THEROX™

AMIHOT II Clinical Summary Report

TherOx, Inc.
17500 Cartwright Road, Suite 100
Irvine, CA 92614-5846
Tel: 949-757-1999

The AMIHOT II Clinical Summary Report was originally submitted in PMA P080005 for the DownStream® AO System. The AMIHOT II Clinical Summary Report has been amended twice, once for the AMIHOT II 12-month data update and once for this Panel Package. The enclosed AMIHOT II Clinical Summary Report begins with background information concerning the current AMI standard of care and the current unmet clinical need, transitioning to a discussion of the SSO_2 Therapy technology, relevant pre-clinical studies, and prior clinical investigations. The bulk of this document is devoted to a comprehensive review of the AMIHOT II clinical trial, including the trial methodology and novel Bayesian statistical design, the study results, and conclusions. This current revision includes a discussion of several alternative Bayesian statistical models that have been included to reflect the most recent Amendments to this PMA.

TABLE OF CONTENTS

1.1 List of Abbreviations and Acronyms 1
1.2 Introduction 7
1.3 Disease State and Current Treatment Options 8
1.3.1 AMI Care in the U.S. 8
1.3.2 Standard of Care – Thrombolytic Therapy vs. PCI 10
1.3.3 Optimization of PCI 12
1.3.4 Adjunctive Therapies in AMI 16
1.3.4.1 Distal Protection Devices in AMI 16
1.3.4.2 Thrombectomy in AMI 17
1.3.4.3 Cooling Devices in AMI 18
1.3.4.4 Pharmacologic Adjunctives in AMI 19
1.3.5 Summary: AMI Standard of Care 21
1.4 Current Outcomes in AMI 22
1.4.1 Major Adverse Cardiac Events (MACE): Summary Data 22
1.4.2 Time to Intervention and Infarct Location: Influence on Patient Outcomes 25
1.4.3 AMI Survival: Progression to CHF 27
1.4.4 The Unmet Meed in AMI 28
1.4.5 SPECT Infarct Size: A Predictive Surrogate Marker 29
1.4.5.1 What is A Clinically Significant Difference in Infarct Size Measured by [redacted]? 30
1.4.5.2 SPECT Infarct Size Synopsis 35
1.4.6 Current Outcomes in AMI: Summary 35
1.5 AO Therapy Administration in AMI – Previous Studies 36
1.5.1 Pre-Clinical Studies of AO Therapy in AMI 36
1.5.1.1 Canine AMI Studies by Spears *et al.* 36

1.5.1.2 Swine Infarct Model: [redacted]c 39
1.5.1.3 Transition to Sub-Selective AO Therapy....40
1.5.1.4 Swine Infarct Studies by Spears *et al.* 41
1.5.1.4.1 Spears Swine Infarct Study No. 1: 90-min Sub-Selective AO Therapy Effectiveness....41
1.5.1.4.2 Spears Swine Infarct Study No. 2: Dose Response 44
1.5.1.4.3 Spears Swine Infarct Study No. 3: AO Therapy 24 Hours Post-AMI 44
1.5.1.5 Summary: Pre-Clinical Evaluations of AO Therapy in AMI....45
1.5.2 Prior Clinical Investigations of AO Therapy in AMI 46
1.5.2.1 Phase I/IA Studies of AO Therapy in AMI 47
1.5.2.1.1 Summary 47
1.5.2.1.2 Differences in Study Parameters between Phase I and Phase IA....49
1.5.2.1.3 Study Methods 50
1.5.2.1.4 Left Ventricular Analysis....50
1.5.2.1.5 Statistical Analysis....52
1.5.2.1.6 Clinical Procedure AMI....52
1.5.2.1.7 Results of Phase I/IA 54
1.5.2.1.8 Phase I/IA Conclusions....58
1.5.2.2 OYSTER-AMI Study....59
1.5.2.2.1 Overview 59
1.5.2.2.2 Results....60
1.5.2.2.3 Conclusions....61
1.5.2.3 AMIHOT I Clinical Trial....62
1.5.2.3.1 Overview 62

1.5.2.3.2 Study Objective 62
1.5.2.3.3 Design 62
1.5.2.3.4 Primary Endpoints 63
1.5.2.3.5 Study Equipment and Methods 64
1.5.2.3.6 Clinical Procedures 65
1.5.2.3.7 Randomization 66
1.5.2.3.8 Post-Randomization Procedures 66
1.5.2.3.9 Endpoint Data Collection 67
1.5.2.3.10 AMIHOT I Study Results 69
1.5.2.3.11 AMIHOT I Summary 78
1.6 Rationale for AMIHOT II Study 79
1.7 AMIHOT II Study Overview and Conduct 80
1.7.1 Device Description 80
1.7.1.1 AO Cartridge 80
1.7.1.2 Patient Connections 83
1.7.1.3 AO System 85
1.7.2 Indications for Use 87
1.7.3 AMIHOT II Study Objective 87
1.7.4 Eligibility Criteria 87
1.7.4.1 Inclusion Criteria 87
1.7.4.2 Exclusion Criteria 88
1.7.5 Randomization Methods 89
1.7.6 Study Endpoints 90
1.7.6.1 Primary Effectiveness Endpoint 90
1.7.6.2 Primary Safety Endpoint 90
1.7.6.3 Secondary Endpoints 90
1.7.7 Study Committees 90
1.7.7.1 Executive Committee 91

1.7.7.2 Steering Committee 91
1.7.7.3 Data and Safety Monitoring Board (DSMB) 93
1.7.7.4 Clinical Events Committee (CEC) 94
1.7.8 Independent Core Laboratories 97
1.7.8.1 [redacted] 97
1.7.8.2 [redacted] (DCRI) – Electronic Electrocardiographic (eECG) Core Laboratory 98
1.7.8.3 [redacted] – SPECT Imaging Core Laboratory 99
1.7.9 AMIHOT II Clinical Procedures, Assessments, and Follow Up 101
1.7.9.1 Patient Evaluation Procedures 101
1.7.9.2 Procedure Medications 101
1.7.9.3 [redacted] Procedures 101
1.7.9.3.1 Patient Anticoagulation 101
1.7.9.3.1.1 Glycoprotein IIb/IIIa Inhibitors 101
1.7.9.3.1.2 Heparin Management 102
1.7.9.3.2 Coronary Angiography 102
1.7.9.3.3 PCI/Stenting Procedure 102
1.7.9.3.4 AO Therapy Procedure 103
1.7.9.3.4.1 Guiding Catheter and Arterial Sheath Selection 103
1.7.9.3.4.2 AO Infusion 104
1.7.9.3.4.3 AO Therapy Device Performance 106
1.7.9.4 Post-Cath Lab In-Hospital Procedures 107
1.7.9.4.1 eECG Monitoring 107

1.7.9.4.2 Cardiac Enzymes, Clinical Chemistry, and Hematology 107
1.7.9.4.3 Patient Management and Hospital Discharge 107
1.7.9.5 [redacted] SPECT Imaging 108
1.7.9.6 30-Day Follow-Up 108
1.7.9.7 6-and12-Month Patient Surveys 108
1.7.9.8 Summary Table: Study Assessments 109
1.7.10 Adverse Event Assessment 109
1.7.10.1 Adverse Event Review Process 112
1.7.10.2 Adverse Event Classification 113
1.7.10.3 Attribution of Adverse Events 114
1.7.10.4 Adverse Event Identification 115
1.7.11 Uniformity of Study Procedures 117
1.7.12 Investigational Site Management and Study Monitoring 117
1.7.12.1 Investigational Sites 117
1.7.12.2 Clinical Site Managers 117
1.7.12.3 Study Monitoring 118
1.7.12.3.1 Pre-Study Visits 118
1.7.12.3.2 Regulatory Approvals 119
1.7.12.3.3 Site Initiation 119
1.7.12.3.4 Interim Monitoring Visits 120
1.7.13 Data Management 120
1.7.13.1 Overview 120
1.7.13.2 Clinical Database Management 121
1.7.13.3 Data Reporting Time Frames 122
1.7.13.4 Data Lock and Transfer 122
1.7.14 Statistical Analysis Overview 123
1.7.14.1 Description of Bayesian Model 123

1.7.14.2 Study Analysis Patient Samples....125
1.7.14.3 General Statistical Analysis Methods....125
1.7.15 IDE-Approved Changes to Investigational Plan....126
1.8 AMIHOT II Study Results....127
1.8.1 Patient Accountability....127
1.8.2 Patient Screening....129
1.8.3 Patient Assignment and Tracking....130
1.8.4 Subject Enrollment by Site....132
1.8.5 Study Data Assessment Compliance....134
1.8.6 Per Protocol Analysis Samples....138
1.8.7 Pre-Randomization Evaluations....139
1.8.7.1 Patient Demographics....140
1.8.7.2 Patient Medical History....142
1.8.7.3 Clinical Complications and Time Intervals....145
1.8.7.4 PCI Data and Cath Lab Information....148
1.8.7.5 Pre-PCI and Post-PCI Angiographic Core Lab Assessments....155
1.8.7.6 Baseline Laboratory Information....160
1.8.7.7 Summary of Baseline Information and Laboratory Data....165
1.8.8 AO Therapy Intra-Procedural Data....166
1.8.8.1 AO Therapy Arterial Access Data....166
1.8.8.2 AO Cartridge Usage and AO Infusion Time....169
1.8.8.3 Causes of Premature AO System Shutdown....172
1.8.8.4 Device Failures....174
1.8.8.5 AO Therapy Delivery Location....175
1.8.8.6 AO Therapy Intra-Procedural Laboratory Assessments....175

1.8.8.7 Summary of AO Therapy Procedural Data.....177
1.8.9 Post-Procedure In-Hospital Evaluations.....177
1.8.9.1 24-Hr Hematology and Clinical Chemistry.....178
1.8.9.2 24-Hr Liver Panel.....181
1.8.9.3 0-24 Hr Cardiac Enzymes.....183
1.8.9.4 Hospital Stay and Discharge Information.....186
1.8.9.5 Summary of In-Hospital Post-Procedural Data.....187
1.8.10 Primary Effectiveness Endpoint: Infarct Size by SPECT Imaging at 14 Days.....187
1.8.10.1 AMIHOT II Infarct Size Results.....188
1.8.10.1.1 ITT Analysis of AMIHOT II Data.....188
1.8.10.1.2 PP Analysis of AMIHOT II Data.....193
1.8.10.1.3 Imputation of Missing Infarct Size Data.....196
1.8.10.2 Analysis of AMIHOT I and II Infarct Size Data Using Simple Pooling.....197
1.8.10.3 Bayesian Analysis of Infarct Size Results: AMIHOT I and II.....201
1.8.10.3.1 Background of Bayesian Model of Effectiveness.....201
1.8.10.3.2 Results of Primary Analysis.....202
1.8.10.3.3 Sensitivity Analysis: Alternative Models.....203
1.8.10.3.4 Additional Bayesian Models to Examine Robustness of Results.....206
1.8.10.3.5 Sensitivity of Model Results to Change in Prior Specification.....219
1.8.10.4 Magnitude of the Treatment Effect.....221

1.8.10.5 Results of Small Infarcts Analysis 222
1.8.10.6 Additional SPECT Imaging Data 227
1.8.10.7 Summary of SPECT Imaging Results 228
1.8.11 Secondary Effectiveness Endpoint: ST Monitoring and ECG Results, 0 – 24 Hrs 230
1.8.11.1 ST-Segment Monitoring Procedure 230
1.8.11.2 % ST Resolution 0 – 6 Hours 232
1.8.11.3 ST Area Results: 0 – 24 Hours 234
1.8.11.4 Additional Quantitative ECG Data 236
1.8.12 AO Therapy Effectiveness Results: Summary 238
1.8.13 AMIHOT II Safety Data Summary 239
1.8.13.1 30-Day Follow Up Clinic Visit 240
1.8.13.2 Primary Composite Safety Endpoint: 30-Day MACE 243
1.8.13.2.1 MACE Definitions 243
1.8.13.2.2 30-Day MACE Assessment Compliance 244
1.8.13.3 30-Day MACE Endpoint Hypothesis and Results 245
1.8.13.3.1 Primary MACE Safety Endpoint ≤ 30 Days, ITT Analysis 245
1.8.13.3.1.1 AMIHOT II Trial Primary Safety Endpoint Summary: ITT Analysis 245
1.8.13.3.1.2 AMIHOT I Trial Primary Safety Endpoint Summary: ITT Analysis 249
1.8.13.3.1.3 Primary Safety Endpoint Testing, Bayesian Methodology: ITT Analysis 249

1.8.13.3.1.4 Alternative Bayesian Models to Test Robustness of Results 252
1.8.13.3.2 Primary MACE Safety Endpoint ≤ 30 Days, PP Analysis 260
1.8.13.3.2.1 AMIHOT II Trial Primary Safety Endpoint Summary: PP Analysis 260
1.8.13.3.2.2 AMIHOT I Trial Primary Safety Endpoint Summary: PP Analysis 262
1.8.13.3.2.3 Primary Safety Endpoint Testing, Bayesian Methodology: PP Analysis.....263
1.8.13.3.3 30-Day MACE Component Events, ITT Analysis 264
1.8.13.3.3.1 Target Vessel Revascularization (TVR) 265
1.8.13.3.3.2 Reinfarction.....267
1.8.13.3.3.3 Stroke 278
1.8.13.3.3.4 Patient Death.....278
1.8.13.4 30-Day MACE Results: Context with Published Trial Data 283
1.8.13.5 30-Day MACE Results: Summary.....283
1.8.13.6 Review of All 30-Day Adverse Event Data: AMIHOT II study 284
1.8.13.6.1 Unanticipated Adverse Device Effects 284

1.8.13.6.2 Anticipated Adverse Events.....284

1.8.13.6.3 Adverse Events Occurring within 30 Days of the Index Procedure.....286

1.8.13.6.3.1 Relationship of Adverse Events Occurring within 30 Days of the Index Procedure 287

1.8.13.6.3.2 Classification of Adverse Events Occurring within 30 Days of the Index Procedure 291

1.8.13.6.3.3 Serious Adverse Events (SAEs) Occurring within 30 Days of the Index Procedure 306

1.8.13.6.3.4 Classification of Serious Adverse Events Occurring within 30 Days of the Index Procedure by Relationship 314

1.8.13.6.3.5 Serious Adverse Events Related to the Index PCI Procedure at 30 Days 326

1.8.13.6.3.6 Serious AO Therapy Device or Procedure Related Adverse Events Occurring within 30 Days of the Index Procedure.....327

1.8.13.6.4 Summary of Bleeding Events 335
1.8.13.6.4.1 Access Site Bleeding.....340
1.8.13.6.4.2 Non-Access Site Bleeding 342
1.8.13.6.4.3 Synopsis of Bleeding Events.....344
1.8.13.6.5 Access Site Events within the First 30 Days 345
1.8.13.6.5.1 Access Site Bleeding: Choice of Infusion Catheter in AO Therapy Patients.....346
1.8.13.6.5.2 Access Site Bleeding: Additional Factors in AO Therapy Patients.....349
1.8.13.6.6 Subset Analyses, MACE and Adverse Events within 30 Days 350
1.8.13.6.6.1 Primary Safety Events by Lesion Location 350
1.8.13.6.6.2 Relationship of Adverse Events Occurring within 30 Days of the Index Procedure by Lesion Location 353
1.8.13.6.6.3 Primary Safety Events by Time to Reperfusion 359
1.8.13.6.6.4 Relationship of Adverse Events Occurring within

30 Days of the Index Procedure by Time to Reperfusion 361
1.8.13.6.6.5 Primary Safety Events by Infusion Catheter Type 366
1.8.13.6.6.6 Relationship of Adverse Events Occurring within 30 Days of the Index Procedure by Infusion Catheter Type.....367
1.8.13.6.7 Safety Summary for 30-Day Events 370
1.8.13.7 Review of All Post-30 Day Adverse Event Data.....371
1.8.13.7.1 Follow Up Assessment at 6 Months Post Procedure 371
1.8.13.7.2 Follow Up Assessment at 12 Months Post Procedure 374
1.8.13.7.3 Post-30 Day MACE Results 377
1.8.13.7.3.1 TVR between 30 Days and 6 Months 381
1.8.13.7.3.2 TVR between 6 Months and 1 Year Follow Up.....382
1.8.13.7.3.3 Reinfarction between 30 Days and 6 Months 383
1.8.13.7.3.4 Reinfarction between 6 Months and 1 Year Follow Up 384
1.8.13.7.3.5 Stroke Events between 30 Days and 6 Months 401

1.8.13.7.3.6 Stroke Events between 6 Months and 1 Year Follow Up 401
1.8.13.7.3.7 Patient Death between 30 Days and 6 Months 402
1.8.13.7.3.8 Patient Death between 6 Months and 1 Year Follow Up 403
1.8.13.7.3.9 Cumulative 1-Year MACE Rates 408
1.8.13.7.4 Unanticipated Adverse Device Effects 409
1.8.13.7.5 Anticipated Adverse Events.....409
1.8.13.7.5.1 Adverse Events Occurring between 30 Days and 6 Months Post Procedure 412
1.8.13.7.5.2 Relationship of Adverse Events Occurring between 30 Days and 6 Months Post Procedure 423
1.8.13.7.5.3 Late Serious Adverse Events.....424
1.8.13.7.5.4 Serious Adverse Events Occurring between 30 Days and 6 Months Post Procedure 434
1.8.13.7.5.5 Relationship of Serious Adverse Events Occurring

between 30 Days and 6 Months Post Procedure 435
1.8.13.7.5.6 Serious Adverse Events Occurring Between 6 Months and 1 Year Post Procedure 435
1.8.13.7.5.7 Relationship of Serious Adverse Events Occurring within 1 Year of the Index Procedure 436
1.8.13.7.5.8 Serious Device or Procedure Related Adverse Events Occurring Post 30 Days 437
1.8.13.7.5.9 Bleeding Events at 6 Months Post Index Procedure 437
1.8.13.7.5.10 Bleeding Events at 1-Year Post Index Procedure 438
1.8.13.7.6 Late Adverse Event Summary 441
1.8.13.8 Summary of Safety-Related Data for AMIHOT II Study 441
1.8.14 Medications.....443
1.8.14.1 Medications Administered up to 7 Days Prior to Admission 444
1.8.14.2 Medications Administered Post-Symptom Onset, Prior to PCI 446

1.8.14.3 Medications Administered in the Cardiac Catheterization Laboratory 449
1.8.14.4 Medications Administered Post Procedure, Prior to Discharge 452
1.8.14.5 Discharge Medications....455
1.8.14.6 Medications Administered Post-Discharge through 30-Day Follow Up 457
1.8.14.7 Medications Summary 459
1.8.15 Protocol Deviations....459
1.8.15.1 Inclusion/Exclusion and Randomization Deviations 460
1.8.15.2 Protocol-Required Labs 462
1.8.15.3 Medication, Study Procedure, and Follow Up Deviations 466
1.8.15.4 Summary of Protocol Deviations....469
1.8.16 Poolability of Site-Specific Data 469
1.8.16.1 Demographic, Clinical and Laboratory Data; and Primary Effectiveness Endpoint, Infarct Size....469
1.8.16.2 Primary Safety Endpoint, 30-Day MACE 470
1.9 AMIHOT II Study Conclusions....471
1.10 Clinical Summary Report Bibliography 472
1.11 Tables, Figures and Listings Index for Clinical Summary Report 481

AMIHOT II Clinical Summary Report

1.1 List of Abbreviations and Acronyms

A list of acronyms and abbreviations used throughout **Section 1** is provided in **Listing 1.**

Listing 1. Acronyms and Abbreviations

[redacted]	
% DS	Percent Diameter Stenosis
ABG	Arterial Blood Gas
ACC	American College of Cardiology
ACE	Angiotension Converting Enzyme
ACT	Activated Clotting Time
AE	Adverse Event
AHA	American Heart Association
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
AMIHOT	Acute Myocardial Infarction With Hyperoxemic Therapy
AN	Area of Necrosis
AO Therapy	Aqueous Oxygen Therapy
AOCS	AO Cartridge Subsystem
apO_2	Arterial Blood Partial Oxygen Pressure (solubilized equivalent)
APSAC	Anisoylated Purified Streptokinase Activator Complex
AR	Area at Risk
[redacted]	[redacted]
ASA	Acetyl Salicylic Acid
AST	Asparatate Aminotransferase
[redacted]	[redacted]
BMC	Blood Mixing Chamber
BMI	Body Mass Index
BMS	Bare Metal Stent
BP	Blood Pressure
BPM	Beats Per Minute
BUN	Blood Urea Nitrogen

CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CARE	Cholesterol and Recurrent Events
CBC	Complete Blood Count
CCS	Canadian Cardiovascular Society
CCL	Cardiac Catheterization Laboratory
CCU	Cardiac Care Unit
CDP	Clinical Discovery Platform
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CI	Clinically Indicated
CK	Creatine Kinase
CK-MB	Creatine Kinase Myocardial-Band Isoenzyme
cm	Centimeter
CORE	Collaborative Organization for RheothRx Evaluation
COURAGE	Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation
CPR	Cardiopulmonary Resuscitation
CRA	Clinical Research Associate
[redacted]	[redacted]
CRF	Case Report Form
CRO	Clinical Research Organization
CSS	Coronary Stent System
CTFC	Corrected TIMI Frame Count
CTO	Chronic Total Occlusion
CVA	Cerebral Vascular Accident
D2B	Door To Balloon
DBP	Diastolic Blood Pressure
DCF	Data Clarification Form
[redacted]	[redacted]

DES	Drug Eluting Stent
DIC	Deviance Information Criterion
dL	Deciliter
DS	Diameter Stenosis
DSMB	Data Safety Monitoring Board
Eecg	Electronic Electrocardiographic
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EECSS	Everolimus Eluting Coronary Stent System
EF	Ejection Fraction
EMERALD	Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris
ER	Emergency Room
EtO	Ethylene Oxide
FDA	Food and Drug Administration
FU	Follow Up
g	grams
GCP	Good Clinical Practice
GERD	Gastro-Esophageal Reflux Disorder
GGPT	Gamma Glutamyl Transferase
GI	Gastrointestinal
GIK	Glucose Insulin Potassium
GP	Glycoprotein
GU	Gastric Ulcer
Hct	Hematocrit
HDL	High Density Lipoprotein
Hgb	Hemoglobin
IABP	Intra-Aortic Balloon Pump
IC	Intra Coronary
ICD	Implantable Cardiac Defibrillator
IDE	Investigational Device Exemption
IFU	Instructions For Use

IMV	Interim Monitoring Visit
IQR	Interquartile Range
IRA	Infarct Related Artery
IRB	Institutional Review Board
ITT	Intent To Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IVUS	Intravascular Ultrasound
LAD	Left Anterior Descending Coronary Artery
LBBB	Left Bundle Branch Block
LCX	Left Circumflex Coronary Artery
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LL	Late Loss
LMWH	Low Molecular Weight Heparin
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Event
mCi	Millicuries
MeDRA	Medical Dictionary fro Regulatory Activities
MDR	Medical Device Reporting
mg	Milligram
MI	Myocardial Infarction
MLD	Minimum Lumen Diameter
mm	Millimeter
mmHg	Millimeter of Mercury
MPO	Myeloperoxidase
MRI	Magnetic Resonance Imaging
NEJM	New England Journal of Medicine
NR-MI-4	National Registry of Myocardial Infarction
NTG	Nitroglycerine
OD	Outer Diameter

OUS	Outside the United States
OYSTER-AMI	Oxygen in ST-Elevation Reperfused Acute Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PES	Paclitaxel-Eluting Stent
PI	Principal Investigator
PO	Per Os
pO_2	Partial Oxygen Pressure (or solubilized equivalent)
PP	Per Protocol
PTCA	Percutaneous Transluminal Coronary Angioplasty
QC	Quality Control
QCA	Quantitative Coronary Angiography
QD	Every Day
RBC	Red Blood Cells
RCA	Right Coronary Artery
RCT	Randomized Clinical Trial
RR	Relative Risk
r-TPA	Recombinant Tissue Plasminogen Activator
RVD	Reference Vessel Diameter
RWMSI	Regional Wall Motion Score Index
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SES	Sirolimus-Eluting Stent
SPECT	Single Photon Emission Computer Tomography
SSO_2	Supersaturated Oxygenation
STEMI	ST-Elevation Myocardial Infarction
STP	Standard Temperature and Pressure (25°C, 1 atmosphere)
TCT	Transcatheter Therapeutics Meeting
TEE	Trans Esophageal Echocardiogram
TIA	Transient Ischemic Neurological Attack

TIMI	Thrombolysis in Myocardial Infarction
TLR	Target Lesion Revascularization
TNK	Tenecteplase
TTC	Triphenyl Tetrazolium Chloride
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effects
Mg	Microgram
UK	United Kingdom
URL	Upper Reference Limit
USA	United States of America
VSD	Ventricular-Septal Defect
WBC	White Blood Cells
WD	Withdrew
WHO	World Health Organization
WMSI	Wall Motion Score Index

1.2 Introduction

Acute myocardial infarction (AMI or MI) occurs when the arterial blood supply to a part of the heart is interrupted, typically by a blood clot from a ruptured plaque. The arterial blockage results in local oxygen deprivation or ischemia, triggering a cascade of inflammatory reactions and processes that lead to infarction, or necrosis of a portion of the myocardium. Typical AMI symptoms include chest pain, shortness of breath, nausea, vomiting, palpitations, sweating, and anxiety. AMI is a medical emergency requiring immediate intervention, and is the worldwide leading cause of death for both men and women. The severity of an AMI is largely dependent on three factors: the extent and location of the occlusion in the coronary artery, the duration of the occlusion, and the amount of supporting collateral circulation adjacent to the infarct area. The more proximal the coronary occlusion within the vessel, the more extensive is the amount of myocardium at risk of infarction. The longer the time period of vessel occlusion, the greater is the amount of irreversible myocardial damage distal to the occlusion. The larger the AMI, the greater is the chance of death due to a mechanical complication or pump failure.

In the progression of an AMI, myocardial cell death first occurs in the area that is most distal to the arterial blood supply. As the duration of the occlusion increases, the area of infarction enlarges and spreads throughout the flow-compromised tissue. The extent of myocardial cell death defines the magnitude of the AMI. Current therapeutic regimens focus on removing the arterial blockage and restoring blood flow. If blood flow can be restored to at-risk myocardium, more heart muscle may be salvaged from irreversible damage or death.

Important risk factors for AMI have been well-studied and include: a previous history of vascular disease such as atherosclerotic coronary heart disease and/or angina, previous MI or stroke, a history of cardiac arrhythmia, age, smoking, excessive alcohol

consumption or abuse of certain narcotics, high triglyceride levels, high LDL (low-density lipoprotein) and low HDL (high density lipoprotein), diabetes, high blood pressure, obesity, and chronic stress[1].

1.3 Disease State and Current Treatment Options

Approximately one third of all AMIs are 'silent', occurring without chest pain or other outward symptoms[2]. Immediate treatment for suspected AMI includes the administration of supplemental oxygen, aspirin, nitroglycerin, and pain relief. Upon hospital admission, the patient receives a number of confirming diagnostic tests, including an electrocardiogram (ECG), a chest X-ray, and blood tests to detect elevated cardiac enzyme levels. Available in-hospital treatment strategies include blood clot-dissolving medications and cardiac catheterization to identify the location of the MI and mechanical intervention to relieve the blockage and restore epicardial blood flow.

Myocardial infarction is a common presentation of ischemic heart disease, the leading cause of death in developed countries. The World Health Organization (WHO) estimated that in 2002, 12.6% of deaths worldwide were from ischemic heart disease[3].

As outlined in this section, the current preferred treatment options for AMI are revascularization by either thrombolytic therapy or percutaneous coronary intervention (PCI) with stenting, in cases where emergency bypass surgery is not indicated. The evolution of current practice will be discussed, in addition to the reasons for failure of several once-promising adjunctive treatments to the current care options.

1.3.1 AMI Care in the U.S.

Heart disease is the leading cause of death in the United States, with a higher aggregate mortality rate than cancer. Coronary heart disease, which nationally affects approximately 7.2 million men and 6.0 million women, is responsible for 1 in 5 deaths in the U.S. According to medical literature, 1.2 million Americans suffer a (new or

recurrent) coronary attack every year, with a 40% mortality rate[4]. The National Registry of Myocardial Infarction (NR-MI-4) estimates that 500,000 ST-elevation myocardial infarctions (STEMI) occur in the United States each year[5]. STEMI is characterized by elevation of more than 1 mm in two contiguous leads from ECG monitoring, and is considered to be the most serious type of myocardial infarction.

AMI symptom recognition and speed of the initial response, particularly for patients who experience cardiac arrest, is extremely important. Primary PCI includes emergent angiography followed by mechanical recanalization of the occluded artery with a balloon catheter (typically including stent placement), without prior administration of thrombolytic therapy[6]. Thrombolytic therapy involves the in-hospital administration of intravenous clot-busting drugs to pharmacologically dissolve the arterial occlusion. Beyond the early critical initial response period and the urgency in re-establishing blood flow to the myocardium, adjunctive pharmacologic strategies are important as well. The American Heart Association (AHA) / American College of Cardiology (ACC) Guidelines[5] make recommendations for STEMI treatment, including the administration of supplemental oxygen therapy (via mask or nasal cannula), nitrate therapy (sublingually or IV), analgesics such as morphine sulfate, aspirin, and beta-blockers.

STEMI patients admitted to the hospital typically undergo a concise and rapid evaluation for reperfusion therapy. Restoration of blood flow in the culprit artery after the onset of STEMI symptoms is a key determinant of short and long term outcomes regardless of whether reperfusion is accomplished by thrombolytic therapy or PCI[7, 8]. The timely use of any type of reperfusion therapy is likely more important than the expanding array of options, if the optimal choice of therapy will delay treatment[5]. However, given a choice of therapeutic options when time is not a deciding factor, an invasive strategy, *i.e.* PCI, is preferred when a cardiac catheterization laboratory (cath lab) is available with surgical back up and the skilled personnel/resources to accommodate high-risk STEMI patients.

Results suggest that every minute of delay in intervention for STEMI adversely affects one-year mortality, for both thrombolytic therapy and primary angioplasty[9, 10].

1.3.2 Standard of Care – Thrombolytic Therapy vs. PCI

The two primary options for AMI care are target vessel revascularization by either thrombolytic therapy or PCI. Rapid re-establishment of infarct vessel patency and microvascular flow provides the best opportunity for minimizing post-MI mortality. Blood flow can be restored by thrombolysis, primary PCI, or facilitated PCI, which involves a combination of both therapies. In comparative studies, primary PCI offers a greater mortality benefit than thrombolysis in patients with AMI[11]. In addition, observed near-term stroke rates and risk of reinfarction have been shown to be significantly lower in patients receiving primary PCI compare with thrombolytic therapy. These clinical outcomes have been demonstrated in data reported in controlled clinical trials; specific results are provided below.

Anderson *et al.*[12] reported on a randomized trial of 1,572 patients with AMI that were randomized to treatment with angioplasty or accelerated treatment with intravenous alteplase. The primary endpoint was a composite of death, reinfarction, and disabling stroke at 30 days. Among patients who underwent randomization at referral hospitals, the primary endpoint was reached in 8.5% of the patients in the angioplasty group, as compared with 14.2% of those in the fibrinolytic group (p=0.002). The results were similar among patients who were enrolled at invasive treatment centers: 6.7% of the patients in the angioplasty group reached the primary end point, as compared with 12.3% in the fibrinolysis group (p=0.001); no significant differences were observed in the component 30-day rates of death (6.6% vs. 7.8%, p=0.35) or stroke (1.1% vs. 2.0%, p=0.15). Ninety-six percent of patients were transferred from referral hospitals to an invasive treatment center. The investigators concluded that a reperfusion strategy involving the transfer of patients to an invasive treatment center for primary angioplasty

is superior to on-site fibrinolysis, provided that the transfer is completed within two hours or less.

Results of other prospective randomized clinical trials have demonstrated improved outcomes for STEMI patients undergoing PCI compared to patients administered thrombolytic therapy. Widimsky *et al.*[13] reported long term outcomes of AMI patients with five-year follow up in the PRAGUE-2 trial. The PRAGUE-2 trial enrolled 850 STEMI patients presenting to community hospitals without cath labs within 12 hours of symptom onset. Patients were randomized into two groups, thrombolytic therapy at the community hospital and interhospital transfer for primary PCI. At 5-year follow up, the composite safety endpoint (death, reinfarction, stroke or revascularization) rate was 53% in the thrombolytic group compared with 40% in the PCI group ($p=<0.001$). This study demonstrated that the early documented clinical benefit in employing PCI in preference to thrombolytics was sustained over a long-term 5-year follow up period.

In another study, De Luca *et al.*[14] examined pre-procedural TIMI flow grade and its effect on mortality in patients with AMI treated by primary angioplasty. The study's review of 1,791 patients treated for AMI between 1994-2001 stratified subjects in high and low-risk groups depending on angiography and other clinical indicators. The study showed that pre-procedural TIMI flow grade 3 is an independent predictor of one-year survival in high-risk patients with AMI treated by primary angioplasty. This result is intuitive and suggests that all efforts should be made to obtain early and optimal restoration of coronary flow, particularly in high-risk patients. Because the use of primary PCI results in high procedural success rates in terms of achieving normal TIMI 3 flow in a matter of minutes, this study provides further evidence of the case for PCI as a preferred reperfusion strategy. In another published study, Mehta *et al.*[15] reported on the effectiveness of PCI compared to thrombolytic therapy in a vulnerable high-risk group, elderly AMI patients. The study results suggest that primary PCI is associated with a

decrease in reinfarction and mortality for in hospital management for this vulnerable elderly population.

Looking at a broader scope of clinical data, the results of 15 trials have been published in an overview of primary PCI compared to thrombolytics. A meta-analysis of 5,253 randomized STEMI patients demonstrated that rescue PCI for failed fibrinolysis significantly reduced the combined rate of 30-day death or reinfarction (10.8% vs. 16.8%) (OR, 0.60; p = 0.012) compared with thrombolytics alone. Fibrinolysis-facilitated PCI was associated with increased 90-day reinfarction as compared with primary PCI alone (5.0% vs. 3.0%) (OR, 1.68; p = 0.013) without significant impact on mortality. The findings support rescue PCI but do not support fibrinolysis-facilitated PCI in lieu of primary PCI alone.

The data cited above is informative and not all-inclusive; ample outcome-based evidence exists that shows consistently improved clinical outcomes in STEMI patients treated with PCI vs. thrombolytics. However, in acknowledgment of operator skill as an influence in STEMI patient outcomes, the AHA recommends that primary PCI for acute STEMI performed at hospitals without established elective PCI programs should be restricted to those institutions capable of performing a minimum number of 36 PCI procedures per year[5].

1.3.3 Optimization of PCI

The practice of PCI has undergone many refinements in achieving early and complete revascularization of the culprit epicardial vessel involved in a patient's AMI. Primary angioplasty using a dilatation balloon was modified to include stenting, and stent deployment, sizing, and design have evolved continuously with the end result of reducing target vessel revascularization rates with the current generation of drug-eluting stents (DES)[16]. Furthermore, clinical evidence shows that a complementary pharmacologic strategy involves the concomitant use of aspirin, glycoprotein IIb/IIIa inhibitors, and

other medicaments. In addition, initiatives to reduce time to presentation at the hospital, and to shorten the in-hospital door-to-balloon times, have contributed to an awareness that 'time is muscle'[17]. Taken together, these improvements demonstrate a clear trend towards achieving early and complete revascularization of the arterial blockage. Specific clinical trial data is presented below that provides the evidence-based evolution of primary PCI to its current clinical practice.

Stone *et al.*[8] reported that among 2,507 patients enrolled in four PAMI trials undergoing primary PCI for AMI, in whom procedural success is high (TIMI flow grade = 3 in > 90% of patients), outcomes are improved by early reperfusion. The study authors reported that patients with pre-PCI TIMI 3 flow had greater baseline left ventricular ejection fraction (LVEF) than patients with TIMI flow < 3 (57±10% vs. 53±11%; p=0.003) and were less likely to present in heart failure (Killip class 2 or 3) (7.0% vs. 11.6%; p=0.009). Six-month mortality was also reduced in patients with greater baseline TIMI flow: 0.5% for TIMI 3, 2.8% with TIMI 2, and 4.4% with TIMI 0/1 (p=0.009). In summary, the study showed that AMI patients undergoing primary PCI with presenting TIMI 3 flow are less likely to develop complications related to left ventricular failure, and exhibit improved survival.

These data suggest the optimal deployment of combination therapy, including both pharmacological strategies to promote early reperfusion and definitive mechanical intervention via PCI for AMI treatment. This combined approach has been the subject of randomized controlled trials, notably the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. The CADILLAC study[18] was a multicenter randomized trial of 2,082 STEMI patients who presented within 12 hours from symptom onset, assigned to one of four groups: PCI alone, PCI + abciximab, PCI w/ stenting, or PCI w/stenting + abciximab. Results showed that for the composite endpoint of death, reinfarction, disabling stroke, and target vessel revascularization, 30-day and 6-month outcomes favored PCI w/ stenting (30 day: 5.7%; 6 mo: 11.5%) over

PCI alone (30 day: 8.3%; 6 mo: 20.0%) ($p < 0.001$ at 6 mo.). Results were nominally better with the addition of abciximab into the treatment regiment, yielding composite endpoint results of 4.4% and 10.2% at 30 days and 6 months, respectively (p = ns with respect to PCI w/ stenting results). The CADILLAC investigators concluded that even if an optimal result is achieved after primary PCI in AMI, early and late outcomes can be further improved with routine stent implantation and the strategic use of abciximab.

Drug-eluting coronary stents (DES) represent the most recent procedural advancement in PCI. Whereas risk factors influencing restenosis and need for target vessel revascularization are well known, risk factors for death and reinfarction, ostensibly due to thrombosis, after drug-eluting coronary stent implantation need to be carefully evaluated. Complicating this picture is the use of different stent-coating agents with different pathophysiological effects, and depositing these agents at different concentrations using different techniques within the stents. Despite this apparent variability, DES are used routinely to treat AMI, and have been evaluated in several randomized clinical trials. The net effect seen in the totality of the data appears to be a marked decrease in target vessel revascularization (TVR), with some controversy over a small but finite risk of in-stent thrombosis.

The German Cypher Stent Registry[19] examined DES data in both AMI and elective cases were from April 2002 to December 2004: 7,445 patients at 122 hospitals, who received at least one sirolimus-eluting stent during PCI, were included. Complete follow-up at a median of 6.6 months was available in 6755 patients (91%). The reported death and non-fatal myocardial infarction rates were 1.8% and 2.3%, respectively. Independent predictors of death or MI were initial presentation with STEMI or non-STEMI (OR 2.21, $p< 0.0001$), cardiogenic shock (OR 3.05, $p= 0.0003$), renal insufficiency (OR 1.74, $p=0.0017$), reduced left ventricular function (OR 1.74, $p=0.0027$), age (per decade) (OR 1.19, $p=0.0058$), diabetes mellitus (OR 1.39, $p=0.0183$), 3-vessel disease (OR 1.32, $p=0.043$), and prior MI (OR 1.35, $p=0.047$), whereas interventional and lesion

characteristics showed no significant association. These results demonstrate that the most powerful predictors of death or MI after sirolimus-eluting stent implantation during PCI are presentation with an acute coronary syndrome, impaired left ventricular ejection fraction, and conventional risk factors for coronary heart disease. DES use did not appear to lead to statistically significant increases in major clinical events in the context of historical rates. Thus, data taken from this large registry population supports DES use from a general clinical perspective; focused data for AMI patients treated with DES is discussed below.

Using the previously discussed CADILLAC trial data as a benchmark, primary PCI with bare metal stenting and concomitant abciximab administration were established as the best available reperfusion strategy for STEMI patients. Focusing the discussion to incremental improvements in moving to DES use in this population, sirolimus-eluting stents (SES), compared to bare metal stents (BMS), have demonstrated reductions in the incidence of TVR at one year with demonstrated equivalency in other clinical outcome measures at one year, as reported in data obtained in the TYPHOON trial[20]. Additionally, a study reported by Newell *et al.*[21] for 306 STEMI patients randomly assigned to either SES or BMS showed marked reductions in 6-month TVR and mortality in SES patients as compared to subjects receiving BMS. Similarly, the PASSION trial[22] evaluated the use of paclitaxel-eluting stents (PES) as compared to BMS for STEMI patients, and showed equivalency in clinical outcome at 30 days and one year. While the use of DES has become routine in AMI management, the primary benefits demonstrated consistently across multiple trials thus far are in the reduction in repeated revascularization procedures.

The currently available standard of care for the STEMI patient has set a high bar that must be exceeded in order to demonstrate further improvements for this high-risk patient group; in order to meet this challenge, it is essential to understand the current patient outcomes in AMI and the associated clinical unmet need that remains unaddressed

despite many incremental refinements in PCI. Before engaging in this discussion, lessons can be learned from several failed attempts to augment the current standard of care in AMI using adjunctive therapies.

1.3.4 Adjunctive Therapies in AMI

At the 2006 Transcatheter Cardiovascular Therapeutics (TCT) meeting, Gregg W. Stone, M.D. gave a presentation[23] focused on the many challenges that face the clinician and patient in contemporary PCI treatment of AMI. As presented by Dr. Stone, performance outcomes leave much room for improvement, and must be addressed by going beyond epicardial flow restoration and focusing on more rapid reperfusion, developing therapies that focus on limiting local myocardial damage and reperfusion injury, and refining cellular-based therapies to repair the tissue post-AMI. Dr. Stone emphasized that bleeding and restenosis must be minimized in this patient group. While some of these topics outlined by Dr. Stone fall beyond the milieu of this discussion, an overview of representative PCI-adjunctive therapies that have been attempted in the area of microvascular improvement and myocardial salvage is relevant. A number of mechanical and pharmaceutical therapies have been used as adjunctive therapies or treatments in the past, but none of the therapies effectively address the underlying issue of local myocardial damage and microvascular dysfunction. Some representative adjunctive therapies and treatment modalities are described herein.

1.3.4.1 Distal Protection Devices in AMI

One of the criticisms of primary PCI for STEMI is the 'no-reflow' condition and microvascular flow stagnation that can occur in the distal coronary artery tree. Distal embolization of thrombus and atheromatous material has been hypothesized to be a factor in the no-reflow phenomenon and microcirculatory dysfunction observed post-AMI. Distal protection devices are designed to physically entrap and/or adsorb both debris and soluble factors that may contribute to the no-reflow condition[24]. These devices have been

in commercial use for a variety of clinical applications, with demonstrated effectiveness in clot retrieval, but have not been proven to be safe and effective in AMI as an adjunctive therapy. To address this issue, The Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris (EMERALD) trial[25] randomized 501 patients with AMI to assess the safety and effectiveness of using the *GuardWire*® (Medtronic, Inc.; Minneapolis, Minnesota) distal protection device. All eligible patients received standard pharmacologic agents and were randomized to either PCI alone (n = 249) or PCI with adjunctive use of the *GuardWire*® distal protection device (n = 252). Results from the EMERALD trial showed no differences in clinical outcomes for patients whether clot retrieval was employed or not. In addition, although distal protection devices are thought to improve distal reperfusion by eliminating the source of no-reflow, the EMERALD data showed no differences in the two randomized cohorts in three telltale surrogate markers: post-PCI myocardial blush score, ST-segment resolution at 30 minutes post-PCI, and infarct size showed statistical equivalency.

Thus, while the atheroembolic debris may be loosened and entrained in the blood flow during primary PCI, the results of the EMERALD trial question the pathophysiological impact of distal embolization during mechanical reperfusion therapy; its impact on the no-reflow condition may perhaps be minor or negligible. In addition to the EMERALD trial, the PROMISE[26] and AIMI Trials[27] have demonstrated neutral or negative effects of these and similar devices on myocardial reperfusion and infarct size. Distal protection devices have not proven to be safe and effective for STEMI intervention and thus have not been incorporated into the standard of care for this patient population.

1.3.4.2 Thrombectomy in AMI

Thrombectomy removal systems are mechanical devices used to remove thrombus from the arterial wall. The effectiveness of thrombectomy in AMI was evaluated using the Possis Medical AngioJet® device in the AIMI trial[27], conducted in 2004. As seen in

evaluations of distal protection devices, the AIMI trial demonstrated no clinical benefit in the use of the device. The primary endpoint of infarct size measured by [redacted] PECT imaging at one month was significantly higher in patients treated with thrombectomy vs. control subjects (12.5% vs. 9.8%; p=0.018). More recently, a study published by Svilaas *et al.*[28] showed that simple aspiration catheters may improve myocardial blush scores and ST-segment resolution but have not been proven to demonstrate clinical benefit. These trial results underscore the assertion that thrombus removal, while instantly gratifying for the interventional cardiologist, has no definitive association with amelioration of the no-reflow condition and microvascular flow impairment and dysfunction post-AMI; these factors must be addressed directly to improve STEMI patient outcomes.

1.3.4.3 Cooling Devices in AMI

Experimental data suggest that myocardial temperature is an important determinant of the extent of tissue necrosis or death during AMI. Endovascular cooling is a relatively new cath-lab based therapeutic approach for AMI. Dixon *et al.*[29] conducted a pilot study of a novel heat-exchange catheter on a series of patients, which involved reducing the patient's core temperature below 34°C prior to performing PCI. This pilot study reported data on 42 AMI patients for the SetPoint Endovascular Temperature Management System (Radiant Medical, Redwood City, CA), demonstrating procedural feasibility but no differences in median infarct size measured at 30 days in this small sample. In a follow-up pivotal study, Otieno[30] summarized the research completed by the participating investigators in the COOL-MI Trial that randomized 392 patients with STEMI to either primary PCI (n=199) or primary PCI with adjunctive endovascular cooling (n=193). The primary endpoint of infarct size at 30 days was equivalent in the two groups, 13.8% in controls vs. 14.1% in the hypothermia group (p=0.83). The nature of the induced hypothermia procedure must be questioned; primary PCI was delayed by administering endovascular cooling. Any adjunctive procedure that delays PCI runs counter to current

initiatives to relieve the primary vessel blockage and restore epicardial perfusion as quickly as possible. An objective evaluation of cooling strategies must question the utility of this approach for in-hospital AMI care, and whether any mechanisms for relieving microvascular dysfunction and improving myocardial salvage are present.

1.3.4.4 Pharmacologic Adjunctives in AMI

Adenosine

Adjunctive pharmacologic strategies in AMI include the use of adenosine in the cath lab; early small studies[31] had suggested that adenosine was a promising therapy to decrease the size of an evolving infarct. To formally test its safety and effectiveness, the AMISTAD-II clinical trial was designed as a randomized, placebo-controlled evaluation of adenosine as an adjunctive complement to either PCI or thrombolytic therapy in AMI treatment[32, 33]. Eligible patients (n = 2,118) all presented with evolving anterior STEMI and were receiving reperfusion therapy in the form of either thrombolytics or primary PCI. Study subjects (n=2118) were randomized to either a 3-hour adenosine infusion (at two different doses) or to a placebo control group. The AMISTAD-II trial results showed that clinical outcomes in STEMI patients undergoing reperfusion therapy were not significantly improved with adenosine; however, promising patient subgroups were identified in post hoc analysis that may yield better outcomes in future studies. Failing to meet the primary study endpoints imposed in the AMISTAD-II trial, adenosine has no indication for STEMI.

Glycoprotein IIb/IIIa Inhibitors

The use of glycoprotein IIb/IIIa inhibitors during primary PCI has become common clinical practice; however, dosimetry and time of administration have not been standardized. Early trials showed that PCI facilitated by a combination of abciximab and reduced dose reteplase were a safe and effective approach[34], and results from the

CADILLAC trial[18] suggest that an optimal cath-lab based AMI treatment strategy involves PCI with stenting plus abciximab. No definitive data have been presented to suggest optimal dosimetry for IIb/IIIa inhibitors, or a preferred agent among the group of abciximab, eptifibatide, and tirofiban.

Glucose Insulin Potassium (GIK)

During myocardial ischemia, the ischemic muscle switches from utilizing fatty acids for metabolism to a glucose oxidation cycle. Accordingly, some researchers have hypothesized that the administration of insulin in the form of combination therapy may be beneficial in AMI, suppressing free fatty acid uptake and maximizing glucose metabolism. Historically, prior to the advent and refinement of PCI, some trials were performed utilizing infusions of glucose insulin potassium (GIK) combination treatments; however, many of these studies are dated, not relevant to current clinical AMI management, and prove difficult to evaluate in context. However, one study[35] has been reported for subjects receiving primary PCI (without stenting) with and without the adjunctive administration of GIK. Study results showed no statistical differences in the primary study endpoint of 30-day mortality between the GIK infusion group (n = 476; 30-day mortality = 4.8%) and the control group (n = 464; 30-day mortality = 5.8%). A significant decrease in 30-day mortality was noted for subjects with no presentation of heart failure in post hoc analysis. Dr. Carl Apstein published a follow-up editorial[36] on GIK use in AMI noting the history of mixed results and lack of definitive evidence for efficacy. Despite numerous studies and a long list of proponents, the use of GIK infusions has never been established as part of the standard of care for AMI.

While the hypothesis of nourishing the ischemic myocardium with GIK infusions has a plausible mechanistic argument, this treatment and other adjunctive pharmacologic therapies are totally dependent on a vascular flow pathway into the ischemic zone. Because of microvascular impairment in the distal myocardial capillary beds, this critical

flow pathway is inoperable and it is unlikely that the drugs can reach their intended target site for maximal effect. The agents may be highly effective when used in combination with an adjunctive therapy that offers access to the target zone.

Gene Therapy

Gene therapy is a relatively new treatment used to regenerate the muscle cells of the myocardium. Globally, there are many studies underway examining gene therapy application in AMI. Stem cell therapy may be given to patients via intracoronary and/or intramuscular means and can be administered by the interventional cardiologist within the cath lab setting. Thus far, no data are available to conduct a meaningful evaluation of the premise, the deployment techniques, dosimetry, preferred cell lines, or the possible efficacy or safety of the practice. To date, publicly presented studies consist of small trials with limited long-term follow up. However, gene therapy may show hope of regenerating infarcted or malfunctioning myocytes and the associated microvasculature, and must be considered a promising technology on the horizon.

1.3.5 Summary: AMI Standard of Care

Acute MI, and specifically STEMI remains the major cause of cardiovascular morbidity. Current evidence shows that when patients have equal access either primary PCI or thrombolytic therapy, primary PCI is the preferred option for care. The current standard of care in primary PCI involves stent implantation, often using a drug-eluting stent, accompanied by adjunctive pharmacologic agents such as aspirin, clopidogrel, glycoprotein IIb/IIIa inhibitors, and anticoagulant therapy. Several adjunctive therapies have sought to improve upon the current standard of care; however, results from controlled randomized studies have not supported the inclusion of additional procedures, devices, or drugs into the currently established treatment regimen. A discussion of current clinical trial outcome data follows in the next section, to provide a means of comparison for future therapies.

1.4 Current Outcomes in AMI

Numerous publications are available outlining current outcomes in interventional trials of AMI therapies. In this section, clinical outcomes will be presented using MACE data from several trials to provide a baseline against which future trials may be compared. Following this discussion, the importance of two key clinical factors will be highlighted, infarct location and time to reperfusion therapy, with emphasis on the clinical impact of these important factors. Lastly, the clinical unmet need is discussed.

1.4.1 Major Adverse Cardiac Events (MACE): Summary Data

Major Adverse Cardiac Event (MACE) rates for treatment of STEMI were obtained from scientific publications describing controlled clinical trials. Studies were identified based upon an ongoing review of relevant published clinical data obtained from the interventional trial literature. The clinical trials selected for review met the following criteria:

- Interventional cardiology trial for acute MI;
- The study was randomized and controlled;
- Reperfusion therapy was employed in each treatment arm;
- The therapies have clinical indication for AMI;
- A minimum of 100 patients were enrolled in each treatment arm; and
- The results were published within the past ten years.

Eleven randomized, controlled clinical trials were selected based on the criteria outlined above. Available MACE data using the individual components of death (all causes), reinfarction, target vessel revascularization, and stroke were compiled from published trial data and are presented in **Table 1**. With the exception of the TYPHOON trial[20], these data represent 30-day MACE rates; data collected at 12 months are reported for this study. Because TYPHOON represents a randomized, controlled evaluation of sirolimus-

eluting stents as compared to bare metal stents for AMI treatment, the data are noteworthy despite the difference in reporting windows and are included in the table.

Several trials do not have published rates for some of the individual MACE component variables; notably, the incidence of stroke is not available for several of the trials. The MACE rates for these studies are therefore conservative due to this exclusion from the composite tally. Despite these differences, a comparative review of the information provided in **Table 1** is valuable.

Table 1. 30-day MACE Data for Recent Acute MI Trials

Trial	Arm	N	Death	Re-infarct	TVR	Stroke	Composite*
ACE[37]	Stent	200	4.0	4.5	1.5	0.5	10.5
	Stent + abciximab	200	3.5	0.5	0.5	0.0	4.5
ADMIRAL[38]	Stent + placebo	151	6.6	2.6	6.6	NR	14.6
	Stent + abciximab	149	3.4	1.3	1.3	NR	6.0
CADILLAC[18]	Stent	512	2.2	1.0	3.3	0.2	5.7
	Stent + abciximab	524	2.7	0.8	1.6	0.2	4.4
	PTCA	518	2.5	0.8	5.6	0.2	8.3
	PTCA + abciximab	528	1.1	0.8	3.4	0.0	4.8
CAPTIM[39]	Pre-hospital thrombolytics	419	3.8	3.7	NR	1.0	8.2**
	PTCA	421	4.8	1.7	NR	0.0	6.2**
EMERALD[25]	Stent	249	2.9	NR	NR	NR	NR
	Stent + distal protection	252	2.1	NR	NR	NR	NR
PASSION[22]	Paclitaxel stent	309	2.6	0.7	2.7	NR	6.0
	Bare metal stent	310	4.2	1.7	3.0	NR	8.9
RAPPORT[40]	PCI	242	2.1	4.1	12.4	NR	16.1
	PCI + abciximab	241	2.5	3.3	9.1	NR	13.3
STENT PAMI[41]	PTCA	448	1.8	1.1	3.8	NR	5.8
	Stent	452	3.5	0.4	1.3	NR	4.6
STOPAMI-3[42]	Stent	305	5.6	NR	2.0	NR	7.6
	PTCA	306	4.9	NR	1.3	NR	6.2
TYPHOON[20] (12 MO)	Sirolimus stent	700	2.2	1.1	3.7	NR	NR
	Bare metal stent	700	2.2	1.4	12.6	NR	NR
ZWOLLE[43]	Streptokinase	201	7.0	9.0	42.8	NR	NR
	PTCA	194	1.0	0.5	12.4	NR	NR

NR = Not Reported
*Composite data include unique MACE
** Composite does not include TVR

As presented in the table, these study data demonstrate significant variability in 30-day mortality between similar therapeutic treatments. Since six of these studies do not include stroke in their composite MACE rates, their MACE rates may be understated. Overall, these studies show that even within the controlled boundaries of PCI and thrombolytic therapy, 30-day safety data can vary significantly, underscoring the need in

an AMI study population to carefully consider the specific study population and key inclusion/exclusion criteria and their potential influence on early events, irrespective of the other trial factors.

Twelve-month MACE data are presented in **Table 1** for the TYPHOON study[20]; 30-day results were not published in the seminal article. The primary end point was target-vessel failure at one year after the procedure, defined as target-vessel–related death, recurrent myocardial infarction, or target-vessel revascularization. The rate of the primary end point was significantly lower in the sirolimus-stent group than in the uncoated-stent group (7.3% vs. 14.3%, p=0.004). This reduction was driven by a decrease in the rate of target-vessel revascularization (5.6% and 13.4%, respectively; p<0.001), with no significant differences in mortality or reinfarction rates. These data, coupled with the PASSION results, allude to the overall safety and effectiveness of drug-eluting stents for STEMI treatment, due to the similar or nominally better mortality and reinfarction rates using DES, and lower TVR occurrence as compared with bare metal stent deployment.

Overall, the data in **Table 1** show significant variance in both mortality and composite event rates at 30 days, in spite of the use of reperfusion therapy in STEMI patients for all cited trials. Thus, 30-day death rates range from 1.0% – 6.6% in the table, while composite event rates range from 4.4% – 16.1%. The underlying patient selection criteria clearly have an impact on outcome in STEMI, and may be responsible for this variability. The next section of the discussion will turn to two important underlying factors in AMI outcome, time to intervention and infarct location.

1.4.2 Time to Intervention and Infarct Location: Influence on Patient Outcomes

Early recognition of symptoms and prompt intervention are critically related to patient outcomes. The AHA and ACC, along with other supporting organizations, have launched a current nationwide hospital initiative called the door-to-balloon, or D2B initiative, with

the goal of increasing the percentage of AMI patients who receive primary angioplasty within 90 minutes of hospital presentation to 75% from its 35% level of 2006. DeLuca *et al.*[10] have reported on the quantitative relationship between time to intervention and outcome in 1791 STEMI patients treated with primary PCI with and without stenting. The study showed that patients with successful reperfusion of the target vessel post-PCI had a significantly shorter ischemic time (P=0.006). After adjustment for age, gender, diabetes, and previous revascularization, each 30 minutes of delay that extended the ischemic time was associated with a relative risk for 1-year mortality of 1.075 (95% CI 1.008 to 1.15; P=0.041). The critical importance of early reperfusion is not specific to PCI but has also been demonstrated in AMI studies of thrombolytic therapy, notably by [redacted] of Harvard[17, 44-46].

The severity of AMI also is highly dependent upon the location of the ischemic infarct created by the arterial blockage. Anterior wall infarction, because of the heavy involvement of the left ventricle caused most commonly by a blockage in the left anterior descending (LAD) coronary artery, is typically the most serious type of infarction. In a study published by Stone *et al.*[47] that was performed to determine the relative prognostic significance of location (anterior or inferior) and type (Q wave or non-Q wave) of infarction, the hospital course and follow-up outcome (mean duration 30.8 months) of 471 patients experiencing their first MI were examined. Results showed that patients with anterior infarction (n=253) had a substantially worse in-hospital and follow-up clinical course compared with those with inferior infarction (n = 218), evidenced by a larger infarct size (21.2 versus 14.9 g Eq/m^2 creatine kinase, MB fraction [CK-MB]), lower admission LVEF (38.1 vs. 55.3%) and higher incidence of heart failure (40.7% vs. 14.7%), in-hospital death (11.9% versus 2.8%), and total cumulative cardiac mortality (27% versus 11%). Each of these comparisons was statistically significant with $p < 0.001$. Anterior wall infarction patients represent a high-risk population that has the

greatest opportunity to benefit from the introduction of novel therapeutic strategies that seek to mitigate the damaging effects of myocardial ischemia brought about by AMI.

1.4.3 AMI Survival: Progression to CHF

The development of congestive heart failure (CHF) can be traced to the evolution of a serious STEMI event for some patients. Heart failure patients exhibit left ventricular enlargement, or LV remodeling, that becomes more pronounced over time as the left ventricle loses more and more pumping efficiency. LV remodeling is quantifiable with direct ventricular volume measurements captured at diastole and systole, over a period of time to monitor progress of the disease.

One of the byproducts of advancement in reperfusion therapy is a shift away from early mortality risk from AMI that increases later in the ischemic disease progression in the form of CHF mortality risk. Early restoration of epicardial coronary blood flow in AMI patients via reperfusion therapy has been proven to improve clinical outcomes. However, because of the inevitable damage caused by the AMI, the effects of the infarction over time lead to LV remodeling. Post-AMI, these changes are inevitable after a portion of the muscle has experienced necrosis; the clinical presentation after significant LV remodeling is ultimately congestive heart failure[48]. Significantly, a review[49] of heart failure studies conducted in the UK showed that recruited patients had an incidence rate of prior MI of 60%; while this finding may overstate the causal relationship between MI and heart failure, their direct relationship is indisputable. In terms of infarct severity, this same review showed that anterior infarction is more commonly associated with progression to heart failure than less severe MI.

After the effects of AMI have progressed into heart failure, the clinical outlook is grim; one population-based study[50] reported that mortality rates in the first year of new onset heart failure are 30-40%. The Cholesterol And Recurrent Events (CARE) trial[51] showed

that patients who experience late-onset CHF have a 10-fold increased risk of death compared with other MI survivors.

While AMI trials do not frequently attempt to correlate therapeutic strategies with long-term heart failure incidence, there is a clear progression from AMI to CHF, with important clinical and lifestyle implications for the patient. Regardless of treatment modality, the prevention of myocardial cell death at the microvascular level, and the early arrest of infarct development, is a key factor in the early prevention of CHF.

1.4.4 The Unmet Need in AMI

Despite advances in reperfusion therapy strategies and better awareness of the need for early patient intervention, AMI patients continue to experience elevated early and late MACE, as well as a heightened risk for CHF development. Clearly, although many current initiatives are underway seeking to further optimize primary reperfusion strategies, including incremental stent design and coating improvements, co-dependent pharmacological administration, and decreasing door-to-balloon time, none of these approaches seems likely to address the critical unmet need for these patients. Namely, the microvascular impairment and flow dysfunction that has been characterized in the at-risk distal capillary beds must be repaired during the acute interventional phase[52]. A better understanding of the natural course of infarct healing and the effect of early reperfusion on ischemic myocardium might contribute to developing new therapies for ischemic heart disease.

Results of experimental studies have shown that microvascular obstruction is related to endothelial swelling, to myocyte edema, and to obstruction of the capillaries by neutrophils, erythrocytes and debris. The presence of microvascular obstruction is associated with greater myocardial damage, based on electrocardiographic and echocardiogaphic criteria. Furthermore, results of clinical studies have indicated that microvascular obstruction is associated with LV remodeling and increased risk of

mortality and morbidity[53].

Addressing this problem at its source requires a new approach to interventional care, and diagnostic tools that seek to measure, directly or indirectly, the results of successful or unsuccessful intervention in the at-risk myocardium. To date, one such diagnostic tool, and the only effective validated measurement with strong clinical correlates, is infarct size measurement wit[redacted] SPECT imaging.

1.4.5 SPECT Infarct Size: A Predictive Surrogate Marker

The best physical measure of the consequences of AMI in post-intervention patients is the quantification of the extent of necrosis or infarction in the muscle. The degree to which microvascular impairment in the myocardium is irreversible and unaffected by therapeutic intervention certainly leads to a greater extent of infarction. [redacted] SPECT imaging is an accurate and reproducible method for measuring infarct size in these patients, is accessible at hospitals that have advanced PCI capabilities, and can be standardized with the help of an expert core laboratory at the [redacted] for comparison of subjects enrolled in randomized studies. Unlike indirect infarct size biomarkers such as creatine kinase (CK) and troponin, which require careful sampling and extrapolation from release kinetics to estimate the extent of myocardial necrosis, SPECT imaging provides a direct picture of the extent of damage to the cardiac muscle, ~~and~~ the infarct location. While cardiac MRI has this capability, a lack of technique standardization and core laboratory analysis has limited this method to single-center studies.

A white paper is presented below that discusses the clinical relevance of infarct size measurements by [redacted] SPECT imaging. The white paper was authored by [redacted] the [redacted] Director at [redacted] ~~and~~ current President of the AHA [redacted] has pioneered the development of SPECT infarct size measurement over the last twenty years; this white paper is included in **Section**

1.4.5.1 below without content editing. For ease of identification, this section is indented and presented in a smaller font size than the surrounding text.

1.4.5.1 What is A Clinically Significant Difference in Infarct Size Measured by [redacted]

[redacted])

SPECT imaging with [redacted] is the best available measurement tool for infarct size. Most of the evidence supporting the validity of this endpoint is summarized in two reviews[54, 55]. This measurement has already served as an endpoint in multiple early pilot studies and in dose-ranging studies. These trials have used this measurement to assess efficacy, either as a primary endpoint or as a component of a composite primary endpoint. Such efforts demand that the trials be designed to detect a difference in infarct size that is clinically meaningful. This document summarizes several lines of evidence in support of the use of a reduction in infarct size of 5% of the left ventricle as a clinically meaningful measure of efficacy in such trials.

I. Relationship to ejection fraction differences observed in randomized trials.

The 5% difference in infarct size was first employed in a study examining the design of randomized trials of acute intervention[56]. This study attempted to "bracket" the range of differences in infarct size (expressed as a percent of the left ventricle) that could be used in the design of randomized trials. At the "high end" of the spectrum, where a treatment would have a truly profound effect, 8% of the left ventricle was employed. For example, in patients with anterior myocardial infarction, mean infarct size might be 18% of the left ventricle with existing reperfusion therapy and 10% of the left ventricle with some new therapy. As detailed in the study, this required a 50% improvement in myocardial salvage over existing therapy. At the other end of the spectrum, a more modest therapeutic effect was represented by 5% of the left ventricle. This effect, which represented a 30% improvement in myocardial salvage over existing therapy, was used because it was felt to be clinically meaningful because of its implications for ejection fraction. As detailed in both that study, and the later review articles, SPECT sestamibi infarct size has been closely inversely associated with both global left ventricular function (ejection fraction and end-systolic volume) and regional left ventricular function (regional wall motion) in multiple different patient cohorts. In one early study[57], discharge infarct size was closely inversely correlated (r=-0.81) with ejection fraction measured six weeks later with a slope of the regression line of approximately 0.5. Thus, a reduction in infarct size of 5% of the left ventricle

would be approximately equivalent to a 2.5 point increase in ejection fraction. Although ejection fraction clearly has limitations as a primary endpoint in reperfusion trials[58], these limitations primarily relate to its insensitivity and the issue of missing values. At the 1992 FDA hearings[59], there was a consensus recognizing the clinical importance of ejection fraction differences.

Despite the limited sensitivity of ejection fraction as an endpoint, multiple studies have shown ejection fraction improvement in association with mortality reduction in placebo-controlled trials of thrombolytic therapy. For example, the European Cooperative Study Group[60] found an ejection fraction at 10 to 22 days of 48.5 in the placebo group and 50.7 in the t-PA group (a 2.2 point difference). Similarly, the ISAM study group[61] found that the ejection fraction at three to four weeks was 53.9 in the placebo group, and 56.8 (a 2.7 point difference) in patients treated with streptokinase. The Western Washington Intravenous Streptokinase trial[62] similarly reported an ejection fraction of 50.7 in the placebo-group compared to an ejection fraction of 54.3 in the streptokinase-treated group, a difference of 3.6 ejection fraction points. Subsequent trials compared one thrombolytic treatment regimen with another. Although the results using ejection fraction were generally disappointing, largely reflecting its low sensitivity, there were generally small improvements in ejection fraction favoring patient groups treated with t-PA, compared to those treated with streptokinase or APSAC. The magnitude of the difference ranged from 0 to 3 points, favoring t-PA. Obviously, the large GUSTO trial subsequently showed a mortality difference of approximately 1% favoring t-PA over streptokinase. Thus, in a much larger data set, the observed modest differences in ejection fraction translated into a clinically significant benefit. *On the basis of these randomized trials of thrombolytic agents, a difference in ejection fraction of approximately two or three points appeared to be associated with a clinically significant difference in overall mortality.* Since an infarct size reduction of 5 % of the left ventricle would represent an increase of about 2.5 ejection fraction points, it appeared likely to be clinically significant, and was therefore chosen for analysis in this early study of sample size.

II. Effect of time to therapy on infarct size and mortality in the CORE trial.

The Collaborative Organization for RheothRx Evaluation (CORE) trial, was an international, multicenter, randomized, dose-ranging study of poloxamer 188 in acute myocardial infarction, which employed sestamibi infarct size in a sizable substudy on more than 1100 patients[62]. This substudy of SPECT imaging has provided important data which are relevant to the issue of a clinically significant difference in infarct size. The first such data examined the impact of time to thrombolytic treatment on infarct size and outcome[63]. Patients who were treated in less than two hours in the CORE trial had a

significant reduction in infarct size compared to all the other groups. The magnitude of this reduction in mean infarct size was 3.1 percent of the left ventricle without adjustment for other factors, and 2.9 percent of the left ventricle after adjustment for previous myocardial infarction, location of infarction, thrombolytic agent used, and treatment with poloxamer 188 (which had no significant effect). In the main CORE trial of 2948 patients, there was a significant reduction in mortality according to time to treatment. Compared to patients treated within two hours, patients treated at two to four hours had an odds ratio for death at 35 days of 1.27 (unadjusted; p=0.0004) or 1.15 (adjusted; p=0.038; Table 4 from reference [62]). This mortality difference confirmed earlier results from the much larger GUSTO I trial[64], which showed a highly significant mortality difference in patients treated in less than two hours. Thus, an approximately 3% difference in infarct size associated with earlier therapy was associated with a clinically significant reduction in mortality.

III. Effect of thrombolytic agent on infarct size and mortality.

A second finding published from the CORE substudy[63] also supports the use of a 5% difference in infarct size. The adjusted effect of the thrombolytic agent used on mean infarct size in the CORE trial is included in the table. Compared to patients treated with streptokinase, t-PA was associated with a reduction in infarct size of 3.5% of the left ventricle (adjusted for time to therapy, previous MI, anterior MI, and poloxamer 188). As previously mentioned, the GUSTO trial demonstrated a clinically significant reduction in mortality associated with t-PA. Although CORE was not designed to compare streptokinase with t-PA, this finding in the infarct size substudy suggested that a reduction in infarct size at 3.5% of the left ventricle is associated with a clinically meaningful difference in early mortality

IV. Relationship of infarct size to late mortality.

Three different published studies have now shown that sestamibi infarct size is associated with a difference in late (greater than 30 days) patient mortality. The first of these[65] reported two-year follow-up in 274 patients at the [redacted]. The measured discharge infarct size was quite small, with a median of 12% to the left ventricle. Despite a low two-year mortality rate of 3%, sestamibi infarct size was highly associated with both overall mortality (Chi-squared = 8.66, p=0.003) and cardiac mortality (Chi-squared = 11.89, p<0.001). A separate multicenter study of 249 patients[66] also showed a similar significant association between sestamibi infarct size at discharge and one-year mortality. However, given the small number of deaths in these series, it is difficult to relate any given magnitude of change in infarct size to subsequent mortality. However, this was subsequently feasible

in the larger report from the CORE trial by Burns *et al.*[67]. In 1,164 patients in the infarct size substudy, six-month mortality was significantly related to infarct size (Chi-squared = 9.1, p=0.03). As indicated in Table 2 of that manuscript, in the "overlap group" of 753 patients who also underwent ejection fraction measurements, the odds ratio for infarct size for six-month mortality was 1.033, i.e., for each one percent increase in infarct size, mortality in the next six months was 1.033 times more likely. A 5% increase in infarct size would therefore mean that six-month mortality was $(1.033)^5 = 1.176$ times more likely. A patient with an infarct size that was greater by 5% of the left ventricle would therefore have a 17.6% greater chance of dying in the next six months. The absolute mortality difference at 6 months is small, because of the low late mortality in most current randomized trials of acute reperfusion therapy in acute ST elevation MI. However, the relative difference of 17.6% is of comparable magnitude to the relative difference of 20-25% that is associated with aspirin therapy for secondary prevention.

Preliminary data from the EMERALD trial has confirmed the results from CORE. There was a highly significant association between infarct size and 6 month mortality. The odds ratio for infarct size for mortality was 1.07, greater than that reported by CORE.

V. Magnitude of reduction in infarct size in a randomized trial with a corresponding reduction in clinical endpoints.

Some would regard this requirement as the "ultimate test" of a surrogate. This requirement had not been met at the time of the publication of our first review, but was subsequently met with the publication in the *New England Journal of Medicine*[68] of a randomized trial comparing coronary stenting plus abciximab with t-PA in acute myocardial infarction. In that study of 140 patients, there was a significant (p=0.02) reduction in final infarct size from 19.4% of the left ventricle in the t-PA group to 14.3% of the left ventricle in the stent group, a difference of 5.1% of the left ventricle. This was associated with a significant (p=.02) reduction in the cumulative incidence of death, reinfarction, or stroke over the next six months in the stent group. A second randomized trial of 162 patients has been reported by the same group[69], again showing a reduction in infarct size of 8% of the left ventricle (and an increase in myocardial salvage of 5.2% of the left ventricle) in patients treated with stenting plus abciximab, compared to patients treated with t-PA plus abciximab. The group treated with stenting plus abciximab again had a reduction in a composite clinical endpoint over the next six months that did not quite achieve statistical significance (p=0.06).

Thus, several different lines of evidence suggest that a reduction in infarct size of 5% of the left ventricle measured by SPECT sestamibi is clinically meaningful. The recent randomized trials from Munich satisfy the most stringent criteria for a surrogate endpoint, i.e., a therapy associated with a reduction in infarct size in a randomized trial has been associated with a reduction in clinical endpoints in the same treatment arm. The first of these studies reported a reduction in infarct size of approximately 5% of the left ventricle. The reduction in infarct size in the second study was 8%. Obviously, both studies were comparatively small, and the 95% confidence limits for the relationship between infarct size and clinical outcomes are therefore quite broad. However, the extensive data summarized above suggesting that two to three point changes in ejection fraction (corresponding to a difference in infarct size of about 5% of the left ventricle) are clinically meaningful, that differences in time to therapy with thrombolytic agents that are associated with differences in infarct size of less than 5% of the left ventricle are also associated with differences in mortality, and that infarct size is significantly related to late mortality, all lend additional support to the use of 5% of the left ventricle as a clinically meaningful difference in infarct size.

Table 2. Ejection fraction measurements in randomized trials comparing different thrombolytic regimens

Author	N	SK/UK/APSAC	tPA
White[70]	270	58 ± 12	58 ± 12
PAIMS[71]	171	53 ± 10	55 ± 10
GAUS[72]	246	52 ± 14	53 ± 12
Anderson[73]	139	51 ± 11	54 ± 12

Table 2 concludes the white paper by [redacted]

1.4.5.2 SPECT Infarct Size Synopsis

In summary, infarct size measured by [redacted] SPECT imaging is a well-established, validated measurement that shows a close correlation with directly measured infarct size in pathology specimens from both animals and humans. Sestamibi infarct size also shows a close correlation with other direct and indirect physiological measurements of heart function in humans, including left ventricular ejection fraction, left ventricular end-systolic volume index, extent of regional wall motion abnormality, infarct size, and myocardial enzyme release. Advantageously, SPECT imaging has been utilized in numerous studies in determining infarct size after AMI, in studies dating back nearly twenty years.

The challenge of demonstrating incremental treatment benefit with an adjunctive regimen superimposed with reperfusion therapy in AMI is usually underestimated. The track record of device trials attempting to demonstrate infarct size reduction by SPECT imaging is not good, as evidenced by several failed trials. The inherent variability in infarct size in patients is substantial, reflecting the underlying variation in several important parameters, including the extent of previous myocardial injury and underlying disease, the extent of myocardium at risk, residual flow to the infarct zone (via collaterals or intermittent antegrade flow), and time to reperfusion. SPECT imaging currently is the best measurement tool available to quantify infarct size for the purpose of controlled study reporting.

1.4.6 Current Outcomes in AMI: Summary

Current AMI treatment strategies have focused almost exclusively on removing the primary flow obstruction in the target coronary artery. However, as mounting evidence suggests, microvascular obstruction plays a significant role in the pathophysiology of MI and impacts the post-MI recovery phase. The "no-reflow" phenomenon[74] indicates lack of adequate tissue perfusion within the infarcted myocardium even after the coronary

artery has been opened using the best available standard-of-care techniques. Angiographic markers of no-reflow have also associated with poorer clinical outcomes, and the clinical significance of microvascular perfusion in the acute MI setting is increasingly apparent. Furthermore, clinical strategies for minimizing reperfusion injury have not yet demonstrated efficacy[75]. The concept of reperfusion will continue to include and refine this concept with new strategies to improve flow at the microvascular level[76]. To sum up the current clinical unmet need in AMI, what is needed is 'angioplasty for the microcirculation'.

1.5 AO Therapy Administration in AMI – Previous Studies

1.5.1 Pre-Clinical Studies of AO Therapy in AMI

Prior to development of the current TherOx® AO System and AO Cartridge, the safety and effectiveness of AO Therapy were examined in several pre-clinical studies. These studies, conducted in collaboration with the [redacted] and Wayne State University, established the effectiveness and mechanism of action of AO Therapy in animal models of acute myocardial infarction. Collectively, these studies consider global heart function, metabolic indicators of myocardial health, and tissue viability post-AMI, comparing animals that have received AO Therapy to appropriate non-treated control animals.

Key study information, including protocol parameters, data, and important conclusions, is summarized below; this information is also provided within PMA Module 2 but is also included here for its relevance in establishing the clinical basis for AO Therapy.

1.5.1.1 Canine AMI Studies by Spears *et al.*

Early studies of hyperoxemic blood reperfusion post-AMI were conducted utilizing a canine model under the direction of J. Richard Spears, M.D. of Wayne State University in Detroit, MI. In work performed in 1998 and published as a peer-reviewed article in 2003[77], Spears *et al.* performed studies on adult mongrel dogs that were subjected to

controlled acute myocardial infarctions by inflating a balloon catheter in the proximal circumflex coronary artery and maintaining occlusion for 90 minutes. After the occlusion period, the balloon was deflated, restoring blood flow to the affected artery, and the animals were randomly assigned into three groups:

- Autologous reperfusion (normoxic physiological blood flow; n = 7)
- Active normoxic reperfusion (100 ml/min of normoxic arterial blood pumped to the left main coronary artery through guide catheter; n = 8)
- Active hyperoxemic reperfusion (100 ml/min of hyperoxemic blood pumped to the left main coronary artery through guide catheter; n = 11)

A ventilator was used to maintain consistent arterial pO_2 (apO_2) levels; the apO_2 averaged 108 ± 8 mmHg for normoxemic control animals. Hyperoxemic reperfusion was provided at a pO_2 level of 530 ± 150 mmHg to the treatment group; hyperoxemia was achieved by mixing normoxic arterial blood with 2.5 – 3.5 ml/min of AO solution with a dissolved concentration of 0.8 – 1.0 ml O_2 (STP)/ml saline. The active reperfusion period was 90 minutes. In both active reperfusion groups, a 30-min autoreperfusion period was observed post-AMI before starting the blood pump.

The three groups were compared with respect to transthoracic echo left ventricular ejection fraction (LVEF), regional wall motion (% fractional shortening of the posterior wall), and ST segment resolution, as well as regional myocardial blood flow assessment. Regional blood flow was examined in the entire autoreperfusion group and in n = 8 of the hyperoxemic treatment group with radio-labeled microsphere injections. Post-sacrifice biopsies enabled radioactivity measurements (and thus regional blood flow assessments) of both normally perfused and post-ischemic myocardial tissue.

The following synopsis of the study results is quoted with permission from Spears *et al.* (2003):

> *"A significant improvement in left ventricular ejection fraction ($p < 0.05$) at 2 hr of reperfusion was noted only in the AO hyperoxemia group (17 ± 6% by two dimensional echo), without a significant reduction in the improvement 1 hr after termination of treatment. During AO hyperoxemic perfusion, ECG ST segment isoelectric deviation normalized, and frequency of ventricular premature contractions was significantly reduced, in contrast to the autoreperfusion control group ($p < 0.05$). Microvascular blood flow, measured as the ischemic/normal left ventricular segment ratio by radiolabeled microspheres immediately after AO hyperoxemic perfusion, was double the value of the autoreperfusion group at 2 hr of reperfusion ($p < 0.05$)."*

As stated above and shown in Figures 1 – 4 of the article, hyperoxemic blood reperfusion post-AMI demonstrated acute signs of improvement in heart function as measured in LVEF, wall motion, and ECG performance, and dramatic difference in regional myocardial blood flow improvement at the end of the reperfusion period. This last result underscores the clinical hypothesis[78-81] that impaired microvascular flow persists in the myocardium even after native flow is restored to the affected coronary artery. This impairment was observed in the study's autoreperfusion group. Restoration of regional myocardial flow in the ischemic zone of the AO-treated hyperoxemic group indicates a reversal in the underlying conditions that cause microvascular impairment. These results provide experimental evidence that AO Therapy addresses the clinical unmet need for regional tissue perfusion improvements.

These significant early results obtained by Spears *et al.* in the canine model were bolstered in subsequent studies of hyperoxemic blood reperfusion in porcine infarct models, performed at the [redacted] and in Dr. Spears' research laboratory at Wayne State University. These studies are summarized in the following sections.

1.5.1.2 Swine Infarct Model: [redacted]

A 1998 study of hyperoxemic blood reperfusion in a porcine myocardial infarct model was conducted jointly between TherOx and St. Mary's Medical Center of the [redacted] in Rochester, MN, under the direction of Robert S. Schwartz, M.D. This work was approved by the [redacted] ACUC committee as protocol number A171-X-97. The study protocol, report, and data are provided in PMA Module 2. The study results were presented by [redacted] co-investigators at the 1998 Transcatheter Cardiovascular Therapeutics conference in Washington, D.C[82].

The [redacted] protocol involved coronary artery balloon occlusion in the left anterior descending (LAD) artery for a period of 60 minutes to induce AMI. The study animals were randomized to either treatment or control groups consisting of n=10 swine in each study arm. The control autoreperfusion group received normoxic native coronary blood flow after the controlled occlusion period; the treatment group received a 60-minute period of active hyperoxemic reperfusion in the left main coronary artery at a blood flow rate of 100 ml/min. The mean systemic arterial pO_2 values were 127 ± 22 and 150 ± 22 mmHg for the control and treatment groups, respectively. The mean hyperoxemic reperfusion pO_2 value was 622 ± 71 mmHg for the treatment group; this level was achieved by extracorporeal mixing of normoxic arterial blood with 2.5 – 3.5 ml/min AO solution with a dissolved oxygen concentration of approximately 1.0 ml O_2 (STP)/ml saline. After treatment, animals were survived for a period of 28 days until sacrifice; two control group animals died within one day of inducing AMI, as expected given the mortality rate for this model. Eighteen animals survived for the day 28 evaluation.

Key data for this study included LVEF measurement before and after occlusion, at 1 and 2 hours post-occlusion, and just prior to sacrifice on day 28 post-occlusion. Histological data were obtained post-sacrifice by sectioning the left ventricle and exposing the sections to a 1.0 % solution of triphenyl tetrazolium chloride (TTC) in 0.2M Tris buffer

(pH = 7.8) at 37°C. TTC staining is a well-established method[83] of infarct size quantification. The histological data for the [redacted] study are expressed in terms of the percentage of the left ventricle that exhibits infarction.

Results from the [redacted] study data showed that LVEF measurements performed before and after LAD occlusion were virtually indistinguishable between the treatment and control groups, as expected. After administration of AO Therapy, LVEF measured at one and two hours post-occlusion was significantly higher in the treatment group than in the control animals (mean scores 53.9 ± 4.0 vs. 43.2 ± 9.9% at one hour; 54.4 ± 4.1 vs. 43.9 ± 10.9% at two hours; $p < 0.001$). This acute improvement observed in ventricular function was sustained at day 28 as a positive trend (treatments: 54.4 ± 6.2% vs. controls: 45.9 ± 7.8%; p=ns). A positive trend was observed in TTC-infarct size measurements as well; the percentage of infarcted left ventricle was 8.2 ± 5.8% vs. 4.9 ± 3.2% in control (n = 8) and treatment (n = 10) animals, respectively. Statistical significance was achieved when large infarct data were considered, isolating the subgroup that exhibited LVEF < 50% post-occlusion (prior to randomization). This subgroup included n = 7 control and n = 7 treatment animals, and yielded infarct size LV% of 9.7 ± 8.3% and 5.1 ± 4.5%, respectively, achieving statistical significance at a level of $p < 0.05$.

1.5.1.3 Transition to Sub-Selective AO Therapy

Taken together, the studies performed at the [redacted] and by Spears *et al.*[77] exhibited promising signs of improved ventricular function, a reduction in the severity of infarction, and improvements in microvascular flow in animals that received post-AMI reperfusion with hyperoxemic blood. In both studies, reperfusion was performed selectively in the left main coronary artery at a flow rate of 100 ml/min. On the strength of these data, TherOx was granted permission by the FDA in January 1999 to conduct a limited 30-patient feasibility trial using AO Therapy in AMI patients (ref. IDE number

[redacted] This study was conducted in two parts, designated Phase I and Phase IA for reference (these studies are discussed in more detail in following sections).

In Phase I, hyperoxemic blood was infused via guide catheter to the left main coronary artery at a flow rate of 100 ml/min, for a period of 60 minutes. After selective AO Therapy was administered to nine patients in the Phase I portion of the study, a decision was made to re-direct the delivery of hyperoxemic blood to the re-vascularized sub-selective artery rather than the left main coronary. In the remaining twenty patients, the hyperoxemic blood flow rate was lowered from 100 to 75 ml/min to match native flow in the smaller target vessel (LAD, circumflex, or RCA), and the treatment duration was increased to 90 minutes. Phase IA was conducted with targeted sub-selective reperfusion using these modified parameters. The participating study physicians advocated these changes because of their belief that placing a smaller infusion catheter more distal into the coronary vasculature would enable more targeted AO delivery to the ischemic zone, offering greater improvements in microcirculatory flow.

A series of animal studies performed in Dr. Spears' laboratory at Wayne State University in Detroit, MI supported the re-direction of hyperoxemic reperfusion to a sub-selective approach.

1.5.1.4 Swine Infarct Studies by Spears *et al.*

1.5.1.4.1 Spears Swine Infarct Study No. 1: 90-min Sub-Selective AO Therapy Effectiveness

Three studies were performed at Wayne State University under the direction of Dr. Spears that established the effectiveness of the sub-selective approach. The first study[84] included (n = 59) swine that were subjected to 60-minute balloon occlusions of the LAD (fourteen animals were excluded for refractory ventricular fibrillation); after 15 minutes of autoreperfusion, animals were randomized to four groups:

- 90-min hyperoxemic reperfusion via AO Therapy
- 90-min hyperoxemic reperfusion with a specialized membrane oxygenator
- Normoxemic active reperfusion (roller pump)
- Autoreperfusion only

Active reperfusion for the first three groups was performed at a flow rate of 50 ml/min, with the infusion catheter placed in the proximal LAD. This flow rate was selected to match the physiologic LAD blood flow rate for the pig model (the corresponding matched LAD blood flow rate in humans is approximately 75 ml/min, the parameter used in the AMIHOT I and II clinical trials). Key data included LVEF comparisons and histological sectioning of the left ventricle (LV) post-sacrifice. Direct measurements were obtained for both the area at risk (AR) and area of necrosis (AN); the area at risk was obtained by re-inflating the balloon catheter just prior to sacrifice and delivering a systemic injection of Evans blue dye. Post-sacrifice infarct size was quantified by TTC staining; hemorrhage was assessed by examining the LV sections prior to TTC exposure.

Hemorrhage and infarct sizes were normalized by expressing the area of necrosis (AN) as a percentage of AR rather than the entire left ventricle. The area at risk ranged between 13 – 18% of the left ventricle for all four study groups. Following TTC staining and digital photography of the heart sections, 1-2 g transmural samples of non-TTC stained necrotic tissue were frozen in liquid nitrogen for subsequent myeloperoxidase (MPO) analysis.

The study results showed that in the AO Therapy and membrane oxygenator treatment groups, the hyperoxemic blood pO_2 levels were 834 ± 104 and 912 ± 53 mmHg, respectively, compared to 148 ± 26 mmHg for the normoxemic control groups. As observed in previous studies, an increase in LVEF was noted during and after hyperoxemic reperfusion as compared to baseline readings and normoxic control LVEF

data. These data appear in Figure 1 of Spears *et al.*[84] Both the AO-infused and membrane oxygenator hyperoxemia groups experienced an acute LVEF increase.

However, upon examination of histological data, only the AO Therapy hyperoxemia group showed a significant infarct size reduction. As shown in Figures 2 and 4 of Spears *et al.*[84], significantly smaller infarct sizes and hemorrhage areas were reported in the AO-treated animals as compared to the other three groups ($p < 0.05$). The membrane oxygenator hyperoxemic group exhibited infarct and hemorrhage characteristics that were statistically indistinguishable from the control groups.

Notably, the significant infarct size reduction reported in the AO-treated group was complemented by MPO assay data shown in Figure 3 of Spears *et al.*[84] As reported in the figure, a significant reduction in MPO was observed in the AO-treated group; all other groups were statistically indistinguishable. Because the presence of elevated MPO levels is a sign of increased leukocyte activation and adhesion, the reduced MPO level observed in the AO-treatment group points to improvement in both myocardial hypoxia and microvascular impairment. Thus, this result corroborates the data obtained in the canine model for improved tissue perfusion, and again is supportive of a general mechanism of microvascular flow improvement.

To strengthen this argument, examination of myocardial tissue biopsies from the ischemic zone provides more evidence of improvement in microvascular flow. In work performed by Spears and co-workers and reported by Bartorelli[85], transmission electron microscopy yielded photos that showed prominent endothelial cell edema and capillary constriction in control animals that did not receive AO Therapy, compared with no observations of these ischemia-related complications in AO-treated animals. Taken together with the improvements observed in overall myocardial perfusion in the canine model, compelling evidence exists to support an underlying mechanism of improved microvascular flow and subsequent reversal of tissue ischemia and its telltale markers.

Pre-clinical mechanism of action data for AO Therapy in AMI models suggests that this treatment modality may have promise in fulfilling the clinical unmet need.

1.5.1.4.2 Spears Swine Infarct Study No. 2: Dose Response

A second swine infarct study is reported by Spears *et al.*[84]; after establishing the merits of the sub-selective approach of hyperoxemic reperfusion, a second porcine infarct study was performed on n = 25 animals. This corollary dose response study had five groups of n = 5 animals each; in addition to a normoxic autoreperfusion group, four AO Therapy groups were examined with hyperoxemic infusion durations of 30, 60, 90, and 180 minutes, respectively. TTC-staining results showed that infarct size trended towards a minimum when the treatment time was 60 or 90 minutes. The infarct size data were at a nominal minimum with a 90-minute treatment time, providing a basis on which to proceed with clinical studies.

1.5.1.4.3 Spears Swine Infarct Study No. 3: AO Therapy 24 Hours Post-AMI

The third key swine infarct study conducted by Spears and co-workers at Wayne State University investigated the effects of AO Therapy with delayed hyperoxemic reperfusion administration, performed at 24 hours post-AMI. The porcine model was nearly identical to the abovementioned swine infarct studies, with the exception that after the 60-min occlusion period, the animals were not treated acutely. Instead, n = 12 animals were survived for 24 hours, then randomly assigned to an AO Therapy (n = 6) or autoreperfusion (n = 6) group. The aim of the study was to determine if the recovery of ischemic tissue that was observed in acute post-occlusion studies would be realized twenty-four hours post infarction. Results showed a statistically significant improvement in LVEF ($p < 0.05$) during and after 90 minutes of AO Therapy administration. In addition, post-sacrifice histological data revealed that the AO-treated group exhibited significantly smaller infarcts than the control group ($p < 0.05$). These improvements observed in delayed AO Therapy administration suggested that a 24-hour treatment

window should be considered in a clinical evaluation of the therapy. The 24-hour data collected by Spears and co-workers were presented at the AHA meeting in November 2000[86]. These data provided the basis for the 24-hr time to intervention window utilized in the AMIHOT I clinical trial.

1.5.1.5 Summary: Pre-Clinical Evaluations of AO Therapy in AMI

The proof of principle and mechanism of action of AO Therapy for the treatment of acute MI has been explored in several animal infarct models. Published study results have demonstrated acute improvements in cardiac function and metabolic indicators of myocardial health, as well as smaller resultant infarcts when AO Therapy is administered post-AMI in animal models. This focal approach to hyperbaric oxygen therapy is novel and does not have a pre-existing body of evidence from which to draw comparisons. The use of Aqueous Oxygen represents a new approach to blood oxygenation, one that is capable of delivering high levels of oxygen to hypoxic tissue in an attempt to reverse myocardial ischemia triggered by a heart attack. The canine and swine infarct models discussed above have yielded the following important safety and effectiveness results from the administration of AO Therapy:

- AO Therapy administration post-AMI acutely improves heart function as measured by LVEF and regional wall motion as compared with non-treated controls.
- AO Therapy administration post-AMI results in tissue salvage, as determined by post-sacrifice histological measurements of infarct size. Control animals exhibit larger infarcts than AO-treated animals.
- The benefits of AO Therapy are realized even when administration is delayed 24 hours post-AMI; the optimal treatment time was determined to be 90 minutes in pre-clinical studies.
- AO Therapy is well tolerated and does not exhibit any identified deleterious effects in controlled pre-clinical studies.

In addition to these observations, TherOx has collected compelling data that supports a microvascular mechanism of action of AO Therapy; this hypothesis is supported by the following experimental results:

- AO Therapy administration post-AMI has exhibited dramatic regional myocardial blood flow improvement compared to non-treated animals.
- A significant reduction in MPO levels was observed in AO-treated animals versus controls. Because the presence of elevated MPO levels is a sign of increased leukocyte activation and adhesion, the reduced MPO levels observed in the AO treatment group may indicate improvements in underlying myocardial perfusion.
- Transmission electron microscopy photographs have shown amelioration of endothelial cell edema and restoration of capillary patency in ischemic zone cross-sectional histological examination of AO-treated animals; non-treated controls exhibit significant edema and vessel constriction at the microvascular level.

Against the backdrop of the current state of AMI care, the limitations of currently available reperfusion therapy, and the need for novel therapeutic approaches to AMI that seek to address deficiencies at the tissue perfusion level, these pre-clinical data are promising and support the feasibility of AO Therapy that may improve clinical outcomes for STEMI patients. Animal model data has its limitations but has the advantage of offering direct histological examination to support the hypothesis of myocardial salvage through local hyperoxemic reperfusion.

1.5.2 Prior Clinical Investigations of AO Therapy in AMI

AO Therapy has been studied for application in acute MI in three separate studies. First, an IDE-sanctioned Phase I pilot study was conducted in the U.S. and Italy beginning in 1999, involving 29 anterior AMI subjects. This study was conducted in two separate

phases: Phase I involved 9 subjects who received AO Therapy selectively, with the hyperoxemic reperfusion provided through a guiding catheter in the left main coronary ostium at a flow rate of 100 ml/min. In Phase IA, the reperfusion was provided sub-selectively in the infarct-related artery through an infusion catheter at a flow rate of 75 ml/min. These studies were conducted using previous generation equipment; however, the physicochemical parameters and route of administration of AO Therapy in Phase IA are the same as the current AO System. Results from the Phase I/IA study are presented in **Section 1.5.2.1**.

The AO System and AO Cartridge were developed in their current configuration after the completion of the Phase I/IA IDE studies. The clinical use of the AO System for administration of AO Therapy was examined in two trials; first, the Supersaturated Oxygen in ST-Elevation Reperfused-AMI, or OYSTER-AMI study, was conducted on anterior STEMI patients by [redacted]. OYSTER-AMI examined the safety and effectiveness of AO Therapy in a 41-patient study (21 AO Therapy subjects, 20 matched control subjects). The OYSTER-AMI study is presented in **Section 1.5.2.2**.

Most significantly, the AMIHOT I study[†] was conducted following IDE approval to examine the safety and effectiveness of AO Therapy in both anterior and inferior STEMI patients undergoing successful reperfusion therapy via PCI up to 24 hours from symptom onset. A summary of the AMIHOT I study, and its significance and tie-in to the AMIHOT II trial, appears in **Section 1.5.2.3**.

1.5.2.1 Phase I/IA Studies of AO Therapy in AMI

1.5.2.1.1 Summary

[†] Note: for consistency of nomenclature and to avoid confusion, the AMIHOT study as formerly termed in IDE submission documents, etc. is termed "AMIHOT I" in this PMA module, to distinguish it from the AMIHOT II study.

The purpose of the Phase I/IA studies was to evaluate the feasibility and safety of AO Therapy in patients undergoing mechanical reperfusion for acute myocardial infarction. In the Phase I study conducted in Q1-Q2 1999, in AMI patients undergoing PCI with or without stent placement, hyperoxemic blood was infused into the left main coronary artery at a flow rate of 100 ml/min for 60 minutes post-PCI. In Phase IA, conducted in Q3-Q4 1999, the hyperoxemic reperfusion was performed sub-selectively into the infarct-related artery at a flow rate of 75 ml/min for 90 minutes post-PCI. Considering both of these phases, Aqueous Oxygen was infused successfully in all cases. No clinical, electrical or hemodynamic instability was observed during the AO infusion. Systemic, pulmonary and pulmonary capillary wedge pressure, all stayed within normal limits. All patients maintained sinus rhythm during and after AO infusion. No adverse events were documented that were related to the AO System or required accessories, or to AO Therapy administration. The Phase I/IA study data were reported by Dixon *et al.*[87] and are summarized below.

Twenty-nine patients were enrolled in the combined study phases (9 patients in Phase I, 20 in Phase IA). To assess ventricular function, left ventriculography was performed pre- and post-AO infusion, and regional wall motion was assessed pre-AO Therapy, during AO infusion, and at 24-hours, 1 and 3-months post-AO Therapy. No change in global LVEF was noted in pre- and immediately post-AO Therapy measurements (48.6 ± 7.3% and 51.1 ± 9.2%, p=ns). Mean chord motion of the infarct zone was also similar in a comparison of pre- and immediately post-AO infusion measurements (-2.3 ± 0.5 vs. –2.2 ± 0.5, p=0.23 for anterior infarction, and –1.9 ± 0.4 vs. –2.2 ± 0.5, p=0.06 for inferior infarction).

Significant LV functional improvement was noted in the 2-D echocardiography analysis of the combined PhaseI/IA data. The baseline EF and wall motion score index (WMSI) were (mean ± SD) 48.6 ± 7.3% and 1.68 ± 0.24, respectively; these measurements were taken immediately post-PCI prior to AO Therapy administration. An improving trend in

EF and significant improvement in WMSI were observed at 24-hours (EF 51.8 ± 6.8%, p=0.08; WMSI 1.48 ± 0.24, p<0.001). Further improvement in ventricular function was demonstrated at 1 and 3 months compared to baseline: EF 1-month 54.4 ± 6.6%, (p<0.001), 3-months 56.0 ± 8.3% (p<0.001) and WMSI 1-month 1.39 ± 0.24 (p<0.001) and 3-months 1.34 ± 0.26 (p<0.001). The analysis demonstrated that these improvements in global LV functional measures were due to recovery of ventricular function in the infarct zone; regional WMSI assessments showed no change in the non-infarct zone[88, 89].

1.5.2.1.2 Differences in Study Parameters between Phase I and Phase IA

Key procedural details of the non-randomized Phase I/IA studies are provided below; the studies were conducted at three investigational sites (two U.S. and one Italian center). The Phase I and IA studies were similar in methodology with the following differences:

PHASE I:

1) Selective infusion through guiding catheter placed in the coronary ostium.
2) Blood flow rate = 100 ml/min
3) AO infusion time = 60 minutes
4) AMI: Total occlusions only.
5) AMI ≤ 12 hours
6) Hyperoxemic pO_2 level: 600 – 700 mmHg

PHASE 1A:

1) Sub-selective infusion through infusion catheter into the infarct-related artery.
2) Blood flow rate = 75 ml/min
3) AO infusion time = 90 minutes
4) AMI: Total and non-total occlusions.
5) AMI ≤ 24 hours
6) Hyperoxemic pO_2 level: 700 – 800 mmHg

1.5.2.1.3 Study Methods

To assess the safety of AO Therapy administration, right heart and arterial pressures, continuous ECG monitoring, oxygen saturations, and 2-D echocardiography were performed pre-AO infusion, at 15-min intervals during the infusion, and immediately post-AO infusion. Blood work was also drawn pre-, during, after, and up to 24 hours post-AO Therapy to assess any potential physiologic changes.

A total of 29 patients were enrolled in the Phase I and IA studies. Nine patients were enrolled in Phase I and 20 patients were enrolled in Phase IA. For the combined studies, 14 patients were enrolled at [redacted] 6 patients were enrolled at [redacted] and 9 patients were enrolled at [redacted]

1.5.2.1.4 Left Ventricular Analysis

Left ventricular function was assessed by left ventriculography and 2-D echocardiography. Left ventriculography was performed pre- and immediately post-AO infusion in the 30° right anterior oblique projection. End-diastolic and end-systolic endocardial contours were traced from a sinus beat by an observer blinded to the infarct vessel and patient outcome. Left ventricular ejection fraction was calculated using the area-length method.

Regional wall motion was determined by the centerline method. Endocardial motion was calculated along 100 chords drawn perpendicular to a centerline midway between the end-diastolic and end-systolic contours. The measured motion of each chord was normalized for heart size by dividing by the end-diastolic perimeter. Regional motion for each chord was expressed in standard deviations per chord above or below normal mean motion for that chord. The *severity* of the regional wall motion abnormality is

represented by the mean chord motion and the *extent* by the number of chords with abnormal motion.

For anterior myocardial infarction, chords 11-66 were used to evaluate the anterior wall and chords 67-80 for the inferior wall. For inferior myocardial infarction the respective chord ranges were 11-50 and 51-80. Chords 1-10 and 81-100 were excluded as per routine practice because they represent movement of the aortic root and mitral valve.

Quantitative angiography was performed and multivessel coronary disease was defined as >50% stenosis in one or more vessels remote from the infarct artery. Patency of the infarct-related artery was classified according to the TIMI flow grades 0-3.

Two-dimensional echocardiography was performed pre- and post-PCI (pre-AO infusion), at 15 minutes intervals during AO infusion, immediately post-AO infusion, and at 24 hours, 1 month and 3 months post-AO infusion. During the AO infusion patients were supine; for all other studies patients were placed in the left lateral decubitus position. Echocardiographic imaging was performed with commercially available equipment and studies were recorded on videotape. Calculations for global and regional wall motion were performed both on-line and off-line. Parasternal long axis and short axis, 4-chamber and 2-chamber views were included for analysis.

The left ventricular wall was divided into 16 segments and regional wall motion for each segment was scored according to the recommendation of the American Society of Echocardiography. Segments were graded as 1 = normal, 2 = hypokinesis, 3 = akinesis, and 4 = dyskinesis. The left ventricular ejection fraction was estimated by tracing the endocardial contour in end-diastole and end-systole. Calculations were performed to allow for serial comparison of images.

1.5.2.1.5 Statistical Analysis

Changes in global left ventricular function and regional wall motion were analyzed using paired t-tests. Results are expressed as (mean ± SD) or percentage. A p value of ≤ 0.05 was considered statistically significant.

1.5.2.1.6 Clinical Procedure

After obtaining an informed consent the study patients were taken to the cardiac catheterization laboratory. Upon entry into the cardiac catheterization laboratory, right and left heart catheterization and coronary angioplasty/stenting was performed as per standard-of-care techniques.

A 7.5F sheath was inserted into a femoral vein for performance of a right heart catheterization with a 7F right heart pressure catheter. Right heart pressures were recorded, and the distal end of the catheter remained in the pulmonary artery for continuous monitoring of pulmonary arterial pressures and for intermittent blood samples.

A 7.5 – 8.5F sheath was inserted into a femoral artery and was used to advance left heart catheters. A 4 – 6F sheath was inserted into the contralateral femoral artery or a radial artery and was used to withdraw blood into the extracorporeal circuit for AO Therapy.

After PCI w/stenting was successfully performed on the culprit lesion, and the angiographic result demonstrated that the patient met the inclusion criteria, left ventriculography was performed. Heparin was administered before and during coronary interventions as per standard clinical practice.

Immediately post-PCI, a 12-lead ECG and 2-D echocardiogram were performed. Blood samples were taken at baseline to measure: cardiac enzymes (CK, CK-MB), CBC with differential, electrolytes, BUN/Creatinine, liver panel (bilirubin, albumin, alkaline

phosphatase, SGOT/SGPT, GGPT, LDH), and Activated Clotting Time (ACT). ACT levels were maintained in the 250 – 300 s range throughout AO Therapy administration by administering heparin as needed.

To deliver AO Therapy, a 7F coronary guide catheter was advanced through the femoral arterial sheath into the coronary ostium (Phase I) or a 5F [redacted] infusion catheter was advanced through the guiding catheter into the infarct related artery (Phase IA). The contralateral or radial arterial sheath was then attached to the proximal end of the AO Loop and the distal end of the AO Loop was then attached to the guide catheter (Phase I) or the infusion catheter (Phase IA), after blood priming of the circuit was complete.

The AO System was then initiated and the blood pump was started until targeted blood flow rates were obtained: 100 ml/min (Phase I) or 75 ml/min (Phase IA). Following approximately 5 minutes of blood flow, infusion of AO solution was initiated. Baseline arterial and pulmonary pressures were recorded along with a 12-lead ECG. Blood samples were drawn from the femoral and pulmonary arteries to assess blood gas measurements.

The AO infusion flow rate was adjusted to achieve a hyperoxemic pO_2 in the ranges of 600-800 mmHg, as measured by blood gas sampling of the distal portion of the return tube set. AO solution was infused continuously for the duration of 60 minutes (Phase I) or 90 minutes (Phase IA). During AO infusion, femoral and pulmonary arterial pressures and saturations, systemic arterial pO_2, ECG, and 2-D echoes of the left ventricle were obtained at 15-minute intervals. ACT measurements were performed at 30-minute intervals.

Post-AO infusion, the circuit priming volume of blood was returned to the patient and the catheters were removed. At 15-min post-AO infusion, femoral and pulmonary pressures and saturations were obtained as well as systemic and AO Loop pO_2s, ECG, and 2-D echoes of the left ventricle. Final left ventriculography was performed. Final blood work

was drawn and included the following: CBC with differential, electrolytes, cardiac enzymes, liver panel and ACT as indicated in the protocols.

1.5.2.1.7 Results of Phase I/IA

Demographic Data

Twenty-nine patients were enrolled (mean age 58.9 ± 12.6 years, male=24, female=5). AO was infused successfully in all cases. The infarct related artery was: left anterior descending (n=19; 65%), right coronary (n=8; 28%), and dominant or co-dominant circumflex (n=2; 7%). Eleven patients (38%) had hypertension, 6 patients (21%) had diabetes, 11 patients (38%) had hypercholesterolemia, 15 patients (52%) smoked or had a history of smoking, 8 patients (28%) had a history of coronary artery disease, 4 patients (14%) had prior coronary interventions, and 6 patients (21%) had a history of prior myocardial infarction. Mean hospital stay was 5.8 ± 2.9 days, and 26 patients (90%) completed follow-up.

Complication/Adverse Event Data

No unanticipated adverse effects were noted throughout the study. No complications or adverse events were noted that were related to the AO System and required accessories, or to AO Therapy administration, as documented in the data collection forms from both study phases and sites.

Adverse event reporting for the combined studies revealed n=9 complications associated with PCI procedures, including: n=6 (21%) hematomas, n=2 (7%) pseudoaneurysms, and n=1 (3.4%) transfusion. These complications are commonly associated with PCI procedures. Additional adverse events reported for the combined studies include the following events classified as related to neither PCI nor AO Therapy: n= 2 (7%) new onsets of congestive heart failure, n=2 (7%) hematomas, n=1 (3.4%) pseudoaneurysm,

n=1 (3.4%) left ventricular thrombus, and n=1 (3.4%) unrelated diagnosis of Chronic Lymphocytic Leukemia, n=1 (3.4%) diagnosis of shortness of breath.

Angiographic Data

Onset of chest pain until reperfusion time was (mean ± SD) 324.8 ± 228.6 minutes. n=11 (38%) patients had single-vessel disease, n=11 (38%) patients had two-vessel disease, and n=7 patients (24%) had triple-vessel disease by angiography. Twenty-two patients (76%) received primary PCI and n=7 (24%) patients had failed thrombolytic therapy and received rescue PCI. Stents were placed in n=27 (93%) patients during their procedure, and n=21 (72%) patients received antiplatelet drugs in the cath lab. The mean diameter stenosis of the infarct related artery was (mean ± SD) 96.2 ± 6.7%, and final angiography demonstrated a diameter stenosis of (mean ± SD) 4.9 ± 6.1% after primary PTCA. n=21 patients (72%) had pre-PCI TIMI flow grade = 0, n=1 (3.4%) had TIMI 1, and n=7 (24%) patients had TIMI 2 flow. Post-PCI, n=3 patients (10%) had TIMI flow grade = 2, and n=26 patients (90%) had TIMI 3 flow. No changes in TIMI flow grade were observed post-AO infusion.

AO Therapy Procedural Data

(Data reported as mean ± SD unless otherwise noted)

Total TherOx infusion time for Phase I was 55.9 ± 9.0 minutes, and for Phase IA was 92.0 ± 5.3 minutes. Sub-selective infusion was performed in n=20 (69%) patients (Phase IA). The blood flow rate in the AO Loop, as measured by continuous ultrasonic flow monitoring, was 101.8 ± 0.2 ml/min in Phase I, and 74.2 ± 0.5 ml/min in Phase IA. The AO solution flow rate was 2.9 ± 0.2 ml/min, and the baseline native arterial systemic pO_2 was 149.4 ± 73.6 mmHg in the combined study data. The systemic arterial pO_2 was observed to increase to 166.7 ± 78.6 at the end of 90 minutes AO infusion ($p = 0.01$).

The hyperoxemic AO Loop pO_2 was 614.8 ± 25.8 mmHg in Phase I and 733.3 ± 42.3 mmHg in Phase IA.

Baseline systolic blood pressure (SBP) was 124.0 ± 16.4 mmHg and did not change significantly during AO infusion: 90-min values = 122.8 ± 17.3 mmHg (p=ns). Similarly, diastolic blood pressure (DBP) was 80.5 ± 11.2 mmHg at baseline vs. 80.7 ± 11.9 mmHg at 90 minutes (p=ns). Pulmonary artery SBP was 36.2 ± 12.7 mmHg at baseline and 31.3 ± 10.3 mmHg at 90 minutes (p=ns), and pulmonary artery DBP was 19.3 ± 5.3 mmHg at baseline and 16.3 ± 5.4 mmHg at 90 minutes (p=ns). Baseline pulmonary capillary wedge pressure was 21.4 ± 9.0 mmHg as compared to 16.0 ± 6.9 mmHg at 90 minutes (p=0.04), and baseline heart rate was 78.4 ± 11.3 bpm as compared to 73.2 ± 14.9 bpm at 90 minutes. Activated clotting times were maintained at 328.2 ± 27.6 seconds during AO infusion.

Laboratory Data

(Data reported as mean ± SD unless otherwise noted)

Laboratory data collected pre-PCI and post-AO infusion showed no clinically significant changes in red blood cell (RBC) count, hemoglobin (Hgb), hematocrit (Hct), platelets, or white blood cells (WBC). The results for the pre/post measurements are as follows: RBC 4.6 ± 0.4 to 4.2 ± 0.4 M/μL, Hgb 14.0 ± 1.1 to 13.1 ± 1.5 g/dL, Hct 41.1 ± 3.3 to 38.1 ± 4.4%, platelets 218.9 ± 40.5 to 208.6 ± 49.3 K/μL, and WBC 11.6 ± 3.3 to 14.7 ± 10.2 K/μL. The white blood cell count was slightly elevated from normal ranges (which is a typical response in the acute myocardial infarction patient), both pre- and post-AO Therapy.

Electrolyte and Blood Urea Nitrogen (BUN)/creatinine data were collected both pre-PCI and post-AO Therapy and showed no clinically significant changes between time points. The results for the pre/post measurements are as follows: Sodium 137.5 ± 3.6 to 135.6 ±

4.4 mEq/L, Potassium 3.9 ± 0.5 to 4.1 ± 0.5 mEq/L, Chloride 104.8 ± 5.6 to 103.3 ± 4.3 mEq/L, Bicarbonate 23.0 ± 3.1 to 23.0 ± 3.0 mEq/L, Magnesium 1.9 ± 0.3 to 1.8 ± 0.3 mEq/L, Calcium 7.3 ± 2.5 to 6.8 ± 2.7 mg/dL, BUN 22.3 ± 11.7 to 20.9 ± 13.0 mg/dL, and Creatinine 0.97 ± 0.25 to 0.91 ± 0.23 mg/dL. No deleterious changes were observed in these parameters as a result of AO Therapy administration.

Liver panel data were collected both pre-PCI and post-AO Therapy as well, and showed no clinically significant changes. The results for the pre/post measurements are as follows: Bilirubin 0.7 ± 0.3 to 0.7 ± 0.4 mg/dL, Albumin 4.0 ± 0.4 to 3.6 ± 0.5 g/dL, Alkaline Phosphotase 75.6 ± 22.1 to 73.7 ± 22.9 U/L, GGPT 33.6 ± 40.0 to 28.3 ± 34.1 U/L, SGOT 97.9 ± 109.6 to 248.7 ± 170.9 U/L, and SGPT 33.8 ± 18.7 to 51.5 ± 28.1 U/L. SGOT and SGPT were elevated above the normal range, as anticipated after an acute myocardial infarction.

Global Left Ventricular Function

(Data reported as mean ± SD unless otherwise noted)

Global LV function was analyzed post-PCI (pre-AO Therapy) and immediately post-AO treatment by left ventriculography. Twenty-six patients had paired ventriculograms for analysis (exclusions: 2 were unsuitable due to ventricular ectopy; 1 patient did not have ventriculography performed per physician request secondary to contrast volume used during PCI). The pre- and post-AO infusion LVEF data assessed by these means were: 50.0 ± 9.2% and 51.1 ± 9.2% (p=ns).

Regional Left Ventricular Function

(Data reported as mean ± SD unless otherwise noted)

Regional left ventricular function was analyzed pre- and post-AO Therapy by the centerline method. The pre- and post-AO Therapy mean chord motion measurements in

the infarct region were: -2.3 ± 0.5 vs. –2.2 ± 0.5 (p=0.23) for anterior infarction and –1.9 ± 0.4 vs. –2.2 ± 0.5 (p=0.06) for inferior infarction. Similarly, the number of hypokinetic or dyskinetic chords in the infarct region did not change pre- to post-AO Therapy.

Echocardiographic Analysis

(Data reported as mean ± SD unless otherwise noted)

Baseline and follow-up echocardiograms were performed in 29 patients. No significant changes were observed in pre- to post-AO infusion LVEF measurements (48.6 ± 7.3 vs. 49.3 ± 6.9%, p=0.20). However, an improving trend in LVEF was demonstrated at 24-hours (51.8 ± 6.8%, p=0.08), and significant improvements were noted at 1-month (54.4 ± 6.6%, p<0.001), and 3-months (56.0 ± 8.3%, p<0.001). Corresponding improvements in global wall motion score index (WMSI) were observed from baseline (WMSI = 1.68 ± 0.24): 24-hour WMSI = 1.48 ± 0.24 (p<0.001), 1-month WMSI = 1.39 ± 0.24 (p<0.001), and 3-month WMSI = 1.34 ± 0.26 (p<0.001) (p values assessed by comparison to baseline).

1.5.2.1.8 Phase I/IA Conclusions

The Phase I/IA studies represent the first clinical evaluations of AO Therapy for the treatment of AMI involving human subjects, following successful reperfusion therapy by PCI. The primary purpose of the Phase I and IA TherOx study was to evaluate the acute safety and feasibility of AO Therapy in this patient population. Procedural and laboratory data from these studies demonstrated that AO infusion was well tolerated and completed in all patients without any clinical, hemodynamic and/or electrical complications. No untoward effects of prolonged intracoronary infusions were noticed on final coronary angiograms. No adverse effects were noted from using the prototype AO System or accessories, and the procedure was successfully completed first in a selective hyperoxemic infusion (Phase I) and also in the preferred sub-selective infusion (Phase IA). An analysis of global and regional left ventricular function as assessed by 2-

D echocardiography showed improving LV function both in measurements of ejection fraction and wall motion score index. Further analysis of wall motion score data revealed that the improvements were specifically in the infarct zone, which is an expected result if the therapy is acting to mitigate myocardial damage. The Phase I/IA study led to refinements in the clinical application of AO Therapy and to the AO System and accessory devices. Following development of the current generation AO System and AO Cartridge, clinical evaluation of AO Therapy continued, first in the OYSTER-AMI study and then significantly in the IDE-approved randomized AMIHOT study.

1.5.2.2 OYSTER-AMI Study

1.5.2.2.1 Overview

Following development of the current configuration AO System and AO Cartridge, clinical evaluation of AO Therapy for AMI treatment was continued in a single-center study conducted in [redacted] under the supervision of [redacted]. This study, termed the "Supersaturated Oxygen in ST-Elevation Reperfused-AMI", or OYSTER-AMI trial[90], investigated LV functional recovery, cardiac enzyme release kinetics, and ST-segment electrocardiographic changes in anterior AMI patients with no prior AMI history.

The study was not randomized but evaluated both AO Therapy patients and a control population of case-matched subjects. The means of AO Therapy administration were the same as both the later AMIHOT I and II studies; 90 minutes of AO infusion was performed with hyperoxemic blood reperfusion provided via sub-selective infusion catheter into the infarct-related artery post-PCI w/ stent placement.

LV functional recovery was evaluated by serial 2-D contrast echocardiography at six time points: immediately post-PCI (baseline), and at 24 hrs, 7 days, 1 month, 3 months, and 6

months post-procedure in both groups. LVEF and wall motion score index (16-segment model) were evaluated at each of these time points.

1.5.2.2.2 Results

A total of 41 subjects were examined in the OYSTER-AMI study, including 21 AO Therapy patients and 20 Control patients. The AO Therapy group had 18 males (86%) as compared to 16 (80%) in the Control group (p=ns). The groups were also comparable in age (mean ± SD): AO Therapy = 62 ± 10.7 yrs vs. Control = 65 ± 9.6 yrs (p=ns); time to presentation (mean ± SD): AO Therapy = 3.5 ± 1.6 hrs vs. Control = 2.8 ± 1.8 hrs (p=ns); and time to reperfusion (mean ± SD): AO Therapy = 4.5 ± 1.5 hrs vs. Control = 5.1 ± 1.2 hrs (p=ns). The two groups had comparable rates of IIb/IIIa inhibitor administration: AO Therapy n = 15 (71.4%) vs. Control n = 13 (65%) (p=ns); rescue PCI: AO Therapy n = 1 (4.7%) vs. Control n = 1 (5.0%) (p=ns); and stent use: AO Therapy n = 21 (100%) vs. Control n = 19 (95%) (p=ns). All patients presented with pre-PCI TIMI flow grade = 0, 1, or 2; over 80% of both groups presented with TIMI 0 or 1 flow (p=ns). The two groups were very well matched in terms of their baseline characteristics, allowing for meaningful comparison of results.

Cardiac enzyme data showed a nominal decrease in peak creatine kinase (CK) and CK-MB levels in the AO Therapy group (CK: 3609 ± 2214 IU/L, CK-MB: 377 ± 219 IU/L) as compared to the Control Group (CK: 4024 ± 2649 IU/L; CK-MB: 327 ± 165 IU/L) (p=ns), and a statistically significant decrease in the time to peak CK, measured from time from symptom onset (AO Therapy = 9.4 ± 3.4 hrs vs. Control = 14.2 ± 5.3 hrs; $p < 0.001$). With cardiac enzyme obtained through 72 hours post-infarction, the CK half life was calculated as well: AO Therapy = 23.4 ± 8.9 hrs vs. Control = 30.5 ± 5.8 hrs ($p<0.01$). The decreases observed in the AO Therapy group in both peak CK enzyme data, time to peak CK, and CK half life translates to less total CK enzyme release.

Because CK enzyme release correlates with myocardial necrosis, these data were considered promising with respect to showing infarct reduction in AO Therapy subjects.

Electrocardiographic data taken from 12-lead ST monitoring showed a statistically significant decrease in ST elevation from baseline (pre-PCI) to 7 days in AO Therapy subjects as compared to controls; on day 7, the decrease in ST elevation in AO Therapy patients was 5.2 mm as compared to 3.8 mm for controls ($p = 0.02$).

Improvements in LVEF and wall motion score index were noted in the AO Therapy group over time as well; post-PCI (baseline) LVEF = 41 ± 7% as compared to 48 ± 8% at 7 days ($p < 0.01$ compared to baseline), 52 ± 9% at 1 month ($p < 0.01$ compared to baseline), and 53 ± 9% at 6 months ($p<0.01$ compared to baseline). The six-month relative improvement was 28%; in contrast, the Control group only improved by a relative 2.5% mean improvement at 6 months ($p<0.01$ as compared to AO Therapy subjects). Similarly, relative improvements in wall motion score index from baseline to six months were 26% in the AO Therapy group as compared to 2.4% in the Control group.

1.5.2.2.3 Conclusions

The OYSTER-AMI study was a successful feasibility study that further bolstered the positive clinical experience with AO Therapy in the Phase I/IA studies, using the current generation AO System and AO Cartridge. The improvements in LV functional recovery, ST elevation recovery, and reduction in cardiac enzyme release observed in OYSTER-AMI suggested that AO Therapy could be used effectively in an anterior STEMI population.

1.5.2.3 AMIHOT I Clinical Trial

1.5.2.3.1 Overview

The safety and effectiveness of AO Therapy were evaluated in a clinical study involving 289 patients at 23 institutions. This Phase II study, termed the Acute Myocardial Infarction with HyperOxemic Therapy, or AMIHOT trial, was conducted from [redacted] when the first patient was enrolled, to [redacted] when the final three-month follow-up assessment was completed. An extensive report of the study was submitted as IDE Supplement [redacted] on [redacted] An executive summary of the study methods, results, and conclusions is provided herein. For clarity, the original AMIHOT trial is referred to within this PMA module as 'AMIHOT I', to distinguish it from the AMIHOT II clinical trial and thus avoid ambiguity.

The TherOx Aqueous Oxygen (AO) System and TherOx AO Cartridge were approved for use in an expanded multicenter investigational clinical trial on [redacted] under IDE number [redacted]. The original request for trial expansion was made in [redacted] and approval for the pivotal trial was received under [redacted].

1.5.2.3.2 Study Objective

The AMIHOT I study objective was to determine whether the adjunctive administration of AO Therapy after PCI and stenting in a group of patients presenting less than or equal to (≤) 24 hours from AMI symptom onset improves left ventricular function and reduces the area of infarction, with no increased incidence of 30-day Major Adverse Cardiac Events (MACE) when compared to a Control group receiving PCI with stenting alone.

1.5.2.3.3 Design

The AMIHOT I clinical trial was prospectively designed as a randomized (1:1), controlled, multicenter trial to assess the safety and effectiveness of intracoronary

perfusion of AO solution and blood following successful PCI in acute myocardial infarction patients. This hyperoxemic intracoronary infusion, which is administered for a period of 90 minutes, is termed 'AO Therapy' in this submission. Patients received standard interventional treatment (PCI with stenting) with or without adjunctive administration of AO Therapy depending on their randomization assignment into either the Control or AO Therapy groups. In addition to the randomized patient cohort, twenty additional run-in patients were administered AO Therapy in the initial training phase of this comparative trial.

1.5.2.3.4 Primary Endpoints

Effectiveness

The AMIHOT I study design included three co-primary effectiveness endpoints as follows:

1. 5% absolute reduction in infarct size as measured by the percent of infarcted left ventricular volume, assessed by [redacted] SPECT imaging at 14(±7) days post PTCA/stent placement, as an indicator of AO treatment effectiveness by test of superiority.
2. 0.2 unit increase in regional wall motion score index (WMSI) in the infarct zone over three months (90 ± 7 days) as evidence of left ventricular function recovery by a test of superiority in the AO treatment group.
3. ST-segment recovery as evidenced by a 50% lower ST-deviation vs. time trend curve area in the AO treatment group during the first three hours of continuous monitoring as an indicator of myocardial ischemia reversal by a test of superiority.

Safety

The composite safety endpoint was based on the number of patients experiencing Major Adverse Cardiac Events (MACE), comprising the total incidences of death, reinfarction, target vessel revascularization, and stroke within one month (30 days) of enrollment.

Results are shown for the MACE rates of the AO Therapy and Control groups in **Table 5** of this document.

All device and procedure-related adverse events were reported by the participating clinical sites and investigated as part of the overall evaluation of device safety. All of the adverse events experienced during the AMIHOT I trial were those that would be anticipated in a PCI procedure. No unanticipated adverse events were encountered during the AMIHOT I trial.

1.5.2.3.5 Study Equipment and Methods

The AO System, AO Cartridge, and accessories described in IDE Supplements [redacted] and [redacted] were used in the AMIHOT I study.

Key AMIHOT I selection criteria considered patients who were diagnosed with acute myocardial infarction (AMI) and admitted to the hospital within 24 hours of symptom onset. Qualifying AMIs met specific electrocardiographic and angiographic criteria prior to randomization, including a > 1 mm ST-segment elevation as measured by ECG in at least two contiguous leads (V1 to V4), and a pre-PCI/stenting angiographic TIMI score of 0, I, or II in the cardiac catheterization laboratory. Successful revascularization with PCI was required for AMIHOT subjects, as measured by a post-procedure TIMI score ≥ II, and qualifying patients were randomized into the study on a 1:1 basis.

AO Therapy patients received an intracoronary 90-minute infusion of hyperoxemic blood post-PCI. The intracoronary infusion of hyperoxemic blood was administered sub-selectively into the infarct-related artery through the [redacted] Infusion Catheter.

1.5.2.3.6 Clinical Procedures

Logging Candidate Patients

Each study center maintained an AMIHOT Patient Selection Log. All patients considered for the AMIHOT clinical trial were recorded in the log. If any candidate patient was excluded from the study, the reasons for the exclusion were recorded in the center's log.

Initial Evaluation

All patients considered for inclusion in the AMIHOT I trial underwent the following screening procedures:

1. Obtained a complete medical history, including history of myocardial infarction, previous coronary interventions, and all medications given within 24 hours prior to procedure.
2. Performed the following baseline labs: Complete blood count (CBC) with differential, cardiac enzymes, electrolytes, BUN/creatinine, liver panel, and arterial blood gas (ABG).
3. Confirmed suitable lesions by coronary angiogram.
4. Confirmed conformance to inclusion/exclusion criteria.
5. Evaluated ECG to determine if patient had experienced a qualifying AMI.
6. Reviewed inclusion/exclusion criteria checklist and obtained patient informed consent prior to PCI.

After obtaining informed consent for the AMIHOT I trial, patients were taken to the cardiac catheterization laboratory where target vessel revascularization was performed by percutaneous coronary intervention (PCI) that included stent placement. All patients underwent PCI with stenting prior to randomization assignment. Post-PCI cine angiography was performed to confirm TIMI flow ≥ II per the study inclusion criteria.

The protocol required an anticoagulation regimen with heparin administration to maintain Activated Clotting Time (ACT) levels ≥ 250 seconds. This level of anticoagulation was required throughout the 90-minute duration of AO Therapy administration.

1.5.2.3.7 Randomization

Each study center received a set of sequentially numbered envelopes containing a slip of paper assigning the patient to either the "Treatment (AO Therapy)" or "Control (PCI only)" group. The assignment slips were generated from a master, computer-generated randomization list that is unique for each study center. Each randomization list was "blocked" to ensure balance in the group assignment within each center.

Patient assignment was based on strict sequential selection from numbered randomization envelopes. The number listed on the envelope assigned to each successive patient enrolled in the study was recorded next to the patient's name in the center's AMIHOT I Patient Selection Log.

1.5.2.3.8 Post-Randomization Procedures

Patients assigned to the Control group received only PCI with stenting. Upon entry into the test group, adjunctive administration of AO Therapy was performed for 90 minutes after successful PCI was completed. The hyperoxemic blood perfusate was delivered through a 5 F [redacted] Infusion Catheter. The femoral arterial access site used for PCI typically was used to place the infusion catheter into the target coronary artery. The infusion catheter was positioned in the infarct-related artery at the investigator's discretion for optimal infusion; the typical placement was inside the stent just at the proximal edge.

Arterial blood gas (ABG) readings were taken before and during AO Therapy administration in order to ensure adequate blood oxygenation for the procedure.

Routine physiological parameters including systolic and diastolic blood pressure, ACT levels, and heart rate and rhythm measurements were taken immediately after completion of PCI for all patients and at 30, 60, and 90 minutes during AO infusion for the AO Therapy group, and finally at 15 minutes post-AO infusion for the AO Therapy group. Additional blood samples were drawn at 8, 16 and 24 hours post-PCI in both the AO Therapy and Control groups; cardiac enzyme levels and other routine diagnostic information were collected from these samples.

1.5.2.3.9 Endpoint Data Collection

ST Segment Resolution

Twelve-lead ECG monitoring was performed continuously for a period of 24 hours post-enrollment. Data were recorded electronically on flash cards and sent to the independent core laboratory for analysis. ST-segment time trend curve areas were measured by the [redacted] at [redacted] (Director: [redacted]). A qualitative description of the endpoint is provided below.

Continuous evaluation of ST-segment resolution more accurately determines both angiographic patency and clinical outcomes than serial static method[91]. The [redacted] method of continuously updated 12-lead ST-segment resolution analysis is a well-established, quantitative marker developed to reflect the speed, quality and stability of reperfusion for patients presenting with acute MI[92, 93]. This method has been shown to be highly reproducible and to have a high correlation with angiographic TIMI flow grades across multiple independent patient populations[94-96]. Continuous ST-segment monitoring also has been shown to be a better predictor of recovery of left ventricular function and clinical outcomes than angiographic TIMI flow grades[97-100], reflecting the continuous physiologic response of myocytes rather than the snap-shot evaluation of epicardial flow characteristics.

Regional Wall Motion Score Index

2D-contrast echocardiograms (ultrasound) were taken for all subjects at four discrete time points: immediately after PCI (baseline) and at 24 hours, 1 month (30 days), and 3 months (90 days) post-PCI. All images were evaluated by the independent [redacted] echocardiography core laboratory ([redacted])

Visual assessment of regional wall motion and associated thickening is commonly used in clinical practice and research. The [redacted] follows the recommendations of the American Society of Echocardiography which has defined a 16 segment system for assessment of left ventricular function that has gained wide acceptance in clinical and research settings[101]. A score is applied to each of these 16 segments: 1 for normal, 2 for hypokinetic (sluggish, but still contracting), 3 for akinetic (not moving), or 4 for dyskinetic (moving opposite direction to expected). The average wall motion score over the abnormal LV segments defines the regional wall motion score index.

Infarct Size

Infarct size for AO Therapy and Control groups was determined using [redacted] SPECT nuclear imaging at 14 days post-procedure. SPECT imaging data interpretation and calculations were used to evaluate infarct size reduction as a percentage of left ventricular volume in both groups. Data were sent to the independent [redacted]) for analysis. **Section 1.3.5.1** provides background and rationale for the clinical significance of an absolute reduction of 5% in infarct size.

1.5.2.3.10 AMIHOT I Study Results

Effectiveness

Results for the Control/AO Therapy group comparisons for the three co-primary effectiveness endpoints demonstrated a nominal improvement in the test group; however, this nominal improvement did not achieve clinical or statistical significance in the entire population. However, two key patient subgroups showed promising results. In particular, AO Therapy patients who were revascularized within 6 hours of AMI symptom onset and who had anterior wall infarctions showed a marked improvement in all three co-primary endpoints as compared to this Control population. This anterior ≤ 6 hour patient subgroup was pre-specified for analysis in the original AMIHOT I Investigational Plan, but the study was not adequately powered for this subgroup population alone. **Tables 3 – 6** below present summary data for the three co-primary effectiveness endpoints for each of the following randomized patient cohorts:

1. All randomized patients (patients treated within 24 hours of symptom onset were included in the AMIHOT I study)
2. Randomized patients treated within 6 hours of symptom onset, regardless of infarct location
3. Randomized patients treated within 6 hours of symptom onset who experienced an anterior location infarct

Table 3. AMIHOT I Infarct Size Results (%LV as measured by Tc-99m SPECT imaging)

	Control Group (median±IQR*) (n)	**AO Therapy Group** (median±IQR) (n)	**p value** (Wilcoxon rank-sum test) **one-sided**
All infarct locations			
0-24 hrs to reperfusion	13.0 ± 26.25 (122)	11.0 ± 27.5 (121)	0.29
0-6 hrs to reperfusion	14.0 ± 26.0 (87)	7.0 ± 21.5 (81)	0.02
Anterior MI			
0-6 hrs to reperfusion	23.0 ± 33.0 (52)	9.0 ± 30.5 (49)	0.04

*IQR = Interquartile range

Infarct size results are expressed as a percentage of the left ventricle, and median values as well as the interquartile ranges (IQR) are displayed in **Table 3**. Available data for all randomized patients were included in the analysis. The results shown in **Table 3** demonstrate a marked reduction in infarct size, as measured by [redacted] SPECT imaging, in the AO Therapy group for the < 6 hour patient cohorts. The all-patient < 24 hour group did not exhibit a statistically significant benefit but showed a favorable trend toward the AO Therapy group, with a 2% absolute reduction in median infarct size, from 13% for Control subjects to 11% in the AO Therapy group.

When data for patients treated within 6 hours of symptom onset are examined, the AO Therapy group exhibited a 7% absolute reduction in infarct size, from 14% in Control subjects to 7% in the AO Therapy group. **Table 3** shows that this reduction is even more pronounced in the data for anterior location AMI subjects treated within 6 hours of symptom onset, where the AO Therapy group exhibited a 14% absolute reduction in infarct size from 23% in the Control group to 9% in the AO Therapy group. This anterior AMI patient cohort represents the most severe acute heart attacks within the general population, as anterior location AMIs are correlated with increased mortality and morbidity and reduced ventricular function. The treatment window suggested by the

data, a time up to six hours post-symptom onset, also is supported in the clinical literature and is a common enrollment criterion in many AMI trials.

Table 4. AMIHOT I Regional Wall Motion Score Index (RWMSI) Improvement Results (change in RWMSI from Baseline – 90 days; negative change = improvement)

ΔRWMSI	Control Group (mean ± SD) (n)	AO Therapy Group (mean ± SD) (n)	p value (t-test) one-sided
All infarct locations			
0-24 hrs to reperfusion	-0.57 ± 0.48 (119)	-0.62 ± 0.53 (115)	0.24
0-6 hrs to reperfusion	-0.56 ± 0.48 (84)	-0.69 ± 0.55 (79)	0.06
Anterior MI			
0-6 hrs to reperfusion	-0.54 ± 0.49 (49)	-0.75 ± 0.57 (49)	0.03

Table 4 displays the results for regional wall motion score index improvement (decrease) at 3 months (90 days) as compared to baseline measurements taken immediately post-PCI; 2-D contrast echocardiography was utilized to record the images for analysis. Wall motion score was evaluated on a 4-point grading scale by the independent echocardiography core laboratory at the [redacted]. As wall motion improves, the score decreases; thus, the improvement is expressed in the table as a negative number.

To obtain a value for ΔRWMSI, a baseline regional wall motion score index was required; if an evaluable 3-month RWMSI was unavailable, the 1-month value was used as the last observation carried forward. Data were not estimated for subjects who lacked either an evaluable baseline or an evaluable 1 or 3-month wall motion score. Because wall motion score experiences monotonic decrease from baseline post-PCI until recovering to a steady-state value, the use of the 1-month value in substitution of the 3-month value is by nature conservatively biased; *i.e.*, any treatment effect to demonstrate superiority will be underestimated. Results show larger decreases, or greater improvement in contractility and muscle recovery, in the AO Therapy group as compared

with Control subjects. In addition, the observed improvement in AO Therapy subjects versus Controls is greatest in the ≤ 6 hr anterior patient population. This result was consistent with the observed trend in the infarct size data.

Tables 5 and 6 display ST-segment resolution data collected during the 0-3 hr and 0-6 hr time intervals post-PCI, respectively (time = 0 is defined as the time of last contrast injection). As outlined previously, continuous ST-segment monitoring is more sensitive than discrete data collection at set time intervals. As a result, the area under the curve trial endpoint enables a comparison of the Control and AO Therapy groups in terms of accumulated ischemic burden.

Table 5. AMIHOT I ST- Deviation Time Trend Curve Area Data: 0 – 3 hrs post-PCI

	Control Group median (95% CI) (n)	**AO Therapy Group median** (95% CI) (n)	**p value** (Wilcoxon rank-sum test) **one-sided**
All infarct locations			
0-24 hrs to reperfusion	0 (0, 34) (117)	0 (0, 186) (120)	0.5
0-6 hrs to reperfusion	0 (0, 34) (83)	0 (0, 132) (75)	0.32
Anterior MI			
0-6 hrs to reperfusion	311 (0, 972) (46)	0 (0, 222) (46)	0.01

Table 6. AMIHOT I ST- Deviation Time Trend Curve Area Data: 0 – 6 hrs post-PCI

	Control Group median (95% CI) (n)	**AO Therapy Group median** (95% CI) (n)	**p value** (Wilcoxon rank-sum test) **one-sided**
All infarct locations			
0-24 hrs to reperfusion	0 (0, 134) (114)	0 (0, 228) (119)	0.32
0-6 hrs to reperfusion	0 (0, 134) (80)	0 (0, 0) (74)	0.25
Anterior MI			
0-6 hrs to reperfusion	600 (34, 1957) (44)	0 (0, 182) (44)	0.002

The AMIHOT I trial endpoint for ST-segment resolution specified that time trend curve areas were to be evaluated during the first three hours post-procedure interval. For Control patients treated with PCI and stenting, this time period is straightforward, and time zero starts with the completion of the last confirming contrast injection in the cardiac catheterization laboratory. However, due to the need for a baseline contrast ECHO measurement and the required 90-min infusion duration, patients in the AO Therapy group had only just completed the hyperoxemic infusion at three hours post-PCI. Therefore, to obtain information three hours post-AO Therapy, the two groups were compared in the 0-6 hour time frame post-PCI as well as the 0-3 hour period specified in the protocol. **Table 6** displays the 0-6 hour ST time trend curve area data and provides

information on whether any acute effects observed during the 0-3 hour period are sustained in the first three hours after AO Therapy has been completed.

Total ischemic area was assessed during the time intervals by the ECG core lab at [redacted] Clinically, an area equal to zero is the best attainable measure and indicates complete or virtually complete ST-segment resolution in the patient's ECG. Increasing areas indicate persistent ECG abnormalities caused by prolonged or unresolved ischemia, and are undesirable. The distributions of the data for the AMIHOT trial were highly skewed, with a large proportion of exactly zero values and a long-tailed distribution of increasingly high areas. Thus, the data displayed in **Tables 5** and **6** frequently show median scores of zero area; p values were calculated for the distributions using a non-parametric Mann-Whitney U test. The 95% lower and upper confidence limits (95% LCL/UCL) are displayed alongside median area values in **Tables 5** and **6**.

Table 5 shows the 0-3 hour data for each of the three patient group comparisons. Consistent with both infarct size and wall motion data, results are nominally better in the AO Therapy group in both the all patient and $\leq$ 6 hr groups, and significantly better in the $\leq$ 6 hr anterior patient group. In addition, irrespective of randomization assignment, approximately 80% of non-anterior infarcts had ST area equal to zero at both the 0-3 and 0-6 hour time points, so this endpoint was not sensitive to detect differences in these subjects. However, the results for < 6 hr anterior AMI subjects demonstrate a strong treatment effect. The median area scores and upper confidence limits of the Control group data are higher than those of the AO Therapy group. Overall, the small sample comparison demonstrated significantly lower ischemic area in the AO Therapy group ($p = 0.01$).

When the data in **Table 6** are considered, covering the interval from 0-6 hrs post-PCI, the disparity between the AO Therapy and Control groups is greater, and the treatment effect in the $\leq$ 6 hr anterior subjects is even stronger than that observed in the 0-3 hr data. At

six hours post-PCI, 61% (27/44) of AO Therapy subjects have zero ischemic area compared to just 34% (15/44) of Control subjects. As displayed in **Table 6**, the median and 95% UCL area scores for the Control group have increased at the 0-6 hour time interval as compared to the 0-3 hour data in **Table 5**. In contrast, the AO Therapy group area scores are virtually unchanged. This result, taken in the context of the small sample group analysis, suggests a continuing ischemic burden in Control subjects as compared to AO Therapy subjects, exhibited in the data by transient ST elevation measured in the 6-hour post-PCI period.

Safety

Safety data revealed no statistically significant differences in the composite primary endpoint of one-month (30 days) Major Adverse Cardiac Event (MACE) rates between the AO Therapy and Control groups. MACE includes the combined incidence of death, reinfarction, target vessel revascularization, and stroke. **Table 7** summarizes the individual event and composite MACE safety data for all randomized subjects. Nine subjects in the AO Therapy group (6.7%) and seven subjects in the Control group (5.2%) experienced MACE. The difference in MACE rates of 1.5% satisfies Blackwelder's test of non-inferiority with a safety delta of 8.0%.

As displayed in **Table 7**, six deaths were documented in the randomized patient population within one month of treatment. Four deaths were observed in the AO Therapy group and two deaths were observed in the Control group. Based on investigator determination, no deaths were attributed to the use or performance of the AO System and AO Cartridge.

Table 7. AMIHOT I 30-day MACE Safety Data

Group	[redacted]				
AO Therapy (n = 134)	4 (3.0%)	3 (2.2%)	3 (2.2%)	1 (0.7%)	9 (6.7%)
Control (n = 135)	2 (1.5%)	3 (2.2%)	3 (2.2%)	2 (1.5%)	7 (5.2%)

Deaths

Seven ~~deaths~~ were documented in the randomized patient population of the AMIHOT I trial during the 90-day follow up period. Three deaths were observed in the Control group (n=135), and four were observed in the AO Therapy group (n=134). One death in the Control group occurred between the 30 and 90-day follow up window and no deaths occurred outside of one month in the AO Therapy group. The death occurring outside the one-month follow-up window in the Control group was, therefore, not included in the MACE safety endpoint calculations shown above.

Demographics and Baseline Characteristics

Two hundred sixty-nine (269) patients were enrolled and randomized into the AMIHOT I trial, including 135 Control subjects and 134 AO Therapy subjects. **Tables 8** and **9** compare key baseline demographic and clinical patient characteristics between the two randomized groups. No statistically significant differences were found in these baseline characteristics that would indicate a bias in the clinical outcome for these patients.

Table 8. AMIHOT I Baseline Patient Characteristics

	Control Group (n=135)	**AO Therapy Group** (n=134)	**p value**
Age (yrs) (mean ± SD)	60±12	60±13	0.99 (t-test)
Gender:			
Male	99 (73.3%)	98 (73.1%)	0.97 (chi-sq)
Female	36 (26.7%)	36 (26.9%)	
Hypertension	66 (48.9%)	71 (53.0%)	0.50 (chi-sq)
Diabetes	15 (11.1%)	17 (12.7%)	0.69 (chi-sq)
Peripheral vascular disease	3 (2.2%)	3 (2.3%)	0.99 (chi-sq)
Previous MI	14 (10.4%)	19 (14.2%)	0.34 (chi-sq)
Previous PCI	10 (7.4%)	16 (11.9%)	0.21 (chi-sq)
Previous CABG	2 (1.5%)	2 (1.5%)	0.99 (chi-sq)
Current smoker	57 (42.2%)	58 (43.3%)	0.86 (chi-sq)
Hyperlipidemia	56 (45.5%)	65 (54.6%)	0.16 (chi-sq)
Rescue PCI	21 (15.6%)	15 (11.2%)	0.29 (chi-sq)
Door-to-balloon time (median) (min)	90	91	0.53 (Wilcoxon rank-sum test)
Time to reperfusion (median) (min)	248	260	0.54 (Wilcoxon rank-sum test)

Table 9. AMIHOT I Baseline Patient Clinical Characteristics

	Control Group (n=135)	**AO Therapy Group** (n=134)	**P value** (chi-sq)
PCI with stenting performed	135 (100%)	134 (100%)	NA
Infarct-related artery			
Left anterior descending coronary artery (LAD)	76 (56.3%)	81 (60.4%)	0.62
Right coronary artery (RCA)	48 (35.6%)	42 (31.3%)	
Circumflex artery (CX)	8 (5.9%)	10 (7.5%)	
Other	3 (2.2%)	1 (0.7%)	
Lesion characteristics:			
Ostial	5 (3.7%)	2 (1.5%)	0.25
Thrombus	80 (59.3%)	93 (69.4%)	0.08
Moderate/heavy calcification	8 (5.9%)	11 (8.2%)	0.46
Chronic total occlusion	7 (5.2%)	1 (0.7%)	0.03
Initial TIMI flow grade (pre-PCI)			
0	102 (75.6%)	101 (75.4%)	0.76
I	19 (14.1%)	16 (11.9%)	
II	14 (10.4%)	17 (12.4%)	
III*	0 (0.0%)	0 (0.0%)	
Final TIMI flow grade (post-PCI)			
0	0 (0.0%)	0 (0.0%)	0.13
I	0 (0.0%)	0 (0.0%)	
II	11 (8.1%)	5 (3.7%)	
III	124 (91.9%)	129 (96.3%)	
Glycoprotein IIb/IIIa inhibitor	114 (84.4%)	120 (89.6%)	0.21

*Initial TIMI flow grade = III was excluded by protocol

1.5.2.3.11 AMIHOT I Summary

The AMIHOT I study was intended to evaluate the safety and effectiveness of AO Therapy in an AMI patient population presenting within 24 hrs from the onset of AMI symptoms. Enrollment was targeted at the most severe infarcts, those upon arrival at the cardiac catheterization laboratory exhibiting compromised flow in the culprit vessel, as determined by an angiographic measure of poor TIMI flow and electrocardiographic demonstration of ST-elevation.

As a novel therapy with limited clinical data, TherOx recognized that key patient subsets may exhibit a stronger treatment effect from AO Therapy administration than others.

Several patient subsets were pre-specified in the AMIHOT I protocol for analysis; however, the trial was insufficiently powered to statistically compare these subgroups. Although a positive therapeutic trend is observed for AO Therapy patients as compared to Control subjects, the results for the entire population did not achieve the requisite level of statistical significance for the three co-primary endpoints. However, when patients treated within six hours of symptom onset are considered, representing approximately 2/3 of the entire cohort, results more strongly favor AO Therapy; in particular, the anterior location AMI cohort exhibited a very strong treatment effect within this six hour population. Infarct size reductions as measured by 14-day [redacted] SPECT imaging are complemented by improved LV contractility in 3-month regional wall motion score improvement as well as post-AMI ischemic burden improvement as measured by recurring ST deviations over the 0-3 and 0-6 hr post-PCI time intervals.

1.6 Rationale for AMIHOT II Study

Results from the AMIHOT I study demonstrated a compelling improvement in left ventricular function and infarct size reduction in high-risk anterior AMI patients treated with PCI within six hours of symptom onset. These consistent effectiveness results, coupled with a comparable 30-day MACE safety profile between the AO Therapy and Control groups, formed the basis of a new trial (AMIHOT II) to build upon the AMIHOT I experience. The need for a validating study for these findings and the framework of the pivotal AMIHOT II trial was discussed in a meeting conducted on November 12, 2004 between FDA and TherOx. Working collaboratively with FDA, TherOx proposed a randomized trial focused upon this vulnerable < 6 hr anterior AMI patient cohort, devising a Bayesian statistical trial design that enabled some degree of borrowing of primary endpoint data from the AMIHOT I trial for the analysis of the AMIHOT II trial. The AMIHOT II trial was approved under IDE number [redacted] in a letter from FDA dated [redacted]

1.7 AMIHOT II Study Overview and Conduct

1.7.1 Device Description

AO Therapy requires the use of three primary components. These include a hardware device called the TherOx® AO System, a single-use disposable device called the TherOx® AO Cartridge and an infusion catheter. The two qualified infusion catheters used in the AMIHOT II trial for AO Therapy were the [redacted] infusion catheter, a Class II device cleared for marketing under 510(k) number [redacted] manufactured by [redacted] and the [redacted] cleared for marketing under [redacted].

The equipment utilized for AO Therapy administration in the AMIHOT II trial was unchanged from the AMIHOT I trial, with the exception of the introduction of the [redacted] catheter.

The AO Cartridge is loaded into and operated by the AO System; the cartridge has a tubing set that connects to an arterial sheath on the patient blood draw side and the infusion catheter on the blood/AO solution patient return side.

1.7.1.1 AO Cartridge

The AO Cartridge, shown in **Figure 1**, is an injection-molded polycarbonate device that creates AO solution from inputs of hospital-supplied oxygen gas and saline solution, mixes the AO solution with the patient's own arterial blood, and delivers oxygen-enriched hyperoxemic blood to the infusion catheter for infusion into the coronary arteries. The methods used in creating the hyperoxemic blood are explained through examination of the three chambers of the AO Cartridge also shown in **Figure 1.**

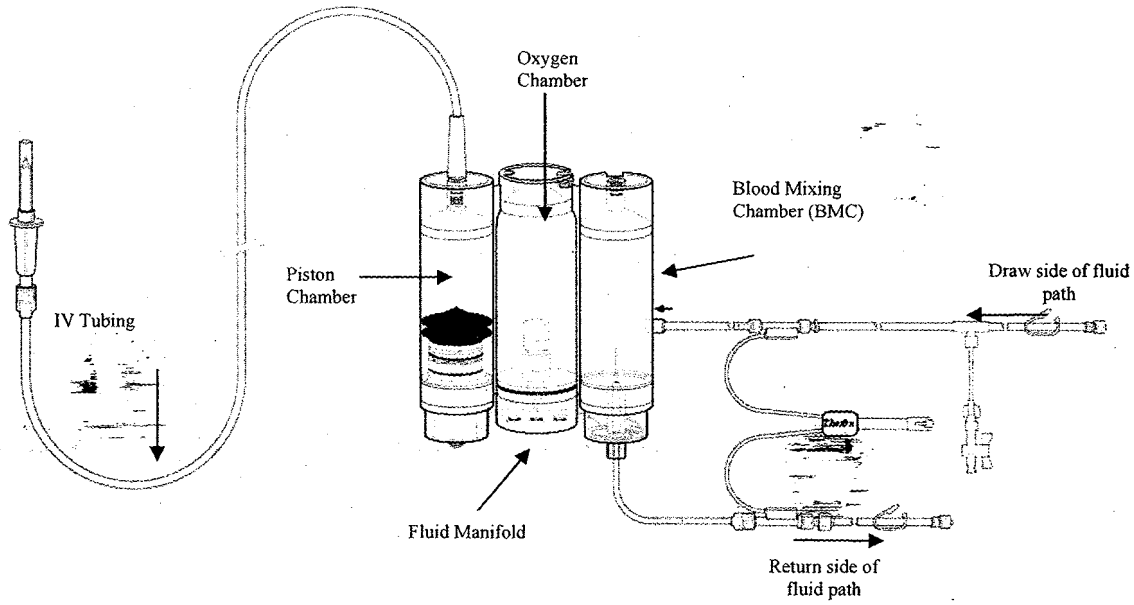


Figure 1. AO Cartridge

Saline is drawn into the Piston Chamber of the AO Cartridge from an IV bag. The Piston Chamber is, in effect, a motor-driven syringe pump that withdraws saline from the IV bag on the downstroke and pushes saline into the central Oxygen Chamber on the upstroke. The saline is pumped through a small nozzle that atomizes the liquid into discrete droplets for efficient oxygen uptake.

Oxygen gas is provided at a pressure of [redacted] or approximately [redacted], to the central Oxygen Chamber. Oxygen is dissolved into the atomized saline droplets to create hyperbaric Aqueous Oxygen, or "AO" solution, with a dissolved oxygen concentration approaching 1.0 ml O_2 (STP)/ml saline. A reservoir of AO solution is maintained at the bottom of the Oxygen Chamber.

AO solution flows continuously from the Oxygen Chamber at a rate of 3 ml/min through a capillary tube into the Blood Mixing Chamber, where it mixes with arterial blood that has been withdrawn from the patient. After combining AO solution with normoxemic

arterial blood, the resultant oxygen-enriched hyperoxemic blood is returned through an infusion catheter at a total flow rate of 75 ml/min to the patient's coronary arteries. The pO_2 level of the AO-infused blood is maintained between 760 – 1000 mmHg.

The AO Cartridge utilizes medical grade polyvinyl chloride (PVC) tubing for blood withdrawal and return to the patient. The cartridge housing is constructed primarily of injection-molded medical grade polycarbonate, a common plastic material used in medical devices. The tubing and Blood Mixing Chamber (BMC) comprise the blood-wetted fluid path of the AO Cartridge.

The production and flow of AO solution are continuous within the AO Cartridge; control of these processes is maintained through the use of the Fluid Manifold shown in **Figure 1**. The Fluid Manifold connects and controls the flow of saline and AO solution between the three chambers of the cartridge with three needle valves and one check valve. The Piston Chamber delivers saline to the Fluid Manifold through a small tube. The saline can be delivered to the Oxygen Chamber through the atomizer to create AO solution, through a dilution port to adjust concentration, or directly to the (BMC) to flush the capillary tube. The AO solution's dissolved oxygen concentration is controlled by the AO System.

The AO Cartridge is equipped with pressure transducers that monitor both the draw side and return side pressures in the device during operation; the transducers connect to the AO System. An IV spike and flexible tube are attached to the Piston Chamber, enabling easy connection to an IV bag during the procedure. The draw and return tubing are equipped with luer connections and manual pinch clamps. The AO Cartridge is a single-use Ethylene Oxide (EtO)-sterilized device.

The draw tubing is connected to the patient with a luer fitting that is attached to the femoral access sheath. The return tube is attached to the infusion catheter that has been

placed at the desired location within the coronary arteries. These connections are addressed in detail below.

1.7.1.2 Patient Connections

The AO Cartridge draw tubing can connect to the same femoral arterial sheath that is used for angioplasty and stenting procedures. Sheath placement may be coaxial (in one femoral artery) or contralateral (in both the right and left femoral arteries), based on the physician's discretion.

The preferred coaxial configuration is shown in **Figure 2** and illustrates how arterial blood is withdrawn from the sidearm. A luer fitting connects the sidearm to the AO Cartridge drawtube.

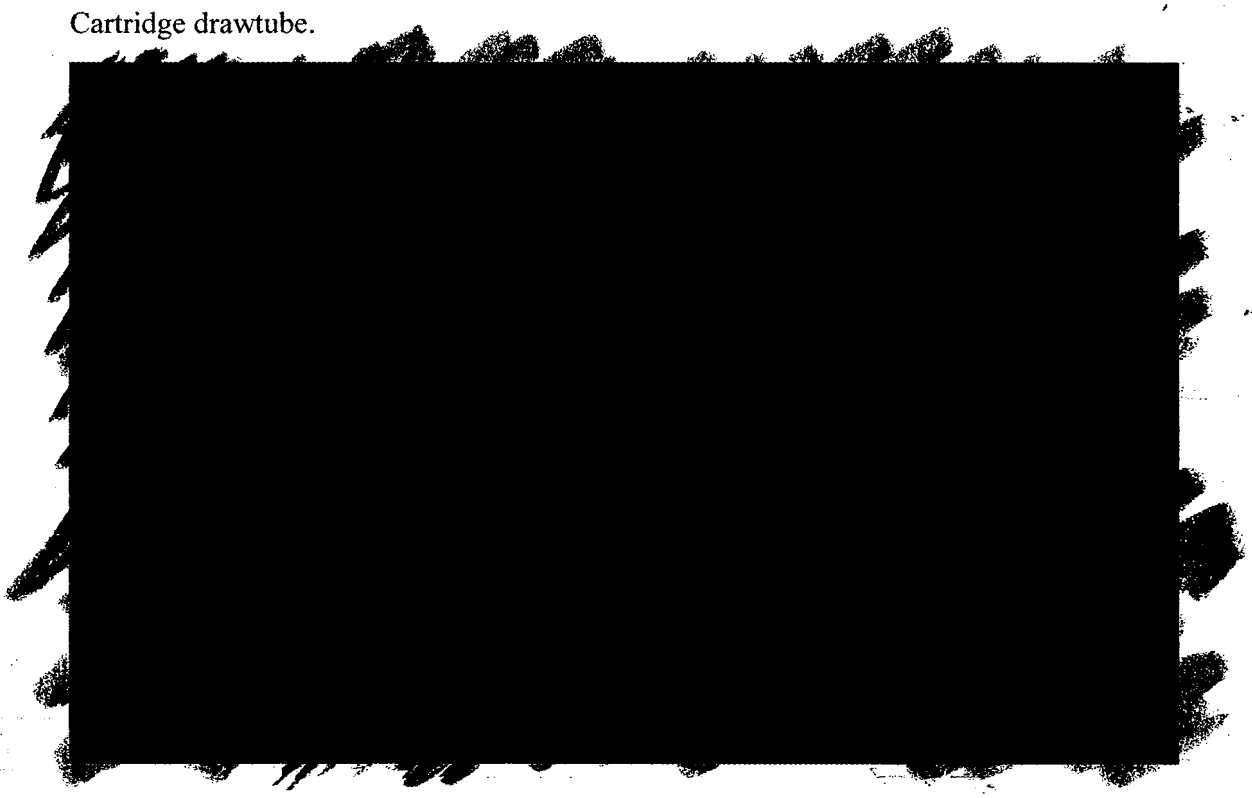


Figure 2. Coaxial Blood Draw/Return Configuration for AO Therapy

Note: Figure 2 depicts an unprimed circuit for illustration purposes only.

The infusion catheter is placed through the guide catheter over a guidewire, to the target location within a coronary artery. The guidewire is removed prior to initiation of treatment. When extracorporeal blood flow is initiated, the infusion catheter and AO Cartridge return tube are wet-connected to ensure that no gaseous emboli are introduced to the patient during priming. Hyperoxemic blood is infused through the infusion catheter shown in **Figure 2**. **Figure 3** provides a schematic of the patient connections during AO Therapy administration.

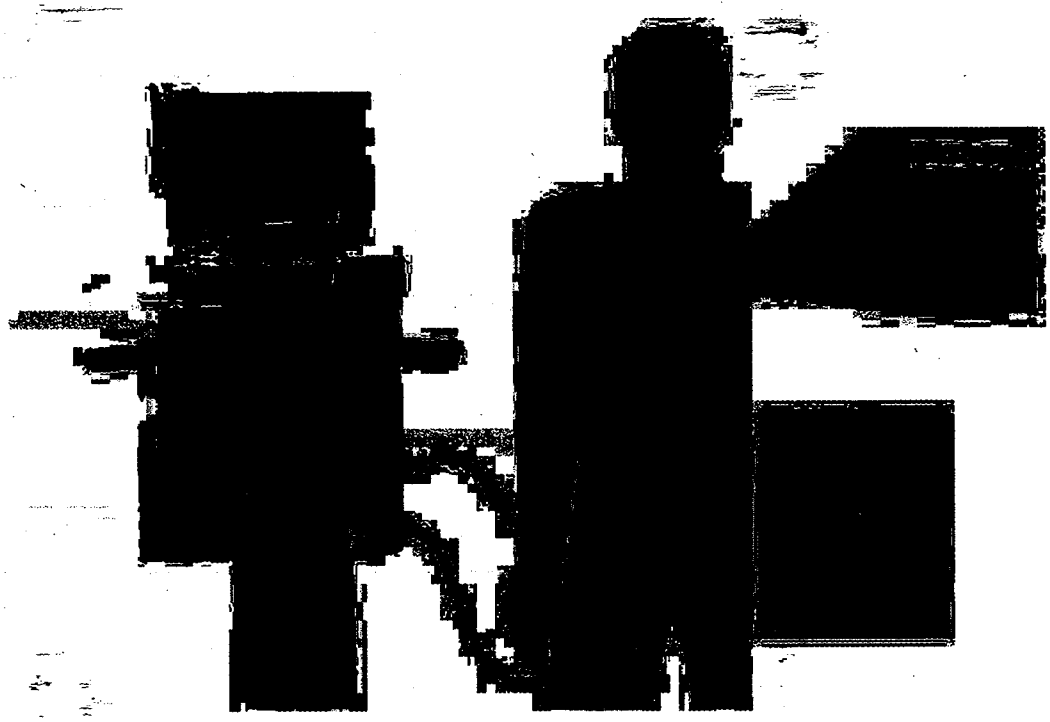


Figure 3. Patient Connections

1.7.1.3 AO System

The AO System, shown in **Figure 4**, is the reusable hardware component that controls and monitors performance and safety during administration of AO Therapy. The mobile AO System stands approximately 5 ft tall with a footprint comparable to many devices that are currently used in a cath lab setting. The system typically is operated in the cardiac catheterization laboratory after the coronary infusion catheter is placed with the aid of fluoroscopy. The rear of the AO System has a built-in compartment that holds an E-bottle of medical-grade oxygen. An IV bag is suspended from a pole attached to the system. The hospital supplies the oxygen gas and sterile saline that are required to make AO solution. The AO System integrates several subsystems mounted on a single system chassis. These subsystems are described below.

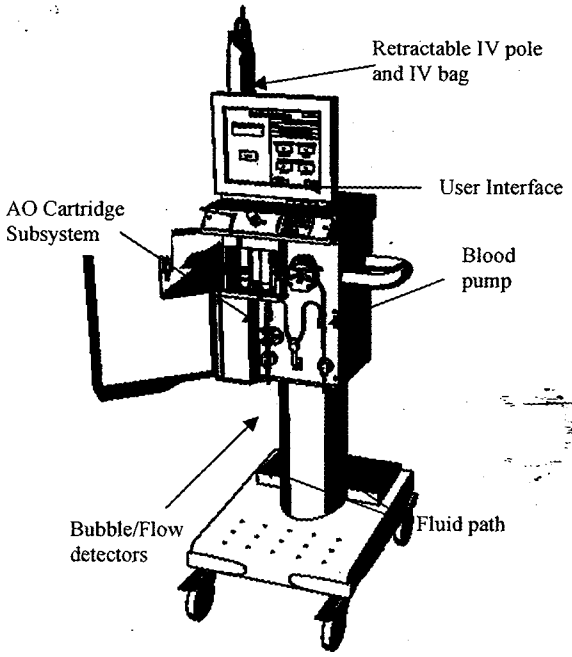


Figure 4. AO System

- The system chassis consists of a main enclosure mounted upon a system base, with four locking wheels. A retractable IV pole is mounted on top of the main enclosure.
- The AO Cartridge Subsystem (AOCS) is mounted inside the main enclosure. The AOCS houses and operates the AO Cartridge (the AOCS does not contact saline or blood). The AOCS provides the oxygen connection for the AO Cartridge, and operates the valves that control the Fluid Manifold. A motor-driven piston ram engages the cartridge piston for operation of the Piston Chamber.
- The blood pump subsystem incorporates a peristaltic pump to withdraw normoxemic arterial blood from the patient's femoral artery, pump the blood through the Blood Mixing Chamber of the AO Cartridge, and return hyperoxemic blood via infusion catheter to the coronary arteries. The blood pump subsystem is equipped with a flow probe and feedback control that maintains a constant reperfusion rate of 75 ml/min during the administration of AO Therapy.
- The bubble detector is an ultrasound-based device that detects and measures the size of individual bubbles that pass through the extracorporeal circuit. The bubble detector will initiate a shutdown of the AO System if a gas volume of 10 microliters or greater is accumulated during AO Therapy administration.
- The Safety Interlock is an independent hardware circuit that shuts down treatment by stopping blood flow. The Safety Interlock continuously monitors system inputs for events that require treatment stoppage. The Safety Interlock contains no software and, in addition to its automatic shutdown capability, has a manually operated emergency stop button to disable AO Therapy regardless of any other input status.
- The User Interface is a touch-screen display that allows the user to initiate, monitor, and end the AO Therapy procedure.
- The TherOx AO System is equipped with an electronic power supply that provides DC power from AC input or from batteries that are self-contained within the system base.

A hospital-supplied oxygen E-bottle with a yoke-type fitting is connected to the AO System pressure regulator to provide the oxygen supply. The pressure regulator controls oxygen gas charging to the AO Cartridge.

1.7.2 Indications for Use

In the AMIHOT II clinical trial, the TherOx AO System was indicated for qualifying patients who had undergone successful revascularization less than or equal to six hours from symptom onset for the treatment of acute anterior myocardial infarction.

1.7.3 AMIHOT II Study Objective

To determine whether intracoronary perfusion of hyperoxemic blood in the AO Therapy group immediately after successful PCI/stenting for the treatment of acute myocardial infarction reduces the area of infarction (% left ventricle) as measured by [redacted] SPECT imaging at 14 days post-PCI, with no worse than a 6% (absolute) increase in the incidence of Major Adverse Cardiac Events (MACE), comprising the combined incidence of death, re-infarction, target vessel revascularization, and stroke at the latter of either 30 days post-PCI or hospital discharge, when compared to a Control group receiving PCI/stenting alone.

1.7.4 Eligibility Criteria

1.7.4.1 Inclusion Criteria

Pre-PCI:

1. Patient must be ≥ 18 years of age
2. AMI must be anterior
3. Patient is experiencing clinical symptoms consistent with anterior AMI of < 6 hour duration from time of symptom onset until admission to the emergency room
4. Complete medical history, history of AMI, previous coronary interventions, list of medications given within last 24 hours
5. 12-lead qualifying ECG criteria: Anterior infarction (ST-segment elevation ≥ 1 mm in two or more contiguous leads between V1 and V4 or new left bundle branch block (LBBB) with documentation of LAD system culprit lesion)
6. Patient provides written, Informed Consent
7. Patient and his/her physician agree to all required follow-up procedures and visits

8. Women of childbearing potential who have a negative pregnancy test (applies to female patients only)

Angiographic Inclusion Criteria: Evaluated after the subject provided signed Informed Consent but prior to randomization:

9. Based on coronary anatomy, PCI is indicated for culprit lesion with anticipated use of an Intra-Coronary Stent
10. TIMI 0, I, or II flow is present on the initial angiographic injection of the infarct-related artery
11. Successful angioplasty as documented by < 50% diameter residual angiographic stenosis within and associated with the culprit lesion and ≥ TIMI II flow and no major complications such as perforation or shock
12. Documented time of reperfusion is ≤ 6 hours from the documented time of symptom onset

1.7.4.2 Exclusion Criteria

Pre-PCI:

13. Patients with ventricular pseudoaneurysm, VSD, or papillary muscle rupture.
14. Absolute contraindications to anticoagulant therapy, including hemorrhagic diathesis or thrombocytopenia
15. Systemic Arterial pO_2 is < 80 mmHg with supplemental oxygen
16. Placement of an intra-aortic balloon pump (IABP)
17. Patient has had coronary bypass surgery during the 30 day period preceding PCI
18. Severe known cardiac valvular stenosis or insufficiency, pericardial disease, or non-ischemic cardiomyopathy
19. Patients requiring cardiopulmonary resuscitation for > 10 minutes
20. Cardiogenic shock (SBP < 80 mm Hg for more than 30 minutes unresponsive to fluids or requiring intravenous pressors or placement of an IABP)
21. Expected survival of less than 6 months due to non-cardiac condition
22. Current participation in other investigational device or drug trials that have not finished the primary efficacy endpoint follow-up parameters
23. Patient has had a hemorrhagic stroke during the 6 month period preceding PCI
24. Physician discretion regarding unacceptability for enrollment

Angiographic Exclusion Criteria: Evaluated after the subject provided signed Informed Consent but prior to randomization:

25. Any proximal coronary diameter stenosis > 40 % that would restrict native flow with the infusion catheter in place

26. Infarct-related vessels that are either saphenous vein grafts and/or small second order coronary vessels that do not supply significant areas of myocardium
27. Presence of a non-stented coronary dissection upon completion of the PCI procedure
28. Unprotected left main diameter stenosis > 60%
29. Severe target vessel calcification or tortuosity
30. Multi – vessel disease that in the judgment of the investigator is best treated with emergent or urgent CABG or additional PCI within 30 days
31. In the investigator's opinion, the target vessel is unsuitable for either placing the infusion catheter or treatment with PCI

1.7.5 Randomization Methods

Patients who met the study's selection criteria were randomized into the AMIHOT II clinical trial after successful enrollment screening and providing Informed Consent.

Patients were randomly assigned, on a 2.8:1 basis, to either the AO Therapy group or the Control group (PCI/stenting). The unbalanced randomization split was derived from the requirements of the Statistical Analysis Plan. Patients were stratified on the basis of time to reperfusion (0-3 hours or >3-6 hours) and lesion location (proximal or non-proximal); therefore, the randomization was performed separately for each of the 4 combinations of these two variables.

The TherOx AMIHOT II clinical trial utilized an automated randomization service, termed the [redacted], operated by the independent [redacted], for all participating investigational sites. The randomization procedure was designed and validated in accordance with the randomization plan outlined in the Statistical Analysis Plan.

1.7.6 Study Endpoints

1.7.6.1 Primary Effectiveness Endpoint

Reduction in infarct size as measured by percent of left ventricular volume, assessed by [redacted] SPECT imaging at 14 days post PCI/stenting, as an indicator of treatment effectiveness by test of superiority.

1.7.6.2 Primary Safety Endpoint

A composite safety endpoint based on the incidence of death, reinfarction, target vessel revascularization, and stroke occurring less than or equal to one month (30 days) after enrollment or until hospital discharge, whichever is later. The composite safety endpoint was evaluated by a test of non-inferiority within a safety delta less than or equal to 6.0%. In addition, all Serious Adverse Events whether they are determined to be device-related or not were investigated and reported as part of the overall evaluation of device safety.

1.7.6.3 Secondary Endpoints

The secondary effectiveness endpoint was ST-segment recovery, as measured by time trend curve areas computed at three, four, and six hours post-procedure. Additional safety data including laboratory variables and non-MACE Adverse Events were analyzed for group comparisons. Secondary endpoints, other than ST-segment recovery, and subgroup analyses will not be used for purposes of making labeling or marketing claims.

1.7.7 Study Committees

The AMIHOT II study utilized four study committees. The Executive and Steering Committees reviewed and approved the study design, and were responsible for general study oversight.

Two additional oversight groups were employed in the AMIHOT II clinical trial, the Data and Safety Monitoring Board (DSMB) and the Clinical Events Committee (CEC). The DSMB was responsible for reviewing the aggregate study results to ensure that patient welfare and safety were being maintained. The DSMB made recommendations on study continuation at each of their meetings. The Clinical Events Committee reviewed and adjudicated all adverse events. In addition, the CEC adjudicated all Primary Safety Endpoints, non-MACE adverse events and Steering Committee Success Endpoints. An independent third party [redacted] managed both the CEC and DSMB. The committees were directed to submit all correspondence through [redacted] Moreover, all Sponsor correspondence to the CEC or DSMB was directed through [redacted] to maintain a level of independence between these oversight committees and the sponsor.

1.7.7.1 Executive Committee

The Executive Committee reviewed and approved final AMIHOT II trial design and the protocol issued to the Data Safety Monitoring Board (DSMB) and clinical sites. This committee was responsible for reviewing the final trial results and determining the methods of presentation and publication. The Executive Committee also had discretion for stopping or otherwise modifying the trial based on recommendations from the DSMB.

The Executive Committee included three (3) interventional cardiologists and (4) Sponsor members.

1.7.7.2 Steering Committee

The primary responsibility of the Steering Committee was to review study logistical concerns raised by the data coordinating center, individual investigational sites and the Sponsor. The Steering Committee monitored enrollment and site compliance with study procedures and made recommendations to enhance both patient recruitment rates and

study compliance. Steering Committee responsibilities included (but were not limited to):

- Provision of guidance on the development of the protocol (including amendments) and study procedures to ensure a timely and smoothly running study that has scientific integrity.
- Review of the boundaries established by the DSMB for critical values and "stopping rules" to be used for making recommendations for early study termination in accordance with the protocol.
- Help in identifying safety issues and events that could affect a recommendation to terminate the study ad provide these concerns to the Executive Committee for consideration.
- Consideration for all recommendations made by the Executive Committee on protocol modifications / study termination.
- Evaluation of specific site data as appropriate to assist alleviating any procedural issue identified by the clinical sites or Sponsor with regard to device operation or patient management.

Per the Manuals of Operations, the Steering Committee convened once as a group and met via teleconference at other non pre-specified intervals. The Steering Committee was composed of three (3) interventional cardiologists and two (2) biostatisticians. The identities of the Steering Committee were disclosed to participating AMIHOT II investigators and vice versa. Steering Committee members refrained from discussing Committee matters with an investigator of the AMIHOT II clinical trial. Any material obtained from the Sponsor or materials/documents generated as part of the Steering Committee were, and remain, confidential.

Each Steering Committee member was required to disclose financial interests in TherOx or its competitors, and report issues related to conflict of interest. The Steering Committee did not review aggregate safety data.

At the inaugural Steering Committee meeting an overview of the AMHOT II clinical program was presented along with the clinical protocol. The Steering Committee was provided with adequate time to deliberate a variety of logistical issues and concerns. The Sponsor provided a brief review of the study status in subsequent teleconferences (number of patients, number of active and inactive centers).

1.7.7.3 Data and Safety Monitoring Board (DSMB)

The primary responsibility of the DSMB was to protect the safety of patients participating in the AMIHOT II clinical study by monitoring data throughout the study. Their additional responsibilities included, but were not limited to:

- Review the protocol (including amendments) and study procedures and establish plans to identify issues that may affect data quality
- Establish boundaries for critical values and "stopping rules" to be used for making recommendations for early study termination in accordance with the protocol
- Identify safety issues and events that could affect a recommendation to terminate the study
- Monitor emerging data to determine whether changes in the design of the study are to be recommended to address patient safety issues
- Notify the Steering Committee of any issues that affect recommendations to modify, continue, or terminate the study and provide advice on these issues
- Evaluate the quality and integrity of study data to determine the impact of operational and procedural problems (*i.e.*, quality control of data, protocol adherence) on patient safety

The DSMB reviewed the cumulative safety data at scheduled intervals to make recommendations regarding continuation of the study. Per the Manual of Operations, they convened to review data at pre-specified intervals. The DSMB was composed of three (3) interventional cardiologists, one (1) noninvasive cardiologist and one (1) biostatistician, all of whom maintained his/her independence from each of the following persons regarding the clinical study:

- Study sponsor
- Principal and Co-Principal Investigators
- Investigators

- Institutions
- Hospitals
- Sub-Investigators
- Additional co-investigators
- Device manufacturers which sponsored or planned to sponsor an acute MI study that is perceived to conflict with AMIHOT II
- Others working with each of the foregoing, regarding the clinical study, which includes not communicating in any manner whatsoever with the afore-described persons about any aspect of the Clinical Study or the Committee

Each board member was required to disclose financial interests in TherOx or its competitors, and report issues related to conflict of interest. In addition, procedures for interactions between DSMB members and investigators or other parties were such that the independence of the members was maintained and bias was minimized.

At each DSMB meeting, there was unanimous agreement by the board that the study should continue and that there were no safety concerns with the AMIHOT II trial that would require permanent or temporary trial stopping or change to the study design.

1.7.7.4 Clinical Events Committee (CEC)

The AMIHOT II Clinical Events Committee (CEC) adjudicated all adverse events. In addition, the CEC reviewed all Primary Safety Endpoints (MACE), non-MACE adverse events and Steering Committee Success Endpoints. The CEC was composed of three (3) interventional cardiologists. Members were not permitted to disclose publicly their membership or activities relating to participation in the TherOx AMIHOT II CEC. It was acknowledged that the CEC member's participation may be known within his/her institution. Members were required to maintain independence from other device manufacturers that had sponsored or will sponsor similar clinical programs, and others working with these manufacturers. Any material obtained from the Sponsor or materials/documents generated as part of the CEC were, and remain, confidential. In

addition, members were to maintain his/her independence from each of the following persons regarding the clinical study:

- Study sponsor
- Principal and Co-Principal Investigators
- Investigators
- Institutions
- Hospitals
- Sub-Investigators
- Additional co-investigators
- Device manufacturers which sponsored or planned to sponsor an acute MI study that is perceived to conflict with AMIHOT II
- Others working with each of the foregoing, regarding the clinical study, which includes not communicating in any manner whatsoever with the afore-described persons about any aspect of the Clinical Study or the Committee

Each committee member was required to disclose financial interests in TherOx or its competitors, and report issues related to conflict of interest. In addition, to the extent possible, the CEC remained blinded to the identity of participating investigators and vice versa. All recommendations/queries were facilitated through [redacted] therefore, as a general course of operation there was no direct site or, if applicable, core lab interaction. If during the course of the study, site identity(ies) became known to one or more Committee members, this information was maintained in strict confidence. To the extent possible, CEC members were blinded to individual patient identities. Patient-identifying information was removed from all medical reports and images.

The committee met prior to initiation of the trial to establish a Manual of Operations and Adverse Event Definitions for expected and commonly occurring adverse events. During the trial, the CEC met at regular intervals to review source documentation and case report form data on adverse events reported by the enrolling sites. The CEC was responsible for the review and adjudication of all adverse events that occurred over the course of the

study. To the extent possible, adverse events were classified in accordance with established adverse event definitions. For each Adverse Event the CEC identified:

- Event Name/MedDRA code: identification of the type of adverse event to the extent possible consistent with event types defined in Adverse Event Definitions.
- Relationship: procedure, device, patient's prior condition, medication, other or unable to determine
- Unanticipated Adverse Device effect: is this event both a serious and device related event and one that is not identified in nature or severity in the study documentation or product labeling.
- Final Adjudication and Event Classification: assignment of event category (serious adverse event, non serious adverse event or not an event)
- Reason if Not an Event (associated symptom of another reported AE, Observation or incidental finding, Inaccurately or incorrectly reported, other)
- Justification for Event Classification
- Information Reviewed: a listing of the documents which were instrumental in arriving at the results of the adjudication.

This information was recorded on adjudication forms for entry into the clinical database. In instances where the sites did not provide sufficient detail to complete the adjudication, supplemental requests and/or queries were submitted to the sites for further clarification, and the event was re-reviewed when the requested information became available. All adjudication decisions were made by unanimous decision. In the event of disagreement by CEC members on the presence or the specifics of an event after all available information had been reviewed, the committee generally elected to adjudicate the event to the most conservative outcome.

All adverse event and safety endpoint data in the PMA application are summarized based on the CEC adjudication of the event. Some events were determined by the CEC to be "Not an Event." The definition of "Not an Event" reads as follows: "Reported events that are symptoms associated with another reported event, duplicate events identified using similar or different nomenclature reported with the same start/stop dates or events

represents observations or incidental findings or determined to be inaccurately/incorrectly reported."

1.7.8 Independent Core Laboratories

The AMIHOT II clinical trial utilized three independent core laboratories for data analysis and interpretation. The core laboratories were blinded to the subjects' randomization assignment and clinical outcome. An overview of the core laboratories is provided below.

1.7.8.1 [redacted]

The [redacted] provided infrastructure, expertise, and independent analysis of index procedure angiograms for the AMIHOT II clinical trial. The [redacted] developed the rationale, measurement, and data assessment for AMIHOT II cath lab angiographic information.

Investigational centers were provided an Angiographic Protocol from the [redacted]. This protocol outlined instructions to each center regarding requirements for acquisition of cineangiographic images, recommendations for minimal guide catheter size, guidelines for use of intra-coronary nitroglycerine (IC NTG) before during and after the coronary intervention, recommendations of specific angiographic views of target lesions before, during and after coronary intervention, recommendations to ensure cardiac cycles viewed are sufficient to assess optimal TIMI flow and Myocardial Blush at baseline and final intervention.

Raw data from the [redacted] were forwarded to the AMIHOT II Data Coordinating Center, [redacted], upon study completion.

113

1.7.8.2 [redacted] Electronic Electrocardiographic (eECG) Core Laboratory

[redacted] is the largest and most experienced academic [redacted] in the world. More than 10 million high-fidelity digital 12-lead ECGs have been analyzed and archived in the lab over the past 20 years. It also is the only such core laboratory in the world to support global point-of-care digital acquisition of ECGs from clinical sites using their own equipment.

The [redacted] has experience with more than 500 sites around the world. Site-friendly data collection spans the full range of patient-care environments, including ambulatory units, pre-hospital settings, emergency departments, chest pain units, cardiac catheterization labs, coronary and intensive care units, operating rooms, general wards, and dialysis, endoscopy, and bronchoscopy wards. Clinical trials include cardiology trials, where eECG data such as measures of ischemia or infarction are used to assess therapeutic efficacy, and non-cardiology trials, where eECG data such as changes in the QT interval are used to assess therapeutic safety.

The eECG Core Laboratory provided an independent interpretation of AMIHOT II ST-Segment monitoring data obtained with the NorthEast 12-lead integrated circuit ST monitors. The AMIHOT II clinical protocol required that all study subjects receive continuous 24 hours ST-Segment monitoring.

Each site's NorthEast device was packaged with two 128-megabyte flash RAM cards for data storage. Each study center coordinator was instructed to notify the [redacted] at t[redacted] by fax at the following number: [redacted] of a patient enrollment. The eECG Core Lab then sent the site a cleared 128-megabyte flash RAM card for use with subsequent patients.

All sites completed at least one successful practice recording prior to enrolling patients. After study enrollment begins, a 48-hour quality control "feedback" loop was maintained by the [redacted] keep sites informed of the quality of the ST-segment data they submitted.

The [redacted] was blinded to patient data with respect to treatment assignment, patient characteristics, and patient outcomes. Data were analyzed and transmitted to the data coordinating center at the conclusion of the AMIHOT II study.

1.7.8.3 [redacted]

The infarct size primary endpoint for AO Therapy and Control groups was determined using [redacted] SPECT nuclear imaging. SPECT imaging data interpretation and calculations were used to evaluate infarct size reduction as a percentage of left ventricular volume in both groups. The nuclear scan was performed fourteen (14) days (±7 days) post-index procedure. Data were sent to the independent [redacted] for analysis.

Prior to study initiation, each enrolling center involved in the AMIHOT II study required validation of their SPECT imaging cameras. Hospitals participating in the AMIHOT II protocol had a good working knowledge of SPECT and performed appropriate quality control to ensure satisfactory image quality. As such, the additional quality control procedures performed as part of the SPECT Core Lab Camera Validation process were not intended to be comprehensive, but rather to assess performance aspects of SPECT systems that may adversely affect image quality. The cardiac phantom, worksheets and instructions for the gamma camera QC (quality control) and cardiac phantom procedures were all sent to enrolling centers from the [redacted] following receipt of the completed SPECT Camera Validation Information worksheet.

Nuclear technologists completed work on the cardiac phantoms in approximately eight (8) hours and returned the phantoms to the [redacted] for review. Once received, the [redacted] lab ran the phantom data analysis and generated a report. If the [redacted] had previously validated the site camera, both the site and the sponsor were notified. SPECT camera validations are good for three years unless there have been camera equipment changes made at the site. SPECT Camera Validation Logs were updated by the Core Lab upon each pass/fail of the phantom and e-mailed to the sponsor typically on a weekly basis.

Fourteen (14±7) days after the index procedure the AMIHOT II patient was required to return to the Nuclear Imaging Department for the follow-up SPECT scan. Per protocol, [redacted] (Cardiolite) was administered by intravenous (IV) injection as described in the approved product labeling, in a dose of 20-30 mCi, with a 20-min waiting period prior to imaging. Per protocol, the imaging camera used was the same camera previously validated by the [redacted]

For each study subject, the sites completed Form 302: Transmittal Form for SPECT Imaging and Form 301:14-Day SPECT Imaging as appropriate and then shipped the SPECT imaging data to the Core Lab.

After each SPECT study was received at [redacted] it was processed and read by qualified and experienced [redacted] staff cardiologists. Form 303: Quantification of Infarct Size form was completed, and copies of this form were sent to the study data coordinating center. Progress and quality of SPECT studies received by [redacted] were reported to the sponsor on the SPECT Study Log.

1.7.9 AMIHOT II Clinical Procedures, Assessments, and Follow Up

1.7.9.1 Patient Evaluation Procedures

The following baseline examinations and tests were performed on patients who agreed to participate in the study by signing the approved Informed Consent:

- Medical History and physical examination
- 12 Lead ECG and application of 24-Hour Holter Monitor
- Administration of study medication
- Cardiac Enzymes
- Clinical Chemistry, Hematology, and Liver Panel

1.7.9.2 Procedure Medications

All enrolled patients were to receive the following protocol required medications:

- Aspirin – 325 mg soluble aspirin given in E.R. or prior to catheterization
- Clopidogrel 300 – 600 mg p.o., then 75 mg p.o.q. daily for a minimum of 1 month in all patients undergoing PCI/stent procedure. (May give up to four hours post procedure.)
- Intravenous Heparin
- Low-flow nasal oxygen (3-5 l/min.) or oxygen mask (5-10 l/min.) to maintain systemic arterial $pO_2 > 80$ mmHg

1.7.9.3 [redacted]

1.7.9.3.1 Patient Anticoagulation

1.7.9.3.1.1 Glycoprotein IIb/IIIa Inhibitors

Use of platelet IIb/IIIa reception inhibitors during the AMIHOT II study was allowed at the physician's discretion, consistent with observing the standard of care in AMI treatment with PCI. The use (or non-use) of these agents, along with the categorical time of administration, was documented for each subject.

1.7.9.3.1.2 Heparin Management

The AMIHOT II study utilized heparin-only per protocol. The target Activated Clotting Time (ACT) was ≥ 250 seconds for all patients assigned to either the Run-In or AO Therapy groups. ACT was measured and recorded as a baseline reading prior to AO Infusion and subsequently every 30 minutes during AO Therapy administration.

1.7.9.3.2 Coronary Angiography

It was recommended that consented patients be transferred to the cath lab quickly to allow adequate time for PCI/stenting and assessment of angiographic inclusion/exclusion criteria. Baseline laboratory results were not necessary before catheterization. After arriving at the catheterization laboratory, patients were prepared for PCI according to standard hospital procedures. Pre-randomization left ventriculography was required per protocol.

Specific instructions were spelled out in anticipation of angiographic data analysis by the angiographic core laboratory. When performing coronary angiography, the entire distal target vessel with capillary and collateral flow was to be shown to allow for assessment of pre-procedure TIMI blush score. Left ventriculography was to be performed in the right anterior oblique view and two consecutive sinus beats were to be available for analysis. Pre and post-PCI angiographic data was sent to the angiographic core laboratory for analysis.

1.7.9.3.3 PCI/Stenting Procedure

Following a successful diagnostic catheterization and identification of the target lesion as suitable for PCI/stenting, additional heparin boluses were administered to maintain the ACT ≥ 250 seconds. If the patient was randomized to the Control group, no additional heparin was required. If the patient is randomized to the AO Therapy group, additional heparin was administered to maintain the ACT at ≥ 250 seconds.

Only commercially available bare metal or drug-eluting stents were used in AMIHOT II patients. Following successful PCI/stenting, with all angiographic inclusion criteria satisfied and in the absence of any angiographic exclusion criteria, patients were randomized.

1.7.9.3.4 AO Therapy Procedure

1.7.9.3.4.1 Guiding Catheter and Arterial Sheath Selection

Coaxial vs. Contralateral Approach

AMIHOT II investigators had the option of utilizing either one or two arterial access sheaths for AO Therapy. When the protocol-recommended COAXIAL approach was employed, blood was withdrawn from the femoral artery via the annular space between the arterial sheath and the guiding catheter. This configuration required a 2-French (F) size difference to enable blood withdrawal at the 72 ml/min flow rate. For example, if the [redacted] infusion catheter was used, a 7F (minimum) guiding catheter was required, necessitating a 9F arterial access sheath.

The protocol allowed for an alternative to the coaxial approach, termed the CONTRALATERAL approach. With contralateral access, a second arterial access site was utilized in the other femoral artery. This configuration allowed the investigator to utilize a smaller sheath on the guiding catheter side (*i.e.* a 7F sheath for a 7F guide) and a 5F or 6F introducer sheath in the contralateral femoral artery. The investigator also had the option of utilizing the radial or brachial artery instead of the contralateral femoral artery for this approach. The ipsilateral placement of a second arterial sheath in the femoral artery was strictly contraindicated due to concerns over potentially serious bleeding.

As part of approved IDE Supplement [redacted], the [redacted] infusion catheter was qualified as an alternative to the [redacted] for AO Therapy delivery. The

guide catheter and arterial sheath size requirements are different for these two catheters. As stated above, the [redacted] infusion catheter requires a 7F guiding catheter, and thus a 9F arterial sheath for coaxial setup. The [redacted] catheter has a slightly smaller outer diameter (O.D.) than the [redacted], requiring a minimum 6F guiding catheter and 8F arterial sheath for coaxial setup.

If contralateral access was utilized, a minimum 5F sheath was required to withdraw blood from the second arterial access site, regardless of the choice of infusion catheter.

Table 10 provides a reference guide for coaxial and contralateral arterial access.

Table 10. Coaxial/Contralateral Arterial Access

	COAXIAL ACCESS	CONTRALATERAL ACCESS	
Access Site	Femoral Artery*	Femoral Artery**	Second Arterial Site***
Sheath	9 French [redacted] 8 French [redacted]	7 French [redacted] 6 French [redacted]	5 – 6 French (either catheter)
Guide Catheter	7 French [redacted] 6 French [redacted]	7 French [redacted] 6 French [redacted]	[redacted]

***Coaxial access:** One femoral artery is used for both PCI/stenting and for withdrawing normoxic arterial blood and returning hyperoxemic blood. This configuration is recommended for AO Therapy.
****Contralateral access:** The femoral artery is used for PCI/stenting and for returning hyperoxemic blood from the AO System.
*****Contralateral access:** A second arterial access site is used for withdrawing blood for delivery to the AO System.

Note: Ipsilateral insertion of a second sheath in a single femoral artery for AO Therapy is strictly contraindicated.

1.7.9.3.4.2 AO Infusion

The following steps were performed during AO Therapy administration, after completion of successful PCI:

Catheter Placement and Patient Set-Up

The guiding catheter was placed at the ostium of the infarct-related artery (IRA). After positioning of the guiding catheter, the infusion catheter was advanced over the guidewire into the IRA. Positioning of the infusion catheter within the IRA was at the discretion of the investigator for optimum infusion, but not distal to the stent.

Prior to initiation of AO Therapy, the investigator removed the guidewire and rechecked the infusion catheter position under fluoroscopy. AO Therapy was initiated in the cardiac catheterization laboratory with no exceptions. Per the device IFU, the recommended procedure was to complete AO Therapy administration in the cath lab, but investigators did have the option of transferring the patient to an appropriate holding area, or the Coronary Care Unit (CCU), after initiating the infusion. In this event, per patient transport instructions, all sheaths were required to be securely attached to the patient and checked for integrity prior to transport. The sheaths were to be secured per standard cath lab procedures. The infusion catheter connection was to be confirmed prior to patient transport.

AO System and AO Cartridge Use

The AO System and AO Cartridge are set up per the AO System Instructions For Use and AO System Operators Manual. An overview is provided here for AO System setup and operation.

Prior to starting blood flow, the AO Cartridge draw tubing was connected to the sidearm of the draw sheath, and after priming the circuit, the return tubing of the AO Cartridge was connected to the proximal end of the infusion catheter. A constant flow rate of 75 ml/min hyperoxemic blood at a pO_2 level of 760-1000 mmHg was established and controlled by the AO System.

Prior to AO Therapy initiation, baseline systemic arterial pO_2 and blood pressure data were recorded. The trained system operator manually adjusted the AO System pO_2 range via the touch-screen display after the baseline systemic arterial pO_2 value was available.

During the 90-min infusion time, physiological parameters such as blood pressure, systemic arterial pO_2, and heart rate/rhythm were recorded at 30-minute intervals. The pO_2 range on the AO System was updated as required based on changes in the patient's systemic arterial pO_2 level.

After 90 minutes of hyperoxemic infusion, the AO System automatically discontinued AO infusion. Normoxic blood continued to circulate through the circuit until the user manually shut down the system, typically within 1-2 minutes after hyperoxemic infusion had stopped.

After shutting down the system, the infusion catheter was withdrawn into the guiding catheter. The AO Cartridge tubing was clamped and disconnected from the sidearm of the arterial sheath and the infusion catheter. The catheters were removed per normal catheterization procedures.

1.7.9.3.4.3 AO Therapy Device Performance

AO System and AO Cartridge device performance information, including date and time of AO Infusion, the number of AO Cartridges used, AO Cartridge tracking information, AO Infusion time, and AO System operating parameters, were recorded for every AMIHOT II clinical case. These data were recorded on discrete log files maintained in the AO System memory; summary information was also recorded for each AO Cartridge onto individual cartridge transducers. Log files and transducer chips were analyzed by TherOx Engineering per established procedures and protocols.

At the conclusion of the trial, data were analyzed for each AO Cartridge utilized during the AMIHOT II study. These data were transferred to [redacted] for inclusion into the AMIHOT II clinical database.

Throughout the study, the Sponsor maintained close contact with active clinical sites in the event that communication was required regarding AO System operation during a case. 24-hour technical support by TherOx Engineering staff was maintained at all times throughout the study. As such, concerns related to device setup, usage, or performance could be relayed immediately by phone to trained system operators for advice and assistance.

1.7.9.4 Post-Cath Lab In-Hospital Procedures

1.7.9.4.1 eECG Monitoring

A continuous 24-hour 12-lead ECG Holter Monitor was placed on patients in the immediately after obtaining Informed Consent. The monitor was removed after 24 hours and recorded data were sent to the [redacted] for analysis. Other ECGs were performed at any time during the index hospitalization as warranted for clinical management.

1.7.9.4.2 Cardiac Enzymes, Clinical Chemistry, and Hematology

Cardiac enzymes (CK, CK-MB and troponins) were drawn at baseline, 8, 16 and 24 hours post-PCI. Clinical chemistry and hematology and liver panel results were obtained at baseline and 24-hours post-PCI.

1.7.9.4.3 Patient Management and Hospital Discharge

No restrictions were placed upon the standard-of-care procedures administered by participating investigational sites in the post-PCI in-hospital period. After leaving the cath lab, patients were sent to the CCU, Step-Down Unit, or Coronary Care Floor at the

investigator's discretion; their transfer location was recorded. Arterial sheath removal and ambulation were conducted per standard hospital care. All medications administered to patients during their hospital stay were recorded.

Timing of hospital discharge was at the investigator's discretion for each individual patient. An appointment for the resting [redacted] scan was made prior to discharge.

1.7.9.5 [redacted] SPECT Imaging

A resting [redacted] scan was performed at 14 days (± 7 days) post-PCI and results sent to the core lab. A phone call was encouraged from the site Clinical Coordinator prior to the scheduled scan date to ensure patient compliance.

1.7.9.6 30-Day Follow-Up

A clinical follow-up visit was required on or after day 30 to be completed no later than day 45 post-PCI per protocol requirements. The purpose of this follow up visit was to assess the patient's health status and to assess definitively whether the patient experienced a MACE event within the 30-day primary endpoint window. If the patient was hospitalized longer than 45 days, the follow-up was to be completed at the time of hospital discharge.

1.7.9.7 6- and 12-Month Patient Surveys

For sponsor tracking purposes, a telephone survey was obtained at the 6-month and 12-month intervals post-PCI (± 30 days) to ascertain patient status.

1.7.9.8 Summary Table: Study Assessments

Table 11 summarizes the required schedule for AMIHOT II study assessments.

Table 11. AMIHOT II Study Assessments

	H&P/Consent	24-Hour ECG	Angiogram	Blood Labs	Blood Pressure	Arterial Blood Gas (ABG)	Heart rate/rhythm	ACT	Sestamibi Imaging	Follow-up Visit	Telephone Survey
Enrollment Screening/ Baseline	♥	♥				♥					
Pre-PCI/Stent		CONTINUOUS	♥	♥				♥			
Post PCI/Stent			♥	♥							
30 min. AO Infusion											
60 min. AO Infusion											
90 min. AO Infusion											
8 hours ± 2 hours				♥							
16 hours± 2 hours				♥							
24 hours± 2 hours				♥							
14 days± 7 days									♥		
30 days +15 days										♥	
6 months±30 days											♥
12 months± 30 days											♥

1.7.10 Adverse Event Assessment

Adverse event data were collected during the AMIHOT II clinical trial on all enrolled patients in accordance with the reporting requirements outlined in the clinical protocol. An Adverse Event is defined as any undesirable experience that is a deviation from the baseline status (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject during the course of the study, whether or not it is related to the devices or procedures described in the Investigational Plan. Adverse events were

1.7.9.8 Summary Table: Study Assessments

Table 11 summarizes the required schedule for AMIHOT II study assessments.

Table 11. AMIHOT II Study Assessments

	H&P/Consent	24-Hour ECG	Angiogram	Blood Labs	Blood Pressure	Arterial Blood Gas (ABG)	Heart rate/rhythm	ACT	Sestamibi Imaging	Follow-up Visit	Telephone Survey
Enrollment Screening/ Baseline	♥	♥				♥					
Pre-PCI/Stent		CONTINUOUS	♥	♥				♥			
Post PCI/Stent			♥	♥							
30 min. AO Infusion											
60 min. AO Infusion											
90 min. AO Infusion											
8 hours ± 2 hours				♥							
16 hours± 2 hours				♥							
24 hours± 2 hours				♥							
14 days± 7 days									♥		
30 days +15 days										♥	
6 months±30 days											♥
12 months± 30 days											♥

1.7.10 Adverse Event Assessment

Adverse event data were collected during the AMIHOT II clinical trial on all enrolled patients in accordance with the reporting requirements outlined in the clinical protocol. An Adverse Event is defined as any undesirable experience that is a deviation from the baseline status (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject during the course of the study, whether or not it is related to the devices or procedures described in the Investigational Plan. Adverse events were

further categorized as serious or non-serious events. An adverse event was defined as serious whenever the adverse event was fatal, life-threatening, disabling, resulted in patient hospitalization or prolongation of hospitalization, or required medical intervention to prevent permanent impairment of a body structure or function (see definition of serious adverse event). According to pre-specified classification, death, reinfarction, urgent target vessel revascularization, major bleeding (including intracranial) requiring transfusion, major clinical events related to AO infusion, and events related to a serious malfunction of the AO System were considered to be the main categories of serious adverse events.

Adverse events were reported per protocol for all enrolled subjects through 30-days post-PCI, or until patient discharge, whichever date occurred later. Additional adverse event data were collected during subsequent clinical visits and via telephone survey at the 6 and 12-month time points.

The study adverse event Case Report Form (CRF) was completed for each adverse event experienced by an individual subject. Serious adverse events (SAEs) were to be reported by fax notification within 24 hours using the Adverse Event and Endpoint Notification CRF. Serious adverse events that were classified as MACE or potential MACE events were detailed on supplemental CRFs: Death, Repeat Revascularization, Suspected MI, and Neurologic Event had specialized CRFs for this reporting. Other SAE details pertaining to repeat angiography and hemorrhagic events were detailed on the supplemental Repeat Angiography and Hemorrhagic/Vascular Event CRFs, respectively.

The AO System Instructions for Use identified potential adverse events, including hazards identified by risk analysis and the inherent condition of the patient population post-AMI. These adverse events include:

- Abrupt vessel closure/spasm
- Acute myocardial infarction (AMI)

- Allergic reactions
- Aneurysm
- Anxiety/dizziness
- Arrhythmias
- Arteriovenous fistula/pseudoaneurysm
- Cardiogenic shock
- Chest pain/angina
- Congestive heart failure
- Death
- Embolism (including air emboli and thromboemboli)
- Hemorrhage
- Hematoma
- Hemolysis
- Hypertension/hypotension
- Infection
- Nausea/vomiting
- Pulmonary edema
- Renal complications
- Stroke/TIA
- Restenosis
- Revascularization (CABG or PCI)
- Tamponade
- Thrombosis
- Vascular damage (dissection, perforation, rupture, or other mechanical injury)

Study investigators were responsible for documenting all adverse events on the appropriate CRFs. TherOx conducted investigational site monitoring to ensure that the completed CRFs matched the medical records and any discrepancies were reviewed with the study center and resolved.

To facilitate AE reporting, the AMIHOT II Clinical Events Committee (CEC) provided a document to sites listing certain events that are not reportable because they are normally expected to occur in conjunction with the index procedure or are associated with customary, standard care of patients undergoing PCI for AMI. This list included events

such as early post-procedure pain at the access site, post-anesthesia/conscious sedation emesis and nausea (within 24 hours), and minor, localized tenderness or swelling atvascular access site.

Source documentation related to the adverse events was collected for all adverse events and reviewed by the Clinical Events Committee (CEC). A Source Document Tracking Checklist was developed and provided to the study monitors to aid in collection of documents deemed necessary for adjudication of each type of reported event. [redacted] preliminarily coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 8.1.[1]

1.7.10.1 Adverse Event Review Process

The CEC and Data and Safety Monitoring Board (DSMB) chairpersons were to be given immediate notification of any potential Unanticipated Adverse Device Effect (UADE) (none reported for this trial) or patient deaths. For patient deaths, the CEC chairperson reviewed CRFs and source documentation and provided a written assessment of the events surrounding the patient death to the DSMB chairperson via [redacted] as the DSMB and CEC were blinded to each other throughout the trial. In addition, all site-reported SAEs were reported to TherOx and the site monitor within 48 hours of fax notification to [redacted].

All other events were provided to CEC members at the time of each scheduled meeting of the committee. Source documentation and original CRFs were available for review. If it was determined by [redacted] that a case was particularly complicated, a pre-review by the CEC chairperson was deemed appropriate to expedite the adjudication process. CEC members reviewed the information provided at the CEC

[1] MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

meeting and determined if additional information/documentation was required.

At the regularly scheduled adjudication meetings, the CEC reviewed the site-reported events against the source documentation and either agreed with or changed the following components: event classification (SAE, non-serious AE), MedDRA code, and event relationship (AO device, AO procedure, index PCI procedure, study medications, coronary artery disease, other comorbid condition, other or unknown). All adjudication was performed in accordance with the CEC Manual of Operations. The CEC had the final decision on adjudication of adverse events.

All adverse events adjudicated were assessed for potential as an endpoint event (30-day MACE). In each case, an Endpoint Event Adjudication Form was completed. Patients were reviewed after 30-day follow-up and categorized as conforming to the definition of a primary endpoint MACE event and the specific type of MACE (Death, TVR, Reinfarction, or Stroke). Secondary safety variables (including late MACE, non-TVR, recurrent MI, severe/life-threatening bleeding, restenosis, incomplete AO Therapy, and the Steering Committee success endpoints of Technical Success, Procedural Success and Clinical Success) were also reviewed and adjudicated. An endpoint adjudication form was completed after each follow-up assessment time period specified for the trial (30 days, 6 months, 1 year). A patient was considered complete for an assessment interval by CEC review if the subject was evaluable for the safety endpoint events through the interval or through the point of death.

Patient-specific documentation concerning each adjudicated adverse event is maintained in a patient binder/folder maintained by [redacted]

1.7.10.2 Adverse Event Classification

The following definitions were used by the CEC when classifying an adverse event:

ADVERSE EVENT: any undesirable experience that is a deviation from the baseline status (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject during the course of the study, whether or not it is related to the devices or procedures described in the Investigational Plan.

SERIOUS ADVERSE EVENT: any adverse event occurring to a subject during the course of the study that is fatal, life-threatening, disabling, results in patient hospitalization or prolongation of hospitalization, or requires medical intervention to prevent permanent impairment of a body structure or function.

UNANTICIPATED ADVERSE DEVICE EFFECT (UADE): any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the study if the effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, patient informed consent, or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

ADVERSE EVENT ATTRIBUTION: Adverse events will be assigned an attribution according to the believed primary cause. Events will be categorized by relationship to AO devices (system/cartridge), AO procedure, PCI procedure, study medications, coronary artery disease, other comorbid condition, or other.

1.7.10.3 Attribution of Adverse Events

Each adverse event was placed into a single category as follows:

AO Device: The clinical event has a reasonable time sequence to use of the investigational devices and is unlikely to be attributed to concurrent disease or other procedures or medications. It is reasonable to believe that the device directly caused or contributed to the adverse event.

AO Procedure: it is reasonable to believe that the event is associated with the AO procedure performed and is not specific to the investigational system used. Other products or medications required specifically for the AO procedure (*e.g.*, [redacted] catheter, sheath) are likely to have contributed to the occurrence of the event.

PCI Procedure: it is reasonable to believe that the event is associated with the patient's PCI procedure in general and is not specific to the investigational devices or procedure. Example: vessel dissection noted after PCI and prior to introduction of AO Therapy.

Study Medications: it is reasonable to believe that the event is associated with the study medications required and is not otherwise specific to the investigational system used (example, bleeding associated with Plavix®).

Coronary Artery Disease: It is reasonable to believe that the event is associated with the patient's coronary artery disease in general and is not specific to the investigational device or procedure.

Comorbid Condition: It is reasonable to believe that the event is directly associated with progression of another pre-existing condition/co-morbidity. Pre-existing conditions that are aggravated or become more severe during or after the procedure, should be evaluated on a case-by-case basis to determine if the event may be more appropriately classified as device-related or procedure-related.

Unknown: The adverse reaction cannot be judged because information is insufficient orcontradictory, and cannot be supplemented or verified.

1.7.10.4 Adverse Event Identification

For purposes of consistent trial reporting and analysis, events were categorized by MedDRA coding. Consistent with the *MedDRA® Term Selection: Points to Consider* document, events were further grouped according to diagnosis when the diagnosis was

identified by the reporter. The diagnosis was categorized as the Primary Event. Associative events were defined as reported/coded events (*e.g.* signs/symptoms) associated with a precipitating primary event/diagnosis (*e.g.* a primary event/diagnosis of GI bleed with associative events of nausea, hematemesis, and anemia).

Each adverse event was identified as falling into one of the following categories:

ADVERSE EVENT IDENTIFICATION: a condition that is one of the following:

a) A unique symptom or event that is a change from the patient's baseline status.
b) A series of symptoms or events that can be categorized as a single entity based on definitions found herein.
c) A specific diagnosis responsible for a clinical change

NOT AN EVENT: Reported events that are symptoms associated with another reported event, duplicate events identified using similar or different nomenclature reported with the same start/stop dates or events represents observations or incidental findings or determined to be inaccurately/incorrectly reported.

a) **OBSERVATION/ INCIDENTAL FINDING:** Abnormal or non-specific findings/observation that may be associated with study activities but has no identifiable clinical correlates and suggests no specific pathophysiological process – such as "painful access" or "tired". Such events will not be considered to be an adverse event unless associated with clinical sequelae or requiring specific intervention. When clinical sequelae occur or when the intervention required exceeds standard response for similar symptom/event, it will be reported as an adverse event.

REQUIRES MORE INFORMATION TO FINALIZE: An adverse event where more data is essential for a proper assessment or the additional data are under examination.

1.7.11 Uniformity of Study Procedures

The AMIHOT II clinical trial was conducted at investigational centers located in the U.S., Canada, and Western Europe. The study was planned and executed by TherOx to ensure uniformity of study procedures at all participating sites. The clinical protocol, randomization procedure, study procedures, case report forms, adverse event reporting, and site management were all conducted as part of an IDE study and thus each site was handled under the same clinical study standard operating procedures. The use of the centralized [redacted] randomization service, independent blinded core laboratories for critical data evaluation, and the independent CEC and DSMB for adverse event reporting and safety oversight was instrumental in achieving study uniformity, transparency across sites and to minimize bias among investigational sites and investigators.

1.7.12 Investigational Site Management and Study Monitoring

An overview of investigational site management and study monitoring practices is presented below.

1.7.12.1 Investigational Sites

The distribution of enrolling AMIHOT II investigational sites is shown below by geographic location:

U.S.: [redacted]

Europe: [redacted]

Canada: [redacted]

1.7.12.2 Clinical Site Managers

Four (4) Site Managers (all registered clinical research associates (CRAs)) managed US and Canadian clinical sites and two (2) Site Managers managed European centers. Site Managers were selected by TherOx, Inc., and were required to have extensive knowledge

and experience in cardiovascular research, with emphasis on interventional cardiology studies. All Site Managers received comprehensive training prior to the study start up per the AMIHOT II Investigational Plan. The training included detailed document reviews of the investigational plan, case report form and instructions, clinical monitoring procedures, and regulatory documentation. In addition, all Site Mangers received hands-on-training in the preparation, set up, and use of the AO System per the Instructions for Use and the companion AO System Operators Manual. All Site Managers completed the required training and were certified by TherOx to train investigational site personnel, proctor cases, and provide 24-hour live case support for participating clinical centers throughout the conduct of the study.

Ongoing device training was provided to the sites on an as-needed basis by both Site Managers and TherOx technical support staff, including AO System hands-on demonstrations. This training increased confidence and safety usage levels at the clinical sites. In addition to direct support provided to investigational sites by the Site Managers, 24-hour 7 days-a-week technical support was provided by the TherOx Engineering Department. Two TherOx technical support staff members were on call at all times to be available to respond to these calls.

1.7.12.3 Study Monitoring

All clinical sites were subject to monitoring visits to ensure that the study was conducted in compliance with all applicable regulations and the study protocol. The chronological sequence for qualifying and monitoring the investigational sites is provided below.

1.7.12.3.1 Pre-Study Visits

AMIHOT II clinical sites were either pre-qualified from previous participation in the AMIHOT I study or had a site-screening visit to assess the capability of the site to meet the protocol requirements. This visit was conducted to ensure that the clinical

investigators understood their role and responsibilities in the investigational study, both with regards to the experimental device and the regulatory requirements. The facilities also were evaluated as part of the screening visit, and an assessment was made to ensure that clinical sites had an adequate study population. Investigational sites that were qualified through this screening process were then allowed to participate in the study.

1.7.12.3.2 Regulatory Approvals

Qualified clinical sites received an invitation to participate in the AMIHOT II study. Upon mutual agreement to participate, the sites were sent a study start-up kit that included the AMIHOT II Investigational Plan and Informed Consent template. The sites then prepared their study paperwork for submission to their Institutional Review Board (IRB). After IRB approval was granted, an IRB letter was issued along with the approved and IRB-stamped Informed Consent.

1.7.12.3.3 Site Initiation

After IRB approval was obtained, a site initiation visit was scheduled with the clinical research coordinator. The site initiation visit's purpose was to train the site personnel in the details of the AMIHOT II Investigational Plan, study case report forms (CRFs) and instructions, operation of the AO System per the Instructions for Use, Regulatory Binder content review, adverse event/protocol deviation reporting, and device accountability and storage. The site initiation ensured that the site study personnel were identified, trained, and certified to perform their delegated duties. At the conclusion of site initiation, a follow-up letter was sent to the site principal investigator (PI) to recap the site initiation visit, affirm the PI's responsibilities in the study, and authorize the clinical site to begin study enrollment.

1.7.12.3.4 Interim Monitoring Visits

Immediately after the clinical site's first enrollment in the study, a monitoring visit was scheduled with the research coordinator per established procedure. Thereafter, interim monitoring visits (IMVs) periodically were scheduled and performed by the assigned Site Manager. These monitoring visits included monitoring of the signed Informed Consent and CRFs to ensure accurate and complete data collection against the patient's medical chart. Monitored case report forms were shipped to the data center for processing. After Any subsequent data queries generated by the data center were sent to the Site Manager for resolution with the site. In addition, all regulatory documentation were reviewed during IMVs and updated as necessary. IMVs also included continuous improvement training per the AMIHOT II Investigational Plan and AO System training per the IFU. A follow-up letter was issued to the site PI at the conclusion of an IMV.

1.7.13 Data Management

1.7.13.1 Overview

[redacted] was contracted to perform all data management activities for the AMIHOT II Clinical Study. [redacted] responsibilities included database development and maintenance, CRF entry, consistency review of Case Report Forms (CRFs), query generation and resolution, reporting of pre-specified Adverse Events to the Clinical Events Committee and DSMB Chairperson, and, in conjunction with the Sponsor, CEC and DSMB meeting preparation and management. In addition, [redacted] was responsible for creation of raw and analysis datasets, data listings, and programming of nearly all safety data tables to support the clinical report. TherOx was responsible for programming of all other data tables included in the clinical report; this activity was performed through the professional statistical consulting firm [redacted]

[redacted]

All data processing and report programming activities performed by [redacted] were conducted in accordance with relevant [redacted] standard operating procedures and the AMIHOT II clinical study Data Management Plan. The AMIHOT II Data Management Plan was authored by [redacted] and approved by the study Sponsor.

1.7.1.2 Clinical Database Management

The Database Management System utilized for the AMIHOT II Study was the [redacted]. This data management system is a web-based data collection and reporting tool developed and hosted by [redacted]. System security and back-up were conducted in accordance with [redacted]' standard operating procedures. [redacted] was validated and verified to be in compliance with federal regulations on electronic records (21 CFR§11).

The Clinical Database for this trial included all CRF data submitted by the sites as well as the Clinical Events Committee CRF data and the [redacted] data. The Data from the [redacted] an [redacted] were provided to [redacted] in electronic format at the completion of the trial. In addition, AO Therapy administration data pertaining to device usage were obtained by TherOx from electronic log files and transducer data chips obtained directly from the AO Systems and used cartridges. These data were provided to [redacted] by TherOx at the completion of the trial. All electronic data were transmitted and validated in accordance with [redacted]'s standard operating procedure for data transfer. Data were reviewed by [redacted] for consistency against the study database and clarifications provided to the core lab and/or TherOx for discrepant data. Final datasets were provided to [redacted] by the [redacted] and TherOx after all discrepancies were corrected.

Data entry was performed by [redacted] data entry staff utilizing a double data entry system. Data verification was completed as discrepancies between the two entries were identified and remediated prior to data commitment to the database. Verified data underwent systematic validation by a combination of computerized validation checks, including checks for logic, consistency, and protocol compliance. In addition, a manual review of all CRFs was performed by the study Clinical Data Manager to identify data issues that were not identified through systematic validation. Data queries were e-mailed to the sites for resolution via Data Clarification Forms (DCFs) in PDF Format.

Adverse events (AEs) were reviewed and coded by [redacted] using MedDRA version 8.1 prior to CEC review. The coding was done solely using patient CRF data in accordance with the study coding guidelines itemized in the Data Management Plan. All AEs were adjudicated by the CEC and MedDRA coding was reviewed and agreed upon, or modified, by the CEC members at that time. Adjudication Case Report Forms were completed and signed by the CEC members and entered into the study database.

1.7.13.3 Data Reporting Time Frames

The data in this regulatory submission includes all patient data through 30-day Follow-up. In addition, for post 30-day patient survey and AE data, the date of May 31, 2007 was utilized as a cut-off for inclusion. If a subject's post 30-day 6 or 12-month follow-up survey date was after 31 May 2007, the follow-up data, as well as all corresponding adverse event data for that time period, were not included in the extracted datasets for this submission.

1.7.13.4 Data Lock and Transfer

A Data Quality Audit was conducted for this trial when the required data necessary to support this regulatory submission were collected and validated. This audit was conducted in accordance with [redacted]'s standard operating procedures for Clinical Data

Quality Auditing and the Data Management Plan. All CRF records were locked prior to audit initiation.

The clinical data were extracted from the database into Microsoft Access files. The Microsoft Access files were then converted to SAS datasets. The raw SAS datasets were utilized to create analysis datasets to support the clinical report data tables. Analysis datasets were then utilized to program the clinical report tables. Analysis datasets and data tables were programmed using SAS version 9.1.3. All analysis datasets and data tables were verified by an independent programmer using either Microsoft Access or Excel.

Final validated datasets and data tables were generated and provided to the sponsor and archived with the study files.

1.7.14 Statistical Analysis Overview

The AMIHOT II study objective, eligible patient population, randomization scheme, and primary endpoints are discussed in **Sections 1.7.3 – 1.7.6**. Some key summary points are presented in this section.

1.7.14.1 Description of Bayesian Model

The study endpoint for effectiveness was superiority of the adjunctive administration of AO Therapy following PCI with stenting, as compared to a Control population receiving PCI with stenting alone. The effectiveness measure was infarct size measurement by Tc-99m SPECT imaging at 14 days. For safety, the endpoint was non-inferiority of the cumulative incidence of 30-day MACE within a safety delta of 6.0%. The target population was anterior AMI successfully revascularized by PCI within six hours of symptom onset.

Bayesian hierarchical modeling was employed to assess these endpoints. In concept, study endpoint success was evaluated for the AMIHOT II study contingent upon the results of the AMIHOT I trial. The model was structured so that the AMIHOT I results were sub-divided into four patient subgroups of interest: anterior vs. non-anterior AMI, treated ≤ 6 or > 6 hours from symptom onset. More specifically, the efficacy endpoint was considered to have been met if there was high posterior probability (more than 95%) of superiority in the AMIHOT II trial conditional on the efficacy data from both trials, and the safety endpoint was satisfied if there was a high posterior probability of non-inferiority in the AMIHOT II trial conditional on the safety data from both trials.

The degree of borrowing from the results of the AMIHOT I study in analyzing the results of the AMIHOT II study was contingent upon the similarity of data in the two trials. A high degree of similarity would have resulted in a large amount of pooling, but dissimilarity of the trials (either in AO Therapy versus Control differences or in overall average efficacy measure or mean MACE rate) would have resulted in a limited amount of pooling. It was thus mathematically impossible for the AMIHOT II trial to trend towards a neutral or negative outcome and still meet the statistical criteria for study success, and the design preserved (frequentist) type I error rates of 5% under the null hypotheses of equal efficacy and inferior safety (*i.e.* the AO Therapy group MACE rate exceeding the Control group rate by at least the safety delta of 6%).

The AMIHOT II trial was not designed or powered to achieve the primary endpoints as a stand-alone study. The study Statistical Analysis Plan was designed using Bayesian methodology whereby data sampling via prior posterior probability distributions modeling from the AMIHOT I study combined with the AMIHOT II study data were analyzed for each of the clinical study endpoints.

1.7.14.2 Study Analysis Patient Samples

An intent-to-treat (ITT) patient sample was used as the primary analysis of both effectiveness and safety data[2]. The ITT sample was defined as all eligible patients randomized into the trial. The ITT analyses included patients who die, are lost to follow up, and patients with protocol deviations. All available data, regardless of whether data were derived within specified time windows, were included in the analysis. For the ITT analysis, patients who did not complete the entire course of treatment with the assigned device were evaluated in the assigned treatment arm.

A per protocol (PP) subset was used as a secondary analysis of the primary effectiveness endpoints. This PP sample consisted of randomized patients not excluded due to major protocol deviations. A major protocol deviation was defined as one that wouldcompromise the evaluation of the endpoint.

1.7.14.3 General Statistical Analysis Methods

All statistical analyses were performed using the ITT patient sample as described above and were considered as primary analyses for the primary effectiveness endpoint and as one of the two analyses for the primary safety endpoint. An additional PP analysis was performed for both the primary safety and effectiveness endpoint. However, because it is unclear for a non-inferiority hypothesis whether the ITT or PP subset is more conservative, both were considered primary for the purpose of evaluating the primary safety endpoint. Samples representing subsets were evaluated in the same manner as the analysis of the ITT and PP samples. Statistical analysis was performed and reported after all patients completed the 30-day follow-up assessment.

Variables were tabulated using descriptive statistics. Continuous variables were presented as means and standard deviations, as well as medians and ranges. For

[2] For safety, a Per Protocol patient sample was considered co-primary.

categorical variables, relative frequencies were provided. The primary effectiveness variable was transformed as described in the Statistical Analysis Plan.

For descriptive purposes, the comparability of the randomized groups at baseline, treatment and control groups were compared with regard to demographic characteristics, medical history, disease status, PCI procedure, and other baseline values using t-tests for independent samples for continuous variables and Mantel-Haenszel chi-square test for trends for categorical and rating scale data with limited (short) scales.

Statistical evaluations of the primary outcomes were performed using the hierarchical Bayesian models specified in the Statistical Analysis Plan. Posterior probabilities in excess of 95% for the defined endpoints were used to reach a positive conclusion about the endpoint in question. The WinBUGS program was used to evaluate the Bayesian models and determine the posterior probability distributions.

1.7.15 IDE-Approved Changes to Investigational Plan

One IDE-approved change was made to the AMIHOT II clinical protocol during the enrollment phase of the study. In [redacted], TherOx submitted a request to FDA to amend the AMIHOT II protocol to include the physician option of using [redacted] infusion catheter as an alternative to the [redacted] infusion catheter for AO delivery. The [redacted] catheter is a 510(k)-cleared general use infusion catheter manufactured by [redacted] whose predicate device was the [redacted] infusion catheter. [redacted] submitted data for the [redacted] catheter under IDE Supplement [redacted] that demonstrated equivalency with the [redacted] in AO Therapy delivery performance.

FDA approved this requested change to the clinical protocol in a letter dated [redacted] subject to IRB review. TherOx obtained the requisite IRB approvals and subsequently incorporated the [redacted] infusion catheter into the AMIHOT II study.

No other changes were made to the AMIHOT II Investigational Plan during the study.

1.8 AMIHOT II Study Results

The results of the AMIHOT II trial are presented in **Section 1.8**, beginning with patient accountability, screening, the topline site enrollment summary, study assessment compliance, and the data analysis populations. This information is covered in **Sections 1.8.1 – 1.8.6**. Group comparisons of the data and a discussion of these results is presented in **Sections 1.8.7 – 1.8.16**, including pre-randomization patient evaluations, AO Therapy intra-procedural data, post-procedure in-hospital evaluations, primary and secondary effectiveness endpoint data, adverse event information, medications, and protocol deviations.

Throughout the tabular data presentation within the clinical report, descriptive statistics for continuous variables are presented as both mean ± standard deviation (SD), as well as median ± interquartile range (IQR), and range (minimum – maximum). Units of measure are provided for continuous variables within each table. For evaluation of group comparisons for continuous variables, two-sided p values were generated from the Mann-Whitney test unless otherwise noted. Categorical variables are presented within the tables as counts and percentages; group comparison p values were generated with the chi-square test for homogeneity unless otherwise noted. When the "exact chi-square" test is mentioned, this refers to the usual chi-square calculations with the p-value determinedfrom the exact distribution of the test statistic.

1.8.1 Patient Accountability

Figure 5 depicts a patient accountability flow chart for the AMIHOT II study.

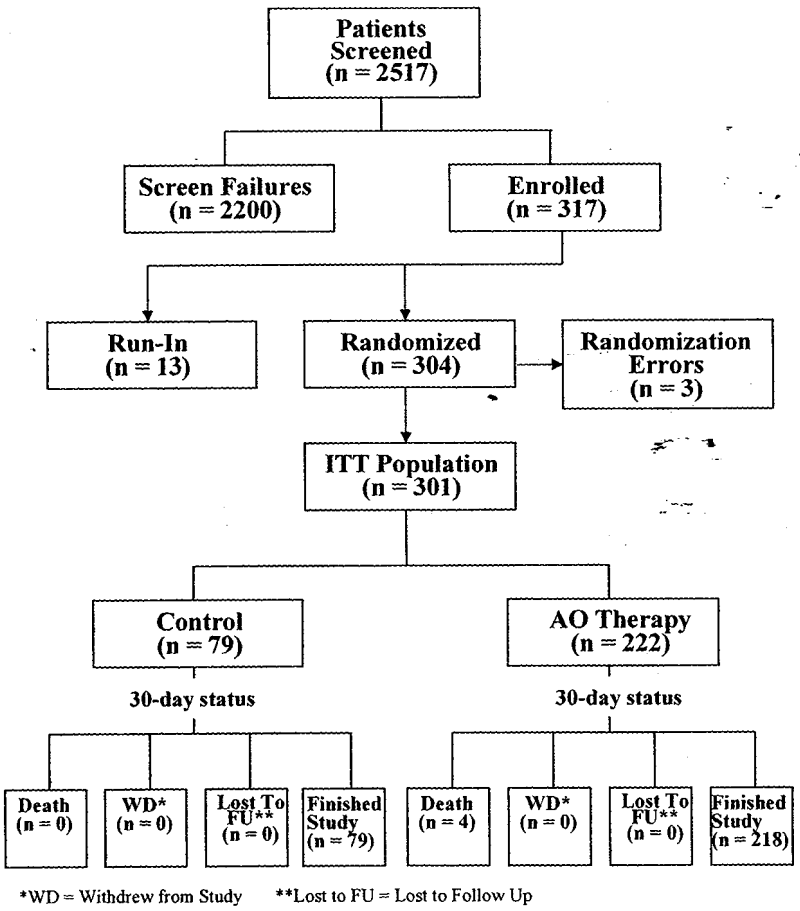


Figure 5. AMIHOT II Patient Accountability Flow Chart

As shown in the figure, a total of 2,517 subjects were screened for potential enrollment in the AMIHOT II trial. Of this total, 2,200 subjects were classified as screen failures, failing to meet the eligibility criteria for the study. A total of 317 subjects were enrolled, including 304 randomized subjects and 13 non-randomized run-in or training cases. Of the 304 randomized subjects, three subjects were randomized simultaneously with investigator assessment that these acute patients did not meet eligibility criteria. There was no intent to treat these three subjects and therefore they are not included in the intent-to-treat (ITT) cohort.

The ITT analysis sample consists of 79 Control subjects and 222 AO Therapy subjects. Unless otherwise specified, the data tables presented in this discussion of AMIHOT II trial results are based upon the ITT sample.

The study's endpoint assessment was performed at 30 days post-procedure. At this time point, the status of all 79 Control and 222 AO Therapy subjects was known. The Control group had zero (0) deaths, zero (0) patients lost to follow up, and zero (0) patient withdrawals, for a total of 79 subjects who finished the study. The AO Therapy group had four (4) deaths, zero (0) patients lost to follow up, and zero (0) patient withdrawals, for a total of 218 subjects who finished the study.

1.8.2 Patient Screening

AMIHOT II screening information is provided in **Table 12**. Screening information was collected and analyzed for all enrolling AMIHOT II investigational sites. As shown in the table, 317/2517 (12.6%) screened patients were enrolled. Of the remaining 2200 patients who were classified as screen failures, the reasons for non-enrollment were categorized in a hierarchical fashion. 1244/2200 (56.5%) screen failures were due to non-anterior AMI, and 338/2200 (15.4%) screen failures were due to out-of-window duration of infarction (> 6 hours). The remaining 617/2200 (28.0%) screen failures were non-qualifying anterior AMI subjects with < 6 hour duration of infarction. The reasons for screen failure of these subjects are provided in the table. The top five (5) reasons for screen failure of these subjects were the need for an intra-aortic balloon pump (IABP)/cardiogenic shock, pre-PCI TIMI 3 flow grade, clinical complications, physician discretion, and patient refusal/inability to obtain consent.

Table 12. Patient Screening

	(N)	(%)
Total number of patients screened	2517	
Number of patients enrolled	317	12.6
Number of patients not enrolled (screen failures)	2200	87.4
Reasons for non-enrollment (hierarchical list):		
Non-anterior AMI	1244	56.5
> 6 hrs from symptom onset	338	15.4
Non-qualifying < 6 hr anterior AMI	617	28.0
Reason for non-qualifying < 6 hr anterior AMI		
IABP†/Cardiogenic Shock	114	18.5
Pre-PCI TIMI flow grade = 3	90	14.6
Clinical Complications	81	13.1
Physician discretion	75	12.2
Patient refused/Unable to consent	75	12.2
PI/sub-PI/coordinator unavailable	45	7.3
Did not meet ECG study criteria	29	4.7
Other	24	3.9
Enrolled in another study	21	3.4
CABG†/PCI indicated < 30 days	20	3.2
Unknown	13	2.1
Drug Abuse	10	1.6
CPR†	7	1.1
Expired	5	0.8
SVG† target vessel	4	0.6
Non-study anticoagulant therapy	3	0.5
Thrombolytics	2	0.3

†IABP=intra-aortic balloon pump; CABG=coronary artery bypass graft; CPR=cardiopulmonary resuscitation; SVG=saphenous vein graft

1.8.3 Patient Assignment and Tracking

Tables 13 and **14** provide additional detail regarding patient assignment and tracking. As seen in **Table 13**, one non-randomized Run-In subject withdrew prior to receiving the 14-day SPECT imaging scan.

In the post-30 day period, the AMIHOT II study includes 6 and 12-month patient surveys, and adverse events are captured by investigational sites during this extended timeframe. In total, three Control subjects and two AO Therapy subjects withdrew post-30 days and could not be contacted for this survey information. **Table 13** also shows that

one Run-In subject was lost to follow up in the post-30 day period. **Table 14** provides summary information concerning patients who withdrew or were lost to follow up.

A total of 0/79 (0.0%) Control subjects and 4/222 (1.8%) AO Therapy subjects were deceased at 30 days. Additionally, 1/79 (1.3%) Control subject and 4/222 (1.8%) AO Therapy subjects died in the post-30 day period, totaling 1/79 (1.3%) and 8/222 (3.6%) expired subjects at any time point.

Table 13 provides the total number of patients categorized as part of the Per Protocol (PP) patient subsets. This pre-specified group was intended to identify subjects who followed the essential protocol elements, received the experimental therapy as intended (for AO Therapy patients), and had the primary study endpoint evaluations. The PP subsets shown in **Table 13** are slightly different for the SPECT and MACE endpoints; this difference reflects the fact that some patients did not have evaluable SPECT data (*i.e.* scan missing or not readable) but did have completed 30-day follow up assessments. In total, 69/79 (87.3%) Control subjects and 175/222 (78.8%) AO Therapy subjects were classified as PP subjects for SPECT endpoint evaluation, and 78/79 (98.7%) Control subjects and 186/222 (83.8%) AO Therapy subjects were classified as PP subjects for MACE endpoint evaluation.

The reason for a lower number of PP subjects in the AO Therapy group is that a number of subjects did not receive the pre-defined duration of therapy (60 minutes) to qualify for the PP analysis. This observation will be addressed in later sections of this report.

Table 13. Patient Assignment and Tracking

	Control Group	AO Therapy Group	Run-In Group
Patients Screened: n = 2517			
Run-In Subjects (n)	NA	NA	13
Randomized Subjects (n)	79	225	NA
Screening Exclusions† (n)	0	3	0
Intent-to-Treat Subjects (n)	79	222	NA
SPECT endpoint Per Protocol Subjects (n/N; %)	69/79 (87.3%)	175/222 (78.8%)	NA
30-day MACE endpoint Per Protocol Subjects (n/N; %)	78/79 (98.7%)	186/222 (83.8%)	NA
Subjects Lost to Follow Up‡:			
Before completing 14-day SPECT scan (n/N; %)	0/79 (0.0%)	0/222 (0.0%)	1/13 (7.7%)
Post SPECT, before completing 30-day follow up (n/N; %)	0/79 (0.0%)	0/222 (0.0%)	0/13 (0.0%)
Post 30 day (n/N; %)	3/79 (3.8%)	2/222 (0.9%)	1/13 (7.7%)
Expired Subjects:			
On or before day 30 (n/N; %)	0/79 (0.0%)	4/222 (1.8%)	0/13 (0.0%)
After day 30 (n/N; %)	1/79 (1.3%)	4/222 (1.8%)	0/13 (0.0%)
At any time (n/N; %)	1/79 (1.3%)	8/222 (3.6%)	0/13 (0.0%)

†3 subjects randomized in error are classified as screening exclusions from the ITT population
‡Includes subjects who withdrew consent and subjects who could not be contacted

Table 14. Reasons for Withdrawal or Loss to Follow-Up

	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)	Run-In Group (n=13) (n/N; %)
Pre-30 days			
Withdrew Consent	0/79 (0.0 %)	0/222 (0.0 %)	1/13 (7.7%)
Post-30 days			
Withdrew Consent	1/79 (1.3%)	1/222 (0.5%)	0/13 (0.0%)
Lost to Follow-Up	2/79 (2.5%)	1/222 (0.5%)	1/13 (7.7%)

1.8.4 Subject Enrollment by Site

AMIHOT II subject enrollment is presented in **Table 15**, organized by investigational site number. Investigational site [redacted]

consisted of two hospitals under a single IRB jurisdiction with a single Primary Investigator [redacted]. These two hospitals are designated [redacted] and [redacted] in the table. The site location (city, ST or country) is provided in the table in addition to a field designating whether the investigational site is in the United States (US) or outside the United States (OUS).

As shown in **Table 15**, site [redacted] was the leading enrolling center in the AMIHOT II study, with 21/79 (26.6%) Control subjects and 50/222 (22.5%) AO Therapy subjects, for a total of 71 subjects. The other sites comprising the top five (5) enrolling centers were site number [redacted] (53 subjects), site number [redacted] (50 subjects), site number [redacted] (28 subjects), and site number [redacted] (26 subjects).

Table 15. Patient Enrollment by Site†

Site Number	Location (City, ST or Country)	US/OUS	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)
[redacted]	[redacted]	[redacted]	**7/79 (8.9%)**	**14/222 (6.3%)**
			0/79 (0.0%)	5/222 (2.3%)
			4/79 (5.1%)	6/222 (2.7%)
			3/79 (3.8%)	12/222 (5.4%)
			0/79 (0.0%)	2/222 (0.9%)
			3/79 (3.8%)	3/222 (1.4%)
			0/79 (0.0%)	2/222 (0.9%)
			0/79 (0.0%)	2/222 (0.9%)
			0/79 (0.0%)	0/222 (0.0%)
			2/79 (2.5%)	2/222 (0.9%)
			7/79 (8.9%)	13/222 (5.9%)
			0/79 (0.0%)	0/222 (0.0%)
			0/79 (0.0%)	1/222 (0.5%)
			6/79 (7.6%)	22/222 (9.9%)
			0/79 (0.0%)	1/222 (0.5%)
			0/79 (0.0%)	2/222 (0.9%)
			0/79 (0.0%)	2/222 (0.9%)
			12/79 (15.2%)	41/222 (18.5%)
			12/79 (15.2%)	38/222 (17.1%)
			21/79 (26.6%)	50/222 (22.5%)
			0/79 (0.0%)	3/222 (1.4%)
			2/79 (2.5%)	1/222 (0.5%)

†Data shown for ITT sample.

1.8.5 Study Data Assessment Compliance

Key study data assessments for the AMIHOT II trial included pre-PCI and post-PCI angiographic evaluation by the [redacted] ST-elevation evaluation by the [redacted] infarct size evaluation by the [redacted] and 30-day MACE assessment by the Clinical Events Committee (CEC).

As shown in **Table 16**, 79/79 (100%) Control subjects and 222/222 (100%) AO Therapy subjects had procedural angiograms submitted to the [redacted]. The high quality of the submitted angiographic data yielded readable pre-PCI images for 78/79 Control subjects (98.7%) and 222/222 (100%) AO Therapy subjects; similarly,

readable post-PCI images totaled 78/79 Control subjects (98.7%) and 221/222 (99.5%) AO Therapy subjects.

Table 16. Angiographic Assessment Imaging Accountability

	Control Group (n=79) (n/N; %)	**AO Therapy Group** (n=222) (n/N; %)
Number of patients with Procedure Angiogram Submitted to Core Lab	79/79 (100.0%)	222/222 (100.0%)
Number of patients with readable images		
Pre PCI assessment available	78/79 (98.7%)	222/222 (100.0%)
Post PCI assessment available	78/79 (98.7%)	221/222 (99.5%)
Post AO assessment available†	NA	44/222 (19.8%)
Number of patients with Follow-up Angiogram Submitted to Core Lab	2/79 (2.5%)	7/222 (3.2%)
Clinical Symptoms	0/79 (0.0%)	3/222 (1.4%)
Other Assessment	2/79 (2.5%)	4/222 (1.8%)

†Not required by protocol

ECG data accountability is presented in **Table 17**. As shown in the table, the [redacted] documented the enrolling ECG for 78/79 (98.7%) Control subjects and 217/222 (97.8%) AO Therapy subjects; study-required 24-hour Holter Monitoring was performed on 79/79 (100%) Control subjects and 221/222 (99.6%) AO Therapy subjects. These high rates of data collection were matched by the generally high quality of the continuous ECG data; 74/79 (93.7%) Control subject ECG recordings were rated as either Excellent or Good, while 197/222 (88.8%) AO Therapy subject ECG recordings achieved these high ratings. As a consequence, the study's secondary effectiveness endpoint, cumulative ST area assessments at 0-3, 0-4, and 0-6 hours post-procedure, were evaluable in 91%-96% of subjects at all time points.

Table 17. Secondary Endpoint: ECG Data Accountability

	Control Group (n=79) (n/N; %)	**AO Therapy Group** (n=222) (n/N; %)
No. of patients with Enrolling ECG documented by Core Lab	78/79 (98.7%)	217/222 (97.8%)
No. of patients with 24-Hr Holter Monitoring performed	79/79 (100%)	221/222 (99.6%)
ST area assessments		
All ST area assessments performed	72/79 (91.1%)	194/222 (87.4%)
0 – 3 Hours	75/79 (94.9%)	202/222 (91.0%)
0 – 4 Hours	73/79 (92.4%)	208/222 (93.7%)
0 – 6 Hours	76/79 (96.2%)	212/222 (95.5%)
0 – 24 Hours	76/79 (96.2%)	206/222 (92.8%)
No. of patients with no Holter Monitoring performed	0/79 (0.0%)	1/222 (0.5%)
Continuous ECG study quality		
Excellent	71/79 (89.9%)	192/222 (86.5%)
Good	3/79 (3.8%)	5/222 (2.3%)
Fair	2/79 (2.5%)	19/222 (8.6%)
Poor	2/79 (2.5%)	2/222 (0.9%)
Technical Failure	1/79 (1.3%)	4/222 (1.8%)

Table 18 shows accountability data for the AMIHOT II study's primary effectiveness endpoint, infarct size evaluation by [redacted] imaging at 14(±7) days post-procedure. A total of 73/79 (92.4%) Control subjects and 211/222 (95.1%) AO Therapy subjects had the nuclear imaging scan performed. Of these performed scans, the overall quality was excellent: only 1/73 (1.4%) Control subject scan and 2/211 (1.0%) AO Therapy subject scans were of Unacceptable quality; as a result, infarct size data were evaluable for 72/79 (91.1%) Controls and 209/222 (94.1%) AO Therapy subjects. The median time to infarct size measurement was 16 days for both groups.

Table 18. SPECT Imaging Accountability

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
Number of patients with SPECT Imaging performed (n/N; %)	73/79 (92.4%)	211/222 (95.1%)	
Imaging performed in window†	66/73 (90.4%)	197/211 (93.4%)	
Imaging performed early (< 7 days)	0/73 (0.0%)	1/211 (0.5%)	
Imaging performed late (>21 days)	7/73 (9.6%)	13/211 (6.2%)	
Time to infarct size measurement (days)			0.40
(mean ± SD) (n)	17.9 ± 8.3 (n=73)	17.1 ± 8.9 (n=211)	
(median ± IQR)	16 ± 5	16 ± 4	
(range)	7 – 66	6 – 122	
Number of patients with no SPECT imaging (n/N; %)	6/79 (7.6%)	11/222 (5.0%)	
Reason not performed (n/N; %)			
Patent withdrew consent	0/6 (0.0%)	0/11 (0.0%)	
Patient lost to follow-up	0/6 (0.0%)	0/11 (0.0%)	
Patient condition deteriorated, unable to perform scan	0/6 (0.0%)	1/11 (9.1%)	
Technical difficulty with SPECT equipment	0/6 (0.0%)	0/11 (0.0%)	
Patient died prior to scan	0/6 (0.0%)	4/11 (36.4%)	
Other	6/6 (100%)	6/11 (54.6%)	
SPECT Image quality (n/N; %)			
Good	28/73 (38.4%)	71/211 (33.7%)	
Acceptable	44/73 (60.3%)	138/211 (65.4%)	
Unacceptable	1/73 (1.4%)	2/211 (1.0%)	

†SPECT imaging assessment required at 14 ± 7 days
*Mann Whitney test

30-day MACE endpoint assessment was performed on 100% of all subjects; the 30-day MACE status of all Control and AO Therapy subjects was known and evaluable by the CEC.

1.8.6 Per Protocol Analysis Samples

The Per Protocol (PP) analysis sample was pre-specified in the AMIHOT II Statistical Analysis Plan. As stated in **Section 1.8.3**, the PP categorization was intended to identify subjects who followed the essential protocol elements, received the experimental therapy as intended (for AO Therapy patients), and completed the primary study endpoint evaluations. **Table 19** shows the PP patient accountability for the AMIHOT II trial. As stated previously, the reason for a lower number of PP subjects in the AO Therapy group is that a number of subjects received incomplete AO Therapy. Incomplete AO Therapy was the disqualifying reason for 33/36 (91.7%) subjects who did not qualify for the 30-day MACE PP analysis and 33/47 (70.2%) subjects who did not qualify for the SPECT PP analysis. Incomplete AO Therapy was a pre-specified PP exclusion criterion consisting of less than 60 min of hyperoxemic reperfusion.

As shown in the table, the SPECT PP sample consisted of 69/79 (87.3%) Control subjects and 175/222 (78.8%) AO Therapy subjects, and the 30-day MACE PP sample consisted of 78/79 (98.7%) Control subjects and 186/222 (83.8%) AO Therapy subjects. As shown in **Table 19**, the pre-specified reasons for exclusion from the SPECT PP sample and 30-day MACE PP sample were slightly different, leading to differences in the group totals. For example, a patient who did not have a SPECT scan but did have a 30-day follow up assessment would be included in the 30-day MACE PP sample but not the SPECT PP sample, in the absence of other disqualifying criteria.

Table 19. Per Protocol Analysis Patient Accountability

	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)
Efficacy Endpoint (SPECT) Per Protocol Subjects	69/79 (87.3%)	175/222 (78.8%)
Reasons for exclusion[†]		
SPECT imaging not performed	6/79 (7.6%)	7/222 (3.2%)
SPECT performed early	0/79 (0.0%)	1/222 (0.5%)
SPECT quality unacceptable	1/79 (1.3%)	1/222 (0.5%)
> 6hrs time to reperfusion	3/79 (3.8%)	1/222 (0.5%)
Proximal disease >40% or unprotected LM stenosis >60%[‡]	0/79 (0.0%)	1/222 (0.5%)
Non-stented dissection present post PCI[‡]	0/79 (0.0%)	2/222 (0.9%)
Elective revascularization prior to 14-day SPECT scan	0/79 (0.0%)	1/222 (0.5%)
Incomplete AO[§]	NA	33/222 (14.9%)
Safety Endpoint (30 day MACE) Per Protocol Subjects	78/79 (98.7%)	186/222 (83.8%)
Reasons for exclusion[†]		
TIMI flow III at baseline[¥]	0/79 (0.0%)	0/222 (0.0%)
Unsuccessful angioplasty[¥]	0/79 (0.0%)	0/222 (0.0%)
Cardiogenic Shock	0/79 (0.0%)	0/222 (0.0%)
CABG w/in 30 days of PCI	0/79 (0.0%)	0/222 (0.0%)
Proximal disease >40% or unprotected LM stenosis >60%[‡]	1/79 (1.3%)	1/222 (0.5%)
Non-stented dissection present post PCI[‡]	0/79 (0.0%)	2/222 (0.9%)
Incomplete AO[§]	NA	33/222 (14.9%)
30-day MACE assessment not available	0/79 (0.0%)	0/222 (0.0%)

[†]In case of multiple reasons for per protocol exclusion, the earliest chronological reason is counted
[‡]Investigator assessment or core lab determination
[§]< 60 min AO infusion, 2 pO_2 readings < 70 mmHg, or more than 3 AO Cartridges
[¥]Investigator assessment

1.8.7 Pre-Randomization Evaluations

AMIHOT II pre-randomization evaluations included data for patient demographics, medical history, physical examination and AMI characteristics, investigator-obtained cath-lab based assessments, [redacted] analysis of pre- and post-PCI data, and baseline laboratory data collection. Data tables are presented within **Section 1.8.7** to present and compare the group data for this information.

1.8.7.1 Patient Demographics

Patient demographic information is presented in **Table 20**. The table displays descriptive statistics and group comparisons for age, gender, ethnicity, height, weight, and body mass index (BMI).

As shown in the table, the median ages in the two groups were well matched at 59 and 60 years for Control and AO Therapy subjects, respectively (p=0.28). The age range was found to be 32 – 89 years in the study. The Control group had a higher percentage of male subjects than the AO Therapy group (87.3% vs. 77.9%), but this nominal difference was not statistically significant (p=0.07). The ethnic breakdown of the two groups was quite similar; a high percentage of AMIHOT II subjects were Caucasian (92.4% of Control subjects and 94.1% of AO Therapy subjects; p=0.07).

Table 20 also shows that height, weight, and BMI were well matched between the two groups, and results did not reveal any statistically significant differences in these parameters.

Table 20. Demographics

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
Age (yrs)			0.28
(mean ± SD) (n)	59.2 ± 11.3 (n=79)	60.9 ± 12.2 (n=222)	
(median ± IQR)	59.0 ± 19.0	60.0 ± 20.0	
(range)	36 – 82	32 – 89	
Gender (n/N; %)			0.07
Male	69/79 (87.3%)	173/222 (77.9%)	
Female	10/79 (12.7%)	49/222 (22.1%)	
Ethnicity (n/N; %)			
Caucasian	73/79 (92.4%)	209/222 (94.1%)	0.07**
Black/African-American	3/79 (3.8%)	5/222 (2.3%)	
American Indian/Alaska Native	0/79 (0.0%)	0/222 (0.0%)	
Asian/Asian American	0/79 (0.0%)	6/222 (2.7%)	
Hispanic or Latino	0/79 (0.0%)	1/222 (0.5%)	
Native Hawaiian or Pacific Islander	0/79 (0.0%)	0/222 (0.0%)	
Other	3/79 (3.8%)	1/222 (0.5%)	
Height (in)			0.15
(mean ± SD) (n)	68.0 ± 4.4 (n=75)	67.3 ± 3.8 (n=213)	
(median ± IQR)	68.0 ± 7	67.0 ± 5	
(range)	57 – 77	57 – 76	
Weight (lb)			0.75
(mean ± SD) (n)	182.5 ± 32.6 (n=76)	184.9 ± 36.8 (n=216)	
(median ± IQR)	180 ± 43	181 ± 51	
(range)	101 – 266	108 – 307	
Weight (kg)			0.75
(mean ± SD) (n)	82.9 ± 14.8 (n=76)	84.1 ± 16.7 (n=216)	
(median ± IQR)	81.8 ± 19.6	82.3 ± 23.2	
(range)	45.9 – 120.9	49.1 – 139.5	
Body Mass Index (BMI) (kg/m^2)			0.23
(mean ± SD) (n)	27.9 ± 4.8 (n=75)	28.7 ± 5.1 (n=211)	
(median ± IQR)	27.1 ± 6.9	28.2 ± 6.5	
(range)	19.7 – 42.3	19.4 – 50.5	

*Mann-Whitney test for continuous data or Chi Square for frequencies unless otherwise noted
**Exact Chi-Square test

1.8.7.2 Patient Medical History

Patient medical history data are shown in **Table 21** for hypertension, diabetes, previous MI, previous PCI of the culprit vessel, previous coronary artery bypass graft (CABG) surgery, prior congestive heart failure (CHF), family history of coronary artery disease (CAD), present Killip class, history of arrhythmia, history of smoking, renal insufficiency, gastrointestinal bleeding or gastric ulcers, and hyperlipidemia.

Slightly less than half of the AMIHOT II subjects had hypertension, 36/79 (45.6%) Control subjects and 104/222 (46.9%) AO Therapy subjects (p=0.85). The percentage of subjects with diabetes was also similar between the two groups; 11/79 (13.9%) Control subjects and 36/222 (16.2%) AO Therapy subjects had either Type I or II diabetes (p=0.63).

The frequencies of previous MI were low – 7/79 (8.9%) Control subjects and 20/222 (9.0%) AO Therapy subjects had experienced a prior myocardial infarction (p=0.97). A small percentage of subjects had experienced prior anterior MI, as seen in the table. A high percentage of AMIHOT II subjects presented with Killip class = 1, evincing no clinical signs of heart failure (94.8% of Control patients and 94.1% of AO Therapy subjects). The balance of patients presented with Killip class = 2, with clinical evidence of early-stage heart failure. No subjects presented with Killip class = 3, and patients with cardiogenic shock – Killip class = 4, were excluded by protocol. Taken together, the relatively small percentage of subjects with previous MI and Killip class > 1, and the absence of subjects with prior CABG surgery, imply that the AMIHOT II patients were experiencing AMI in otherwise well-functioning hearts. This represents a good patient population to evaluate the effect of an experimental therapy to ameliorate infarct size, one that is largely absent of direct evidence of baseline myocardial damage in their medical history.

The number of patients presenting with a history of smoking was high, 49/79 (62.0%) Control subjects and 135/222 (60.8%) AO Therapy subjects (p=0.85). Likewise, there was a high incidence of family CAD history in both groups (50.6% Control vs. 44.6% AO Therapy, p=0.36) and similar rates of hyperlipidemia (43.0% Control vs. 45.1% AO Therapy, p=0.76).

Overall, the patient medical history data presented in **Table 21** are consistent with an anterior AMI population; the factors that are present with a high percentage of occurrence, including hypertension, family history of CAD, smoking, and hyperlipidemia, are all known risk factors for AMI. No significant group differences in these high-risk or other medical history characteristics were found.

Table 21. Medical History

	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)	p value*
Hypertension†	36/79 (45.6%)	104/222 (46.9%)	0.85
Diabetes mellitus	11/79 (13.9%)	36/222 (16.2%)	0.63
Type I	1/79 (1.3%)	5/222 (2.3%)	1.0**
Type II	10/79 (12.7%)	31/222 (14.0%)	0.85**
Primary Treatment:			0.26**
Diet	1/79 (1.3%)	11/222 (5.0%)	
Oral medication only	8/79 (10.1%)	14/222 (6.3%)	
Any Insulin	1/79 (1.3%)	6/222 (2.7%)	
Oral medication and insulin	1/79 (1.3%)	5/222 (2.3%)	
Previous MI‡	7/79 (8.9%)	20/222 (9.0%)	0.97
Anterior	3/79 (3.8%)	5/222 (2.3%)	
Inferior	0/79 (0.0%)	6/222 (2.7%)	
Posterior	0/79 (0.0%)	0/222 (0.0%)	
Lateral	0/79 (0.0%)	1/222 (0.5%)	
Other	0/79 (0.0%)	0/222 (0.0%)	
Unknown	4/79 (5.1%)	8/222 (3.6%)	
Previous PCI‡ of target lesion/vessel	8/79 (10.1%)	13/222 (5.9%)	0.20
With stent placement	8/79 (10.1%)	9/222 (4.1%)	0.08**
Previous CABG‡	0/79 (0.0%)	0/222 (0.0%)	
Prior CHF‡ within 6 months (Killip class > 1)	0/79 (0.0%)	1/222 (0.5%)	1.00**
Present Killip Class:			1.00**
1	73/77 (94.8%)	206/219 (94.1%)	
2	4/77 (5.2%)	13/219 (5.9%)	
Family history of CAD‡	40/79 (50.6%)	99/222 (44.6%)	0.36
History of arrhythmia (within 6 months)	3/79 (3.8%)	7/222 (3.2%)	0.73**
Atrial fibrillation/flutter	0/79 (0.0%)	5/222 (2.3%)	
Ventricular block	0/79 (0.0%)	0/222 (0.0%)	
Other§	3/79 (3.8%)	2/222 (0.9%)	
History of cigarette smoking	49/79 (62.0%)	135/222 (60.8%)	0.85
Current smoker (within 30 days)	34/79 (43.0%)	85/222 (38.3%)	0.46
Prior smoker	15/79 (19.0%)	50/222 (22.5%)	0.51
Renal insufficiency (creatinine > 1.5 mg/dL)	2/79 (2.5%)	6/222 (2.7%)	1.00**
GI‡/GU‡ bleeding within 6 months	1/79 (1.3%)	0/222 (0.0%)	0.26**
Hyperlipidemia¥	34/79 (43.0%)	100/222 (45.1%)	0.76
Other Significant Medical History	33/79 (41.8%)	79/222 (35.6%)	0.33

†From the AMIHOT II CEC manual of definitions, Hypertension is defined as: Systolic BP>140 mmHg, or diastolic BP>90 mmHg, or requiring medication.
‡MI = Myocardial infarction; PCI = Percutaneous coronary intervention; CABG = Coronary artery bypass grafting; CHF = Congestive heart failure; CAD = Coronary artery disease; GI = gastrointestinal; GU = gastric ulcer
§History of Arrhythmia Other: Atrial tachycardia, VF, VT/VF on arrival (Control); RBBB, Unknown (AO Therapy
¥Cholesterol > 200, or LDL > 100, or requiring medication
*Mann-Whitney test for continuous data and Chi-Square test for frequencies unless otherwise noted.
**Exact Chi-Square or Fisher's Exact test

1.8.7.3 Clinical Complications and Time Intervals

Table 22 shows the frequency of certain clinical complications present in AMIHOT II subjects prior to undergoing cath lab procedures. Data also are presented in the table for several key time intervals, including symptom onset to emergency room (ER) arrival, symptom onset to reperfusion, and door-to-balloon (D2B) time. The number of subjects partitioned to the 0 – 3 and > 3 – 6 hour symptom onset to reperfusion strata through [redacted] randomization is shown, as well as the actual distribution of subjects to these strata[†].

The [redacted] lab clinical complications recorded for the AMIHOT II study included cardiac arrest, pacemaker placement, defibrillation, respiratory arrest, cardioversion, use of an intra-aortic balloon pump (IABP), cardiopulmonary resuscitation (CPR), hypotension requiring vasopressors, and cardiogenic shock.

IABP use and cardiogenic shock were protocol exclusion criteria; the incidence rate for these complications was 0% in both study groups. Overall, the observed incidence rates for these [redacted] lab complications were low. The most prevalent complications were defibrillation, observed in 8/79 (10.1%) Control subjects and 13/222 (5.9%) AO Therapy subjects (p=0.20), and cardiac arrest, observed in 3/79 (3.8%) Control subjects and 9/222 (4.1%) AO Therapy subjects (p=1.0). No significant differences were found in the group comparisons of the individual clinical complications or in the group comparison of the aggregate totals.

Table 22 also shows key time interval data for AMI intervention; this discussion will refer to the data in terms of median ± IQR values. Symptom onset to ER arrival times were 90 ± 90 min and 109.5 ± 110 min for the Control and AO Therapy groups,

[†] The number of subjects randomized to the 0-3/>3-6 strata differ from the true number of subjects in these strata due to human errors during the automated randomization process in choosing the correct strata. See **Section 1.8.16** for further details.

142 of 505

respectively. The nominal 19.5 min difference observed in the median times was not statistically significant (p=0.39). D2B times were similar as well, 75 ± 72 min for Control subjects and 77 ± 68 min for AO Therapy subjects (p=0.63). Symptom onset to reperfusion times were 171 ± 147 min for Control subjects and 194.5 ± 111 min for AO Therapy subjects (p=0.42). As seen in the range values for symptom onset to reperfusion times, a few patients were included in the study whose infarct duration exceeded the protocol-mandated six-hour window. A total of three (3) Control subjects and one (1) AO Therapy subject had symptom onset to reperfusion times greater than six hours.

Patients were stratified through randomization into 0-3 hr and >3-6 hr groups; the number of patients randomized into each of these strata is shown in **Table 22**. However, a number of stratification errors occurred during the trial, leading to a disparity in the actual number of subjects in these 0-3 and >3-6 hr categories as compared to the number of patients randomized into these strata (see **Section 1.8.15**, Protocol Deviations). **Table 22** shows the true patient breakdown as "Time Stratification (actual)". As seen in the table, the net effect of the stratification errors was to create an imbalance in the groups; a higher percentage of Control subjects had 0-3 hour symptom onset to reperfusion time than AO Therapy subjects, 43/79 (54.4%) vs. 95/222 (42.8%). The disparity in the group totals for actual time stratification was found to be statistically significant (p=0.01). Because a shorter time to reperfusion is associated with improved outcome, as outlined in **Section 1.4.2**, the effect of this imbalance would be expected to be conservative with respect to proving superiority of the experimental therapy, *ceteris paribus*.

Table 22. Cardiac Complications and MI Time Intervals

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
Clinical Complications (prior to [redacted] procedure): (n/N; %)	10/79 (12.7%)	17/222 (7.7%)	0.18
Cardiac Arrest	3/79 (3.8%)	9/222 (4.1%)	1.0**
Pacemaker	0/79 (0.0%)	0/222 (0.0%)	
Defibrillation	8/79 (10.1%)	13/222 (5.9%)	0.20
Respiratory Arrest	1/79 (1.3%)	4/222 (1.8%)	1.0**
Cardioversion	1/79 (1.3%)	0/222 (0.0%)	0.26**
IABP	0/79 (0.0%)	0/222 (0.0%)	
CPR	1/79 (1.3%)	5/222 (2.3%)	1.0**
Hypotension requiring pressors	0/79 (0.0%)	1/222 (0.5%)	1.0**
Cardiogenic Shock	0/79 (0.0%)	0/222 (0.0%)	
Other†	3/79 (3.8%)	5/222 (2.3%)	0.44**
Time Intervals			
Symptom Onset to ER arrival (min)			0.39
(mean ± SD) (n)	118.5 ± 79.1 (n=73)	122.2 ± 73.6 (n=218)	
(median ± IQR)	90 ± 90	109.5 ± 110	
(range)	20 – 362	10 – 390	
Symptom Onset to Reperfusion (min)			0.42
(mean ± SD) (n)	205.1 ± 83.8 (n=79)	208.9 ± 73.6 (n=222)	
(median ± IQR)	171 ± 147	194.5 ± 111	
(range)	56 – 408	65 – 437	
Time Stratification [redacted]			0.65
Randomized to 0 – 3 hr group (n/N; %)	39/79 (49.4%)	103/222 (46.4%)	
Randomized to 3 – 6 hr group (n/N; %)	40/79 (50.6%)	119/222 (53.6%)	
Time Stratification (actual)			0.01**
0 ≤ 3 hr (n/N; %)	43/79 (54.4%)	95/222 (42.8%)	
> 3 ≤ 6 hr (n/N; %)	33/79 (41.8%)	126/222 (56.8%)	
> 6 hr (n/N; %)‡	3/79 (3.8%)	1/222 (0.5%)	
Door to Balloon Time (min)			0.63
(mean ± SD) (n)	90.1 ± 61.5 (n=73)	89.3 ± 53.7 (n=218)	
(median ± IQR)	75 ± 72	77 ± 68	
(range)	16 – 297	17 – 303	

‡protocol deviation
*Mann-Whitney test for continuous data and Chi Square test for frequencies unless otherwise noted
**Exact Chi-Square test

1.8.7.4 PCI Data and [redacted] Information

Myocardial infarction characteristics, percutaneous coronary intervention (PCI) data, and additional cath lab information are presented in **Tables 23 – 25**. These tables also include investigator assessments of certain angiographic data; some of these data were also assessed by the independent angiographic core laboratory and are presented in **Section 1.8.7.5**.

The index PCI infarct characteristics are presented in **Table 23**. Procedural left ventricular ejection fraction (LVEF), left main diameter stenosis, the reference vessel diameter, maximum stenosis proximal to the target lesion, and in-vessel anterior infarct location are provided in the table.

Procedural LVEF (median ± IQR) was 40 ± 10% in both groups (p=0.53). Left main diameter stenosis, reference vessel diameter and maximum stenosis proximal to the target lesion were also similar between the two groups, exhibiting no significant differences.

The in-vessel anterior infarct location was categorized by specific location with respect to the left anterior descending (LAD) coronary artery. The distributions of infarcts in the proximal LAD, mid LAD, distal LAD, first diagonal branch of the LAD, and second diagonal branch of the LAD were very similar between the two groups (p=0.64).

Patients were stratified through randomization into two infarct location categories: proximal LAD and non-proximal LAD. The number of patients randomized into each of these strata is shown in **Table 23**. However, a number of stratification errors occurred during the trial, leading to a disparity in the actual number of subjects in these proximal LAD and non-proximal LAD categories as compared to the number of patients randomized into these strata. **Table 23** shows the true patient breakdown as "Actual Infarct Classification". In spite of the stratification errors, the actual infarct location classifications are similar between the two groups, with 37/79 (46.8%) Control subjects

and 106/222 (47.7%) AO Therapy subjects with infarcts in the proximal LAD category. A statistical comparison of actual infarct classification reveals no significant differences between the two groups (p=0.89).

Table 24 shows the index PCI procedural characteristics. This table displays the frequencies of PCI (100% of both groups), stent implantation, rescue PCI, untreated post-PCI dissection, post-stent dilatation, and [redacted]ab glycoprotein IIb/IIIa inhibitor usage. Pre-PCI and post-PCI TIMI flow grade and % stenosis are shown in the table, as well as the number and total length of deployed stents, and stent type.

As shown in the table, all patients in the study received mechanical reperfusion with PCI. Stenting was performed in 77/79 (97.5%) Control subjects and 220/222 (99.1%) AO Therapy subjects. A small percentage of subjects were rescue PCI patients, totaling 7/79 (8.9%) Control subjects and 11/222 (5.0%) AO Therapy subjects (p=0.27). A comparison in the total number of stents deployed per patient shows that the two groups were very similar; for subjects who were stented, 54/77 (70.1%) Control subjects and 147/220 (66.8%) AO Therapy subjects received one (1) stent. As seen in **Table 24**, the distributions of stent types were also very similar between the two groups, both with respect to bare metal stents (BMS) vs. drug-eluting stents (DES), and with respect to the breakdown of the use of sirolimus-eluting stents (Cypher) vs. paclitaxel-eluting stents (Taxus).

The rates of glycoprotein (GP) IIb/IIIa inhibitor use were comparable in both study groups (p=0.57). **Table 24** shows that in-cath lab use rates of GP IIb/IIIa were 51/79 (64.6%) and 151/222 (68.0%) in the Control and AO Therapy groups, respectively.

Investigator-assessed variables such as pre-PCI and post-PCI TIMI flow grade and diameter stenosis were evaluated in a standardized fashion by the angiographic core laboratory. That analysis must be viewed as the preferred method for quantitative comparison of the groups for several key angiographic variables. However, it is worth

166 of 505

noting that a statistical comparison of these variables as assessed by the investigators in **Table 24** reveals no statistical differences between the groups.

Index PCI access equipment data, the use of additional procedures and/or devices in the cath lab, and information regarding additional non-target treated lesions are presented in **Table 25**. As shown in the table, the femoral access sheath and guide catheter sizes exhibited a high degree of similarity between the two groups. The most common femoral access sheath size was 6 French (F) for both groups; taken together, 6F and 7F femoral sheaths were used in 63/79 (79.7%) Control subjects and 162/222 (73.0%) AO Therapy subjects. Consistent with these data, 6F and 7F guide catheters were the most commonly employed sizes and were used in the overwhelming majority of subjects in both study groups.

Table 25 displays the use of additional non-required [redacted]ab procedures/devices recorded for AMIHOT II subjects prior to randomization, including IABP use, temporary pacemaker placement, defibrillation/cardioversion, CPR, transfusions, filter wire use, distal protection devices, brachytherapy, and thrombectomy. As shown in the table, these additional procedures/devices were used sparingly or not at all with the exception of thrombectomy. These devices were employed in 17/79 (21.5%) Control subjects and 50/222 (22.5%) AO Therapy subjects (p=0.85).

The number of subjects who had additional lesions treated, as assessed by the [redacted]s shown in **Table 25**. No statistical differences were noted in the number or location of these additional lesions treated during the index PCI procedure.

Table 23. Index PCI[†]: Infarct Characteristics[‡]

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
Procedural LVEF[†] (%)			0.53
(mean ± SD) (n)	41.3 ± 9.1 (n=70)	40.2 ± 8.6 (n=196)	
(median ± IQR)	40 ± 10	40 ± 10	
(range)	20 – 71	25 – 65	
Left Main Diameter Stenosis (%)			0.77
(mean ± SD) (n)	1.7 ± 6.8 (n=79)	2.1 ± 7.7 (n=221)	
(median ± IQR)	0 ± 0	0 ± 0	
(range)	0 – 39	0 – 45	
Presence of Multivessel CAD (n/N; %)	37/79 (46.8%)	108/222 (48.7%)	0.78
Location of anterior infarct: (n/N; %)			0.64**
Proximal LAD	37/79 (46.8%)	106/222 (47.7%)	
Mid LAD	41/79 (51.9%)	109/222 (49.1%)	
Distal LAD	0/79 (0.0%)	5/222 (2.3%)	
First diagonal branch of LAD	1/79 (1.3%)	1/222 (0.5%)	
Second diagonal branch of LAD	0/79 (0.0%)	1/222 (0.5%)	
Other	0/79 (0.0%)	0/222 (0.0%)	
Infarct Classification fo[redacted]			0.26
Proximal	38/79 (48.1%)	123/222 (55.4%)	
Non-Proximal	41/79 (51.9%)	99/222 (44.6%)	
Actual Infarct Classification (n/N; %)			0.89
Proximal	37/79 (46.8%)	106/222 (47.7%)	
Non-Proximal	42/79 (53.2%)	116/222 (52.3%)	
Involvement of bifurcation w/ target lesion (n/N; %)	12/79 (15.2%)	45/222 (20.3%)	0.32
Reference vessel diameter (mm)			0.61
(mean ± SD) (n)	3.2 ± 0.4 (n=79)	3.2 ± 0.4 (n=220)	
(median ± IQR)	3.0 ± 0.5	3.0 ± 0.5	
(range)	2.5 – 4.3	2.0 – 4.5	
Maximum stenosis proximal to target lesion (%)			0.90
(mean ± SD) (n)	4.7 ± 13.4 (n=79)	4.1 ± 11.7 (n=222)	
(median ± IQR)	0 ± 0	0 ± 0	
(range)	0 – 75	0 – 70	

[†]PCI = Percutaneous coronary intervention; LVEF = left ventricle ejection fraction
[‡]Investigator assessments
*Mann-Whitney test for continuous data and Chi-Square test for frequencies unless otherwise noted.
**Exact Chi-Square test

Table 24. Index PCI: Procedural Characteristics[†]

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
PCI[‡] (any) (n/N: %)	79/79 (100.0%)	222/222 (100.0%)	
PCI with stenting performed (n/N; %)	77/79 (97.5%)	220/222 (99.1%)	0.28**
Rescue PCI[§] (n/N; %)	7/79 (8.9%)	11/222 (5.0%)	0.27**
Pre-PCI diameter stenosis (%)			0.26
(mean ± SD) (n)	98.7 ± 2.7 (n=79)	98.8 ± 3.1 (n=222)	
(median ± IQR)	100 ± 1	100 ± 1	
(range)	90 – 100	80 – 100	
Post-PCI diameter stenosis (%)			0.59
(mean ± SD) (n)	5.8 ± 10.3 (n=79)	4.6 ± 8.9 (n=222)	
(median ± IQR)	0 ± 5	0 ± 5	
(range)	0 – 30	0 – 25	
Initial TIMI flow grade (pre-PCI) (n/N; %)			0.53
0	51/79 (64.6%)	155/222 (69.8%)	
1	6/79 (7.6%)	19/222 (8.6%)	
2	22/79 (27.9%)	48/222 (21.6%)	
Final TIMI flow grade (post-PCI) (n/N; %)			0.40**
2	6/79 (7.6%)	11/222 (4.9%)	
3	73/79 (92.4%)	211/222 (95.1%)	
Number of stents placed[¥] (n/N; %)			0.93**
1	54/77 (70.1%)	147/220 (66.8%)	
2	18/77 (23.4%)	57/220 (25.9%)	
3	4/77 (5.2%)	14/220 (6.4%)	
4	1/77 (1.3%)	2/220 (0.9%)	
(mean ± SD) (n)	1.4 ± 0.6 (n=77)	1.4 ± 0.7 (n=220)	0.60
(median ± IQR)	1 ± 1	1 ± 1	
(range)	1 – 4	1 – 4	
Total length of deployed stents (mm)			0.45
(mean ± SD) (n)	26.9 ± 12.5 (n=77)	28.1 ± 14.0 (n=220)	
(median ± IQR)	23 ± 14	24 ± 15	
(range)	12 – 76	8 – 94	

[†]Investigator assessments
[‡]PCI = Percutaneous coronary intervention
[§]Prior thrombolytic therapy for this admission
[¥] Evaluated for patients with stents
*Mann-Whitney test for continuous data and Chi-Square test for frequencies unless otherwise noted.
**Exact Chi-Square or Fisher's test

Table 24 (Continued). Index PCI: Procedural Characteristics[†]

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
Stent Type (n/N; %)[¤]			0.55
Bare Metal Stent	37/77 (48.1%)	97/220 (44.1%)	0.55
Any Drug Eluting Stent (DES)	40/77 (52.0%)	123/220 (55.9%)	0.55
Cypher	15/77 (19.5%)	42/220 (19.1%)	
Taxus	22/77 (28.6%)	69/220 (31.4%)	
Any Other DES	3/77 (3.9%)	12/220 (5.5%)	
Untreated dissection present post-PCI (n/N; %)	0/79 (0.0%)	2/222 (0.9%)	1.00**
Post-stent dilatation performed (n/N; %)	27/79 (34.2%)	85/222 (38.3%)	0.52
Glycoprotein IIb/IIIa inhibitor (any) (n/N; %)[£]	51/79 (64.6%)	151/222 (68.0%)	0.57
ReoPro (abciximab)	35/79 (44.3%)	109/222 (49.1%)	
Aggrastat (tirofiban)	7/79 (8.9%)	15/222 (6.8%)	
Integrilin (eptifibatide)	9/79 (11.4%)	27/222 (12.2%)	
Other	0/79 (0.0%)	0/222 (0.0%)	

[†]Investigator assessments
[¤]N for stent type = number of patients receiving stent in group
[£]Note: one high enrolling center routinely administered IIb/IIIa inhibitors post-PCI in the CCU; this usage is not counted in the table data
*Mann-Whitney test for continuous data and Chi-Square test for frequencies unless otherwise noted.
**Exact-Chi Square or Fisher's test

Table 25. Index PCI Procedure: Access Equipment and Additional Procedures/Devices

	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)	p value*
Femoral Access Sheath Size:			0.44
6F	36/79 (45.6%)	95/222 (42.8%)	
7F	29/79 (36.7%)	67/222 (30.2%)	
8F	8/79 (10.1%)	26/222 (11.7%)	
9F	6/79 (7.6%)	33/222 (14.9%)	
Other	0/79 (0.0%)	1/222 (0.5%)	
Guide Catheter Size:			0.91**
6F	38/79 (48.1%)	110/222 (49.6%)	
7F	40/79 (50.6%)	108/222 (48.7%)	
8F	1/79 (1.3%)	2/222 (0.9%)	
Other	0/79 (0.0%)	2/222 (0.9%)	
Additional procedures or devices used (pre-randomization)†	19/79 (24.1%)	55/222 (24.8%)	0.90
IABP‡	0/79 (0.0%)	0/222 (0.0%)	
Temporary pacemaker	1/79 (1.3%)	2/222 (0.9%)	1.0**
Defibrillation/cardioversion	4/79 (5.1%)	5/222 (2.3%)	0.25**
CPR‡ ≤ 10 min	0/79 (0.0%)	1/222 (0.5%)	1.0**
Transfusions	0/79 (0.0%)	0/222 (0.0%)	
Filter Wire	0/79 (0.0%)	0/222 (0.0%)	
Distal Protection	0/79 (0.0%)	0/222 (0.0%)	
Brachytherapy	0/79 (0.0%)	0/222 (0.0%)	
Thrombectomy	17/79 (21.5%)	50/222 (22.5%)	0.85
Other	2/79 (2.5%)	3/222 (1.4%)	0.61**
Additional non-target lesions treated (during index PCI)§			
Number of additional lesions treated			0.54**
0	69/79 (87.3%)	201/222 (90.5%)	
1	10/79 (12.7%)	20/222 (9.0%)	
2	0/79 (0.0%)	1/222 (0.5%)	
Location of additional lesions treated			
Additional LAD/branch vessel lesion	7/79 (8.9%)	14/222 (6.3%)	1.0**
RCA distribution	1/79 (1.3%)	3/222 (1.4%)	1.0**
Circumflex distribution	2/79 (2.5%)	3/222 (1.4%)	1.0**
Ramus	0/79 (0.0%)	2/222 (0.9%)	1.0**

‡IABP = Intra-aortic balloon pump; CPR = Cardiopulmonary resuscitation
§As determined by angiographic core laboratory
*Chi-Square test unless otherwise specified
**Exact Chi-Square or Fisher's Exact test

1.8.7.5 Pre-PCI and Post-PCI Angiographic Core Lab Assessments

Pre-randomization pre-PCI and post-PCI angiographic data analyzed by the [redacted] are presented in **Tables 26 – 29**. **Tables 26** and **27** show data for pre-PCI and post-PCI quantitative assessments, and **Tables 28** and **29** display pre-PCI and post-PCI qualitative assessments.

Table 26 shows group data for pre-PCI reference vessel diameter, in-segment minimum lumen diameter, in-segment % diameter stenosis, TIMI flow grade, corrected TIMI frame count (CTFC), and blush score. As shown in the table, results for reference vessel diameter, in-segment minimum lumen diameter, and in-segment % diameter stenosis are very similar for the two groups.

As presented in **Table 26**, pre-PCI TIMI flow was nominally worse in the AO Therapy group. As shown, 51/73 (69.9%) Control subjects and 163/216 (75.5%) AO Therapy subjects exhibited TIMI 0/1 flow; a comparison of the overall TIMI flow distribution was not statistically significant (p=0.07). A comparison of blush score results showed nominally lower scores in the AO Therapy group; this observation is in qualitative agreement with TIMI flow measurements. More subjects in the AO Therapy group had blush score = 0/1 (170/197; 86.3%) than in the Control group (52/67; 77.6%). A statistical comparison of the blush score distributions showed that these nominal differences were not statistically significant (p=0.21). The quantitative CTFC results were not evaluable in a sufficient number of subjects to draw meaningful conclusions.

Table 27 displays group data for post-PCI reference vessel diameter, in-segment minimum lumen diameter, in-stent reference diameter, in-stent minimum lumen diameter, in-segment % diameter stenosis, in-stent % diameter stenosis, TIMI flow grade, corrected TIMI frame count (CTFC), and blush score.

The post-PCI results shown in **Table 27** are in good qualitative agreement with the pre-PCI results displayed in **Table 26**. As shown in **Table 27**, results for post-PCI reference vessel diameter, in-segment minimum lumen diameter, in-stent reference diameter, in-stent minimum lumen diameter, in-segment % diameter stenosis, and in-stent % diameter stenosis are very similar for the two groups.

As observed in the pre-PCI TIMI flow and blush score data, post-PCI results for these two categorical indicators of normal blood flow were nominally worse in the AO Therapy group, but not reaching the level of statistical significance. A higher percentage of Control subjects (66/71; 93.0%) had normal TIMI 3 flow post-PCI than AO Therapy subjects (190/215; 88.4%). However, a statistical comparison of the TIMI flow distributions showed no significant differences between the groups (p=0.23). Results for post-PCI blush score mirrored these findings. CTFC was evaluable in significantly more subjects post-PCI than pre-PCI, and was nominally lower in the Control group (40 ± 26) than in AO Therapy subjects (48 ± 22) (median ± IQR). While higher CTFC is indicative of qualitatively poorer coronary arterial flow, this nominal difference was not statistically significant (p=0.08).

Taken together, the pre-PCI and post-PCI [redacted] assessments shown in **Tables 26** and **27** demonstrate that the two study groups were well matched with respect to their PCI characteristics.

The pre-PCI and post-PCI qualitative [redacted] assessments are shown in **Tables 28** and **29**. Pre-PCI evaluations of target vessel eccentricity, tortuosity, calcification, ulceration, and signs of thrombus revealed no significant differences between the groups in these qualitative assessments. Similarly, post-PCI evaluations of thrombus, evidence of vessel dissection, staining, perforation, and distal embolization revealed no significant group differences or unexpected findings.

Table 26. Pre-PCI Procedure: Angiographic Core Lab Quantitative Assessments

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
Reference Vessel Diameter (mm)			0.44
(mean ± SD) (n)	2.78 ± 0.42 (n=78)	2.86 ± 0.48 (n=222)	
(median ± IQR)	2.78 ± 0.66	2.85 ± 0.56	
(range)	1.77 – 3.60	1.75 – 4.59	
In Segment Minimum Lumen Diameter (mm)			0.92
(mean ± SD) (n)	0.17 ± 0.30 (n=78)	0.17 ± 0.33 (n=222)	
(median ± IQR)	0.00 ± 0.24	0.00 ± 0.22	
(range)	0.00 – 1.25	0.00 – 1.80	
In Segment % Diameter Stenosis			0.89
(mean ± SD) (n)	93.91 ± 11.09 (n=78)	93.87 ± 11.31 (n=222)	
(median ± IQR)	100.00 ± 7.78	100.00 ± 7.15	
(range)	47.48 – 100.00	47.21 – 100.00	
TIMI flow grade (n/N; %)			0.07
0/1	51/73 (69.9%)	163/216 (75.5%)	
2	10/73 (13.7%)	37/216 (17.1%)	
3	12/73 (16.4%)	16/216 (7.4%)	
Corrected TIMI frame count			0.46
(mean ± SD) (n)	75.2 ± 31.4 (n=19)	79.6 ± 30.3 (n=39)	
(median ± IQR)	66 ± 27	76 ± 40	
(range)	36 – 164	30 – 158	
Blush Score† (n/N; %)			0.21
0/1	52/67 (77.6%)	170/197 (86.3%)	
2	10/67 (14.9%)	16/197 (8.1%)	
3	5/67 (7.5%)	11/197 (5.6%)	

†Blush score key: 0 = None; 1 = Mild; 2 = Moderate; 3 = Normal
*Mann-Whitney test for continuous data and Chi-Square test for frequencies unless otherwise noted.

Table 27. Post-PCI Procedure: Angiographic Core Lab Quantitative Assessments

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
Reference Vessel Diameter (mm)			0.17
(mean ± SD) (n)	2.79 ± 0.43 (n=78)	2.89 ± 0.48 (n=221)	
(median ± IQR)	2.78 ± 0.68	2.89 ± 0.59	
(range)	1.85 – 3.75	1.76 – 4.48	
In Segment Minimum Lumen Diameter (mm)			0.45
(mean ± SD) (n)	2.28 ± 0.45 (n=78)	2.33 ± 0.47 (n=221)	
(median ± IQR)	2.27 ± 0.66	2.31 ± 0.61	
(range)	1.33 – 3.41	1.09 – 4.10	
In Stent Reference Diameter (mm)			0.71
(mean ± SD) (n)	2.85 ± 0.43 (n=78)	2.88 ± 0.50 (n=218‡)	
(median ± IQR)	2.79 ± 0.63	2.87 ± 0.65	
(range)	1.95 – 4.01	1.58 – 4.23	
In Stent Minimum Lumen Diameter (mm)			0.65
(mean ± SD) (n)	2.65 ± 0.41 (n=78)	2.69 ± 0.48 (n=219)	
(median ± IQR)	2.62 ± 0.61	2.67 ± 0.70	
(range)	1.84 – 3.59	1.49 – 4.26	
In Segment % Diameter Stenosis			0.14
(mean ± SD) (n)	18.37 ± 10.66 (n=78)	19.55 ± 8.42 (n=221)	
(median ± IQR)	17.04 ± 15.20	19.50 ± 11.97	
(range)	0.23 – 52.58	0.69 – 42.73	
In Stent % Diameter Stenosis			0.72
(mean ± SD) (n)	6.64 ± 5.92 (n=78)	6.55 ± 8.08 (n=219)	
(median ± IQR)	5.04 ± 7.20	5.70 ± 7.03	
(range)	-8.33 – 27.56	-6.63 – 89.12	

*Mann-Whitney test for continuous data and Chi-Square test for frequencies unless otherwise noted.
‡A single out of range value of 18.1 was excluded from analysis

Table 27 (continued). Post-PCI Procedure: [redacted] Quantitative Assessments

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
TIMI flow grade (n/N; %)			0.23**
0/1	2/71 (2.8%)	3/215 (1.4%)	
2	3/71 (4.2%)	22/215 (10.2%)	
3	66/71 (93.0%)	190/215 (88.4%)	
Corrected TIMI frame count			0.08
(mean ± SD) (n)	44.4 ± 19.1 (n=59)	49.2 ± 20.2 (n=162)	
(median ± IQR)	40 ± 26	48 ± 22	
(range)	18 – 108	20 – 154	
Blush Score† (n/N; %)			0.11
0 /1	2/55 (3.6%)	20/149 (13.4%)	
2	11/55 (20.0%)	22/149 (14.8%)	
3	42/55 (76.4%)	107/149 (71.8%)	

†Blush score key: 0 = None; 1 = Mild; 2 = Moderate; 3 = Normal
*Mann-Whitney test for continuous data and Chi-Square test for frequencies unless otherwise noted.
**Exact Chi-Square or Fisher's Exact test

Table 28. Pre-PCI Procedure: [redacted]litative Assessments

	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)	p value*
Eccentricity	9/78 (11.5%)	20/222 (9.0%)	0.52
Tortuosity†			1.0**
0	78/78 (100.0%)	220/221 (99.5%)	
1	0/78 (0.0%)	1/221 (0.5%)	
2	0/78 (0.0%)	0/221 (0.0%)	
Calcification†			0.11
0	44/72 (61.1%)	127/216 (58.8%)	
1	27/72 (37.5%)	71/216 (32.9%)	
2	1/72 (1.4%)	18/216 (8.3%)	
Ulceration	2/77 (2.6%)	4/221 (1.8%)	0.65**
Thrombus	46/73 (63.0%)	157/218 (72.0%)	0.15

†For both tortuosity and calcification categorical classification keys: 0 = None; 1 = Moderate; 2 = Severe
*Chi-Square test unless otherwise indicated.
**Fisher's Exact test

Table 29. Post-PCI Procedure: [redacted] Qualitative Assessments

	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)	p value*
Thrombus	0/75 (0.0%)	2/219 (0.9%)	1.0
Dissection†			0.44
0	71/72 (98.6%)	215/216 (99.5%)	0.03
A			
B			
C	1/72 (1.4%)	1/216 (0.5%)	0.46
D			
E			
F			
Staining	0/68 (0.0%)	0/205 (0.0%)	
Perforation	0/71 (0.0%)	0/213 (0.0%)	
Distal Embolization			0.68
Main Branch	1/78 (1.3%)	6/218 (2.8%)	
Side Branch	0/78 (0.0%)	0/218 (0.0%)	

†Dissection classification key: 0 = None; A = Minor radiolucencies within the coronary lumen with contrast injection with no persistence after dye clearing; B = Double lumen separated by radiolucent area during contrast injection with minimal or no persistence after dye clearing; C = Extraluminal cap with persistence of contrast after dye clearance from the coronary lumen; D = Spiral luminal filling defects; E = Any dissection A to D with reduced flow; F = Any dissection A to D with vessel closure and TIMI 0 flow
*Fisher's Exact test

1.8.7.6 Baseline Laboratory Information

Tables 30 and **31** display pre-randomization baseline laboratory values for the AMIHOT II study. Baseline hematology, clinical chemistry, and hemodynamic data are presented in **Table 30**. Liver panel data are presented in **Table 31**. **Table 32** contains reference laboratory normal values for parameters presented in the tables. In the following discussion, data are presented as (median ± IQR) unless otherwise noted.

Table 30 displays hematology data for white blood cell (WBC) concentration, hemoglobin (hgb), hematocrit (hct), and platelets. As observed in the table, these parameters are comparable between the two groups. WBC concentrations are elevated in both groups vs. normal levels, as expected in AMI patients. WBC counts are elevated in

AMI patients following a normal clinical course. The nominal increase in WBC in AO Therapy subjects (11.1 ± 45) as compared with Control patients (10.3 ± 3.5) was not found to be statistically significant (p=0.11). Hemoglobin, hematocrit, and platelet levels were all found to be within normal range in both groups, with comparable baseline values. As shown in the table, creatinine levels were also found to be comparable between the two groups.

The hemodynamic information presented in **Table 30** also shows that the two study groups were well-matched in terms of blood pressure, heart rate, and heart rhythm baseline measurements. No significant differences in these parameters were observed between the two groups.

Baseline liver panel data are displayed in **Table 31**. Data for the randomized groups exhibit a lack of dissimilarity for the measured parameters. Slight trends in increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are observed in the Control group as compared to AO Therapy subjects, but these differences are neither statistically nor clinically significant. AST levels are higher for both the Control and AO Therapy groups as compared to laboratory normal ranges in **Table 32**; this enzyme is expected to be elevated in a patient population presenting with acute MI.

Table 30. Baseline Laboratory Data: Hematology and Clinical Chemistry, Hemodynamic Information

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
WBC† (K/μl)			0.11
(mean ± SD) (n)	10.6 ± 3.2 (n=79)	11.3 ± 3.5 (n=216)	
(median ± IQR)	10.3 ± 3.5	11.1 ± 4.5	
(range)	3.0 – 21.2	4.2 – 23.7	
Hemoglobin (g/dL)			0.27
(mean ± SD) (n)	14.6 ± 1.5 (n=79)	14.4 ± 1.6 (n=218)	
(median ± IQR)	14.7 ± 1.8	14.3 ± 2.1	
(range)	9.9 – 18.1	9.6 – 18.5	
Hematocrit (%)			0.52
(mean ± SD) (n)	42.5 ± 3.8 (n=76)	42.2 ± 4.5 (n=211)	
(median ± IQR)	43.0 ± 4.1	42.4 ± 6.6	
(range)	31.8 – 51.6	27.7 – 52.6	
Platelets (K/μl)			0.49
(mean ± SD) (n)	240.2 ± 67.4 (n=78)	248.3 ± 71.6 (n=216)	
(median ± IQR)	229.5 ± 71	240 ± 85.5	
(range)	85 – 443	116 – 513	
Creatinine (mg/dL)			0.13
(mean ± SD) (n)	1.0 ± 0.2 (n=78)	1.0 ± 0.3 (n=219)	
(median ± IQR)	1.0 ± 0.3	1.0 ± 0.3	
(range)	0.6 – 1.7	0.5 – 2.6	

†WBC = White blood cells
*Mann-Whitney test for continuous data and Chi-Square test for frequencies unless otherwise noted.
**Exact Chi-Square test

Table 30 (continued). Baseline Laboratory Data: Hematology and Clinical Chemistry, Hemodynamic Information

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
Systolic BP (mmHg)			0.74
(mean ± SD) (n)	129.8 ± 22.6 (n=77)	129.9 ± 20.6 (n=212)	
(median ± IQR)	130 ± 26	130 ± 23	
(range)	94 – 211	85 – 234	
Diastolic BP (mmHg)			0.57
(mean ± SD) (n)	81.2 ± 12.1 (n=77)	80.1 ± 13.9 (n=212)	
(median ± IQR)	80 ± 12	80 ± 18	
(range)	57 – 125	42 – 130	
Heart Rate (bpm)			0.95
(mean ± SD) (n)	77.5 ± 14.9 (n=76)	77.6 ± 15.5 (n=210)	
(median ± IQR)	78 ± 19.5	78 ± 18	
(range)	53 – 140	35 – 147	
Heart Rhythm (n/N; %)			0.81**
Sinus Rhythm	71/79 (89.9%)	195/219 (89.0%)	0.63
Sinus Bradycardia	5/79 (6.3%)	11/219 (5.0%)	0.77**
Sinus Tachycardia	2/79 (2.5%)	7/219 (3.2%)	1.0**
Atrial Fibrillation	1/79 (1.3%)	2/219 (0.9%)	1.0**
Other	0/79 (0.0%)	4/219 (1.8%)	0.58**

*Mann-Whitney test for continuous data and Chi-Square test for frequencies unless otherwise noted.
**Exact Chi-Square test

Table 31. Baseline Laboratory Data: Liver Panel

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
Total Bilirubin (mg/dL)			0.35
(mean ± SD) (n)	0.6 ± 0.3 (n=73)	0.6 ± 0.3 (n=205)	
(median ± IQR)	0.5 ± 0.4	0.5 ± 0.4	
(range)	0.1 – 1.5	0.1 – 2.2	
Direct Bilirubin (mg/dL)			0.31
(mean ± SD) (n)	0.13 ± 0.11 (n=70)	0.12 ± 0.11 (n=200)	
(median ± IQR)	0.10 ± 0.14	0.10 ± 0.12	
(range)	0.00 – 0.60	0.00 – 0.78	
Albumin (g/dL)			0.43
(mean ± SD) (n)	3.8 ± 0.5 (n=67)	3.8 ± 0.5 (n=179)	
(median ± IQR)	3.9 ± 0.7	3.8 ± 0.6	
(range)	1.8 – 4.9	1.7 – 5.9	
Alkaline Phosphatase (U/L)			0.74
(mean ± SD) (n)	84.2 ± 34.1 (n=73)	86.8 ± 43.2 (n=202)	
(median ± IQR)	75 ± 29	74 ± 33	
(range)	31 – 219	23 – 306	
AST† (SGOT) (U/L)			0.37
(mean ± SD) (n)	82.3 ± 111.6 (n=73)	67.8 ± 92.0 (n=208)	
(median ± IQR)	32 ± 59	33 ± 45	
(range)	9 – 555	8 – 660	
ALT† (SGPT) (U/L)			0.11
(mean ± SD) (n)	35.4 ± 19.4 (n=73)	32.8 ± 21.5 (n=207)	
(median ± IQR)	29 ± 21	28 ± 25	
(range)	10 – 111	6 – 141	
GGTP† (U/L)			0.80
(mean ± SD) (n)	44.2 ± 55.1 (n=69)	38.7 ± 31.9 (n=184)	
(median ± IQR)	28 ± 26	27.5 ± 28.5	
(range)	9 – 425	7 – 218	
LDH† (U/L)			0.86
(mean ± SD) (n)	262.2 ± 163.5 (n=65)	268.7 ± 219.7 (n=181)	
(median ± IQR)	197 ± 136	204 ± 132	
(range)	109 – 1021	48 – 2442	

†AST = Aspartate aminotransferase; ALT = alanine aminotransferase; GGTP = Gamma Glutamyl Transferase; LDH = lactate dehydrogenase
*Mann-Whitney test

Table 32. Normal Ranges: Laboratory Data[102]

Panel	Parameter		Normal Range
Hematology	WBC		3.8-10.8 k/μL
	HGB	Male	13.8-17.2 g/dL
		Female	12.0-15.6 g/dL
	HCT	Male	41-50%
		Female	35-46%
	Platelets		130-400 k/μL
Renal Function	Creatinine		0.4-1.5 mg/dL
Liver Panel	Total Bilirubin		0.0-1.3 mg/dL
	Direct Bilirubin		0.0-0.4 mg/dL
	Albumin		3.5-5.0 gm/dL
	Alkaline Phosphatase		20-125 U/L
	AST (SGOT)		≤ 42 U/L
	ALT (SGPT)		≤ 48 U/L
	GGPT (GPT)		12-55 U/L
	LDH		≤ 270 U/L

1.8.7.7 Summary of Baseline Information and Laboratory Data

Tables 20 – 31 comprise the routine baseline data collected during the AMIHOT II trial, including patient demographics and medical history information, PCI specifics, angiographic evaluations, and hematology, clinical chemistry, and liver panel data. Collectively, these data demonstrate a lack of dissimilarity between the Control and AO Therapy groups. However, stratification errors during randomization did contribute to an imbalance between the study groups with more Control subjects in the 0-3 hr time to reperfusion group, as discussed in **Section 1.8.7.3**. The anticipated effect of this imbalance would be conservative with respect to establishing superiority with AO Therapy, because shorter time to reperfusion is associated with improved clinical outcomes. Aside from this issue, the homogeneity in the baseline results provides a basis for group comparisons in post-procedural laboratory results, surrogate endpoint data, and safety outcomes.

1.8.8 AO Therapy Intra-Procedural Data

AO Therapy intra-procedural data are presented in **Section 1.8.8**. Data and discussion are presented for AO Therapy arterial access information, device usage parameters, including intra-procedural time intervals, hemodynamic and laboratory data during AO Therapy administration, and device failures.

1.8.8.1 AO Therapy Arterial Access Data

The AO Therapy procedure requires the placement of an infusion catheter within the target coronary artery to perform the hyperoxemic infusion. The outer diameter (OD) of the infusion catheter dictates the size of the guide catheter (and therefore the size of the arterial access sheath) used for the procedure.

During the AMIHOT II study, two catheters were used to perform the AO infusion. The [redacted] infusion catheter was the only qualified infusion catheter for AO Therapy at the beginning of the study. When enrollment was approximately two-thirds completed, an alternative to the [redacted] was introduced, the [redacted] infusion catheter. The [redacted] catheter has a slightly smaller OD than the [redacted], enabling the use of a smaller 6F guide catheter as compared to the 7F guide necessary for the [redacted]

Physicians had two arterial access options for blood withdrawal into the extracorporeal circuit. The protocol-recommended option was coaxial access, where blood was withdrawn through the annular space between the guide catheter and arterial sheath, exiting the sheath sidearm. To enable the pumping of blood through this annular space, a 2F size differential was required between the sheath and guide catheter. Therefore, the coaxial configuration dictated a 6F/8F guide/sheath combination for the [redacted] catheter, in contrast to a 7F/9F combination for the [redacted]. If the required sheath size was larger than the sheaths used for index PCI arterial access, patients randomized to AO Therapy needed to have the index PCI sheath up-sized to an 8F or 9F sheath, depending

on which infusion catheter was used for AO infusion. As a consequence, for physicians who preferred not to up-size the existing index PCI sheath, the alternative blood withdrawal configuration was to use a second 5F or 6F arterial sheath in the contralateral femoral artery (or another major artery if this was warranted).

Tables 33 and **34** display the arterial access data obtained for the AMIHOT II study. As shown in **Table 33**, 160/222 (72.1%) AO Therapy subjects had the protocol-recommended coaxial blood draw configuration, as compared to the remaining 62/222 (27.9%) who had the contralateral configuration. Nearly half of AMIHOT II subjects required the use of a different guide catheter than the index PCI procedure, indicative of the need to up-size the access equipment. A total of 118/222 (53.2%) AO Therapy subjects had a 9F access sheath; this choice is indicative of the preferred coaxial draw configuration and the exclusive use of the [redacted] catheter until later in the trial. As shown in **Table 33**, the [redacted] catheter was used in 147/222 (66.2%) AO Therapy subjects compared to 75/222 (33.8%) patients who received the infusion with the [redacted] catheter.

Table 34 shows a comparison of arterial access variables for patients infused with the [redacted] vs. the [redacted] catheters. One striking difference is that only 88/147 (59.9%) of [redacted] patients had coaxial draw access employed, compared with 72/75 (96.0%) of [redacted] subjects. This difference is certainly due to the option of the 8F sheath size with this arrangement. The desire of practitioners to avoid the 9F sheath led to 59/147 (40.1%) [redacted] subjects to have the contralateral configuration, compared to only 3/72 (4.2%) [redacted] patients.

The significance of these data become more clear in the discussion of access site bleeding events in later sections of this report.

Table 33. AO Therapy Procedure: Arterial Access Data

	AO Therapy Group (n=222) (n/N; %)
Guide Catheter Introducer Sheath	
Access Site:	
LFA	3/222 (1.4%)
RFA	219/222 (98.7%)
Sheath Size:	
7F	55/222 (24.8%)
8F	48/222 (21.6%)
9F	118/222 (53.2%)
10F	1/222 (0.5%)
Draw Sheath Approach:	
Coaxial	160/222 (72.1%)
Contralateral femoral artery	62/222 (27.9%)
Sheath Size:	
5F	30/222 (13.5%)
6F	32/222 (14.4%)
Guide Catheter Used for AO Therapy	
Same as Index PCI procedure	116/222 (52.3%)
Other	106/222 (47.8 %)
Hemostasis Valve:	
Touhy Borst	84/221 (38.0%)
Sure Seal	137/221 (62.0%)
Infusion Catheter	
[redacted]	147/222 (66.2%)
[redacted]	75/222 (33.8%)
Number of infusion catheters used:	
1	213/222 (96.0%)
2	8/222 (3.6%)
3	1/222 (0.5%)

Table 34. Sheath Size Usage in AO Therapy Procedures by Infusion Catheter Type

	Infusion Catheter Type	
	[redacted] Catheter (n=147)	[redacted] Catheter (n=75)
Coaxial	88/147 (59.9%)	72/75 (96.0%)
AO Therapy Access/Draw Sheath		
8F	0/88 (0.0%)	42/72 (58.3%)
9F	87/88 (98.9%)	30/72 (41.7%)
10F	1/88 (1.1%)	0/72 (0.0%)
Contralateral	59/147 (40.1%)	3/75 (4.0%)
AO Therapy Access Sheath		
7F	52/59 (88.1%)	3/3 (100.0%)
8F	6/59 (10.2%)	0/3 (0.0%)
9F	1/59 (1.7%)	0/3 (0.0%)
Draw Sheath		
5F	30/59 (50.8%)	0/3 (0.0%)
6F	29/59 (49.2%)	3/3 (100.0%)

1.8.8.2 AO Cartridge Usage and AO Infusion Time

Table 35 shows detailed AO Therapy procedural data and AO Cartridge device usage information. Time interval data are displayed for the time from reperfusion (opening of the vessel via PCI) to the initiation of AO Therapy, the duration of time elapsed from the start to finish of AO Therapy, and the time from symptom onset to initiation of AO Therapy, the time from symptom onset to completion of AO Therapy. The convention of using (median ± IQR) to describe the continuous data are followed herein.

Table 35. AO Therapy Procedure: Device Usage Information

	AO Therapy Group (n=222)
Time Intervals	
Reperfusion to initiation of AO Therapy (min)	
(mean ± SD) (n)	57 ± 28.9 (n=214)
(median ± IQR)	52 ± 28
(range)	18 – 240
Start to Finish of AO Therapy (min)	
(mean ± SD) (n)	86.5 ± 27.6 (n=222)
(median ± IQR)	90 ± 6
(range)	0 – 167
Symptom Onset to initiation of AO Therapy (min)	
(mean ± SD) (n)	266 ± 77.5 (n=214)
(median ± IQR)	250 ± 106
(range)	101 – 540
Symptom onset to completion of AO Therapy (min)	
(mean ± SD) (n)	355.6 ± 79.8 (n=214)
(median ± IQR)	343.5 ± 121
(range)	191 – 630
AO Infusion Time (min)	
(mean ± SD)	81.2 ± 25.5 (n=222)
(median ± IQR)	90 ± 0
(range)	0 – 114
0-59 min infusion time (n/N; %)	25/222 (11.3%)
60-89 min infusion time (n/N; %)	9/222 (4.1%)
90 min infusion time (n/N; %)	165/222 (74.3%)
>90 min infusion time (n/N; %)	23/222 (10.4%)
[redacted]	
[redacted]	1/222 (0.5%)
[redacted]	150/222 (67.6%)
[redacted]	48/222 (21.6%)
[redacted]	20/222 (9.0%)
[redacted]	3/222 (1.4%)
[redacted]	1.4 ± 0.7
[redacted]	1 ± 1
[redacted]	0 – 4

Table 35 (continued). AO Therapy Procedure: Device Usage Information

	AO Therapy Group (n=222)
[redacted]	
[redacted]	152/216 (70.4%)
[redacted]	5/216 (2.3%)
[redacted]	53/216 (24.5%)
[redacted]	6/216 (2.8%)
[redacted]	
[redacted]	318
[redacted]	181/318 (56.9%)
[redacted]	137/318 (43.1%)
[redacted]	
[redacted]	42/137 (30.7%)
[redacted]	39/137 (28.5%)
[redacted]	11/137 (8.0%)
[redacted]	19/137 (13.9%)
[redacted]	3/137 (2.2%)
[redacted]	23/137 (16.8%)
[redacted]	

As seen in **Table 35**, the time delay from reperfusion of the target vessel to initiation of AO Therapy was 52 ± 28 minutes (median ± IQR). The shortest delay was only 18 minutes, while in one case this delay was 240 minutes. The probable causes of this variability in the time interval between reperfusion and AO Therapy initiation were additional cath lab procedural issues, the requirements for protocol-specific angiographic measurements, and delays in AO System set up and readiness for infusion. The time interval from symptom onset to AO Therapy initiation was 250 ± 106 minutes, and the time interval from symptom onset to AO Therapy completion was 343.5 ± 121 minutes. Therefore, a majority of AO Therapy subjects had been administered the experimental procedure within the critical 6-hour window post-symptom onset.

Table 35 also displays AO infusion time data. The protocol-prescribed infusion time was 90 minutes. The AO System is programmed to deliver this time duration of infusion with a single AO Cartridge. However, during the AMIHOT II study, a total of 34/222 (15.3%) AO Therapy patients received less than 90 minutes infusion time. 25/222 AO Therapy patients (11.3%) received less than 60 minutes of infusion time.

An argument can be made based upon pre-clinical study data (see **Section 1.5.1**) that 60 minutes or more AO Therapy infusion time is efficacious. Accepting this argument, that leaves 11.3% of AO Therapy subjects who did not receive an effective dose of therapy. This is a significant handicap in trying to prove effectiveness in an adjunctive therapy. Therefore, this issue is an important discussion point with regard to a novel therapy that admittedly has an operator learning curve.

[redacted]

[redacted]

1.8.8.5 AO Therapy Delivery Location

Table 35 also provides information for AO delivery location. All AMIHOT II AO Therapy cases were initiated in the cath lab per the Instructions for Use. However, because the AO System is designed for limited mobile operation, in some cases patients were transferred from the cath lab to the CCU or cath lab holding area after the extracorporeal blood flow was initiated. Investigational sites were trained for AO System mobile operation in the event that patients needed to be moved from the cath lab due to resource constraints. In all, 152/216 (70.4%) AO Therapy subjects had the infusion completed within the cath lab, while 58/216 (26.9%) were transferred to either the CCU or cath lab holding area to complete the infusion.

1.8.8.6 AO Therapy Intra-Procedural Laboratory Assessments

Table 36 displays hemodynamic and laboratory data obtained at 30-min intervals during AO Therapy administration, including blood pressure measurement, heart rate and rhythm, arterial blood gas (ABG) information, and activated clotting time (ACT). Data are displayed at 4 time points: t = 0 (pre-infusion), 30 min, 60 min, and 90 min. ABG data were necessary because the patient's systemic arterial pO_2 level is a user-supplied input to the AO System.

The results displayed in **Table 36** demonstrate that patient vital signs were remarkably stable from the pre-infusion time point through the completion of AO Therapy administration. ABG values were steady as well; the focal hyperoxemic intracoronary infusion provided by AO Therapy does not change systemic blood gas values.

Table 36. Hemodynamic and Laboratory Data During AO Therapy†

	Post-Stent (pre-infusion)	30 min	60 min	90 min
Systolic BP (mmHg)				
(mean ± SD) (n)	124.9 ± 17.4 (n=221)	125.2 ± 17.3 (n=201)	128.0 ± 19.8 (n=196)	126.4 ± 17.6 (n=192)
(median ± IQR)	125 ± 23	124 ± 23	125 ± 25	123 ± 20
(range)	76 – 180	76 – 175	70 – 186	90 – 182
Diastolic BP (mmHg)				
(mean ± SD) (n)	78.5 ± 12.9 (n=221)	80.7 ± 13.7 (n=201)	82.1 ± 13.8 (n=196)	80.4 ± 13.9 (n=192)
(median ± IQR)	80 ± 15	80 ± 17	80 ± 18.5	80 ± 19
(range)	41 – 120	38 – 119	50 – 124	41 – 119
Heart Rate (bpm)				
(mean ± SD) (n)	76.5 ± 15.7 (n=221)	72.9 ± 12.9 (n=201)	72.5 ± 12.5 (n=196)	72.6 ± 11.8 (n=192)
(median ± IQR)	75 ± 17	72 ± 15	71 ± 15	71 ± 14
(range)	34 – 187	46 – 110	40 – 124	41 – 109
ABG data				
PH				
(mean ± SD) (n)	7.38 ± 0.06 (n=221)	7.38 ± 0.06 (n=200)	7.37 ± 0.05 (n=196)	7.38 ± 0.05 (n=188)
(median ± IQR)	7.38 ± 0.07	7.38 ± 0.07	7.38 ± 0.06	7.38 ± 0.05
(range)	7.20 – 7.62	7.25 – 7.64	7.21 – 7.63	7.22 – 7.61
HCO_3 (mmol/L)				
(mean ± SD) (n)	22.9 ± 2.5 (n=221)	22.9 ± 2.4 (n=199)	22.9 ± 2.4 (n=194)	22.7 ± 2.4 (n=188)
(median ± IQR)	22.9 ± 2.8	23.0 ± 2.8	23.0 ± 2.5	22.9 ± 2.9
(range)	14.5 – 29.5	14.4 – 30.2	15.1 – 31.8	15.1 – 29.3
pCO_2 (mmHg)				
(mean ± SD) (n)	39.2 ± 7.5 (n=221)	39.2 ± 7.4 (n=200)	39.4 ± 7.1 (n=195)	38.9 ± 6.9 (n=188)
(median ± IQR)	39.0 ± 9.0	38.5 ± 7.6	39.0 ± 7.0	38.9 ± 7.7
(range)	18.0 – 65.1	17.3 – 66.4	18.0 – 73.0	20.3 – 68.3
Systemic arterial pO_2 (mmHg)				
(mean ± SD) (n)	140.5 ± 72.4 (n=221)	140.7 ± 61.1 (n=200)	144.0 ± 57.8 (n=196)	139.9 ± 51.3 (n=187)
(median ± IQR)	114.7 ± 74.7	125.1 ± 64.6	133.3 ± 69.2	127.5 ± 62.0
(range)	34.5 – 460.0	53.0 – 452.0	51.0 – 403.0	63.0 – 378.0
O_2 saturation (%)				
(mean ± SD) (n)	97.7 ± 3.8 (n=220)	98.2 ± 2.2 (n=195)	98.2 ± 3.7 (n=194)	98.5 ± 1.6 (n=186)
(median ± IQR)	98.9 ± 2.5	99.0 ± 1.6	99.0 ± 1.7	99.0 ± 1.6
(range)	62.0 – 100.0	85.0 – 100.0	62.0 – 100.0	91.0 – 100.0

†If multiple assessments were made at a given time point, the last assessment was used for data analysis. If pre-infusion data were missing, screening data were used to replace the missing values (if available).

1.8.8.7 Summary of AO Therapy Procedural Data

AO Therapy is a first-of-a-kind adjunctive procedure administered in the [redacted]. As expected with a novel therapy, trained operators typically experience a learning curve in using the AO System. Because the AO System is designed with conservative safety mechanisms, this learning curve may involve the use of additional AO Cartridges before the AO Therapy set-up and operational techniques are mastered. The data presented above demonstrate that in spite of these operational challenges, the vast majority of AO Therapy subjects did receive the prescribed 90-minute infusion.

Early in the study, AMIHOT II investigators used only the [redacted] infusion catheter for AO delivery. As discussed above, physicians were evenly split on whether they preferred to up-size a single arterial access sheath to 9F or place a second sheath in the contralateral femoral artery for blood withdrawal. The IDE-approved protocol change initiated during the study to give investigators the option of the [redacted] catheter led to a more uniform selection of the coaxial draw configuration, using a single 8F sheath. Because the [redacted] catheter is no longer available commercially, the device labeling submitted in this PMA specifies the exclusive use of the TherOx-supplied infusion catheter.

AO Therapy intra-procedural data show that patients were stable and that the infusion was well-tolerated.

1.8.9 Post-Procedure In-Hospital Evaluations

Post-procedure in-hospital evaluations are discussed in **Section 1.8.9**. These evaluations include 24-hour laboratory values for hematology, clinical chemistry, and liver panel. In addition, baseline – 24 hr cardiac enzyme data are presented herein.

1.8.9.1 24-Hr Hematology and Clinical Chemistry

Tables 37 and **38** display 24-hr hematology and clinical chemistry data for both the AO Therapy and Control groups. As shown in **Table 37**, both hemoglobin (hgb) and hematocrit (hct) were significantly lower in AO Therapy subjects 24 hours post-procedure (p=0.0005 for both comparisons). At 24 hours, hgb levels (g/dL) were 13.6 ± 2.0 in Controls as compared to 12.9 ± 1.8 in AO Therapy subjects (data shown as median ± IQR). Similarly, 24-hr hct levels (%) were 40.1 ± 5.7 in Controls as compared to 38.5 ± 5.9 in AO Therapy subjects. Other hematology parameters were similar between the two groups, and while creatinine levels showed a significant difference (p=0.04), median values were identical and this change is not clinically meaningful.

The difference in hematocrit and hemoglobin levels can be explained partially by referring to data cited earlier within this report. Because hemoglobin and hematocrit levels are both representations of red blood cell concentration, this discussion focuses on hematocrit changes for ease of illustration. **Table 38** shows baseline and 24-hour hematocrit values for both study groups. As seen in the table, both the AO Therapy and Control groups experienced a significant drop in hematocrit from baseline – 24 hrs. This drop is due to both dilution caused by administration of IV saline, and blood loss. To calculate the additional incremental hematocrit decrease (hct_{AO}), we used the following formula:

hct_{AO} (%) = [hct (baseline AO) – hct (24-hr AO)] – [hct (baseline Control) – hct (24-hr Control)]

Thus, using the median hematocrit data from **Table 38**:

hct_{AO} = [42.4 – 38.5] – [43.0 – 40.1] = 1.0%

Using median values, hct_{AO} = 1.0%. Drawing upon the discussion presented in **Section 1.8.8.2**, it was noted that used AO Cartridges are discarded without attempting to return the blood to the patient. Because human blood volume is approximately 7.0% of body

mass[103], and AMIHOT II patients were ~ 82 kg (see **Table 20**), AMIHOT II patients had on average approximately 5.7 L blood volume. AO Cartridges have a priming volume of approximately 60 ml; therefore, every discarded AO Cartridge resulted in a blood loss of 60/5700 ~ 1.1% total blood volume, or equivalently, 0.011 x 42.4% = 0.47% of hematocrit loss. From **Table 35**, 318 AO Cartridges were used for 222 AO Therapy subjects, or an average of 318/222 = 1.43 cartridges per case. The mean expected blood loss (%) is thus 1.43 x 0.47 = 0.67%, thus accounting for approximately 2/3 of hct_{AO} (1.0%). Using this estimate, it is reasonable to conclude that much of the incremental hematocrit drop observed in AMIHOT II AO Therapy subjects was due to routine AO Cartridge use; the rest may be accounted for through additional fluid loading from the infusion, and bleeding.

From the standpoint of patient safety, an incremental drop of 1-2% of hematocrit generally does not cause concern, unless this decrease caused a patient with an already-low hematocrit to fall below the desired normal range.

Table 37. 24-Hr Laboratory Data: Hematology and Clinical Chemistry

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
WBC† (K/μl)			0.23
(mean ± SD) (n)	10.9 ± 3.1 (n=77)	11.3 ± 3.1 (n=211)	
(median ± IQR)	10.0 ± 3.8	10.9 ± 3.4	
(range)	4.9 – 18.5	4.9 – 24.7	
Hemoglobin (g/dL)			0.0005
(mean ± SD) (n)	13.6 ± 1.5 (n=77)	12.9 ± 1.5 (n=211)	
(median ± IQR)	13.6 ± 2.0	12.9 ± 1.8	
(range)	8.9 – 17.2	9.5 – 16.8	
Hematocrit (%)			0.0005
(mean ± SD) (n)	40.1 ± 4.1 (n=76)	38.1 ± 4.2 (n=208)	
(median ± IQR)	40.1 ± 5.7	38.5 ± 5.9	
(range)	25.8 – 49.0	27.6 – 48.8	
Platelets (K/μl)			0.50
(mean ± SD) (n)	222.1 ± 65.8 (n=75)	227.0 ± 65.8 (n=206‡)	
(median ± IQR)	215 ± 72	219.5 ± 82	
(range)	111 – 487	87 – 494	
Creatinine (mg/dL)			0.04
(mean ± SD) (n)	1.0 ± 0.3 (n=74)	1.1 ± 0.3 (n=209)	
(median ± IQR)	1.0 ± 0.2	1.0 ± 0.3	
(range)	0.6 – 2.2	0.5 – 2.3	

†WBC = White blood cells
‡A single out of range value of 8 was excluded from analysis of AO Therapy platelet data
*Mann-Whitney test

Table 38. Baseline – 24-Hr Hematocrit Data

	Baseline	24 Hr	p value*
Control Subjects			
Hematocrit (%)			<0.0001
(mean ± SD) (n)	42.5 ± 3.8 (n=76)	40.1 ± 4.1 (n=76)	
(median ± IQR)	43.0 ± 4.1	40.1 ± 5.7	
(range)	31.8 – 51.6	25.8 – 49.0	
AO Therapy Subjects			
Hematocrit (%)			<0.0001
(mean ± SD) (n)	42.2 ± 4.5 (n=211)	38.1 ± 4.2 (n=208)	
(median ± IQR)	42.4 ± 6.6	38.5 ± 5.9	
(range)	27.7 – 52.6	27.6 – 48.8	

*Signed Rank test

1.8.9.2 24-Hr Liver Panel Data

24-hr liver panel data are shown in **Table 39**. As seen in the table, the 24-hr results for all parameters are highly comparable for the two groups; only one enzyme, gamma glutamyl transferase (GGTP), shows a statistically significance difference (p=0.008). GGTP values for both groups are within the normal expected range (see **Table 32**), and the relative increase observed in this enzyme level in Control subjects at 24 hours is not clinically significant. In addition, because the GGTP level in AO Therapy subjects was lower, the group difference does not raise a clinical concern.

Table 39. 24-Hr Laboratory Data: Liver Panel

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
Total Bilirubin (mg/dL)			0.47
(mean ± SD) (n)	0.8 ± 0.4 (n=66)	0.8 ± 0.4 (n=200)	
(median ± IQR)	0.8 ± 0.6	0.7 ± 0.5	
(range)	0.2 – 2.2	0.2 – 2.9	
Direct Bilirubin (mg/dL)			0.29
(mean ± SD) (n)	0.18 ± 0.12 (n=64)	0.17 ± 0.13 (n=198)	
(median ± IQR)	0.20 ± 0.13	0.14 ± 0.10	
(range)	0.00 – 0.51	0.00 – 0.87	
Albumin (g/dL)			0.13
(mean ± SD) (n)	3.6 ± 0.5 (n=64)	3.5 ± 0.5 (n=180)	
(median ± IQR)	3.6 ± 0.6	3.6 ± 0.6	
(range)	1.7 – 4.4	1.1 – 4.5	
Alkaline Phosphatase (U/L)			0.31
(mean ± SD) (n)	77.9 ± 29.8 (n=64)	77.1 ± 34.1 (n=196)	
(median ± IQR)	74.5 ± 33.5	67.5 ± 32.5	
(range)	36 – 219	32 – 255	
AST† (SGOT) (U/L)			0.46
(mean ± SD) (n)	223.5 ± 154.6 (n=68)	209.6 ± 150.4 (n=205)	
(median ± IQR)	191.5 ± 177.5	182 ± 171	
(range)	35 – 843	18 – 823	
ALT† (SGPT) (U/L)			0.29
(mean ± SD) (n)	65.2 ± 36.5 (n=71)	60.1 ± 34.8 (n=204)	
(median ± IQR)	61 ± 38	52 ± 45.5	
(range)	14 – 202	8 – 178	
GGTP† (U/L)			0.008
(mean ± SD) (n)	47.5 ± 55.1 (n=64)	34.6 ± 30.2 (n=179)	
(median ± IQR)	31.5 ± 36	24 ± 26	
(range)	7 – 415	6 – 201	
LDH† (U/L)			0.99
(mean ± SD) (n)	756.3 ± 506.6 (n=66)	773.4 ± 534.5 (n=173)	
(median ± IQR)	626.5 ± 534	644 ± 628	
(range)	109 – 2745	148 – 3587	

†AST = Aspartate aminotransferase; ALT = alanine aminotransferase; GGTP = Gamma Glutamyl Transferase; LDH = lactate dehydrogenase
*Mann-Whitney test

1.8.9.3 0-24 Hr Cardiac Enzymes

Cardiac enzyme data were collected at baseline (t=0), 8 hours, 16 hours, and 24 hours post-procedure. Data are shown in **Table 40** for creatine kinase (CK), creatine kinase-MB (CK-MB), Troponin I, and Troponin T levels at each of these time points.

As shown in **Table 40**, measured CK and CK-MB levels were comparable for the two study groups at all time points. The wide range of reported enzyme levels is indicative of the highly variable course of myocardial infarction in terms of proliferating infarction. Troponin I and T were collected for informational purposes at participating AMIHOT II centers; the troponin data shown in **Table 40** do not reveal clinically meaningful group differences.

Table 40. Cardiac Enzymes: Baseline (time = 0) to 24 hrs

		Control Group (n=79)	AO Therapy Group (n=222)	p value*
Creatine kinase (CK) (IU/L)				
0 hr	(mean ± SD) (n)	579.1 ± 962.3 (n=74)	496.7 ± 772.9 (n=213)	0.79
	(median ± IQR)	176 ± 398	193 ± 337	
	(range)	35 – 5069	25 – 4498	
8 hr	(mean ± SD) (n)	2546.2 ± 1718.1 (n=79)	2690.4 ± 2078.4 (n=218)	0.91
	(median ± IQR)	2317 ± 2273	2108 ± 3008	
	(range)	13.2 – 9299	7.0 – 9515	
16 hr	(mean ± SD) (n)	1767.1 ± 1184.6 (n=78)	1846.9 ± 1317.2 (n=218)	0.97
	(median ± IQR)	1577 ± 1142	1590.5 ± 1827	
	(range)	11.8 – 6623	23.0 – 7182	
24 hr	(mean ± SD) (n)	1202.1 ± 836.6 (n=75)	1301.0 ± 931.8 (n=209)	0.50
	(median ± IQR)	1090 ± 1010	1150 ± 1134	
	(range)	17.7 – 4461	17.6 – 5415	
Creatine kinase-MB (CK-MB) (ng/ml)				
0 hr	(mean ± SD) (n)	60.1 ± 103.6 (n=75)	53.0 ± 87.4 (n=203)	0.84
	(median ± IQR)	15.0 ± 53.7	17.1 ± 47.9	
	(range)	0.3 – 471.0	0.2 – 527.6	
8 hr	(mean ± SD) (n)	286.8 ± 175.0 (n=79)	288.7 ± 234.7 (n=217)	0.32
	(median ± IQR)	252.0 ± 253.9	224.0 ± 278.6	
	(range)	25.0 – 925.5	0.2 – 1496.0	
16 hr	(mean ± SD) (n)	175.7 ± 113.8 (n=78)	183.4 ± 177.5 (n=216)	0.72
	(median ± IQR)	148.6 ± 128.8	145.9 ± 151.3	
	(range)	18.7 – 605.1	0.2 – 1938.7	
24 hr	(mean ± SD) (n)	97.5 ± 60.8 (n=75)	103.0 ± 89.3 (n=209)	0.85
	(median ± IQR)	89.0 ± 96.5	83.7 ± 84.7	
	(range)	12.4 – 266.2	6.4 – 886.2	

*Mann-Whitney test

Table 40 (continued). Cardiac Enzymes: Baseline (time = 0) to 24 hrs

		Control Group (n=79)	AO Therapy Group (n=222)	p value*
Troponin I (ng/ml)				
0 hr	(mean ± SD) (n)	17.6 ± 47.0 (n=50)	14.0 ± 41.4 (n=144)	0.28
	(median ± IQR)	0.7 ± 10.9	0.5 ± 4.9	
	(range)	0.0 – 247.8	0.0 – 234.5	
8 hr	(mean ± SD) (n)	188.9 ± 169.6 (n=50)	136.7 ± 149.2 (n=136)	0.02
	(median ± IQR)	122.5 ± 251.8	87.0 ± 147.4	
	(range)	6.0 – 546.9	0.0 – 553.1	
16 hr	(mean ± SD) (n)	115.2 ± 105.9 (n=48)	90.7 ± 89.2 (n=131)	0.12
	(median ± IQR)	78.8 ± 98.4	63.9 ± 92.0	
	(range)	4.3 – 442.7	0.0 – 395.7	
24 hr	(mean ± SD) (n)	70.0 ± 57.9 (n=47)	59.1 ± 54.9 (n=126)	0.14
	(median ± IQR)	55.0 ± 65	44.6 ± 56.2	
	(range)	3.6 – 228.1	0.0 – 256.8	
Troponin T (ng/ml)				
0 hr	(mean ± SD) (n)	0.3 ± 0.8 (n=28)	0.6 ± 1.9 (n=69)	0.11
	(median ± IQR)	0.1 ± 0.2	0.1 ± 0.3	
	(range)	0.0 – 3.6	0.0 – 12.5	
8 hr	(mean ± SD) (n)	6.3 ± 5.3 (n=26)	13.9 ± 51.3 (n=74)	0.15
	(median ± IQR)	5.9 ± 7.8	6.8 ± 7.7	
	(range)	0.2 – 21.8	0.3 – 446.5	
16 hr	(mean ± SD) (n)	3.7 ± 2.7 (n=21)	5.5 ± 4.3 (n=63)	0.10
	(median ± IQR)	4.2 ± 5.2	4.0 ± 4.9	
	(range)	0.2 – 8.0	0.6 – 20.6	
24 hr	(mean ± SD) (n)	3.0 ± 2.3 (n=26)	4.9 ± 4.3 (n=67)	0.04
	(median ± IQR)	2.5 ± 4.0	3.8 ± 4.3	
	(range)	0.1 – 7.7	0.3 – 24.4	

*Mann-Whitney test

1.8.9.4 Hospital Stay and Discharge Information

Hospital stay and discharge information are shown in **Table 41**. As shown in the table, the median hospital stay was 1 day longer for AO Therapy subjects than Control patients (p=0.03). The difference in ICU/CCU stay was not statistically significant (p=0.27). Approximately two-thirds of study subjects were discharged home after completing their hospital stay.

Table 41. Hospital Discharge Information

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
AICD placement during hospitalization (any) (n/N; %)	0/79 (0.0%)	3/222 (1.4%)	0.57**
Prophylactic	0/79 (0.0%)	2/222 (0.9%)	
Therapeutic	0/79 (0.0%)	1/222 (0.5%)	
Days in hospital			0.03
(mean ± SD) (n)	4.7 ± 4.1 (n=79)	5.7 ± 6.9 (n=222)	
(median ± IQR)	4.0 ± 4.0	5.0 ± 4.0	
range	1 – 23	0 – 93	
Days in ICU/CCU			0.27
(mean ± SD) (n)	2.7 ± 1.4 (n=79)	3.0 ± 2.0 (n=221)	
(median ± IQR)	2.0 ± 1.0	3.0 ± 2.0	
range	0 – 9	0 – 20	
Days in step-down unit			0.03
(mean ± SD) (n)	2.7 ± 3.7 (n=79)	3.5 ± 6.4 (n=221)	
(median ± IQR)	2.0 ± 4.0	2.0 ± 4.0	
range	0 – 21	0 – 88	
Patient discharged to: (n/N; %)			0.70**
Home	51/79 (64.6%)	142/222 (64.0%)	
Extended care facility	15/79 (19.0%)	47/222 (21.2%)	
Patient died	0/79 (0.0%)	3/222 (1.4%)	
Other	13/79 (16.5%)	30/222 (13.5%)	

*Mann-Whitney test for continuous variables or Chi-Square test for frequencies unless otherwise noted.
**Exact Chi-Square or Fisher's Exact test

1.8.9.5 Summary of In-Hospital Post-Procedural Data

Post-procedural in-hospital data for the AMIHOT II trial included laboratory assessments for hematology, clinical chemistry, and liver function assessed at 24 hours, cardiac enzyme collection at 8 hour intervals up to 24 hours post-procedure, and hospital stay assessments. Results from these evaluations showed that both the Control and AO Therapy groups experienced a drop in hematocrit and hemoglobin levels over 24 hours; the incremental drop observed in AO Therapy subjects correlates with AO Cartridge use. Despite the relative drop in these measures, both remained within normal clinical range for AO Therapy subjects at 24 hours post-procedure.

No noteworthy differences were observed between Control and AO Therapy in 24-comparisons of other assessments. A statistically significant increase in hospital stay of one additional day was observed in the AO Therapy group. The length of stay in the ICU/CCU was comparable. The overall difference of one day may be attributed to conservative treatment for subjects undergoing the experimental therapy, because investigators and staff were not blinded to the patient assignment.

ST-segment resolution monitored via continuous ECG up to 24 hours post-procedure is addressed separately in **Section 1.8.11**.

1.8.10 Primary Effectiveness Endpoint: Infarct Size by SPECT Imaging at 14 Days

The primary effectiveness endpoint for the AMIHOT II study was based upon infarct size measurement by 14(±7)-day SPECT imaging. Details regarding the collection of SPECT imaging data and analysis by the independent [redacted] at the [redacted] are provided in **Section 1.7.9.5**.

Infarct size results are shown below for both the ITT and PP samples as described previously. The presentation of these data is structured, so that results are shown first for

the AMIHOT II trial alone and then in the context of the Bayesian hierarchical model for the combined analysis of the AMIHOT I and II results.

1.8.10.1 AMIHOT II Infarct Size Results

1.8.10.1.1 ITT Analysis of AMIHOT II Data

Results are shown in **Table 42** for AMIHOT II infarct size results for the ITT analysis. This table represents a secondary analysis of data based upon a frequentist paradigm. Because the AMIHOT II study was designed and powered within the context of Bayesian hierarchical modeling of both AMIHOT I and II data, evidence of superiority was not required or expected from AMIHOT II data alone. **Table 42** shows available results for all evaluable subjects, irrespective of the measurement time window. Referring to **Table 18**, 72/79 (91.1%) Control subjects and 209/222 (94.1%) AO Therapy subjects had SPECT scans that were submitted to the core laboratory and were of sufficient quality to permit infarct size measurement. The results shown in **Table 42** are based on these evaluable data.

Infarct size results are displayed in **Table 42** as median ± IQR for all subjects, and for key patient subsets of interest. Patients were categorized for the purposes of exploring the effects of time to reperfusion, infarct location within the target LAD vessel, age, gender, prior MI, diabetes, pre- and post-PCI TIMI flow grade, baseline LVEF, stent type (BMS or DES), AO Therapy infusion time, the number of AO Cartridges used, the choice of infusion catheter, and geographic location. Two-sided p values were calculated for individual comparisons using the Mann-Whitney test; interaction p values for patient subsets were calculated using two-way ANOVA with infarct size results expressed on the log-transformed scale (ln (infarct size + 10)). These p values should be interpreted cautiously because these comparisons were not corrected for multiple comparisons.

Table 42 shows that infarct size was 26.5 ± 35.5% in AMIHOT II Control patients, as compared to 20 ± 31% in AO Therapy patients (p=0.10). Although the AMIHOT II trial was not powered to demonstrate superiority, this 6.5% absolute reduction in median infarct size shows a trend toward establishing superiority of AO Therapy. The Bayesian hierarchical model that incorporates data from the AMIHOT I trial is presented later in this section and supports this result.

Table 42 shows that shorter time to reperfusion (0-3 hrs vs. >3 – 6 hrs) appears to favor AO Therapy subjects as well; Control subjects with 0 – 3 time to reperfusion had significantly larger infarct size (32 ± 35%) as compared to AO Therapy subjects (14 ± 27%; p = 0.004). This result is consistent with the previously discussed AMIHOT I results, for which shorter reperfusion times on a longer time scale (0-6 hrs. vs. > 6 hrs) favored AO Therapy subjects as well. However, because the AMIHOT II Control group is stratified into small sample sizes for these comparisons, no firm conclusions can be drawn from these data.

Subjects with target vessel lesions located more distally in the LAD vessel appeared to show a stronger treatment effect as well; Control subjects with non-proximal LAD lesions had larger infarct size (21.5 ± 30%) as compared to AO Therapy subjects (14 ± 26%; p = 0.017). Results for patients older than the median age of 60 years also favored AO Therapy; Control subjects older than 60 had greater infarct size (29.5 ± 36%) compared to AO Therapy subjects (19 ± 32%; p = 0.031).

Small sample size caveats apply to these qualitative comparisons of patient subsets, but the results are suggestive of a treatment effect from the adjunctive use of AO Therapy that is more effective in patients with shorter time to primary intervention, with more available circulation for the convective transfer of hyperoxemic blood flow. The results on the second page of **Table 42**, showing that patients with greater TIMI flow (as

measured by the core lab) have greater infarct size reduction with AO Therapy, is also supportive of the general mechanism of action.

None of the patient subgroups examined in **Table 42** showed a statistically significant increase in infarct size in the AO Therapy group.

No trend was observed in infarct size in patients receiving less than 60 minutes of infusion, but an examination of the AO Therapy-specific procedural variables in **Table 42** yields the result that infarct size may increase with the use of additional cartridges. While these results must be interpreted cautiously due to small cell sizes, the findings highlight the importance of receiving an effective duration of AO infusion without interruptions and delays that result from multiple cartridge use.

Table 42. Infarct Size at 14 Days (% of Left Ventricle), Evaluation of Infarct Size for AMIHOT II ITT Analysis†
(infarct size values presented as median data with interquartile range (IQR))

	Control Group (n=79) (median ± IQR) (n)	**AO Therapy Group** (n=222) (median ± IQR) (n)	**p value***
All Patients	26.5 ± 35.5 (n=72)	20 ± 31 (n=209)	0.10
Time strata (randomized)			**0.3**
0 – 3 hrs to reperfusion	31 ± 35 (n=37)	15.5 ± 30.5 (n=96)	0.06
> 3 hrs to reperfusion	24 ± 35 (n=35)	24 ± 30 (n=113)	0.7
Time strata (actual)			**0.026**
0 – 3 hrs to reperfusion	32 ± 35 (n=41)	14 ± 27 (n=88)	0.004
> 3 hrs to reperfusion	21 ± 30 (n=31)	26 ± 32 (n=121)	0.6
Infarct location (randomized)			**0.059**
Proximal LAD	28 ± 37 (n=35)	25 ± 32 (n=117)	0.9
Non-proximal LAD	23 ± 35 (37)	14 ± 28 (n=92)	0.009
Infarct location (actual)			**0.11**
Proximal LAD	29.5 ± 36 (n=34)	30 ± 33.5 (n=100)	0.9
Non-proximal LAD	21.5 ± 30 (n=38)	14 ± 26 (n=109)	0.017
Age			**0.11**
Age < 60 (median)	20 ± 35 (n=42)	21 ± 30 (n=101)	0.9
Age ≥ 60 (median)	29.5 ± 36 (n=30)	19 ± 32 (n=108)	0.031
Gender			**0.2**
Male	24 ± 36 (n=65)	20 ± 31 (n=167)	0.3
Female	38 ± 27 (n=7)	20.5 ± 23 (n=42)	0.044
Prior Myocardial Infarction			**0.9**
Prior MI	37 ± 39 (n=6)	32 ± 32 (n=19)	0.7
No Prior MI	24 ± 36 (n=65)	19 ± 29 (n=189)	0.13
Diabetes			**0.7**
Diabetic (Type I or II)	20 ± 39 (n=10)	21 ± 26.5 (n=32)	0.8
Non-diabetic	28 ± 35 (n=61)	19.5 ± 31 (n=172)	0.09

†Available data for ITT patients analyzed as per Statistical Analysis Plan
*two-sided p value calculated using Mann-Whitney test; interaction p values shown in bold calculated using 2-way ANOVA on the log-transformed scale

Table 42 (continued). Infarct Size at 14 Days (% of Left Ventricle), Evaluation of Infarct Size for AMIHOT II ITT Analysis[†]
(infarct size values presented as median data with interquartile range (IQR))

	Control Group (n=79) (median ± IQR) (n)	**AO Therapy Group** (n=222) (median ± IQR) (n)	**p value***
Pre-PCI TIMI flow grade[‡]			**0.10**
0/I	31.5 ± 34 (n=46)	26.5 ± 30 (n=154)	0.5
II	24.5 ± 27 (n=10)	6 ± 19 (n=34)	0.033
III	8 ± 30 (n=10)	2 ± 17 (n=15)	0.3
II/III	19 ± 28.5 (n=20)	4 ± 19 (n=49)	0.030
Post-PCI TIMI flow grade[‡]			**0.9**
0-II	43 ± 36 (n=5)	26 ± 18 (n=21)	0.7
III	24 ± 37 (n=59)	20 ± 31 (n=181)	0.3
Baseline LVEF[§]			**0.8**
LVEF < 40%	33 ± 23 (n=29)	29 ± 28 (n=69)	0.2
LVEF ≥ 40%	18.5 ± 29.5 (n=36)	14 ± 30 (n=116)	0.15
Stent Type			**0.2**
DES[¥]	31 ± 27 (n=35)	21 ± 31 (n=117)	0.09
BMS[¥]	18 ± 34 (n=35)	19 ± 27 (n=90)	0.9
AO Therapy variables:			
< 60 min AO infusion	NA	19 ± 43 (n=20)	NA
≥ 60 ≤ 90 min AO infusion	NA	20 ± 27.5 (n=168)	NA
> 90 min AO infusion	NA	31 ± 36 (n=21)	NA
1 Cartridge	NA	17 ± 26 (n=141)	NA
2 Cartridges	NA	22 ± 34 (n=45)	NA
> 2 Cartridges	NA	31 ± 35 (n=23)	NA
[redacted] Catheter	NA	17 ± 34.5 (n=136)	NA
[redacted] Catheter	NA	24 ± 23 (n=73)	NA
Site Location			**0.5**
US	29.5 ± 36 (n=30)	26 ± 31 (n=85)	0.5
OUS	23.5 ± 34 (n=42)	17 ± 26.5 (n=124)	0.10

[†]Available data for ITT patients analyzed as per Statistical Analysis Plan
[‡]Angiographic core laboratory assessment
[§]Investigator assessment
[¥]DES = drug-eluting stent; BMS = Bare metal stent
*two-sided p value calculated using Mann-Whitney test; interaction p values shown in bold calculated using 2-way ANOVA on the log-transformed scale

1.8.10.1.2 PP Analysis of AMIHOT II Data

Table 43 shows infarct size results for the AMIHOT II Per Protocol (PP) analysis. This pre-specified analysis was described previously in **Sections 1.8.3** and **1.8.6**. The PP sample sizes for SPECT infarct size evaluation were n=69 for the Control group and n=175 for the AO Therapy group.

As seen in **Table 43**, the infarct size reduction observed in AO Therapy subjects in the PP analysis was larger than in the ITT analysis. Control subjects had a larger infarct size (28 ± 36%) than AO Therapy subjects (20 ± 28%), representing an absolute infarct size reduction of 8% ($p = 0.06$). This infarct size reduction is greater in magnitude than the results seen in the ITT analysis in **Table 42**, and is anticipated because of the relatively high number of failure-to-treat AO Therapy subjects who did not receive an effective duration of AO infusion. Because these subjects are by definition excluded from the PP analysis, the treatment effect of AO Therapy is magnified in **Table 43**.

The analysis of patient subgroups in **Table 43** shows the same qualitative trends observed in the ITT analysis data of **Table 42**.

Table 43. Infarct Size at 14 Days (% of Left Ventricle), Evaluation of Infarct Size for AMIHOT II PP Analysis†
(infarct size values presented as median data with interquartile range (IQR))

	Control Group (n=69) (median ± IQR) (n)	**AO Therapy Group** (n=175) (median ± IQR) (n)	**p value***
All Patients	28 ± 36 (n=69)	20 ± 28 (n=175)	0.06
Time strata (randomized)			**0.5**
0 – 3 hrs to reperfusion	31 ± 35 (n=37)	16 ± 28 (n=79)	0.08
> 3 – 6 hrs to reperfusion	24.5 ± 35 (n=32)	21 ± 26.5 (n=96)	0.4
Time strata (actual)			**0.047**
0 – 3 hrs to reperfusion	32 ± 35 (n=41)	14 ± 26 (n=73)	0.004
> 3 hrs to reperfusion	20 ± 29 (n=28)	24 ± 32 (n=102)	0.8
Infarct location (randomized)			**0.07**
Proximal LAD	28 ± 37 (n=33)	22 ± 32 (n=93)	0.9
Non-proximal LAD	25 ± 35.5 (n=36)	14 ± 27 (n=82)	0.007
Infarct location (actual)			**0.2**
Proximal LAD	31 ± 36 (n=33)	28.5 ± 33 (n=82)	0.6
Non-proximal LAD	21 ± 29.5 (n=36)	14 ± 26 (n=93)	0.029
Age			**0.17**
Age < 59 (median)	21.5 ± 34 (n=34)	21 ± 28 (n=81)	0.8
Age ≥ 59 (median)	28 ± 39 (n=35)	18.5 ± 31 (n=94)	0.026
Gender			**0.4**
Male	24.5 ± 36.5 (n=64)	19 ± 28 (n=142)	0.13
Female	40 ± 17 (n=5)	21 ± 19 (n=33)	0.08
Prior Myocardial Infarction			**0.9**
Prior MI	37 ± 39 (n=6)	31 ± 29 (n=16)	0.5
No Prior MI	24.5 ± 37 (n=62)	19 ± 27 (n=158)	0.09
Diabetes			**0.8**
Diabetic (Type I or II)	20 ± 39 (n=10)	20.5 ± 34 (n=26)	0.6
Non-diabetic	28 ± 36 (n=58)	19.5 ± 27 (n=144)	0.052

†Available data for PP patients analyzed as per Statistical Analysis Plan
*two-sided p value calculated using Mann-Whitney test; interaction p values shown in bold calculated using 2-way ANOVA on the log-transformed scale

Table 43 (continued). Infarct Size at 14 Days (% of Left Ventricle), Evaluation of Infarct Size for AMIHOT II PP Analysis †
(infarct size values presented as median data with interquartile range (IQR))

	Control Group (n=69) (median ± IQR) (n)	**AO Therapy Group** (n=175) (median ± IQR) (n)	**p value***
Pre-PCI TIMI flow grade‡			**0.2**
0/I	32 ± 37 (n=43)	24.5 ± 27 (n=130)	0.24
II	24.5 ± 27 (n=10)	6 ± 24 (n=25)	0.056
III	8 ± 30 (n=10)	3 ± 17 (n=14)	0.4
II/III	19 ± 28.5 (n=20)	4 ± 21 (n=39)	0.048
Post-PCI TIMI flow grade‡			**0.6**
0-II	43 ± 36 (n=5)	31 ± 27 (n=18)	1.0
III	24.5 ± 37 (n=56)	19.5 ± 30 (n=150)	0.14
Baseline LVEF§			**0.9**
LVEF < 40%	36.5 ± 22 (n=28)	26 ± 26 (n=61)	0.10
LVEF ≥ 40%	18 ± 30 (n=35)	14 ± 30 (n=99)	0.15
Stent Type			**0.2**
DES¥	31 ± 27 (n=33)	21 ± 33 (n=100)	0.059
BMS¥	18.5 ± 34 (n=34)	20 ± 26 (n=73)	0.8
AO Therapy variables:			
< 60 min AO infusion	NA	NA	NA
≥ 60 ≤ 90 min AO infusion	NA	19 ± 27 (n=159)	NA
> 90 min AO infusion	NA	26 ± 36.5 (n=16)	NA
1 Cartridge	NA	17 ± 26 (n=126)	NA
2 Cartridges	NA	22 ± 34 (n=37)	NA
> 2 Cartridges	NA	30.5 ± 22 (n=12)	NA
[redacted] Catheter	NA	17 ± 31 (n=111)	NA
[redacted] Catheter	NA	23 ± 20.5 (n=64)	NA
Site Location			**0.7**
US	28 ± 36 (n=29)	23 ± 33 (n=74)	0.3
OUS	26 ± 34.5 (n=40)	17 ± 26 (n=101)	0.09

†Available data for PP patients analyzed as per Statistical Analysis Plan
‡Angiographic core laboratory assessment
§Investigator assessment
¥DES = drug-eluting stent; BMS = Bare metal stent
*two-sided p value calculated using Mann-Whitney test; interaction p values shown in bold calculated using 2-way ANOVA on the log-transformed scale

1.8.10.1.3 Imputation of Missing Infarct Size Data

Reasonable efforts were made to obtain complete data for all patients; however, missing observations did occur due to patients lost to follow-up or noncompliance with required assessments. In order to account for this, and to be able to perform the ITT analysis on the primary outcomes, the missing outcomes were imputed.

[redacted]

In addition, to evaluate the impact of data imputation on the outcomes, a secondary analysis ignoring missing responses also was conducted, as shown in the previous section. **Table 44** shows the infarct size results for the AMIHOT II study with and without the effects of imputation. As seen in the table, the overall impact of the additional imputed data is minor. The AMIHOT II study results using only available data show an absolute median infarct size reduction of 6.5% in the AO Therapy group. Using the 1st and 2nd order imputation methods described above, the associated infarct size reductions are 6.0% and 6.7%, respectively, in good agreement with the non-imputed results.

Table 44. Infarct Size at 14 Days (% of Left Ventricle), Frequentist Evaluation of Infarct Size for ITT Analysis, Sensitivity of Imputation Methods†
(infarct size values presented as median data with interquartile range (IQR))

	Control Group (median ± IQR) (n)	**AO Therapy Group** (median ± IQR) (n)	**P value***
No imputation (available data)	26.5 ± 35.5 (n=72)	20 ± 31 (n=209)	0.10
1st Order Imputation	26.3 ± 35.5 (n=79)	20.3 ± 30.9 (n=222)	0.10
2nd Order Imputation	26.9 ± 35.3 (n=79)	20.2 ± 30.8 (n=222)	0.07

†Analysis performed three ways: No imputation, 1st order imputation, 2nd order imputation methods.
*Two-sided p value calculated using Mann-Whitney test.

1.8.10.2 Analysis of AMIHOT I and II Infarct Size Data Using Simple Pooling

Prior to presenting the results of the Bayesian hierarchical model for infarct size reduction, additional analyses are presented herein for the combined analysis of AMIHOT II infarct size data and AMIHOT I anterior < 6 hr patient infarct size data. This model provides an idealized scenario for combining trial data for the subgroup of interest. The Bayesian hierarchical model conservatively considers other AMIHOT I patient subgroups (*i.e.* non-anterior infarcts and > 6 – 24 hr infarcts), so this pooled model can be thought of as a simplified construct, but one that is instructive with respect to understanding the magnitude of the treatment effect in the target population.

A correction for study level has been made to account for the overall baseline differences in the AMIHOT I and II infarct size results. This pooled analysis is shown in **Tables 45** and **46** for the ITT and PP samples, respectively.

As shown in **Table 45**, this pooled analysis shows an absolute infarct size reduction of 6.5%, from 25 ± 35% in the Control group to 18.5 ± 31% in the AO Therapy group (p=0.023). The magnitude of the treatment effect is equivalent to the overall reduction observed in the AMIHOT II study, as presented in **Table 42**. The patient subgroup data

are informative, and show where clear trends are evident in favor of a stronger treatment effect. As observed in the AMIHOT II data alone, the pooled analysis shows that the treatment effect is strongest in patients older than median age (59 yrs) (p=0.013), female subjects (p=0.028), patients with no prior MI (p=0.026), non-diabetic patients (p=0.005), patients with pre-PCI TIMI flow grade = 2 or 3 (p=0.002), patients with post-PCI TIMI flow grade = 3 (p=0.01), and patients with baseline LVEF < 40% (p=0.034). While these results are exploratory in nature, it is noteworthy that no patient subgroups exhibited a statistically significant negative treatment effect, and that some of the patient subgroups representing high-risk patients had smaller infarcts with AO Therapy.

As shown in **Table 46**, the AMIHOT I and II pooled PP analysis is consistent with the overall findings shown in **Table 43**. **Table 46** shows that absolute infarct size reduction in the pooled analysis is 8%, from 26.5 ± 36% in Control subjects to 18.5 ± 30% in AO Therapy subjects (p=0.017).

While the pooled analysis is not the primary analysis model for the AMIHOT II study, this analysis is a fair representation of the treatment effect size, in terms of the percentage infarct size reduction observed in patients with anterior infarction treated with PCI within 6 hours.

Table 45. Infarct Size at 14 Days (% of Left Ventricle), Pooled Evaluation of Infarct Size for AMIHOT I anterior < 6 hr and AMIHOT II ITT Analysis[†]
(infarct size values presented as median data with interquartile range (IQR))

	Control Group (n=132) (median ± IQR) (n)	**AO Therapy Group** (n=274) (median ± IQR) (n)	**p value***
All Patients	25 ± 35 (n=124)	18.5 ± 31 (n=258)	0.023
Time strata (actual)			**0.7**
0 – 3 hrs to reperfusion	19.5 ± 37 (n=57)	11.5 ± 27 (n=112)	.055
> 3 hrs to reperfusion	26.5 ± 28 (n=67)	24 ± 33 (n=146)	0.2
Age			**0.2**
Age < 59 (median)	19.5 ± 30 (n=65)	18.5 ± 29 (n=119)	0.4
Age ≥ 59 (median)	27.5 ± 37 (n=59)	18.5 ± 33 (n=139)	0.017
Gender			**0.16**
Male	23.5 ± 35 (n=107)	19.5 ± 31 (n=203)	0.16
Female	31.5 ± 33 (n=17)	15.5 ± 28 (n=55)	0.013
Prior Myocardial Infarction			**0.9**
Prior MI	41.5 ± 41 (n=11)	30.5 ± 34 (n=23)	0.8
No Prior MI	23 ± 33.5 (n=112)	17.5 ± 30 (n=234)	0.028
Diabetes			**0.15**
Diabetic (Type I or II)	14.5 ± 30 (n=16)	19.5 ± 25.5 (n=36)	0.6
Non-diabetic	27.5 ± 34 (n=107)	17.5 ± 31 (n=217)	0.007
Pre-PCI TIMI flow grade[‡]			**0.007**
0/I	27.5 ± 32 (n=97)	21.5 ± 32 (n=207)	0.3
II/III	17.5 ± 38 (n=27)	2.5 ± 13.5 (n=51)	0.001
Post-PCI TIMI flow grade[‡]			**0.18**
0-II	14.5 ± 20 (n=11)	27.5 ± 33 (n=10)	0.4
III	26.5 ± 36 (n=113)	18 ± 31 (n=248)	0.012
Baseline LVEF[§]			**0.6**
LVEF < 40%	33.5 ± 26 (n=59)	23.5 ± 31 (n=95)	0.034
LVEF ≥ 40%	16.5 ± 27 (n=57)	12.5 ± 28 (n=139)	0.19
AO Therapy variables:			
< 60 min AO infusion	NA	13.5 ± 42.5 (n=24)	NA
≥ 60 ≤ 90 min AO infusion	NA	18.5 ± 28 (n=213)	NA
> 90 min AO infusion	NA	29.5 ± 36 (n=21)	NA
Site Location			**0.8**
US	28.5 ± 37 (n=55)	22.5 ± 30 (n=110)	0.164
OUS	21.5 ± 31 (n=69)	15 ± 28.5 (n=148)	0.06

[†]Available data for ITT patients analyzed using pooled AMIHOT I and II data with study level correction
[‡]Investigator assessments
[§]Baseline LVEF assessed by ECHO core lab in AMIHOT I, by investigator in AMIHOT II
*Two-sided p value calculated using Mann-Whitney test; interaction p values shown in bold calculated using 2-way ANOVA on the log-transformed scale

Table 46. Infarct Size at 14 Days (% of Left Ventricle), Pooled Evaluation of Infarct Size for AMIHOT I Anterior < 6 hr and AMIHOT II PP Analysis[†]
(infarct size values presented as median data with interquartile range (IQR))

	Control Group (n=121) (median ± IQR) (n)	**AO Therapy Group** (n=219) (median ± IQR) (n)	**p value***
All Patients	26.5 ± 36 (n=121)	18.5 ± 30 (n=219)	0.017
Time strata (actual)			**0.9**
0 – 3 hrs to reperfusion	19.5 ± 37 (n=57)	12.5 ± 27 (n=93)	0.07
> 3 hrs to reperfusion	27 ± 29.5 (n=64)	22.5 ± 34 (n=126)	0.13
Age			**0.19**
Age < 59 (median)	20 ± 30.5 (n=64)	19 ± 26.5 (n=104)	0.4
Age ≥ 59 (median)	27.5 ± 37 (n=57)	18.5 ± 31 (n=115)	0.013
Gender			**0.2**
Male	23.5 ± 35 (n=106)	19.5 ± 30 (n=173)	0.10
Female	31.5 ± 37 (n=15)	17 ± 28 (n=46)	0.028
Prior Myocardial Infarction			**0.9**
Prior MI	41.5 ± 41 (n=11)	29.5 ± 35 (n=20)	0.6
No Prior MI	23.5 ± 34 (n=109)	18.5 ± 30 (n=198)	0.026
Diabetes			**0.2**
Diabetic (Type I or II)	14.5 ± 30 (n=16)	19.5 ± 34 (n=30)	0.8
Non-diabetic	27.5 ± 34.5 (n=104)	18.5 ± 30 (n=184)	0.005
Pre-PCI TIMI flow grade[‡]			**0.012**
0/I	28 ± 33 (n=94)	21 ± 29 (n=176)	0.2
II/III	17.5 ± 38 (n=27)	2.5 ± 15.5 (n=43)	0.002
Post-PCI TIMI flow grade[‡]			**0.14**
0-II	12.5 ± 16 (n=9)	27.5 ± 33 (n=10)	0.3
III	27 ± 36 (n=112)	18.5 ± 30) (n=209)	0.01
Baseline LVEF[§]			**0.5**
LVEF < 40%	35 ± 23 (n=58)	22.5 ± 31 (n=85)	0.015
LVEF ≥ 40%	15.5 ± 28 (n=56)	12.5 ± 28 (n=119)	0.2
AO Therapy variables:			
< 60 min AO infusion	NA	NA	NA
≥ 60 ≤ 90 min AO infusion	NA	18.5 ± 30 (n=203)	NA
> 90 min AO infusion	NA	24.5 ± 36.5 (n=16)	NA
Site Location			**0.9**
US	28.5 ± 37 (n=54)	21.5 ± 33 (n=97)	0.10
OUS	21.5 ± 31 (n=67)	15.5 ± 27 (n=122)	0.07

[†]Available data for ITT patients analyzed using pooled AMIHOT I and II data with study level correction
[‡]Investigator assessments
[§]Baseline LVEF assessed by ECHO core lab in AMIHOT I, by investigator in AMIHOT II
*Two-sided p value calculated using the Mann-Whitney test; interaction p values shown in bold calculated using 2-way ANOVA on the log-transformed scale

1.8.10.3 Bayesian Analysis of Infarct Size Results: AMIHOT I and II

1.8.10.3.1 Background of Bayesian Model for Effectiveness

For simplicity of this evaluation, it was necessary to develop a transformation of the primary endpoint infarct size that would, to a degree, remove the skewness of the data (which includes a number of exactly zero values). Transformations of the form Y = log(X + c) were considered, where "log" denotes the natural logarithm. Consideration of a wide variety of choices for c gave reasonable approximations of normality, and extremely similar statistical inference, but a value of c=10 was chosen based on the distribution of the AMIHOT I trial data in designing the AMIHOT II study. It is useful to present backtransformed results from the Bayesian model; this was done using the well-known technique of smearing[105].

The AMIHOT II trial enrolled anterior infarct patients with times to reperfusion of less than or equal to 6 hours (LT6). The previous AMIHOT I study can be regarded as being composed of 4 mutually exclusive subgroups: anterior/LT6, anterior/GT6, non-anterior/LT6, non-anterior/GT6. The Bayesian hierarchical model was used to analyze both the AMIHOT I data and the AMIHOT II results. In this model, the posterior mean effect size in any particular subgroup is shrunk towards the overall mean. This procedure gives a formal methodology to account for the reduction of the target population. The model also includes random study effects. As a result, if the difference between the AO Therapy and Control means for the AMIHOT II study was different from that seen in the AMIHOT I trial, the analysis would not permit a high degree of borrowing. This allows the type I error to be kept to a reasonable level even though the prior information is centered over a favorable outcome. The log-transformed values (as discussed above) in each subgroup are assumed to be normally distributed with a mean and standard deviation specific to the subgroup-treatment (AO Therapy versus Control) combination. The effectiveness endpoint was considered to have been met if there was high posterior

probability (more than 95%) of superiority in the AMIHOT II trial conditional on the effectiveness data from both trials.

1.8.10.3.2 Results of Primary Analysis

Table 47 shows the results for the Bayesian analysis of infarct size reduction using the pre-specified hierarchical model described in the Statistical Analysis Plan. The data were transformed as described above in order to remove some degree of skewness. **Table 47** shows the Control and AO Therapy group infarct size results as (mean ± SE) on this logarithmic scale. Sample sizes are provided for both the AMIHOT I and II studies. For discussion purposes, this model is referred to as M1.

The important output of the Bayesian hierarchical model is the posterior probability of superiority, which indicates the degree of certainty that the AO Therapy group infarct size is smaller than that of the Control group. The study endpoint required that the posterior probability of superiority be greater than 95.0%, taking into account data from all ITT subjects, and providing for imputation of data for subjects without a readable SPECT scan. The 2nd order imputation analysis factors in the most background information about the patients missing data and is considered the primary analysis result.

The results of the infarct size analyses in **Table 47** demonstrate that the study endpoint was met successfully for the ITT analysis, with or without imputation; the posterior probability of superiority = 95.1% using available data without imputation, 95.5% using 1st order imputation, and 96.9% using 2nd order imputation. Furthermore, the results are statistically significant in the PP analysis as well, in spite of a reduction in the sample size. The PP analysis posterior probability of superiority was 95.2%. No imputed results are necessary for PP analysis, which as defined does not include missing data because acquiring a readable SPECT scan is a criterion for inclusion.

Sufficient Monte Carlo simulations were performed to ensure one-tenth-of-one-percent precision for these calculated posterior probabilities.

Table 47. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Sensitivity of Imputation Methods†: Model M1 (Pre-specified Model) (infarct size values presented on log-transformed scale with mean and standard error (SE))

	Control Group (mean ± SE) (n§)	**AO Therapy Group** (mean ± SE) (n§)	**Difference#** (± SE)	**Posterior Probability of Superiority***
ITT Analysis				
No imputation (available data)	3.42 ± 0.06 (n=52/68; 72)	3.30 ± 0.04 (n=49/71; 209)	-0.12 ± 0.07	95.1%
1st Order Imputation	3.42 ± 0.06 (n=53/79; 79)	3.30 ± 0.04 (n=52/81; 222)	-0.12 ± 0.07	95.5%
2nd Order Imputation	3.43 ± 0.06 (n=53/79; 79)	3.30 ± 0.04 (n=52/81; 222)	-0.13 ± 0.07	96.9%
PP Analysis‡	3.40 ± 0.06 (n=52/68; 69)	3.28 ± 0.04 (n=44/65; 175)	-0.12 ± 0.07	95.2%

†Analysis performed three ways: No imputation, 1st order imputation, 2nd order imputation methods
‡No imputation (available data)
§Sample size for Bayesian Evaluation given as (x/y; z) where x = number of Anterior ≤ 6 hours in AMIHOT I, y = number of other subjects in AMIHOT I and z = number of subjects in AMIHOT II (all Anterior ≤ 6 hours).
#Posterior mean difference between AO and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the average AO Therapy Group infarct size is smaller than the Control Group infarct size.

1.8.10.3.3 Sensitivity Analysis: Alternative Prior Assumptions for Pre-specified Bayesian Model

A sensitivity analysis was conducted on the Bayesian primary effectiveness endpoint evaluation by varying two of the assumptions for prior distributions on the hyperparameters. The first model of these alternative models (M2) changes the prior distribution for the standard deviation of the study random effects in the control group. This change allows the average control infarct size to be more variable between AMIHOT I and II. The second of these alternative models (M3) makes a similar change

to the prior distribution for the standard deviation of the study treatment effects. This change allows the treatment effect to be more variable between AMIHOT I and II.

Results using these alternative models are presented below in **Tables 48** and **49**. Results for M2 are shown in **Table 48**. The net effect of the parameter adjustment in this model as compared to M1 is to allow for more variability in Control group infarct size. Because the AMIHOT II trial featured larger infarct size results than the AMIHOT I study, the M2 value for this parameter is more appropriate than the setting in the pre-specified M1 value. In particular, the prior distributions used in M1 put very little weight on the possibility of a Control group infarct size for AMIHOT II of higher than 25%, whereas the M2 model allows for this amount of variation in the two studies. Results from M2 produce higher posterior probabilities of superiority than the pre-specified model M1. The posterior probabilities of superiority for the ITT analyses are 96.6%, 96.9%, and 97.9% for available data, 1st order imputation, and 2nd order imputation, respectively. Results for the M2 PP analysis yield a posterior probability of 96.4% that infarct size is smaller in the AO Therapy group.

Results for M3 appear in **Table 49**. The net effect of the parameter adjustment used to construct M3 is conservative; as such, there is a slight reduction in the calculated posterior probabilities in M3 as compared to M1, as seen in the table.

In order to gauge the appropriateness of models M1, M2, and M3, the Deviance Information Criterion[106] was calculated. The Deviance Information Criterion (DIC) is a measure of model fit, with smaller values corresponding to better fit of the model to the data. DIC calculations in a multiple imputation setting are not straightforward, but for the available data, model M2 had the strongest support in the data (DIC = 974.8), followed by model M1 (DIC = 975.1), and then model M3 (DIC = 975.2). Thus, the model fit is slightly preferable in M2, and this is also the model that gives reasonable a

priori possibility for the Control group infarct size to be greater than 25% in the AMIHOT II study.

Table 48. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Sensitivity of Imputation Methods[†]: Model M2 (Allows More Variability Between Studies in Control Group Levels)
(infarct size values presented on log-transformed scale with mean and standard error (SE))

	Control Group (mean ± SE) (n[§])	**AO Therapy Group** (mean ± SE) (n[§])	**Difference**[#] (± SE)	**Posterior Probability of Superiority***
ITT Analysis				
No imputation (available data)	3.44 ± 0.06 (n=52/68; 72)	3.30 ± 0.04 (n=49/71; 209)	-0.13 ± 0.07	96.6%
1st Order Imputation	3.44 ± 0.06 (n=53/79; 79)	3.31 ± 0.04 (n=52/81; 222)	-0.13 ± 0.07	96.9%
2nd Order Imputation	3.45 ± 0.06 (n=53/79; 79)	3.31 ± 0.04 (n=52/81; 222)	-0.14 ± 0.07	97.9%
PP Analysis[‡]	3.42 ± 0.06 (n=52/68; 69)	3.29 ± 0.04 (n=44/65; 175)	-0.13 ± 0.07	96.4%

[†]Analysis performed three ways: No imputation, 1st order imputation, 2nd order imputation methods
[‡]No imputation (available data)
[§]Sample size for Bayesian Evaluation given as (x/y; z) where x = number of Anterior ≤ 6 hours in AMIHOT I, y = number of other subjects in AMIHOT I and z = number of subjects in AMIHOT II (all Anterior ≤ 6 hours).
[#]Posterior mean difference between AO and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the average AO Therapy Group infarct size is smaller than the Control Group infarct size.

Table 49. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Sensitivity of Imputation Methods†: Model M3 (Allows More Variability Between Studies in Treatment Effects)
(infarct size values presented on log-transformed scale with mean and standard error (SE))

	Control Group (mean ± SE) (n§)	AO Therapy Group (mean ± SE) (n§)	Difference# (± SE)	Posterior Probability of Superiority*
ITT Analysis				
No imputation (available data)	3.41 ± 0.06 (n=52/68; 72)	3.31 ± 0.04 (n=49/71; 209)	-0.11 ± 0.07	92.8%
1st Order Imputation	3.42 ± 0.06 (n=53/79; 79)	3.31 ± 0.04 (n=52/81; 222)	-0.11 ± 0.07	93.4%
2nd Order Imputation	3.43 ± 0.06 (n=53/79; 79)	3.30 ± 0.04 (n=52/81; 222)	-0.12 ± 0.07	95.2%
PP Analysis‡	3.40 ± 0.06 (n=52/68; 69)	3.29 ± 0.05 (n=44/65; 175)	-0.12 ± 0.07	94.1%

†Analysis performed three ways: No imputation, 1st order imputation, 2nd order imputation methods
‡No imputation (available data)
§Sample size for Bayesian Evaluation given as (x/y; z) where x = number of Anterior ≤ 6 hours in AMIHOT I, y = number of other subjects in AMIHOT I and z = number of subjects in AMIHOT II (all Anterior ≤ 6 hours).
#Posterior mean difference between AO and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the average AO Therapy group infarct size is smaller than the Control group infarct size.

1.8.10.3.4 Additional Bayesian Models to Examine Robustness of Results

A series of additional Bayesian hierarchical models were developed to examine the robustness of the results to different choices of model parameters, prior distributions, and the degree of borrowing from AMIHOT I data. These models were not part of the pre-specified Statistical Analysis Plan but were developed in concert with FDA's request to examine the sensitivity of the study results to a number of factors. For simplicity, these models are referred to in the text as "OL", "H1", "H2", etc. with the following brief descriptions of the purpose of each of the models:

Model OL: Analyzes the data through a non-parametric ordinal logistic model that also allows for the straightforward calculation of the magnitude of the median infarct size reduction.

Model H1: An alternative Bayesian hierarchical model similar to our pre-specified model M1, but has 6 additional random effects terms, leading to higher degrees of borrowing from AMIHOT I where this is warranted.

Model H2: A variant of model H1 to incorporate the two-way ANOVA mean model for the subgroup effect, to account for the potential interaction between infarct location and time to reperfusion in the AMIHOT I data.

Model H3: A variant of model H1 to incorporate a term for possible center effects from the AMIHOT I and II investigational sites.

Model H4: A variant of model H1 that includes the time to reperfusion as a continuous variable and treatment by time to reperfusion interaction effects

The following discussion addresses the findings of these models.

Model OL

The data are re-analyzed using an ordinal logistic regression model with categories corresponding to quintiles of infarct size [redacted] Model OL is specified as follows:

[redacted] (Model OL)

where [redacted] This model specification should allow for more flexibility in the model, and may lead to higher degrees of borrowing from AMIHOT I where this is warranted.

Superiority is adjudicated by the posterior probability computation

[redacted]

The results of running model OL are shown in **Table 49a** below for both the available data and for the primary imputed data.

Table 49a. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint Using Ordinal Logistic Regression Model (Model OL)

	Control Group (Median ± SE)‡	**AO Therapy Group** (Median ± SE)‡	**Odds Ratio** (95% CI)#	**Posterior Probability of Superiority***
No imputation (available data)				
Model OL	25.5 ± 2.9	18.8 ± 1.5	1.61 (1.07, 2.43)	99.0%
Multiple Imputation (S2)				
Model OL	26.1 ± 2.9	18.7 ± 1.5	1.69 (1.12, 2.54)	99.4%

‡Posterior mean and standard deviation of the median infarct size calculated for each draw from the posterior sample assuming a step function distribution with probabilities π_{ijt}.
#Posterior median and (2.5th, 97.5th) percentiles of [redacted]
*Probability [redacted] given AMIHOT I and II data.

The ordinal logistic regression model assumes proportional odds, *i.e.* that μ_{ijt} describes the common log-odds increment between each successive outcome category. This assumption is a reasonable approximation from several standpoints:

- First, a non-Bayesian ordinal logistic regression was performed for just the AMIHOT II data using these cutpoints with the single explanatory variable of treatment vs. control arm. The common odds ratio for the arm predictor is estimated as 1.53 (p=0.08), with the treatment group more likely to have lower categories of infarct size than the control group. The score test for the proportional odds assumption is non-significant (p=0.86).

- Second, a non-Bayesian ordinal logistic regression was performed for the AMIHOT II data pooled with the AMIHOT I data from the subgroup interest with explanatory variables of treatment vs. control arm and study. The common odds ratio for the arm predictor is now estimated as 1.69 (p=0.009), again reflecting that the treatment group was more likely to have lower categories of infarct size than the control group. The score test for the proportional odds assumption remains non-significant (p=0.22).

- Third, four separate Bayesian dichotomous models were fit for each of the four category cutpoints [redacted] The model used for each of these four dichotomous

logistic regressions was in every other way identical to model OL. The similarity of the odds ratios for the four dichotomous models to the common odds ratio from the OL model can be seen **Table 49b** below.

Table 49b. Results of Ordinal Logistic Regression Model (Model OL) for the Quintile Cutpoints

	Odds Ratio (95% CI)[#]	**Posterior Probability of Superiority***
No Imputation (available data)		
Model OL	1.61 (1.07, 2.43)	99.0%
0% vs. >0%	1.62 (0.89, 3.04)	94.7%
0-7% vs. >7%	1.47 (0.92, 2.44)	94.6%
0-21% vs. >21%	1.43 (0.93, 2.27)	95.2%
0-39% vs. >39%	1.51 (0.91, 2.53)	94.4%

[#]Posterior median and (2.5^{th}, 97.5^{th}) percentiles of $\varphi \equiv \exp(\omega_2 + \alpha_{12} - \alpha_{11} + \beta_{22} - \beta_{21})$.
*Probability $\omega_2 + \alpha_{12} - \alpha_{11} + \beta_{22} - \beta_{21} > 0$ given AMIHOT I and II data.

The OL model is thus able to aggregate the evidence of superiority across all four dichotomous cutpoints, and the assumption of common odds ratio that is needed for this aggregation is satisfied.

Model H1

[redacted]

[redacted]. It is similar to our pre-specified model, but has 6 additional random effects terms. This model specification should allow for more flexibility in the model, and may lead to higher degrees of borrowing from AMIHOT I where this is warranted. The complete model is written as

[redacted] (Model H1)

The results from the model H1 are presented below in **Table 49c**, alongside the results from the pre-specified model M1.

Table 49c. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint Using New Hierarchical Model (Model H1)

	Control Group (mean ± SE)	**AO Therapy Group** (mean ± SE)	**Difference#** (± SE)	**Posterior Probability of Superiority***
No Imputation (available data)				
Pre-specified Model (M1)	3.42 ± 0.06	3.30 ± 0.04	-0.12 ± 0.07	95.1%
New Hierarchical Model (H1)	3.45 ± 0.06	3.31 ± 0.04	-0.15 ± 0.07	97.7%
Multiple Imputation S2				
Pre-specified Model (M1)	3.43 ± 0.06	3.30 ± 0.04	-0.13 ± 0.07	96.9%
New Hierarchical Model (H1)	3.46 ± 0.06	3.31 ± 0.04	-0.16 ± 0.07	98.4%

#Posterior mean difference between AO Therapy and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the average AO Therapy Group infarct size is smaller than the Control Group infarct size.

As anticipated, the new hierarchical model H1 is able to more effectively borrow information from AMIHOT I in estimating the AMIHOT II treatment effect. This results in a larger estimated difference and posterior probability of superiority.

Model H2

Model H1 is modified to incorporate the two-way ANOVA mean model for the subgroup effect. Index j for subgroup is replaced by two indices for reperfusion time [redacted]

[redacted] (Model H2)

The results of model H2 are presented below in **Table 49d**, and are quite similar to the new hierarchical model H1.

Table 49d. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, New Hierarchical Model (Model H2)

	Control Group (mean ± SE)	**AO Therapy Group** (mean ± SE)	**Difference#** (± SE)	**Posterior Probability of Superiority***
No Imputation (available data)				
New Hierarchical Model (H1)	3.45 ± 0.06	3.31 ± 0.04	-0.15 ± 0.07	97.7%
Two-Way ANOVA Mean Structure Model (H2)	3.45 ± 0.06	3.31 ± 0.04	-0.14 ± 0.07	97.3%
Multiple Imputation S2				
New Hierarchical Model (H1)	3.46 ± 0.06	3.31 ± 0.04	-0.16 ± 0.07	98.4%
Two-Way ANOVA Mean Structure Model (H2)	3.46 ± 0.06	3.31 ± 0.04	-0.15 ± 0.07	98.4%

#Posterior mean difference between AO Therapy and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the average AO Therapy Group infarct size is smaller than the Control Group infarct size.

Model H3

Model H1 is adjusted to incorporate random site (indexed by *s*) and site-by-treatment effects. The resultant model H3 is defined as:

[redacted]

[redacted] (Model H3)

The results of model H3 are presented below in **Table 49e**, and show that the incorporation of site effects results in small differences in comparison to the base model H1 without incorporation of site effects; posterior probabilities are slightly smaller because the site effects are estimated with vague prior distributions, resulting in a very slight loss of power. However, as seen in the table, the inclusion of site effects does not impact the study results in a material way.

Table 49e. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Incorporation of Site Effects into New Hierarchical Model (Model H3)

	Control Group (mean ± SE)	**AO Therapy Group** (mean ± SE)	**Difference#** (± SE)	**Posterior Probability of Superiority***
No Imputation (available data)				
New Hierarchical Model (H1)	3.45 ± 0.06	3.31 ± 0.04	-0.15 ± 0.07	97.7%
Random Site Effects (H3)	3.46 ± 0.07	3.32 ± 0.06	-0.14 ± 0.08	96.6%
Multiple Imputation S2				
New Hierarchical Model (H1)	3.46 ± 0.06	3.31 ± 0.04	-0.16 ± 0.07	98.4%
Random Site Effects (H3)	3.47 ± 0.07	3.31 ± 0.05	-0.15 ± 0.08	97.7%

#Posterior mean difference between AO Therapy and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the average AO Therapy Group infarct size is smaller than the Control Group infarct size.

Model H4

With respect to formal analysis of the primary effectiveness endpoint, the requested inclusion of time to reperfusion as a continuous variable and treatment by time to reperfusion interaction effects are incorporated into the new hierarchical model H1. For

illustrative purposes, these model results are calculated using available study data (no imputation). The directional effects of these additional parameters on the model results are translatable to other imputation schemes and models. The results are shown in comparison to the model H1 below in **Table 49f** for effectiveness. As shown in the table, the effects of these parameters are minor, and do not impact the study results.

Table 49f. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Incorporation of Time to Reperfusion and Treatment by Time Interaction Effects into Models M1 and H1[†]

	Control Group (mean ± SE)	**AO Therapy Group** (mean ± SE)	**Difference**[#] (± SE)	**Posterior Probability of Superiority***
Base Model				
New Hierarchical Model (H1)	3.45 ± 0.06	3.31 ± 0.04	-0.15 ± 0.07	97.7%
Incorporation of Time to Reperfusion as Continuous Variable and Treatment by Time Interaction				
New Hierarchical Model H4[&]	3.45 ± 0.06	3.31 ± 0.04	-0.15 ± 0.07	97.9%

[†]Results shown for available data (no imputation)
[#]Posterior mean difference between AO Therapy and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the average AO Therapy Group infarct size is smaller than the Control Group infarct size.
[&]Results adjusted to mean reperfusion time in AMIHOT II study (t=3.46 hours)

Model Results Using Informative (Borrowing) and Non-Informative (Non-Borrowing) Priors

The results for models M1, H1, H2, H3, and OL are shown below in **Tables 49g** and **49h**, comparing the results using informative (borrowing) and non-informative (non-borrowing) priors. The results are provided using available data for illustrative purposes and are applicable to model variants with imputation. For each model, inference was performed on the transformed infarct size in both the Control and AO Therapy groups conditioning on both studies (borrowing) and on only the AMIHOT II study (non-borrowing). An indication of the extent of borrowing is given by the relative efficiency (*i.e.*, the ratio of the posterior variances for non-borrowing over borrowing). This relative efficiency is displayed as an effective sample size borrowed from AMIHOT I (n_{borrow} is defined by the relative efficiency times the AMIHOT II sample size for the group).

With respect to the primary effectiveness endpoint, the new hierarchical models (H1 and H2) have smaller effective borrowing sample sizes, but have much higher posterior probability of superiority as compared to the pre-specified model M1. Thus, the new hierarchical models borrow more effectively from AMIHOT I through weighting the data from the other subgroups (non-anterior and/or > 6 hr infarcts) less heavily than does model M1. The large effective borrowing sample sizes for the site effect model (H3) reflect that the model is poorly determined when using only AMIHOT II data, but is estimated much more precisely when AMIHOT I data are also considered; as such, the n_{borrow} metric is not as appropriate for this model. Finally, the OL model borrows more than does model H1 from the AMIHOT I data. The results from model OL are quite similar to the results from dichotomizing at any of the four category boundaries, and this observation carries over to the borrowing behavior of the dichotomous models (data not shown). In comparison to previously presented dichotomizations, model OL is the most

statistically powerful and clinically relevant because it analyzes the continuum of the data rather than binary categorization.

Table 49g. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Comparison of Informative (Borrowing) and Non-Informative (Non-Borrowing) Priors, Models M1, H1, H2, and H3[†]

	Control Group (mean ± SE)	**AO Therapy Group** (mean ± SE)	**Difference**[#] (± SE)	**Posterior Probability of Superiority***
Informative Prior (Borrowing)	*(n=52/68; 72)*[†]	*(n=49/71; 209)*[†]		
Pre-specified Model (M1)	3.42 ± 0.06 *(n_{borrow}=28)*[&]	3.30 ± 0.04 *(n_{borrow}=43)*[&]	-0.12 ± 0.07	95.1%
New Hierarchical Model (H1)	3.45 ± 0.06 *(n_{borrow}=22)*[&]	3.31 ± 0.04 *(n_{borrow}=29)*[&]	-0.15 ± 0.07	97.7%
Two-Way ANOVA Mean Structure Model (H2)	3.45 ± 0.06 *(n_{borrow}=21)*[&]	3.31 ± 0.04 *(n_{borrow}=25)*[&]	-0.14 ± 0.07	97.3%
Random Site Effects (H3)	3.46 ± 0.07 *(n_{borrow} ~ 72)*[&]	3.32 ± 0.06 *(n_{borrow}~209)*[&]	-0.14 ± 0.08	96.6%
Non-Informative Prior (Non-Borrowing)	*(n=72)*	*(n=209)*		
Pre-specified Model (M1)	3.45 ± 0.07	3.31 ± 0.05	-0.13 ± 0.08	94.0%
New Hierarchical Model (H1)	3.45 ± 0.07	3.31 ± 0.04	-0.14 ± 0.09	94.5%
Two-Way ANOVA Mean Structure Model (H2)	3.45 ± 0.07	3.31 ± 0.04	-0.14 ± 0.09	94.5%
Random Site Effects (H3)	3.48 ± 0.10	3.35 ± 0.08	-0.13 ± 0.11	89.3%

[†]Results shown for available data (no imputation)
[#]Posterior mean difference between AO Therapy and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the average AO Therapy Group infarct size is smaller than the Control Group infarct size.
[&]The sample size n_{borrow} is computed as the relative gain in efficiency of the model using both AMIHOT I and AMIHOT II data to the model using only AMIHOT II data (i.e. the ratio of the posterior variances minus 1) times the sample size in AMIHOT II.

Table 49h. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint Using Ordinal Logistic Regression Model (Model OL), Comparison of Informative (Borrowing) and Non-Informative (Non-Borrowing) Priors

	Control Group (median ± SE)‡	AO Therapy Group (median ± SE)‡	Odds Ratio (95% CI)#	Posterior Probability of Superiority*
Informative Prior (Borrowing)	*(n=52/68; 72)*†	*(n=49/71; 209)*†		
Model OL	25.5 ± 2.9 *(n_{borrow}=36)*&	18.8 ± 1.5 *(n_{borrow}=64)*&	1.61 (1.07, 2.43)	99.0%
Non-Informative Prior (Non-Borrowing)	*(n=72)*	*(n=209)*		
Model OL	25.6 ± 3.6	19.1 ± 1.7	1.53 (0.93, 2.47)	95.4%

‡Posterior mean and standard deviation of the median infarct size calculated for each draw from the posterior sample assuming a step function distribution with probabilities π_{it}, [redacted]

&The sample size n_{borrow} is computed as the relative gain in efficiency of the model using both AMIHOT I and AMIHOT II data to the model using only AMIHOT II data (i.e. the ratio of the posterior variances minus 1) times the sample size in AMIHOT II.

1.8.10.3.5 Sensitivity of Model Results to Change in Prior Specification

The results presented herein for indicate that the study conclusions with respect to effectiveness are quite robust to changes in the specification of prior distributions. The original pre-specified model M1 gave posterior probabilities for superiority of 95.1% (available data) and 96.9% (with 2nd order imputation strategy S2), with other reasonable imputation strategies leading to similar conclusions. In retrospect, the pre-specified model was not particularly suited to the overall shift in infarct size seen between the two studies (infarct size increased in AMIHOT II), and had difficulty borrowing effectively from the subgroup of interest (anterior < 6 hr infarcts) in AMIHOT I. A more appropriate alternative prior specification for model M1 was provided in model M2 and yielded a higher posterior probability of superiority. Similarly, the new hierarchical structure used in Models H1 or H2 is strongly preferable to model M1, exhibiting higher posterior probabilities. The exploratory analysis of site effects in model variant H3 has

no appreciable effect upon study results. Lastly, a non-parametric version of the analysis (the ordinal logistic regression model OL) provides an excellent fit to the data and results in a very strong demonstration of superiority.

These new models were not pre-specified and were not tuned to have appropriately low type I error at the boundaries (as was model M1). However, adjusting the prior distributions in models H1 and OL to be much less informative results in posterior probabilities in excess of 95% for superiority, as shown below in **Tables 49i** and **49j**.

In summary, the primary endpoint results for both safety and effectiveness are robust and resilient to a wide array of choices for both the Bayesian model and the prior distributions, and are not sensitive to the inclusion of site effects or other variables such as time to reperfusion.

Table 49i. Sensitivity of Model OL to Change in Prior Distributions

	Control Group (Median ± SE)‡	**AO Therapy Group** (Median ± SE)‡	**Odds Ratio** (95% CI)#	**Posterior Probability of Superiority***
No Imputation (available data)				
Model OL	25.5 ± 2.9	18.8 ± 1.5	1.61 (1.07, 2.43)	99.0%
Model OL** with all SDs given weakly informative prior distributions U(0.01, 0.67)	25.4 ± 3.1	18.9 ± 1.5	1.58 (1.00, 2.49)	97.5%

‡Posterior mean and standard deviation of the median infarct size calculated for each draw from the posterior sample assuming a step function distribution with probabilities π_{ijt}.

[redacted]

**Model OL with all SDs given weakly informative prior distributions U(0.01, 0.67)

Table 49j. Sensitivity of Model H1 to Change in Prior Distributions

	Control Group (mean ± SE)	**AO Therapy Group** (mean ± SE)	**Difference#** (± SE)	**Posterior Probability of Superiority***
No Imputation (available data)				
New Hierarchical Model (H1)	3.45 ± 0.06	3.31 ± 0.04	-0.15 ± 0.07	97.7%
New Hierarchical Model (H1)**	3.45 ± 0.07	3.31 ± 0.04	-0.14 ± 0.08	96.3%

#Posterior mean difference between AO Therapy and Control groups incorporating data from AMIHOT I study ~~into the~~ hierarchical model.
*Posterior probability that the average AO Therapy Group infarct size is smaller than the Control Group infarct size.
**Model H1 with all SDs given weakly informative prior distributions U(0.01, 0.67)

1.8.10.4 Magnitude of the Treatment Effect

The magnitude of the infarct size reduction exhibited from the adjunctive administration of AO Therapy is an important parameter that can be used to correlate expected long-term benefit for patients. Both the AMIHOT II study results and the simple pooled analysis of AMIHOT I anterior < 6 hr patients and AMIHOT II subjects yielded absolute median infarct size reductions of 6.5%. A 6.5% infarct size reduction exceeds the 5.0% benchmark established in the white paper by [redacted] in **Section 1.4.5.1**.

The Bayesian hierarchical model M1, through the use of log-transformed data, is an effective tool for evaluating whether a statistically significant treatment effect has been observed, but direct back-transformation of the results is very misleading. As discussed above, a smearing approach[105] can be used to improve the calibration. To do this, the parameter estimates are exponentiated, multiplying by the smearing factor which is the average of the exponentiated residuals, and then subtract the offset constant, c = 10. Taking the primary results of M1 from **Table 46**, the smeared retransformation of the available study data yields infarct sizes of 26.4% and 22.3% for the Control and AO Therapy groups, respectively. The corresponding estimates from Model H1 (**Table 49c**)

are 26.9% vs. 21.8% for Control and AO groups, respectively. One difficulty with this approach is that it yields a well-calibrated estimate of the mean on the transformed scale in each group, but the standard summary measure for infarct size is the median, owing to the nature of the distributions. Another difficulty in direct interpretation, is that the hierarchical Bayesian approach conservatively down-weights the treatment effect for AMIHOT II in the model, owing to the presence of less favorable AMIHOT I subgroups.

The alternative Bayesian hierarchical Model OL is better suited for this analysis because the non-parametric model does not require the transformation and back-transformation of the data on the log scale. As shown in **Table 11.46b** above, the calculated median infarct sizes for the respective Control and AO Therapy groups are 25.5% and 18.8% (no imputation). These results yield an infarct size reduction of 6.7%, consistent with the other methods of calculation.

Translated into a relative change, the AMIHOT II data yield a relative infarct size reduction of (AO – Control)/(Control) x 100% = 6.5/20 x 100% = 24.5%. In the previously presented pooled model, this relative reduction is 26.0%, consistent with the AMIHOT II results alone. In the Bayesian Model OL, the relative reduction is 26.3%, providing another consistent estimate of the relative treatment effect.

1.8.10.5 Results of Small Infarcts Analysis

An additional secondary analysis was performed to explore the treatment effect with respect to the relative number of small infarcts, defined as $\leq$ 5.0%. The rationale behind this exploratory analysis is that infarct size is a highly variable outcome from a clinical standpoint; some patients have large resultant infarcts regardless of treatment modality or baseline characteristics. Statistically, the resultant data sets are known to create skewed, long-tailed distributions rather than normally distributed outcomes centered by a mean value. To illustrate this point, **Figures 6** and **7** show infarct size histograms for the AMIHOT I anterior < 6 cohort and the AMIHOT II study, respectively. As seen in the

figures, both studies show a left-shift in the distributions of AO Therapy infarct size with respect to Control; qualitatively, this left-shift shows a greater proportion of the smallest infarcts at the left end of the distribution. Graphically, each histogram bar represents a 5% increment; therefore, the first histogram bar shows the proportion of subjects with infarct size between 0 – 5%, inclusive.

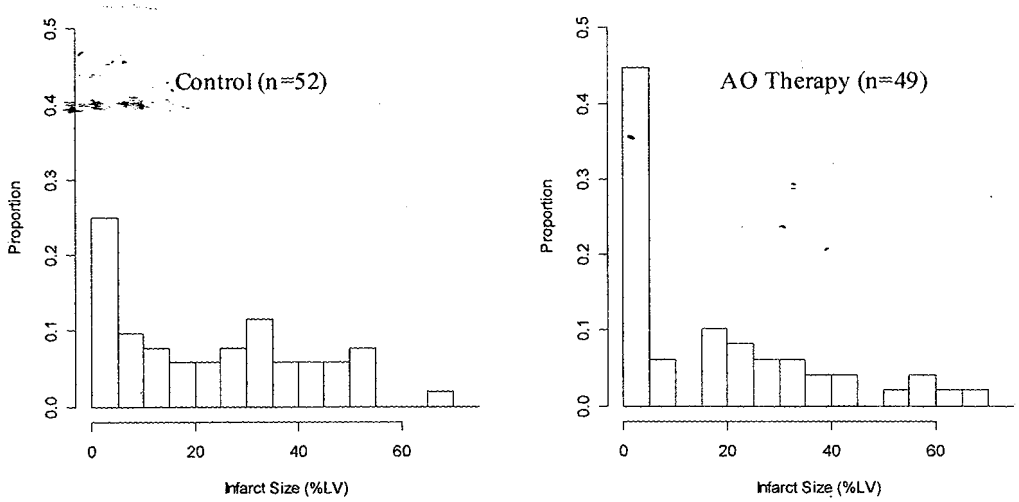


Figure 6. AMIHOT I Anterior < 6 Hr Subjects Infarct Size Distributions

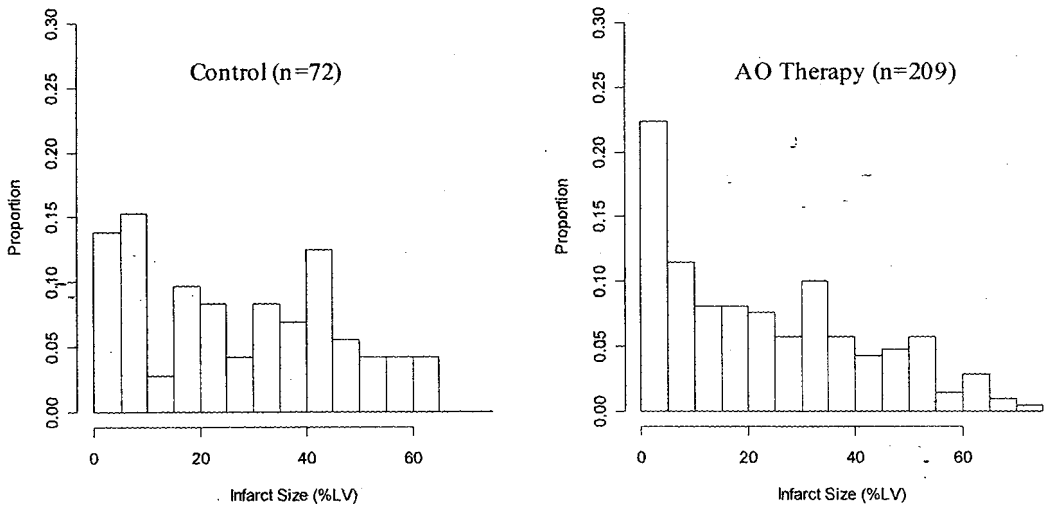


Figure 7. AMIHOT II Infarct Size Distributions

From a clinical standpoint, an effective adjuvant therapy must be able to increase the proportion of small infarcts to be viable. The best clinical outcome possible is a small infarction; a measured infarct size of 0% indicates miniscule necrosis as detected by SPECT imaging.

To formally test whether the AMIHOT I and II data exhibited a greater proportion of small infarcts in the AO Therapy group, the relative risk (RR) was calculated first for the anterior < 6 hr population, and was further explored using Bayesian hierarchical modeling. For the anterior < 6 hr analysis, standard exact chi-squared tests (for inference on AMIHOT I and AMIHOT II individually) and Mantel-Haenszel tests (for examining the pooled results from both trials) were used to perform inference on the relative probability ("risk") of having a small infarct size in AO versus control groups. The Bayesian hierarchical approach used a model similar to the pre-specified MACE endpoint model, where the log odds of small infarct size was assumed to be the sum of an overall mean, study effects for control group and treatment difference, and subgroup effects for control group and treatment difference. The posterior probability that the relative rate of small infarct size was more than 1 in AMIHOT II conditional on the data for both trials was calculated for the Bayesian analysis. **Tables 50 – 52** show the results of these analyses, performed both for exactly 0% infarcts and for infarcts 0 – 5% (inclusive) in magnitude.

Tables 50 and **51** display relative risk results for ITT and PP analyses of the AMIHOT I anterior < 6 hr patients, AMIHOT II, and the study level-adjusted pooled combination of these data. Two important observations are made from these data. First, the AMIHOT I and II studies exhibited differences in the proportions of small infarcts. As shown in the tables and seen graphically in **Figures 6** and 7, infarct sizes were larger in AMIHOT II in this patient population across the board. However, the relative proportions of small infarcts between the study groups are relatively constant. The calculated RR is in the range of 1.6 – 1.8 in favor of a greater tendency for small infarction in the AO Therapy

group. The results of the pooled model are statistically significant for RR > 1.0 for both 0% and 0 – 5% infarcts, for both ITT and PP analyses of these data ($p<0.05$ for all four cases).

This result is supported in the more conservative Bayesian model, which also considers data from non-anterior infarction and > 6 hr infarction from the AMIHOT I study. As shown in **Table 52**, the calculated RR from the Bayesian model is ~ 1.5 for all comparisons in favor of a greater tendency for small infarction in the AO Therapy group. These results are statistically significant with calculated posterior probabilities of superiority greater than 95% for RR > 1.0 in the 0 – 5% infarct size comparisons.

This analysis of small infarction is exploratory in nature but the results are compelling; any adjuvant therapy that seeks to improve upon standard-of-care outcomes for infarction by augmenting the standard of care can be expected to work highly effectively in some subjects, minimizing the damage from prolonged ischemia. AO Therapy appears to have this effect when adjunctively administered post-PCI.

Table 50. Patients with Small Infarct Size (0-5%) at 14 days. ITT Analysis.

	Control Group (n/N; %)	AO Therapy Group (n/N; %)	Relative Risk#	p value*
0% Infarct Size				
AMIHOT I anterior < 6 hours	10/52 (19.2%)	17/49 (34.7%)	1.80	0.11
AMIHOT II	6/72 (8.3%)	30/209 (14.4%)	1.72	0.2
Pooled†	- -	- -	1.76	0.03**
0 - 5% Infarct Size				
AMIHOT I anterior < 6 hours	13/52 (25.0%)	22/49 (44.9%)	1.80	0.04
AMIHOT II	10/72 (13.9%)	47/209 (22.5%)	1.62	0.13
Pooled†	- -	- -	1.70	0.01**

†Pooled Relative Risk estimated using Mantel-Haenszel method
#Relative Risk (AO Therapy Probability/Control Probability)
*Exact Chi-Square test
**Mantel-Haenszel test

Table 51. Patients with Small Infarct Size (0-5%) at 14 days. PP Analysis.

	Control Group (n/N; %)	AO Therapy Group (n/N; %)	Relative Risk#	p value*
0% Infarct Size				
AMIHOT I anterior < 6 hours	10/52 (19.2%)	15/44 (34.1%)	1.77	0.11
AMIHOT II	6/69 (8.7%)	26/175 (14.9%)	1.71	0.3
Pooled†	- -	- -	1.74	0.04**
0 - 5% Infarct Size				
AMIHOT I anterior < 6 hours	13/52 (25.0%)	19/44 (43.2%)	1.73	0.08
AMIHOT II	10/69 (14.5%)	40/175 (22.9%)	1.58	0.16
Pooled†	- -	- -	1.65	0.02**

†Pooled Relative Risk estimated using Mantel-Haenszel method
#Relative Risk (AO Therapy Probability/Control Probability)
*Exact Chi-Square test
**Mantel-Haenszel test

Table 52. Patients with Small Infarct Size (0-5%) at 14 days. Bayesian Evaluation of Relative Probability of Small Infarct Size in AO Therapy versus Control[†]

	Control Group (Probability[‡] ± SE)	AO Therapy Group (Probability[‡] ± SE)	Relative Risk[#]	Posterior Probability of Superiority*
0% Infarct Size				
ITT	0.105 ± 0.029	0.156 ± 0.024	1.494	92.2%
PP	0.110 ± 0.030	0.162 ± 0.027	1.482	92.0%
0 - 5% Infarct Size				
ITT	0.153 ± 0.035	0.234 ± 0.028	1.539	97.1%
PP	0.161 ± 0.036	0.238 ± 0.030	1.489	96.0%

[†]Analysis performed using available data; no imputation
[‡]Probability of infarct size = 0% or ≤ 5%
[#]Relative Risk (AO Therapy Probability/Control Probability)
*Posterior Probability of Superiority that Relative Risk > 1.0

1.8.10.6 Additional SPECT Imaging Data

Additional data obtained from the [redacted] are shown in **Table 53**. Data are provided for the sestamibi dose (mCi), the specific infarct location, the likely coronary territories, and the number of perfusion defects. For the categorical variables of infarct location and coronary territories, multiple classifications are possible for a single patient.

Table 53. Additional [redacted] Data

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
Sestamibi Dose (mCi)			0.89
(mean ± SD) (n)	25.0 ± 4.3 (n=73)	24.8 ± 4.2 (n=211)	
(median ± IQR)	24.3 ± 7.9	24.3 ± 7.4	
(range)	18.6 – 35.6	13.5 – 35.1	
Location† (n/N; %)			
Anterior	56/72 (77.8%)	131/209 (62.7)	0.02
Anterolateral	3/72 (4.2%)	3/209 (1.4%)	0.18**
Inferolateral	0/72 (0.0%)	5/209 (2.4%)	0.33**
Inferior	34/72 (47.2%)	87/209 (41.6%)	0.41
Inferoseptal	25/72 (34.7%)	49/209 (23.4%)	0.06
Anteroseptal	34/72 (47.2%)	83/209 (39.7%)	0.27
Apical	49/72 (68.1%)	127/209 (60.8%)	0.27
Indeterminate	4/72 (5.6%)	25/209 (12.0%)	0.12
Likely Coronary Territories‡ (n/N; %)			
LAD	59/72 (81.9%)	151/209 (72.3%)	0.10
LCF	0/72 (0.0%)	3/209 (1.4%)	0.57**
RCA (if dominant)	21/72 (29.2%)	39/209 (18.7%)	0.06
RCA or LCF	11/72 (15.3%)	49/209 (23.4%)	0.14
Indeterminate	6/72 (8.3%)	25/209 (12.0%)	0.40
Number of Perfusion defects (n/N; %)			0.08**
None	3/72 (4.2%)	25/209 (12.0%)	0.05
Single, but doesn't meet criteria	2/72 (2.8%)	5/209 (2.4%)	1.0**
Single	41/72 (56.9%)	113/209 (54.1%)	0.88
Single, but a second doesn't meet criteria	0/72 (0.0%)	5/209 (2.4%)	0.33**
Possibly two	5/72 (6.9%)	22/209 (10.5%)	0.34
Probably two	20/72 (27.8%)	39/209 (18.7%)	0.14
Multiple	1/72 (1.4%)	0/209 (0.0%)	0.26**

†Multiple infarct locations are possible for individual subject data
‡Multiple likely coronary territories are possible for individual subject data
*Mann Whitney test for continuous data, Chi-Square test for categorical data unless otherwise indicated
**Exact Chi-Square or Fisher's Exact test

1.8.10.7 Summary of SPECT Imaging Results

The study endpoint for effectiveness was superiority of the adjunctive administration of AO Therapy following PCI with stenting, as compared to a Control population receiving PCI with stenting alone. The effectiveness measure was infarct size measurement by [redacted]

imaging at 14 days. The target population was anterior AMI successfully revascularized by PCI within six hours of symptom onset.

Bayesian hierarchical modeling was employed to assess this endpoint. In concept, study endpoint success was evaluated for the AMIHOT II study contingent upon the results of the AMIHOT I trial. Results obtained from the pre-specified model demonstrated that the efficacy endpoint was met successfully, with a high posterior probability (> 95%) of superiority in the AMIHOT II trial conditional on the efficacy data from both trials. This finding was robust with respect to various imputation methods and a sensitivity analysis of key parameters used in the Bayesian hierarchical model.

The degree of borrowing from the results of the AMIHOT I study in analyzing the results of the AMIHOT II study was contingent upon the similarity of data in the two trials. A high degree of similarity would have resulted in a large amount of pooling, but dissimilarity of the trials (either in AO Therapy versus Control differences or in overall average efficacy measure or mean MACE rate) would have resulted in a limited amount of pooling. It was thus mathematically impossible for the AMIHOT II trial to trend towards a neutral or negative outcome and still meet the statistical criteria for study success. In fact, the AMIHOT II study results did show a strong trend towards effectiveness and an infarct size reduction that was comparable to AMIHOT I study results. The resultant combination of these data in the Bayesian model was conservative with respect to the pooling of other AMIHOT I subgroups.

The best estimate of the magnitude of the median infarct size reduction observed with the adjuvant use of AO Therapy is an absolute reduction of 6.5%, or in other terms a relative reduction of ~ 25%, as compared to study patients receiving PCI alone. This level of median infarct size reduction has been correlated with long-term clinical benefit in previous studies of infarct size in AMI.

Because of the inherent variability in measuring infarct size, an exploratory analysis was performed on small infarcts (0 – 5%). This exploratory analysis showed compelling results in favor of an increased tendency for small infarcts in patients treated with AO Therapy as compared to Control subjects. This result was consistent for both AMIHOT I and II subjects in the target population, and was observed in a more conservative analysis using Bayesian hierarchical modeling.

The robustness of the results observed using the pre-specified Bayesian hierarchical model was tested using a series of alternative Bayesian models. The resultant posterior probabilities of superiority calculated using these alternative models all exceeded the 95.0% threshold for superiority.

1.8.11 Secondary Effectiveness Endpoint: ST Monitoring and ECG Results, 0 – 24 Hours

1.8.11.1 ST-Segment Monitoring Procedure

A continuous 24-hour 12-lead ECG Holter Monitor was placed on patients in the immediately after obtaining Informed Consent. The monitor was removed after 24 hours and recorded data were sent to the [redacted] for analysis. Other ECGs were performed at any time during the index hospitalization as warranted for clinical management. The [redacted] provided an independent interpretation of ST-Segment monitoring data obtained with the NorthEast 12-lead integrated circuit ST monitors.

ECG study quality, lead documented as most deviated on enrollment, deviation level value at peak deviation on enrollment and during monitoring period, presence of recurrent ischemia, area under ST-deviation vs. time trend curve during the monitoring period and percent of ST-segment resolution at regular intervals during the monitoring period were recorded for study subjects. ST-segment time trend curve areas were

evaluated at 0-3, 0-4, and 0-6 hours post-PCI as a secondary effectiveness endpoint. The analyses of these secondary effectiveness areas were performed using a basic frequentist paradigm based on AMIHOT II study data.

1.8.11.2 % ST Resolution 0 – 6 Hours

Qualitatively, reversal of ST-segment elevation post-AMI is indicative of ischemia reversal in the myocardium at-risk. A higher degree of ST resolution indicates a restoration of normal function, with 100% being complete resolution of the ECG abnormality.

Table 54 shows data for % ST resolution measured at discrete time points from t = 0 to 6 hours; here t = 0 is the documented time of last contrast injection post-PCI in the cath lab. As shown in the table, the Control group had slightly better ST resolution than the AO Therapy group at t = 0, prior to randomization. At this time point, median % ST resolution was 63.8% in Control subjects compared to 61.5% in AO Therapy subjects (p=0.14). As shown in the table, no statistical differences were observed between the two groups at t = 30, 60, 90, 120, 180, or 360 minutes.

Table 54. % ST Resolution (0-6 hrs)

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
ST resolution (%) at t =			
0 min†			
(mean ± SD) (n)	65.2 ± 25.3 (n=73)	59.0 ± 25.1 (n=187)	0.14
(median ± IQR)	63.8 ± 40.4	61.5 ± 34.5	
(range)	14.5 – 100.0	0.0 – 100.0	
30 min			
(mean ± SD) (n)	70.5 ± 22.6 (n=75)	68.6 ± 22.6 (n=204)	0.60
(median ± IQR)	70.6 ± 34.7	71.4 ± 29.5	
(range)	7.4 – 100.0	0.0 – 100.0	
60 min			
(mean ± SD) (n)	72.4 ± 20.3 (n=73)	73.0 ± 20.7 (n=200)	0.68
(median ± IQR)	73.4 ± 25.7	75.5 ± 26.8	
(range)	18.8 – 100.0	10.1 – 100.0	
90 min			
(mean ± SD) (n)	74.8 ± 20.3 (n=77)	74.7 ± 19.1 (n=209)	0.93
(median ± IQR)	75.2 ± 25.1	76.8 ± 21.6	
(range)	22.3 – 100.0	12.6 – 100.0	
120 min			
(mean ± SD) (n)	75.9 ± 19.5 (n=77)	74.9 ± 19.4 (n=209)	0.63
(median ± IQR)	79.2 ± 23.2	78.2 ± 23.3	
(range)	29.8 – 100.0	18.8 – 100.0	
180 min			
(mean ± SD) (n)	77.1 ± 17.6 (n=74)	76.0 ± 18.4 (n=213)	0.67
(median ± IQR)	76.6 ± 22	77.4 ± 22.8	
(range)	32.7 – 100.0	14.7 – 100.0	
240 min			
(mean ± SD) (n)	76.4 ± 17.8 (n=77)	75.6 ± 18.2 (n=215)	0.83
(median ± IQR)	77.7 ± 24.9	78.2 ± 21.4	
(range)	32.0 – 100.0	10.5 – 100.0	
360 min			
(mean ± SD) (n)	78.1 ± 16.8 (n=77)	75.9 ± 18.6 (n=213)	0.50
(median ± IQR)	79.2 ± 25.4	78.3 ± 22.9	
(range)	33.0 – 100.0	7.9 – 100.0	

†t = 0 min defined as time of last contrast injection
*Mann-Whitney test

1.8.11.3 ST Area Results: 0 – 24 Hours

Results for accumulated ischemic burden measured through cumulative ST-elevation time trend curve areas are presented in **Tables 55** and **56** for the ITT and PP samples. Data are presented as (median ± IQR) values in the tabled for the time intervals 0 – 3, 0 – 4, 0 – 6, and 0 – 24 hours. The most striking observation from the tables is that the median accumulated ST area in both the AO Therapy and Control groups, at any time point, is exactly equal to zero. This is surprising because one would expect to see accumulated ischemic burden in an anterior AMI population with relatively large infarct size. In contrast, AMIHOT I anterior < 6 hr Control subjects exhibited median ST curve areas of 311 μV-min at 0 – 3 hours and 600 μV-min at 0 – 6 hours (see **Section 1.5.2.3.10**); because these AMIHOT I patients had smaller documented infarct size than their counterpart AMIHOT II subjects, and thus a lesser degree of ischemia, one could have anticipated ST areas to increase in the current study, not decrease to zero. Overall, because the data set exhibits such a high percentage of zero values, very little inference can be obtained from the group comparisons of this measure. As expected, calculated p values for the group comparisons do not reveal statistically significant differences.

The Statistical Analysis Plan called for a number of group comparisons of ST time trend curve areas by patient subgroup. These tables are not included for discussion here because no significant findings were noted in the results.

Table 55. Secondary Endpoint: ST Time Trend Curve Area (Total Ischemic Area): 0-3, 0-4, 0-6, 0-24 hrs† (ITT Analysis)

	ST area (μV-min) (median ± IQR)	p value*
0 – 3 Hours		0.69
Control (n=75)	0 ± 1244	
AO Therapy (n=202)	0 ± 1270	
0 – 4 Hours		0.55
Control (n=73)	0 ± 1243	
AO Therapy (n=208)	0 ± 988	
0 – 6 Hours		0.82
Control (n=76)	0 ± 1244	
AO Therapy (n=212)	0 ± 1178	
0 – 24 Hours		0.81
Control (n=76)	0 ± 1497	
AO Therapy (n=206)	0 ± 1680	

†Area under the curve calculated for each time frame specified; time zero defined as the time of last contrast injection.
*Mann-Whitney test

Table 56. Secondary Endpoint: ST Time Trend Curve Area (Total Ischemic Area): 0-3, 0-4, 0-6, 0-24 hrs (PP Analysis)

	ST area (μV-min) (median ± IQR)	p value*
0 – 3 Hours		0.64
Control (n=65)	0 ± 1294	
AO Therapy (n=167)	0 ± 862	
0 – 4 Hours		0.84
Control (n=63)	0 ± 1294	
AO Therapy (n=169)	0 ± 861	
0 – 6 Hours		0.66
Control (n=66)	0 ± 1294	
AO Therapy (n=174)	0 ± 862	
0 – 24 Hours		0.86
Control (n=66)	0 ± 1580	
AO Therapy (n=172)	0 ± 1320	

*Mann-Whitney test

1.8.11.4 Additional Quantitative ECG Data

Additional quantitative ECG data are presented in **Table 57**, including the enrolling and peak ECG levels, accumulated absolute area totals (ischemic and non-ischemic) from 0 – 3, 0 – 4, 0 – 6, and 0 – 24 hours, and the presence of recurring ischemia (yes or no).

The results shown in **Table 57** do not reveal any significant group differences in the measured parameters.

Table 57. Additional Quantitative ECG Data

	Control Group (n=79)	AO Therapy Group (n=222)	p value*
Enrolling ECG level (μV)			0.54
(mean ± SD) (n)	398.1 ± 210.5 (n=78)	385.3 ± 227.6 (n=217)	
(median ± IQR)	400 ± 300	400 ± 300	
(range)	50 – 1000	-300 – 1200	
Peak ECG level (0-24 hrs) (μV)			0.86
(mean ± SD) (n)	685.0 ± 462.1 (n=74)	653.3 ± 451.1 (n=195)	
(median ± IQR)	600 ± 493	575 ± 425	
(range)	125 – 3100	-1843 – 2387	
Absolute Area (ischemic and non-ischemic) (μV-min)			
0-3 hrs			0.74
(median ± IQR) (n)	6,589 ± 4,262 (n=75)	6,222 ± 4,137 (n=202)	
(range)	2,095 – 32,971	2,261 – 27,557	
0-4 hrs			0.68
(median ± IQR) (n)	8,163 ± 5,314 (n=73)	7,944.5 ± 5,273 (n=208)	
(range)	2,691 – 37,640	2,991 – 29,122	
0-6 hrs			0.88
(median ± IQR) (n)	11,729 ± 7,727 (n=76)	11,525 ± 7,270 (n=212)	
(range)	4,231 – 46,459	4,074 – 36,752	
0-24 hrs			0.30
(median ± IQR) (n)	39,499.5 ± 20,903 (n=76)	33,823.5 ± 22,418 (n=206)	
(range)	14,033 – 95,838	11,763 – 105,656	
Presence of Recurring Ischemia (n/N; %)	4/79 (5.1%)	17/222 (7.7%)	0.53

*The Mann-Whitney test was used to compare the continuous variables and the Chi Square test was used for the categorical variables

1.8.12 AO Therapy Effectiveness Results: Summary

The primary effectiveness endpoint for the AMIHOT II study was achieved, as demonstrated in the data presented above. A reduction in infarct size as measured by [redacted] imaging at 14 days was definitively proven with consistent data obtained in two distinct studies. After the promising AMIHOT I subset of anterior < 6 hr patients was identified, the goal of the AMIHOT II trial was to validate these results in a meaningful way. The AMIHOT II study design relied on repeating this beneficial treatment effect in reducing infarct size in order to achieve success. Having successfully achieved the study endpoint for superiority in infarct size reduction, AO Therapy has succeeded where other adjunctive therapies have failed. The task of proving superiority in improving myocardial salvage in PCI-adjunctive therapies has thus far been an insurmountable goal for thrombectomy, distal protection, and cooling therapies. AO Therapy stands apart from these earlier efforts in achieving this endpoint. It is notable that a significant reduction in infarct size was achieved in patients with anterior MI in whom the infarct size is large despite effective reperfusion therapy. Thus, AO Therapy has significant potential to reduce infarct size and improve the prognosis of the highest risk patients, those most in need of additional therapies to improve outcomes.

Ultimately, the success of this novel therapy must be judged in consideration of the risk-benefit assessment, taking into consideration the safety profile of the device and weighing that against the documented benefit. The following sections will discuss device safety in detail, focusing on the adverse event profile for the AMIHOT II clinical study.

1.8.13 AMIHOT II Safety Data Summary

This section presents a summary of safety for all Intent-to-Treat (ITT) patients treated in the randomized phase of the AMIHOT II clinical trial. For the primary safety endpoint of 30-Day Major Adverse Cardiac Events (MACE), a Per Protocol (PP) analysis is also performed.

This safety summary is divided into two (2) sections: 1) 30-Day Safety Evaluation, and 2) Late Safety Evaluation (> 30 days to 1 year). All data presented in the Safety Evaluation are presented using the ITT patient sample as described previously. Thus, data are presented for 222 AO Therapy patients and 79 Control subjects. Within each table, the incidence of each event is tabulated by group (including number of events and number of patients with an event as well as percentage of patients in the total population with an event). All adverse events and safety endpoint events were reviewed and adjudicated by the independent Clinical Events Committee (CEC) as previously described in **Section 1.7.7.4**. The types and numbers of these events are summarized in the following tables as adjudicated by the CEC.

A Data and Safety Monitoring Board (DSMB) was utilized for safety review throughout the study. As specified in the study protocol and described previously in **Section 1.7.7.3**, the independent DSMB conducted periodic reviews of the composite safety endpoint. The DSMB reviewed the cumulative safety data at scheduled intervals to make recommendations regarding continuation of the study. At each DSMB meeting there was unanimous agreement by the board that the study should continue and that there were no safety concerns with the AMIHOT II trial that would require permanent or temporary trial stopping or change to the study design.

1.8.13.1 30-Day Follow Up Clinic Visit

A follow up evaluation was required at 30-days post procedure. This assessment consisted of an office visit with a medical history. No further imaging studies were required. **Table 58** provides a review of the 30-day follow-up assessment compliance and subject status for the AMIHOT II trial.

Table 58. 30-Day Follow Up Information

	Control Group (n=79) (n/N; %)	**AO Therapy Group** (n=222) (n/N; %)
30-day follow up completed	79/79 (100.0%)	217/222 (97.7%)
Method:		
Patient visit	69/79 (87.3%)	203/222 (91.4%)
Telephone contact with patient	10/79 (12.7%)	12/222 (5.4%)
Contact with patient's family	0/79 (0.0%)	1/222 (0.5%)
Other	0/79 (0.0%)	1/222 (0.5%)
Timing:		
Assessment performed in window†	60/79 (76.0%)	177/222 (79.7%)
Assessment performed early (< 30 days)	13/79 (16.5%)	16/222 (7.2%)
Assessment performed late (> 45 days)	6/79 (7.6%)	24/222 (10.8%)
30-day follow up not completed	0/79 (0.0%)	5/222 (2.3%)
Reason why not completed:		
Subject died	0/79 (0.0%)	5‡/222 (2.3%)
Subject lost to follow up	0/79 (0.0%)	0/222 (0.0%)
Subject withdrew from study	0/79 (0.0%)	0/222 (0.0%)
Other	0/79 (0.0%)	0/222 (0.0%)
Hospitalized since hospital discharge?	9/79 (11.4%)	17/217 (7.8%)

†30-day assessment required at 30 + 15 days
‡One of the 5 deaths occurred 32 days post-procedure; this patient's MACE status was known through medical records at 30 days even though formal follow up was incomplete.

All eligible subjects in the ITT patient sample completed a 30-day follow up assessment, including 217/222 (97.7%) AO Therapy patients and 79/79 (100%) Control patients. 5/222 (2.3%) AO Therapy subjects died prior to completing 30-day follow up (four (4) prior to day 30 and one (1) on day 32), and were thus ineligible for follow up. However,

all Adverse Events through the point of death were reviewed and adjudicated by the CEC, and these patients are considered complete through study exit.

The majority of patients who completed 30-day evaluations had an office visit, including. 203/222 (91.4%) AO Therapy patients and 69/79 (87.3%) Control patients. A total of 14/222 (6.3%) AO Therapy patients and 10/79 (12.7%) Control patients who underwent a 30-day follow-up assessment did not return for an office visit.

Of these fourteen (14) AO Therapy patients, a telephone interview was conducted for twelve (12) patients (5.4%) and one patient (0.5%) contact was made with their family in lieu of a telephone interview. This patient was still hospitalized at a local facility at the time of the planned follow up visit, and information regarding the patient's health status was obtained through a telephone conversation with her son. Subsequently, this patient completed all required assessments at both 6-months and 12-months and complete information was obtained on her health status at 30-days. One additional AO Therapy patient who did not undergo an office visit was imprisoned and not able to return for an office visit. Consequently, a telephone contact with the prison health service was substituted for an office visit. Ten (10) patients in the Control group did not complete an in-person office visit. In all ten (10) patients (12.7%), a telephone contact with the patient was substituted for an office visit.

In all patients who did not return for an office visit (24 patients total between the two study groups), a sufficient amount of information was collected regarding the occurrence of any Adverse Events or Major Adverse Cardiac Events (MACE) primary safety endpoints. All available information was reviewed by the Clinical Events Committee and was considered to be satisfactory for assessment of the primary safety study endpoint.

The 30-day assessment was required to be performed no sooner than day 30 and up to 15 days after day 30; 177/222 (79.7%) AO Therapy patients and 60/79 (75.9%) Control subjects completed the follow up assessment within this specified time interval. 16/222

(7.2%) AO Therapy patients and 13/79 (16.5%) Control subjects had an early assessment prior to 30 days. These early follow up assessments occurred in the range of 20 to 29 days, at an average of 27 days. In all cases either a later assessment was available (6 months or 1 year) or subjects were contacted by the clinical site at some point after the 30th day to document the presence or absence of MACE endpoint events occurring between the day of the early 30-day assessment and the 30th day post procedure.

24/222 (10.8%) AO Therapy patients and 6/79 (7.6%) Control patients completed a late follow up assessment at greater than 45 days post procedure. Late assessments occurred between 46 and 102 days post procedure, with an average of 55 days. The majority of late follow up visits were caused by scheduling issues surrounding patients' return for an office visit. Of these 30 patients who had a late 30-day assessment, 28 subjects returned for an office visit, while two patients underwent a late telephone assessment. Follow up assessments were completed in all living patients within 102 days post procedure. Sufficient information was obtained to enable an accurate assessment of 30-day MACE for each of these subjects.

Following initial hospital discharge, 17/217 (7.8%) AO Therapy patients and 9/79 (11.4%) Control patients underwent a rehospitalization. These patients presented with associated "Serious Adverse Events" (SAEs) resulting in rehospitalization. A description of Serious Adverse Events experienced by both patient populations is provided in **Section 1.8.13.6.3.3**.

The randomized phase 30-day safety summary which follows is divided into two (2) sections: 1) a review of the primary composite safety endpoint (30-day MACE) and 2) a review of all reported adverse event data.

1.8.13.2 Primary Composite Safety Endpoint: 30-Day MACE

1.8.13.2.1 MACE Definitions

The composite safety endpoint for the AMIHOT II clinical trial is the incidence of Major Adverse Cardiac Events (MACE) including death, reinfarction, target vessel revascularization, and stroke within 30 days. The components of this composite safety endpoint are defined as follows:

30-Day Stroke: Neurological deficit lasting 24 hours or longer, or lasting less than 24 hours with a brain imaging study showing infarction. Stroke events occurring within the 30-day (or hospital discharge) MACE window will be considered primary safety endpoint events.

30-Day Reinfarction: Presence of recurrent ischemic symptoms thought to be of cardiac origin of at least 20 minutes duration and redevelopment of ST-Segment elevation in two (2) or more contiguous precordial leads and/or worsening of existing Q waves or development of new pathologic Q waves in the precordial leads. For defining reinfarctions occurring 96 hours or more after the index event, re-elevation of CK-MB isoenzyme may be utilized as a substitute for ST segment changes. Note: degree of ST change cannot be stipulated during periprocedural phase because it may be related to underlying persistent ST segment changes related to presentation event. Reinfarction events occurring within the 30-day (or hospital discharge) MACE window will be considered primary safety endpoint events if they occur in the region of the originally treated infarct location.

30-Day TVR (Target Vessel Revascularization): Revascularization of AMIHOT II study-related vessel by means of PCI or CABG. Target Vessel Revascularization events occurring within the 30-day (or hospital discharge) MACE window will be considered

primary safety endpoint events. Any intervention performed in the cath lab at the time of treatment will not be considered a TVR.

30-Day Death: Including all deaths occurring from time of randomization through day 30 or until hospital discharge, whichever is later.

All reported study primary safety endpoints were reviewed by the CEC and classified according to the definitions outlined above into the appropriate MACE event category. De-identified source documentation and clinical imaging were provided to the CEC for review and adjudication of the primary safety endpoints. The primary endpoint of 30-Day MACE includes all MACE events occurring through the 30th day post procedure.

1.8.13.2.2 30-Day MACE Assessment Compliance

The CEC reviewed all available information on study subjects to determine if the data were sufficient to completely adjudicate for the primary safety endpoint through day 30. A MACE assessment was considered "complete" if by CEC review, the subject was evaluable for the MACE safety endpoints through the 30th day post procedure or through the point of death if the subject died prior to 30 days. A subject was considered "available" for MACE safety evaluation if the subject was either "complete" or had a MACE endpoint event but was not considered complete through the 30th day (*e.g.* subject had a target vessel revascularization prior to day 30 and was subsequently lost to follow-up).

As described above, 87.3% of Control patients and 91.4% of AO Therapy patients had completed a 30-Day follow up office visit. Five (5) AO Therapy patients who died prior to the 30-day follow-up assessment had detailed information available and were considered assessable for the primary MACE endpoint through study exit. The remaining subjects had phone contacts or other available information judged by the CEC to be sufficient for assessment of the primary safety endpoint. No subjects in the

randomized ITT cohort withdrew or were lost to follow-up prior to the 30-day assessment. Subjects with follow-up assessment prior to day 30 had later assessments sufficient to allow CEC evaluation of the MACE outcome through the 30th day. MACE assessments were complete and available for all 222/222 (100%) patients in the AO Therapy group and all 79/79 (100%) patients in the Control group.

1.8.13.3 30-Day MACE Endpoint Hypothesis and Results

In accordance with the study protocol, the composite primary safety 30-day MACE endpoint was evaluated by a test of non-inferiority within a safety delta of 6.0%. The planned primary study hypothesis test involves a Bayesian hierarchical analysis incorporating data from both the previous AMIHOT I trial and the current AMIHOT II trial as described in the study Statistical Analysis Plan.

Primary Safety Endpoint results are presented for both the ITT analysis sample and for the safety PP sample. For the ITT analysis, data are presented in the following format: 1) A presentation of 30-Day MACE results for the ITT sample in the AMIHOT II trial; 2) A summary of the 30-Day MACE results from the AMIHOT I trial and 3) The Bayesian hierarchical analysis of the composite primary endpoint demonstrating study success.

An analysis of the primary safety endpoint in the safety PP patient sample is presented using a similar presentation format. The primary endpoint analysis summary sections are then followed by a detailed summary of the primary endpoint event components.

1.8.13.3.1 Primary MACE Safety Endpoint ≤ 30 Days, ITT Analysis

1.8.13.3.1.1 AMIHOT II Trial Primary Safety Endpoint Summary: ITT Analysis

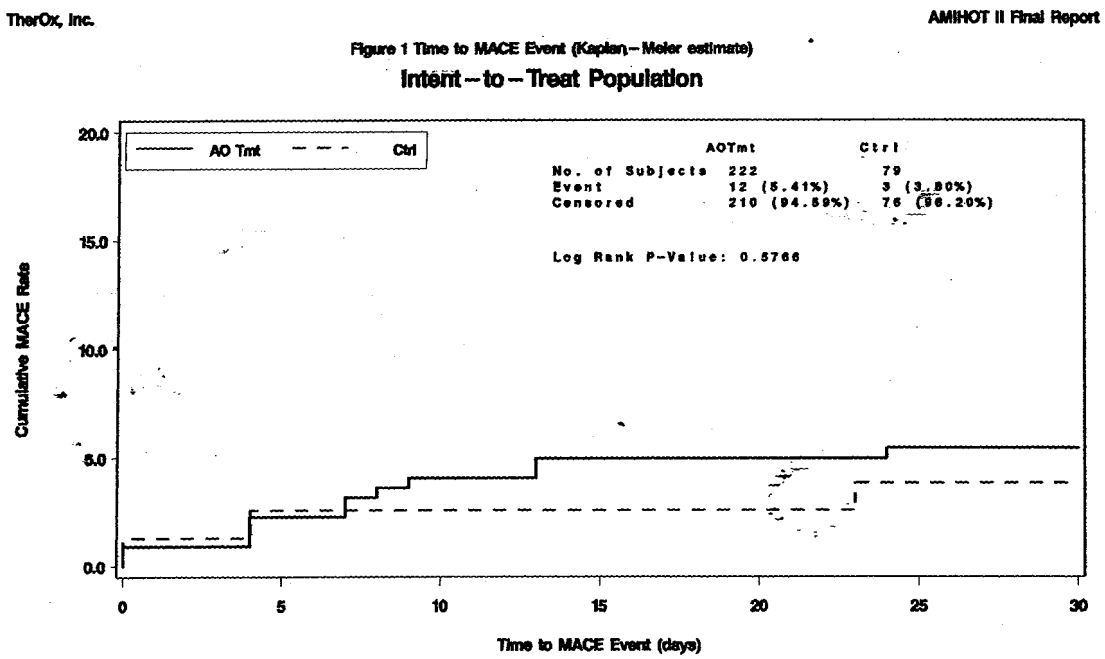
The AMIHOT II composite 30-day primary safety MACE endpoint of death, reinfarction, target vessel revascularization or stroke within 30 days is presented in **Table 59**; a Kaplan-Meier curve is shown in **Figure 8.** A total of 12/222 (5.4%) AO Therapy patients

and 3/79 (3.8%) Control patients experienced a MACE event within 30 days of the index procedure. As seen in the table, direct comparison of the composite MACE event rate and the MACE component rates by frequentist methods using Fisher's Exact Test suggests no statistically significant differences between the AO Therapy group and the Control group. The MACE rates overall were low given the study patient population which consists of individuals suffering from anterior acute myocardial infarction. Anterior AMI patients have a higher incidence of significant morbidity and mortality than those with non-anterior MI. This patient population has been reported elsewhere to have 30-day MACE rates in the range of 4.4% to 10.5%.[18, 37] In the AMIHOT II study, patients met strict inclusion/exclusion criteria prior to enrollment, including recent onset of symptoms (within 6 hours), successful and uncomplicated PCI procedure with the intention of intra-coronary stent placement, no significant concurrent cardiac morbidity or need for further intervention within 30 days, and no cardiogenic shock or periods of cardiopulmonary resuscitation (CPR) for > 10 minutes. The low overall MACE rate in both groups likely reflects the selective nature of the study population.

Table 59. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT II ITT Analysis

	Randomization Group				
	Control (N=79)		AO Therapy (N=222)		
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
MACE Assessment complete at 30 days	[redacted]	79/79(100.0%)	[redacted]	222/222 (100.0%)	-----
MACE Assessment available at 30 days†	[redacted]	79/79 (100.0%)	[redacted]	222/222(100.0%)	-----
Composite 30-Day MACE	5	3/79 (3.8%)	19	12/222 (5.4%)	0.7665
Death	0	0/79 (0.0%)	4	4/222 (1.8%)	0.5761
Target Vessel Revascularization‡	3	3/79 (3.8%)	9	8/222 (3.6%)	1.0000
TVR: Clinically Driven	[redacted]	2/79 (2.5%)	[redacted]	8/222 (3.6%)	1.0000
TVR: Objective evidence of ischemia in AMIHOT II lesion	2	2/79 (2.5%)	5	4/222 (1.8%)	0.6547
TVR: Target Lesion Revascularization	3	3/79 (3.8%)	8	7/222 (3.2%)	0.7256
TVR: Urgent or Emergent	[redacted]	2/79 (2.5%)	[redacted]	8/222 (3.6%)	1.0000
Reinfarction	2	2/79 (2.5%)	6	4/222 (1.8%)	0.6547
Stroke	0	0/79 (0.0%)	0	0/222 (0.0%)	-----

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
‡AMIHOT II main vessel or branches
*Fisher's Exact test



No. at Risk

AOTmt	222	217	213	211	211	206	195
Ctrl	79	77	77	77	77	74	63

Figure 8. 30-Day MACE Kaplan-Meier Estimate, AMIHOT II ITT Analysis

1.8.13.3.1.2 AMIHOT I Trial Primary Safety Endpoint Summary: ITT Analysis

An overview of the safety endpoint in the prior AMIHOT I trial is presented in **Table 60.** As a reminder, in the AMIHOT I trial, the overall patient population included a 24-hour window for both inferior and anterior acute myocardial infarction. The cumulative 30-day MACE rates in the prior AMIHOT I trial were 5.2% for the Control group and 6.7% for the AO Therapy group. These rates are comparable to the rates observed in the AMIHOT II study.

Table 60. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I ITT Analysis

	Randomization Group				
	Control (N=135)		AO Therapy (N=134)		
Adverse Event	**Events**† (n)	**Pts with Events** (n/N; %)	**Events**† (n)	**Pts with Events** (n/N; %)	**p value***
Composite 30-Day MACE	10	7/135 (5.2%)	11	9/134 (6.7%)	0.6176
Death	[redacted]	2/135 (1.5%)	[redacted]	4/134 (3.0%)	0.4470
Target Vessel Revascularization‡	[redacted]	3/135 (2.2%)	[redacted]	3/134 (2.2%)	1.0000
Reinfarction	[redacted]	3/135 (2.2%)	[redacted]	3/134 (2.2%)	1.0000
Stroke	[redacted]	2/135 (1.5%)	[redacted]	1/134 (0.7%)	1.0000

†Event count: count of number of unique event types experienced per patient
‡AMIHOT I main vessel or branches; further TVR subcategorization was not available as in AMIHOT II analysis
*Fisher's Exact Test

1.8.13.3.1.3 Primary Safety Endpoint Testing, Bayesian Methodology: ITT Analysis

The primary safety endpoint was non-inferiority of the cumulative incidence of 30-day MACE within a safety delta of 6.0%, assessed through Bayesian hierarchical modeling. In concept, study endpoint success was evaluated for the AMIHOT II study contingent upon the results of the AMIHOT I trial. The model was structured so that the AMIHOT I results were sub-divided into four patient subgroups of interest: anterior vs. non-anterior AMI, treated ≤ 6 or > 6 hours from symptom onset. More specifically, the safety

endpoint was satisfied if there was a high posterior probability of non-inferiority (> 95%) in the AMIHOT II trial conditional on the safety data from both trials. For the safety endpoint analysis, the ITT and PP analyses were considered co-primary.

The exact specification of the Bayesian model is as follows. [redacted] The model which we denote "Safety Model M1" is specified as follows:

[redacted]

(Safety Model M1)

[redacted]

The degree of borrowing from the results of the AMIHOT I study in analyzing the results of the AMIHOT II study was contingent upon the similarity of data in the two trials. A high degree of similarity would have resulted in a large amount of pooling, but dissimilarity of the trials (either in AO Therapy versus Control differences or in overall average efficacy measure or mean MACE rate) would have resulted in a limited amount of pooling. It was thus mathematically impossible for the AMIHOT II trial to trend towards a neutral or negative outcome and still meet the statistical criteria for study

success, and the design preserved (frequentist) type I error rates of no more than 5% under the null hypothesis of inferior safety (*i.e.* the AO Therapy group MACE rate exceeding the Control group rate by at least the safety delta of 6%).

The study was not designed or powered to achieve the study endpoints ~~as a~~ stand-alone trial outside of this Bayesian framework. Thus, the study relied upon a reasonable degree of similarity between AMIHOT I and AMIHOT II data in order to be able to pool some of the positive evidence from the AMIHOT I trial in analyzing the AMIHOT II endpoints.

Table 61 shows the results of the Bayesian analysis of 30-day MACE rates for the AMIHOT I and II studies within the framework of the model. MACE rate data are displayed as (mean ± SE) for the composite safety endpoint. The difference in MACE rates is also displayed in addition to the calculated posterior probability of non-inferiority. As seen in the table, the 30-day MACE rates for both the Control and AO Therapy groups are very similar, 5.0 ± 1.4% and 5.9 ± 1.4%, respectively. The posterior probability of non-inferiority was 99.5%. Sufficient Monte Carlo simulations were performed to ensure precision to one-tenth-of-one-percent. The AMIHOT II primary safety endpoint was achieved in the ITT analysis.

Table 61. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I & II ITT Bayesian Analysis

	Control Group (mean ± SE) (%) (n†)	**AO Therapy Group** (mean ± SE) (%) (n†)	**Difference#** (± SE) (%)	**Posterior Probability of Non-Inferiority***
ITT Analysis	5.0 ± 1.4 (n=53/79; 79)	5.9 ± 1.4 (n=52/81; 222)	0.9 ± 2.0	99.5%

†Sample size for Bayesian Evaluation given as (x/y; z) where x = number of Anterior ≤ 6 hours in AMIHOT I, y = number of other subjects in AMIHOT I and z = number of subjects in AMIHOT II (all Anterior ≤ 6 hours).
#Posterior mean difference between MACE event rate in AO and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the AO Therapy group MACE rate is not more then 6 percentage points larger than the Control group rate.

1.8.13.3.1.4 Alternative Bayesian Models to Test Robustness of Results

A series of additional Bayesian hierarchical models were developed to examine the robustness of the results to different choices of model parameters, prior distributions, and the degree of borrowing from AMIHOT I data. These models were not part of the pre-specified Statistical Analysis Plan but were developed in concert with FDA's request to examine the sensitivity of the study results to a number of factors. In **Section 1.8.10.3.4**, a discussion is provided for these models with respect to evaluation of the primary effectiveness endpoint. This section defines the safety endpoint versions of these additional models and addresses their effect upon primary safety endpoint results. For simplicity, these models are referred to in the text as "Safety Model H1", "Safety Model H2", etc. with the following brief descriptions of the purpose of each of the models:

Safety Model H1: An alternative Bayesian hierarchical model similar to our pre-specified Safety M1, but has 6 additional random effects terms, leading to higher degrees of borrowing from AMIHOT I where this is warranted.

Safety Model H2: A variant of Safety Model H1 to incorporate the two-way ANOVA mean model for the subgroup effect, to account for the potential interaction between infarct location and time to reperfusion in the AMIHOT I data.

Safety Model H3: A variant of Safety Model H1 to incorporate a term for possible center effects from the AMIHOT I and II investigational sites.

Safety Model H4: A variant of Safety Model H1 that includes the time to reperfusion as a continuous variable and treatment by time to reperfusion interaction effects.

The following discussion addresses the findings of these models.

Safety Model H1

[redacted]

[redacted] This model specification should allow for more flexibility in the model, and may lead to higher degrees of borrowing from AMIHOT I where this is warranted. The complete model is written as

[redacted] (Safety Model H1)

The new hierarchical model Safety H1 was used to evaluate the primary safety endpoint of 30-day MACE. These results are shown in comparison to the pre-specified Safety Model M1 below in **Table 61a**. The strength of evidence for non-inferiority is unaffected by the adjustment to the hierarchical modeling.

Table 61a. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I & II ITT Bayesian Analysis, New Hierarchical Model (Model H1)

	Control Group (mean ± SE)(%)	**AO Therapy Group** (mean ± SE)(%)	**Difference#** (± SE)(%)	**Posterior Probability of Non-Inferiority***
Pre-specified Safety Model M1	5.0 ± 1.4	5.9 ± 1.4	0.9 ± 2.0	99.5%
New Hierarchical Safety Model H1	4.5 ± 1.5	5.6 ± 1.3	1.2 ± 1.9	99.5%

#Posterior mean difference between MACE event rate in AO and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the AO Therapy group MACE rate is not more then 6 percentage points larger than the Control group rate.

Safety Model H2

[redacted] The resultant Safety Model H2 is defined as:

[redacted]

(Safety Model H2)

Safety Model H2 was used to evaluate the primary safety endpoint of 30-day MACE. These results are shown in comparison to model H1 below in **Table 61b**, and demonstrate again that the models lead to very similar levels of evidence for non-inferiority.

Table 61b. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I & II ITT Bayesian Analysis, New Hierarchical Model (Model H2)

	Control Group (mean ± SE)(%)	**AO Therapy Group** (mean ± SE)(%)	**Difference#** (± SE)(%)	**Posterior Probability of Non-Inferiority***
New Hierarchical Safety Model H1	4.5 ± 1.5	5.6 ± 1.3	1.2 ± 1.9	99.5%
Two-Way ANOVA mean structure (Safety Model H2)	4.5 ± 1.5	5.6 ± 1.3	1.2 ± 1.9	99.5%

#Posterior mean difference between MACE event rate in AO and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the AO Therapy group MACE rate is not more then 6 percentage points larger than the Control group rate.

Safety Model H3

[redacted] The resultant Safety Model H3 is defined as:

[redacted] (Safety Model H3)

Similarly, Saefty Model H3 was used to evaluate the primary safety endpoint of 30-day MACE with the incorporation of site effects. These results are shown in comparison to Safety Model H1 without site effects below in **Table 61c**. As observed with the primary effectiveness endpoint, the inclusion of site effects into the model for primary safety evaluation results in a slightly smaller posterior probability, but does not impact study results in a material way.

Table 61c. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I & II ITT Bayesian Analysis, New Hierarchical Model (Safety Model H3)

	Control Group (mean ± SE) (%)	**AO Therapy Group** (mean ± SE) (%)	**Difference#** (± SE) (%)	**Posterior Probability of Non-Inferiority***
New Hierarchical Safety Model H1 (No Site Effects)	4.5 ± 1.5	5.6 ± 1.3	1.2 ± 1.9	99.5%
Safety Model H3 (with Site Effects)	4.1 ± 1.7	5.5 ± 1.7	1.3 ± 2.1	98.3%

#Posterior mean difference between MACE event rate in AO and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the AO Therapy group MACE rate is not more then 6 percentage points larger than the Control group rate.

Safety Model H4

With respect to formal analysis of the primary safety endpoint, [redacted]

[redacted]

[redacted] The results are shown in comparison to these base models below in **Table 61d**. As shown in the table, the inclusion of these effects into the model has a negligible impact upon the study results.

Table 61d. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I & II ITT Bayesian Analysis, Incorporation of Time to Reperfusion and Treatment by Time Interaction Effects into Safety Model H1

	Control Group (mean ± SE)(%)	**AO Therapy Group** (mean ± SE)(%)	**Difference#** (± SE)(%)	**Posterior Probability of Non-Inferiority***
Base Model				
New Hierarchical Safety Model H1	4.5 ± 1.5	5.6 ± 1.3	1.2 ± 1.9	99.5%
Incorporation of Time to Reperfusion as Continuous Variable and Treatment by Time Interaction				
Hierarchical Safety Model H4[&]	4.6 ± 1.6	5.6 ± 1.4	1.0 ± 2.1	99.4%

#Posterior mean difference between MACE event rate in AO and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the AO Therapy group MACE rate is not more then 6 percentage points larger than the Control group rate.

Model Results Using Informative (Borrowing) and Non-Informative (Non-Borrowing) Priors

The results for Safety Models M1, H1, H2, and H3 are shown below in **Table 61e**, comparing the results using informative (borrowing) and non-informative (non-borrowing) priors. The results are provided using available data for illustrative purposes and are applicable to model variants with imputation. For each model, [redacted]

[redacted]

With respect to the primary safety endpoint, the pre-specified Safety Model M1 achieved a moderate level of borrowing from the safety information in AMIHOT I. Safety Models H1 and H2 are able to achieve higher levels of borrowing. For Safety Model H3, [redacted]. In summary, the aggregate effect of borrowing in the models of primary safety endpoint data is similar, and the study results are not sensitive to the choice of model.

Table 61e. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I & II ITT Bayesian Analysis, Comparison of Informative (Borrowing) and Non-Informative (Non-Borrowing) Priors, Safety Models M1, H1, H2, H3

	Control Group (mean ± SE) (%)	**AO Therapy Group** (mean ± SE) (%)	**Difference#** (± SE) (%)	**Posterior Probability of Non-Inferiority***
Informative Prior (Borrowing)	*(n=53/79; 79)* †	*(n=52/81; 222)* †		
Safety Model M1	5.0 ± 1.4 *(n_{borrow}=52)* &	5.9 ± 1.4 *(n_{borrow}=37)* &	0.9 ± 2.0	99.5%
Safety Model H1	4.5 ± 1.5 *(n_{borrow}=75)* &	5.6 ± 1.3 *(n_{borrow}=77)* &	1.2 ± 1.9	99.5%
Safety Model H2	4.4 ± 1.5 *(n_{borrow}=75)* &	5.6 ± 1.3 *(n_{borrow}=80)* &	1.1 ± 1.9	99.6%
Safety Model H3	4.1 ± 1.7 *(n_{borrow}=0)* &	5.5 ± 1.7 *(n_{borrow}=0)* &	1.3 ± 2.1	98.3%
Non-Informative Prior (Non-Borrowing)	*(n=79)*	*(n=222)*		
Safety Model M1	3.8 ± 2.2	5.8 ± 1.6	2.0 ± 2.7	95.0%
Safety Model H1	3.9 ± 2.2	5.4 ± 1.5	1.5 ± 2.6	97.0%
Safety Model H2	3.9 ± 2.2	5.4 ± 1.5	1.5 ± 2.6	97.0%
Safety Model H3	1.6 ± 1.5	3.9 ± 1.7	2.3 ± 2.2	95.6%

†Sample size for Bayesian Evaluation given as (x/y; z) where x = number of Anterior ≤ 6 hours in AMIHOT I, y = number of other subjects in AMIHOT I and z = number of subjects in AMIHOT II (all Anterior ≤ 6 hours).
#Posterior mean difference between MACE event rate in AO and Control groups incorporating data from AMIHOT I study into the hierarchical model.
*Posterior probability that the AO Therapy group MACE rate is not more then 6 percentage points larger than the Control group rate.
&The sample size n_{borrow} is computed as the relative gain in efficiency of the model using both AMIHOT I and AMIHOT II data to the model using only AMIHOT II data (i.e. the ratio of the posterior variances minus 1) times the sample size in AMIHOT II.

1.8.13.3.2 Primary MACE Safety Endpoint ≤ 30 Days, PP Analysis

As prespecified in the AMIHOT II study clinical protocol and Statistical Analysis Plan, the primary MACE safety endpoint analysis is considered primary for both the ITT and PP analyses. The PP safety sample consists of randomized patients not excluded due to major protocol deviations. A detailed breakout of exclusion criteria for this patient population is presented in **Section 1.8.6**. As discussed in that section and presented in **Table 19**, The AMIHOT II PP safety sample consists of 186 AO Therapy patients and 78 Control subjects.

Endpoint results are presented for the Per Protocol analysis as follows: 1) A presentation of 30-Day MACE results for the Per Protocol sample in the AMIHOT II trial; 2) A summary of the 30-Day MACE results for the Per Protocol analysis from the AMIHOT I trial and 3) The Bayesian hierarchical analysis of the composite primary endpoint demonstrating study success for the Per Protocol sample.

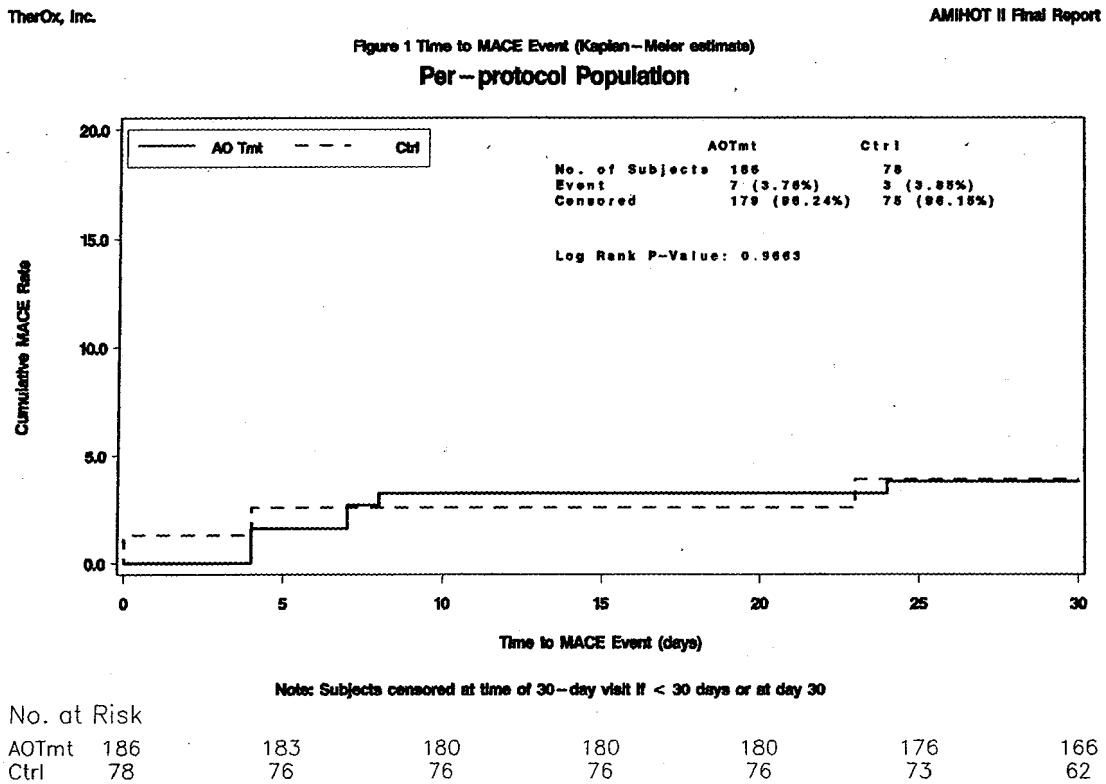
1.8.13.3.2.1 AMIHOT II Trial Primary Safety Endpoint Summary: PP Analysis

The AMIHOT II composite 30-day primary safety MACE endpoint of death, reinfarction, target vessel revascularization or stroke is presented in **Table 62** for the PP analysis; a Kaplan-Meier curve is shown in **Figure 9**. A total of 7/186 (3.8%) AO Therapy patients exhibited 13 MACE events, as compared to five (5) MACE events in 3/78 (3.8%) Control patients. As shown in the table, direct comparison of the composite MACE event rate and the individual MACE component rates by frequentist methods using Fisher's Exact test suggests no statistically significant differences between the AO Therapy group and the Control group.

Table 62. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT II PP Analysis

	Randomization Group				
	Control (N=78)		AO Therapy (N=186)		
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
MACE Assessment complete at 30 days	[redacted]	78/78 (100.0%)	[redacted]	186/186 (100.0%)	-----
MACE Assessment available at 30 days†	[redacted]	78/78 (100.0%)	[redacted]	186/186 (100.0%)	-----
Composite 30-Day MACE	5	3/78 (3.8%)	13	7/186 (3.8%)	1.0000
Death	0	0/78 (0.0%)	2	2/186 (1.1%)	1.0000
Target Vessel Revascularization‡	3	3/78 (3.8%)	6	5/186 (2.7%)	0.6972
TVR: Clinically Driven	[redacted]	2/78 (2.6%)	[redacted]	5/186 (2.7%)	1.0000
TVR: Objective evidence of ischemia in AMIHOT II lesion	2	2/78 (2.6%)	4	3/186 (1.6%)	0.6339
TVR: Target Lesion Revascularization	3	3/78 (3.8%)	5	4/186 (2.2%)	0.4249
TVR: Urgent or Emergent	[redacted]	2/78 (2.6%)	[redacted]	5/186 (2.7%)	1.0000
Reinfarction	2	2/78 (2.6%)	5	3/186 (1.6%)	0.6339
Stroke	0	0/78 (0.0%)	0	0/186 (0.0%)	-----

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
‡AMIHOT II main vessel or branches
* Fisher's Exact test



No. at Risk

AOTmt	186	183	180	180	180	176	166
Ctrl	78	76	76	76	76	73	62

Figure 9. 30-Day MACE Kaplan-Meier Estimate, AMIHOT II PP Analysis

1.8.13.3.2.2 AMIHOT I Trial Primary Safety Endpoint Summary: PP Analysis

The AMIHOT I composite 30-day primary safety MACE endpoint of death, reinfarction, target vessel revascularization or stroke is presented in **Table 63** for the PP sample. A total of 9/119 (7.6%) AO Therapy patients exhibited 11 MACE events, as compared to ten (10) MACE events in 7/124 (5.6%) Control patients. As shown in the table, direct comparison of the composite MACE event rate and the individual MACE component rates by frequentist methods using Fisher's Exact test suggests no statistically significant differences between the AO Therapy group and the Control group.

Table 63. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I PP Analysis

	Randomization Group				
	Control (N=124)		AO Therapy (N=119)		
Adverse Event	**Events†** (n)	**Pts with Events** (n/N; %)	**Events†** (n)	**Pts with Events** (n/N; %)	**p value***
Composite 30-Day MACE	10	7/124 (5.6%)	11	9/119 (7.6%)	0.6112
Death	[redacted]	2/124 (1.6%)	[redacted]	4/119 (3.4%)	0.4389
Target Vessel Revascularization‡	[redacted]	3/124 (2.4%)	[redacted]	3/119 (2.5%)	1.0000
Reinfarction	[redacted]	3/124 (2.4%)	[redacted]	3/119 (2.5%)	1.0000
Stroke	[redacted]	2/124 (1.6%)	[redacted]	1/119 (0.8%)	1.0000

†Event count: count of number of unique event types experienced per patient
‡AMIHOT I main vessel or branches; TVR subcategorization was not available as in AMIHOT II analysis
*Fisher's Exact Test

1.8.13.3.2.3 Primary Safety Endpoint Testing, Bayesian Methodology: PP Analysis

Table 64 shows the results of the Bayesian analysis of 30-day MACE rates for the AMIHOT I and II studies within the framework of Safety Model M1, as described previously. As seen in the table, the 30-day MACE rates for both the Control and AO Therapy PP groups are very similar, 5.1 ± 1.5% and 4.7 ± 1.5%, respectively (mean ± SE). The posterior probability of non-inferiority was 99.9%. Sufficient Monte Carlo simulations were performed to ensure precision to one-tenth-of-one-percent. The AMIHOT II primary safety endpoint was achieved in the PP analysis.

Table 64. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I & II PP Bayesian Analysis

	Control Group (mean ± SE) (%) (n†)	**AO Therapy Group** (mean ± SE) (%) (n†)	**Difference#** (± SE) (%)	**Posterior Probability of Non-Inferiority***
PP Analysis	5.1 ± 1.5 (n=51/73; 78)	4.7 ± 1.5 (n=47/72; 186)	-0.4 ± 2.0	99.9%

†Sample size for Bayesian Evaluation given as (x/y; z) where x = number of Anterior ≤ 6 hours in AMIHOT I, y = number of other subjects in AMIHOT I and z = number of subjects in AMIHOT II (all Anterior ≤ 6 hours).

#Posterior mean difference between MACE event rate in AO and Control groups incorporating data from AMIHOT I study (see **Appendix 18**) into the hierarchical model described in **Appendices 9** and **10**.
*Posterior probability that the AO Therapy group MACE rate is not more then 6 percentage points larger than the Control group rate.

1.8.13.3.3 30-Day MACE Component Events, ITT Analysis

Further detail on the 30-day MACE component events for the ITT patient sample is provided in the following sections. As shown previously, **Table 59** includes a breakdown of the 30-day primary safety endpoint MACE event components (death, reinfarction, target vessel revascularization, and stroke). As discussed, 19 MACE events occurred in 12/222 (5.4%) AO Therapy patients, and five (5) MACE events occurred in 3/79 (3.8%) Control group patients. Four (4) AO Therapy group patients and two (2) Control patients experienced more than one MACE event. In all six (6) of these patients with more than one MACE component event, the patient presented with reinfarction thatwas treated with target vessel revascularization.

1.8.13.3.3.1 Target Vessel Revascularization (TVR)

A total of 8/222 (3.6%) AO Therapy patients and 3/79 (3.8%) Control patients underwent TVR procedures within the first 30 days. Within the AO Therapy group, TVR in combination with reinfarction occurred in four (4) patients. One patient [redacted] presented with two (2) episodes of reinfarction, one at day four (4) and one at day six (6), both requiring treatment with revascularization procedures involving the target lesion.

All nine (9) TVR procedures in the eight (8) AO Therapy patients were clinically driven and required urgent or emergent treatment. Eight (8) of these nine (9) revascularizations involved PCI with stent placement, while one patient underwent coronary artery bypass grafting (CABG). These TVR procedures occurred between 0 and 24 days post-procedure. Of these nine (9) episodes, six (6) incidents occurred in five (5) patients who initially presented with chest pain and were documented to have stent occlusion. One patient ([redacted]) exhibited chest discomfort, nausea and malaise in the absence of stent occlusion, while one patient [redacted] presented with dyspnea and stenosis [redacted] Patient [redacted] did not present with active symptomatology, but had a prior medical history of multivessel coronary artery disease (CAD). Angiographic imaging obtained during the initial PCI revealed occlusions within four (4) coronary vessels. The patient subsequently underwent an urgent 4-Vessel CABG at 13 days post-procedure.

Eight (8) TVR procedures in seven (7) patients (3.2%) involved revascularization of the AMIHOT II lesion. One patient ([redacted]) underwent TVR without Target Lesion Revascularization (TLR). This patient originally received stent placement with two (2) stents at the bifurcation of the LAD coronary artery and first diagonal branch, with the LAD designated as the target lesion. He required revascularization of the first diagonal branch at 24 days post procedure. As the first diagonal branch is part of the

AMIHOT II Vessel but not the AMIHOT II designated lesion, the patient was categorized as having undergone TVR but not TLR.

Only one patient [redacted] had TVR that was determined to be related to the AO Therapy procedure, specifically the infusion catheter. This patient presented with chest discomfort, nausea and malaise at eight (8) days post procedure. Angiography revealed a hazy lesion within the proximal stent with no critical obstruction. No images on the initial films after the AO Therapy procedure were available, and the CEC could not exclude a mechanical issue related to the catheter that may have produced a lesion evidenced on follow-up angiography. Consequently, the conservative approach was taken to attribute this finding to the infusion catheter.

In the Control population, 3/79 (3.8%) patients required treatment with TVR, for a total of three (3) events. Two (2) patients presented with chest pain, while one patient exhibited dyspnea. All three (3) patients required revascularization of the AMIHOT II target lesion. Revascularization occurred in the range of 0-23 days post procedure.

Two (2) of the three (3) Control patients with a MACE event exhibited a combination of the MACE endpoints of reinfarction resulting in TVR with PCI. One of these patients exhibited an acute occlusion (within 1 hour of the index procedure) with chest pain and electrocardiogram (EKG) changes, while the second experienced a subacute thrombosis presenting as progressive dyspnea at four (4) days post procedure. These procedures were both urgent/emergent, clinically driven, and with objective evidence of ischemia in the AMIHOT II lesion.

One Control patient underwent TVR through an elective bypass procedure without any objective evidence of ischemia in the AMIHOT II lesion. This patient, who had a history of aortic valve stenosis, presented on day 23 with angina due to extensive coronary artery disease and severe symptomatic aortic stenosis. The patient underwent elective CABG

with five (5) distal anastamoses, reimplantation of coronary arteries, mitral valvuloplasty and a Benman procedure.

There were no significant differences in the incidence of TVR between the study groups. An abbreviated narrative for each patient who underwent Target Vessel Revascularization is presented in **Table 65**.

1.8.13.3.3.2 Reinfarction

A total of 4/222 (1.8%) AO Therapy patients exhibited six (6) reinfarction events. All four (4) patients had an associated TVR procedure and were described above. Two (2) patients [redacted] each experienced two (2) separate incidents of reinfarction. All six (6) episodes of reinfarction were adjudicated by the CEC to be related to the Index PCI procedure. None of these incidents were determined to be related to the AO device or procedure.

Within the AO Therapy population, reinfarction occurred at between 4 and 13 days post procedure. All episodes of reinfarction initially presented as chest pain, and were caused by a subacute stent thrombosis.

In comparison, 2/79 (2.5%) Control patients each experienced one reinfarction event. All episodes were determined to be related to the Index PCI procedure, and occurred at day 0 and day 4 post-procedure. One of these patients exhibited an acute occlusion (within 1 hour of the index procedure) with chest pain and EKG changes, while the second experienced a subacute thrombosis presenting as progressive dyspnea at four (4) days post-procedure.

Reinfarction rates in the AO Therapy group (1.8%) and Control group (2.5%) were similar. **Table 65** provides an abbreviated narrative for patients experiencing reinfarction.

Table 65. Brief Narratives for Patients Undergoing Reinfarction and/or Target Vessel Revascularization within 30 Days

ID	Subjects Undergoing Target Vessel Revascularization and/or Reinfarction ≤ 30 Days
[redacted]	[redacted]

ID	Subjects Undergoing Target Vessel Revascularization and/or Reinfarction ≤ 30 Days
[redacted]	[redacted]

ID	Subjects Undergoing Target Vessel Revascularization and/or Reinfarction ≤ 30 Days
[redacted]	[redacted]

ID	Subjects Undergoing Target Vessel Revascularization and/or Reinfarction ≤ 30 Days
[redacted]	[redacted]

ID	Subjects Undergoing Target Vessel Revascularization and/or Reinfarction ≤ 30 Days
[redacted]	[redacted]

ID	Subjects Undergoing Target Vessel Revascularization and/or Reinfarction ≤ 30 Days
[redacted]	[redacted]

ID	Subjects Undergoing Target Vessel Revascularization and/or Reinfarction ≤ 30 Days
[redacted]	[redacted]

ID	Subjects Undergoing Target Vessel Revascularization and/or Reinfarction ≤ 30 Days
[redacted]	[redacted]

ID	Subjects Undergoing Target Vessel Revascularization and/or Reinfarction ≤30 Days
[redacted]	[redacted]

ID	Subjects Undergoing Target Vessel Revascularization and/or Reinfarction ≤ 30 Days
[redacted]	[redacted]

ID	Subjects Undergoing Target Vessel Revascularization and/or Reinfarction ≤ 30 Days
[redacted]	[redacted]

1.8.13.3.3.3 Stroke

No patients randomized to either group experienced stroke, with an incidence rate of 0%.

1.8.13.3.3.4 Patient Death

There were a total of four (4) deaths which occurred within 30 days post procedure, all occurring in the AO Therapy group (1.8%). All four (4) deaths were determined to be cardiac-related deaths. Three (3) deaths were adjudicated by the Clinical Events Committee to be related to the patient's primary disease state (coronary artery disease). Of these three (3) deaths, two (2) patients expired from myocardial rupture within the territory of the LAD at 4 and 9 days, respectively. One patient passed from hypoxic

encephalopathy resulting from a cardiac arrest that occurred prior to enrollment. This patient was a protocol deviation for the AMIHOT II trial and should have been excluded per protocol, as she had presented with a loss of consciousness for over five minutes prior to trial enrollment.

The fourth death was determined by the CEC to be related to the AO Therapy procedure. Patient [redacted] initially underwent a difficult and complicated index PCI procedure associated with prolonged periods of no reflow. A TIMI flow of only Grade 2 was able to be established post procedure. At four minutes into the AO Therapy procedure, the patient experienced an arrhythmia consisting of ventricular tachycardia and ventricular fibrillation. These events culminated in cardiac arrest. Standard resuscitative measures were employed including multiple attempts at defibrillation. Late during the course of the event an angiogram was performed which demonstrated mid-LAD and distal circumflex artery occlusions. It cannot be determined if this finding was primarily related to the low flow/cardiac arrest (most likely) or primary stent occlusion (less likely secondary to no preceding new EKG changes). The patient was treated with thrombolytic therapy. Despite continued resuscitative measures, no sustainable hemodynamic status was achieved and efforts were terminated after two hours. During resuscitative measures, residual slow flow was present. This adjudication by the Clinical Events Committee was a conservative judgment based primarily on event timing, as the patient experienced cardiac arrest four (4) minutes post-initiation of AO Therapy.

Death within 30 days of the index procedure was rare in this study and on the low end of rates reported for other acute MI trials, particularly in light of the fact that only anterior MI patients were enrolled. Recent acute MI trials have reported death rates in the range of 1.1% to 6.6%[18, 38].

Table 66 provides an abbreviated patient narrative for each patient death occurring within the first 30 days after randomization.

Table 66. Patient Death Occurring ≤ 30 Days

ID	Subjects Who Died at ≤ 30 Days Post Procedure
[redacted]	[redacted]

ID	Subjects Who Died at ≤ 30 Days Post Procedure
[redacted]	[redacted]

ID	Subjects Who Died at ≤ 30 Days Post Procedure
[redacted]	[redacted]
[redacted]	[redacted]

1.8.13.4 30-Day MACE Results: Context with Published Trial Data

Within the AMIHOT II trial, the 30-day MACE rates for the ITT patient sample were comparable between the AO Therapy group (5.4%) and the Control group (3.8%). In addition, these observed rates are quite low given the anterior MI patient population being studied. The 5.4% incidence of MACE in the AO Therapy group is comparable to the rates presented in current trials examining various therapies for acute myocardial infarction. Recent studies report an incidence of 30-Day MACE in the range of 4.4% (CADILLAC)[18] to 10.5% (ACE)[37]. In trials where stroke is not included within the MACE endpoint, recent studies present a MACE incidence in the range of 4.6% (STENT PAMI)[41] to 16.1% (RAPPORT)[40]. The CAPTIM[39] trial did not include TVR within the primary MACE endpoint, as the endpoint consisted of only patient death, reinfarction, and stroke. Results indicated a MACE incidence in the range of 6.2% for patients treated with PTCA, and 8.2% for patients treated with pre-hospital thrombolytics. In the context of these and other contemporary AMI trials, the AMIHOT II 30-day MACE rates are comparable, although it is understood that these inter-study comparisons have limitations. The Per Protocol analysis MACE rate results were similar to those obtained for the Intent-to-Treat analysis.

1.8.13.5 30-Day MACE Results: Summary

The pre-specified analysis of the primary safety endpoint hypothesis of non-inferiority in 30-day MACE rate was evaluated using a hierarchical Bayesian model that incorporated both AMIHOT and AMIHOT II MACE data. Non-inferiority between the AO Therapy and Control study arms was demonstrated to within the required 6% non-inferiority margin for both the ITT and PP analyses. This finding was demonstrated to be robust with respect to analysis of alternative Bayesian models that included various interaction effects and prior specifications.

In conclusion, the AMIHOT II study met its primary safety hypothesis, demonstrating that AO Therapy is non-inferior within the safety margin to standard PCI treatment with respect to the incidence of 30-day Major Adverse Cardiac Events. The 30-day MACE rates in this trial were low considering the nature of the patients enrolled. Component MACE event rates (death, reinfarction, stroke and target vessel revascularization) were similar between groups and in line with expected rates from the literature. There were no AO device-related events. The AO Therapy procedure was adjudicated to be the cause of the MACE event in only two (2) instances, and these were both noted by the Clinical Events Committee to be conservatively adjudicated as such. Review of the literature for recent AMI trials suggests that the safety profile of AO Therapy as characterized by the 30-day MACE rate is comparable to the safety profile for standard of care for patients undergoing treatment for AMI. These results support the safety of AO Therapy for use in the intended patient population.

1.8.13.6 Review of All 30-Day Adverse Event Data: AMIHOT II Study

1.8.13.6.1 Unanticipated Adverse Device Effects

There were no unanticipated adverse device effects reported by the participating investigational centers at any time during the AMIHOT II clinical trial.

1.8.13.6.2 Anticipated Adverse Events

During the course of the AMIHOT II clinical trial, adverse events were collected on all enrolled patients in accordance with the reporting requirements outlined in the clinical protocol. An Adverse Event is defined as any undesirable experience that is a deviation from the baseline status (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject during the course of the study, whether or not it is related to the devices or procedures described in the Investigational Plan.

The AMIHOT II Clinical Events Committee provided a document to the sites listing certain events that are not reportable because they are normally expected to occur in conjunction with the index procedure or are associated with customary, standard care of patients undergoing percutaneous interventions for acute myocardial infarction. This list included events such as early post-procedure pain at the access site, post-anesthesia/ conscious sedation emesis and nausea (within 24 hours), and minor, localized tenderness or swelling at vascular access site.

Per the protocol, adverse events were reported for all randomized and Run-In subjects through 30-days post-PCI, or until patient discharge, whichever date occurred later. Additional adverse event data were collected during hospital visits and via telephone survey at the 6 and 12-month time points. As such, the adverse event summary presented is an extensive review of clinical experience of the intended patient population during the observation period.

For purposes of consistent trial reporting and analysis, events were categorized by MedDRA coding. Consistent with the *MedDRA® Term Selection: Points to Consider* document (Release 3.3, June 2004) events were further grouped according to diagnosis when the diagnosis was identified by the reporter.

Adverse Event review and adjudication was performed on a regular basis by the Clinical Events Committee throughout the clinical trial. The CEC was responsible for the review and adjudication of all adverse events that occurred over the course of the study. To the extent possible, adverse events were classified in accordance with established adverse event definitions. For each Adverse Event, the CEC identified the Event Name/MedDRA code, event relationship (device, procedure, etc), and event category (serious, non-serious, not an event).

As outlined in the CEC Manual of Operations, an Adverse Event is identified as a condition that involves one of the following: A unique symptom or event that is a change from the patient's baseline status, a series of symptoms or events that can be categorized as a single entity, or a specific diagnosis responsible for a clinical change. The CEC adjudicated some of the site-reported adverse events to be "Not An Event." These incidents were determined to be symptoms associated with another reported event, duplicate events identified using similar or different nomenclature reported with the same start/stop dates or events representing observations or incidental findings or determined to be inaccurately/incorrectly reported.

Adverse events occurring from the time of randomization through exactly 30 days post procedure (including peri-procedural events) are presented separately from those occurring after day 30 (post 30-day events). This enables an accurate description of any morbidity and mortality potentially associated with AO Therapy to be separated from post 30-day events that may be more related to the underlying disease process.

1.8.13.6.3 Adverse Events Occurring within 30 Days of the Index Procedure

In the AMIHOT II study, a total of 119/222 (53.6%) AO Therapy patients and 37/79 (46.8%) Control patients presented with one or more adverse events during study follow-up.

Patients were enrolled in the AMIHOT II trial following acute myocardial infarction, representing an often seriously ill medical/surgical population. The subsequent rates of Adverse Events are consistent with those expected from a high-risk patient population. Patients randomized to the AO Therapy group exhibited a similar incidence of Adverse Events (53.6%) compared to patients randomized to the control group (46.8%) despite the fact that patients randomized to the AMIHOT II Therapy group received an additional 90 minutes of catheterization time in addition to increased anticoagulation therapy, and a requirement to up-size arterial access sheaths to accommodate the [redacted] infusion

catheter or undergo a second arterial stick to allow for placement of the draw sheath. Increased procedure time would also be expected to subsequently increase the rates of Adverse Events.

1.8.13.6.3.1 Relationship of Adverse Events Occurring within 30 Days of the Index Procedure

In accordance with the CEC Manual of Operations, Adverse Events were assigned a single most probable attribution hierarchically as follows: AO Device (System or Cartridge), AO Procedure [redacted] Infusion Catheter or [redacted] Infusion Catheter, Arterial Supply Sheath, Other), PCI Procedure, Study Medications, Coronary Artery Disease, Comorbid Condition, or Unknown. **Table 67** presents the breakdown of all Adverse Events and Serious Adverse Events in the AMIHOT II trial by relationship.

Table 67. Overall Summary of Adjudicated Adverse Events within First 30 Days

	Randomization Group				
	Control (N=79)		AO Therapy (N=222)		
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Assessment Complete	[redacted]	79/79 (100.0%)	[redacted]	222/222 (100.0%)	[redacted]
Assessment Available †	[redacted]	79/79 (100.0%)	[redacted]	222/222 (100.0%)	[redacted]
Any Adverse Event	58	37/79 (46.8%)	256	119/222 (53.6%)	0.3633
AO device related AE	[redacted]		0	0/222 (0.0%)	[redacted]
AO procedure related AE	[redacted]		46	40/222 (18.0%)	[redacted]
Index PCI procedure related AE	16	14/79 (17.7%)	43	34/222 (15.3%)	0.5931
Coronary Artery Disease related AE	23	17/79 (21.5%)	94	64/222 (28.8%)	0.3003
Study Medication related AE	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
Other relationship ‡	18	15/79 (19.0%)	62	46/222 (20.7%)	0.8709
Unknown relationship	1	1/79 (1.3%)	9	9/222 (4.1%)	0.4627
Serious Adverse Event	19	15/79 (19.0%)	89	57/222 (25.7%)	0.2844
AO device related AE	[redacted]		0	0/222 (0%)	[redacted]
AO procedure related AE	[redacted]		17	14/222 (6.3%)	[redacted]

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available
‡Including pre-existing condition, concurrent condition, concurrent intervention and other relationships
*Fisher's Exact test

Table 67 (continued). Overall Summary of Adjudicated Adverse Events within First 30 Days

	Randomization Group				
	Control (N=79)		AO Therapy (N=222)		
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Index PCI procedure related AE	4	4/79 (5.1%)	17	14/222 (6.3%)	1.0000
Coronary Artery Disease related AE	9	8/79 (10.1%)	42	32/222 (14.4%)	0.4408
Study Medication related AE	0	0/79 (0.0%)	0	0/222 (0.0%)	-----
Other relationship ‡	6	5/79 (6.3%)	10	10/222 (4.5%)	0.5480
Unknown relationship	0	0/79 (0.0%)	3	3/222 (1.4%)	0.5706
Adverse Event related to AMIHOT II Vessel	8	5/79 (6.3%)	26	20/222 (9.0%)	0.6353

‡Including pre-existing condition, concurrent condition, concurrent intervention and other relationships
*Fisher's Exact test

As seen in **Table 67**, the majority of Adverse Events for both the AO Therapy group (28.8%) and the Control group (21.5%) were adjudicated by the Clinical Events Committee to be related to the patient's coronary artery disease (CAD). Additionally, 34/222 (15.3%) AO Therapy patients and 14/79 (17.7%) Control patients presented with an Adverse Event determined to be related to the Index PCI procedure. Overall in both groups, over half of all adverse events were categorized as related to the patient's baseline CAD or Index PCI procedure. These results are consistent with expected rates in a patient population receiving immediate treatment for AMI.

Within this total incidence of Adverse Events, 57/222 (25.7%) AO Therapy patients presented a total of 89 events determined to be a "Serious Adverse Event" (SAE). Similarly, 15/79 (19.0%) Control patients demonstrated a total of 19 SAEs. The distribution of SAEs by relationship category was similar to the dispersion of Adverse Events. The majority of events were determined to be related to coronary artery disease (14.4% AO Therapy, 10.1% Control group) and the Index PCI procedure (6.3% AOTherapy, 5.1% Control group).

Adverse Events were also categorized by the Clinical Events Committee as Target Vessel related, Access site related or Other. 20/222 (9.0%) AO Therapy patients and 5/79 (6.3%) Control patients demonstrated an Adverse Event related to the AMIHOT II Target Vessel. No statistically significant difference was found in the rate of target vessel-related events between the two study groups.

Events were categorized as related to the AO device or procedure only for subjects in the AO Therapy group. This category was not applicable to the Control group. No Adverse Events were adjudicated to be related to the AO device. A total of 40/222 (18.0%) AO Therapy patients presented a total of 46 Adverse Events determined to be related to the AO procedure. Within these forty (40) patients, 14/222 (6.3%) AO Therapy subjects presented a total of seventeen (17) Serious Adverse Events determined to be related to the

AO procedure. Serious Adverse Events related to the AO procedure are discussed in detail in **Section 1.8.13.6.3.6.**

1.8.13.6.3.2 Classification of Adverse Events Occurring Within 30 Days of the Index Procedure

A detailed summary of the types and numbers of adverse events according to MedDRA categorization for System Organ Class and Preferred Term as adjudicated by the Clinical Events Committee is included in the following pages in **Table 68**.

Table 68. Summary of All Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Assessment Complete	[redacted]	[redacted]	79/79 (100.0%)	[redacted]	222/222 (100.0%)	[redacted]
Assessment Available †	[redacted]	[redacted]	79/79 (100.0%)	[redacted]	222/222 (100.0%)	[redacted]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	[redacted]	1	1/79 (1.3%)	8	7/222 (3.2%)	0.6855
	ANEMIA	1	1/79 (1.3%)	7	7/222 (3.2%)	0.6855
	THROMBOCYTOPENIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
CARDIAC DISORDERS	[redacted]	22	17/79 (21.5%)	87	65/222 (29.3%)	0.2389
	ACCELERATED IDIOVENTRICULAR RHYTHM	1	1/79 (1.3%)	2	2/222 (0.9%)	1.0000
	ANGINA PECTORIS	3	3/79 (3.8%)	9	9/222 (4.1%)	1.0000
	AORTIC VALVE STENOSIS	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	ATRIAL FIBRILLATION	2	2/79 (2.5%)	9	9/222 (4.1%)	0.7338

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
*Fisher's Exact test

Table 68 (continued). Summary of All Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	ATRIAL FLUTTER	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	CARDIAC ARREST	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	CARDIAC FAILURE CONGESTIVE	5	5/79 (6.3%)	17	16/222 (7.2%)	1.0000
	CARDIAC TAMPONADE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	CARDIOGENIC SHOCK	1	1/79 (1.3%)	5	5/222 (2.3%)	1.0000
	CORONARY ARTERY DISEASE	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	CORONARY ARTERY OCCLUSION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	CORONARY ARTERY STENOSIS	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	INTRACARDIAC THROMBUS	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
	MYOCARDIAL ISCHEMIA	0	0/79 (0.0%)	4	4/222 (1.8%)	0.5761

*Fisher's Exact test

Table 68 (continued). Summary of All Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	MYOCARDIAL RUPTURE	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
	PALPITATIONS	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	PERICARDIAL EFFUSION	1	1/79 (1.3%)	7	7/222 (3.2%)	0.6855
	PERICARDITIS	2	2/79 (2.5%)	7	7/222 (3.2%)	1.0000
	PULMONARY EDEMA	0	0/79 (0.0%)	4	4/222 (1.8%)	0.5761
	SICK SINUS SYNDROME	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	SUPRAVENTRICULAR TACHYCARDIA	3	3/79 (3.8%)	1	1/222 (0.5%)	0.0568
	VENTRICULAR FIBRILLATION	0	0/79 (0.0%)	3	3/222 (1.4%)	0.5693
	VENTRICULAR TACHYCARDIA	2	2/79 (2.5%)	8	8/222 (3.6%)	1.0000

*Fisher's Exact test

Table 68 (continued). Summary of All Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AQ Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
GASTROINTESTINAL DISORDERS	[redacted]	1	1/79 (1.3%)	5	5/222 (2.3%)	1.0000
	ABDOMINAL PAIN UPPER	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	DIARRHEA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	GASTROESOPHOGEAL REFLUX DISEASE	1	1/79 (1.3%)	0	0/222 (0%)	0.2625
	HEMATEMESIS	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	VOMITING	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	[redacted]	6	6/79 (7.6%)	18	15/222 (6.8%)	0.7995
	ADVERSE DRUG REACTION	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
	CHEST PAIN	4	4/79 (5.1%)	7	5/222 (2.3%)	0.2485

*Fisher's Exact test

Table 68 (continued). Summary of All Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	DRUG WITHDRAWAL SYNDROME	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	EDEMA PERIPHERAL	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	HYPOTHERMIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	PYREXIA	2	2/79 (2.5%)	6	6/222 (2.7%)	1.0000
HEPATOBILIARY DISORDERS	[redacted]	1	1/79 (1.3%)	1	1/222 (0.5%)	0.4567
	CHOLECYSTITIS	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	HEPATITIS C	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
IMMUNE SYSTEM DISORDERS	[redacted]	1	1/79 (1.3%)	7	7/222 (3.2%)	0.6855
	DRUG HYPERSENSITIVITY	1	1/79 (1.3%)	3	3/222 (1.4%)	1.0000
	HYPERSENSITIVITY	0	0/79 (0.0%)	4	4/222 (1.8%)	0.5761

*Fisher's Exact test

Table 68 (continued). Summary of All Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
INFECTIONS AND INFESTATIONS	[redacted]	3	3/79 (3.8%)	18	17/222 (7.7%)	0.3005
	BACTEREMIA	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
	CATHETER SITE INFECTION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	PHARYNGITIS	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	PNEUMONIA	1	1/79 (1.3%)	5	5/222 (2.3%)	1.0000
	URINARY TRACT INFECTION	2	2/79 (2.5%)	9	9/222 (4.1%)	0.7338
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	[redacted]	3	3/79 (3.8%)	16	11/222 (5.0%)	1.0000
	CORONARY ARTERY DISSECTION	0	0.0 (0.0%)	1	1/222 (0.5%)	1.0000
	DRUG TOXICITY	1	1 (1.3%)	1	1/222 (0.5%)	0.4567

*Fisher's Exact test

Table 68 (continued). Summary of All Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	IMPLANT SITE HEMATOMA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	STENT OCCLUSION	2	2/79 (2.5%)	12	9/222 (4.1%)	0.7338
	TRAUMATIC HEMATOMA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
METABOLISM AND NUTRITION DISORDERS	[redacted]	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
	DIABETES MELLITUS	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	GOUT	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	[redacted]	2	2/79 (2.5%)	0	0/222 (0.0%)	0.0682
	ARTHRALGIA	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	SACRAL PAIN	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625

*Fisher's Exact test

Table 68 (continued). Summary of All Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
NERVOUS SYSTEM DISORDERS	[redacted]	1	1/79 (1.3%)	5	5/222 (2.3%)	1.0000
	AGITATION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	CONVULSION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	DIZZINESS	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	HEADACHE	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	HYPOXIC ENCEPHALOPATHY	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	TRANSIENT ISCHEMIC ATTACK	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
PSYCHIATRIC DISORDERS	[redacted]	1	1/79 (1.3%)	4	4/222 (1.8%)	1.0000
	ANXIETY	1	1/79 (1.3%)	2	2/222 (0.9%)	1.0000
	DELIRIUM	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	DEPRESSION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

*Fisher's Exact test

Table 68 (continued). Summary of All Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
RENAL AND URINARY DISORDERS	[redacted]	2	2/79 (2.5%)	11	11/222 (5.0%)	0.5252
	HEMATURIA	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
	NEPHROLITHIASIS	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	RENAL FAILURE ACUTE	1	1/79 (1.3%)	8	8/222 (3.6%)	0.4540
	URINARY RETENTION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	[redacted]	1	1/79 (1.3%)	4	4/222 (1.8%)	1.0000
	DYSPNEA	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	PLEURAL EFFUSION	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
	PNEUMONIA ASPIRATION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

*Fisher's Exact test

Table 68 (continued). Summary of All Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	RESPIRATORY DISORDER	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	[redacted]	1	1/79 (1.3%)	3	3/222 (1.4%)	1.0000
	ECCHYMOSIS	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	HERPES ZOSTER	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	RASH	1	1/79 (1.3%)	1	1/222 (0.5%)	0.4567
VASCULAR DISORDERS	[redacted]	12	11/79 (13.9%)	67	57/222 (25.7%)	0.0409
	AORTIC ANEURYSM	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	ARTERIOVENOUS FISTULA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	CAROTID ARTERY STENOSIS	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625

*Fisher's Exact test

Table 68 (continued). Summary of All Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	CATHETER SITE HEMATOMA	8	8/79 (10.1%)	39	39/222 (17.6%)	0.1488
	CATHETER SITE HEMORRHAGE	1	1/79 (1.3%)	1	1/222 (0.5%)	0.4567
	HEMORRHAGE	0	0/79 (0.0%)	4	4/222 (1.8%)	0.5761
	HYPERTENSION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	HYPOTENSION	0	0/79 (0.0%)	11	10/222 (4.5%)	0.0681
	RETROPERITONEAL HEMORRHAGE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	SYNCOPE VASOVAGAL	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
	THROMBOPHLEBITIS	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	UROGENITAL HEMORRHAGE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	CATHETER SITE HEMATOMA	8	8/79 (10.1%)	39	39/222 (17.6%)	0.1488
	VASCULAR PSEUDOANEURYSM	2	2/79 (2.5%)	4	4/222 (1.8%)	0.6547

*Fisher's Exact test

As shown in **Table 68**, the majority of Adverse Events occurring within the AMIHOT II trial were classified under either the System Organ Class (SOC) of Cardiac Disorder (29.3% AO Therapy, 21.5% Control) or Vascular Disorder (25.7% AO Therapy, 13.9% Control).

Other more common events included Adverse Events classified under the SOCs of Infections and Infestations (7.7% AO Therapy, 3.8% Control), General Disorders and Administration Site Conditions (6.8% AO Therapy, 7.6% Control), Injury, Poisoning and Procedural Complications (5.0% AO Therapy, 3.8% Control), and Renal and Urinary Disorders (5.0% AO Therapy, 2.5% Control).

Events occurring less frequently (*i.e.* at a rate less than 4% for both populations) included Adverse Events categorized under the SOCs of Blood and Lymphatic System Disorders, Gastrointestinal Disorders, Hepatobiliary Disorders, Immune System Disorders, Metabolism and Nutrition Disorders, Musculoskeletal and Connective Tissue Disorders, Nervous System Disorders, Psychiatric Disorders, Respiratory, Thoracic and Mediastinal Disorders, and Skin and Subcutaneous Tissue Disorders.

No statistically significant differences were found at the SOC level between the two study groups except for in the category of Vascular Disorders (25.7% AO Therapy, 13.9% Control, p=0.04). A discussion of events classified under Cardiac Disorders, Vascular Disorders, and Injury, Poisoning, and Procedural Complications are presented in the following section, as these three (3) categories are most related to the patient's disease state and treatment.

A total of 65/222 (29.3%) AO Therapy subjects presented with an Adverse Event classified as a cardiac disorder, compared to 17/79 (21.5%) Control patients. Most commonly, these events were episodes of congestive heart failure, angina/myocardial ischemia, or ventricular tachycardia. These are common periprocedural events in acute MI patients and occurred at a rate in this trial that is consistent with that reported in other

AMI trials[18, 37-41]. No statistically significant differences were noted between the two patient groups by direct comparison of the rates. MACE events within the first 30 days were detailed previously.

A total of 57/222 (25.7%) AO Therapy patients demonstrated a vascular disorder, compared to 11/79 (13.9%) Control patients. This difference was statistically significant when compared by Fisher's Exact test (p=0.04). Bleeding and vascular access events are well-known side effects of percutaneous intervention for acute myocardial infarction. Vascular events were common in both study groups. The AO Therapy procedure involves an increased procedure time of approximately 90 minutes, with a larger arterial access sheath size (9 French) and an increased anticoagulant medication regime. All of these factors may have contributed to a higher rate of bleeding and vascular access events. A further detailed discussion of bleeding events is provided in **Section 1.8.13.6.4** "Summary of Bleeding Events" and a discussion of vascular access site events is provided in **Section 1.8.13.6.5** "Access Site Events Within the First 30 Days".

A total of 11/222 (5.0%) AO Therapy patients experienced a total of 16 Adverse Events classified under "Injury, Poisoning and Procedural Complications". Within these 11 individuals, nine (9) patients (4.1%) exhibited 12 episodes of stent occlusions. Additional events included one patient with each of the following events: Coronary artery dissection (0.5%), drug toxicity (0.5%), implant site hematoma (0.5%) and traumatic hematoma (0.5%). The majority of these events (10/16 events, 62.5%) were determined to be caused by the Index PCI procedure. Two patients presented a total of three (3) events (stent occlusion, implant site hematoma, and traumatic hematoma) determined to be related to coronary artery disease. Traumatic hematoma in the neck in one patient was determined to be related to coronary artery disease, specifically intubation prior to randomization from the initial acute myocardial infarction. A second patient [redacted] presented with stent occlusion and implant site hematoma, both determined to be related to coronary artery disease. This patient had a previous medical

history of myocardial infarction, hypertension, and a family history of coronary artery disease. At 19 days post procedure he presented with ventricular tachycardia and ventricular fibrillation, leading to placement of an ICD. A repeat angiography revealed stenosis within his previously placed stent within the LAD. He exhibited a hematoma that had formed within the ICD implantation site. Both the stent occlusion and implant site hematoma were determined by the Clinical Events Committee to be caused by coronary artery disease. Three (3) additional episodes of stent occlusion classified under "Injury Poisoning and Procedural Complications" were determined to be related to the AO Therapy procedure.

A total of 3/79 (3.8%) Control patients exhibited three (3) Adverse Events classified under "Injury Poisoning and Procedural Complications". Events experienced by patients randomized to the Control population included one patient with drug toxicity (1.3%) and two patients with stent occlusion (2.5%). Both episodes of stent occlusion were determined to be related to the Index PCI procedure, while drug toxicity was related to the patient's statin medication.

No statistically significant differences were found in the incidence of Injury, Poisoning and Procedural complications between the AO Therapy and Control groups, despite the longer procedure performed in patients who received AO Therapy.

Overall, the type and frequency of Adverse Events experienced in the AMIHOT II trial were similar to those expected in the patient population under study and largely comparable between the two groups. Further discussion of events by seriousness and relationship is provided in the subsequent sections.

1.8.13.6.3.3 Serious Adverse Events (SAEs) Occurring within 30 Days of the Index Procedure

An adverse event is determined to be "Serious" whenever the adverse event is fatal, life-threatening, disabling, or results in patient hospitalization or prolongation of hospitalization. For each reported Adverse Event, the investigator made a determination as to whether or not this event met the definition of serious. As part of the adjudication process, the Clinical Events Committee reviewed and made a final determination as to whether or not the event met the definition of serious.

Table 69 provides a summary of all SAEs by SOC and PT. A total of 57/222 (25.7%) AO Therapy patients presented a total of 89 events determined to be a "Serious Adverse Event". Similarly, 15/79 (19.0%) Control patients exhibited a total of 19 SAEs. The majority of events were determined to be "Serious" due to a requirement for prolonged hospitalization. The incidence of SAEs was not significantly different between the two study groups. As described above, the slightly higher incidence of SAEs in the AO Therapy group may have been caused by the longer procedure time, extended anticoagulation treatment, and vascular access requirements involved in the AO Therapy procedure.

Table 69. Summary of All Serious Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Assessment Complete	[redacted]	[redacted]	79/79 (100.0%)	[redacted]	222/222 (100.0%)	[redacted]
Assessment Available †	[redacted]	[redacted]	79/79 (100.0%)	[redacted]	222/222 (100.0%)	[redacted]
All serious adverse events	[redacted]	19	15/79 (19.0%)	89	57/222 (25.7%)	0.2828
BLOOD AND LYMPHATIC SYSTEM DISORDERS	[redacted]	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	ANEM[redacted]	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
CARDIAC DISORDERS	[redacted]	9	8/79 (10.1%)	41	33/222 (14.9%)	0.3436
	ANGINA PECTORIS	1	1/79 (1.3%)	4	4/222 (1.8%)	1.0000
	AORTIC VALVE STENOSIS	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	ATRIAL FIBRILLATION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	CARDIAC ARREST	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available
*Fisher's Exact test

Table 69 (continued). Summary of All Serious Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	CARDIAC FAILURE CONGESTIVE	4	4/79 (5.1%)	8	8/222 (3.6%)	0.5208
	CARDIAC TAMPONADE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	CARDIOGENIC SHOCK	1	1/79 (1.3%)	5	5/222 (2.3%)	1.0000
	CORONARY ARTERY DISEASE	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	CORONARY ARTERY OCCLUSION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	CORONARY ARTERY STENOSIS	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	MYOCARDIAL ISCHEMIA	0	0/79 (0.0%)	4	4/222 (1.8%)	0.5761
	MYOCARDIAL RUPTURE	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
	PERICARDITIS	1	1/79 (1.3%)	2	2/222 (0.9%)	1.0000
	PULMONARY EDEMA	0	0/79 (0.0%)	4	4 (1.8%)	0.5761

*Fisher's Exact test

Table 69 (continued). Summary of All Serious Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	SICK SINUS SYNDROME	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	VENTRICULAR FIBRILLATION	0	0/79 (0.0%)	3	3/222 (1.4%)	0.5693
	VENTRICULAR TACHYCARDIA	0	0/79 (0.0%)	3	3/222 (1.4%)	0.5693
GASTROINTESTINAL DISORDERS	[redacted]	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	GASTROESOPHOGEAL REFLUX DISEASE	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	[redacted]	2	2/79 (2.5%)	6	5/222 (2.3%)	1.0000
	ADVERSE DRUG REACTION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	CHEST PAIN	2	2/79 (2.5%)	2	2/222 (0.9%)	0.2823
	HYPOTHERMIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

*Fisher's Exact test

Table 69 (continued). Summary of All Serious Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	PYREXIA	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
INFECTIONS AND INFESTATIONS	[redacted]	0	0/79 (0.0%)	3	3/222 (1.4%)	0.5693
	BACTEREMIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	PNEUMONIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	URINARY TRACT INFECTION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	[redacted]	2	2/79 (2.5%)	15	11/222 (5.0%)	0.5252
	CORONARY ARTERY DISSECTION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	DRUG TOXICITY	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	STENT OCCLUSION	2	2/79 (2.5%)	12	9/222 (4.1%)	0.7338
	TRAUMATIC HEMATOMA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

*Fisher's Exact test

Table 69 (continued). Summary of All Serious Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
NERVOUS SYSTEM DISORDERS	[redacted]	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
	HYPOXIC ENCEPHALOPATHY	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	TRANSIENT ISCHEMIC ATTACK	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
PSYCHIATRIC DISORDERS	[redacted]	1	1/79 (1.3%)	1	1/222 (0.5%)	0.4567
	ANXIETY	1	1/79 (1.3%)	1	1/222 (0.5%)	0.4567
RENAL AND URINARY DISORDERS	[redacted]	1	1/79 (1.3%)	4	4/222 (1.8%)	1.0000
	HEMATURIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	RENAL FAILURE ACUTE	1	1/79 (1.3%)	3	3/222 (1.4%)	1.0000

*Fisher's Exact test

Table 69 (continued). Summary of All Serious Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	[redacted]	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
	PNEUMONIA ASPIRATION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	RESPIRATORY DISORDER	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
VASCULAR DISORDERS	[redacted]	3	2/79 (2.5%)	14	12/222 (5.4%)	0.3699
	CAROTID ARTERY STENOSIS	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	CATHETER SITE HEMATOMA	0	0/79 (0.0%)	3	3/222 (1.4%)	0.5693
	CATHETER SITE HEMORRHAGE	1	1/79 (1.3%)	1	1/222 (0.5%)	0.4567
	HEMORRHAGE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

*Fisher's Exact test

Table 69 (continued). Summary of All Serious Adverse Events within 30 Days by SOC and PT

		Randomization Group				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	HYPOTENSION	0	0/79 (0.0%)	4	3/222 (1.4%)	0.5693
	RETROPERITONEAL HEMORRHAGE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	VASCULAR PSEUDOANEURYSM	1	1/79 (1.3%)	4	4/222 (1.8%)	1.0000

*Fisher's Exact test

As seen in **Table 69**, no significant differences were found in the incidence of SAEs between the two study groups with regard to event category or SOC. As was the case with overall adverse events, the majority of SAEs were classified into the categories of "Cardiac Disorders", "Vascular Disorders" and "Injury, Poisoning and Procedural Complications". A total of 33/222 (14.9%) AO Therapy patients and 8/79 (10.1%) Control patients exhibited a SAE classified in the System Organ Class of "Cardiac Disorders". 12/222 (5.4%) AO Therapy patients and 2/79 (2.5%) Control patients presented a SAE classified under "Vascular Disorders". Additionally, 11/222 (5.0%) AO Therapy patients and 2/79 (2.5%) Control patients exhibited a SAE classified under "Injury, Poisoning, and Procedural Complications".

1.8.13.6.3.4 Classification of Serious Adverse Events Occurring within 30 Days of the Index Procedure by Relationship

SAEs were categorized further according to MedDRA Preferred Term (PT), System Organ Class (SOC) by relationship (causality). Patients in both study groups presented with a similar incidence of events with comparable underlying causes. No significant differences were found in frequency and type of SAE by relationship between AO Therapy and Control patients. A summary of all Serious Adverse Events within 30 days by SOC, PT and Relationship to Patient is provided in **Table 70.**

Table 70. Summary of All Serious Adverse Events within 30 Days by SOC, PT and Relationship by Patient

			Randomization Group				
Relationship	**Category**	**Adverse Event**	**Control (N=79)**		**AO Therapy (N=222)**		
	System Organ Class	**MedDRA PT**	**Events (n)**	**Pts with Events (n/N; %)**	**Events (n)**	**Pts with Events (n/N; %)**	**p value***
Assessment Complete			[redacted]	79/79 (100.0%)	[redacted]	222/222 (100.0%)	[redacted]
Assessment Available†			[redacted]	79/79 (100.0%)	[redacted]	222/222 (100.0%)	[redacted]
Any Relationship	All serious adverse events		19	15/79 (19.0%)	89	57/222 (25.7%)	0.2828
AO procedure related AE	All serious adverse events		[redacted]		17	14/222 (6.3%)	[redacted]
	CARDIAC DISORDERS		[redacted]		5	5/222 (2.3%)	[redacted]
		ANGINA PECTORIS	[redacted]		1	1/222 (0.5%)	[redacted]
		CARDIAC ARREST	[redacted]		1	1/222 (0.5%)	[redacted]
		CARDIOGENIC SHOCK	[redacted]		3	3/222 (1.4%)	[redacted]
	INJURY, POISONING AND PROCEDURAL COMPLICATIONS		[redacted]		3	3/222 (1.4%)	[redacted]
		STENT OCCLUSION	[redacted]		3	3/222 (1.4%)	[redacted]

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available
*Fisher's Exact test

Table 70 (continued). Summary of All Serious Adverse Events within 30 Days by SOC, PT and Relationship by Patient

			Randomization Group				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		[redacted]	[redacted]	1	1/222 (0.5%)	[redacted]
		PNEUMONIA ASPIRATION	[redacted]	[redacted]	1	1/222 (0.5%)	[redacted]
	VASCULAR DISORDERS		[redacted]	[redacted]	8	8/222 (3.6%)	[redacted]
		CATHETER SITE HEMATOMA	[redacted]	[redacted]	3	3/222 (1.4%)	[redacted]
		CATHETER SITE HEMORRHAGE	[redacted]	[redacted]	1	1/222 (0.5%)	[redacted]
		HYPOTENSION	[redacted]	[redacted]	1	1/222 (0.5%)	[redacted]
		VASCULAR PSEUDOANEURYSM	[redacted]	[redacted]	3	3/222 (1.4%)	[redacted]
Index PCI procedure related AE	All serious adverse events		4	4/79 (5.[illegible]%)	17	14/222 (6.3%)	0.7896

*Fisher's Exact test

Table 70 (continued). Summary of All Serious Adverse Events within 30 Days by SOC, PT and Relationship by Patient

			Randomization Group				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	CARDIAC DISORDERS		0	0/79 (0.0%)	3	3/222 (1.4%)	0.5693
		CARDIAC TAMPONADE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		CORONARY ARTERY OCCLUSION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		MYOCARDIAL ISCHEMIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		PYREXIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	INFECTIONS AND INFESTATIONS		0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		BACTEREMIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	INJURY, POISONING AND PROCEDURAL COMPLICATIONS		2	2/79 (2.5%)	10	8/222 (3.6%)	1.0000

*Fisher's Exact test

Table 70 (continued). Summary of All Serious Adverse Events within 30 Days by SOC, PT and Relationship by Patient

			Randomization Group				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
		CORONARY ARTERY DISSECTION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		DRUG TOXICITY	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		STENT OCCLUSION	2	2/79 (2.5%)	8	6/222 (2.7%)	1.0000
	RENAL AND URINARY DISORDERS		1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
		RENAL FAILURE ACUTE	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	VASCULAR DISORDERS		1	1/79 (1.3%)	2	2/222 (0.9%)	1.0000
		CATHETER SITE HEMORRHAGE	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
		RETROPERITONEAL HEMORRHAGE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		VASCULAR PSEUDOANEURYSM	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

*Fisher's Exact test

Table 70 (continued). Summary of All Serious Adverse Events within 30 Days by SOC, PT and Relationship by Patient

			Randomization Group				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Coronary Artery Disease related AE	All serious adverse events		9	8/79 (10.1%)	42	32/222 (14.4%)	0.4405
	CARDIAC DISORDERS		8	7/79 (8.9%)	31	26/222 (11.7%)	0.6750
		ANGINA PECTORIS	1	1/79 (1.3%)	3	3/222 (1.4%)	1.0000
		ATRIAL FIBRILLATION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		CARDIAC FAILURE CONGESTIVE	4	4/79 (5.1%)	7	7/222 (3.2%)	0.4872
		CARDIOGENIC SHOCK	1	1/79 (1.3%)	2	2/222 (0.9%)	1.0000
		CORONARY ARTERY DISEASE	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
		CORONARY ARTERY STENOSIS	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		MYOCARDIAL ISCHEMIA	0	0/79 (0.0%)	3	3/222 (1.4%)	0.5693
		MYOCARDIAL RUPTURE	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000

*Fisher's Exact test

Table 70 (continued). Summary of All Serious Adverse Events within 30 Days by SOC, PT and Relationship by Patient

			Randomization Group				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
		PERICARDITIS	1	1/79 (1.3%)	2	2/222 (0.9%)	1.0000
		PULMONARY EDEMA	0	0/79 (0.0%)	4	4/222 (1.8%)	0.5761
		VENTRICULAR FIBRILLATION	0	0/79 (0.0%)	3	3/222 (1.4%)	0.5693
		VENTRICULAR TACHYCARDIA	0	0/79 (0.0%)	3	3/222 (1.4%)	0.5693
	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		0	0/79 (0.0%)	3	3/222 (1.4%)	0.5693
		CHEST PAIN	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
		PYREXIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	INJURY, POISONING AND PROCEDURAL COMPLICATIONS		0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
		STENT OCCLUSION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

*Fisher's Exact test

Table 70 (continued). Summary of All Serious Adverse Events within 30 Days by SOC, PT and Relationship by Patient

			Randomization Group				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
		TRAUMATIC HEMATOMA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	NERVOUS SYSTEM DISORDERS		0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		HYPOXIC ENCEPHALOPATHY	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	PSYCHIATRIC DISORDERS		1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
		ANXIETY	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
	RENAL AND URINARY DISORDERS		0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
		RENAL FAILURE ACUTE	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
	VASCULAR DISORDERS		0	0/79 (0.0%)	3	2/222 (0.9%)	1.0000
		HYPOTENSION	0	0/79 (0.0%)	3	2/222 (0.9%)	1.0000

*Fisher's Exact test

Table 70 (continued). Summary of All Serious Adverse Events within 30 Days by SOC, PT and Relationship by Patient

			Randomization Group				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Other relationship *	All serious adverse events		6	5/79 (6.3%)	10	10/222 (4.5%)	0.5505
	CARDIAC DISORDERS		1	1/79 (1.3%)	2	2/222 (0.9%)	1.0000
		AORTIC VALVE STENOSIS	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
		CARDIAC FAILURE CONGESTIVE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		SICK SINUS SYNDROME	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	GASTROINTESTINAL DISORDERS		1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
		GASTROESOPHOGEAL REFLUX DISEASE	1	1/79 (1.3%)	0	0/222 (0%)	0.2625
	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		2	2/79 (2.5%)	1	1/222 (0.5%)	0.1696
		ADVERSE DRUG REACTION	0	0/79 (0%)	1	1/222 (0.5%)	1.0000

[†]Including pre-existing condition, concurrent condition, concurrent intervention and other relationships
*Fisher's Exact test

Table 70 (continued). Summary of All Serious Adverse Events within 30 Days by SOC, PT and Relationship by Patient

			Randomization Group				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
		CHEST PAIN	2	2/79 (2.5%)	0	0/222 (0.0%)	0.0682
	INFECTIONS AND INFESTATIONS		0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
		PNEUMONIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		URINARY TRACT INFECTION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	NERVOUS SYSTEM DISORDERS		0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		TRANSIENT ISCHEMIC ATTACK	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	PSYCHIATRIC DISORDERS		0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		ANXIETY	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	RENAL AND URINARY DISORDERS		0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		HEMATURIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

*Fisher's Exact test

Table 70 (continued). Summary of All Serious Adverse Events within 30 Days by SOC, PT and Relationship by Patient

			Randomization Group				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		RESPIRATORY DISORDER	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	VASCULAR DISORDERS		2	1/79 (1.3%)	1	1/222 (0.5%)	0.4567
		CAROTID ARTERY STENOSIS	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
		HEMORRHAGE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		VASCULAR PSEUDOANEURYSM	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
Unknown relationship	All serious adverse events		0	0/79 (0.0%)	3	3/222 (1.4%)	0.5693
	BLOOD AND LYMPHATIC SYSTEM DISORDERS		0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

*Fisher's Exact test

Table 70 (continued). Summary of All Serious Adverse Events within 30 Days by SOC, PT and Relationship by Patient

			Randomization Group				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
		ANEMIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		HYPOTHERMIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	RENAL AND URINARY DISORDERS		0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		RENAL FAILURE ACUTE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

*Fisher's Exact test

As seen in **Table 70**, the majority of SAEs were determined by the Clinical Events Committee to be related to the patient's primary disease state. A total of 32/222 (14.4%) AO Therapy patients and 8/79 (10.1%) Control patients experienced a SAE determined to be related to coronary artery disease. Additionally, 14/222 (6.3%) AO Therapy patients and 4/79 (5.1%) Control patients demonstrated a SAE related to the Index Procedure. These results are consistent with incidence rates expected in an AMI patient population.

14/222 (6.3%) AO Therapy patients exhibited a total of 17 SAEs that were believed to be related to AO Therapy procedure. The majority of these events were access site related, and consisted of vascular events such as catheter site hematoma and pseudoaneurysm. Most vascular events were determined to be "Serious" due to an increased hospitalization time or due to the need for treatment with blood transfusion. None of the bleeding events determined to be related to the AO procedure were classified as a "Severe/Life Threatening Bleeding Event". The majority of events resolved within a short period of time following the index procedure, and did not involve any lasting clinical sequelae. No AO Device related Serious Adverse Events were noted in the AMIHOT II study.

1.8.13.6.3.5 Serious Adverse Events Related to the Index PCI Procedure at 30 Days

A total of 14/222 (6.3%) AO Therapy patients and 4/79 (5.1%) Control patients demonstrated an SAE related to the Index Procedure. Within the AO Therapy group, the most frequent type of SAE in this category was stent occlusion in six (6) patients (2.7%). All other SAE attributed to the Index Procedure each involved one patient (0.5%) and included the following categories: Cardiac tamponade, coronary artery occlusion (non AMIHOT II lesion), myocardial ischemia, pyrexia, bacteremia, coronary artery dissection, drug toxicity, retroperitoneal hemorrhage and vascular pseudoaneurysm. Five (5) of the fourteen (14) patients had symptom onset during AO Therapy. These events included two episodes of stent occlusion, coronary artery occlusion, coronary artery

disease, and cardiac tamponade. Although these patients demonstrated symptom onset during the AO procedure, the event was determined by the Clinical Events Committee to be related to the Index PCI procedure.

Of the four (4) Control patients who experienced a SAE related to the Index PCI procedure, stent occlusion occurred in two patients (2.5%), followed by catheter site hemorrhage in one patient (1.3%) and acute renal failure in one patient (1.3%).

No significant differences were found between the AO Therapy and Control group in the incidence of SAEs related to the Index PCI procedure.

1.8.13.6.3.6 Serious AO Therapy Device or Procedure Related Adverse Events Occurring within 30 Days of the Index Procedure

There were no AMIHOT II SAEs with relationship attributed to the AO Device (*i.e.* AO System or Cartridges). A total of 14/222 (6.3%) study subjects experienced a total of 17 AO Therapy Procedure-Related Serious Adverse Events. The most frequent categories of procedure-related adverse events were cardiogenic shock in three (3) patients (1.4%), stent occlusion in three (3) patients (1.4%), catheter site hematoma in three (3) patients (1.4%) and vascular pseudoaneurysm in three (3) patients (1.4%). Additionally, the following AO Therapy procedure-related SAEs were each experienced by a single patient: Angina pectoris (0.5%), cardiac arrest (0.5%), aspiration pneumonia (0.5%), catheter site hemorrhage (0.5%), and hypotension (0.5%).

These events were considered to be Serious primarily due to the requirement for prolonged hospitalization (47% of the AO Procedure-Related SAEs). Other reasons for the "Serious" categorization included a serious anomaly requiring medical intervention to prevent impairment (5 events), persistent disability (1 event) and death (1 event). Events resulting in death or disability are explained below.

Cardiac arrest resulting in death occurred in [redacted]. This patient presented with arrhythmia shortly after initiation of the AO Therapy procedure, consisting of ventricular tachycardia and fibrillation and culminating in cardiac arrest. Cardiac arrest was adjudicated as Target Vessel Related and was determined to be related to the AO Therapy procedure, specifically to the [redacted] catheter placement. However, this patient underwent a difficult and complicated PCI procedure associated with prolonged periods of no reflow. The adjudication of cardiac arrest as related to the AO Therapy procedure was a conservative decision based on event timing. This death has been summarized previously in **Section 1.8.13.3.3.4.**

[redacted] presented with a pseudoaneurysm at the vascular access site, which resolved without treatment on a follow-up ultrasound three (3) months later. Due to the longer time period to resolution of this event, it was determined to be a "Serious Adverse Event" through resulting in persistent disability.

A detailed description of each AO Procedure-Related SAE is provided in **Table 71.**

Table 71. Patients Presenting a Serious AO Device or Procedure Related Adverse Event Occurring within 30 Days of the Index Procedure

ID	Patients Presenting a Serious AO Device or Procedure Related Adverse Event Occurring Within ≤ 30 Days
[redacted]	[redacted]
[redacted]	[redacted]

ID	Patients Presenting a Serious AO Device or Procedure Related Adverse Event Occurring Within ≤ 30 Days
[redacted]	[redacted]
[redacted]	[redacted]

ID	Patients Presenting a Serious AO Device or Procedure Related Adverse Event Occurring Within ≤ 30 Days
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

ID	Patients Presenting a Serious AO Device or Procedure Related Adverse Event Occurring Within ≤ 30 Days
[redacted]	[redacted]
[redacted]	[redacted]

ID	Patients Presenting a Serious AO Device or Procedure Related Adverse Event Occurring Within ≤ 30 Days
[redacted]	[redacted]
[redacted]	[redacted]

ID	Patients Presenting a Serious AO Device or Procedure Related Adverse Event Occurring Within ≤ 30 Days
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

In addition to the above-described serious device or procedure related events, twenty-nine (29) non-serious Adverse Events in the AO Therapy group were determined to be related to the AO Therapy procedure. These occurrences were almost exclusively related to the vascular access site and primarily consisted of catheter site hematoma (84.8% of all events). Other events included a single episode of hypotension (3.6%), ecchymosis (3.6%), vasovagal syncope (3.6%), angina pectoris (3.6%), and catheter site infection (3.6%).

1.8.13.6.4 Summary of Bleeding Events

Access site bleeding events and other bleeding or anemia events are summarized together in **Table 72** according to severity. Bleeding events in this clinical trial included events such as catheter site hemorrhage or hematoma, retroperitoneal hemorrhage, hematuria, epistaxis and cardiac tamponade. As with all adverse events in this trial, bleeding events were adjudicated by the CEC and were further categorized by severity during this review. These events are categorized according to the following definitions:

Severe/Life Threatening Bleeding: Bleeding that is intracranial or that results in substantial hemodynamic compromise requiring treatment.

Moderate Bleeding: Bleeding requiring transfusion defined as any blood loss requiring transfusion of blood products.

Mild Bleeding: Bleeding that does not require transfusion or results in hemodynamic compromise.

Table 72. Bleeding Events by Bleeding Category within First 30 Days

			Randomization Group				
			Control (N=79)		AO Therapy (N=222)		
Location	**Bleeding Category‡**	**Adverse Event**	**Events (n)**	**Pts with Events (n/N; %)**	**Events (n)**	**Pts with Events (n/N; %)**	**p value***
Assessment Complete	[redacted]		[redacted]	79/79 (100.0%)	[redacted]	222/222 (100.0%)	[redacted]
Assessment Available †				79/79 (100.0%)		222/222 (100.0%)	
All Bleeding Events			10	10/79 (12.7%)	58	55/222 (24.8%)	0.0259
All Severe/Life Threatening Bleeding Events			1	1/79 (1.3%)	3	3/222 (1.4%)	1.0000
Access Site			9	9/79 (11.4%)	41	41/222 (18.5%)	0.1628
	Mild	CATHETER SITE HEMATOMA	8	8/79 (10.1%)	34	34/222 (15.3%)	0.3443
	Moderate	CATHETER SITE HEMATOMA	0	0/79 (0.0%)	5	5/222 (2.3%)	0.3309
		CATHETER SITE HEMORRHAGE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
‡Mild Bleeding: Bleeding that does not require transfusion or result in hemodynamic compromise.
Moderate Bleeding: Bleeding requiring transfusion defined as any blood loss requiring transfusion of blood products.
Severe/Life Threatening Bleeding: Bleeding that is intracranial or that results in substantial hemodynamic compromise requiring treatment.
*Fisher's Exact test

Table 72 (continued). Bleeding Events by Bleeding Category within First 30 Days

			Randomization Group				
			Control (N=79)		AO Therapy (N=222)		
Location	**Bleeding Category‡**	**Adverse Event**	**Events (n)**	**Pts with Events (n/N; %)**	**Events (n)**	**Pts with Events (n/N; %)**	**p value***
	Severe	CATHETER SITE HEMORRHAGE	1	1/79 (1.3%)	0	0/222 (0.0%)	0.2625
		RETROPERITONEAL HEMORRHAGE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
Non-Access Site	[redacted]		1	1/79 (1.3%)	17	16/222 (7.2%)	0.0504
	Mild	ANEMIA	0	0/79 (0.0%)	6	6/222 (2.7%)	0.3458
		HEMATURIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		IMPLANT SITE HEMATOMA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		UROGENITAL HEMORRHAGE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000

‡Mild Bleeding: Bleeding that does not require transfusion or result in hemodynamic compromise.
Moderate Bleeding: Bleeding requiring transfusion defined as any blood loss requiring transfusion of blood products.
Severe/Life Threatening Bleeding: Bleeding that is intracranial or that results in substantial hemodynamic compromise requiring treatment.
*Fisher's Exact test

Table 72 (continued). Bleeding Events by Bleeding Category within First 30 Days

			Randomization Group				
			Control (N=79)		AO Therapy (N=222)		
Location	**Bleeding Category‡**	**Adverse Event**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	Moderate	ANEMIA	1	1/79 (1.3%)	1	1/222 (0.5%)	0.4567
		HEMORRHAGE	0	0/79 (0.0%)	4	4/222 (1.8%)	0.5761
		TRAUMATIC HEMATOMA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
	Severe	CARDIAC TAMPONADE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
		HEMATURIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
Events Requiring Transfusion	[redacted]		1	1/79 (1.3%)	14	14/222 (6.3%)	0.1276

‡Mild Bleeding: Bleeding that does not require transfusion or result in hemodynamic compromise.
Moderate Bleeding: Bleeding requiring transfusion defined as any blood loss requiring transfusion of blood products.
Severe/Life Threatening Bleeding: Bleeding that is intracranial or that results in substantial hemodynamic compromise requiring treatment.
*Fisher's Exact test

Overall, 55/222 (24.8%) AO Therapy patients experienced a bleeding event compared to 10/79 (12.7%) Control patients. This difference in overall bleeding rate was statistically significant (p=0.03). The majority of the bleeding events which occurred in the trial for both study groups were access site related and were primarily mild access site hematomas. There was a trend toward an increased incidence within the AO Therapy group of patients experiencing a bleeding event in each of the Access Site and Non-Access Site Bleeding categories. However, no statistically significant differences were identified between the two groups in any specific category of bleeding.

AO Therapy subjects had a requirement for larger size sheaths (up to 9 French) in order to accommodate the [redacted]™ infusion catheter, in conjunction with an additional requirement for further anticoagulation during the 90-minute infusion of AO Therapy. These factors may have contributed to the increased bleeding rate.

During the study, as mentioned previously, the [redacted] infusion catheter was introduced as an alternative to the [redacted]. As discussed in **Section 1.8.8.1**, the [redacted] catheter has a smaller outer diameter (O.D.) than the [redacted]. This feature enabled the use of a smaller guide catheter (6F) with the [redacted] catheter than required by the [redacted] (7F). The net result was that physicians utilized the AO Therapy coaxial draw configuration almost exclusively with the [redacted] catheter, involving a single arterial stick with an 8F sheath. In contrast, during the first 2/3 of the enrollment phase, when the [redacted] was the exclusive AO delivery catheter, physicians utilized either a single 9F arterial sheath or used a second arterial stick in the contralateral femoral artery for the blood withdrawal site. The impact that this choice had upon access site bleeding will be discussed in the following sections.

1.8.13.6.4.1 Access Site Bleeding

Access site bleeding occurred in 41/222 (18.5%) AO Therapy patients and 9/79 (11.4%) Control patients. This difference was not statistically significant. The majority of access site bleeding was caused by a mild catheter site hematoma in 34/222 (15.3%) AO Therapy patients and 8/79 (10.1%) Control patients. Other events experienced by patients in the AO Therapy group included moderate catheter site hematoma (5/222; 2.3%) and a moderate catheter site hemorrhage in one patient (0.5%).

One patient randomized to receive AO Therapy demonstrated an episode of retroperitoneal hemorrhage, classified as a Severe/Life threatening bleeding access site event (0.5%). This event was determined to be related to the Index PCI procedure, with no relationship to the AO Therapy procedure. In the Control group, one patient demonstrated an episode of catheter site hemorrhage (1.3%) determined to be a Severe/Life threatening bleeding. These events were determined to be "Severe" as they resulted in substantial hemodynamic compromise requiring treatment. Abbreviated patient narratives for these two patients who experienced severe bleeding are provided in **Table 73.** Overall, the differences in the incidence, type and severity of Access Site Bleeding Events between AO Therapy and Control patients were not statistically significant.

Table 73. Severe/Life Threatening Access Site Bleeding

ID	Severe/Life Threatening Access Site Bleeding
[redacted]	[redacted]
[redacted]	[redacted]

1.8.13.6.4.2 Non-Access Site Bleeding

A total of 15/222 (6.8%) AO Therapy patients and 1/79 (1.3%) Control patient presented with non-access site bleeding. This nominal difference was not found to be statistically significant (p=0.08). The majority of non-access site bleeding events in the AO Therapy group (8 patients) were classified as mild, including five (5) patients who demonstrated mild anemia (2.3%).

Additionally, one AO Therapy patient each (0.5%) exhibited the Adverse Events of hematuria, an implant site hematoma, or urogenital hemorrhage. Each of these events was related to another procedure outside of AO Therapy treatment. Implant site hematoma was determined to be associated with implantation of an ICD to treat ventricular fibrillation. The episodes of hematuria and urogenital hemorrhage were associated with Foley catheter placement, and were unrelated to the AO Therapy procedure.

A total of 6/222 (2.7%) AO Therapy patients and 1/79 (1.3%) Control patient presented with a non-access bleeding event classified as Moderate. Of this group, one AO Therapy patient (0.5%) and one Control subject (1.3%) each experienced moderate anemia. Additionally, four (4) AO Therapy patients (1.8%) demonstrated hemorrhage. One episode of hemorrhage was determined to be associated with the patient's initial index PCI procedure, and one episode was determined to have an unknown cause. Two episodes of hemorrhage were determined to be related to the patient's "Other Comorbid Condition", as one patient presented with gastritis, and a second patient experienced dysplasia.

Additionally, one AO Therapy patient (0.5%) exhibited a moderate bleeding event of traumatic hematoma. Traumatic hematoma of the neck was determined to be associated with an intubation procedure involved in the initial treatment of acute myocardial infarction. There were no significant differences between the two groups.

Two patients assigned to receive AO Therapy demonstrated a non-access site bleeding event classified as Severe/Life threatening Bleeding. One patient presented with cardiac tamponade (0.5%), while another patient demonstrated hematuria (0.5%). These events were determined to be "Severe" as they resulted in substantial hemodynamic compromise requiring treatment. Patient narratives for each patient who experienced severe bleeding are provided in **Table 74.**

Table 74. Severe/Life Threatening Non Access Site Bleeding

ID	Severe/Life Threatening Non-Access Site Bleeding
[redacted]	[redacted]

ID	Severe/Life Threatening Non-Access Site Bleeding
[redacted]	[redacted]

1.8.13.6.4.3 Synopsis of Bleeding Events

Bleeding is a known complication associated with PCI in the treatment of acute myocardial infarction. Bleeding complications have been associated with heparin dose, ACTs, procedure time, and use of IIIB/IIA inhibitors. The AO Therapy procedure involved the additional insertion of a larger size introducer sheath or use of a second contralateral vascular access site for a draw sheath, both of which may have contributed to increased bleeding. For example, 53.2% of AO Therapy patients had a 9F arterial access introducer sheath, primarily with the coaxial blood draw configuration with the [redacted] infusion catheter. In contrast, a 9F sheath was used during the initial PCI procedure in only 7.6% of Control patients, with the more common sizes being 6F and

7F. Use of larger sheath sizes and/or multiple vascular access sites is likely to have contributed to an increased rate of bleeding events. Access site bleeding is explored further in the following sections.

1.8.13.6.5 Access Site Events within the First 30 Days

Table 75 presents a summary of the AMIHOT II access site complications by study group.

Table 75. Access Site Events within First 30 Days

	Randomization Group				
	Control (N=79)		AO Therapy (N=222)		
Location	**Events (n)**	**Pts with Events (n/N; %)**	**Events (n)**	**Pts with Events (n/N; %)**	**p value***
Assessment Complete	[redacted]	79/79 (100.0%)	[redacted]	222/222 (100.0%)	[redacted]
Assessment Available†	[redacted]	79/79 (100.0%)	[redacted]	222/222 (100.0%)	[redacted]
Any Access Site Complication	10	10/79 (12.7%)	54	50/222 (22.5%)	0.0711
ARTERIOVENOUS FISTULA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
BACTEREMIA	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
CATHETER SITE HEMATOMA	8	8/79 (10.1%)	39	39/222 (17.6%)	0.1488
CATHETER SITE HEMORRHAGE	1	1/79 (1.3%)	1	1/222 (0.5%)	0.4567
CATHETER SITE INFECTION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
ECCHYMOSIS	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
HYPOTENSION	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
PYREXIA	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
RETROPERITONEAL HEMORRHAGE	0	0/79 (0.0%)	1	1/222 (0.5%)	1.0000
SYNCOPE VASOVAGAL	0	0/79 (0.0%)	2	2/222 (0.9%)	1.0000
VASCULAR PSEUDOANEURYSM	1	1/79 (1.3%)	4	4/222 (1.8%)	1.0000

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
*Fisher's Exact test

As presented in the table, 50/222 (22.5%) AO Therapy patients compared to 10/79 (12.7%) Control patients experienced an access site complication (p=0.07). The most

common access site complication involved catheter site hematoma, occurring in 39/222 (17.6%) AO Therapy patients and 8/79 (10.1%) Control patients. Other complications included vascular pseudoaneurysm in 4/222 (1.8%) AO Therapy patients and 1/79 (1.3%) Control patient, and catheter site hemorrhage occurring in one AO Therapy patient (0.5%) and one Control patient (1.3%).

Additional access site related events in the AO Therapy population included two (2) patients with vasovagal syncope (0.9%) and two patients with bacteremia (0.9%). One patient each experienced one of the following events: Arteriovenous fistula, catheter site infection, ecchymosis, hypotension, pyrexia, and retroperitoneal hemorrhage.

1.8.13.6.5.1 Access Site Bleeding: Choice of Infusion Catheter in AO Therapy Patients

The difference in the overall rate of Access Site events between AO Therapy patients and Control patients did not achieve statistical significance. Although the higher incidence of events in the treatment group cannot be ignored, data indicates that the use of the [redacted] catheter may decrease the rate of access site events associated with the AO Therapy procedure. Access site complications are presented below in **Table 76** for AO Therapy subjects, categorized by the choice of infusion catheter. As seen in the table, in comparison to patients receiving therapy with the [redacted] catheter, patients who received treatment with the [redacted] catheter exhibited a statistically significant decreased event rate of from 27.2% to 13.3% (p=0.026). Furthermore, the 13.3% [redacted] catheter access site complication rate is comparable to rates presented by the Control group (12.7%).

Table 76. Access Site Events within First 30 Days by Infusion Catheter Type

	AO Therapy Group				
	[redacted] (N=147)		[redacted] (N=75)		
Location	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Assessment Complete	[redacted]	147/147 (100.0%)	[redacted]	75/75 (100.0%)	[redacted]
Assessment Available†	[redacted]	147/147 (100.0%)	[redacted]	75/75 (100.0%)	[redacted]
Any Access Site Complication	44	40/147 (27.2%)	10	10/75 (13.3%)	0.0264
ARTERIOVENOUS FISTULA	1	1/147 (0.7%)	0	0/75 (0.0%)	1.0000
BACTEREMIA	2	2/147 (1.4%)	0	0/75 (0.0%)	0.5506
CATHETER SITE HEMATOMA	31	31/147 (21.1%)	8	8/75 (10.7%)	0.0627
CATHETER SITE HEMORRHAGE	1	1/147 (0.7%)	0	0/75 (0.0%)	1.0000
CATHETER SITE INFECTION	0	0/147 (0.0%)	1	1/75 (1.3%)	0.3378
ECCHYMOSIS	1	1/147 (0.7%)	0	0/75 (0.0%)	1.0000
HYPOTENSION	1	1/147 (0.7%)	0	0/75 (0.0%)	1.0000
PYREXIA	1	1/147 (0.7%)	0	0/75 (0.0%)	1.0000
RETROPERITONEAL HEMORRHAGE	1	1/147 (0.7%)	0	0/75 (0.0%)	1.0000
SYNCOPE VASOVAGAL	2	2/147 (1.4%)	0	0/75 (0.0%)	0.5506
VASCULAR PSEUDOANEURYSM	3	3/147 (2.0%)	1	1/75 (1.3%)	1.0000

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
*Fisher's Exact test

Although AO Therapy patients had a higher incidence of bleeding events than Control patients, these events were primarily mild hematomas that resolved without transfusion or interventional procedures. Furthermore, delivery of AO Therapy with the [redacted] catheter resulted in an access site event rate directly in line with the access site event rate in the Control group. Because the [redacted] catheter is no longer commercially available, the [redacted] catheter is the exclusive AO delivery catheter for future use, and the reduced bleeding rates observed with its adoption are indicative of expectations in commercial practice.

Looking further at these data, use of the [redacted] catheter was used with the coaxial (single arterial access site) blood draw in 72/75 (96%) of patients, as discussed previously. As shown in **Table 76a**, the rate of access site complications was significantly higher in AO Therapy patients with contralateral arterial access (two sites) as compared to the coaxial draw. This factor explains the bleeding reduction with the [redacted] catheter.

Table 76a. Access Site Complications within 30 Days by Draw Sheath Configuration

	AO Therapy Group				
	Coaxial (N=160)		Contralateral (N=62)		
Location	**# of Events**	**n (%) of Pts with Events**	**# of Events**	**n (%) of Pts with Events**	**p-value***
Assessment Complete	[redacted]	160 (100.0%)	[redacted]	62 (100.0%)	[redacted]
Assessment Available†	[redacted]	160 (100.0%)	[redacted]	62 (100.0%)	[redacted]
Any Access Site Complication	23	22 (13.8%)	31	28 (45.2%)	<.0001
ARTERIOVENOUS FISTULA	0	0 (0%)	1	1 (1.6%)	0.2793
BACTEREMIA	0	0 (0%)	2	2 (3.2%)	0.0771
CATHETER SITE HEMATOMA	16	16 (10.0%)	23	23 (37.1%)	<.0001
CATHETER SITE HEMORRHAGE	1	1 (0.6%)	0	0 (0%)	1.0000
CATHETER SITE INFECTION	1	1 (0.6%)	0	0 (0%)	1.0000
ECCHYMOSIS	1	1 (0.6%)	0	0 (0%)	1.0000
HYPOTENSION	0	0 (0%)	1	1 (1.6%)	0.2793
PYREXIA	0	0 (0%)	1	1 (1.6%)	0.2793
RETROPERITONEAL HEMORRHAGE	1	1 (0.6%)	0	0 (0%)	1.0000
SYNCOPE VASOVAGAL	1	1 (0.6%)	1	1 (1.6%)	0.4815
VASCULAR PSEUDOANEURYSM	2	2 (1.3%)	2	2 (3.2%)	0.3113

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
*Fisher's Exact test

1.8.13.6.5.2 Access Site Bleeding: Additional Factors in AO Therapy Patients

Fifty (50) patients randomized to receive AO Therapy presented a total of 54 events determined to be access site related. Out of all access site Adverse Events for the AO treatment group, 23/54 events (42.6%) involved the coaxial therapeutic approach, while 31/54 events (57.4%) utilized the contralateral approach.

A total of 39 episodes of catheter-site hematomas were determined to be access-site related. Seventeen of these events (43.6%) involved AO therapy administered through the coaxial approach, while 22 events (56.5%) involved the contralateral approach. Mild and Moderate catheter site hematomas were similarly distributed with respect to vascular access approach. Although the one single access site event determined to be "Severe" (retroperitoneal hematoma) involved the coaxial approach, this event was determined to be related to the index PCI procedure, with no relationship to the AO Therapy procedure.

Four (4) episodes of vascular pseudoaneurysm were determined to be access site related. The incidence of these events was evenly divided between both blood draw configurations, with two (2) patients receiving AO Therapy through the coaxial approach, and two (2) patients through the contralateral approach.

In summation, despite the fact that the coaxial approach requires an arterial access sheath that is 2F larger than the guide catheter, there did not appear to be any significant differences in the incidence of access site events. The larger catheter size associated with the coaxial approach may have been offset by a requirement for only one arterial access site puncture compared to the two (2) associated with the contralateral approach. Introduction of the [redacted] catheter allowed for decreased sheath size with a coaxial approach and appears to have decreased the incidence of access site complications.

1.8.13.6.6 Subset Analyses, MACE and Adverse Events within 30 Days

Several covariates warrant more detailed discussion as they relate to the AMIHOT II trial results. The variables of Target Lesion Location (proximal vs. non-proximal) and Time to Reperfusion (0 - 3.0 hours compared to >3.0 - 6.0 hours) were utilized as randomization stratification variables, while infusion catheter type is important for evaluating the AO therapy procedure results. Comparisons for a number of subsets with corresponding discussions are included in the following sections, including:

- Lesion Location (Proximal/Non-Proximal), Randomization stratification variable
- Time to Reperfusion (0-3 hrs, >3-6 hrs), Randomization stratification variable
- Infusion Catheter type ([redacted]

These subset analyses are exploratory in nature, as the AMIHOT II trial was not designed to evaluate and make conclusions concerning clinical outcomes within subset populations. This study was not powered to detect clinically meaningful differences within subsets. Additionally, p values used to compare within the subset groups were not adjusted for multiple comparisons and therefore should also be interpreted with caution.

1.8.13.6.6.1 Primary Safety Events by Lesion Location

One important covariate identified prior to study initiation with potential to impact study outcome involved lesion categorization into "proximal" and "non-proximal." Location of lesion within the LAD distribution is known to be associated with safety outcomes in AMI trials[107-109]. Patients with proximal lesions are more likely to experience adverse events, including MACE events, within the first 30 days than those with non-proximal lesions. As such, an evaluation of results was performed with patients "proximal" or "non proximal" location. This analysis is based on lesion location as reported by the investigator.

A summary of the Primary Safety Endpoint by Lesion Location is provided below in **Table 77.** AMIHOT II lesions were classified as "proximal" if the lesions were located from the origin of the LAD to the takeoff of the first side branch. Lesions in the AMIHOT II trial were similarly distributed between proximal and non-proximal. A total of 106/222 (47.8%) AO Therapy patients and 37/79 (46.8%) Control patients presented with an AMIHOT II lesion that was located in the proximal location. The balance of patients was treated for lesions located in the mid or distal LAD distributions.

As seen in **Table 77**, the composite 30-day MACE rate for proximal LAD lesions was 2.7% in the Control group and 6.6% in the AO Therapy group. In the non-proximal lesion subset, composite 30-day MACE rates were 4.8% for the Control group and 4.3% for AO Therapy group. The distribution of component MACE events in the subgroups was similar to that seen in the overall trial population. Within these subgroups, the composite 30-day MACE rates were similar between the two study groups. These results suggest that in the AMIHOT II study the primary safety endpoint results were not importantly impacted by lesion location.

Table 77. Primary Safety Events (within 30 Days) by Target Lesion Location (Per Investigator Assessment)

	Proximal				Non-proximal			
	Control (N=37)		AO Therapy (N=106)		Control (N=42)		AO Therapy (N=116)	
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)
MACE Assessment complete at 30 days		37/37 (100.0%)		106/106 (100.0%)		42/42 (100.0%)		116/116 (100.0%)
MACE Assessment available at 30 days†		37/37 (100.0%)		106/106 (100.0%)		42/42 (100.0%)		116/116 (100.0%)
Composite 30-Day MACE	1	1/37 (2.7%)	10	7/106 (6.6%)	4	2/42 (4.8%)	9	5/116 (4.3%)
Death	0	0/37 (0.0%)	2	2/106 (1.9%)	0	0/42 (0.0%)	2	2/116 (1.7%)
Target Vessel Revascularization‡	1	1/37 (2.7%)	5	5/106 (4.7%)	2	2/42 (4.8%)	4	3/116 (2.6%)
TVR: Clinically Driven		0/37 (0.0%)		5/106 (4.7%)		2/42 (4.8%)		3/116 (2.6%)
TVR: Objective evidence of ischemia in AMIHOT II lesion	0	0/37 (0.0%)	2	2/106 (1.9%)	2	2/42 (4.8%)	3	2/116 (1.7%)
TVR: Target Lesion Revascularization	1	1/37 (2.7%)	5	5/106 (4.7%)	2	2/42 (4.8%)	3	2/116 (1.7%)
TVR: Urgent or Emergent		0/37 (0.0%)		5/106 (4.7%)		2/42 (4.8%)		3/116 (2.6%)
Reinfarction	0	0/37 (0.0%)	3	2/106 (1.9%)	2	2/42 (4.8%)	3	2/116 (1.7%)
Stroke	0	0/37 (0.0%)	0	0/106 (0.0%)	0	0/42 (0.0%)	0	0/116 (0.0%)

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
‡AMIHOT main vessel or branches

1.8.13.6.6.2 Relationship of Adverse Events Occurring within 30 Days of the Index Procedure by Lesion Location

A summary of the AMIHOT II trial Adjudicated Adverse Events by Lesion Location is provided below in **Table 78.** As shown in the table, the overall incidences of Adverse Events in the lesion subsets were similar to those observed for the AMIHOT II trial overall. In the proximal lesion subset, 64/106 (60.4%) AO Therapy patients experienced an adverse event, compared to 19/37 (51.4%) Control patients. For the non-proximal lesion subset, 55/116 (47.4%) AO Therapy patients experienced an adverse event, compared to 18/42 (42.9%) Control patients.

The Serious Adverse Event rates in the lesion subsets were also similar in the two treatment groups. In the proximal lesion subset, 31/106 (29.2%) AO Therapy patients and 7/37 (18.9%) Control patients had a SAE. Within the subset of patients with non-proximal lesions, 26/116 (22.4%) AO Therapy patients and 8/42 (19.0%) Control patients experienced a SAE. As described above, proximal lesions would be expected to have an increased incidence of adverse events.

In addition, the distribution of events by relationship in the subgroups was similar to that seen in the overall trial population. With regard to adverse events adjudicated to be related to the AO procedure, 22/106 (20.8%) proximal lesion patients and 18/116 (15.5%) non-proximal lesion patients had an event in this category. This difference was not found to be statistically significant. The majority of these events were minor, consisting of hematoma or edema at the catheter infusion site. No events were determined to be related to the AO device. Of interest is the fact that in the proximal lesion subset, a higher percentage of Control patients (21.6%) presented with an event determined to be related to the Index PCI procedure compared to AO Therapy patients (14.2%). One explanation for the higher observed incidence of AO procedure related events in the proximal lesion subset could be that the relationship of Adverse Events is

often based on timing. Consequently, events occurring during the AO procedure may be adjudicated to be therapy-related due to the timing of event onset. As patients in the Control population did not undergo any additional procedures, a higher percentage of events are likely to be attributed to the index PCI procedure. Serious AO procedure related adverse event rates were similar in proximal (6.6%) and non-proximal (6.0%) lesion subsets.

Adverse events associated with the AMIHOT II Vessel were also evaluated within the subsets of proximal and non-proximal lesions. In the proximal lesion subset, 12/106 (11.3%) AO Therapy patients experienced fifteen (15) AMIHOT II vessel-related events and one patient (2.7%) randomized to the Control group exhibited an Adverse Event determined to be Target Vessel Related. For the AO Therapy population, events mainly consisted of stent occlusion (7 events). Other events included angina pectoris (2 events) and one episode of each of the following events: intracardiac thrombus, ventricular fibrillation, cardiac tamponade, cardiogenic shock, coronary artery disease, and myocardial ischemia. One Control patient had aortic stenosis prompting surgery that resulted in target vessel revascularization so this event was categorized as target vessel related by the CEC. These events were primarily adjudicated to be PCI related or CAD related.

In the non-proximal lesion subset, 6.9% of AO Therapy patients experienced 11 Adverse Events determined to be related to the AMIHOT II Vessel and 9.5% of Control patients demonstrated seven (7) Adverse Events determined to be related to the AMIHOT II Vessel. As evidenced in the proximal vessel, the majority of events experienced by patients randomized to receive AO Therapy consisted of stent occlusion (5 patients). Other events included two episodes of cardiogenic shock and one episode of each of the following events: hypotension, myocardial ischemia, cardiac arrest, and ventricular tachycardia. Similarly, the majority of events presented within the Control population consisted of stent occlusion (2 events) and congestive heart failure (2 events). Other

events included one episode of each of the following events: coronary artery disease, cardiogenic shock and accelerated idioventricular rhythm. There were no significant differences in the incidence of AMIHOT II Vessel related Adverse Events between study groups within these two lesion subgroups. Overall, adverse events related to the AMIHOT vessel occurred in approximately 8% of patients.

There were no significant differences between study groups in adverse event profile when separately evaluating the subsets of patients who presented with a target lesion in the proximal location, and patients presenting with a target lesion located in a non-proximal location. The Adverse Event rates, Serious Adverse Event rates, and Device/Procedure Related Adverse Event rates were similar between the two study groups within these subgroups. The safety profile of the subsets evaluated is similar in nature to the safety profile observed in the overall study results. Proximal lesion patients on the whole had somewhat higher adverse event rates than non-proximal lesion patients, consistent with results observed in other AMI trials.

Table 78. Overall Summary of Adjudicated Adverse Events within First 30 Days by Lesion Location (Per Investigator Assessment)

	Proximal				Non-proximal			
	Control (N=37)		AO Therapy (N=106)		Control (N=42)		AO Therapy (N=116)	
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)
Assessment Complete		37/37 (100.0%)		106/106 (100.0%)		42/42 (100.0%)		116/116 (100.0%)
Assessment Available †		37/37 (100.0%)		106/106 (100.0%)		42/42 (100.0%)		116/116 (100.0%)
Any Adverse Event	28	19/37 (51.4%)	153	64/106 (60.4%)	30	18/42 (42.9%)	103	55/116 (47.4%)
AO device related AE			0	0/106 (0%)			0	0/116 (0.0%)
AO procedure related AE			27	22/106 (20.8%)			19	18/116 (15.5%)
Index PCI procedure related AE	10	8/37 (21.6%)	20	15/106 (14.2%)	6	6/42 (14.3%)	23	19/116 (16.4%)
Coronary Artery Disease related AE	11	8/37 (21.6%)	59	38/106 (35.8%)	12	9/42 (21.4%)	35	26/116 (22.4%)
Study Medication related AE	0	0/37 (0.0%)	1	1/106 (0.9%)	0	0/42 (0%)	1	1/116 (0.9%)

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.

Table 78 (continued). Overall Summary of Adjudicated Adverse Events within First 30 Days by Lesion Location (Per Investigator Assessment)

	Proximal				Non-proximal			
	Control (N=37)		AO Therapy (N=106)		Control (N=42)		AO Therapy (N=116)	
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)
Other relationship ‡	7	6/37 (16.2%)	42	30/106 (28.3%)	11	9/42 (21.4%)	20	16/116 (13.8%)
Unknown relationship	0	0/37 (0.0%)	4	4/106 (3.8%)	1	1/42 (2.4%)	5	5/116 (4.3%)
Serious Adverse Event	7	7/37 (18.9%)	52	31/106 (29.2%)	12	8/42 (19.0%)	37	26/116 (22.4%)
AO device related AE	[redacted]		0	0/106 (0.0%)	[redacted]		0	0/116 (0.0%)
AO procedure related AE	[redacted]		9	7/106 (6.6%)	[redacted]		8	7/116 (6.0%)
Index PCI procedure related AE	1	1/37 (2.7%)	8	6/106 (5.7%)	3	3/42 (7.1%)	9	8/116 (6.9%)
Coronary Artery Disease related AE	4	4/37 (10.8%)	28	20/106 (18.9%)	5	4/42 (9.5%)	14	12/116 (10.3%)
Study Medication related AE	0	0/37 (0.0%)	0	0/106 (0.0%)	0	0/42 (0.0%)	0	0/116 (0.0%)

‡Including pre-existing condition, concurrent condition, concurrent intervention and other relationships

Table 78 (continued). Overall Summary of Adjudicated Adverse Events within First 30 Days by Lesion Location (Per Investigator Assessment)

	Proximal				Non-proximal			
	Control (N=37)		AO Therapy (N=106)		Control (N=42)		AO Therapy (N=116)	
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)
Other relationship‡	2	2/37 (5.4%)	5	5/106 (4.7%)	4	3/42 (7.1%)	5	5/116 (4.3%)
Unknown relationship	0	0/37 (0.0%)	2	2/106 (1.9%)	0	0/42 (0.0%)	1	1/116 (0.9%)
Adverse Event related to AMIHOT II Vessel	1	1/37 (2.7%)	15	12/106 (11.3%)	7	4/42 (9.5%)	11	8/116 (6.9%)

‡Including pre-existing condition, concurrent condition, concurrent intervention and other relationships

1.8.13.6.6.3 Primary Safety Events by Time to Reperfusion

A second critical covariate identified prior to study initiation that had a potential to impact study outcomes was the time from symptom onset to coronary artery reperfusion. As stated previously, literature suggests that patients with shorter time to reperfusion have better long-term safety outcomes[12, 17, 44]. As such, an evaluation of MACE endpoint results was performed with patients stratified according to time to reperfusion. Patients were stratified according to measured reperfusion times of 0 to 3.0 hours and 3.0 to 6.0 hours. Four (4) patients with an actual time to reperfusion of > 6 hours are included in the 3-6 hour group for this analysis.

A summary of the Primary Safety Endpoint by Time to Reperfusion is provided in **Table 79.** Subjects were similarly divided into these two subgroups; 95/222 (42.8%) AO Therapy patients and 43/79 (54.5%) Control had time to reperfusion from 0 to 3.0 hours from symptom onset. The balance of patients had times to reperfusion greater than 3.0 hours from point of symptom onset.

In the 0-3 hour subgroup, 7/95 (7.4%) AO Therapy patients and one Control patient (2.3%) experienced a 30-day MACE endpoint event. In the 3-6 hour subgroup, 5/127 (3.9%) AO Therapy patients and 2/36 (5.6%) Control patients experienced a 30-day MACE endpoint event. The distribution of component MACE events in the subgroups was similar to that seen in the overall trial population. Within these subgroups, the composite 30-day MACE rates were similar between the two treatment groups. In addition, composite 30-day MACE rates in the subsets of patients achieving reperfusion within three (3) hours and those achieving reperfusion more than three (3) hours from symptom onset were similar, suggesting that in this study the primary safety endpoint results were not importantly impacted by time to reperfusion.

Table 79. Primary Safety Events (within 30 Days) by Time to Reperfusion (Actual)

	0-3 hours				>3-6 hours[†]			
	Control (N=43)		AO Therapy (N=95)		Control (N=36)		AO Therapy (N=127)	
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)
MACE Assessment complete at 30 days		43/43 (100.0%)		95/95 (100.0%)		36/36 (100.0%)		127/127 (100.0%)
MACE Assessment available at 30 days[‡]		43 (100.0%)		95/95 (100.0%)		36/36 (100.0%)		127/127 (100.0%)
Composite 30-Day MACE	2	1/43 (2.3%)	10	7/95 (7.4%)	3	2/36 (5.6%)	9	5/127 (3.9%)
Death	0	0/43 (0.0%)	2	2/95 (2.1%)	0	0/36 (0.0%)	2	2/127 (1.6%)
Target Vessel Revascularization[§]	1	1/43 (2.3%)	5	5/95 (5.3%)	2	2/36 (5.6%)	4	3/127 (2.4%)
TVR: Clinically Driven		1/43 (2.3%)		5/95 (5.3%)		1/36 (2.8%)		3/127 (2.4%)
TVR: Objective evidence of ischemia in AMIHOT II lesion	1	1/43 (2.3%)	2	2/95 (2.1%)	1	1/36 (2.8%)	3	2/127 (1.6%)
TVR: Target Lesion Revascularization	1	1/43 (2.3%)	4	4/95 (4.2%)	2	2/36 (5.6%)	4	3/127 (2.4%)
TVR: Urgent or Emergent		1/43 (2.3%)		5/95 (5.3%)		1/36 (2.8%)		3/127 (2.4%)
Reinfarction	1	1/43 (2.3%)	3	2/95 (2.1%)	1	1/36 (2.8%)	3	2/127 (1.6%)
Stroke	0	0/43 (0.0%)	0	0/95 (0.0%)	0	0/36 (0.0%)	0	0/127 (0.0%)

[†]Includes 4 subjects with > 6 hours of Time to Reperfusion.
[‡]Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
[§]AMIHOT main vessel or branches

1.8.13.6.6.4 Relationship of Adverse Events Occurring within 30 Days of the Index Procedure by Time to Reperfusion

A summary of the AMIHOT II trial Adjudicated Adverse Events by Time to Reperfusion is provided in **Table 80.** The overall incidences of Adverse Events in the time to reperfusion subsets were similar to those observed for the AMIHOT II trial overall. In the 0-3 hour subset, 53/95 (55.8%) AO Therapy patients presented with a total of one-hundred nineteen (119) Adverse Events, compared to 20/43 (46.5%) Control patients with a total of thirty-five (35) Adverse Events. In the >3-6 hour subset, 66/127 (52.0%) AO Therapy patients experienced one-hundred thirty-seven (137) Adverse Events and 17/36 (47.2%) Control patients demonstrated a total of twenty-three (23) Adverse Events.

The SAE rates in the time to reperfusion subsets are provided in the table. In the 0-3 hour subset, 29/95 (30.5%) AO Therapy patients and 7/43 (16.3%) Control patients experienced a SAE. Within the >3-6 hour patient subset, 28/127 (22.0%) AO Therapy patients and 8/36 (22.2%) Control patients experienced a SAE.

The distribution of events by relationship in the subgroups was similar to that seen in the overall trial population. With regard to adverse events adjudicated to be related to the AO procedure, 16/95 (16.8%) AO Therapy patients with 0-3 hours to reperfusion and 24/127 (18.9%) patients with >3-6 hours to reperfusion had an event in this category. This difference was not statistically significant. Serious AO procedure related adverse event rates were equal in the 0-3 hour subset (6.3%) and >3-6 hour (6.3%) patient subsets.

A total of 12/95 (12.6%) AO Therapy patients and 2/43 (4.7%) Control patients in the 0-3 hour group presented an Adverse Event related to the AMIHOT II vessel. These results are consistent with trends observed for the total patient cohort. In the >3-6 hour subgroup, 8/127 (6.3%) AO Therapy patients 3/36 (8.3%) Control patients demonstrated

an Adverse Event determined to be related to the AMIHOT II vessel. No statistically significant differences were found between the two study groups.

Although not statistically significant, AO Therapy patients in the 0-3 hour subset had a higher incidence of SAEs. Additionally, compared to the Control population, these patients exhibited a nominally higher incidence of events determined to be related to the Target Vessel. These results are consistent with trends presented over the course of the AMIHOT II trial. However, the majority of events resolved within minimal time period following symptom onset. Although AO Therapy patients may have experienced an increased incidence of events occurring in the short term, these events for the most part resolved without lasting clinical sequelae.

There were no significant differences between the two study groups in the adverse event profile (SAEs, AEs, AMIHOT II vessel related AEs) when evaluating separately the subsets of patients who had reperfusion within three (3) hours of symptom onset and those with reperfusion more than three (3) hours from symptom onset. The safety profile of the subsets evaluated is similar in nature to the safety profile observed in the overall study results. In addition, the safety profile of subjects in the 0-3 hour time to reperfusion group is not substantially different than that for the >3-6 hour time to reperfusion group, suggesting time to reperfusion does not have had a significant impact on the safety profile in this trial.

Table 80. Overall Summary of Adjudicated Adverse Events within First 30 Days by Time to Reperfusion (Actual)

	0-3 hours				>3-6 hours†			
	Control (N=43)		AO Therapy (N=95)		Control (N=36)		AO Therapy (N=127)	
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)
Assessment Complete	[redacted]	43/43 (100.0%)	[redacted]	95/95 (100.0%)	[redacted]	36/36 (100.0%)	[redacted]	127/127 (100.0%)
Assessment Available ‡	[redacted]	43/43 (100.0%)	[redacted]	95/95 (100.0%)	[redacted]	36/36 (100.0%)	[redacted]	127/127 (100.0%)
Any Adverse Event	35	20/43 (46.5%)	119	53/95 (55.8%)	23	17/36 (47.2%)	137	66/127 (52.0%)
AO device related AE	[redacted]		0	0/95 (0.0%)	[redacted]		0	0/127 (0%)
AO procedure related AE	[redacted]		19	16/95 (16.8%)	[redacted]		27	24/127 (18.9%)
Index PCI procedure related AE	[redacted]	7/43 (16.3%)	24	19/95 (20.0%)	7	7/36 (19.4%)	19	15/127 (11.8%)
Coronary Artery Disease related AE	15	10/43 (23.3%)	41	29/95 (30.5%)	8	7/36 (19.4%)	53	35/127 (27.6%)
Study Medication related AE	0	0/43 (0.0%)	2	2/95 (2.1%)	0	0/36 (0.0%)	0	0/127 (0.0%)

†Includes 4 subjects with > 6 hours of Time to Reperfusion.
‡Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.

Table 80 (continued). Overall Summary of Adjudicated Adverse Events within First 30 Days by Time to Reperfusion (Actual)

	0-3 hours				>3-6 hours†			
	Control (N=43)		AO Therapy (N=95)		Control (N=36)		AO Therapy (N=127)	
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)
Other relationship *	11	9/43 (20.9%)	28	21/95 (22.1%)	7	6/36 (16.7%)	34	25/127 (19.7%)
Unknown relationship	0	0/43 (0.0%)	5	5/95 (5.3%)	1	1/36 (2.8%)	4	4/127 (3.1%)
Serious Adverse Event	9	7/43 (16.3%)	42	29/95 (30.5%)	10	8/36 (22.2%)	47	28/127 (22.0%)
AO device related AE	[redacted]		0	0/95 (0.0%)	[redacted]		0	0/127 (0%)
AO procedure related AE	[redacted]		7	6/95 (6.3%)	[redacted]		10	8/127 (6.3%)
Index PCI procedure related AE	1	1/43 (2.3%)	8	7/95 (7.4%)	3	3/36 (8.3%)	9	7/127 (5.5%)
Coronary Artery Disease related AE	4	4/43 (9.3%)	21	18/95 (18.9%)	5	4/36 (11.1%)	21	14/127 (11.0%)
Study Medication related AE	0	0/43 (0.0%)	0	0/95 (0.0%)	0	0/36 (0.0%)	0	0/127 (0.0%)

†Includes 4 subjects with > 6 hours of Time to Reperfusion.
*Including pre-existing condition, concurrent condition, concurrent intervention and other relationships

Table 80 (continued). Overall Summary of Adjudicated Adverse Events within First 30 Days by Time to Reperfusion (Actual)

	0-3 hours				>3-6 hours†			
	Control (N=43)		AO Therapy (N=95)		Control (N=36)		AO Therapy (N=127)	
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)
Other relationship *	4	3/43 (7.0%)	5	5/95 (5.3%)	2	2/36 (5.6%)	5	5/127 (3.9%)
Unknown relationship	0	0/43 (0.0%)	1	1/95 (1.1%)	0	0/36 (0.0%)	2	2/127 (1.6%)
Adverse Event related to AMIHOT II Vessel	3	2/43 (4.7%)	14	12/95 (12.6%)	5	3/36 (8.3%)	12	8/127 (6.3%)

†Includes 4 subjects with > 6 hours of Time to Reperfusion.
*Including pre-existing condition, concurrent condition, concurrent intervention and other relationships

1.8.13.6.6.5 Primary Safety Events by Infusion Catheter Type

As discussed previously, AO Therapy was delivered first exclusively through the [redacted] infusion catheter, then primarily through the [redacted] catheter after an IDE-approved [redacted] protocol change was implemented to enable this physician option. It was anticipated that the [redacted] catheter might provide some potential benefit with respect to decreased bleeding incidence due to the previously discussed advantages with smaller sheath size, single arterial stick, etc. And, in fact, the data presented with regard to access site bleeding support this hypothesis. In this section, the results for the Primary Safety Endpoint MACE rates were summarized by infusion catheter type to assess the impact of infusion catheter type on 30-day MACE.

Table 81 includes a breakdown of Primary Safety Events by Infusion Catheter Type. A total of 147/222 (66.2%) AO Therapy patients received infusion through the [redacted] catheter. Out of this patient population, 6/147 (4.1%) patients demonstrated a total of eleven (11) 30-day MACE events. In comparison, 75/222 (33.8%) patients received AO Therapy with the [redacted] catheter. Out of this patient population, 6/75 (8.0%) patients presented a total of eight (8) 30-day MACE events.

Infusion catheter type does not appear to have an impact on the primary safety endpoint 30-day MACE rate.

Table 81. Primary Safety Events (within 30 Days) by Infusion Catheter Type

	AO Therapy			
	[redacted] (N=147)		[redacted] (N=75)	
Adverse Event	**Events (n)**	**Pts with Events (n/N; %)**	**Events (n)**	**Pts with Events (n/N; %)**
MACE Assessment complete at 30 days	[redacted]	147/147 (100.0%)	[redacted]	75/75 (100.0%)
MACE Assessment available at 30 days†	[redacted]	147/147 (100.0%)	[redacted]	75/75 (100.0%)
Composite 30-Day MACE	11	6/147 (4.1%)	8	6/75 (8.0%)
Death	2	2/147 (1.4%)	2	2/75 (2.7%)
Target Vessel Revascularization‡	5	4/147 (2.7%)	4	4/75 (5.3%)
TVR: Clinically Driven	[redacted]	4/147 (2.7%)	[redacted]	4/75 (5.3%)
TVR: Objective evidence of ischemia in AMIHOT II lesion	3	2/147 (1.4%)	2	2/75 (2.7%)
TVR: Target Lesion Revascularization	5	4/147 (2.7%)	3	3/75 (4.0%)
TVR: Urgent or Emergent	[redacted]	4/147 (2.7%)	[redacted]	4/75 (5.3%)
Reinfarction	4	2/147 (1.4%)	2	2/75 (2.7%)
Stroke	0	0/147 (0.0%)	0	0/75 (0.0%)

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
‡AMIHOT main vessel or branches

1.8.13.6.6.6 Relationship of Adverse Events Occurring Within 30 Days of the Index Procedure by Infusion Catheter Type

A summary of the AMIHOT II trial Adjudicated Adverse Events by Infusion Catheter Type is provided in **Table 82**. A total of 81/147 (55.1%) AO Therapy patients who received infusion with the [redacted] catheter presented a total of one-hundred eighty-two (182) Adverse Events. In comparison, 38/75 (50.7%) AO Therapy patients who received infusion with the [redacted] catheter demonstrated a total of seventy-four (74) Adverse Events.

Within the [redacted] catheter subset, 40/147 (27.2%) patients presented a total of sixty-five (65) SAEs, compared to 17/75 (22.7%) [redacted] patients with a total of twenty-

four (24) SAEs. Meanwhile, 12/147 (8.2%) patients who received AO Therapy with the [redacted] catheter presented a total of eighteen (18) events related to an AMIHOT II vessel. Similarly, 8/75 (10.7%) patients who received AO Therapy with the [redacted] catheter exhibited an Adverse Event related to the AMIHOT II vessel.

No noteworthy differences were noted overall in the rate of Adverse Events or Serious Adverse Events between patients receiving AO Therapy with the [redacted] catheter or [redacted] catheter. Incidence rates tended to be lower in the [redacted] catheter group.

Table 82. Overall Summary of Adjudicated Adverse Events within First 30 Days by Infusion Catheter Type

	AO Therapy			
	[redacted] (N=147)		[redacted] (N=75)	
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)
Assessment Complete	[redacted]	147/147 (100.0%)	[redacted]	75/75 (100.0%)
Assessment Available †	[redacted]	147/147 (100.0%)	[redacted]	75/75 (100.0%)
Any Adverse Event	182	81/147 (55.1%)	74	38/75 (50.7%)
AO device related AE	0	0/147 (0.0%)	0	75/75 (0.0%)
AO procedure related AE	33	28/147 (19.0%)	13	12/75 (16.0%)
Index PCI procedure related AE	32	25/147 (17.0%)	11	9/75 (12.0%)
Coronary Artery Disease related AE	68	44/147 (29.9%)	26	20/75 (26.7%)
Study Medication related AE	1	1/147 (0.7%)	1	1/75 (1.3%)
Other relationship ‡	41	31/147 (21.1%)	21	15/75 (20.0%)
Unknown relationship	7	7/147 (4.8%)	2	2/75 (2.7%)
Serious Adverse Event	65	40/147 (27.2%)	24	17/75 (22.7%)
AO device related AE	0	0/147 (0.0%)	0	0/75 (0.0%)
AO procedure related AE	13	10/147 (6.8%)	4	4/75 (5.3%)
Index PCI procedure related AE	13	10/147 (6.8%)	4	4/75 (5.3%)
Coronary Artery Disease related AE	28	20/147 (13.6%)	14	12/75 (16.0%)
Study Medication related AE	0	0/147 (0.0%)	0	0/75 (0.0%)
Other relationship ‡	8	8/147 (5.4%)	2	2/75 (2.7%)
Unknown relationship	3	3/147 (2.0%)	0	0/75 (0.0%)
Adverse Event related to AMIHOT II Vessel	18	12/147 (8.2%)	8	8/75 (10.7%)

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
‡Including pre-existing condition, concurrent condition, concurrent intervention and other relationships

1.8.13.6.7 Safety Summary for 30-Day Events

The Primary Safety Endpoint for the AMIHOT II trial involving the incidence of 30-Day MACE was determined to be similar between patients randomized to the AO Therapy group (5.4%) and the control group (3.8%). This study met its primary endpoint, supporting non-inferiority between AO Therapy and standard treatment for acute myocardial infarction to within a 6% delta as demonstrated with the pre-specified Bayesian hierarchical analysis.

Similarly, when the breakdown of separate MACE events of death, reinfarction, target vessel revascularization and stroke within 30 days was compared between the two study arms, no significant differences were found between the two groups.

All Adverse Events and Serious Adverse Events were summarized according to PT, SOC, and relationship of the event. For both study groups, the majority of both Serious and Non-Serious Adverse Events were classified as a cardiac disorder. These events were determined primarily to be related to the patient's underlying coronary artery disease.

AO Therapy patients did display a higher incidence of vascular events (p=0.04) and bleeding events (p=0.04) compared to the Control group. Although not statistically significant, AO Therapy patients displayed a higher incidence of Access Site Adverse Events. However, this increased incidence appears to have been mitigated through the introduction of an alternative infusion catheter, the TherOx-supplied [redacted] during the study. The [redacted] catheter is the device that will be used in future administration of AO Therapy, in either an investigational or post-market setting.

A total of 40/222 (18.0%) AO Therapy patients presented a total of forty-six (46) Adverse Events that were determined to be related to the AO procedure. These occurrences were almost exclusively related to the vascular access site and primarily consisted of catheter site hematoma (84.8% of all events).

Although an increased incidence of Adverse Events was observed with AO Therapy, the majority of events resolved quickly after onset and was not associated with residual effects. For example, 57/222 (25.7%) AO Therapy patients exhibited a total of eighty-nine (89) Serious Adverse Events within the first 30 days. Of these events, 80.9% (72 events) had resolved completely with no residual effects. Nine (9) of the 89 events (10.2%) had resolved with ongoing effects. In contrast, only 2.3% of events (2 events) had not resolved at the time of patient follow-up. Five (5) events (5.7%) were associated with patient death, and the outcome of one event was unknown. Therefore, AO Therapy may involve an increased incidence of short term, bleeding events, although this risk may no longer be present when the [redacted] catheter is used. However, the majority of events resolved quickly with minimal intervention, and did not exert any long-term side effects.

No differences were noted between the incidence of any type of Adverse Event between AO Therapy and Control patients at 6-month or 1-year follow up. These findings suggest that the use of AO Therapy as an adjunctive treatment for AMI is not associated with an increased risk of serious adverse events associated with lasting clinical sequelae.

1.8.13.7 Review of All Post 30-Day Adverse Event Data

1.8.13.7.1 Follow Up Assessment at 6 Months Post-Procedure

A follow-up telephone survey was required at 6 months post-procedure. All patients were eligible for 6-month follow-up, and reported 6-month follow-up assessment data are complete for the AMIHOT II study. **Table 83** summarizes the 6-month telephone survey data.

Table 83. Six Month Patient Follow Up Survey[†]

	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)
Number of patients eligible to be contacted[†]	79/79 (100%)	222/222 (100%)
Number of patients contacted	75/79 (94.9%)	214/222 (96.4%)
Assessment performed in window[‡]	70/75 (93.3%)	207/214 (96.7%)
Assessment performed early	0/75 (0.0%)	0/214 (0.0%)
Assessment performed late	5/75 (6.7%)	7/214 (3.3%)
Number of patients not contacted	4/79 (5.1%)	8/222 (3.6%)
Reasons why patients not contacted		
Not available	2/79 (2.5%)	0/222 (0.0%)
Withdrew Consent	1/79 (1.3%)	0/222 (0.0%)
Deceased	1/79 (1.3%)	8/222 (3.6%)
Lost to follow up	0/79 (0.0%)	0/222 (0.0%)
Other	0/79 (0.0%)	0/222 (0.0%)
Number of patients rehospitalized for cardiovascular care since last study visit?	8/75 (10.7%)	39/214 (18.2%)
Rehospitalized patients: No. of times		
1	8/75 (10.7%)	32/214 (15.0%)
2	0/75 (0.0%)	6/214 (2.8%)
> 2	0/75 (0.0%)	1/214 (0.5%)
CHF diagnosis since last study visit		
Yes	4/75 (5.3%)	8/214 (3.7%)
No	71/75 (94.7%)	206/214 (96.3%)
Improvement in subject's ability to perform physical activity		
Yes	60/74 (81.1%)	178/214 (83.2%)
No	14/74 (18.9%)	36/214 (16.8%)
Subject self assessment: overall health status (1-5; 1=poor, 5=excellent)		
1	1/74 (1.4%)	2/214 (0.9%)
2	3/74 (4.1%)	13/214 (6.1%)
3	9/74 (12.2%)	40/214 (18.7%)
4	36/74 (48.7%)	104/214 (48.6%)
5	25/74 (33.8%)	55/214 (25.7%)
Mean ± SD	4.1 ± 0.9	3.9 ± 0.9

[†]For patient follow-up data current as of December 14, 2007. All patients were available for follow-up as of December 14, 2007.
[‡]Six month assessment required at 6 ± 1 months

A total of 214/222 (96.4%) AO Therapy patients and 75/79 (94.9%) Control patients completed a telephone follow-up assessment. A follow-up assessment was not obtained for 8/222 (3.6%) AO Therapy patients because of death. Within the Control patient population, one patient had died (1.3%), one patient had withdrawn consent (1.3%) and two patients were unable to be contacted (2.5%).

A 6-month assessment was required at 6 months ± 30 days. A total of 207/214 (96.7%) AO Therapy patients and 70/75 (93.3%) Control patients who completed a 6-month follow-up assessment did so within the appropriate time interval. No assessments were performed early. From the total number of patients contacted, 7/214 (3.3%) patients in the AO Therapy group and 5/75 (6.7%) patients in the Control group completed a late assessment occurring after 210 days post-procedure. Late assessments occurred in the range of 212 to 286 days, with an average of 228 days post-procedure.

Following hospital discharge, 39/214 (18.2%) AO Therapy patients and 8/75 (10.7%) Control patients had undergone rehospitalization for cardiovascular care between the 30-day and 6-month follow-up. Thirty two (32) patients in the AO Therapy group (15.0%) had experienced one hospitalization, while six (6) patients (2.8%) had undergone two hospitalizations since the initial index procedure. One patient (0.5%) in the AO Therapy group was hospitalized more than two times since the initial index procedure. Similarly, eight (8) patients in the Control group (10.7%) had undergone one hospitalization, with no Control patients requiring a second hospital stay.

Patients in both study groups received a new diagnosis of congestive heart failure (CHF). Eight (8) patients in the AO Therapy group (3.7%) compared to four (4) patients in the Control group (5.3%) were diagnosed with CHF at 6 months post-procedure.

The majority of patients in both study groups displayed an improvement at 6-month follow-up. A total of 178/214 (83.2%) AO Therapy patients and 60/74 (81.1%) Control

patients experienced an improvement in their ability to perform physical activity. Furthermore, the majority of patients reported overall health status as good. On a 5-point self-assessment of overall health status, with "1" = Poor and "5" = Excellent, AO Therapy patients earned an average score of 3.9 ± 0.9, while Control patients reported an average score of 4.1 ± 0.9.

1.8.13.7.2 Follow Up Assessment at 12 Months Post Procedure

A follow-up telephone survey was required at 12 months post-procedure. All patients were eligible for 12-month follow-up. **Table 84** summarizes the 12-month telephone survey data for the AMIHOT II study.

Table 84. Twelve Month Patient Follow Up Survey[†]

	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)
Number of patients eligible to be contacted[†]	79/79 (100.0%)	222/222 (100.0%)
Number of patients contacted	75/79 (94.9%)	212/222 (95.5%)
Assessment performed in window[‡]	73/75 (97.3%)	207/212 (97.6%)
Assessment performed early	0/75 (0.0%)	1/212 (0.5%)
Assessment performed late	2/75 (2.7%)	4/212 (1.9%)
Number of patients not contacted	4/79 (5.1%)	10/222 (4.5%)
Reasons why patients not contacted		
Not available	0/79 (0.0%)	0/222 (0.0%)
Withdrew Consent	1/79 (1.3%)	1/222 (0.5%)
Deceased	1/79 (1.3%)	8/222 (3.6%)
Lost to follow up	2/79 (2.5%)	1/222 (0.5%)
Other	0/79 (0.0%)	0/222 (0.0%)
Number of patients rehospitalized for cardiovascular care since last study visit?	3/74 (4.1%)	19/212 (9.0%)
Rehospitalized patients: No. of times		
1	2/74 (2.7%)	18/212 (8.5%)
2	1/74 (1.4%)	1/212 (0.5%)
> 2	0/74 (0.0%)	0/212 (0.0%)
CHF diagnosis since last study visit		
Yes	1/73 (1.4%)	4/212 (1.9%)
No	72/73 (98.6%)	208/212 (98.1%)
Improvement in subject's ability to perform physical activity		
Yes	57/73 (78.1%)	183/211 (86.7%)
No	16/73 (21.9%)	28/211 (13.3%)
Subject self assessment: overall health status (1-5; 1=poor, 5=excellent)		
1	1/72 (1.4%)	4/211 (1.9%)
2	1/72 (1.4%)	4/211 (1.9%)
3	13/72 (18.1%)	32/211 (15.2%)
4	26/72 (36.1%)	102/211 (48.3%)
5	31/72 (43.1%)	69/211 (32.7%)
Mean ± SD	4.2 ± 0.9	4.1 ± 0.8

[†]For patient follow-up data current as of December 14, 2007. Patient considered available for follow-up contact if procedure date ± 1 year <= December 14, 2007.
[‡]Twelve month assessment required at 12 ± 1 mos

A total of 212/222 (95.5%) AO Therapy patients and 75/79 (94.9%) Control patients completed a 12-month telephone survey. An assessment was not completed for 10/222 (4.5%) AO Therapy patients and 4/79 (5.1%) Control patients. Of the ten (10) AO Therapy patients (4.5%), one patient had withdrawn consent (0.5%), one patient was lost to follow up (0.5%) and eight (8) patients had died (3.6%). In the Control group, one patient had died (1.3%), one patient had withdrawn consent (1.3%) and two patient were lost to follow up (2.5%).

A 12-month assessment was required at 12 months ± 30 days. A total of 207/212 (97.6%) AO Therapy patients and 73/75 (97.3%) Control patients completed a 12-month assessment within the appropriate time interval. Within the AO Therapy group, 1/212 (0.5%) patients had an assessment performed early and 4/212 (2.4%) AO Therapy patients had an assessment performed late. No Control patients were assessed early but 2/75 (3.3%) Control patients had a late assessment at greater than 395 days post-procedure. Late assessments occurred in the range of 400 to 707 days, with an average of 494 days post-procedure.

Between the 6-month and the12-month assessment, a total of 19/212 (9.0%) AO Therapy patients and 3/74 (4.1%) Control patients had been rehospitalized. One of the patients within the AO Therapy group (0.5%) was hospitalized twice as was one patient within the Control group (1.4%). Of the AO Therapy group, 4/212 (1.9%) patients received an additional diagnosis of heart failure as did 1/73 (1.4%) patient from the Control group.

The majority of patients in both treatment groups reported a significant health improvement at 12-month follow up. A total of 183/211 (86.7%) AO Therapy patients and 57/73 (78.1%) Control patients displayed an improvement in their ability to perform physical activity. Furthermore, on a 5-point self assessment of overall health status, with "1" = Poor and "5" = Excellent, the majority of patients reported a good overall health

status, with an average score of 4.1 ± 0.8 in AO Therapy patients, and an average of 4.2 ± 0.9 in Control patients.

1.8.13.7.3 Post-30 Day MACE Results

A MACE assessment for the 6-month and 12-month periods was considered "complete" if by Clinical Events Committee review, the subject was evaluable for the safety endpoints through the respective 180th day or 365th day post procedure or through the point of death. A subject was considered "available" for MACE safety evaluation if the subject was either "complete" or had a safety endpoint event but was not considered complete through the 180th or 365th day (*e.g.* subject had a TVR prior to day 180 and was subsequently lost to follow-up). MACE events of death, reinfarction, target vessel revascularization and stroke at the 6-month and 12-month follow-up are presented in **Table 85**.

MACE assessments at six months were available in 222/222 (100.0%) AO Therapy patients and 78/79 (98.7%) Control patients. Twelve-month MACE assessments were available in 220/222 (73.4%) AO Therapy patients and 75/79 (70.9%) Control patients. Information on all events (MACE and any adverse events) occurring within the time frame of post AO Therapy until 6-month or 12-month follow-up was collected and reviewed. The relationship and severity of all events were adjudicated by the Clinical Events Committee.

As seen in the **Table 85**, between 30 days and 6 months post-procedure, a total of 15/222 (6.8%) patients in the AO Therapy group had experienced a total of twenty (20) MACE events. [redacted] underwent two separate target vessel revascularization procedures. [redacted] each exhibited two separate MACE events. Both patients experienced an episode of reinfarction requiring treatment with target vessel revascularization. A total of 3/78 (3.8%) patients in the Control group experienced four (4) MACE events between 30 days and 6 months following the index procedure.

[redacted] experienced an episode of reinfarction requiring treatment with target vessel revascularization. The incidence of late MACE events was consistent with that reported in other acute MI trials[18, 37, 38, 40, 41] and not significantly different between the study groups.

Between 180 days and 365 days post procedure a total of 5/220 (2.3%) patients in the AO Therapy group experienced a total of eight (8) MACE events. [redacted] each experienced an episode of reinfarction requiring treatment with target vessel revascularization. [redacted] underwent two separate target vessel revascularization procedures and [redacted] each underwent one target vessel revascularization. Two patients in the Control group (2.7%) demonstrated a single episode of TVR.

The events in **Table 85** include a breakdown of each occurrence of the MACE event components (death, reinfarction, target vessel revascularization, and stroke), between 30 days and 6 months, and between 6 months and 12 months post-procedure.

Table 85. Late MACE (>30 Days to 1 Year), Randomized Subjects

	>30 days - 6 months					>6 months - 1 year				
	Control (n=79)		AO Therapy (n=222)			Control (n=79)		AO Therapy (n=222)		
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
MACE Assessment complete at interval		77/79 (97.5%)		222/222 (100.0%)	0.0682		75/79 (94.9%)		220/222 (99.1%)	0.1125
MACE Assessment available at interval†		78//79 (98.7%)		222/222 (100.0%)	0.2625		75/79 (94.9%)		220/222 (99.1%)	0.1125
Composite MACE >30 days to 1 year	4	3/78 (3.8%)	20	15/222 (6.8%)	0.4196	2	2/75 (2.7%)	8	5/220 (2.3%)	1.0000
Death	1	1/78 (1.3%)	4	4/222 (1.8%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
Target Vessel Revascularization‡	2	2/78 (2.6%)	10	9/222 (4.1%)	0.7338	2	2/75 (2.7%)	6	5/220 (2.3%)	1.0000
TVR: Clinically Driven		2/78 (2.6%)		9/222 (4.1%)	0.7338		1/75 (1.3%)		3/220 (1.4%)	1.0000
TVR: Objective evidence of ischemia in AMIHOT II lesion	2	2/78 (2.6%)	7	6/222 (2.7%)	1.0000	1	1/75 (1.3%)	4	3/220 (1.4%)	1.0000
TVR: Target Lesion Revascularization	2	2/78 (2.6%)	9	9/222 (4.1%)	0.7338	2	2/75 (2.7%)	6	5/220 (2.3%)	1.0000
TVR: Urgent or Emergent		1/78 (1.3%)		4/222 (1.8%)	1.0000		1/75 (1.3%)		3/220 (1.4%)	1.0000

† Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
‡ AMIHOT main vessel or branches
* Fisher's Exact test†

Table 85 (continued). Late MACE (>30 Days to 1 Year), Randomized Subjects

	>30 days - 6 months					>6 months - 1 year				
	Control (n=79)		AO Therapy (n=222)			Control (n=79)		AO Therapy (n=222)		
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Reinfarction	1	1/78 (1.3%)	5	4/222 (1.8%)	1.0000	0	0/75 (0.0%)	2	2/220 (0.9%)	1.0000
Stroke	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

*Fisher's Exact test

within the stent, with collateral filling of the LAD via the right coronary artery. The patient required three balloon dilatations to treat this thrombosis.

1.8.13.7.3.2 TVR between 6 Months and 1 Year Follow Up

Five (5) patients in the AO Therapy group (2.3%) required treatment with TVR between 6 months and 1 year, for a total of six (6) events [redacted] underwent two attempted TVR procedures of the LAD, both of which were unsuccessful due to a chronic total occlusion. Three of these five (5) patients experienced events that were clinically driven and characterized as urgent or emergent. None of these incidents of TVR were determined to be related to either the AO device or AO Therapy procedure.

Three of the five (5) AO Therapy patients (1.4%) treated with TVR demonstrated objective evidence of ischemia within the AMIHOT II lesion. Of the other two (2) AO Therapy patients treated with TVR, one patient [redacted] did not manifest any clinical symptoms or objective evidence of ischemia. This patient had a known history of multivessel disease; a 60% diameter stenosis of the AMIHOT II lesion was detected during a routine follow up angiography requiring treatment with PCI. The other patient [redacted] experienced a recurrent myocardial infarction occurring secondary to presumed occlusion of the diagonal LAD branch (non-target lesion).

Of the five (5) patients in the AO Therapy group treated with TVR, three patients (1.4%) required revascularization due to restenosis. Of the other two (2) AO Therapy patients treated with TVR, one patient [redacted] exhibited late stent thrombosis at 263 days post procedure. He presented with severe chest pain in conjunction with ST-elevation on EKG and received urgent thrombolytic treatment with TNK. A catheterization procedure revealed that the previously placed LAD stent was widely patent, with no visible thrombus. The event was adjudicated by the Clinical Events Committee to be probable stent thrombus related to the Index PCI Procedure. The other patient [redacted] had an EKG which revealed ST segment elevation in leads V1-V4 consistent with actute

anterior septal MI, in addition to elevated cardiac enzymes. The patient initially received treatment with thrombolytic therapy in the form of TNK. Cardiac catherization revealed a patent stent in the left LAD, with a 0% stenosis of the AMIHOT lesion. However, a high grade 99% ostial stenosis of the diagonal branch proximal to the previously placed stent within the diagonal branch was noted and stented with a Taxus™ stent deployed in-stent within the left anterior descending artery, with a kissing balloon PTCA in both stents with good angiographic result. The Clinical Events Committee adjudicated the event to be stent occlusion related to the index PCI procedure.

Two patients enrolled in the Control group of the AMIHOT II trial (2.7%) required TVR during this time interval. [redacted] demonstrated objective evidence of ischemia within the AMIHOT II Lesion, requiring target lesion revascularization. The procedure was characterized as clinically driven and urgent or emergent. [redacted] underwent an elective CABG procedure due to the presence of triple vessel disease, involving the LAD, right coronary artery, and left circumflex artery. No objective evidence of ischemia was present within the AMIHOT II vessel.

The incidence of TVR/TLR > 30 days post index procedure in the two treatment groups was similar (2.3% AO Therapy, 2.7% Control). **Table 86** lists patient narratives for patients undergoing TVR between 30 days and 1-year follow-up.

1.8.13.7.3.3 Reinfarction between 30 Days and 6 Months

Four patients in the AO Therapy group (1.8%) demonstrated reinfarction between 30 days and 6 months, for a total of five (5) incidents. None of these incidents of reinfarction were determined to be related to either the AO device or AO Therapy procedure. Three of the four (4) patients with reinfarction had TVR performed. One patient [redacted] did not have TVR performed and was instead treated with medical therapy only. In comparison, one Control patient (1.3%) experienced one episode of reinfarction and had TVR performed.

1.8.13.7.3.4 Reinfarction Between 6 Months and 1 Year Follow-Up

Two patients in the AO Therapy group (0.9%) demonstrated an episode of reinfarction during the post-procedure interval between 6 months and one year. [redacted] demonstrated an episode of reinfarction determined to be related to the Index PCI procedure and [redacted] experienced a reinfarction presumably due to the occlusion of the diagonal branch of the LAD. These incidents of reinfarction did not demonstrate any relationship to the AO device or AO Therapy procedure. No Control patients demonstrated an incident of reinfarction during this time interval. Late TVR and Reinfarction events (> 30 days) were infrequent. No statistically significant differences between the AO Therapy and Control group were noted. **Table 86** provides an abbreviated patient narrative for all patients experiencing reinfarction and/or undergoing TVR between 30 days and 1 year.

Table 86. Patients undergoing Reinfarction and/or Target Vessel Revascularization Between 30 days and 1- Year Follow-Up

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 0 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Yea

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

ID	Subjects Undergoing Reinfarction and Target Vessel Revascularization Between 30 days and 6 Months, and 6 Months and 1-Year

1.8.13.7.3.5 Stroke Events between 30 Days and 6 Months

One patient in the AO Therapy group (0.5%) experienced a stroke between 30 days and 6months. No patients randomized to the Control group experienced stroke.

1.8.13.7.3.6 Stroke Events between 6 Months and 1-Year Follow Up

No patients in either the AO Therapy or Control groups experienced stroke between 6 months and 1-year follow-up.

Table 87 provides a patient narrative for the patient who experienced stroke between 30 days and 12-month follow-up.

Table 87. Subject with Late Stroke between 30 Days and 1-Year Follow-Up

ID	Subject with Late Stroke Between 30 Days and 1-Year Follow-Up

1.8.13.7.3.7 Patient Death between 30 Days and 6 Months

Four (4) patients in the AO Therapy group (1.8%) and one patient in the Control group (1.3%) died between 30 days and 6 months. All deaths were CEC-adjudicated to occur from pre-existing conditions and none were related to either the AO device or AO Therapy procedure.

1.8.13.7.3.8 Patient Death between 6 Months and 1-Year Follow-Up

No patients randomized to AO Therapy or the Control group had died during the interval between 6 months and 1-year follow up. The incidence of death occurring after 30 days was low and was similar in both study groups. **Table 88** provides a patient narrative for each late patient death.

Table 88. Late Patient Deaths (> 30 Days)

ID	Patient Deaths > 30 Days Post Procedure

ID	Patient Deaths > 30 Days Post Procedure

ID	Patient Deaths > 30 Days Post Procedure

ID	Patient Deaths > 30 Days Post Procedure

ID	Patient Deaths > 30 Days Post Procedure
[redacted]	[redacted]
[redacted]	[redacted]

1.8.13.7.3.9 Cumulative 1-Year MACE Rates

Table 89 presents a cumulative accounting of MACE events through the 1-year assessment.

Table 89. Cumulative MACE to 1 Year

	Control (n=79)		AO Therapy (n=222)		
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
MACE Assessment complete through 1 year		75/79 (94.9%)		220/222 (99.1%)	0.8518
MACE Assessment available† through 1 year		77/79 (97.5%)		220/222 (99.1%)	0.9259
Composite Cumulative MACE‡	11	8/77 (10.4%)	47	28/220 (12.7%)	0.6905
Death	1	1/77 (1.3%)	8	8/220 (3.6%)	0.4555
Target Vessel Revascularization§	7	7/77 (9.1%)	25	19/220 (8.6%)	1.0000
TVR: Clinically Driven		5/77 (6.5%)		18/220 (8.2%)	0.8064
TVR: Objective evidence of ischemia in AMIHOT II lesion	5	5/77 (6.5%)	16	11/220 (5.0%)	0.7714
TVR: Target Lesion Revascularization	7	7/77 (9.1 %)	23	18/220 (8.2%)	0.8165
TVR: Urgent or Emergent		4/77 (5.2%)		13/220 (5.9%)	1.0000
Reinfarction	3	3/77 (3.9%)	13	9/220 (4.1%)	1.0000
Stroke	0	0/77 (0.0%)	1	1/220 (0.5%)	1.0000

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
‡For Cumulative summaries, subjects who died prior to 1 year are considered to have assessment complete through 1 year.
§AMIHOT main vessel or branches
*Fisher's Exact test

At 1-year follow up, 28/220 (12.7%) AO Therapy patients exhibited a total of forty-seven (47) MACE events. In comparison, 8/77 (10.4%) Control patients presented a total of eleven (11) events. Both populations exhibited similar rates of death, TVR, reinfarction and stroke through 1 year. Within the AO Therapy group, the overall MACE rate throughout 1-year follow-up is entirely reflective of patients with a history of coronary artery disease and previous myocardial infarction. Based upon these data, AO Therapy does not increase risk for late MACE events.

1.8.13.7.4 Unanticipated Adverse Device Effects

There were no unanticipated adverse device effects reported by the participating investigational centers at any time during the AMIHOT II clinical trial, throughout 1-year follow-up.

1.8.13.7.5 Anticipated Adverse Events

Table 90 presents an overall summary of adverse events that occurred during the AMIHOT II clinical trial more than 30 days following the index procedure. The table is divided into events occurring from >30 days to 6 months, and those occurring from >6 months to 1 year. The majority of these events reflect chronic morbidity associated with the patient's underlying disease state. The occurrence of adverse events after 30 days was similar in the AO Therapy and Control groups. No significant differences were found between the two patient populations. Events were determined to be related primarily to the patient's underlying disease state. The events presented at follow up are consistent with those expected for patients with a history of coronary artery disease.

Table 90. Overall Summary of Adjudicated Late Adverse Events (>30 Days to 1 Year)

	>30days - 6 months					>6 months - 1 year				
	Control (N=79)		AO Therapy (N=222)			Control (N=79)		AO Therapy (N=222)		
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Assessment Complete		77/79 (97.5%)		222/222 (100.0%)			75/79 (94.9%)		220/222 (99.1%)	
Assessment Available†		78/79 (98.7%)		222/222 (100.0%)			75/79 (94.9%)		220/222 (99.1%)	
Any Adverse Event	21	14/78 (17.9%)	81	55/222 (24.8%)	0.2746	10	7/75 (9.3%)	36	24/220 (10.9%)	0.8293
AO device related AE			0	0/222 (0.0%)				0	0/220 (0.0%)	
AO procedure related AE			0	0/222 (0.0%)				0	0/220 (0.0%)	
Index PCI procedure related AE	2	2/78 (2.6%)	6	6/222 (2.7%)	1.0000	0	0/75 (0.0%)	3	3/220 (1.4%)	0.5706
Coronary Artery Disease related AE	3	2/78 (2.6%)	38	28/222 (12.6%)	0.0083	6	3/75 (4.0%)	21	15/220 (6.8%)	0.4214
Study Medication related AE	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
Other relationship‡	15	9/78 (11.5%)	36	26/222 (11.7%)	1.0000	4	4/75 (5.3%)	11	8/220 (3.6%)	0.5168

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
‡Including pre-existing condition, concurrent condition, concurrent intervention and other relationships
*Fisher's Exact test

Table 90 (continued). Overall Summary of Adjudicated Late Adverse Events (>30 Days to 1 Year)

	>30days - 6 months					>6 months - 1 year				
	Control (N=79)		AO Therapy (N=222)			Control (N=79)		AO Therapy (N=222)		
Adverse Event	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Unknown relationship	1	1/78 (1.3%)	1	1/222 (0.5%)	0.4528	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
Serious Adverse Event	10	9/78 (11.5%)	56	41/222 (18.5%)	0.2162	7	5/75 (6.7%)	24	20/220 (9.1%)	0.6353
AO device related AE			0	0/222 (0.0%)				0	0/220 (0.0%)	
AO procedure related AE			0	0/222 (0.0%)				0	0/220 (0.0%)	
Index PCI procedure related AE	2	2/78 (2.6%)	6	6/222 (2.7%)	1.0000	0	0/75 (0.0%)	3	3/220 (1.4%)	0.5706
Coronary Artery Disease related AE	3	2/78 (2.6%)	30	24/222 (10.8%)	0.0328	5	3/75 (4.0%)	16	14/220 (6.4%)	0.5735
Study Medication related AE	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
Other relationship‡	4	4/78 (5.1%)	19	14/222 (6.3%)	1.0000	2	2/75 (2.7%)	4	3/220 (1.4%)	0.6076
Unknown relationship	1	1/78 (1.3%)	1	1/222 (0.5%)	0.4528	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
Adverse Event related to AMIHOT II Vessel	2	2/78 (2.6%)	12	11/222 (5.0%)	0.5258	1	1/75 (1.3%)	6	5/220 (2.3%)	1.0000

‡Including pre-existing condition, concurrent condition, concurrent intervention and other relationships

*Fisher's Exact test

1.8.13.7.5.1 Adverse Events Occurring between 30 Days and 6 Months Post Procedure

A total of 55/222 (24.8%) AO Therapy patients and 14/78 (17.9%) Control patients demonstrated one or more adverse events between 30 days and 6 months. The majority of these events were cardiac disorders. In all, 30/218 (13.5%) AO Therapy patients presented with an adverse event classified as a cardiac disorder compared to 4/78 (5.1%) Control patients. A detailed summary of late adverse events categorized by SOC and PT is included in **Table 91.**

A total of 24/220 (10.9%) AO Therapy patients and 7/75 (9.3%) Control patients demonstrated one or more adverse events between 6 months and 1-year follow up. Events occurring between 6 months and 1 year were primarily cardiac disorder events. Fourteen (14) AO Therapy patients (6.4%) and three (3) Control patients (4.0%) presented with an adverse event classified as a cardiac disorder. One AO Therapy patient (0.5%) and one Control patient (1.3%) demonstrated an episode of coronary artery restenosis classified under "Injury Poisoning and Procedural Complications".

The types and numbers of these events are summarized in **Table 91** as adjudicated by the Clinical Events Committee. No significant differences were found between the study groups.

Table 91. Summary of Late Adverse Events (>30 Days to 1 Year) by SOC and PT

		>30 days - 6 months					>6 months - 1 year				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Assessment Complete†			77/79 (97.5%)		222/222 (100.0%)			75/79 (94.9%)		220/222 (99.1%)	
Assessment Available†			78/79 (98.7%)		222/222 (100.0%)			75/79 (94.9%)		220/222 (71.6%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS		1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	ANEMIA	1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
CARDIAC DISORDERS		4	4/78 (5.1%)	39	30/222 (13.5%)	0.0597	5	3/75 (4.0%)	19	14/220 (6.4%)	0.5744
	ACUTE MYOCARDIAL INFARCTION	0	0/78 (0.0%)	3	3/222 (1.4%)	0.5705	0	0/75 (0.0%)	3	3/220 (1.4%)	0.5734
	ANGINA PECTORIS	0	0/78 (0.0%)	11	10/222 (4.5%)	0.0686	3	1/75 (1.3%)	7	6/220 (2.7%)	0.6829
	ATRIAL FIBRILLATION	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
*Fisher's Exact test

Table 91 (continued). Summary of Late Adverse Events (>30 Days to 1 Year) by SOC and PT

		>30 days - 6 months					>6 months - 1 year				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	ATRIAL FLUTTER	0	0/78 (0.0%)	2	2/222 (0.9%)	1.0000	0	0/75 (0.0%)	2	2/220 (0.9%)	1.0000
	BRADYARRHYTHMIA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	CARDIAC FAILURE CONGESTIVE	0	0/78 (0.0%)	11	8/222 (3.6%)	0.1173	2	2/75 (2.7%)	4	3/220 (1.4%)	0.6042
	DYSPNEA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	ISCHEMIC CARDIOMYOPATHY	0	0/78 (0.0%)	4	4/222 (1.8%)	0.5758	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	MYOCARDIAL ISCHEMIA	2	2/78 (2.6%)	2	2/222 (0.9%)	0.2781	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	PALPITATIONS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	PULMONARY EDEMA	1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	SUPRAVENTRICULAR TACHYCARDIA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

*Fisher's Exact test

Table 91 (continued). Summary of Late Adverse Events (>30 Days to 1 Year) by SOC and PT

		>30 days - 6 months					>6 months - 1 year				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	VENTRICULAR TACHYCARDIA	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
ENDOCRINE DISORDERS	[redacted]	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	HYPERTHYROIDISM	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
GASTROINTESTINAL DISORDERS	[redacted]	0	0/78 (0.0%)	4	4/222 (1.8%)	0.5758	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	COLONIC POLYP	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	DIARRHEA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	ESOPHAGITIS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	HEMORRHOIDS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	PANCREATITIS ACUTE	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

*Fisher's Exact test

Table 91 (continued). Summary of Late Adverse Events (>30 Days to 1 Year) by SOC and PT

		>30 days - 6 months					>6 months - 1 year				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	[redacted]	2	2/78 (2.6%)	6	6/222 (2.7%)	1.0000	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	CHEST PAIN	0	0/78 (0.0%)	3	3/222 (1.4%)	0.5705	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	CHEST PRESSURE	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	EDEMA PERIPHERAL	1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	FATIGUE	1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
HEPATOBILIARY DISORDERS	[redacted]	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	CHOLECYSTITIS ACUTE	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
INFECTIONS AND INFESTATIONS	[redacted]	2	2/78 (2.6%)	4	3/222 (1.4%)	0.6077	0	0/75 (0.0%)	3	3/220 (1.4%)	0.5734
	GASTROENTERITIS	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/56 (0.0%)	1	1/220 (0.5%)	1.0000

*Fisher's Exact test

Table 91 (continued). Summary of Late Adverse Events (>30 Days to 1 Year) by SOC and PT

		>30 days - 6 months					>6 months - 1 year				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	INFLUENZA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	PNEUMONIA	1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	SYSTEMIC CANDIDA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	URINARY TRACT INFECTION	1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	VIRAL INFECTION	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		2	2/78 (2.6%)	6	6/222 (2.7%)	1.0000	1	1/75 (1.3%)	4	4/220 (1.8%)	1.0000
	CORONARY ARTERY RESTENOSIS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	1	1/75 (1.3%)	1	1/220 (0.5%)	0.4445
	LOWER LIMB FRACTURE	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	STENT OCCLUSION	1	1/78 (1.3%)	4	4/222 (1.8%)	1.0000	0	0/75 (0.0%)	3	3/220 (1.4%)	0.5734

*Fisher's Exact test

Table 91 (continued). Summary of Late Adverse Events (>30 Days to 1 Year) by SOC and PT

		>30 days - 6 months					>6 months - 1 year				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Eve nts** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	SUBDURAL HEMATOMA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
METABOLISM AND NUTRITION DISORDERS	[redacted]	2	2/78 (2.6%)	2	2/222 (0.9%)	0.2781	1	1/75 (1.3%)	0	0/220 (0.0%)	0.2542
	DIABETES MELLITUS	2	2/78 (2.6%)	1	1/222 (0.5%)	0.1667	1	1/75 (1.3%)	0	0/220 (0.0%)	0.2542
	DIABETIC COMA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	[redacted]	1	1/78 (1.3%)	2	2/222 (0.9%)	1.0000	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	MYALGIA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	PAIN IN EXTREMITY	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	PAIN IN JAW	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
NERVOUS SYSTEM DISORDERS	[redacted]	1	1/78 (1.3%)	6	5/222 (2.3%)	1.0000	1	1/75 (1.3%)	1	1/220 (0.5%)	0.4445
	CEREBROVASCULAR ACCIDENT	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

*Fisher's Exact test

Table 91 (continued). Summary of Late Adverse Events (>30 Days to 1 Year) by SOC and PT

		>30 days - 6 months					>6 months - 1 year				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	DEMENTIA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	DIZZINESS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	1	1/75 (1.3%)	0	0/220 (0.0%)	0.2542
	EPILEPSY	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	PARESTHESIA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	RADIAL NERVE PALSY	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	SYNCOPE	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	TRANSIENT ISCHEMIC ATTACK	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
PSYCHIATRIC DISORDERS	[redacted]	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	DEPRESSION	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

*Fisher's Exact test

Table 91 (continued). Summary of Late Adverse Events (>30 Days to 1 Year) by SOC and PT

		>30 days - 6 months					>6 months - 1 year				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
RENAL AND URINARY DISORDERS	[redacted]	0	0/78 (0.0%)	2	2/222 (0.9%)	1.0000	2	2/75 (2.7%)	3	2/220 (0.9%)	0.2682
	HEMATURIA	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	1	1/75 (1.3%)	1	1/220 (0.5%)	0.4445
	NEPHROLITHIASIS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	RENAL FAILURE ACUTE	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	1	1/75 (1.3%)	1	1/220 (0.5%)	0.4445
	URINARY RETENTION	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	[redacted]	2	2/78 (2.6%)	2	2/222 (0.9%)	0.2781	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	COUGH	1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	EPISTAXIS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

*Fisher's Exact test

Table 91 (continued). Summary of Late Adverse Events (>30 Days to 1 Year) by SOC and PT

		>30 days - 6 months					>6 months - 1 year				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	SLEEP APNEA SYNDROME	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	[redacted]	0	0/78 (0.0%)	2	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	DECUBITUS ULCER	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	HERPES ZOSTER	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	RASH	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
SURGICAL AND MEDICAL PROCEDURES	[redacted]	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	IMPLANTABLE DEFIBRILLATOR INSERTION	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

Table 91 (continued). Summary of Late Adverse Events (>30 Days to 1 Year) by SOC and PT

		>30 days - 6 months					>6 months - 1 year				
Category	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
VASCULAR DISORDERS	[redacted]	2	2/78 (2.6%)	3	3/222 (1.4%)	0.6077	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	ARTERIOSCLEROSIS	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	CATHETER SITE HEMATOMA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	DEEP VEIN THROMBOSIS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	HYPERTENSION	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	HYPOTENSION	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	SYNCOPE VASOVAGAL	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

*Fisher's Exact test

1.8.13.7.5.2 Relationship of Adverse Events Occurring between 30 Days and 6 Months Post Procedure

Coronary artery disease was determined by the Clinical Events Committee to be the most common reason for post 30-day Adverse Events in both the AO Therapy group (38/81 events; 46.9 %) and the Control group (3/21 events; 14.3%). Six (6) patients in the AO Therapy group (2.7%) and two patients in the Control group (2.6%) demonstrated an adverse event related to the Index PCI procedure. These results are consistent with those expected in a patient population with a history of coronary artery disease and previous myocardial infarction. No events were determined to be related to either the AO device or AO Therapy procedure.

Eleven (11) AO Therapy patients (5.0%) and two (2) Control patients (2.6%) demonstrated adverse events related to the AMIHOT II Vessel. Within the AO Therapy group, three patients experienced acute myocardial infarctions (1.4%), four (4) patients experienced a stent occlusion (1.8%) and four (4) patients experienced angina pectoris (1.8%). Within the Control group, one patient experienced myocardial ischemia (1.3%) and one patient experienced stent occlusion (1.3%).

The majority of adverse events occurring between 6 months and 1 year for both groups were also determined to be related to the patient's coronary artery disease. Fifteen (15) AO Therapy patients (6.8%) experienced twenty-one (21) adverse events and three Control patients (4.0%) experienced six (6) adverse events that were determined by the CEC to have been related to coronary artery disease. Three (3) AO Therapy patients (1.4%) and no Control patients demonstrated an adverse event related to the Index PCI procedure. These results are consistent with those expected in a patient population receiving immediate treatment for AMI.

Five (5) AO Therapy patients (2.3%) and one Control patient (1.3%) demonstrated an adverse event related to the AMIHOT II Vessel between 6 months and 1-year follow-up.

Of the five (5) AO Therapy patients, three experienced stent occlusion (1.4%), one patient experienced coronary artery restenosis (0.5%) and one patient experienced two separate episodes of angina pectoris (0.5%). Within the Control group, one patient experienced coronary artery restenosis (1.8%).

The type and frequency of late adverse events (>30 days) observed in the AMIHOT II trial is expected of a population with chronic coronary artery disease and a history of myocardial infarction. There were no significant differences between groups in the incidence or type of adverse events occurring post 30 days.

1.8.13.7.5.3 Late Serious Adverse Events

Late serious adverse events are summarized in **Table 92** categorized by PT, SOC, and relationship.

Table 92. Summary of Late Serious Adverse Events (>30 Days to 1 Year) by SOC, PT and Relationship by Patient

			>30 days - 6 months					>6 months - 1 year				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Assessment Complete				77/79 (97.5%)		222/222 (100.0%)			75/79 (94.9%)		220/222 (99.1%)	
Assessment Available†				78/79 (98.7%)		222/222 (100.0%)			75/79 (94.9%)		220/222 (99.1%)	
Any Relationship	All serious adverse events		10	9/78 (11.5%)	56	41/222 (18.5%)	0.2156	7	5/75 (6.7%)	24	20/220 (9.1%)	0.6353
Index PCI procedure related AE	All serious adverse events		2	2/78 (2.6%)	6	6/222 (2.7%)	1.0000	0	0/75 (0.0%)	3	3/220 (1.4%)	0.5734
	CARDIAC DISORDERS		1	1/78 (1.3%)	3	3/222 (1.4%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		ACUTE MYOCARDIAL INFARCTION	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		ANGINA PECTORIS	0	0/78 (0.0%)	2	2/222 (0.9%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		MYOCARDIAL ISCHEMIA	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
*Fisher's Exact test

Table 92 (continued). Summary of Late Serious Adverse Events (>30 Days to 1 Year) by SOC, PT and Relationship by Patient

			>30 days - 6 months					>6 months - 1 year				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
	INJURY, POISONING AND PROCEDURAL COMPLICATIONS		1	1/78 (1.3%)	3	13/222 (1.4%)	1.0000	0	0/75 (0.0%)	3	3/220 (1.4%)	0.5734
		CORONARY ARTERY RESTENOSIS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		STENT OCCLUSION	1	1/78 (1.3%)	2	2/222 (0.9%)	1.0000	0	0/75 (0.0%)	3	3/220 (1.4%)	0.5734
Coronary Artery Disease related AE	All serious adverse events		3	2/78 (2.6%)	30	24/222 (10.8%)	0.0327	5	3/75 (4.0%)	16	14/220 (6.4%)	0.5744
	CARDIAC DISORDERS		2	2/78 (2.6%)	28	23/222 (10.4%)	0.0322	4	3/75 (4.0%)	14	12/220 (5.5%)	0.7676
		ACUTE MYOCARDIAL INFARCTION	0	0/78 (0.0%)	2	2/222 (0.9%)	1.0000	0	0/75 (0.0%)	3	3/220 (1.4%)	0.5734
		ANGINA PECTORIS	0	0/78 (0.0%)	9	8/222 (3.6%)	0.1173	2	1/75 (1.3%)	6	5/220 (2.3%)	1.0000

*Fisher's Exact test

Table 92 (continued). Summary of Late Serious Adverse Events (>30 Days to 1 Year) by SOC, PT and Relationship by Patient

			>30 days - 6 months					>6 months - 1 year				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
		ATRIAL FLUTTER	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
		CARDIAC FAILURE CONGESTIVE	0	0/78 (0.0%)	9	7/222 (3.2%)	0.1962	2	2/75 (2.7%)	2	2/220 (0.9%)	0.2682
		ISCHEMIC CARDIOMYOPATHY	0	0/78 (0.0%)	4	4/222 (1.8%)	0.5758	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		MYOCARDIAL ISCHEMIA	1	1/78 (1.3%)	2	2/222 (0.9%)	1.0000	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
		PALPITATIONS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		PULMONARY EDEMA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
		VENTRICULAR TACHYCARDIA	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	INJURY, POISONING AND PROCEDURAL COMPLICATIONS		0	0/78 (0.0%)	2	2/222 (0.9%)	-----	1	1/75 (1.3%)	1	1/220 (0.5%)	0.4445

*Fisher's Exact test

Table 92 (continued). Summary of Late Serious Adverse Events (>30 Days to 1 Year) by SOC, PT and Relationship by Patient

			>30 days - 6 months					>6 months - 1 year				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
		CORONARY ARTERY RESTENOSIS	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	1	1/75 (1.3%)	1	1/220 (0.5%)	0.4445
		STENT OCCLUSION	0	0/78 (0.0%)	2	2/222 (0.9%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	SURGICAL AND MEDICAL PROCEDURES		1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		IMPLANTABLE DEFIBRILLATOR INSERTION	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	VASCULAR DISORDERS		0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
		HYPOTENSION	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
Other relationship‡	All serious adverse events		4	4/78 (5.1%)	19	14/222 (6.3%)	1.0000	2	2/75 (2.7%)	4	3/220 (1.4%)	0.6042
	BLOOD AND LYMPHATIC SYSTEM DISORDERS		1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

‡Including pre-existing condition, concurrent condition, concurrent intervention and other relationships
*Fisher's Exact test

Table 92 (continued). Summary of Late Serious Adverse Events (>30 Days to 1 Year) by SOC, PT and Relationship by Patient

			>30 days - 6 months					>6 months - 1 year				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
		ANEMIA	1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	CARDIAC DISORDERS		0	0/78 (0.0%)	3	3/222 (1.4%)	0.5705	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		ATRIAL FLUTTER	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		BRADYARRHYTHMIA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		SUPRAVENTRICULAR TACHYCARDIA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	GASTROINTESTINAL DISORDERS		0	0/78 (0.0%)	2	2/222 (0.9%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		ESOPHAGITIS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		PANCREATITIS ACUTE	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		0	0/78 (0.0%)	2	2/222 (0.9%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

*Fisher's Exact test

Table 92 (continued). Summary of Late Serious Adverse Events (>30 Days to 1 Year) by SOC, PT and Relationship by Patient

			>30 days - 6 months					>6 months - 1 year				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
		CHEST PAIN	0	0/78 (0.0%)	2	2/222 (0.9%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	HEPATOBILIARY DISORDERS		0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
		CHOLECYSTITIS ACUTE	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	INFECTIONS AND INFESTATIONS		0	0/78 (0.0%)	3	2/222 (0.9%)	1.0000	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
		GASTROENTERITIS	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
		PNEUMONIA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		SYSTEMIC CANDIDA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		URINARY TRACT INFECTION	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	INJURY, POISONING AND PROCEDURAL COMPLICATIONS		1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

*Fisher's Exact test

Table 92 (continued). Summary of Late Serious Adverse Events (>30 Days to 1 Year) by SOC, PT and Relationship by Patient

			>30 days - 6 months					>6 months - 1 year				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
		LOWER LIMB FRACTURE	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2635	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		SUBDURAL HEMATOMA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	METABOLISM AND NUTRITION DISORDERS		0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		DIABETIC COMA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	NERVOUS SYSTEM DISORDERS		1	1/78 (1.3%)	2	2/222 (0.9%)	1.0000	1	1/75 (1.3%)	0	0/220 (0.0%)	0.2542
		CEREBROVASCULAR ACCIDENT	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		DIZZINESS	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	1	1/75 (1.3%)	0	0/220 (0.0%)	0.2542
		EPILEPSY	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

*Fisher's Exact test

Table 92 (continued). Summary of Late Serious Adverse Events (>30 Days to 1 Year) by SOC, PT and Relationship by Patient

			>30 days - 6 months					>6 months - 1 year				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
		TRANSIENT ISCHEMIC ATTACK	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	RENAL AND URINARY DISORDERS		0	0/78 (0.0%)	2	2/222 (0.9%)	1.0000	1	1/75 (1.3%)	2	1/220 (0.5%)	0.4445
		HEMATURIA	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
		NEPHROLITHIASIS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		RENAL FAILURE ACUTE	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	1	1/75 (1.3%)	0	0/220 (0.0%)	0.2542
		URINARY RETENTION	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	VASCULAR DISORDERS		1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		DEEP VEIN THROMBOSIS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		HYPERTENSION	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

*Fisher's Exact test

Table 92 (continued). Summary of Late Serious Adverse Events (>30 Days to 1 Year) by SOC, PT and Relationship by Patient

			>30 days - 6 months					>6 months - 1 year				
Relationship	**Category**	**Adverse Event**	**Control** (N=79)		**AO Therapy** (N=222)			**Control** (N=79)		**AO Therapy** (N=222)		
	System Organ Class	**MedDRA PT**	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***	**Events** (n)	**Pts with Events** (n/N; %)	**Events** (n)	**Pts with Events** (n/N; %)	**p value***
Unknown relationship	All serious adverse events		1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
		CHEST PAIN	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	NERVOUS SYSTEM DISORDERS		0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		PARESTHESIA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	VASCULAR DISORDERS		1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		ARTERIOSCLEROSIS	1	1/78 (1.3%)	0	0/222 (0.0%)	0.2600	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

*Fisher's Exact test

1.8.13.7.5.4 Serious Adverse Events Occurring between 30 Days and 6 Months Post Procedure

A total of 41/222 (18.5 %) AO Therapy patients demonstrated a total of fifty-six (56) serious adverse events between 30 days and 6 months. By comparison, 9/78 (11.5%) Control patients demonstrated a total of ten (10) serious adverse events in this interval.

More than half of these events experienced by the AO Therapy patients were classified under "Cardiac Disorders". Events included acute myocardial infarction (3 patients), angina pectoris (10 patients), atrial flutter (1 patient), bradyarrhythmia (1 patient), congestive heart failure (7 patients), ischemic cardiomyopathy (4 patients), myocardial ischemia (2 patients), palpitations (1 patient), pulmonary edema (1 patient) and supraventricular tachycardia (1 patient).

Serious adverse events classified under "Cardiac Disorders" in the Control group included myocardial ischemia (2 patients) and ventricular tachycardia (1 patient).

One patient (0.5%) in the AO Therapy group and two (2) patients (2.6%) in the Control group presented with a SAE classified under "Vascular Disorders" between 30 days and 6 months. The AO Therapy patient exhibited deep vein thrombosis. One Control patient experienced hyertension while the other Control patient [redacted] died after 30 days with minimal detail except a death certificate noting arteriosclerosis (the adjudicated AE term) as the cause of death.

Six (6) AO Therapy patients (2.7%) and two (2) Control patients (2.6%) demonstrated a SAE classified under "Injury, Poisoning, and Procedural Complications". One patient in the AO Therapy group exhibited coronary artery restenosis, one patient presented with subdural hematoma and four (4) patients presented with stent occlusion. One patient in the Control group displayed a lower limb fracture and one patient had a stent occlusion.

1.8.13.7.5.5 Relationship of Serious Adverse Events Occurring between 30 Days and 6 Months Post Procedure

The majority of serious adverse events were determined by the Clinical Events Committee to be related to coronary artery disease. Twenty-four (24) AO Therapy patients (10.8%) and two (2) Control patients (2.6%) presented a serious adverse event believed to be related to coronary artery disease.

Six (6) AO Therapy patients (2.7%) and two (2) Control patients (2.6%) demonstrated a SAE between 30 days and 6 months that was determined to be related to the Index Procedure. Of the six (6) AO Therapy subjects, two (2) patients experienced the serious adverse event of angina pectoris, one patient experienced an episode of acute myocardial infarction, two (2) patients experienced a stent occlusion and one patient demonstrated an episode of coronary artery restenosis. Within the Control group, one patient demonstrated an episode of stent occlusion and one patient demonstrated myocardial ischemia.

These results are consistent with that expected in a population of patients with a history of coronary artery disease and previous myocardial infarction. Both adverse events and serious adverse events reflect a chronic condition associated with the patient's underlying disease state.

1.8.13.7.5.6 Serious Adverse Events Occurring Between 6 Months and 1 Year Post Procedure

Between 6 months and 1-year follow-up, 20/220 AO Therapy patients (9.1%) demonstrated twenty-four (24) serious adverse events. A total of 5/75 (6.7%) Control patients presented a total of seven (7) SAEs during this time interval. No significant differences were found between the two study groups.

Twelve (12) AO Therapy patients (5.5%) and three (3) Control patients (4.0%) demonstrated a SAE classified as under "Cardiac Disorders". For AO Therapy patients, events consisted of acute myocardial infarction (3 patients), congestive heart failure (2 patients), angina pectoris (6 episodes in 5 patients), atrial flutter (1 patient) myocardial ischemia (1 patient) and pulmonary edema (1 patient). Two Control patients exhibited congestive heart failure and one patient exhibited two episodes of angina pectoris.

The remaining SAEs were spread across all categories. One AO Therapy patient presented with a serious adverse event classified under "Vascular Disorders", as evidenced by one episode of hypotension. No Control patients exhibited any events classified under vascular disorders. Three (3) patients in the AO Therapy group exhibited stent occlusion while no patients in the Control group experienced stent occlusion. Additionally, one patient in the AO Therapy group and one patient in the Control group demonstrated the serious adverse event of coronary artery restenosis, classified under "Injury, Poisoning, and Procedural Complications." No significant differences were found in the incidence or type of serious adverse events between the two study groups.

Other SAEs presented by AO Therapy patients include cholecystitis (1 patient), gastroenteritis (1 patient), hematuria (1 patient), urinary retention (1 patient) and chest pain (1 patient). The Control group had one patient experience dizziness and one patient experience acute renal failure during the 6-month to 1-year interval.

1.8.13.7.5.7 Relationship of Serious Adverse Events Occurring within 1 Year of the Index Procedure

The majority of serious adverse events were determined by the Clinical Events Committee to be related to the patient's underlying disease state. A total of 14/220 (6.4%) AO Therapy patients and 3/75 (4.0%) Control patients presented a SAE determined to be related to coronary artery disease. Three patients in the AO Therapy group (1.4%)

experienced a stent occlusion while no Control patients demonstrated a SAE related to the Index Procedure.

1.8.13.7.5.8 Serious Device or Procedure Related Adverse Events Occurring Post 30 Days

No AO Therapy patients demonstrated a serious adverse event determined to be related to the AO Device or AO Therapy procedure after day 30. Additionally, there were no non-serious adverse events in the AO Therapy group after day 30 that were determined to be related to the AO device or AO Therapy procedure. Because AO Therapy is an infusion with no implantable component, and no mechanical manipulation of the heart, the absence of late device/procedure-related adverse events of any kind is a logical and expected outcome.

1.8.13.7.5.9 Bleeding Events At 6 Months Post Index Procedure

Table 93 provides a summary of late bleeding events in the AMIHOT II trial, divided into those occurring between 30 days and 6 months, and those occurring between 6 months and 1-year follow-up.

The incidence of late bleeding events was similar in the AO Therapy and Control groups. Four (4) AO Therapy patients (1.8%) and one Control patient (1.3%) demonstrated an episode of bleeding between 30 days and 6 months. One AO Therapy patient (0.5%) and one Control patient (1.3%) demonstrated a bleeding event that required a transfusion. No significant differences were found between the study groups.

One patient in the AO Therapy group (0.5%) experienced a single episode of access site bleeding, classified as mild catheter site hematoma, between 30 days and 6 months. No patients within the Control group presented with access site bleeding.

Three AO Therapy patients (1.4%) and one Control patient (1.3%) demonstrated a total of four (4) episodes of non-access site bleeding between 30 days and 6 months. One AO Therapy patient (0.5%) and one Control patient (1.3%) each presented a single episode of moderate anemia. A mild epistaxis was experienced by one AO Therapy patient (0.5%). Additionally, one patient in the AO Therapy group presented one incident of severe non-access site bleeding (0.5%). This patient presented a subdural hematoma, classified as "Severe" bleeding. This event reflects a pre-existing condition (trauma event prior to the index procedure), and did not demonstrate any relationship to the AO device or AO Therapy procedure. All late bleeding events were completely resolved, with no residual clinical sequelae.

1.8.13.7.5.10 Bleeding Events at 1-Year Post Index Procedure

One patient in the AO Therapy group (0.5%) and one patient in the Control group (1.3%) demonstrated an episode of bleeding between 6 months and 1 year. These events were determined to be Non-Access Site related. Neither event required a blood transfusion. Specifically, the AO Therapy patient demonstrated an episode of mild hematuria and the Control patient demonstrated an episode of moderate hematuria. No severe/life threatening bleeding events were recorded in the AMIHOT II trial between 6 months and 1 year. The incidence of bleeding events more than 30 days post index procedure in this trial was minimal and comparable between the two study groups.

Table 93. Bleeding Events by Bleeding Category after 30 Days

			Randomization Group									
			6 months					12 months				
			Control (N=79)		AO Therapy (N=222)			Control (N=79)		AO Therapy (N=222)		
Location	**Bleeding Category‡**	**Adverse Event**	**Events (n)**	**Pts with Events (n/N; %)**	**Events (n)**	**Pts with Events (n/N; %)**	**p value***	**Events (n)**	**Pts with Events (n/N; %)**	**Events (n)**	**Pts with Events (n/N; %)**	**p value***
Assessment Complete				77/79 (97.5%)		222/222 (100.0%)			75/79 (94.9%)		220/222 (99.1%)	
Assessment Available†				78/79 (98.7%)		222/222 (100.0%)			75/79 (94.9%)		220/222 (99.1%)	
All Bleeding Events			1	1/78 (1.3%)	4	4/222 (1.8%)	1.0000	1	1/75 (1.3%)	1	1/220 (0.5%)	0.4445
All Severe/Life Threatening Bleeding Events			0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
Access Site			0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
	Mild	CATHETER SITE HEMATOMA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

†Complete or event reported in the interval. Event rate denominators utilize number of subjects with assessment available.
‡Mild Bleeding: Bleeding that does not require transfusion or result in hemodynamic compromise.
Moderate Bleeding: Bleeding requiring transfusion defined as any blood loss requiring transfusion of blood products.
Severe/Life Threatening Bleeding: Bleeding that is intracranial or that results in substantial hemodynamic compromise requiring treatment.
*Fisher's Exact test

Table 93 (continued). Bleeding Events by Bleeding Category after 30 Days

			Randomization Group									
			6 months					12 months				
			Control (N=79)		AO Therapy (N=222)			Control (N=79)		AO Therapy (N=222)		
Location	**Bleeding Category†**	**Adverse Event**	**Events (n)**	**Pts with Events (n/N; %)**	**Events (n)**	**Pts with Events (n/N; %)**	**p value***	**Events (n)**	**Pts with Events (n/N; %)**	**Events (n)**	**Pts with Events (n/N; %)**	**p value***
Non-Access Site			1	1/78 (1.3%)	3	3/222 (1.4%)	1.0000	1	1/75 (1.3%)	1	1/220 (0.5%)	0.4445
	Mild	EPISTAXIS	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		HEMATURIA	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	0	0/75 (0.0%)	1	1/220 (0.5%)	1.0000
	Moderate	ANEMIA	1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
		HEMATURIA	0	0/78 (0.0%)	0	0/222 (0.0%)	-----	1	1/75 (1.3%)	0	0/220 (0.0%)	0.2542
	Severe	SUBDURAL HEMATOMA	0	0/78 (0.0%)	1	1/222 (0.5%)	1.0000	0	0/75 (0.0%)	0	0/220 (0.0%)	-----
Events Requiring Transfusion			1	1/78 (1.3%)	1	1/222 (0.5%)	0.4530	0	0/75 (0.0%)	0	0/220 (0.0%)	-----

†Mild Bleeding: Bleeding that does not require transfusion or result in hemodynamic compromise.
Moderate Bleeding: Bleeding requiring transfusion defined as any blood loss requiring transfusion of blood products.
Severe/Life Threatening Bleeding: Bleeding that is intracranial or that results in substantial hemodynamic compromise requiring treatment.
*Fisher's Exact test

1.8.13.7.6 Late Adverse Event Summary

No significant differences were found between the AO Therapy group and Control group in the incidence or type of adverse events and serious adverse events occurring after 30 days. The incidence and type of adverse events and serious adverse events occurring between 30 days and 1-year follow up are consistent with those expected in a patient population with coronary artery disease and a history of previous myocardial infarction. No causal relationship was found by the CEC between any late events and the AO device or AO Therapy procedure. These data emphasize the comparable profile of safety between AO Therapy and PCI for the treatment of myocardial infarction.

1.8.13.8 Summary of Safety-Related Data for AMIHOT II Study

The prospective AMIHOT II multi-center randomized clinical investigation was undertaken to assess the safety and effectiveness of the AO Therapy procedure in patients presenting with anterior acute myocardial infarction treated with PCI within six hours of symptom onset. The randomized, controlled study enrolled subjects from the specified target population who were treated according to the protocol. The resulting scientific evidence supports the following conclusions regarding the safety of AO Therapy.

Patients assigned to receive adjunctive AO Therapy following PCI experienced a similar incidence of MACE events assessed at 30 days when compared to patients treated with PCI alone. The primary study endpoint hypothesis of non-inferiority in 30-day MACE rates within a non-inferiority delta of 6% was achieved. Late MACE rates at 6 months and up to one year showed that MACE events remain consistent with rates expected in this patient population.

No significant differences were found in the incidence of MACE component events (Target Vessel Revascularization, Reinfarction, Stroke, or Patient Death) at 30 days, 6 months and one year between AO Therapy patients and Control patients.

AO Therapy patients demonstrated a similar incidence, type, and relationship of Serious Adverse Events assessed at 30 days, 6 months, and one year, when compared to Control patients. A general review of Serious Adverse Events also reveals that the types and frequencies of adverse events observed in this clinical study were entirely consistent with this patient population based upon published medical literature.

AO Therapy patients presented with a higher incidence of vascular disorder events and a higher incidence of bleeding events. AO Therapy patients received an additional 90 minutes of catheterization time and extended anticoagulation therapy during the 90-minute infusion period. More significantly, AO Therapy patients enrolled prior to the introduction of the [redacted] catheter required a 9F arterial sheath or a second contralateral arterial sheath in order to accommodate the [redacted] infusion catheter. Increased procedure time and anticoagulation in conjunction with the increased needs for vascular access would be expected to subsequently increase the rates of Vascular and Bleeding Adverse Events. The majority of these observed events consisted of mild bleeding events associated with the access site. These events resolved quickly without any long-term residual effects. No significant differences were found between the study groups in the incidence of Vascular and Bleeding Adverse Events at 6 months and one year.

Importantly, the incidence of access site events decreased with the use of the TherOx [redacted] catheter, thus enabling smaller sheath sizes (8F) used for coaxial delivery of AO Therapy with only a single arterial puncture. The overall incidence of access site complications in the [redacted] catheter group (13.3%) was found to be significantly less than rates associated with the [redacted] catheter (27.2%), and similar to the rates within in the Control group (12.7%). Because the [redacted] catheter is the exclusive AO delivery catheter for future investigational and post-market administration of AO Therapy, the lower access site complication rates associated with its use are likely representative of rates that would be observed in a post-market setting.

The types and frequencies of other adverse events observed in this clinical study were similar across groups and entirely consistent with this patient population.

In summation, the 30-day MACE rate in the AMIHOT II trial was very low overall (5.4%) considering the patient population under study. AO Therapy patients had a similar 30-day MACE rate to that observed in Control patients. The primary safety hypothesis of non-inferiority (with a delta of 6%) in 30-day MACE rate between AO Therapy and Control groups was achieved using a Bayesian hierarchical model that incorporated data from the prior AMIHOT I trial. The type and frequency of other adverse events which occurred in this trial suggest that AO Therapy is associated with a safety profile which is largely similar to that seen with current percutaneous treatment modalities, including PCI, balloon angioplasty, and stent placement. Improvements in the infusion catheter used for AO delivery (*i.e.* introduction of the [redacted] catheter) have reduced the rate of access site complications, directly in line with that observed for standard PCI therapy. No late events (>30 days to 1 year) were observed that suggest late safety concerns associated with the use of this device. AO Therapy can be delivered safely to patients presenting with anterior AMI within 6 hours of symptom onset.

1.8.14 Medications

Medication use in patients enrolled in the AMIHOT II trial is summarized in the following sections. Compliance with medications required by clinical protocol is summarized in **Section 1.8.15.** Required study medications included Aspirin 325 mg in the emergency room or prior to catheterization, Clopidogrel 300-600 mg po (may be given up to four hours post-procedure), followed by 75 mg po qd for a minimum of 1 month, and I.V. heparin during the index procedure/AO therapy to maintain ACT greater than or equal to 250 seconds. In addition to these required study medications, patients enrolled in the AMIHOT II trial were often being treated with cardiac medications for their cardiovascular disease and other associated medical conditions. Common

medications for patients with cardiovascular disease include nitrates, beta blockers, calcium channel blockers, ACE inhibitors, diuretics, anti-arrhythmics, lipid lowering agents, and anticoagulants. AMIHOT II patients were treated for their acute anterior MI with medications typically utilized in this setting including nitrates, beta blockers, antiplatelets, anticoagulants, analgesics, antiemetics, and antianxiety medications[5]. Additional medications were administered as required to address comorbid conditions or complications that occurred during hospitalization or within 30 days of hospitalization.

Medications were categorized for the AMIHOT II trial into common classifications of cardiac-related agents. Medications used during the trial were summarized by class of medication. **Tables 94 – 100** summarize the most commonly used medications administered to patients prior to admission (within 7 days), Post-Symptom Onset and Prior to PCI, in the Cardiac Catheterization Laboratory, Post Procedure through Discharge, Discharge and Post-Discharge through 30-Day Follow Up. These tables present the number and proportion of patients in each group taking the specified class of medication at the tabulated time period.

1.8.14.1 Medications Administered up to 7 Days Prior to Admission

Medication usage within the seven (7) days preceding admission for the index MI event is detailed in **Table 94.** Prior to admission for acute MI, the most commonly prescribed classes of medications in both treatment groups were lipid lowering agents (statins), antiplatelets (aspirin) and beta-blockers. ACE-inhibitors, calcium channel blocking agents and diuretics were also commonly prescribed medications for this patient population. These medications were prescribed in approximately 10-20% of both patient groups. A small percentage of patients were being treated with anticoagulants for conditions such as atrial fibrillation and recent hip surgery. One patient with glycoprotein IIb/IIIa inhibitor use had a recent MI (7 days prior). The medication usage profile of subjects in this trial is consistent with that of this patient population. No

significant differences were found between the two groups with respect to medications administered within 7 days of admission for the index procedure.

Table 94. Medications Administered up to 7 Days Prior to Admission

Medication Category	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)	p value*
Glycoprotein IIb/IIIa inhibitors (any)	1/79 (1.3%)	0/222 (0.0%)	0.26**
ReoPro (abciximab)	0/79 (0.0%)	0/222 (0.0%)	
Aggrastat (tirofiban)	1/79 (1.3%)	0/222 (0.0%)	
Integrilin (eptifibatide)	0/79 (0.0%)	0/222 (0.0%)	
Other	0/79 (0.0%)	0/222 (0.0%)	
Antiplatelets	17/79 (21.5%)	40/222 (18.0%)	0.50
ASA†	15/79 (19.0%)	37/222 (16.7%)	0.64
Clopidogrel	3/79 (3.8%)	7/222 (3.2%)	0.73**
Ticlopidine	0/79 (0.0%)	0/222 (0.0%)	
Clopidogrel or Ticlopidine	3/79 (3.8%)	7/222 (3.2%)	0.73**
Other	0/79 (0.0%)	1/222 (0.5%)	1.0**
Anticoagulants	3/79 (3.8%)	3/222 (1.4%)	0.19**
Heparin	0/79 (0.0%)	0/222 (0.0%)	
Bivalirudin	0/79 (0.0%)	0/222 (0.0%)	
LMWH†	2/79 (2.5%)	0/222 (0.0%)	
Other	1/79 (1.3%)	3/222 (1.4%)	
Thrombolytics (any)	0/79 (0.0%)	0/222 (0.0%)	
Adenosine	0/79 (0.0%)	0/222 (0.0%)	
ACE† inhibitors	9/79 (11.4%)	29/222 (13.1%)	0.70
Angiotension receptor blockers	4/79 (5.1%)	10/222 (4.5%)	0.76**
Beta blockers	12/79 (15.2%)	37/222 (16.7%)	0.76
Calcium channel blockers	5/79 (6.3%)	25/222 (11.3%)	0.21
Alpha blockers	6/79 (7.6%)	7/222 (3.2%)	0.11**
Diuretics	10/79 (12.7%)	20/222 (9.0%)	0.35
Digitalis	1/79 (1.3%)	0/222 (0.0%)	0.26**
Vasopressors	0.79 (0.0%)	0/222 (0.0%)	
Inotropes	0/79 (0.0%)	0/222 (0.0%)	
Nitrates	2/79 (2.5%)	8/222 (3.6%)	1.0**
Analgesics	3/79 (3.8%)	22/222 (9.9%)	0.09
Antiarrhythmics	0/79 (0.0%)	1/222 (0.5%)	1.0**
Statins	16/79 (20.3%)	42/222 (18.9%)	0.80
Other	26/79 (32.9%)	59/222 (26.6%)	0.28

†ASA = acetyl salicylic acid, common name: aspirin; LMWH = low molecular weight heparin; ACE = angiotension converting enzyme
*Chi-Square test unless otherwise noted
**Exact Chi-Square or Fisher's Exact test

1.8.14.2 Medications Administered Post-Symptom Onset, Prior to PCI

Medication usage following symptom onset and prior to initiation of the Index Procedure is summarized in **Table 95**. Aspirin administration was required by protocol during this time window and compliance with this requirement was high in both groups (92.4% Control group, 95.5% AO Therapy group). Clopidogrel administration could occur up to 4 hours post procedure. Approximately 37% of Control subjects and 39% of AO Therapy subjects had clopidogrel administered prior to the Index PCI procedure. Approximately 85% of subjects had clopidogrel administered either prior to PCI or in the cardiac cath lab (see **Table 97**). Compliance with study medications is discussed further in **Section 1.8.15.**

In addition to protocol-required medications, study patients were administered medications to treat the MI or to prepare for the index PCI procedure. Glycoprotein IIb/IIIa inhibitors were administered prior to PCI in 8.9% of Control group subjects and 11.3% of AO Therapy subjects. Heparinization was initiated prior to PCI in 69.6% of Control patients and 62.2% of AO Therapy patients. Thrombolytic therapy use was infrequent in both groups with 8.9% of Control group patients and 5.0% of AO Therapy patients undergoing lytic therapy prior to PCI. As anticipated in an acute MI population, nitrate use was high in both groups (83.5% of Control patients and 80.2% of AO Therapy patients), and administration of analgesics was common (51.9% Control, 46.0% AO Therapy). Beta Blockers were administered in approximately 30% of subjects in both groups. Vasopressor use was required in only two (2) Control subjects and one (1) AO Therapy subject prior to PCI (all in subjects who underwent defibrillation or cardioversion prior to enrollment). No patient in either group had treatment with inotropes prior to the index PCI procedure. Antiarrhythmic therapy was utilized to treat arrhythmias that occurred prior to PCI in approximately 9% of AO Therapy patients and 6% of Control patients. Other medications administered during this time interval included antiemetics and antianxiety medications as well as medications for treatment of

chronic conditions such as gastroesophageal reflux disorder (GERD) and diabetes. Medication administration post symptom onset and prior to PCI was similar in the two study groups; no significant differences were found in the data shown in **Table 95**.

Table 95. Medications Administered Post-Symptom Onset, Prior to PCI

Medication Category	Control Group (n=79) n/N (%)	AO Therapy Group (n=222) n/N (%)	p value*
Glycoprotein IIb/IIIa inhibitors (any)	7/79 (8.9%)	25/222 (11.3%)	0.55
ReoPro (abciximab)	1/79 (1.3%)	13/222 (5.9%)	
Aggrastat (tirofiban)	4/79 (5.1%)	6/222 (2.7%)	
Integrilin (eptifibatide)	2/79 (2.5%)	6/222 (2.7%)	
Other	0/79 (0.0%)	0/222 (0.0%)	
Antiplatelets	75/79 (94.9%)	213/222 (96.0%)	0.75**
ASA†	73/79 (92.4%)	212/222 (95.5%)	0.38**
Clopidogrel	29/79 (36.7%)	87/222 (39.2%)	0.70
Ticlopidine	0/79 (0.0%)	0/222 (0.0%)	
Clopidogrel or Ticlopidine	29/79 (36.7%)	87/222 (39.2%)	0.70
Other	0/79 (0.0%)	0/222 (0.0%)	
Anticoagulants	59/79 (74.7%)	154/222 (69.4%)	0.37
Heparin	55/79 (69.6%)	138/222 (62.2%)	0.24
Bivalirudin	0/79 (0.0%)	0/222 (0.0%)	
LMWH†	6/79 (7.6%)	16/222 (7.2%)	0.91
Other	0/79 (0.0%)	0/222 (0.0%)	
Thrombolytics (any)	7/79 (8.9%)	11/222 (5.0%)	0.27**
r-TPA†	0/79 (0.0%)	2/222 (0.9%)	
Streptokinase (SK)	0/79 (0.0%)	0/222 (0.0%)	
APSAC†	0/79 (0.0%)	0/222 (0.0%)	
TNK†	5/79 (6.3%)	7/222 (3.2%)	
Other	2/79 (2.5%)	2/222 (0.9%)	
Adenosine	0/79 (0.0%)	0/222 (0.0%)	
ACE† inhibitors	1/79 (1.3%)	3/222 (1.4%)	1.0**
Angiotension receptor blockers	0/79 (0.0%)	0/222 (0.0%)	
Beta blockers	22/79 (27.9%)	67/222 (30.2%)	0.70
Calcium channel blockers	1/79 (1.3%)	1/222 (0.5%)	0.46**
Alpha blockers	0/79 (0.0%)	0/222 (0.0%)	
Diuretics	2/79 (2.5%)	2/222 (0.9%)	0.28**
Digitalis	0/79 (0.0%)	0/222 (0.0%)	
Vasopressors	2/79 (2.5%)	1/222 (0.5%)	0.17**
Inotropes	0/79 (0.0%)	0/222 (0.0%)	
Nitrates	66/79 (83.5%)	178/222 (80.2%)	0.51
Analgesics	41/79 (51.9%)	102/222 (46.0%)	0.36
Antiarrhythmics	7/79 (8.9%)	13/222 (5.9%)	0.36
Statins	2/79 (2.5%)	2/222 (0.9%)	0.28**
Other	10/79 (12.7%)	34/222 (15.3%)	0.57

†ASA = acetyl salicylic acid; common name: aspirin; LMWH = low molecular weight heparin; r-TPA = recombinant tissue plasminogen activator; APSAC = anisoylated purified streptokinase activator complex; TNK = Tenecteplase; ACE = angiotension converting enzyme
*Chi-Square test unless otherwise noted
**Exact Chi-Square or Fisher's Exact test

1.8.14.3 Medications Administered in the [redacted]

Table 96 presents a summary of the medications administered in the cath lab for both Control and AO Therapy patients. Glycoprotein IIb/IIIa inhibitor use in this setting was prevalent (64.6% of Control subjects, 68.0% of AO Therapy subjects), with abciximab the most commonly administered medication in this category. The overall use of glycoprotein IIb/IIIa inhibitors would have been even higher except for the standard practice at one study site. At investigational site 024, patients were started on IIb/IIIa inhibitors upon arrival to the CCU. IIb/IIIa inhibitor is currently accepted standard practice in acute MI unless contraindications are present (Class IIa recommendation by AHA/ACC, Weight of evidence/opinion is in favor of usefulness/efficacy[5]).

Analgesics and nitrates were other commonly used medications in the cardiac catheterization lab. Vasopressor and inotrope usage in the cardiac catheterization lab was minimal and occurred to treat complications such as hypotension and cardiogenic shock. As previously discussed, cardiogenic shock occurred in a total of five (5) AO Therapy patients (2.3%), and one (1) Control patient (1.3%). Inotrope administration was required in these six subjects to treat this complication. Medications categorized in the "Other" category included antiemetics, antibiotics and sedatives.

Subjects in the Control group had a slightly lower incidence of heparin use in the cath lab (87.3% Control, 95.1% AO Therapy, p=0.02), although the overall difference in use of anticoagulants in the cath lab between the two groups was not statistically significant. Control patients with short PCI procedures who underwent heparin administration prior to presentation in the cath lab may not have had a need for additional heparin dosing. AO Therapy patients were anticipated to have an increased use of heparin in the catheterization lab due to procedural requirements.

Control patients had a slightly higher use of adenosine in the catheterization lab (8.9% Control, 2.7% AO Therapy, p=0.05). Since the higher rate was in the Control group, this

represents patient experience prior to randomization (patients were randomized after completion of the PCI procedure which represents the end of the cath lab period for Control patients). Further data on all events resulting in adenosine administration in these patients prior to randomization is not available. The increased use of adenosine in the catheterization lab in Control patients is not likely to impact the study's primary endpoints.

Aside from these noted differences, medication usage in the cath lab was similar between the two study groups.

Table 97 shows the medications administered either pre-PCI or in the cath lab. A more complete assessment of anticoagulant use is seen in this table, but no important group differences were found in the combined treatment of these data.

Table 96. Medications Administered in the [redacted]

Medication Category	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)	p value*
Glycoprotein IIb/IIIa inhibitors (any)	51/79 (64.6%)	151/222 (68.0%)	0.57
ReoPro (abciximab)	35/79 (44.3%)	109/222 (49.1%)	
Aggrastat (tirofiban)	7/79 (8.9%)	15/222 (6.8%)	
Integrilin (eptifibatide)	9/79 (11.4%)	27/222 (12.2%)	
Other	0/79 (0.0%)	0/222 (0.0%)	
Antiplatelets	42/79 (53.2%)	118/222 (53.2%)	0.99
ASA†	16/79 (20.3%)	41/222 (18.5%)	0.73
Clopidogrel	38/79 (48.1%)	106/222 (47.8%)	0.96
Ticlopidine	0/79 (0.0%)	2/222 (0.9%)	1.0**
Clopidogrel or Ticlopidine	38/79 (48.1%)	108/222 (48.7%)	0.93
Other	0/79 (0.0%)	0/222 (0.0%)	
Anticoagulants	71/79 (89.9%)	212/222 (95.5%)	0.09**
Heparin	69/79 (87.3%)	211/222 (95.1%)	0.02
Bivalirudin	2/79 (2.5%)	1/222 (0.5%)	0.17**
LMWH†	0/79 (0.0%)	0/222 (0.0%)	
Other	0/79 (0.0%)	0/222 (0.0%)	
Thrombolytics (any)	0/79 (0.0%)	1/222 (0.5%)	1.0**
r-TPA†	0/79 (0.0%)	1/222 (0.5%)	
Streptokinase (SK)	0/79 (0.0%)	0/222 (0.0%)	
APSAC†	0/79 (0.0%)	0/222 (0.0%)	
TNK†	0/79 (0.0%)	0/222 (0.0%)	
Other	0/79 (0.0%)	0/222 (0.0%)	
Adenosine	7/79 (8.9%)	6/222 (2.7%)	0.05**
ACE† inhibitors	0/79 (0.0%)	2/222 (0.9%)	1.0**
Angiotension receptor blockers	0/79 (0.0%)	0/222 (0.0%)	
Beta blockers	5/79 (6.3%)	17/222 (7.7%)	0.70
Calcium channel blockers	4/79 (5.1%)	13/222 (5.9%)	1.0**
Alpha blockers	0/79 (0.0%)	0/222 (0.0%)	
Diuretics	6/79 (7.6%)	10/222 (4.5%)	0.38**
Digitalis	0/79 (0.0%)	0/222 (0.0%)	
Vasopressors	1/79 (1.3%)	11/222 (5.0%)	0.19**
Inotropes	1/79 (1.3%)	5/222 (2.3%)	1.0**
Nitrates	50/79 (63.3%)	138/222 (62.2%)	0.86
Analgesics	27/79 (34.2%)	81/222 (36.5%)	0.71
Antiarrhythmics	3/79 (3.8%)	15/222 (6.8%)	0.42**
Statins	0/79 (0.0%)	0/222 (0.0%)	
Other	10/79 (12.7%)	40/222 (18.0%)	0.27

†ASA = acetyl salicylic acid, common name: aspirin; LMWH = low molecular weight heparin; r-TPA = recombinant tissue plasminogen activator; APSAC = anisoylated purified streptokinase activator complex; TNK = Tenecteplase; ACE = angiotension converting enzyme
*Chi-Square test unless otherwise noted
**Exact Chi-Square or Fisher's Exact test

Table 97. Medications Administered Pre-PCI or in th[redacted] (inclusive)

Medication Category	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)	p value*
Glycoprotein IIb/IIIa inhibitors (any)	51/79 (64.6%)	156/222 (70.3%)	0.35
ReoPro (abciximab)	35/79 (44.3%)	111/222 (50.0%)	
Aggrastat (tirofiban)	7/79 (8.9%)	17/222 (7.7%)	
Integrilin (eptifibatide)	9/79 (11.4%)	28/222 (12.6%)	
Other	0/79 (0.0%)	0/222 (0.0%)	
Antiplatelets	76/79 (96.2%)	219/222 (98.7%)	0.19**
ASA†	74/79 (93.7%)	214/222 (96.4%)	0.34**
Clopidogrel	66/79 (83.5%)	188/222 (84.7%)	0.81
Ticlopidine	0/79 (0.0%)	2/222 (0.9%)	1.0**
Clopidogrel or Ticlopidine	66/79 (83.5%)	190/222 (85.6%)	0.66
Other	0/79 (0.0%)	0/222 (0.0%)	
Anticoagulants	79/79 (100.0%)	221‡/222 (99.6%)	1.0**
Heparin	78/79 (98.7%)	220/222 (99.1%)	1.0**
Bivalirudin	2/79 (2.5%)	1/222 (0.5%)	0.17**
LMWH†	6/79 (7.6%)	16/222 (7.2%)	0.91
Other	0/79 (0.0%)	0/222 (0.0%)	

†ASA = acetyl salicylic acid, common name: aspirin; LMWH = low molecular weight heparin;
‡One subject was listed as "unknown"; ACT levels support heparin usage
*Chi-Square test unless otherwise noted
**Exact Chi-Square or Fisher's Exact test

1.8.14.4 Medications Administered Post Procedure, Prior to Discharge

Post procedure and prior to hospital discharge, AMIHOT II study patients received the protocol-required medications (clopidogrel and aspirin) as well as other medications typically administered to post-MI patients. At one investigational site, ticlopidine was administered as a therapeutic equivalent for clopidogrel (see **Section 1.8.15**) post procedure through 30-day follow-up per hospital practice.

Commonly administered medications in this time period are presented in **Table 98.** The listed medications include IIb/IIIa inhibitors, anticoagulants (including LMWH), ACE inhibitors, beta blockers, diuretics, analgesics, and statins. The only noted difference between the two study groups in medication administration during this time period was

for anticoagulant use. AO Therapy patients had a higher rate of anticoagulant usage during the post procedure, prior to discharge time period (55.7% Control, 69.4% AO Therapy, p=0.03) that appears to be related to an increase in LMWH utilization. As noted in the following section, the proportion of subjects discharged on anticoagulants was no different between the two groups. Aside from this one noted difference, the medication regimen in the "Post Procedure, Prior to Discharge" time period was consistent with standard post-MI therapy and comparable between the two study groups.

Table 98. Medications Administered Post Procedure, Prior to Discharge

Medication Category	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)	p value*
Glycoprotein IIb/IIIa inhibitors (any)	52/79 (65.8%)	144/222 (64.9%)	0.88
ReoPro (abciximab)	32/79 (40.5%)	89/222 (40.1%)	
Aggrastat (tirofiban)	12/79 (15.2%)	30/222 (13.5%)	
Integrilin (eptifibatide)	8/79 (10.1%)	25/222 (11.3%)	
Other	0/79 (0.0%)	0/222 (0.0%)	
Antiplatelets	79/79 (100.0%)	221/222 (99.6%)	1.0**
ASA†	78/79 (98.7%)	211/222 (95.1%)	0.19**
Clopidogrel	71/79 (89.9%)	195/222 (87.8%)	0.63
Ticlopidine	8/79 (10.1%)	26/222 (11.7%)	0.70
Clopidogrel or Ticlopidine	79/79 (100.0%)	221/222 (99.6%)	1.0**
Other	1/79 (1.3%)	2/222 (0.9%)	1.0**
Anticoagulants	44/79 (55.7%)	154/222 (69.4%)	0.03
Heparin	18/79 (22.8%)	59/222 (26.6%)	0.51
Bivalirudin	0/79 (0.0%)	0/222 (0.0%)	
LMWH†	37/79 (46.8%)	125/222 (56.3%)	0.15
Other	4/79 (5.1%)	19/222 (8.6%)	0.32
Thrombolytics (any)	0/79 (0.0%)	0/222 (0.0%)	
Adenosine	0/79 (0.0%)	1/222 (0.5%)	1.0**
ACE† inhibitors	67/79 (84.8%)	190/222 (85.6%)	0.87
Angiotension receptor blockers	2/79 (2.5%)	7/222 (3.2%)	1.0**
Beta blockers	78/79 (98.7%)	213/222 (96.0%)	0.46**
Calcium channel blockers	3/79 (3.8%)	10/222 (4.5%)	1.0**
Alpha blockers	4/79 (5.1%)	3/222 (1.4%)	0.08**
Diuretics	23/79 (29.1%)	78/222 (35.1%)	0.33
Digitalis	1/79 (1.3%)	8/222 (3.6%)	0.45**
Vasopressors	1/79 (1.3%)	6/222 (2.7%)	0.68**
Inotropes	1/79 (1.3%)	8/222 (3.6%)	0.45**
Nitrates	40/79 (50.6%)	112/222 (50.5%)	0.98
Analgesics	27/79 (34.2%)	73/222 (32.9%)	0.83
Antiarrhythmics	7/79 (8.9%)	19/222 (8.6%)	0.93
Statins	71/79 (89.9%)	195/222 (87.8%)	0.63
Other	55/79 (69.6 %)	150/222 (67.6%)	0.74

†ASA = acetyl salicylic acid, common name: aspirin; LMWH = low molecular weight heparin; ACE = angiotension converting enzyme
*Chi-Square test unless otherwise noted
**Exact Chi-Square or Fisher's Exact test

1.8.14.5 Discharge Medications

Table 99 provides a summary of discharge medications for AMIHOT II subjects. As seen in the table, the discharge medication profile in this trial is similar to the standard of care for post-MI pharmacological therapy in the patient population studied. The most common classes of discharge medications in both groups were antiplatelets (protocol-required), lipid lowering agents, beta blockers, ACE inhibitors and nitrates. Medications in the other category generally included medications to treat comorbid conditions such as diabetes and reflux disorder. Three (3) patients were discharged on glycoprotein IIb/IIIa inhibitors to a local hospital or extended care facility. Discharge medication patterns were comparable between the two study groups.

Table 99. Discharge Medications

Medication Category	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)	p value*
Glycoprotein IIb/IIIa inhibitors (any)	2/79 (2.5%)	1/222 (0.5%)	0.17**
ReoPro (abciximab)	0/79 (0.0%)	0/222 (0.0%)	
Aggrastat (tirofiban)	2/79 (2.5%)	1/222 (0.5%)	
Integrilin (eptifibatide)	0/79 (0.0%)	0/222 (0.0%)	
Other	0/79 (0.0%)	0/222 (0.0%)	
Antiplatelets	79/79 (100.0%)	219/222 (98.7%)	0.57**
ASA†	75/79 (94.9%)	209/222 (94.1%)	1.0**
Clopidogrel	70/79 (88.6%)	189/222 (85.1%)	0.44
Ticlopidine	9/79 (11.4%)	28/222 (12.6%)	0.78
Clopidogrel or Ticlopidine	79/79 (100.0%)	217/222 (97.8%)	0.33**
Other	1/79 (1.3%)	2/222 (0.9%)	1.0**
Anticoagulants	17/79 (21.5%)	44/222 (19.8%)	0.74
Heparin	0/79 (0.0%)	0/222 (0.0%)	
Bivalirudin	0/79 (0.0%)	0/222 (0.0%)	
LMWH†	13/79 (16.5%)	21/222 (9.5%)	
Other	5/79 (6.3%)	23/222 (10.4%)	
Thrombolytics (any)	0/79 (0.0%)	0/222 (0.0%)	
Adenosine	0/79 (0.0%)	0/222 (0.0%)	
ACE† inhibitors	67/79 (84.8%)	188/222 (84.7%)	0.98
Angiotension receptor blockers	2/79 (2.5%)	6/222 (2.7%)	1.0**
Beta blockers	76/79 (96.2%)	209/222 (94.1%)	0.57**
Calcium channel blockers	2/79 (2.5%)	8/222 (3.6%)	1.0**
Alpha blockers	3/79 (3.8%)	4/222 (1.8%)	0.38**
Diuretics	18/79 (22.8%)	58/222 (26.1%)	0.56
Digitalis	0/79 (0.0%)	5/222 (2.3%)	0.33**
Vasopressors	0/79 (0.0%)	1/222 (0.5%)	1.0**
Inotropes	0/79 (0.0%)	0/222 (0.0%)	
Nitrates	27/79 (34.2%)	65/222 (29.3%)	0.42
Analgesics	3/79 (3.8%)	10/222 (4.5%)	1.0**
Antiarrhythmics	4/79 (5.1%)	8/222 (3.6%)	0.52**
Statins	72/79 (91.1%)	198/222 (89.2%)	0.62
Other	41/79 (51.9%)	130/222 (58.6%)	0.30

†ASA = acetyl salicylic acid, common name: aspirin; LMWH = low molecular weight heparin; ACE = angiotension converting enzyme
*Chi-Square test unless otherwise noted
**Exact Chi-Square or Fisher's Exact test

1.8.14.6 Medications Administered Post-Discharge through 30-Day Follow Up

Medication usage between discharge and 30-day Follow-up is summarized in **Table 100**. Aspirin and clopidogrel were protocol-required medications during this time interval. As seen in the table, all patients received antiplatelet agents during this time period, and the majority of patients were treated with both aspirin and clopidogrel as required.

The commonly used medications aside from antiplatelets during this time period were ACE inhibitors, beta blockers and statins, followed by diuretics and nitrates. This medication profile is consistent with standard of care pharmacologic therapy for post-MI patients. No significant differences were noted in medication usage during the post discharge to 30-day follow-up time period.

Table 100. Medications Administered Post-Discharge through 30-Day Follow Up

Medication Category	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)	p value*
Glycoprotein IIb/IIIa inhibitors (any)	0/79 (0.0%)	2/217 (0.9%)	1.0**
ReoPro (abciximab)	0/79 (0.0%)	0/217 (0.0%)	
Aggrastat (tirofiban)	0/79 (0.0%)	0/217 (0.0%)	
Integrilin (eptifibatide)	0/79 (0.0%)	2/217 (0.9%)	
Other	0/79 (0.0%)	0/217 (0.0%)	
Antiplatelets	79/79 (100%)	217/217 (100.0%)	
ASA†	75/79 (94.9%)	204/217 (94.0%)	1.0**
Clopidogrel	69/79 (87.3)	187/217 (86.2%)	0.80
Ticlopidine	9/79 (11.4%)	27/217 (12.4%)	0.81
Clopidogrel or Ticlopidine	78/79 (98.7%)	214/217 (98.6%)	1.0**
Other	1/79 (1.3%)	2/217 (0.9%)	1.0**
Anticoagulants	8/79 (10.1%)	26/217 (12.0%)	0.66
Heparin	1/79 (1.3%)	1/217 (0.5%)	
Bivalirudin	1/79 (1.3%)	0/217 (0.0%)	
LMWH†	1/79 (1.3%)	1/217 (0.5%)	
Other	6/79 (7.6%)	25/217 (11.5%)	
Thrombolytics (any)	0/79 (0.0%)	0/217 (0.0%)	
Adenosine	0/79 (0.0%)	0/217 (0.0%)	
ACE† inhibitors	67/79 (84.8%)	180/217 (82.9%)	0.70
Angiotension receptor blockers	3/79 (3.8%)	15/217 (6.9%)	0.42**
Beta blockers	76/79 (96.2%)	203/217 (93.5%)	0.57**
Calcium channel blockers	2/79 (2.5%)	12/217 (5.5%)	0.37**
Alpha blockers	4/79 (5.1%)	4/217 (1.8%)	0.22**
Diuretics	20/79 (25.3%)	61/217 (28.1%)	0.63
Digitalis	0/79 (0.0%)	6/217 (2.8%)	0.35**
Vasopressors	0/79 (0.0%)	1/217 (0.5%)	1.0**
Inotropes	0/79 (0.0%)	0/217 (0.0%)	
Nitrates	24/79 (30.4%)	59/217 (27.2%)	0.59
Analgesics	6/79 (7.6%)	14/217 (6.5%)	0.73
Antiarrhythmics	0/79 (0.0%)	8/217 (3.7%)	0.11**
Statins	72/79 (91.1%)	203/217 (93.5%)	0.48
Other	46/79 (58.2%)	125/217 (57.6%)	0.92

†ASA = acetyl salicylic acid, common name: aspirin; LMWH = low molecular weight heparin; ACE = angiotension converting enzyme
*Chi-Square test unless otherwise indicated
**Fisher's Exact test

1.8.14.7 Medications Summary

The medication usage profile of AMIHOT II subjects was consistent across all time intervals with standard practice for pharmacologic treatment of AMI patients. Compliance with protocol-required medications was high and comparable in both study groups. No differences were found between the two groups with respect to medications administered within 7 days of admission for the index procedure, post symptom onset and prior to PCI, discharge medications, and medications administered between discharge and 30 days.

Heparin use was somewhat higher in the catheterization lab in AO Therapy subjects (95.1% vs. 87.3%). This difference is anticipated because AO Therapy patients were required to have measured ACT levels > 250 s throughout the procedure. AO Therapy patients also had a higher rate of anticoagulant usage during the post procedure, prior to discharge time period (55.7% Control, 69.4% AO Therapy), primarily related to an increase in LMWH utilization. The proportion of subjects discharged on anticoagulants was no different between the two groups.

The medication usage in this trial was consistent with standard of care pharmacologic therapy for AMI patients.

1.8.15 Protocol Deviations

During the course of the study, the sites together with clinical monitors tracked all protocol deviations. These deviations were recorded on Case Report Forms based on the category of deviation and the reason. A summary of the deviations for the intention to treat (ITT) cohort is provided herein based on specific classification of deviations including: a) Inclusion/Exclusion and Randomization; b) Protocol Required Laboratory Testing and c) Medication, Study Procedures and Follow Up.

1.8.15.1 Inclusion/Exclusion and Randomization Deviations

Table 101 provides a summary of the number and percentage of each type of deviation related to enrollment of patients into the study. The most common deviation noted in the interactive voice response system [redacted] screening/enrollment process was noted as errors on the designation of randomization stratification factors at the time or randomization (time to reperfusion and location of lesion). Both the Control group and the AO Therapy group experienced [redacted] deviations at a similar level of about 10%, which was not unreasonably high. The [redacted] related deviations were inadvertent and did not affect the patient's procedural process or outcomes. The deviations occurred across all study sites in the trial. In each instance, the staff at the study site was contacted and retrained on the process for randomization, and reminded of the importance of accuracy in supplying the stratification variables at the time of randomization.

The most common deviations related to inclusion and exclusion criteria were associated with obtaining systemic arterial pO_2 according to protocol (either not performed prior to randomization or the pO_2 being below 80 mm Hg which is an exclusion criteria). The rate of this deviation was slightly higher in the AO Therapy group, but since this deviation occurred prior to randomization, this observation is a random finding. Systemic arterial pO_2 was not performed prior to randomization in 2.5% of Control subjects and 9.5% of AO Therapy subjects. Systemic arterial pO_2 was below 80 mmHg in 2.5% of Control subjects and 7.2% of AO Therapy subjects. Ability to maintain pO_2 over 80 mmHg is important to the success of AO Therapy. Subjects with these deviations were excluded from the per protocol analysis of effectiveness.

Two (2) AO Therapy patients and two (2) Control patients were enrolled without the anticipated use of an intracoronary stent. In all four (4) instances, there was a previously placed stent within the target lesion. These patients were not excluded from the per protocol analysis as the deviations were not considered major. The patients did have

intracoronary stents existing and the fact that stents were not placed at the time of the index procedure was not anticipated to impact the primary effectiveness or safety endpoints.

Four (4) subjects (three Control and one AO Therapy) were enrolled with symptom onset to reperfusion time > 6 hours. These subjects were believed to have reperfusion within 6 hours of symptom onset at the time of randomization, but later review of documentation revealed slightly longer time to reperfusion (6.3 to 7.3 hours). Because the time to reperfusion is considered a critical variable affecting the primary study endpoints, these patients are all excluded from the per protocol analyses.

Importantly, there were no deviations related to the informed consent process. All patients had a signed informed consent prior to enrollment into the study and all patients signed the appropriate version of the consent.

Table 101. Protocol Deviations by Classification (IE Criteria and Randomization)

Classification	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)
Informed Consent not Signed	0/79 (0.0%)	0/222 (0.0%)
Signed wrong version informed consent	0/79 (0.0%)	0/222 (0.0%)
I/E Criteria		
Not Qualifying anterior or not < 6 hr AMI	3/79 (3.8%)	1/222 (0.5%)
No Anticipated use of an Intra-Coronary Stent	2/79 (2.5%)	2/222 (0.9%)
Pre-PCI TIMI flow grade > II	0/79 (0.0%)	0/222 (0.0%)
Post-PCI TIMI flow grade < II	0/79 (0.0%)	0/222 (0.0%)
Systemic arterial pO_2 < 80 mmHg	2/79 (2.5%)	16/222 (7.2%)
Systemic arterial pO_2 not performed prior to randomization	2/79 (2.5%)	21/222 (9.5%)
Patient has a VSD	0/79 (0.0%)	0/222 (0.0%)
Presence of unstented dissection post PCI	0/79 (0.0%)	2/222 (0.9%)
Proximal stenosis > 40%	1/79 (1.3%)	1/222 (0.5%)
Elective CABG/PCI indicated < 30 days	0/79 (0.0%)	1/222 (0.5%)
Cardiogenic shock	0/79 (0.0%)	0/222 (0.0%)
Incorrect patient stratification via IVRS		
Mistake in designation of 0-3/3-6 hrs	8/79 (10.1%)	20/222 (9.0%)
Mistake in designation of proximal/non-proximal	9/79 (11.4%)	20/222 (9.0%)

1.8.15.2 Protocol-Required Labs

Deviations associated with the laboratory requirements outlined in the protocol are summarized in **Table 102** based on the labs that were inadvertently not performed, those that were performed outside of the specified time window and those that were categorized as "other". The only deviation categorized as "other" was for activated clotting times (ACTs) being below 250 seconds prior to treatment assignment. This deviation occurred at a very low rate (less than 4 %) and was related to the fact that ACTs can normally vary as part of optimizing anticoagulation administration.

Baseline labs were to be performed prior to first contrast injection, and post-procedure labs were performed at 24 (± 2) hours. This window was very tight and frequently

missed. Cardiac enzymes were required at 8, 16 and 24 hours (all ± 2 hours). Again strict adherence to these windows was challenging.

The most common lab deviation was related to the liver panel test either not being performed or being performed outside of the specified window. In many instances, the liver panel deviation category of "not done" represents a component of the panel not performed (for example Albumin, GGTP or LDH) and not the entire liver panel being incomplete. Deviations that were out of window include instances where baseline labs were collected after the first contrast injection. These deviations were considered oversight by staff in the majority of cases and the staff was retrained. Liver panel deviations were high at one site in particular (site number 023).

As seen in **Table 102**, 27.8% of Control subjects and 30.2% of AO Therapy subjects did not have complete liver panels at baseline (primarily LDH or albumin not done), and similar percentages of patients (30.4% Control, 31.5% AO Therapy) did not have post-procedure liver panel blood work drawn. Retraining was preformed to address these deviations at frequent intervals.

The rate of liver panel-related deviations was similar between the AO Therapy and Control groups and was therefore not considered to be associated with the treatment assignment. It is also not a blood panel that was utilized as part of patient eligibility or any study endpoint. Liver panel results in patients for whom data were collected are included in **Sections 1.8.7.6 and 1.8.9.2.** Liver enzymes did not deviate from the expected normal range for acute MI patients in either study group.

It can also be seen in **Table 102** that a number of deviations occurred that were associated with incomplete cardiac enzyme data collection. Because the patients are enrolled based on the ECG and angiographic evidence of an acute MI (STEMI), the deviations of cardiac enzymes at baseline did not have impact on patient eligibility. Frequently in the case of cardiac enzymes not done, the deviation was specific to

troponin not performed in subjects where CK and CK-MB was obtained. Again, these deviations were primarily considered oversight by the staff and staff retraining was performed to encourage future compliance with the study protocol. Site [redacted] also had a higher than average incidence of lab deviations of this type, with approximately half of the randomized cohort subjects with troponin levels not obtained at some point in the post- procedure interval as required.

In those patients where the cardiac enzymes were not performed or were taken outside of the specified window, the cases were adjudicated by the CEC in a conservative manner when there was any sign of a cardiac event. In the presence of signs or symptoms of a cardiac event and the lack of appropriate cardiac enzymes to rule out a myocardial infarction, the events were adjudicated conservatively as a myocardial infarction.

All other laboratory protocol deviations occurred at a low rate and there were no dramatic discrepancies noted between the AO Therapy and Control groups.

Table 102. Protocol Deviations by Classification (Labs)

Classification	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)
Labs – Not Done		
Pre-Assignment cardiac enzymes	9/79 (11.4%)	27/222 (12.2%)
Pre-Assignment hematology	3/79 (3.8%)	12/222 (5.4%)
Pre-Assignment creatinine	1/79 (1.3%)	3/222 (1.4%)
Pre-Assignment arterial blood gas	2/79 (2.5%)	24/222 (10.8%)
Pre-Assignment liver panel	22/79 (27.8%)	67/222 (30.2%)
Pre-Assignment ACT	5/79 (6.3%)	17/222 (7.7%)
Post-Procedure cardiac enzymes	16/79 (20.3%)	53/222 (23.9%)
Post-Procedure hematology	5/79 (6.3%)	15/222 (6.8%)
Post-Procedure creatinine	6/79 (7.6%)	14/222 (6.3%)
Post-Procedure liver panel	24/79 (30.4%)	70/222 (31.5%)
Labs – Out of Window		
Pre-Assignment cardiac enzymes	11/79 (13.9%)	25/222 (11.3%)
Pre-Assignment hematology	13/79 (16.5%)	19/222 (8.6%)
Pre-Assignment creatinine	13/79 (16.5%)	19/222 (8.6%)
Pre-Assignment arterial blood gas	15/79 19.0%)	23/222 (10.4%)
Pre-Assignment pO_2	14/79 (17.7%)	20/222 (9.0%)
Pre-Assignment liver panel	19/79 (24.1%)	31/222 (14.0%)
Pre-Assignment ACT	2/79 (2.5%)	5/222 (2.3%)
Post-Procedure cardiac enzymes	21/79 (26.6%)	82/222 (36.9%)
Post-Procedure hematology	13/79 (16.5%)	51/222 (23.0%)
Post-Procedure creatinine	11/79 (13.9%)	51/222 (23.0%)
Post-Procedure liver panel	12/79 (15.2%)	51/222 (23.0%)
Labs – Other		
Pre-Assignment cardiac enzymes	0/79 (0.0%)	0/222 (0.0%)
Pre-Assignment hematology	0/79 (0.0%)	0/222 (0.0%)
Pre-Assignment creatinine	0/79 (0.0%)	0/222 (0.0%)
Pre-Assignment arterial blood gas	0/79 (0.0%)	0/222 (0.0%)
Pre-Assignment liver panel	0/79 (0.0%)	0/222 (0.0%)
Pre-Assignment ACT < 250	3/79 (3.8%)	4/222 (1.8%)
Post-Procedure cardiac enzymes	0/79 (0.0%)	0/222 (0.0%)
Post-Procedure hematology	0/79 (0.0%)	0/222 (0.0%)
Post-Procedure creatinine	0/79 (0.0%)	0/222 (0.0%)
Post-Procedure liver panel	0/79 (0.0%)	0/222 (0.0%)

1.8.15.3 Medication, Study Procedure, and Follow Up Deviations

Table 103 provides a summary of the deviations that were reported that relate to the protocol study specifics including the required study medications, the procedural requirements, and the follow up assessments. These clinical cases for these acute MI patients are often times very critical with a heightened close scrutiny of the patient and therefore some of the protocol-required lab values are not normally part of their patient surveillance.

As observed in **Table 103**, the most common category of protocol deviation was intra-AO Therapy assessments. The most common deviations in this category were ACT, ABG and/or pO_2 assessment not being performed during the treatment. These lab values were provided to supplement procedural information regarding the patient but were not utilized in assessing the study endpoints. These labs were to be obtained every 30 minutes during the AO infusion. If pre-infusion pO_2 levels were not above 80, this test was to be repeated after the patient was given supplemental oxygen. The labs were frequently missed at only one of the required time points (most commonly at 90 minutes when the procedure was completed and the additional information was no longer useful in guiding AO Therapy).

Incomplete AO Therapy administration was also a frequent deviation, occurring in 32/222 (14.4%) of study subjects. These deviations are discussed in detail in **Section 1.8.8.3.** Patients in whom there was a failure to administer at least 60 minutes of AO Therapy were not included in the pre-specified per protocol analysis. Procedural deviations are summarized in detail below.

Medication deviations were for the most part infrequent and similar in the two treatment groups. Deviations with regard to aspirin administration were the most common, and were primarily use of an alternative aspirin dose (300 mg vs. 325 mg) at the European sites. Again, the staff was retrained to try to reduce the occurrence of these deviations in

the future. Clopidogrel deviations occurred primarily as a result of contraindications to this medication. At one site, a blanket protocol deviation was obtained by the sponsor to allow use of ticlopidine in place of clopidogrel post procedure through 30-day follow-up. Per hospital practice, this site used ticlopidine as a therapeutic equivalent for clopidogrel.

The most common follow up deviations are those associated with the 30-day follow up visit. The deviations consisted of the 30-day follow up visit being performed outside of the specified window of 30-45 days or being performed via telephone rather than an in office visit. These deviations occurred at a similar rate between the AO Therapy and Control groups. It is critical to note that, despite these deviations, a 30-day evaluation was available for all patients. When only an early 30-day visit was available, the site was asked to contact the patient after day 30 to ensure no primary safety endpoint events occurred through the 30th day. In all cases, the data was determined by the Clinical Events Committee to be sufficient for evaluation of the primary study safety endpoint. This resulted in the study population having no missing safety endpoint data, which is critical in any clinical trial.

SPECT scans either not available or not analyzable were noted as protocol deviations for 6/79 (7.6%) Control subjects and 7/222 (3.2%) AO Therapy subjects. For the ITT analysis, these and other cases of unavailable data were imputed as predefined in the study protocol and Statistical Analysis Plan. SPECT scans were out of window for an additional 7/79 (8.9%) Control patients and 14/222 (6.3%) AO Therapy patients. SPECT scan deviations occurred at a similar rate in the two treatment groups.

Table 103. Protocol Deviations by Classification (Medication, Study Procedures, Follow Up)

Classification	Control Group (n=79) (n/N; %)	AO Therapy Group (n=222) (n/N; %)
Failure to Follow Study Medication Regimen – Baseline to Hospital Discharge		
Asprin therapy	10/79 (12.7%)	31/222 (14.0%)
Anticoagulation therapy	1/79 (1.3%)	2/222 (0.9%)
Clopidogrel	4/79 (5.1%)	10/222 (4.5%)
Supplemental oxygen	0/79 (0.0%)	0/222 (0.0%)
Failure to Follow Study Medication Regimen–Hospital Discharge- 30 day Follow-up		
Clopidogrel	1/79 (1.3%)	8/222 (3.6%)
Procedural deviations		
LVEF not done or done out of window	9/79 (11.4%)	28/222 (12.6%)
Patient Randomized prior to last contrast	6/79 (7.6%)	15/222 (6.8%)
Angiographic Assessment not done or not analyzable	2/79 (2.5%)	1/222 (0.5%)
Other Procedural Deviation	0/79 (0.0%)	0/222 (0.0%)
AO Therapy		
Arterial access setup	NA	2/222 (0.9%)
ACT < 250 s	NA	12/222 (5.4%)
ACT Not done	NA	48/222 (21.6%)
Labs Pre-Infusion or During AO Therapy		
ABG not done	NA	42/222 (18.9%)
pO_2 not done	NA	60/222 (27.0%)
pO_2 < 80 mmHg	NA	9/222 (4.1%)
AO infusion = 0 min	NA	6/222 (2.7%)
AO infusion < 60 min	NA	19/222 (8.6%)
AO infusion ≥ 60, < 90 min	NA	7/222 (3.2%)
Post Procedure		
ST monitoring data not obtained or analyzable	0/79 (0.0%)	3/222 (1.4%)
ST monitoring not begun until after first contrast or Post PCI	15/79 (19.0%)	47/222 (21.2%)
14-day SPECT scan not obtained or analyzable	6/79 (7.6%)	7/222 (3.2%)
14-day SPECT scan done out of window	7/79 (8.9%)	14/222 (6.3%)
30-day follow up data not obtained	0/79 (0.0%)	0/222 (0.0%)
30-day follow up done out of window	17/79 (21.5%)	38/222 (17.1%)
30-day follow up obtained by phone	9/79 (11.4%)	14/222 (6.3%)
6 month follow up data not obtained	2/79 (2.5%)	0/222 (0.0%)
6 month follow up done out of window	5/79 (6.3%)	7/222 (3.2%)
6 month follow up obtained by medical records	1/79 (1.3%)	1/222 (0.5%)
1 year follow up data not obtained	2/79 (2.5%)	1/222 (0.5%)
1 year follow up done out of window	2/79 (2.5%)	5/222 (2.3%)
1 year follow up obtained by phone, signed letter or medical records	1/79 (1.3%)	1/222 (0.5%)

1.8.15.4 Summary of Protocol Deviations

The protocol deviations observed in the AMIHOT II clinical trial are consistent with the type of deviations that are commonly noted in any clinical trial. The frequency of deviations was comparable between the study groups. In addition, the majority of frequently occurring deviations noted were not considered to impact the patient outcomes or study endpoints. In instances where the deviation was considered important to the study endpoints, a per protocol analysis was performed that excluded subjects with these deviations. The conclusions from the per protocol analysis were consistent with those obtained for the ITT analysis in this study. Therefore, it can be concluded that the protocol deviations observed in this study are reasonable and unlikely to have impacted the assessment of study outcomes.

1.8.16 Poolability of Site-Specific Data

1.8.16.1 Demographic, Clinical and Laboratory Data; and Primary Effectiveness Endpoint, Infarct Size

Both demographic variables and the primary effectiveness variable, infarct size, were evaluated for comparability across the study sites (where all sites with fewer than 10 enrolled subjects were pooled together into one group) leaving a total of 9 groups [redacted] and the pooled smaller sites).

With respect to the demographic, clinical and laboratory variables, not unexpectedly there were some statistically significant differences across the study sites, although with the specific randomization scheme employed in the trial, this would not have had an untoward effect on group comparability.

Most importantly, with respect to the primary effectiveness endpoint, infarct size, poolability was evaluated in a basic two-way analysis of variance model with the main effects of study group and site and the key site-by-group interaction. A log (X + 10)

transformation (where X = infarct size (%)) was used (as in the primary Bayesian analysis) to attempt to approximate a Gaussian distribution for the outcome. The resulting site-by-group interaction effect was not significant (p=0.26). As such, the results for this outcome were pooled across the study sites and analyzed as such.

1.8.16.2 Primary Safety Endpoint, 30-Day MACE

The results for the occurrence of the MACE endpoint by study site were evaluated to determine whether it was reasonable to pool the data across the various investigational sites in the trial. Centers that included fewer than ten patients were pooled together into one group consisting of a total of 33 patients. Of the remaining eight large centers (at least 10 patients), three sites (cente[redacted]) reported no MACE events in either study arm and could not be evaluated in the poolability analysis. The remaining six groups (centers [redacted] and the combined small sites) were evaluated using a test for the homogeneity of odds ratios using the Zelen statistic and the determination of an exact p-value based on the approach using the methodology contained in the program StatXact (using a SAS call procedure). The results showed a p-value of 0.15 for the test of a common odds ratio, indicating a lack of evidence for a site-by-treatment interaction. When the data were examined in terms of just U.S.-based versus non-U.S.-based sites, the p-value for the Zelen statistic was 0.25, again indicating a lack of evidence for this interaction. As a result, the findings for the MACE endpoint across the sites were pooled together to provide the final analyses of this primary endpoint.

It is worth noting that study site numbe[redacted] had the only MACE endpoints in the Control group. However, the extremely low rates (compared to the results for this endpoint reported in the relevant clinical literature) for all of the study sites and the study groups along with the statistical analysis noted above suggest that this finding for this

particular center is not unreasonable. As a result, the decision to pool the study sites for the primary safety analysis was considered to be appropriate.

1.9 AMIHOT II Study Conclusions

The AMIHOT II clinical trial was a prospective, multicenter, randomized evaluation of the safety and effectiveness of AO Therapy administered adjunctively in a population of anterior AMI patients revascularized by PCI with stenting within six hours of symptom onset. The primary effectiveness endpoint, superiority in infarct size reduction measured by SPECT imaging at 14 days, was achieved. The absolute median infarct size reduction was 6.5% in AO Therapy patients, translating into an approximate 25% relative reduction as compared to the Control group. Bayesian hierarchical modeling was used to evaluate the study endpoint hypothesis; infarct size results from the AMIHOT I and II studies yielded a statistically significant outcome, with a calculated posterior probability of superiority of 96.9% that infarct size is smaller in AO Therapy patients. The study's primary safety endpoint was non-inferiority in the occurrence of 30-day MACE, evaluated within a safety margin of 6.0%. In the AMIHOT II study, 30-day MACE rates were comparable between the study groups (Control 3.8%; AO Therapy 5.4%). Bayesian hierarchical modeling demonstrated a posterior probability of non-inferiority of 99.5% in consideration of AMIHOT I and II combined 30-day MACE data. Analysis of other non-endpoint safety data showed that AO Therapy may be associated with an increase in bleeding at the arterial access site; however, this increase was partially mitigated during the trial with the introduction of a smaller infusion catheter. In conclusion, AO Therapy is safe and effective as an adjunctive therapy in anterior AMI patients treated with PCI within six hours of symptom onset when used in accordance with its labeling.

1.10 Clinical Summary Report Bibliography

1. Risk Factors and Coronary Heart Disease. 2007. (Accessed June 19, 2007, at http://www.americanheart.org/print_presenter.jhtml;jsessionid=DTRYZHNDVE4UECQFCXPSDQ?identifier=4726.)
2. Myocardial Infarction. 2007. (Accessed January 8, 2008, at http://en.wikipedia.org/wiki/Myocardial_infarction.)
3. The World Health Report 2004 -- Changing History; 2004.
4. Heart Attack and Angina Statistics. 2007. (Accessed May 7, 2007, at http://www.americanheart.org/presenter.jhtml?identifier-4591.)
5. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004;110:588-636.
6. Keeley EC, Grines CL. Primary coronary intervention for acute myocardial infarction. JAMA 2004;291:736-9.
7. De Luca G, Suryapranata H, Zijlstra F, et al. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. J Am Coll Cardiol 2003;42:991-7.
8. Stone GW, Cox D, Garcia E, et al. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. Circulation 2001;104:636-41.
9. Deaths--Leading Causes. National Center for Health Statistics, 2007. (Accessed at www.cdc.gov/nchs/fastats/lcod.htm.)
10. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation 2004;109:1223-5.
11. Cox DA, Stone GW, Grines CL, et al. Outcomes of optimal or "stent-like"balloon angioplasty in acutemyocardial infarction: the CADILLAC trial. J Am Coll Cardiol 2003;42:971-7.
12. Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med 2003;349:733-42.
13. Widimsky P, Bilkova D, Penicka M, et al. Long-term outcomes of patients with acute myocardial infarction presenting to hospitals without catheterization laboratory and randomized to immediate thrombolysis or interhospital transport for primary percutaneous coronary intervention. Five years' follow-up of the PRAGUE-2 Trial. Eur Heart J 2007;28:679-84.

14. De Luca G, Ernst N, Zijlstra F, et al. Preprocedural TIMI flow and mortality in patients with acute myocardial infarction treated by primary angioplasty. J Am Coll Cardiol 2004;43:1363-7.
15. Mehta RH, Sadiq I, Goldberg RJ, et al. Effectiveness of primary percutaneous coronary intervention compared with that of thrombolytic therapy in elderly patients with acute myocardial infarction. Am Heart J 2004;147:253-9.
16. Drug-Eluting Stent Overview. 2006. (Accessed October 30, 2006, 2006, at http://www.angioplasty.org.)
17. Gibson M. Time is Myocardium and Time is Outcomes. Circulation 2001;104:2632-4.
18. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957-66.
19. Zahn R, Hamm CW, Schneider S, et al. Predictors of death or myocardial infarction during follow-up after coronary stenting with the sirolimus-eluting stent. Results from the prospective multicenter German Cypher Stent Registry. Am Heart J 2006;152:1146-52.
20. Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med 2006;355:1093-104.
21. Newell MC, Henry CR, Sigakis CJ, et al. Comparison of safety and efficacy of sirolimus-eluting stents versus bare metal stents in patients with ST-segment elevation myocardial infarction. Am J Cardiol 2006;97:1299-302.
22. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. N Engl J Med 2006;355:1105-13.
23. Stone GW. Shifting Paradigms in Pharmacologic and Interventional Therapies for ACS and AMI. In: Transcatheter Cardiovascular Therapeutics Conference. Washington, DC: Cardiovascular Research Foundation; 2006.
24. Salloum J, Tharpe C, Vaughan D, Zhao DX. Release and elimination of soluble vasoactive factors during percutaneous coronary intervention of saphenous vein grafts: analysis using the PercuSurge GuardWire distal protection device. J Invasive Cardiol 2005;17:575-9.
25. Stone GW, Webb J, Cox DA, et al. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. JAMA 2005;293:1063-72.
26. Limbruno U, De Caterina R. EMERALD, AIMI, and PROMISE: is there still a potential for embolic protection in primary PCI? Eur Heart J 2006;27:1139-45.
27. Bridenbaker ML. AIMI: AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction. In: Transcatheter Cardiovascular Therapeutics Conference. Washington, DC: Cardiovascular Research Foundation; 2004:1-4.

28. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 2008;358:557-67.
29. Dixon SR, Whitbourn RJ, Dae MW, et al. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. J Am Coll Cardiol 2002;40:1928-34.
30. Otieno HA. Acute Myocardial Infarction in 2004: Reperfusion, Support, and Pharmacology. Cardiac Interventions 2004:16-21.
31. Miller KE. Adenosine for Reducing Infarction Size in Acute MI. American Family Physician 2000:1-2.
32. Kloner RA, Forman MB, Gibbons RJ, Ross AM, Alexander RW, Stone GW. Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. Eur Heart J 2006;27:2400-5.
33. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW. A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). J Am Coll Cardiol 2005;45:1775-80.
34. Herrmann HC, Moliterno DJ, Ohman EM, et al. Facilitation of early percutaneous coronary intervention after reteplase with or without abciximab in acute myocardial infarction: results from the SPEED (GUSTO-4 Pilot) Trial. J Am Coll Cardiol 2000;36:1489-96.
35. van der Horst IC, Zijlstra F, van 't Hof AW, et al. Glucose-insulin-potassium infusion inpatients treated with primary angioplasty for acute myocardial infarction: the glucose-insulin-potassium study: a randomized trial. J Am Coll Cardiol 2003;42:784-91.
36. Apstein CS. The benefits of glucose-insulin-potassium for acute myocardial infarction (and some concerns). J Am Coll Cardiol 2003;42:792-5.
37. Antoniucci D, Rodriguez A, Hempel A, et al. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. J Am Coll Cardiol 2003;42:1879-85.
38. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344:1895-903.
39. Bonnefoy E, Lapostolle F, Leizorovicz A, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. Lancet 2002;360:825-9.
40. Brener SJ, Barr LA, Burchenal JE, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators. Circulation 1998;98:734-41.
41. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1999;341:1949-56.

42. Kastrati A, Mehilli J, Nekolla S, et al. A randomized trial comparing myocardial salvage achieved by coronary stenting versus balloon angioplasty in patients with acute myocardial infarction considered ineligible for reperfusion therapy. J Am Coll Cardiol 2004;43:734-41.
43. Zijlstra F, Hoorntje JC, de Boer MJ, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999;341:1413-9.
44. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. Circulation 2002;105:1909-13.
45. Gibson CM, de Lemos JA, Antman EM. Time is muscle in primary PCI: the strength of the evidence grows. Eur Heart J 2004;25:1001-2.
46. Gibson CMM, Sabina A.; McCabe, Carolyn H.; Giugliano, Robert P.; Cannon, Christopher P.; Antman, Elliott; Braunwald, Eugene. Time is Muscle: Delays in Time from Symptom Onset to Fibrinolytic Administration in ST Elevation MI are Associated with Proper Myocardial Perfusion. Boston, MA: TIMI Study Group; 2003.
47. Stone PH, Raabe DS, Jaffe AS, et al. Prognostic significance of location and type of myocardial infarction: independent adverse outcome associated with anterior location. J Am Coll Cardiol 1988;11:453-63.
48. Cleland JG, McGowan J. Heart failure due to ischaemic heart disease: epidemiology, pathophysiology and progression. J Cardiovasc Pharmacol 1999;33 Suppl 3:S17-29.
49. Cowie MRL, Larry; Tabberer, Maggie. Heart Failure After Myocardial Infarction: A Neglected Problem? British Journal of Cardiology 2005;12:205-8.
50. Cowie MR, Wood DA, Coats AJ, et al. Survival of patients with a new diagnosis of heart failure: a population based study. Heart 2000;83:505-10.
51. Lewis EF, Moye LA, Rouleau JL, et al. Predictors of late development of heart failure in stable survivors of myocardial infarction: the CARE study. J Am Coll Cardiol 2003;42:1446-53.
52. Baks T, van Geuns RJ, Biagini E, et al. Effects of primary angioplasty for acute myocardial infarction on early and late infarct size and left ventricular wall characteristics. J Am Coll Cardiol 2006;47:40-4.
53. Lund GK, Stork A, Saeed M, et al. Acute myocardial infarction: evaluation with first-pass enhancement and delayed enhancement MR imaging compared with 201Tl SPECT imaging. Radiology 2004;232:49-57.
54. Gibbons RJ, Christian TF, Hopfenspirger M, Hodge DO, Bailey KR. Myocardium at risk and infarct size after thrombolytic therapy for acute myocardial infarction: implications for the design of randomized trials of acute intervention. J Am Coll Cardiol 1994;24:616-23.

55. Gibbons RJ, Valeti US, Araoz PA, Jaffe AS. The quantification of infarct size. J Am Coll Cardiol 2004;44:1533-42.
56. Gibbons RJ, Miller TD, Christian TF. Infarct size measured by single photon emission computed tomographic imaging with (99m)Tc-sestamibi: A measure of the efficacy of therapy in acute myocardial infarction. Circulation 2000;101:101-8.
57. Christian TF, Behrenbeck T, Pellikka PA, Huber KC, Chesebro JH, Gibbons RJ. Mismatch of left ventricular function and infarct size demonstrated by technetium-99m isonitrile imaging after reperfusion therapy for acute myocardial infarction: identification of myocardial stunning and hyperkinesia. J Am Coll Cardiol 1990;16:1632-8.
58. Califf RM, Harrelson-Woodlief L, Topol EJ. Left ventricular ejection fraction may not be useful as an end point of thrombolytic therapy comparative trials. Circulation 1990;82:1847-53.
59. In: Cardiovascular and renal drugs advisory committee in collaboration with the blood products advisory committee, subcommittee; 1992.
60. Van der Werf F A. Intravenous tissue plasminogen activator and size of infarct, left ventricular function, survival in acute myocardial infarction. British Medical Journal 1988;297:1374-9.
61. Group ISAMS. A prospective trial of intravenous streptokinase in acute myocardial infarction (I.S.A.M.) Mortality, morbidity, and infarct size at 21 days. The I.S.A.M. Study Group. The New England Journal of Medicine 1986;314:1465-71.
62. Kennedy JW, Martin GV, Davis KB, et al. The Western Washington Intravenous Streptokinase in Acute Myocardial Infarction Randomized Trial. Circulation 1988;77:345-52.
63. Chareonthaitawee P, Gibbons RJ, Roberts RS, Christian TF, Burns R, Yusuf S. The impact of time to thrombolytic treatment on outcome in patients with acute myocardial infarction. For the CORE investigators (Collaborative Organisation for RheothRx Evaluation). Heart 2000;84:142-8.
64. Newby LK, Rutsch WR, Califf RM, et al. Time from symptom onset to treatment and outcomes after thrombolytic therapy. GUSTO-1 Investigators. J Am Coll Cardiol 1996;27:1646-55.
65. Miller TD, Christian TF, Hopfenspirger MR, Hodge DO, Gersh BJ, Gibbons RJ. Infarct size after acute myocardial infarction measured by quantitative tomographic 99mTc sestamibi imaging predicts subsequent mortality. Circulation 1995;92:334-41.
66. Miller TD, Hodge DO, Sutton JM, et al. Usefulness of technetium-99m sestamibi infarct size in predicting posthospital mortality following acute myocardial infarction. Am J Cardiol 1998;81:1491-3.
67. Burns RJ, Gibbons RJ, Yi Q, et al. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. J Am Coll Cardiol 2002;39:30-6.

68. Schomig AK, Adnan; Dirschinger, Josef; Mehilli, Julinda; Schricke, Ullrich; Pache, Jurgen; Martinoff, Stefan; Neumann, Franz-Josef; Schwaiger, Markus. Coronary Stenting Plus Platelet Glycoprotein IIb/IIIa Blockade Compared With Tissue Plasminogen Activator in Acute Moycardial Infarction. The New England Journal of Medicine 2000;343:385-91.
69. Kastrati A, Mehilli J, Dirschinger J, et al. Myocardial salvage after coronary stenting plus abciximab versus fibrinolysis plus abciximab in patients with acute myocardial infarction: a randomised trial. Lancet 2002;359:920-5.
70. White HD, Rivers JT, Maslowski AH, et al. Effect of intravenous streptokinase as compared with that of tissue plasminogen activator on left ventricular function after first myocardial infarction. N Engl J Med 1989;320:817-21.
71. Magnani B. Plasminogen Activator Italian Multicenter Study (PAIMS): comparison of intravenous recombinant single-chain human tissue-type plasminogen activator (rt-PA) with intravenous streptokinase in acute myocardial infarction. J Am Coll Cardiol 1989;13:19-26.
72. Neuhaus KL, Tebbe U, Gottwik M, et al. Intravenous recombinant tissue plasminogen activator (rt-PA) and urokinase in acute myocardial infarction: results of the German Activator Urokinase Study (GAUS). J Am Coll Cardiol 1988;12:581-7.
73. Anderson JL, Becker LC, Sorensen SG, et al. Anistreplase versus alteplase in acute myocardial infarction: comparative effects on left ventricular function, morbidity and 1-day coronary artery patency. The TEAM-3 Investigators. J Am Coll Cardiol 1992;20:753-66.
74. Chaitman BR, Lim MJ. No reflow and the quest to achieve optimal perfusion during the acute phase of myocardial infarction. J Am Coll Cardiol 2004;44:313-5.
75. Faxon DP. Coronary interventions and their impact on post myocardial infarction survival. Clin Cardiol 2005;28:I38-44.
76. Luo AK, Wu KC. Imaging microvascular obstruction and its clinical significance following acute myocardial infarction. Heart Fail Rev 2006;11:305-12.
77. Spears JR, Prcevski P, Xu R, et al. Aqueous oxygen attenuation of reperfusion microvascular ischemia in a canine model of myocardial infarction. ASAIO J 2003;49:716-20.
78. Kaul S, Ito H. Microvasculature in acute myocardial ischemia: part I: evolving concepts in pathophysiology, diagnosis, and treatment. Circulation 2004;109:146-9.
79. Kaul S, Ito H. Microvasculature in acute myocardial ischemia: part II: evolving concepts in pathophysiology, diagnosis, and treatment. Circulation 2004;109:310-5.
80. Bolognese L, Carrabba N, Parodi G, et al. Impact of microvascular dysfunction on left ventricular remodeling and long-term clinical outcome after primary coronary angioplasty for acute myocardial infarction. Circulation 2004;109:1121-6.
81. Hillis GS, Mulvagh SL, Pellikka PA, et al. Comparison of intravenous myocardial contrast echocardiography and low-dose dobutamine echocardiography for predicting left

ventricular functional recovery following acute myocardial infarction. Am J Cardiol 2003;92:504-8.
82. B Kantor CJM, A.R. Camrud, L.J. Camrud, J.L. Allen, D.R. Holmes, R.S. Schwartz. Coronary Reperfusion with Aqueous Oxygen Improves Left Ventricular Ejection Fraction and May Reduce Mortality in an Ischemic Porcine Model. Am J Cardiol 1998;84:86S (TCT-231).
83. Fishbein MC, Meerbaum S, Rit J, et al. Early phase acute myocardial infarct size quantification: validation of the triphenyl tetrazolium chloride tissue enzyme staining technique. Am Heart J 1981;101:593-600.
84. Spears JR, Henney C, Prcevski P, et al. Aqueous oxygen hyperbaric reperfusion in a porcine model of myocardial infarction. J Invasive Cardiol 2002;14:160-6.
85. Bartorelli AL. Hyperoxemic perfusion for treatment of reperfusion microvascular ischemia in patients with myocardial infarction. Am J Cardiovasc Drugs 2003;3:253-63.
86. Spears J. Reperfusion Microvascular Ischemia: Attenuation with Aqueous Oxygen. Circulation 2000;102:646(3132).
87. Dixon SR, Bartorelli AL, Marcovitz PA, et al. Initial experience with hyperoxemic reperfusion after primary angioplasty for acute myocardial infarction: results of a pilot study utilizing intracoronary aqueous oxygen therapy. J Am Coll Cardiol 2002;39:387-92.
88. Dixon SR. Early recovery of infarct zone function with hyperoxemic reperfusion after primary percutaneous transluminal coronary angioplasty. American Journal of Cardiology 2000;86 (Suppl. 8A) 8i.
89. Dixon SR. Global and regional left ventricular function after intracoronary hyperoxemic perfusion with the Aqueous Oxygen system in acute myocardial infarction: TherOx study. Circulation 2000;102 (Suppl.):II-386.
90. Trabattoni D. Cardiac Enzyme Kinetic, St-segment Evolutionary Changes and Left Ventricular Function Recovery in Patients with Anterior AMI Treated with Primary PCI Followed by LAD Hyperoxemic Blood Infusion. In: 34th Congresso Nazionale di Cardiolgia. Florence, Italty; 2003.
91. Veldkamp RF, Green CL, Wilkins ML, et al. Comparison of continuous ST-segment recovery analysis with methods using static electrocardiograms for noninvasive patency assessment during acute myocardial infarction. Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 7 Study Group. Am J Cardiol 1994;73:1069-74.
92. Krucoff MW, Croll MA, Pope JE, et al. Continuously updated 12-lead ST-segment recovery analysis for myocardial infarct artery patency assessment and its correlation with multiple simultaneous early angiographic observations. Am J Cardiol 1993;71:145-51.
93. Veldkamp RF, Pope JE, Sawchak ST, Wagner GS, Califf RM, Krucoff MW. ST-segment recovery as an endpoint in acute myocardial infarction trials. Past, present, and future. J Electrocardiol 1993;26 Suppl:256-61.

94. Klootwijk P, Langer A, Meij S, et al. Non-invasive prediction of reperfusion and coronary artery patency by continuous ST segment monitoring in the GUSTO-I trial. Eur Heart J 1996;17:689-98.
95. Krucoff MW, Croll MA, Pope JE, et al. Continuous 12-lead ST-segment recovery analysis in the TAMI 7 study. Performance of a noninvasive method for real-time detection of failed myocardial reperfusion. Circulation 1993;88:437-46.
96. Krucoff MW, Green CE, Satler LF, et al. Noninvasive detection of coronary artery patency using continuous ST-segment monitoring. Am J Cardiol 1986;57:916-22.
97. Andrews J, Straznicky IT, French JK, et al. ST-Segment recovery adds to the assessment of TIMI 2 and 3 flow in predicting infarct wall motion after thrombolytic therapy. Circulation 2000;101:2138-43.
98. Langer A, Krucoff MW, Klootwijk P, et al. Prognostic significance of ST segment shift early after resolution of ST elevation in patients with myocardial infarction treated with thrombolytic therapy: the GUSTO-I ST Segment Monitoring Substudy. J Am Coll Cardiol 1998;31:783-9.
99. Moons KG, Klootwijk P, Meij SH, et al. Continuous ST-segment monitoring associated with infarct size and left ventricular function in the GUSTO-I trial. Am Heart J 1999;138:525-32.
100. Shah A, Wagner GS, Granger CB, et al. Prognostic implications of TIMI flow grade in the infarct related artery compared with continuous 12-lead ST-segment resolution analysis. Reexamining the "gold standard" for myocardial reperfusion assessment. J Am Coll Cardiol 2000;35:666-72.
101. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358-67.
102. Mark H. Beers RB, ed. The Merck Manual of Diagnosis and Therapy. 17th ed: Merck and Company; 1999.
103. J. R. Cameron JGS, Roderick M. Grant. In: Physics of the Body. 2nd ed. Madison, WI: Medical Physics Publishing Corporation; 1999:394.
104. R.J.A. Little DBR. Statistical Analysis with Missing Data. 2nd ed. New York: John Wiley & Sons, Inc.; 2002.
105. Duan N. Smearing estimate: a nonparametric retransformation method. J Am Stat Ass 1983;78:605-10.
106. Spiegelhalter DJ, Best DJ, Carlin BP, van der Linde A. Bayesian measures of model complexity and fit (with discussion). J Roy Stat Soc, Series B 2002;64:583-639.
107. Alidoosti M, Salarifar M, Zeinali AM, Kassaian SE, Dehkordi MR. Comparison of outcomes of percutaneous coronary intervention on proximal versus non-proximal left anterior descending coronary artery, proximal left circumflex, and proximal right coronary artery: a cross-sectional study. BMC Cardiovasc Disord 2007;7:7.

108. Elsman P, van t Hof AW, Hoorntje JC, et al. Effect of coronary occlusion site on angiographic and clinical outcome in acute myocardial infarction patients treated with early coronary intervention. Am J Cardiol 2006;97:1137-41.
109. Leborgne L, Cheneau E, Wolfram R, et al. The proximal location of stenosis in the left anterior descending coronary artery is not a predictive factor of worse outcome in the era of the stent. Cardiovasc Radiat Med;3:127-32.

1.11 Tables, Figures and Listings Index for Clinical Summary Report

List of Tables **Page Number**

Table 1. 30-Day MACE Data for Recent Acute MI Trials 24
Table 2. Ejection Fraction Measurements in Randomized Trials Comparing Different Thrombolytic Regimens 34
Table 3. AMIHOT I Infarct Size Results 70
Table 4. AMIHOT I Regional Wall Motion Score Index (RWMSI) Improvement Results 71
Table 5. AMIHOT I ST-Deviation Time Trend Curve Area Data: 0-3 hrs Post-PCI 73
Table 6. AMIHOT I ST-Deviation Time Trend Curve Area Data: 0-6 hrs Post-PCI 73
Table 7. AMIHOT I 30-Day MACE Safety Data 76
Table 8. AMIHOT I Baseline Patient Characteristics 77
Table 9. AMIHOT I Baseline Patient Clinical Characteristics 78
Table 10. Coaxial/Contralateral Arterial Access 104
Table 11. AMIHOT II Study Assessments 109
Table 12. Patient Screening 130
Table 13. Patient Assignment and Tracking 132
Table 14. Reasons for Withdrawal or Loss to Follow-up 132
Table 15. Patient Enrollment by Site 134
Table 16. Angiographic Assessment Imaging Accountability 135
Table 17. Secondary Endpoint. ECG Data Accountability 136
Table 18. SPECT Imaging Accountability 137
Table 19. Per Protocol Analysis Patient Accountability 139
Table 20. Demographics 141
Table 21. Medical History 144
Table 22. Cardiac Complications and MI Time Intervals 147
Table 23. Index PCI: Infarct Characteristics 151
Table 24. Index PCI: Procedural Characteristics 152
Table 25. Index PCI Procedure: Access Equipment and Additional Procedures/Devices 154
Table 26. Pre-PCI Procedure: Angiographic Core Lab Quantitative Assessments 157
Table 27. Post-PCI Procedure: Angiographic Core Lab Quantitative Assessments 158
Table 28. Pre-PCI Procedure: Angiographic Core Lab Qualitative Assessments 159

Table 29. Post PCI Procedure: Angiographic Core Lab Qualitative Assessments 160
Table 30. Baseline Laboratory Data: Hematology and Clinical Chemistry, Hemodynamic Information 162
Table 31. Baseline Laboratory Data: Liver Panel 164
Table 32. Normal Ranges: Laboratory Data 165
Table 33. AO Therapy Procedure: Arterial Access Data 168
Table 34. Sheath Size Usage in AO Therapy Procedures by Infusion Catheter Type 169
Table 35. AO Therapy Procedure: Device Usage Information 170
Table 36. Hemodynamic and Laboratory Data during AO Therapy 176
Table 37. 24-Hr Laboratory Data: Hematology and Clinical Chemistry 180
Table 38. Baseline – 24-Hr Hematocrit Data 181
Table 39. 24-Hr Laboratory Data: Liver Panel 182
Table 40. Cardiac Enzymes: Baseline (Time = 0) to 24 hrs 184
Table 41. Hospital Discharge Information 186
Table 42. Infarct Size at 14 Days (% of Left Ventricle), Evaluation of Infarct Size for AMIHOT II ITT Analysis 191
Table 43. Infarct Size at 14 Days (% of Left Ventricle), Evaluation of Infarct Size for AMIHOT II PP Analysis 194
Table 44. Infarct Size at 14 Days (% of Left Ventricle), Frequentist Evaluation of Infarct Size for ITT Analysis, Sensitivity of Imputation Methods 197
Table 45. Infarct Size at 14 Days (% of Left Ventricle), Pooled Evaluation of Infarct Size for AMIHOT I Anterior < 6 hr and AMIHOT II ITT Analysis 199
Table 46. Infarct Size at 14 Days (% of Left Ventricle), Pooled Evaluation of Infarct Size for AMIHOT I Anterior < 6 hr and AMIHOT II PP Analysis 200
Table 47. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Sensitivity of Imputation Methods: Model M1 203
Table 48. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Sensitivity of Imputation Methods: Model M2 205
Table 49. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Sensitivity of Imputation Methods: Model M3 206
Table 49a. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint Using Ordinal Logistic Regression Model (Model OL) 210
Table 49b. Results of Ordinal Logistic Regression Model (Model OL) for the Quintile Cutpoints 211
Table 49c. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint Using New Hierarchical Model (Model H1) 213

Table 49d. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, New Hierarchical Model (Model H2) 214
Table 49e. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Incorporation of Site Effects into New Hierarchical Model (Model H3) 215
Table 49f. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Incorporation of Time to Reperfusion and Treatment by Time Interaction Effects into Models M1 and H1 216
Table 49g. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint, Comparison of Informative (Borrowing) and Non-Informative (Non-Borrowing) Priors, Models M1, H1, H2, and H3 218
Table 49h. Infarct Size at 14 Days (% of Left Ventricle), Bayesian Evaluation of Primary Endpoint Using Ordinal Logistic Regression Model (Model OL), Comparison of Informative (Borrowing) and Non-Informative (Non-Borrowing) Priors 219
Table 49i. Sensitivity of Model OL to Change in Prior Distributions 220
Table 49j. Sensitivity of Model H1 to Change in Prior Distributions 221
Table 50. Patients with Small Infarct Size (0-5%) at 14 Days. ITT Analysis 226
Table 51. Patients with Small Infarct Size (0-5%) at 14 Days. PP Analysis 226
Table 52. Patients with Small Infarct Size (0-5%) at 14 Days. Bayesian Evaluation of Relative Probability of Small Infarct Size in AO Therapy versus Control 227
Table 53. Additional [redacted] Data 228
Table 54. % ST Resolution (0-6 hrs) 233
Table 55. Secondary Endpoint: ST Time Trend Curve Area (Total Ischemic Area): 0-3, 0-4, 0-6, 0-24 hrs (ITT Analysis) 235
Table 56. Secondary Endpoint: ST Time Trend Curve Area (Total Ischemic Area): 0-3, 0-4, 0-6, 0-24 hrs (PP Analysis) 235
Table 57. Additional Quantitative ECG Data 237
Table 58. 30-Day Follow Up Information 240
Table 59. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT II ITT Analysis 247
Table 60. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I ITT Analysis 249
Table 61. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I and II ITT Bayesian Analysis 252
Table 61a. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I & II ITT Bayesian Analysis, New Hierarchical Model (Model H1) 254
Table 61b. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I & II ITT Bayesian Analysis, New Hierarchical Model (Model H2) 225
Table 61c. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I

& II ITT Bayesian Analysis, New Hierarchical Model (Model H3) 256
Table 61d. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I & II ITT Bayesian Analysis, Incorporation of Time to Reperfusion and Treatment by Time Interaction Effects into Model H1 257
Table 61e. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I & II ITT Bayesian Analysis, Comparison of Informative (Borrowing) and Non-Informative (Non-Borrowing) Priors, Models M1, H1, H2, H3 259
Table 62. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT II PP Analysis 261
Table 63. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I PP Analysis 263
Table 64. Primary Safety Endpoint Evaluation (30-Day MACE): AMIHOT I & II PP Bayesian Analysis 263
Table 65. Brief Narratives for Patients Undergoing Reinfarction and/or Target Vessel Revascularization within 30 Days 268
Table 66. Patient Death Occurring ≤ 30 Days 280
Table 67. Overall Summary of Adjudicated Adverse Events within First 30 Days 288
Table 68. Summary of All Adverse Events within 30 Days by SOC and PT 292
Table 69. Summary of All Serious Adverse Events within 30 Days by SOC and PT 307
Table 70. Summary of All Adverse Events within 30 Days by SOC, PT and Relationship by Patient 315
Table 71. Patients Presenting a Serious AO Device or Procedure Related Adverse Event Occurring within 30 Days of the Index Procedure 329
Table 72. Bleeding Events by Bleeding Category within First 30 Days 336
Table 73. Severe/Life Threatening Access Site Bleeding 341
Table 74. Severe/Life Threatening Non-Access Site Bleeding 343
Table 75. Access Site Events within First 30 Days 345
Table 76. Access Site Events within First 30 Days by Infusion Catheter Type ...347
Table 76a. Access Site Complications within 30 Days by Draw Sheath Configuration 348
Table 77. Primary Safety Events (within 30 Days) by Target Lesion Location ...352
Table 78. Overall Summary of Adjudicated Adverse Events within First 30 Days by Lesion Location 356
Table 79. Primary Safety Events (within 30 Days) by Time to Reperfusion 360
Table 80. Overall Summary of Adjudicated Adverse Events within First 30 Days by Time to Reperfusion 363
Table 81. Primary Safety Events (within 30 Days) by Infusion Catheter Type ...367

Table 82. Overall Summary of Adjudicated Adverse Events within First 30 Days by Infusion Catheter Type 369
Table 83. Six-Month Patient Follow Up Survey 372
Table 84. Twelve-Month Patient Follow Up Survey 375
Table 85. Late MACE (>30 Days to 1 Year), Randomized Subjects 379
Table 86. Patients Undergoing Target Vessel Revascularization and Reinfarction between 30 Days and 12-Month Follow Up 385
Table 87. Subject with Late Stroke between 30 Days and 12-Month Follow Up 402
Table 88. Late Patient Deaths (> 30 Days) 403
Table 89. Cumulative MACE to 1 Year 408
Table 90. Overall Summary of Adjudicated Late Adverse Events (>30 Days to 1 Year) 410
Table 91. Summary of Late Adverse Events (>30 Days to 1 Year) by SOC and PT 413
Table 92. Summary of Late Serious Adverse Events (>30 Days to 1 Year) by SOC, PT, and Relationship by Patient 425
Table 93. Bleeding Events by Bleeding Category after 30 Days 439
Table 94. Medications Administered Up to 7 Days Prior to Admission 445
Table 95. Medications Administered Post-Symptom Onset, Prior to PCI 449
Table 96. Medications Administered in the Cardiac Catheterization Laboratory 451
Table 97. Medications Administered Pre-PCI or in [redacted] (inclusive) 452
Table 98. Medications Administered Post Procedure, Prior to Discharge 454
Table 99. Discharge Medications 456
Table 100. Medications Administered Post-Discharge through 30-Day Follow Up 458
Table 101. Protocol Deviations by Classification (IE Criteria and Randomization) 462
Table 102. Protocol Deviations by Classification (Labs) 465
Table 103. Protocol Deviations by Classification (Medication, Study Procedures, Follow Up) 468

List of Figures

Figure 1. AO Cartridge 81
Figure 2. Coaxial Blood Draw/Return Clinical Configuration for AO Therapy 83
Figure 3. Patient Connections 84
Figure 4. AO System 85
Figure 5. AMIHOT II Patient Accountability Flow Chart 128
Figure 6. AMIHOT I Anterior < 6 Hr Subjects Infarct Size Distributions 223

Figure 7. AMIHOT II Infarct Size Distributions 223
Figure 8. 30-Day MACE Kaplan-Meier Estimate, AMIHOT II ITT Analysis....248
Figure 9. 30-Day MACE Kaplan-Meier Estimate, AMIHOT II PP Analysis 262

Listings

Listing 1. Acronyms and Abbreviations 1