Cangrelor

Presentation to the
Cardiovascular and Renal Advisory Committee

The Medicines Company
April 15th 2015

Cangrelor Introduction

Loretta M. Itri, MD, FACP
Executive Vice President
Global Health Science and Regulatory Affairs
The Medicines Company

Regulatory History of Cangrelor

Date	Regulatory Milestone
November 2009	FDA Meeting to discuss results of C-PCI and C-Platform
September 2010	FDA comments on C-PHOENIX protocol
February 2013	Pre-NDA meeting for C-PHOENIX
April 2013	Original NDA submitted
February 2014	Cardiovascular & Renal Drugs Advisory Committee Meeting
April 2014	Complete Response Letter (CRL)
August 2014	FDA Meeting to discuss CRL
September 2014	FDA Meeting to discuss NDA Resubmission
December 2014	NDA resubmission
March 2015	FDA meeting to discuss NDA review & Advisory Committee

What Has Been Done Since February 2014 Advisory Committee Meeting?

- Withdrew bridging indication
- Restricted the PCI indication to reflect the C-PHOENIX population and to be consistent with American practice
- Performed efficacy analyses to reflect clinically meaningful endpoints
  - Excluded intraprocedural stent thrombosis (IPST) and used conservative MI definitions
  - Utilized investigator assessment at the time of randomization instead of derived patient type
- Re-evaluated the C-PHOENIX bleeding data
- Provided additional analyses on transitioning to oral therapy
  - Evaluated timing of endpoint events in C-PHOENIX following Cangrelor infusion
- Benefit:Risk assessment

Proposed Restricted Indication

FDA Briefing Document

Cangrelor is indicated as an adjunct to PCI for the reduction in risk of periprocedural ischemic complications including myocardial infarction and stent thrombosis in patients in whom treatment with an oral $P2Y_{12}$ platelet inhibitor prior to PCI is not feasible and when glycoprotein IIb/IIIa receptor antagonists are not anticipated to be used.

Today's Agenda

Introduction	**Loretta M. Itri, MD, FACP** Executive Vice President Global Health Science and Regulatory Affairs The Medicines Company
American Practice	**J. Jeffrey Marshall, MD, FACC, FSCAI** Director Cardiac Catheterization Lab Northeast Georgia Medical Center
Clinical Development and C-PHOENIX Efficacy	**Efthymios N. Deliargyris, MD, FACC, FSCAI** Vice President and Medical Director Acute Cardiovascular Care The Medicines Company
Safety Profile	**Loretta M. Itri, MD, FACP** Executive Vice President Global Health Science and Regulatory Affairs The Medicines Company
Benefit:Risk	**Robert Harrington, MD, FACC, FSCAI** Arthur L Bloomfield Professor of Medicine Chairman of the Department of Medicine Stanford University

Available Experts

Robert J. Levine, MD, FACP, FACC	**Yale University** Bioethics
Ken Mahaffey, MD, PhD, FACC	**Stanford University** CHAMPION Program Clinical Event Committee Chair
David Schneider, MD, PhD, FACC	**University of Vermont** Clinical Pharmacology
Janet Wittes, PhD	**Statistics Collaborative, Inc.** Biostatistics
Cynthia Dinella, PharmD	**Advyzom** Global Regulatory
Andrew Friedman, PharmD	**The Medicines Company** Regulatory
Jayne Prats, PhD	**The Medicines Company** Clinical Pharmacology
Peter Wijngaard, PhD	**The Medicines Company** Clinical Development
Brad Zerler, PhD	**The Medicines Company** Nonclinical

The Heart Center of Northeast Georgia Medical Center

American Practice

J. Jeffrey Marshall, MD, FACC, FSCAI

Director, Cardiac Catheterization Lab
Northeast Georgia Medical Center

Past President, Society for Cardiovascular Angiography and Interventions (SCAI) 2012 - 2013

The Heart Center of Northeast Georgia Medical Center

Objectives

- Ad hoc PCI is standard of care in the United States
- There is a window of vulnerability for thrombotic complications (predominantly MI) in PCI
- SCAI has defined the most clinically relevant MI outcomes
- Anti-platelet agents are required, but there is marked variability in American practice
- Therapy should balance anti-thrombotic and bleeding complications

The Heart Center of Northeast Georgia Medical Center

Outline

- PCI in America - ad hoc PCI
- Window of vulnerability
- Complications of PCI
- Antiplatelet agents
- Unmet need in PCI
- Conclusions

The Heart Center of Northeast Georgia Medical Center

Current American Practice

- 950,000 PCIs are performed in the United States each year[1]
- Patient population[2]
  - Stable angina: 74%
  - Acute coronary syndromes (ACS): 26%
    - NSTE-ACS: 2/3
    - STEMI: 1/3

1. Go AS, et al. Circulation. 2014;129;e28-e292; 2. NCDR Cath-PCI Registry Rolling 12 month 2014Q2

The Heart Center of Northeast Georgia Medical Center

Ad Hoc PCI – The Standard of Care in the US

- Ad hoc PCI: Performance of diagnostic angiogram and PCI in the same setting
- SCAI consensus statement regarding ad hoc PCI
  - Most PCI procedures (>90%) are done as ad hoc
  - Safety and efficacy similar between ad hoc and delayed PCI
  - Potential advantages of ad hoc over delayed PCI:
    - Efficiency
    - Patient convenience

Blankenship JC, et.al. *Catheter Cardiovasc Interv.* 2013;81:748-758

Complications of PCI

Thrombotic

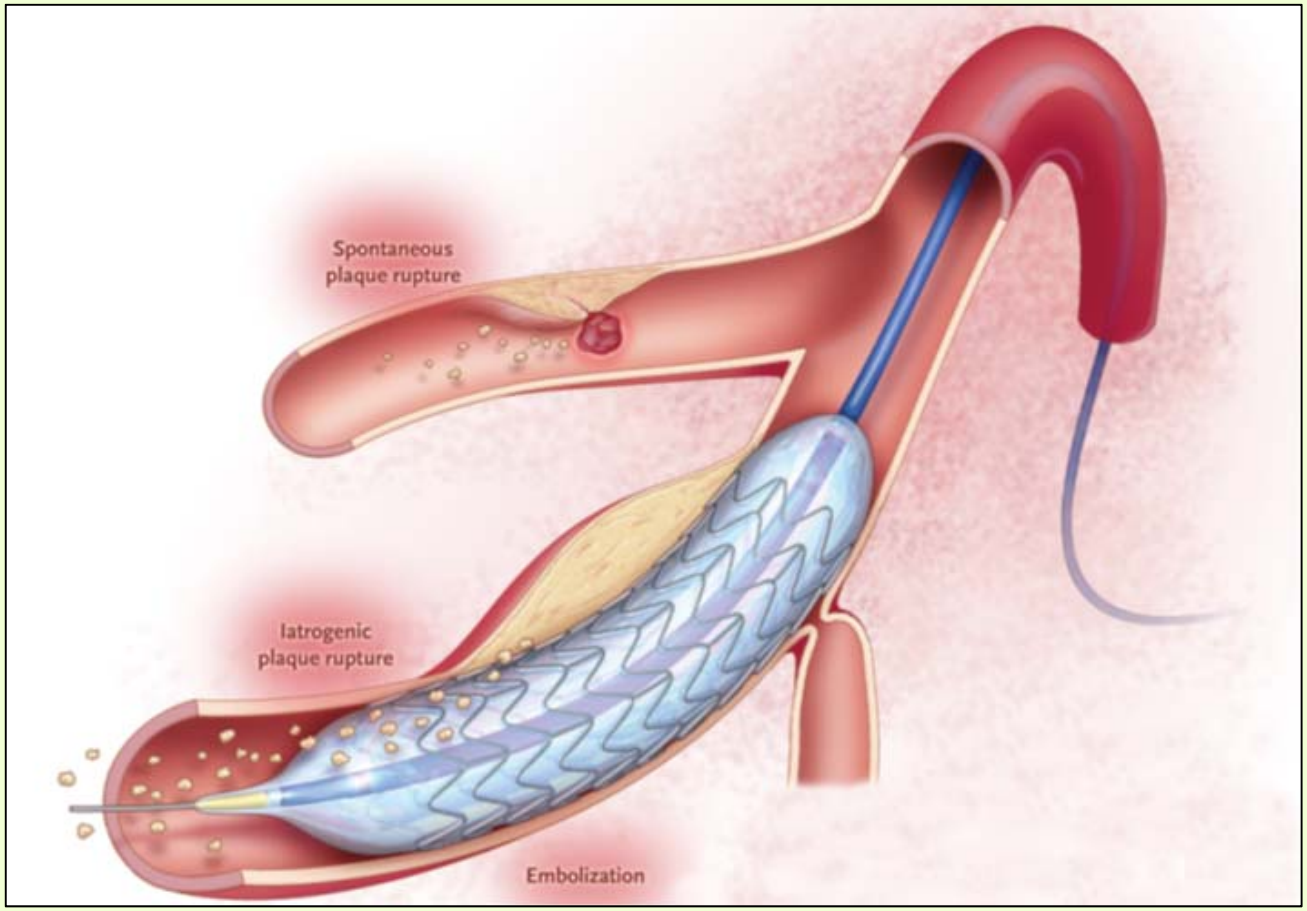
- Myocardial infarctions

Mechanical

- Perforations
- Dissections

PCI Failure

- Stent thrombosis
- Ischemia driven revascularization



Prasad A and Herrmann J. *N Engl J Med*. 2011;364:453-464

Window of Vulnerability

Thrombotic

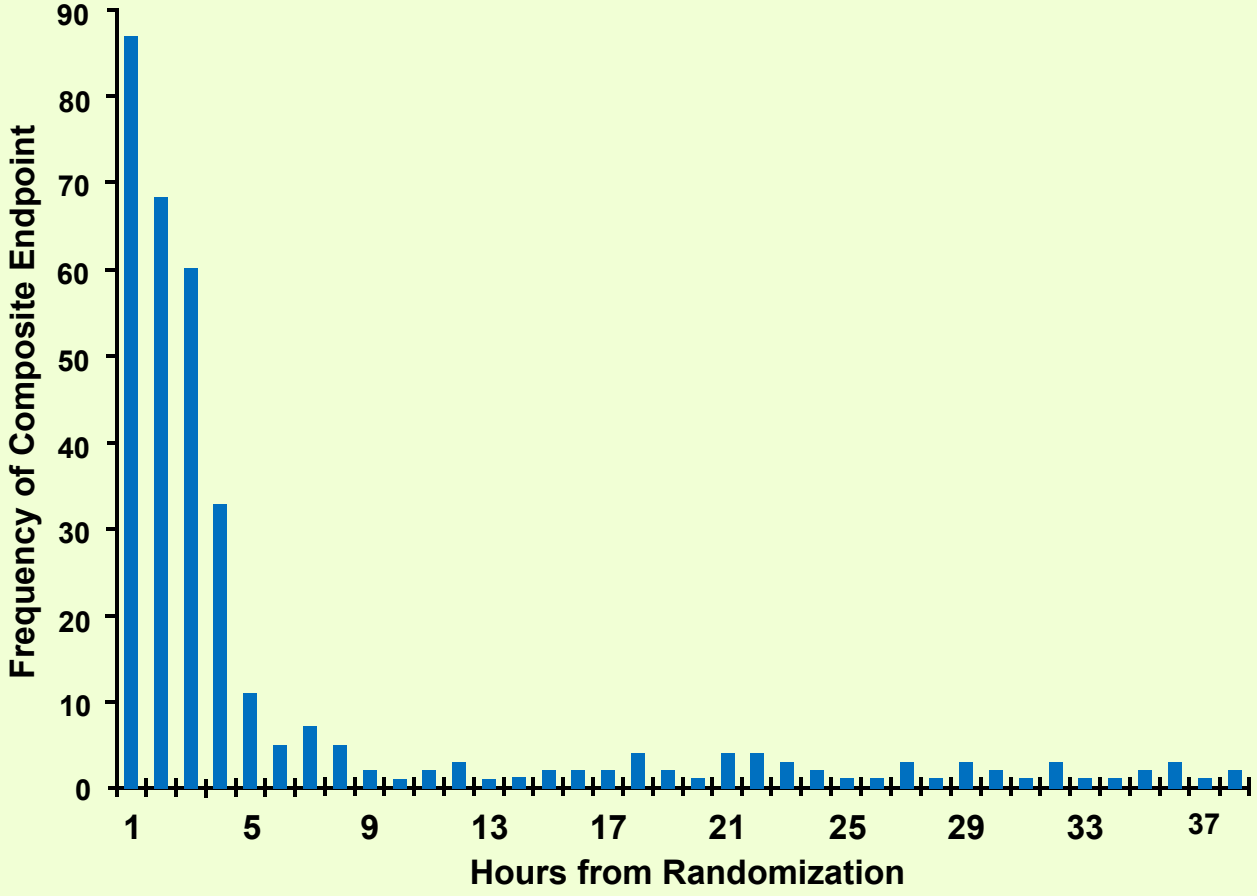
- Myocardial infarctions

Mechanical

- Perforations
- Dissections

PCI Failure

- Stent thrombosis
- Ischemia driven revascularization



Thel M, et al. *Am J Cardiol*. 2000;85:427-434.

The Heart Center of Northeast Georgia Medical Center

Periprocedural MIs are Associated With Increased Mortality

	Mortality	
CPK-MB	**1 year**	**2 years**
Normal	3.4%	7.0%
1-3x ULN	5.9%	8.6%
3-5x ULN	4.5%	8.3%
5-8x ULN	4.5%	6.3%
>8x ULN	11.2%	14.5%
Q-wave	38.6%	38.6%

7147 consecutive patients at Washington Hospital Center

Stone GW. *Circ* 2001;104:642-647

The Heart Center of Northeast Georgia Medical Center

Society for Cardiac Angiography and Interventions (SCAI) Consensus on Periprocedural MI

- Address the need for accurate detection of peri-procedural MI
  - Complex process especially for biomarker (+) patients
- Define a threshold for clinically meaningful events with prognostic importance
- SCAI MI Definition created and published in 2013
  - ≥10 X ULN CK-MB elevations, or
  - ≥5 X ULN CK-MB and new Q waves or LBBB

The Heart Center of Northeast Georgia Medical Center

Platelet Inhibition Therapeutic Options

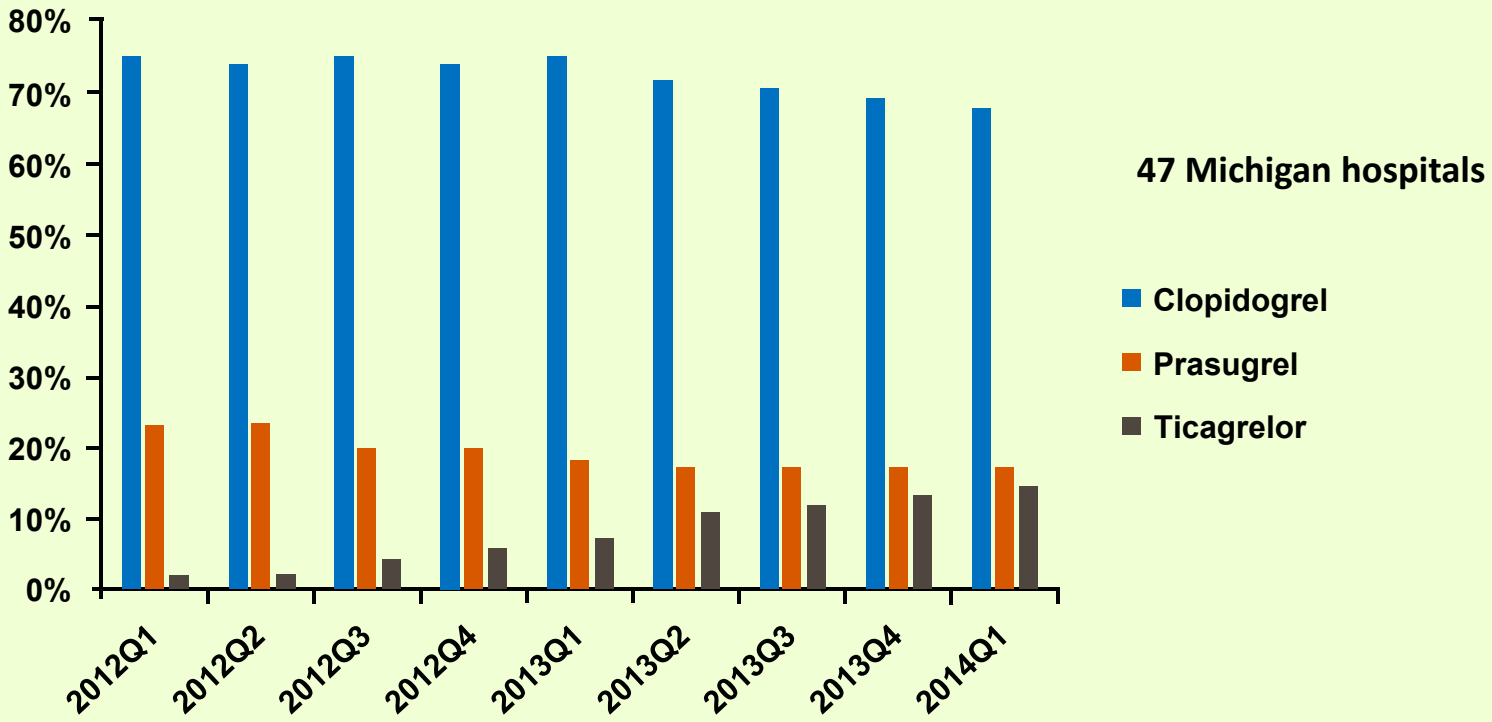
Agent	Route	Onset of effect
Cyclooxygenase (COX) inhibitors		
Aspirin	PO	Fast
$P2Y_{12}$ inhibitors		
Clopidogrel	PO	(>2 hours - 600 mg)
Prasugrel	PO	(<1 hour)
Ticagrelor	PO	(<2 hours)
GP IIb/IIIa Inhibitors		
Abciximab	IV	Immediate
Eptifbatide	IV	Immediate
Tirofiban	IV	Immediate

Use of GP IIb/IIIa Inhibitors is Declining in PCI

Source: Premier Research database, data on file, The Medicines Company
Adult patients undergoing PCI between Jan 01, 2004 and Sept 30, 2014 in the Premier Hospital system.; n=1,143,502

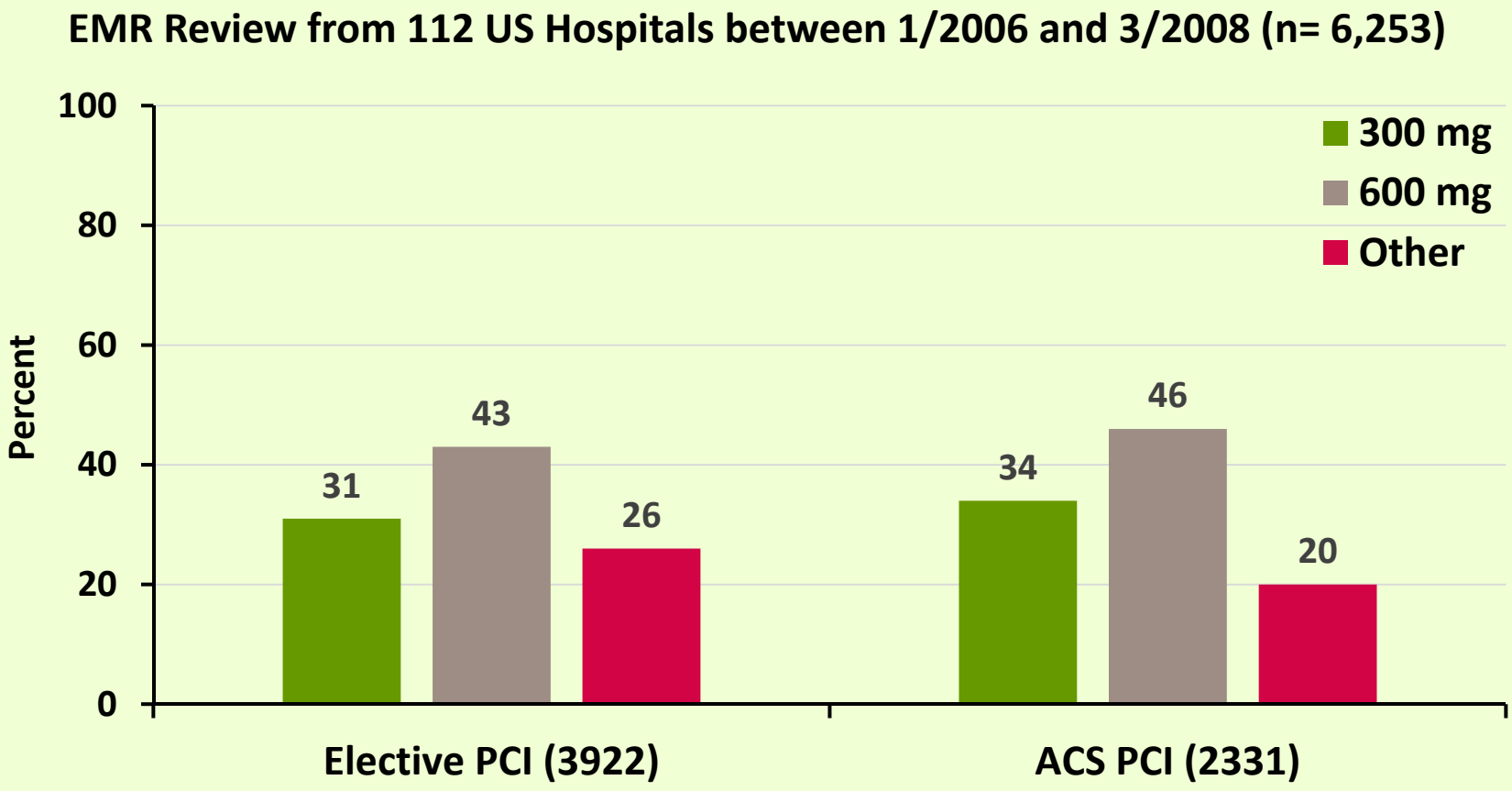
$P2Y_{12}$ Inhibitors Given to Every PCI Patient Clopidogrel is the Most Frequent Choice in US Today

BCBS Michigan Registry Data
Use of Clopidogrel, Prasugrel, and Ticagrelor by Quarter
64,590 patients undergoing PCI from January 2012 to January 2014



Karve A, et al. *Am J Cardiol*. 2015 Mar 12. pii: S0002-9149(15)00893-0.

Loading Dose of Clopidogrel Varies in American Practice



PCI = Percutaneous coronary intervention; **Elective PCI** = No primary diagnosis of acute coronary syndrome (ACS) during or within 14 days before PCI; **ACS-PCI** = Primary diagnosis of ACS during or within 14 days before PCI

Dean BB et al. *Am J Health-Syst Pharm* 2010;67:1430-7

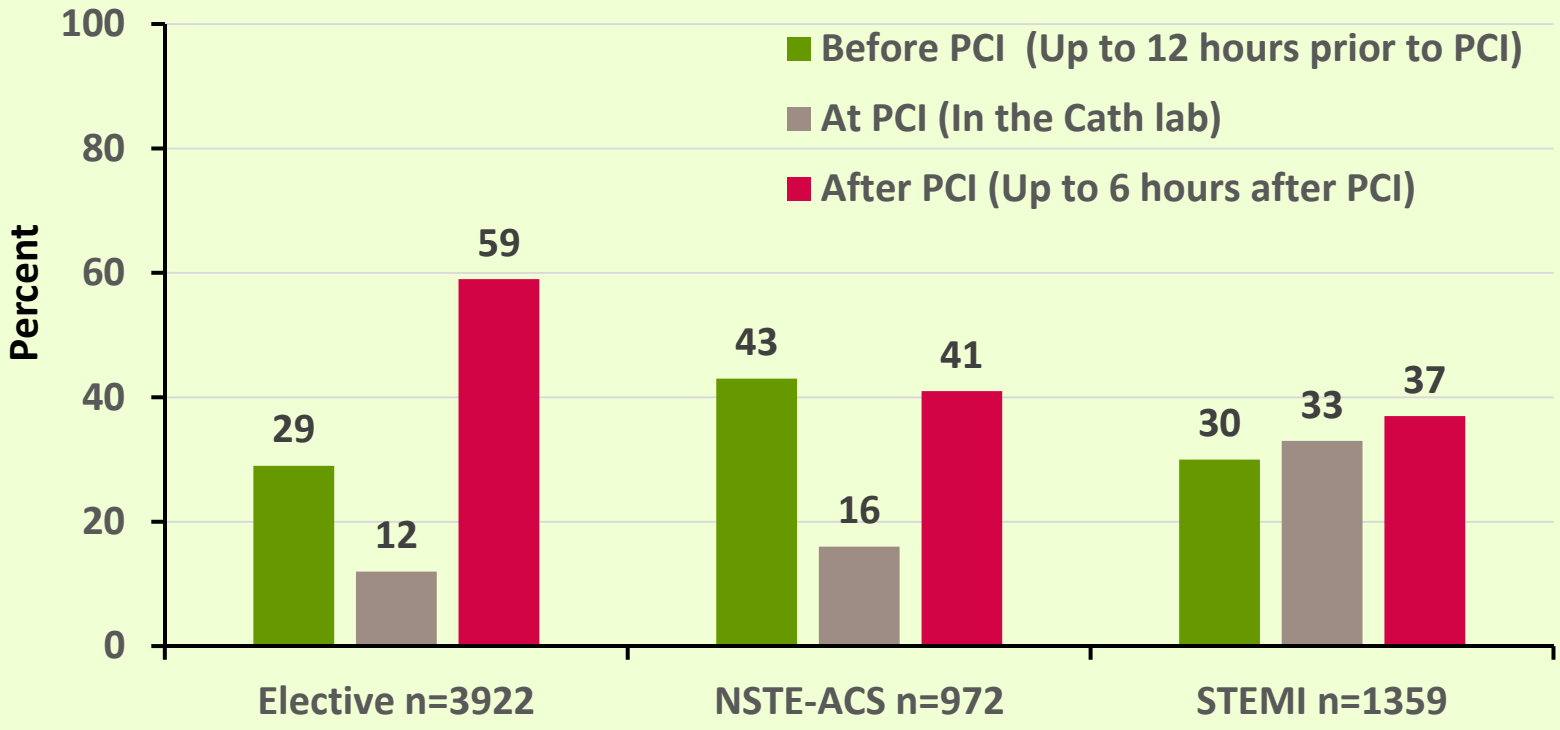
The Heart Center of Northeast Georgia Medical Center

Variable Timing of $P2Y_{12}$ Inhibitor Administration

- Guidelines are not definitive on timing of oral $P2Y_{12}$ inhibitors reflecting inconclusive evidence
  - Different ways interventionalists practice PCI
  - All are relevant and acceptable
- Preference for treatment is based on local practice patterns and how you, your peers and colleagues interpret the data and practice
  - Older patients, patients referred from non-cardiologists
  - Patients with possible left main disease, prior bypass patients, or risk for bleeding
  - Patients on warfarin/afib patients

Timing of Clopidogrel Administration Varies in American Practice

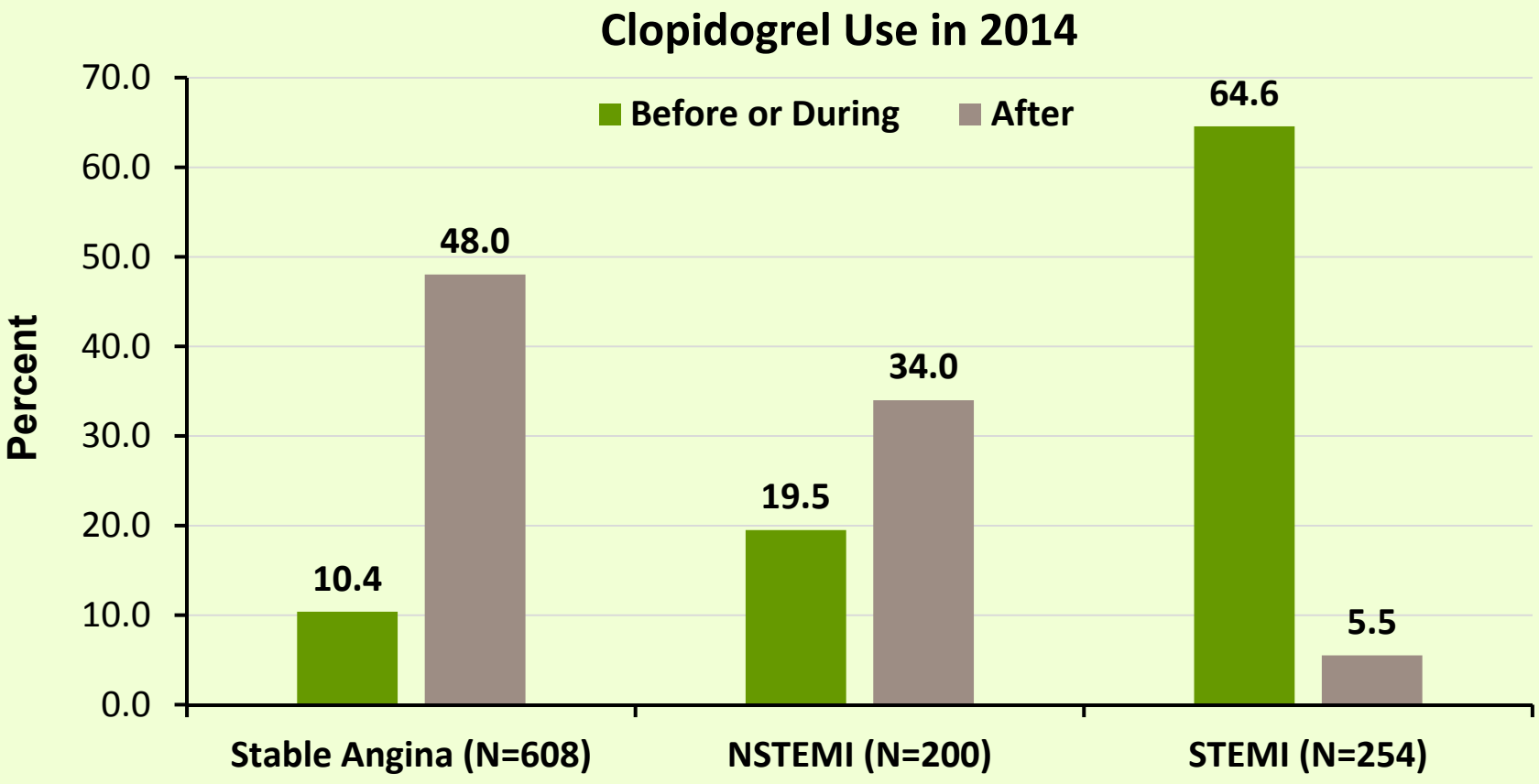
EMR Review from 112 US Hospitals between 1/2006 and 3/2008 (n= 6,253)



PCI = Percutaneous coronary intervention; **Elective PCI** = No primary diagnosis of acute coronary syndrome (ACS) during or within 14 days before PCI; **ACS-PCI** = Primary diagnosis of ACS during or within 14 days before PCI; **UA/NSTEMI** = Unstable angina/non-ST-elevation myocardial infarction; **STEMI** = ST-elevation myocardial infaction

Dean BB et al. *Am J Health-Syst Pharm* 2010;67:1430-7

Timing of Clopidogrel Administration at Northeast Georgia Medical Center



The Heart Center of Northeast Georgia Medical Center

Current American PCI Practice: Conclusions

- Ad hoc PCI is standard of care in the United States
- There is a window of vulnerability for thrombotic complications (predominantly MI) in PCI
- SCAI has defined the most clinically relevant MI outcomes
- Anti-platelet agents are required, but there is marked variability in American practice
- Therapy should balance anti-thrombotic and bleeding complications

Cangrelor Development and C-PHOENIX Efficacy

Efthymios N. Deliargyris, MD, FACC, FSCAI
Vice President and Medical Director
Acute Cardiovascular Care
The Medicines Company

Objectives

- C-PHOENIX trial is consistent with American practice
- C-PHOENIX met the prespecified primary endpoint; cangrelor reduced the occurrence of periprocedural thrombotic events
- Sensitivity analyses of the most clinically meaningful events were consistent with the primary results
- The benefit was observed across subgroups

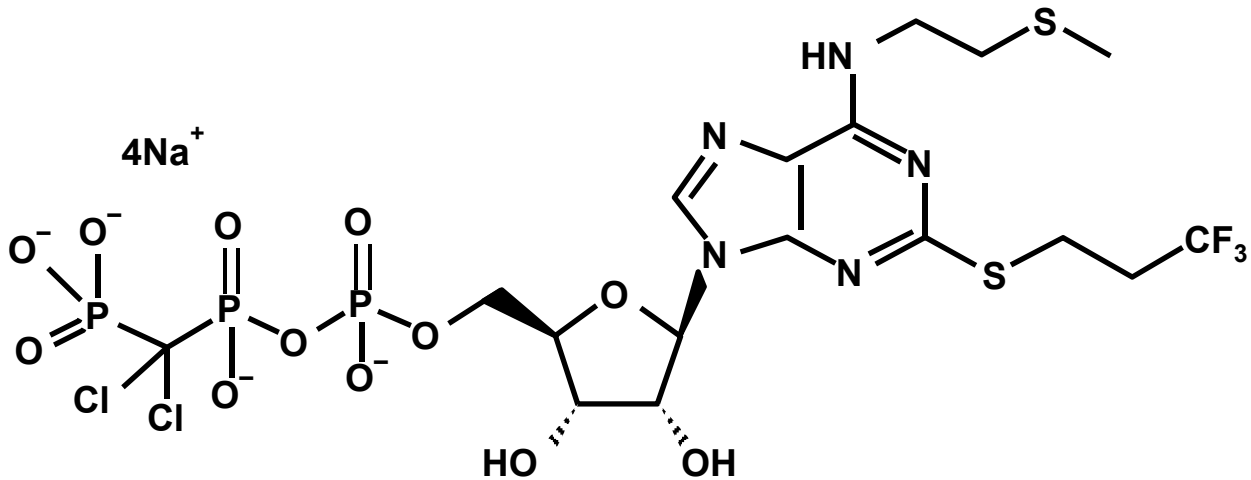
Topics for Discussion

- Clinical profile of cangrelor
- Design of C-PHOENIX
  - Patient population
  - Relevance to American practice
- Efficacy results
  - Protocol pre-specified
  - Sensitivity analyses
    - Subgroups
  - Topics of interest
- Conclusions

Cangrelor Pharmacology

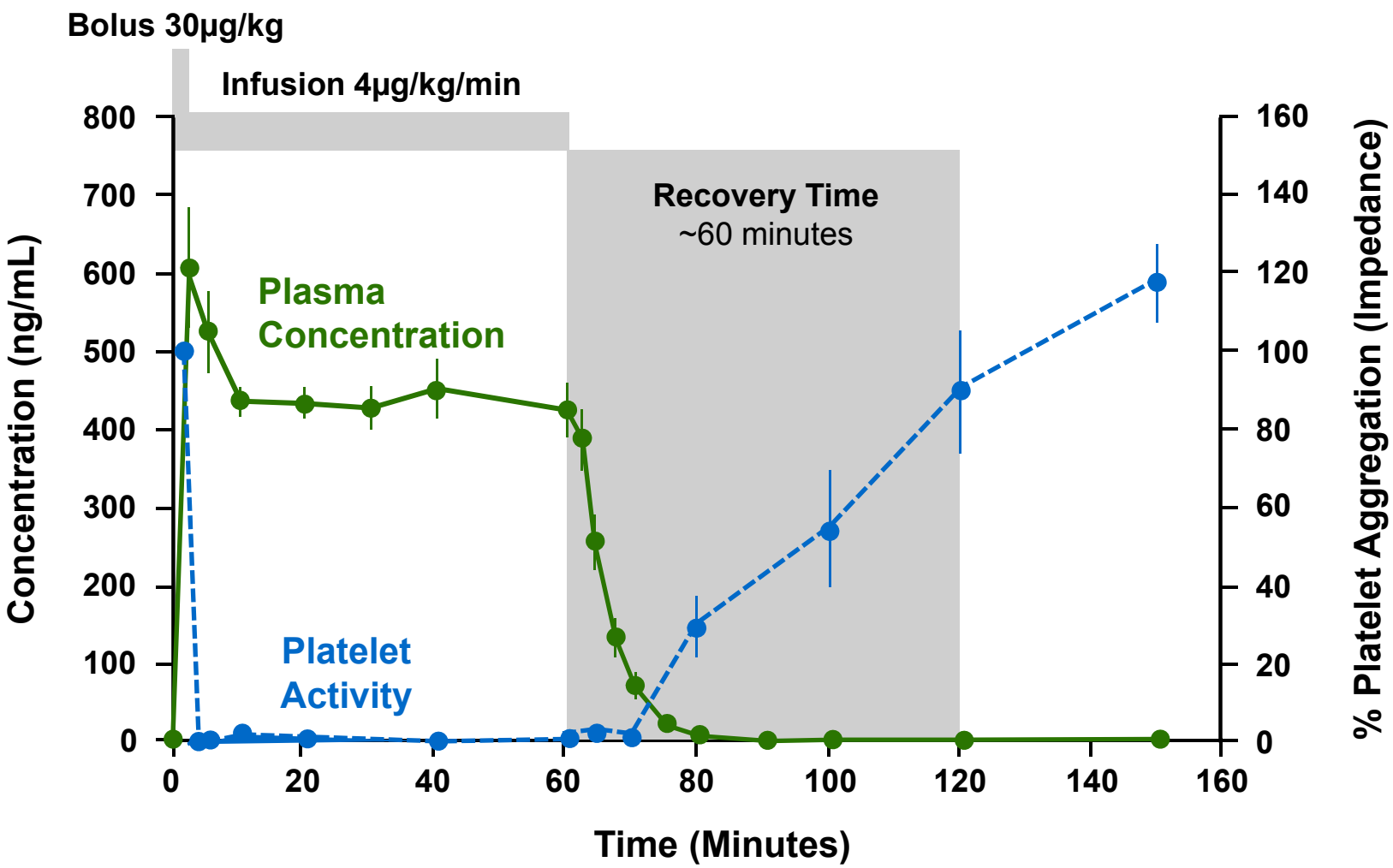
$P2Y_{12}$ Receptor Inhibitor as Adjunct to PCI

- *Immediate onset:* IV, direct-acting
- *Consistent effect:* Not influenced by age, gender, renal function, or genetic variations
- *Rapid offset:* Reversible; half-life of 3-6 minutes; clearance independent of organ function; return of complete platelet function within one hour



Cangrelor Pharmacokinetic and Pharmacodynamic Profile

TMC-CAN-04-02



Overview of Development Program

- 7 Phase I and 8 Phase II studies were conducted in healthy volunteers, patients with renal impairment and patients with coronary artery disease
  - Safety and tolerability
  - Dose and regimen
  - Transition to oral agents
- 2 Phase III studies (C-PCI, C-PLATFORM)
  - Did not meet primary endpoint
  - Demonstrated potential utility in preventing periprocedural events
- C-PHOENIX was designed to test Cangrelor as an adjunct to PCI to prevent periprocedural MI and stent thrombosis

C-PHOENIX

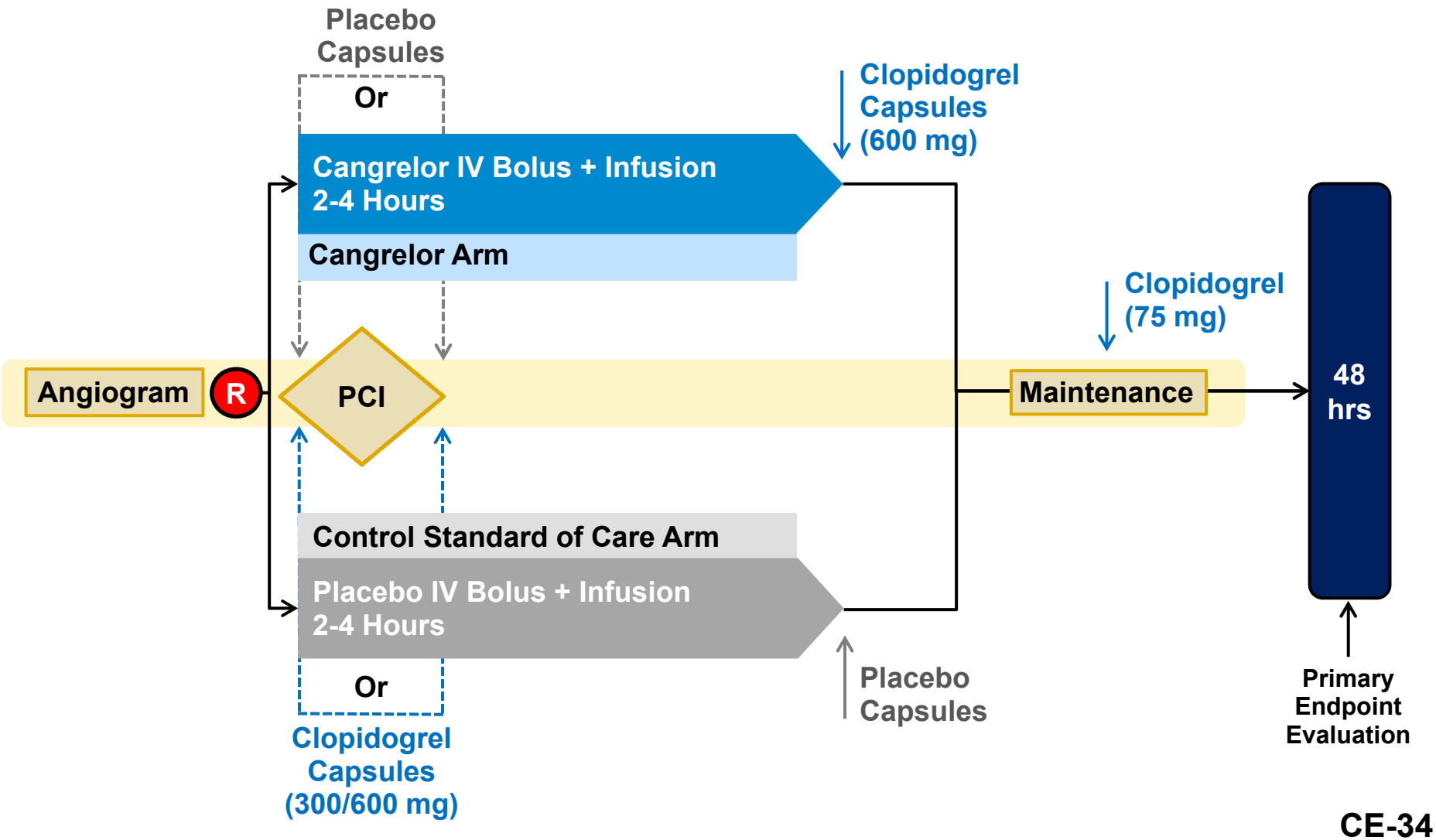
C-PHOENIX: Pivotal Phase 3 Trial

- Randomized (1:1), double blind, double dummy trial
- Comparator: Clopidogrel according to Standard of Care
- Population: Patients undergoing PCI
- Key inclusion criteria:
  - SA/NSTE-ACS: Confirmed need for PCI (by angiography)
  - STEMI: Intent for emergent PCI
- Key exclusion criteria:
  - Pretreated with a $P2Y_{12}$ inhibitor in the past 7 days
  - Patients using or planning to use GP IIb/IIIa inhibitors

Patient Stratification

- Baseline status:
  - Normal: No evidence of evolving MI
    - Stable angina
    - NSTE-ACS: No ongoing symptoms, normal ECG, and normal biomarkers
  - Abnormal: Evidence of evolving MI
    - STEMI
    - NSTE-ACS: Ongoing symptoms, ischemia on ECG, or increased biomarkers
- Clopidogrel loading dose
  - 300 mg or 600 mg
- Site

C-PHOENIX: Study Design



Pre-specified Study Efficacy Endpoints (48 hours)

- Primary efficacy composite endpoint:
  - Death/MI/IDR/ST within 48 hours
    - Myocardial infarction (UDMI) definition:
      - CK-MB ≥3x ULN if baseline normal
      - CK-MB >50% increase from baseline + objective evidence of ischemia if baseline abnormal
    - Ischemic driven revascularization (IDR)
    - Stent thrombosis (ST) definitions:
      - Academic Research Consortium (ARC) ST: After PCI procedure
      - Intraprocedural ST (IPST): During PCI procedure
  - Event determination by a Clinical Events Committee (CEC)
- Key secondary endpoint: Incidence of stent thrombosis within 48 hours

C-PHOENIX Statistical Considerations

- Assuming event rate of 5.1% in the clopidogrel arm and 3.9% in the cangrelor arm (24.5% reduction in odds ratio)
- Sample size of 10,900 with power of 85% at the two-sided significance level of 0.05 with an interim analysis at 70%
- Primary efficacy analysis
  - Composite endpoint (Death/MI/IDR/ST) at 48 hours
  - mITT population
  - Two-sided overall alpha level at 0.050 (nominal final alpha at 0.047 adjusting for 70% IA)
  - Logistic regression to adjust for baseline status (normal vs abnormal) and loading dose (300 mg vs 600 mg)
- Additional analyses for other endpoints and subgroups
  - Crude analysis without adjustment, χ^2 test, OR (95% CI)

Results

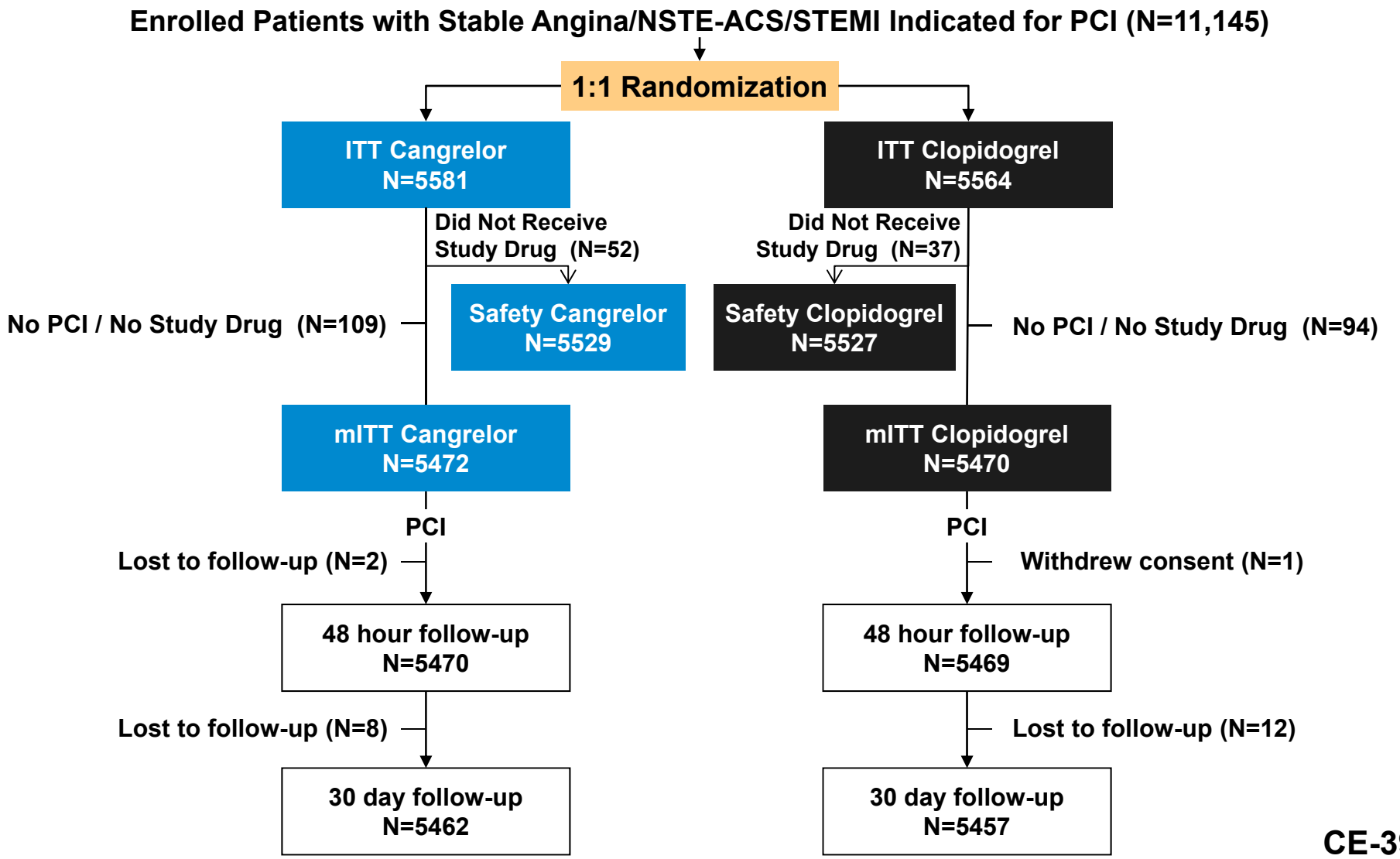
Study Enrollment

	n	Enrollment %
Number of Countries	12	
Number of Enrolling Sites	153*	
USA	63	38%
Europe	74	58%
Asia/Pacific	9	3%
South America	7	1%

* Out of the total 161 activated sites.

Patient Disposition

C-PHOENIX



Baseline Characteristics
C-PHOENIX (ITT)

	Cangrelor N=5581 n (%)	Clopidogrel N=5564 n (%)
Age, mean ± SD	64.0 ± 11.0	63.8 ± 11.0
≥65, n (%)	2689 (48.2)	2662 (47.8)
≥75, n (%)	1033 (18.5)	1000 (18.0)
Male, n (%)	3982 (71.3)	4042 (72.6)
Race, n (%)		
White	5231 (93.8)	5206 (93.7)
Asian	173 (3.1)	177 (3.2)
Black/African American	156 (2.8)	152 (2.7)
Other	18 (0.3)	22 (0.4)
Patient baseline status, n (%)		
Normal – no evolving MI	3587 (64.3)	3564 (64.1)
Abnormal – evolving MI	1994 (35.7)	2000 (35.9)
Patient types, n (%)		
SA	3220 (57.7)	3208 (57.7)
ACS	2361 (42.3)	2356 (42.3)
NSTE-ACS	1479 (26.5)	1435 (25.8)
STEMI	882 (15.8)	921 (16.6)

Medical History
C-PHOENIX (ITT)

	Cangrelor N=5581 n (%)	Clopidogrel N=5564 n (%)
Diabetes Mellitus	1546 (27.8)	1559 (28.1)
Hypertension	4460 (80.1)	4406 (79.4)
Hyperlipidemia	3412 (69.0)	3380 (68.9)
Cerebrovascular event	276 (5.0)	252 (4.5)
Previous MI	1111 (20.0)	1191 (21.6)
Previous PCI	1261 (23.0)	1344 (24.2)
Previous CABG	581 (10.4)	509 (9.2)
Congestive heart failure	565 (10.1)	592 (10.7)

Clopidogrel Dose and Timing
C-PHOENIX (ITT)

- Clopidogrel dose* - sites
  - 6 sites dosed only 300 mg
  - 118 sites dosed only 600 mg
  - 27 sites dosed both
- Clopidogrel dose** - patients
  - 4064 (73%) received 600 mg
  - 1427 (26%) received 300 mg
- United States: 99% of patients received 600 mg
- Clopidogrel timing***
  - 3442 (62%) before start of PCI – Median time: -5 minutes
  - 1997 (36%) after start of PCI – Median time: 20 minutes

* 2 sites did not dose

** 73 (1%) patients did not receive a dose

*** 125 (2%) patients with missing time

Prespecified Primary Efficacy Endpoint Met at 48 Hours

C-PHOENIX (mITT)

Primary Analysis Adjusted[1]	Cangrelor N=5470 n (%)	Clopidogrel N=5469 n (%)	OR (95% CI)	p-value
Death/MI/IDR/ST	257 (4.7)	322 (5.9)	0.78 (0.66, 0.93)	0.005
Secondary Efficacy Endpoints				
Death	18 (0.3)	18 (0.3)	1.00 (0.52, 1.92)	>0.99
MI	207 (3.8)	255 (4.7)	0.80 (0.67, 0.97)	0.02
IDR	28 (0.5)	38 (0.7)	0.74 (0.45, 1.20)	0.22
ST (key secondary endpoint)	46 (0.8)	74 (1.4)	0.62 (0.43, 0.90)	0.01

[1]Using logistic model adjusted for baseline status and clopidogrel dose.

Prespecified Efficacy Endpoint Met at 30 Days

C-PHOENIX (mITT)

Analysis Adjusted	Cangrelor N=5462* n (%)	Clopidogrel N=5457** n (%)	OR (95% CI)	p-value
Death/MI/IDR/ST	326 (6.0)	380 (7.0)	0.85 (0.73, 0.99)	0.03
Individual components				
Death	60 (1.1)	55 (1.0)	1.09 (0.76, 1.58)	0.64
MI	225 (4.1)	272 (5.0)	0.82 (0.68, 0.98)	0.03
IDR	56 (1.0)	66 (1.2)	0.85 (0.59, 1.21)	0.36
ST	71 (1.3)	104 (1.9)	0.68 (0.50, 0.92)	0.01

99.8% follow-up complete at 30 days
* 10 patients lost to follow-up; ** 13 patient lost to follow-up.

Sensitivity Analyses

FDA Requested Sensitivity Analyses

Clinical Meaningful Endpoints

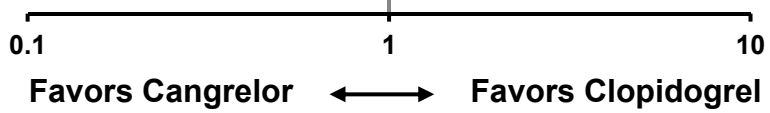
Sensitivity Composite Endpoint	Definition
Death/MI/IDR/ARC-ST	Remove IPST
Death/SCAI MI/IDR/ARC-ST	Remove IPST Use SCAI MI definition*
Death/≥10 ULN MI/IDR/ARC-ST	Remove IPST Include only MI with CK-MB ≥10X ULN
Death/Clinical MI/IDR/ARC-ST	Remove IPST Include only MI with clinical evidence
Death/IDR/ARC-ST	Remove IPST Remove all MI
Site Death/MI/IDR/ST	Site reported events only

*SCAI MI: CK-MB ≥10X ULN, or CK-MB ≥5X ULN with new Q waves in 2 leads or new LBBB

Protocol-Defined and Sensitivity Analyses of Primary Efficacy Endpoints at 48 Hours

C-PHOENIX (mITT)

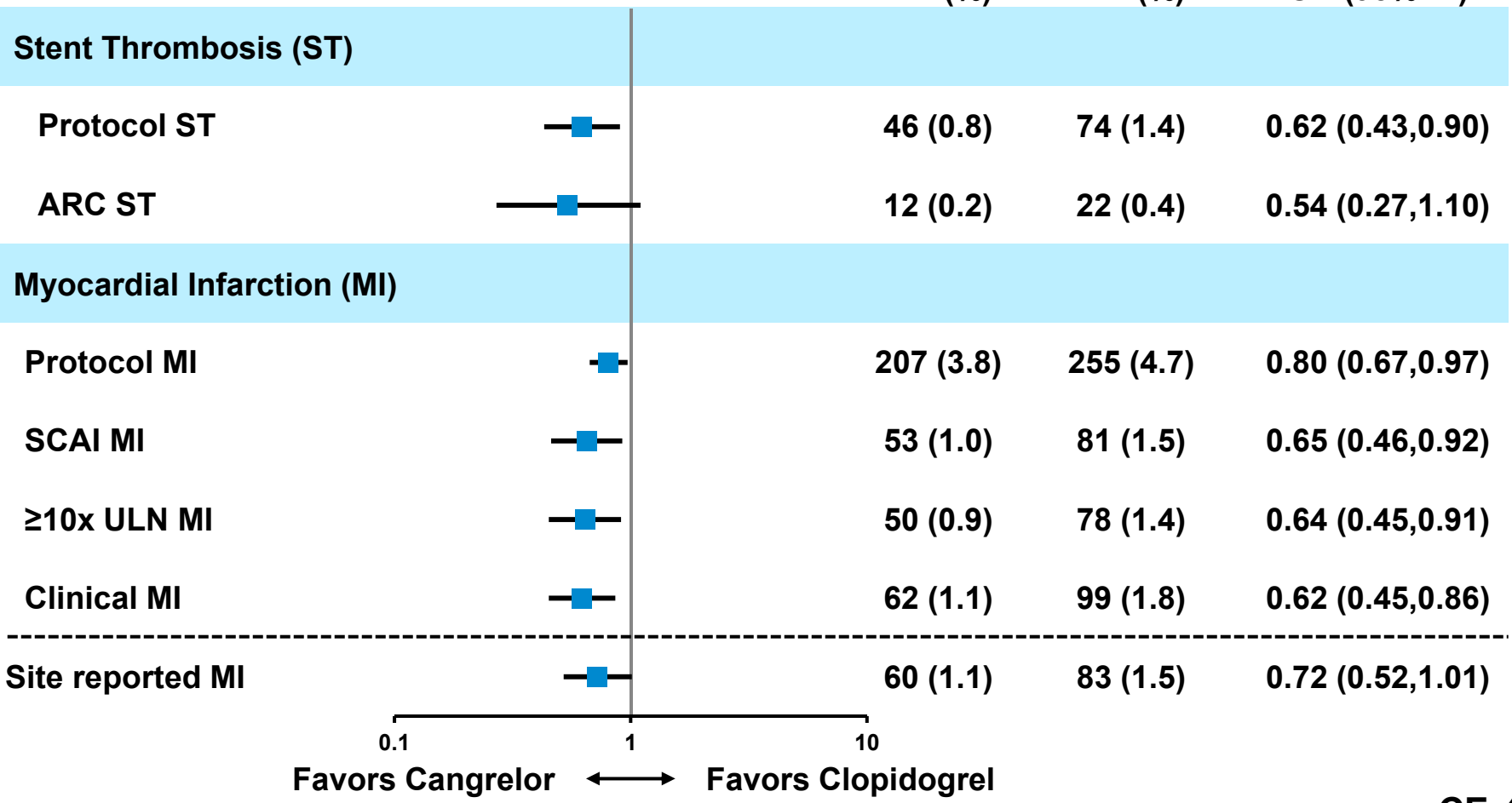
	Cangrelor N=5470 n (%)	Clopidogrel N=5469 n (%)	OR (95% CI)
Protocol Defined Primary Endpoint			
Death/MI/IDR/ST	257 (4.7)	322 (5.9)	0.78 (0.66, 0.93)
Sensitivity Analyses			
Death/MI/IDR/ARC-ST	230 (4.2)	286 (5.2)	0.80 (0.67, 0.95)
Death/SCAI MI/IDR/ARC-ST	79 (1.4)	114 (2.1)	0.69 (0.52, 0.92)
Death/≥10 ULN MI/IDR/ARC-ST	77 (1.4)	111 (2.0)	0.69 (0.51, 0.92)
Death/Clinical MI/IDR/ARC-ST	86 (1.6)	130 (2.4)	0.66 (0.50, 0.86)
Death/IDR/ARC-ST	43 (0.8)	54 (1.0)	0.79 (0.53, 1.19)
Site Death/MI/IDR/ST	96 (1.8)	121 (2.2)	0.79 (0.60, 1.03)



Sensitivity Analyses of the ST and MI Endpoints at 48 Hours

PHOENIX (mITT)

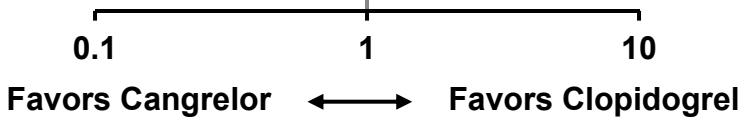
	Cangrelor N=5470 n/N (%)	Clopidogrel N=5469 n/N (%)	OR (95% CI)
Stent Thrombosis (ST)			
Protocol ST	46 (0.8)	74 (1.4)	0.62 (0.43,0.90)
ARC ST	12 (0.2)	22 (0.4)	0.54 (0.27,1.10)
Myocardial Infarction (MI)			
Protocol MI	207 (3.8)	255 (4.7)	0.80 (0.67,0.97)
SCAI MI	53 (1.0)	81 (1.5)	0.65 (0.46,0.92)
≥10x ULN MI	50 (0.9)	78 (1.4)	0.64 (0.45,0.91)
Clinical MI	62 (1.1)	99 (1.8)	0.62 (0.45,0.86)
Site reported MI	60 (1.1)	83 (1.5)	0.72 (0.52,1.01)



Consistent Effect Across All Subgroups Death/MI (SCAI)/IDR/ARC-ST at 48 Hours

C-PHOENIX (mITT)

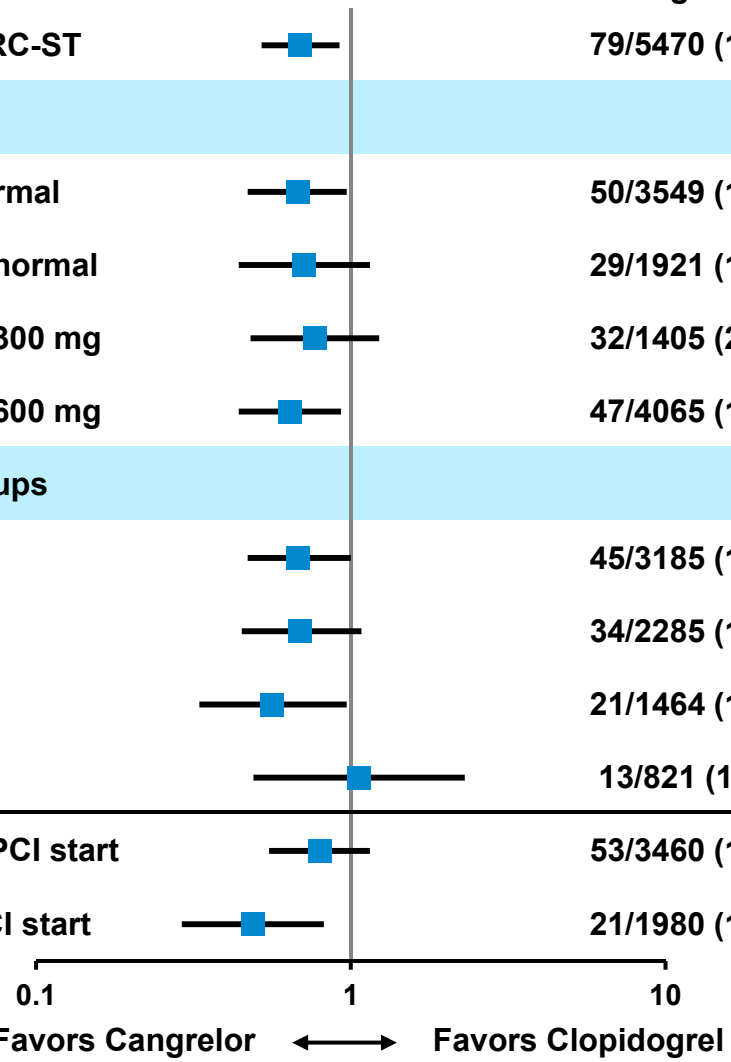
	Cangrelor	Clopidogrel	OR [95% CI]	P [Int]
Death/SCAI MI/IDR/ARC-ST	79/5470 (1.4)	114/5469 (2.1)	0.69 (0.52, 0.92)	
Subgroups				
Male	57/3913 (1.5)	72/3976 (1.8)	0.80 (0.56, 1.14)	0.131
Female	22/1557 (1.4)	42/1493 (2.8)	0.50 (0.29, 0.83)	
Race: white	73/5130 (1.4)	106/5119 (2.1)	0.68 (0.51, 0.92)	0.676
Race: non-white	6/337 (1.80)	7/343 (2.0)	0.87 (0.29, 2.62)	
Age ≥ 75	17/1021 (1.7)	26/987 (2.6)	0.63 (0.34, 1.16)	0.736
Age < 75	62/4449 (1.4)	88/4482 (2.0)	0.71 (0.51, 0.98)	
United States	25/2048 (1.2)	50/2049 (2.4)	0.49 (0.30, 0.80)	0.085
Outside US	54/3422 (1.6)	64/3420 (1.9)	0.84 (0.58, 1.21)	



Consistent Effect Across All Subgroups Death/MI (SCAI)/IDR/ARC-ST at 48 Hours

C-PHOENIX (mITT)

	Cangrelor	Clopidogrel	OR [95% CI]	P [Int]
Death/SCAI MI/IDR/ARC-ST	79/5470 (1.4)	114/5469 (2.1)	0.69 (0.52, 0.92)	
Stratified Subgroups				
Patient Status: Normal	50/3549 (1.4)	73/3524 (2.1)	0.68 (0.47, 0.97)	0.865
Patient Status: Abnormal	29/1921 (1.5)	41/1945 (2.1)	0.71 (0.44, 1.15)	
Clopidogrel Dose 300 mg	32/1405 (2.3)	41/1401 (2.9)	0.77 (0.48, 1.23)	0.535
Clopidogrel Dose 600 mg	47/4065 (1.2)	73/4068 (1.8)	0.64 (0.44, 0.93)	
Not Stratified Subgroups				
Investigator: SA	45/3185 (1.4)	65/3171 (2.0)	0.68 (0.47, 1.00)	0.967
Investigator: ACS	34/2285 (1.5)	49/2298 (2.1)	0.69 (0.45, 1.08)	
NSTE-ACS	21/1464 (1.4)	36/1428 (2.5)	0.56 (0.33, 0.97)	0.187
STEMI	13/821 (1.6)	13/870 (1.5)	1.06 (0.49, 2.30)	
Oral Dose Before PCI start	53/3460 (1.5)	66/3442 (1.9)	0.80 (0.55, 1.15)	0.131
Oral Dose After PCI start	21/1980 (1.1)	43/1996 (2.2)	0.49 (0.29, 0.82)	



Topics of Interest

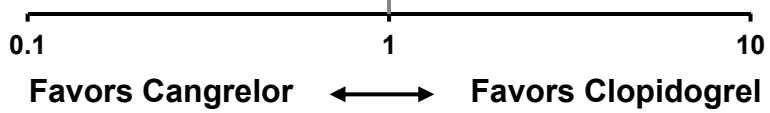
Outcomes in Sites with Clopidogrel 600 mg use only

Risk during transition of Cangrelor to Clopidogrel

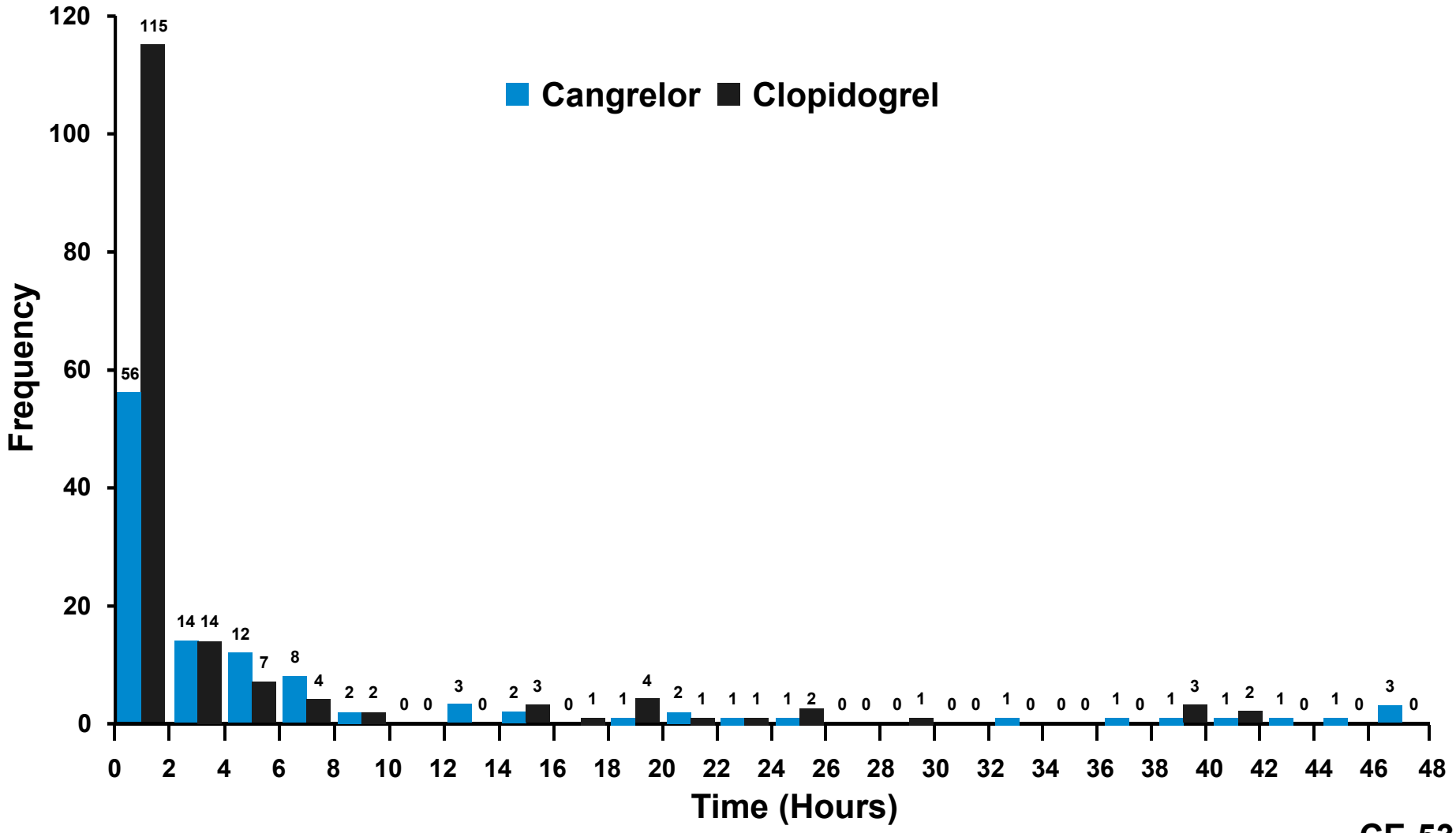
Similar Efficacy Observed at Sites Using 600 mg Clopidogrel Only

C-PHOENIX (mITT)

	Cangrelor N=2290 n (%)	Clopidogrel N=2310 n (%)	OR (95% CI)
Protocol Defined Primary Endpoint			
Death/MI/IDR/ST	99 (4.3)	140 (6.1)	0.70 (0.54, 0.91)
Sensitivity Analyses			
Death/MI/IDR/ARC-ST	89 (3.9)	125 (5.4)	0.71 (0.54, 0.93)
Death/SCAI MI/IDR/ARC-ST	26 (1.1)	47 (2.0)	0.55 (0.34, 0.90)
Death/≥10 ULN MI/IDR/ARC-ST	24 (1.0)	46 (2.0)	0.52 (0.32, 0.86)
Death/Clinical MI/IDR/ARC-ST	36 (1.6)	62 (2.7)	0.58 (0.38, 0.88)
Death/IDR/ARC-ST	13 (0.6)	21 (0.9)	0.62 (0.31, 1.25)
Site Death/MI/IDR/ST	51 (2.2)	68 (2.9)	0.75 (0.52, 1.08)



Timing of Events
Death, SCAI MI, IDR, ARC-ST
C-PHOENIX (mITT)



C-PHOENIX Efficacy Conclusions

- C-PHOENIX trial is consistent with American practice
- C-PHOENIX met the prespecified primary endpoint; cangrelor reduced the occurrence of periprocedural thrombotic events
- Sensitivity analyses of the most clinically meaningful events were consistent with the primary results
- The benefit was observed across subgroups

Cangrelor Safety Profile

Loretta M. Itri, MD, FACP
Executive Vice President
Global Health Science and Regulatory Affairs
The Medicines Company

Topics for Discussion

- Safety analysis populations:
  - C-PHOENIX (N=11,056)
  - CHAMPION Pool (N=25,107)
- Summary of adverse events within 48 hours
- Serious adverse events
- Adverse events leading to discontinuation
- Deaths
- Special safety topics
  - Bleeding events
  - Dyspnea
  - Hypersensitivity
  - Renal adverse events
- Transition to oral $P2Y_{12}$ inhibitors
- Conclusions

Summary of Adverse Events

C-PHOENIX, CHAMPION Pool (Safety Population)

	C-PHOENIX		CHAMPION Pool	
	Cangrelor N=5529 n (%)	Clopidogrel N=5527 n (%)	Cangrelor N=12,565 n (%)	Clopidogrel N=12,542 n (%)
Any AE	1125 (20.3)	1064 (19.3)	2933 (23.3)	2778 (22.1)
Any SAE	122 (2.2)	105 (1.9)	295 (2.3)	287 (2.3)
Death	18 (0.3)	20 (0.4)	34 (0.3)	47 (0.4)
AE leading to discon of study drug	31 (0.6)	21 (0.4)	75 (0.6)	52 (0.4)

Serious Adverse Events

≥0.1% Patients in C-PHOENIX
C-PHOENIX, CHAMPION Pool (Safety Population)

Preferred Terms	C-PHOENIX		CHAMPION Pool	
	Cangrelor N=5529 n (%)	Clopidogrel N=5527 n (%)	Cangrelor N=12,565 n (%)	Clopidogrel N=12,542 n (%)
Patients with at least one SAE	122 (2.2)	105 (1.9)	295 (2.3)	287 (2.3)
Cardiogenic shock	12 (0.2)	6 (0.1)	24 (0.2)	25 (0.2)
Coronary artery dissection	9 (0.2)	6 (0.1)	14 (0.1)	11 (0.1)
Hypotension	7 (0.1)	3 (0.1)	15 (0.1)	15 (0.1)
Pulmonary edema	6 (0.1)	3 (0.1)	10 (0.1)	9 (0.1)
Ventricular fibrillation	6 (0.1)	7 (0.1)	22 (0.2)	15 (0.1)
Cardiac arrest	5 (0.1)	8 (0.1)	10 (0.1)	17 (0.1)

Patients with AE Leading to Discontinuation of Study Drug

≥2 Patients in C-PHOENIX

Preferred Terms	C-PHOENIX		CHAMPION Pool	
	Cangrelor N=5529 n	Clopidogrel N=5527 n	Cangrelor N=12,565 n	Clopidogrel N=12,542 n
Patients with at least one AE leading to discon of study drug	31 (0.6%)	21 (0.4%)	75 (0.6%)	52 (0.4%)
Coronary artery dissection	6	5	11	8
Coronary artery perforation	5	4	14	7
Dyspnea	4	0	8	1
Cardio-respiratory arrest	3	0	3	0
Anaphylactic reaction	2	0	2	0
Cardiac arrest	2	1	3	3
Arterial rupture	1	3	1	3
Hypotension	1	2	5	6
Bradycardia	0	2	1	2
Coronary artery occlusion	0	2	0	3
Hypersensitivity	0	2	0	3

Deaths Within 48 Hours

C-PHOENIX, CHAMPION Pool (Safety Population)

Preferred Terms*	C-PHOENIX		CHAMPION Pool	
	Cangrelor N=5529 n	Clopidogrel N=5527 n	Cangrelor N=12,565 n	Clopidogrel N=12,542 n
Any deaths within 48 hours	18 (0.3%)	20 (0.4%)	34 (0.3%)	47 (0.4%)
Cardiogenic shock	4	2	7	14
Acute myocardial infarction	3	2	4	4
Thrombosis in device	3	3	3	4
Myocardial infarction	2	0	2	2
Cardiac arrest	1	2	1	4
Cardiac failure	1	1	1	1
Coronary artery dissection	1	0	1	0
Renal failure acute	1	0	2	0
Aortic dissection	1	0	1	0
Aspiration	1	0	1	0
Cardiac failure congestive	0	1	1	1
Coronary artery disease	0	1	0	1
Coronary artery occlusion	0	2	0	2
Myocardial rupture	0	3	0	4
Pulmonary oedema	0	1	0	2
Ventricular asystole	0	1	0	1
Ventricular fibrillation	0	1	0	2

* Terms based on C-PHOENIX.

Special Safety Topics

Bleeding Events

- Standardized Scales
- Cases of Intracranial Hemorrhage (ICH)
- Cases of Death Within 48 hrs

Bleeding Definitions

Bleed Classification	Definition
GUSTO severe	• Intracranial bleeding or • Resulting in hemodynamic compromise requiring treatment (includes fatal bleeding)
GUSTO moderate	• Requiring blood transfusion
TIMI major	• Intracranial bleeding or • Any bleeding associated with clinically overt signs associated with a drop in hemoglobin of > 5 g/dL (or when hemoglobin is not available, an absolute drop in hematocrit >15%)
TIMI minor	• Clinically overt sign of bleeding (including observations by imaging techniques) that is associated with a fall in hemoglobin of ≥3 g/dL and ≤5 g/dL (or when hemoglobin is not available, an absolute drop in hematocrit ≥9% and ≤15%

FDA BD Table 14.

Summary of Bleeding

C-PHOENIX, CHAMPION Pool (Safety Population)

	C-PHOENIX			CHAMPION Pool		
	Cangrelor N=5529 n (%)	Clopidogrel N=5527 n (%)	OR (95% CI)	Cangrelor N=12,565 n (%)	Clopidogrel N=12,542 n (%)	OR (95% CI)
Non-CABG bleeding	857 (15.5)	602 (10.9)	1.50 (1.34, 1.68)	2197 (17.5)	1697 (13.5)	1.35 (1.26,1.45)
GUSTO						
Severe/Moderate	32 (0.6)	20 (0.4)	1.60 (0.92, 2.81)	104 (0.8)	80 (0.6)	1.30 (0.97,1.74)
Severe	11 (0.2)	6 (0.1)	1.83 (0.68, 4.96)	30 (0.2)	23 (0.2)	1.30 (0.76,2.24)
Moderate	21 (0.4)	14 (0.3)	1.50 (0.76, 2.96)	75 (0.6)	57 (0.5)	1.32 (0.93,1.86)
TIMI						
Major or minor	45 (0.8)	17 (0.3)	2.66 (1.52, 4.65)	126 (1.0)	81 (0.6)	1.56 (1.18,2.06)
Major	12 (0.2)	6 (0.1)	2.00 (0.75, 5.34)	35 (0.3)	29 (0.2)	1.21 (0.74,1.97)
Minor	33 (0.6)	11 (0.2)	3.01 (1.52, 5.96)	91 (0.7)	52 (0.4)	1.75 (1.25,2.47)
Any Blood Transfusion	25 (0.5)	17 (0.3)	1.47 (0.79, 2.73)	90 (0.7)	71 (0.6)	1.27 (0.93,1.73)

Cases of Intracranial Hemorrhage Within 48 Hours of Start of Study Drug

C-PHOENIX

Treatment	Relevant Prior History	Age/ Sex	Event / Timing	Comments	Outcome
Cangrelor	A-Fib TIA	76 F	Right upper extremity weakness, slurred speech of 5 min duration post discharge 21 hrs. post-PCI	History multiple TIAs and similar symptoms; CT- Subarachnoid hemorrhage "probably old" Discharged Day 2	Resolved without sequelae
Cangrelor	HTN	64 M	Frontal headache, sense of RUE "detachment" 33 hrs. post PCI	CT- L posterior frontal hemorrhage w/ minimal subarachnoid extension Discharged Day 4	Resolved without sequelae
Cangrelor	Vertigo	65 F	Head injury due to syncope with fall; superficial occipital bleeding 9.5 hrs. post PCI	CT-small subarachnoid bleed Discharged Day 8	Resolved without sequelae
Clopidogrel	None	76 M	Head injury due to fall 8 hrs. post PCI	CT- Paracerebral hematoma over right hemisphere Discharged Day 2	Resolved without sequelae

Patients With Bleeding Events Who Died Within 48 Hours of Study Drug Start

Treatment	Age/Sex	Diagnosis	Timing of Bleeding Event	Cause of Death
Cangrelor	75 M	SA	During PCI	Aortic root dissection, hemorrhage, hemodynamic instability
Cangrelor	74 F	STEMI	During PCI	Dissection of LAD artery with cardiac tamponade
Cangrelor	62 F	STEMI	23 hrs. post-PCI	Cardiac arrest, V Fib, GI hemorrhage, hematemesis
Cangrelor	85 F	STEMI	3 hrs. post-PCI	Cardiac arrest with resuscitation x 2; acute renal failure; family requested DNR; Pt discharged and died during transport to home; GI hemorrhage and hematuria occurred 3 hrs post PCI

Special Safety Topics

Dyspnea
Hypersensitivity
Renal adverse events
Transition to Oral $P2Y_{12}$ Inhibitors

Dyspnea
C-PHOENIX, CHAMPION Pool (Safety Population)

	C-PHOENIX		CHAMPION Pool	
	Cangrelor N=5529 n	Clopidogrel N=5527 n	Cangrelor N=12,565 n	Clopidogrel N=12,542 n
Any Dyspnea AE	65 (1.2%)	18 (0.3%)	148 (1.2%)	50 (0.4%)
Mild	46	14	96	34
Moderate	18	4	51	15
Severe	1	0	1	1
Any Dyspnea SAE	1	0	3	1
Dyspnea leading to study drug D/C	4	0	10	3
Death	0	0	0	0

Hypersensitivity

	C-PHOENIX		CHAMPION Pool	
	Cangrelor N=5529 n	Clopidogrel N=5527 n	Cangrelor N=12,565 n	Clopidogrel N=12,542 n
Hypersensitivity AE	23 (0.4%)	32 (0.6%)	71 (0.6%)	65 (0.5%)
Mild	16	19	50	45
Moderate	4	11	17	18
Severe	3	2	4	2
SAE Hypersensitivity	3	2	5	2
Hypersensitivity leading to D/C	0	0	1	2
Death	0	0	0	0

Renal Adverse Events

C-PHOENIX, CHAMPION POOL (Safety Population)

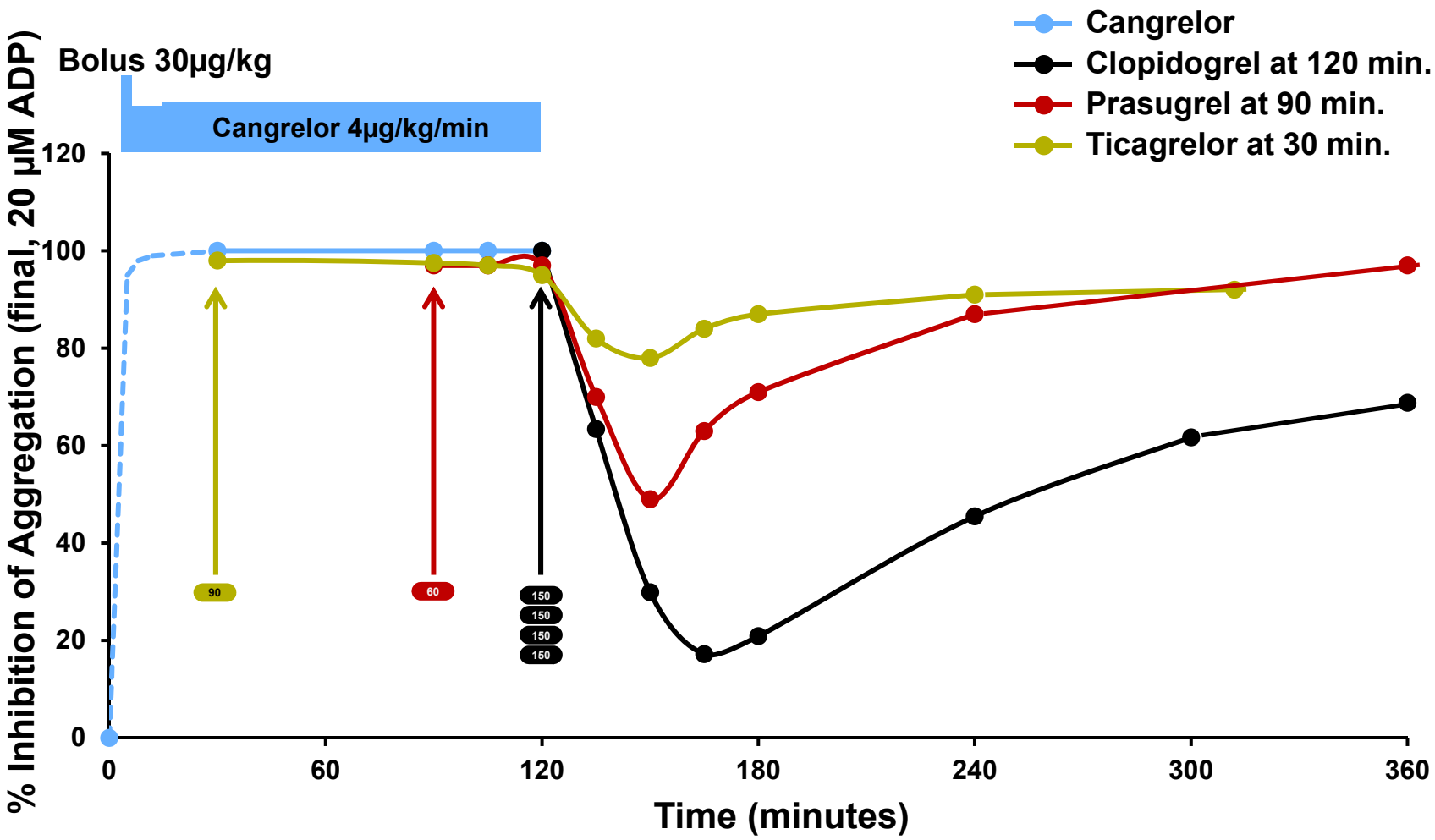
	C-PHOENIX*		CHAMPION Pool	
	Cangrelor N=5529 n	Clopidogrel N=5527 n	Cangrelor N=12,565 n	Clopidogrel N=12,542 n
Renal Failure AE	25 (0.5%)	20 (0.4%)	68 (0.5%)	50 (0.4%)
Mild	16	10	37	20
Moderate	7	10	25	26
Severe	2	0	6	4
Any Renal SAE	9	6	23	12
Renal Failure leading to study drug D/C	2	0	8	6
Death	1	0	1	0

*Renal function data not specifically collected in the PHOENIX trial

Transition to Oral $P2Y_{12}$ Inhibitors

Transition From Cangrelor to Oral $P2Y_{12}$ Inhibitors

MDCO-CAN-12-03, MDCO-CAN-13-01, MDCO-CAN-13-02



Safety Summary

- AEs, SAEs, AEs leading to discontinuation, and deaths within 48 hours similar between Cangrelor and clopidogrel in a study population of >25,000 patients
- Bleeding events, including serious bleeding events were observed more frequently in the Cangrelor arm vs. clopidogrel
- Dyspnea occurred more frequently with Cangrelor
- Renal and hypersensitivity adverse events infrequent and similar between treatment groups
- Transition:
  - Clopidogrel: At end of Cangrelor infusion
  - Prasugrel: Up to 1 hour before end of Cangrelor infusion
  - Ticagrelor: At any time during Cangrelor infusion

Benefit:Risk Profile of Cangrelor

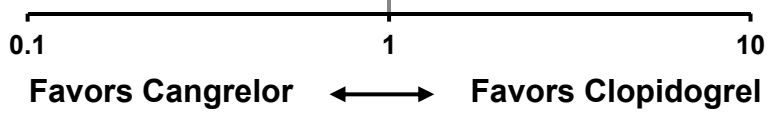
Robert Harrington, MD, FACC, FSCAI
Arthur L. Bloomfield Professor of Medicine
Chairman of Medicine
Stanford University

Unmet Need in PCI Therapy

- 950,000 PCI are performed to treat CAD in the United States each year
- Most PCI procedures (>90%) are ad hoc
  - Single session: diagnostic angiogram and PCI
- $P2Y_{12}$ inhibitors are recommended for all PCI patients and practice patterns are variable
- Bleeding risk must always be balanced against ischemic protection
- Cangrelor offers a new option when existing therapies are suboptimal

Cangrelor Efficacy
C-PHOENIX (mITT)

	Cangrelor N=5470 n (%)	Clopidogrel N=5469 n (%)	OR (95% CI)
Protocol Defined Primary Endpoint			
Death/MI/IDR/ST	257 (4.7)	322 (5.9)	0.78 (0.66, 0.93)
Sensitivity Analyses			
Death/MI/IDR/ARC-ST	230 (4.2)	286 (5.2)	0.80 (0.67, 0.95)
Death/SCAI MI/IDR/ARC-ST	79 (1.4)	114 (2.1)	0.69 (0.52, 0.92)
Death/≥10 ULN MI/IDR/ARC-ST	77 (1.4)	111 (2.0)	0.69 (0.51, 0.92)
Death/Clinical MI/IDR/ARC-ST	86 (1.6)	130 (2.4)	0.66 (0.50, 0.86)
Death/IDR/ARC-ST	43 (0.8)	54 (1.0)	0.79 (0.53, 1.19)
Site Death/MI/IDR/ST	96 (1.8)	121 (2.2)	0.79 (0.60, 1.03)



Bleeding Risk
C-PHOENIX (Safety Population)

	Cangrelor N=5529 n (%)	Control N=5527 n (%)	OR (95% CI)
Non-CABG bleeding	857 (15.5)	602 (10.9)	1.50 (1.34, 1.68)
GUSTO			
Severe/Moderate	32 (0.6)	20 (0.4)	1.60 (0.92, 2.81)
Severe	11 (0.2)	6 (0.1)	1.83 (0.68, 4.96)
Moderate	21 (0.4)	14 (0.3)	1.50 (0.76, 2.96)
TIMI			
Major or minor	45 (0.8)	17 (0.3)	2.66 (1.52, 4.65)
Major	12 (0.2)	6 (0.1)	2.00 (0.75, 5.34)
Minor	33 (0.6)	11 (0.2)	3.01 (1.52, 5.96)

Overall Benefit Risk

FDA Analyses from FDA Briefing Book

PHOENIX Events and Number Needed to Treat

Events	Cangrelor n	Clopidogrel n	Number Needed to Treat
Death	18	18	--
SCAI MI, IDR, ARC-ST	61	96	156
SCAI MI	48	80	171
IDR	13	16	1822
ARC-ST	0	0	--

If a subject had more than one event at 48 hours, then worst outcome counted (death>MI>IDR>ST).

PHOENIX Events and Number Needed to Harm

Events	Cangrelor n	Clopidogrel n	Number Needed to Harm
GUSTO severe or moderate bleed	32	20	461
GUSTO severe	11	6	1106
GUSTO moderate	21	14	790
TIMI major or minor bleed	45	17	198
TIMI major	12	6	922
TIMI minor	33	11	251

The Potential Role of Cangrelor in Clinical Practice

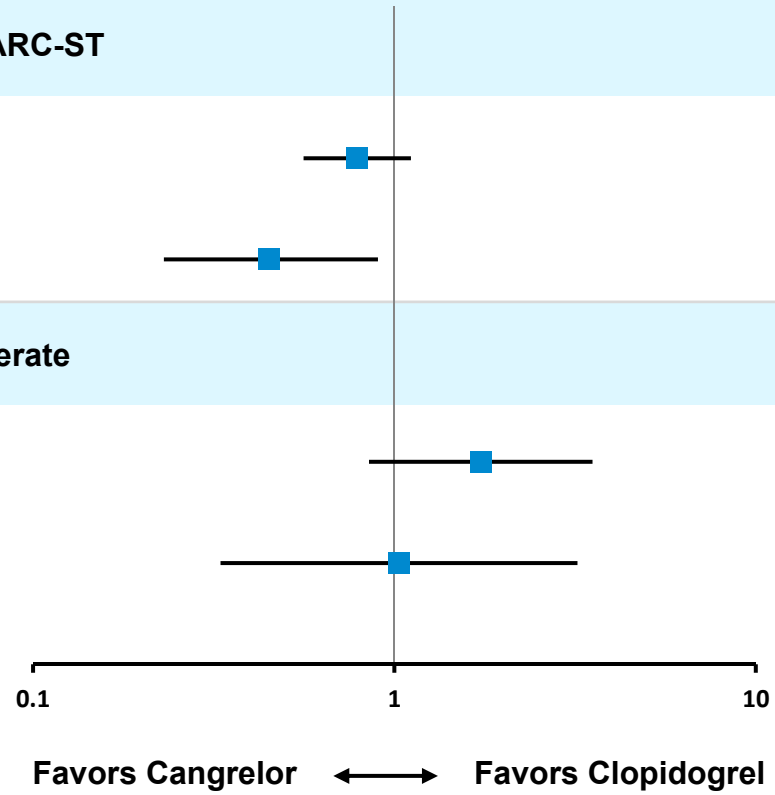
- How I would use Cangrelor in practice:
  - Patients who are not preloaded with oral $P2Y_{12}$ inhibitors
  - Patients undergoing ad hoc PCI
  - Physicians choose not to administer or patients are unable to receive:
    - Oral $P2Y_{12}$ inhibitors periprocedurally
    - Glycoprotein IIb/IIIa receptor antagonists

Cangrelor Offers a Favorable Benefit-Risk Profile

- Significant reductions in clinically important PCI-related thrombotic events
  - Sensitivity analyses support the consistency of the efficacy benefit
- More bleeding events, including more serious bleeding events were observed in the Cangrelor arm vs. clopidogrel
- Cangrelor prevents more clinically meaningful MI events than is associated with serious bleeds
- Benefits of administration of Cangrelor as an adjunct to PCI outweigh the risks

Backup Slides Shown

Anticoagulant Subgroup
C-PHOENIX (mITT and Safety Population)

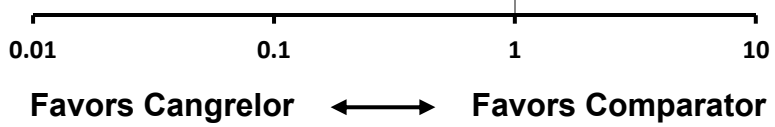


	Cangrelor	Clopidogrel	OR (95% CI)
Death/SCAI MI/IDR/ARC-ST			
Heparin only	60/3800 (1.6)	75/3766 (2.0)	0.79 (0.56, 1.11)
Angiomax only	12/1014 (1.2)	27/1045 (2.6)	0.45 (0.23, 0.90)
GUSTO Severe/Moderate			
Heparin only	21/3838 (0.5)	12/3799 (0.3)	1.74 (0.85, 3.53)
Angiomax only	6/1021 (0.6)	6/1055 (0.6)	1.03 (0.33, 3.21)

Subgroup Analysis of Death/SCAI MI/IDR/ARC-ST at 48 Hour (3 of 4)

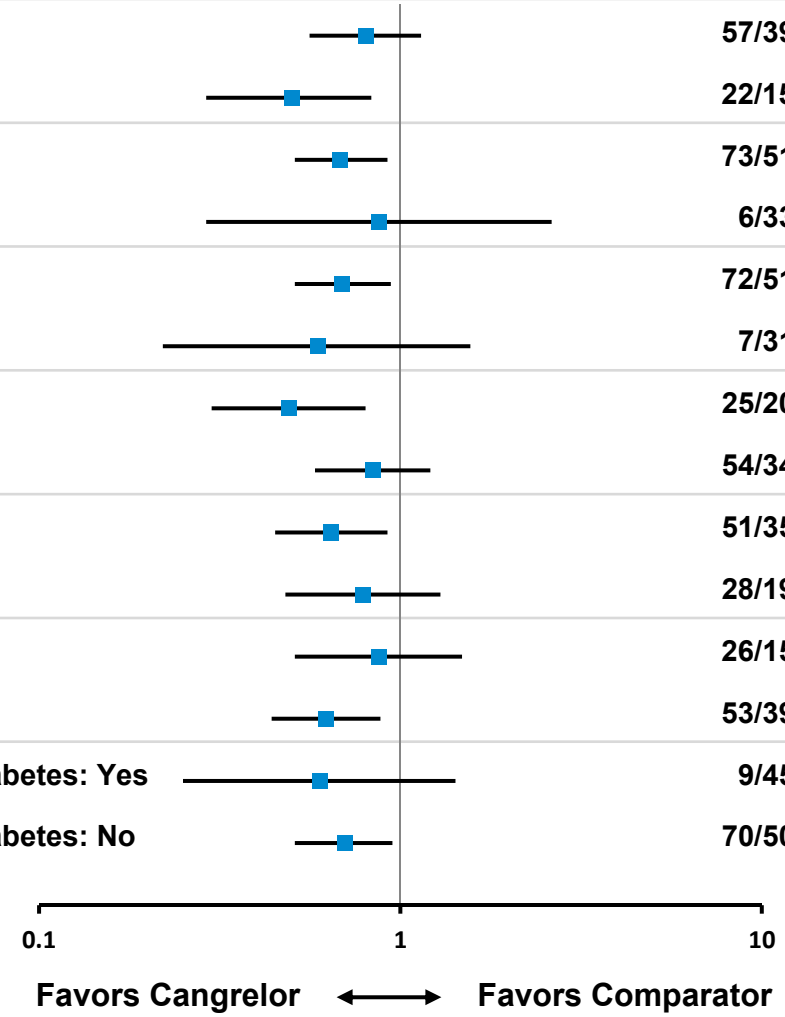
C-PHOENIX (mITT)

	Cangrelor	Clopidogrel	OR [95% CI]	P [Int]
Prior MI	18/1092 (1.6)	31/1175 (2.6)	0.62 (0.34,1.11)	0.595
No Prior MI	61/4347 (1.4)	80/4255 (1.9)	0.74 (0.53,1.04)	
Prior TIA/Stroke	2/271 (0.7)	6/244 (2.5)	0.29 (0.06,1.48)	0.272
No Prior TIA/Stroke	77/5182 (1.5)	107/5207 (2.1)	0.72 (0.54,0.97)	
History of PAD: Yes	4/447 (0.9)	17/385 (4.4)	0.20 (0.07,0.59)	0.011
History of PAD: No	75/4958 (1.5)	96/5033 (1.9)	0.79 (0.58,1.07)	
History of CHF: Yes	12/552 (2.2)	14/584 (2.4)	0.90 (0.41,1.97)	0.477
History of CHF: No	67/4906 (1.4)	99/4871 (2.0)	0.67 (0.49,0.91)	
Heparin Only	60/3800 (1.6)	75/3766 (2.0)	0.79 (0.56,1.11)	0.150
Angiomax Only	12/1014 (1.2)	27/1045 (2.6)	0.45 (0.23,0.90)	
Femoral	65/4053 (1.6)	92/4011 (2.3)	0.69 (0.50,0.96)	0.860
Radial	14/1408 (1.0)	22/1444 (1.5)	0.65 (0.33,1.27)	
# Vessels = 1	59/4543 (1.3)	84/4603 (1.8)	0.71 (0.51,0.99)	0.335
# Vessels ≥2	14/878 (1.6)	26/817 (3.2)	0.49 (0.26,0.95)	



Subgroup Analysis of Death/SCAI MI/IDR/ARC-ST at 48 Hour (2 of 4)

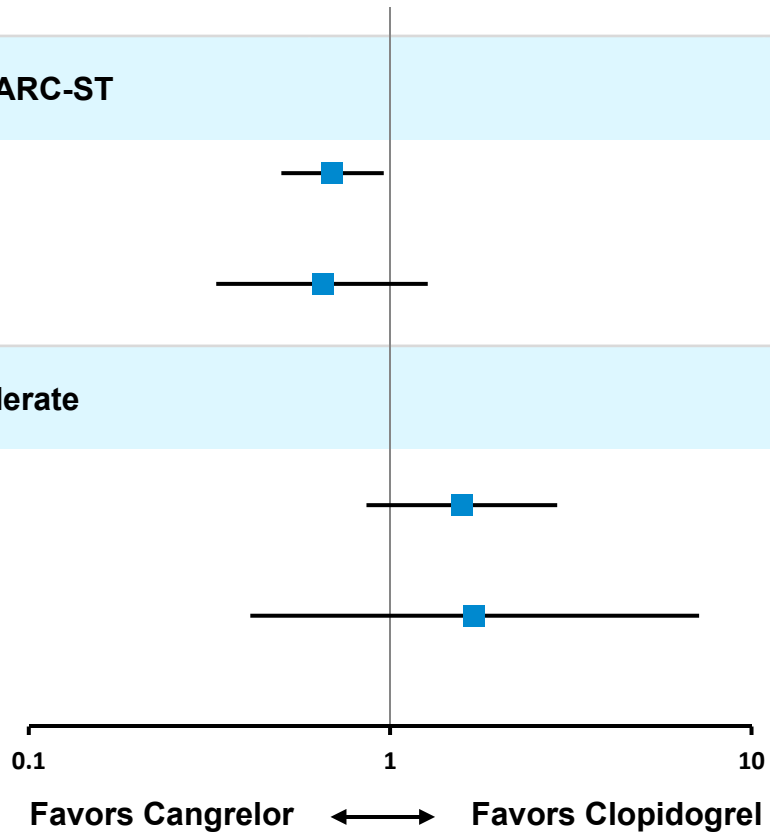
C-PHOENIX (mITT)



	Cangrelor	Clopidogrel	OR [95% CI]	P [Int]
Male	57/3913 (1.5)	72/3976 (1.8)	0.80 (0.56,1.14)	0.131
Female	22/1557 (1.4)	42/1493 (2.8)	0.50 (0.29,0.83)	
Race: White	73/5130 (1.4)	106/5119 (2.1)	0.68 (0.51,0.92)	0.676
Race: Non-white	6/337 (1.8)	7/343 (2.0)	0.87 (0.29,2.62)	
Weight ≥ 60	72/5155 (1.4)	104/5201 (2.0)	0.69 (0.51,0.94)	0.747
Weight < 60	7/315 (2.2)	10/268 (3.7)	0.59 (0.22,1.56)	
United States	25/2048 (1.2)	50/2049 (2.4)	0.49 (0.30,0.80)	0.085
Rest of World	54/3422 (1.6)	64/3420 (1.9)	0.84 (0.58,1.21)	
Biomarker Normal	51/3519 (1.4)	77/3431 (2.2)	0.64 (0.45,0.92)	0.506
Biomarker Abnormal	28/1946 (1.4)	37/2034 (1.8)	0.79 (0.48,1.29)	
Diabetes: yes	26/1519 (1.7)	30/1535 (2.0)	0.87 (0.51,1.48)	0.295
Diabetes: no	53/3943 (1.3)	84/3927 (2.1)	0.62 (0.44,0.88)	
Insulin-Dependent Diabetes: Yes	9/459 (2.0)	13/404 (3.2)	0.60 (0.25,1.42)	0.754
Insulin-Dependent Diabetes: No	70/5011 (1.4)	101/5056 (2.0)	0.70 (0.51,0.95)	

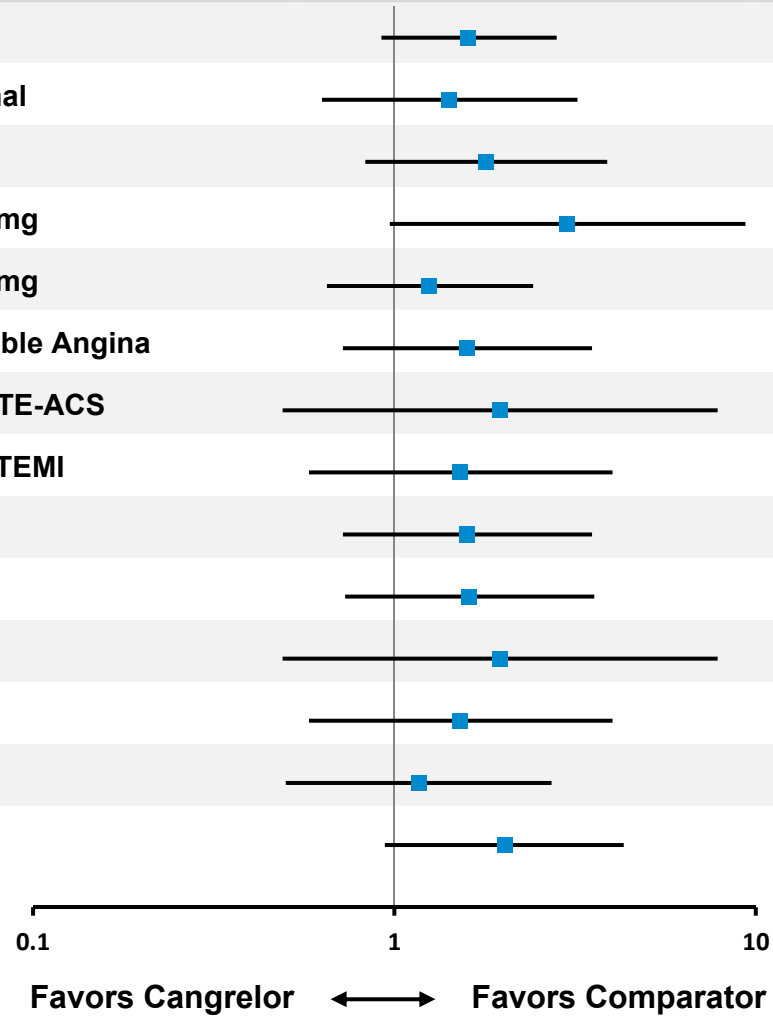
Access Site Subgroup

C-PHOENIX (mITT and Safety Population)



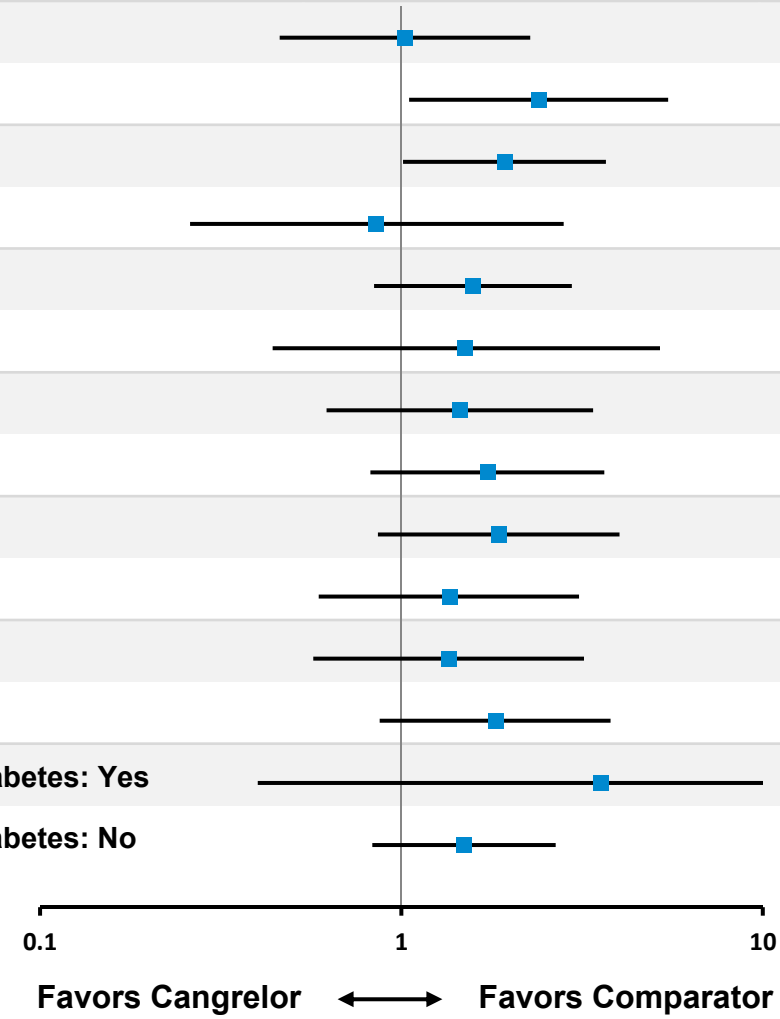
	Cangrelor	Clopidogrel	OR (95% CI)
Death/SCAI MI/IDR/ARC-ST			
Femoral	65/4053 (1.6)	92/4011 (2.3)	0.69 (0.50,0.96)
Radial	14/1408 (1.0)	22/1444 (1.5)	0.65 (0.33,1.27)
GUSTO Severe/Moderate			
Femoral	27/4052 (0.7)	17/4012 (0.4)	1.58 (0.86, 2.90)
Radial	5/1411 (0.4)	3/1444 (0.2)	1.71 (0.41, 7.16)

Figure 6: Forest Plot for 48 Hour Non-CABG GUSTO Severe/Moderate Bleeding by Subgroup (Safety Population) (1 of 4)



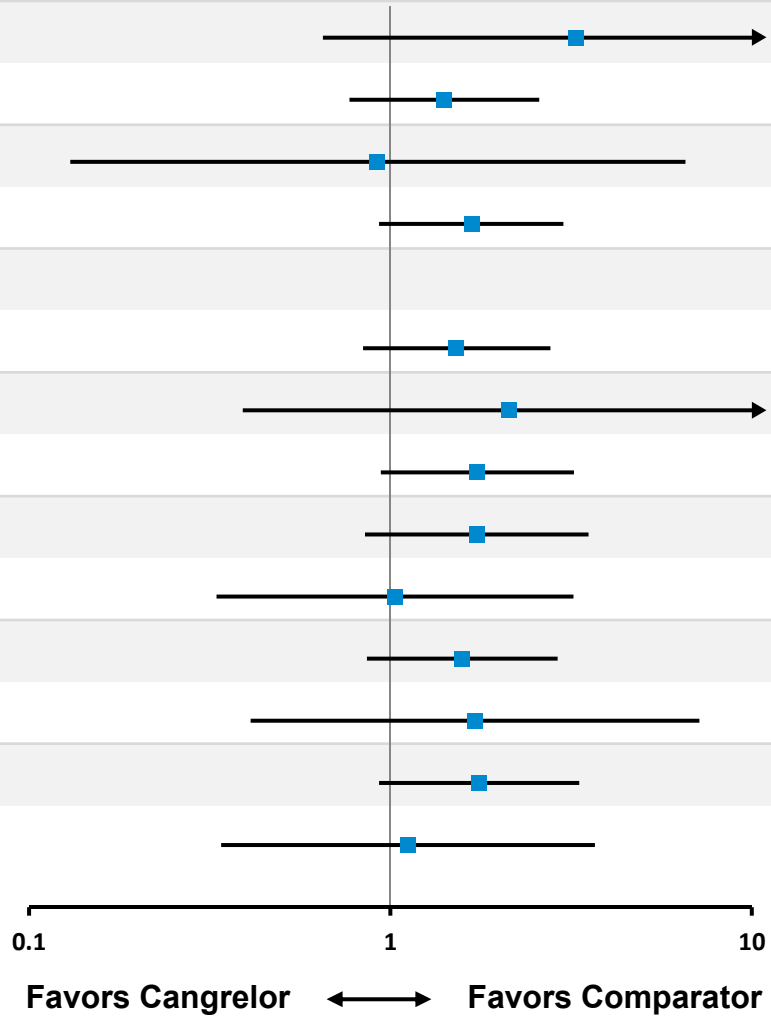
	Cangrelor	Clopidogrel	OR [95% CI]
Overall	32/5529 (0.6)	20/5527 (0.4)	1.60 (0.92, 2.81)
Patient Status Abnormal	14/1963 (0.7)	10/1988 (0.5)	1.42 (0.63, 3.21)
Patient Status Normal	18/3566 (0.5)	10/3539 (0.3)	1.79 (0.83, 3.88)
Clopidogrel Dose 300 mg	12/1428 (0.8)	4/1425 (0.3)	3.01 (0.97, 9.36)
Clopidogrel Dose 600 mg	20/4101 (0.5)	16/4102 (0.4)	1.25 (0.65, 2.42)
IVRS Patient Type: Stable Angina	16/3201 (0.5)	10/3184 (0.3)	1.59 (0.72, 3.52)
IVRS Patient Type: NSTE-ACS	6/1468 (0.4)	3/1433 (0.2)	1.96 (0.49, 7.84)
IVRS Patient TypeP: STEMI	10/860 (1.2)	7/910 (0.8)	1.52 (0.58, 4.01)
IVRS SA	16/3201 (0.5)	10/3184 (0.3)	1.59 (0.72, 3.52)
IVRS ACS	16/2328 (0.7)	10/2343 (0.4)	1.61 (0.73, 3.57)
IVRS NSTE-ACS	6/1468 (0.4)	3/1433 (0.2)	1.96 (0.49, 7.84)
IVRS STEMI	10/860 (1.2)	7/910 (0.8)	1.52 (0.58, 4.01)
Age ≥ 75	12/1025 (1.2)	10/996 (1.0)	1.17 (0.50, 2.72)
Age < 75	20/4504 (0.4)	10/4531 (0.2)	2.02 (0.94, 4.31)

Figure 6: Forest Plot for 48 Hour Non-CABG GUSTO Severe/Moderate Bleeding by Subgroup (Safety Population) (2 of 4)



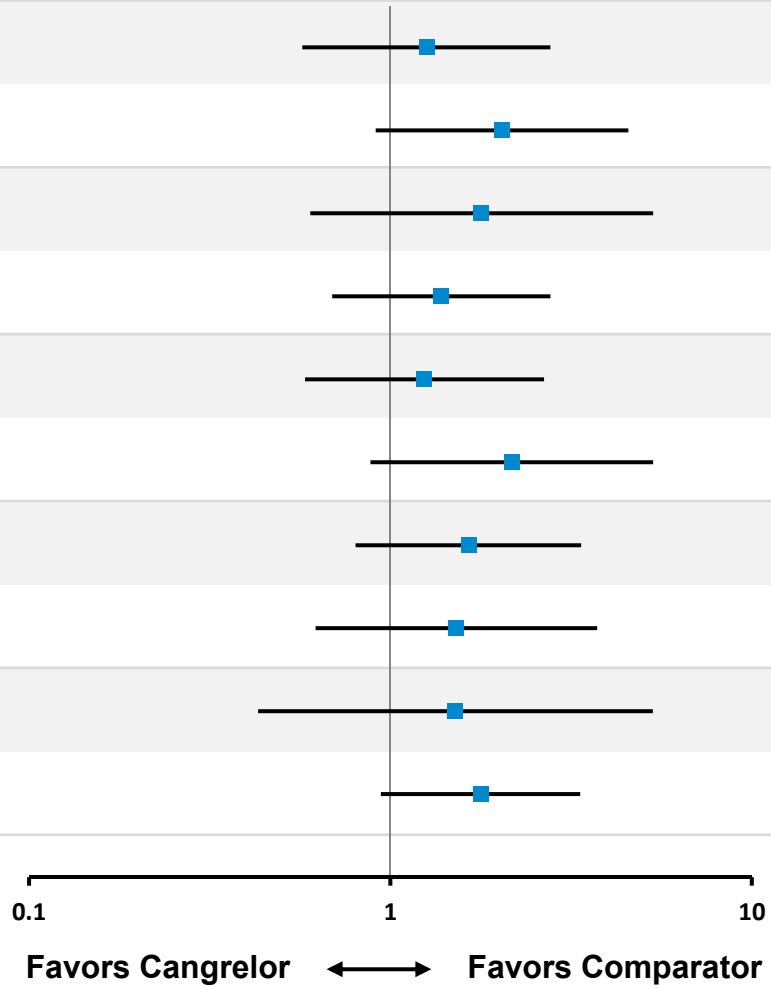
	Cangrelor	Clopidogrel	OR [95% CI]
Male	12/3946 (0.3)	12/4018 (0.3)	1.02 (0.46, 2.27)
Female	20/1583 (1.3)	8/1509 (0.5)	2.40 (1.05, 5.47)
Race: White	27/5188 (0.5)	14/5175 (0.3)	1.93 (1.01, 3.68)
Race: Non-white	5/338 (1.5)	6/345 (1.7)	0.85 (0.26, 2.81)
Weight ≥ 60	25/5210 (0.5)	16/5255 (0.3)	1.58 (0.84, 2.96)
Weight < 60	7/319 (2.2)	4/272 (1.5)	1.50 (0.44, 5.19)
United States	13/2062 (0.6)	9/2062 (0.4)	1.45 (0.62, 3.39)
Most of World	19/3467 (0.5)	11/3465 (0.3)	1.73 (0.82, 3.64)
Biomarker Normal	19/3540 (0.5)	10/3458 (0.3)	1.86 (0.86, 4.01)
Biomarker Abnormal	13/1983 (0.7)	10/2064 (0.5)	1.36 (0.59, 3.10)
Diabetes: yes	12/1535 (0.8)	9/1547 (0.6)	1.35 (0.57, 3.20)
Diabetes: no	20/3986 (0.5)	11/3972 (0.3)	1.82 (0.87, 3.79)
Insulin-Dependent Diabetes: Yes	4/461 (0.9)	1/408 (0.2)	3.56 (0.40, 32.00)
Insulin-Dependent Diabetes: No	28/5068 (0.6)	19/5119 (0.4)	1.49 (0.83, 2.67)

Figure 6: Forest Plot for 48 Hour Non-CABG GUSTO Severe/Moderate Bleeding by Subgroup (Safety Population) (3 of 4)



	Cangrelor	Clopidogrel	OR [95% CI]
Prior MI	6/1101 (0.5)	2/1187 (0.2)	3.25 (0.65, 16.12)
No Prior MI	26/4397 (0.6)	18/4299 (0.4)	1.41 (0.77, 2.58)
Prior TIA/Stroke	2/275 (0.7)	2/252 (0.8)	0.92 (0.13, 6.55)
No Prior TIA/Stroke	30/5236 (0.6)	18/5256 (0.3)	1.68 (0.93, 3.01)
History of PAD: yes	5/448 (1.1)	0/389 (0.0)	
History of PAD: no	27/5016 (0.5)	18/5086 (0.4)	1.52 (0.84, 2.77)
History of CHF: yes	4/557 (0.7)	2/592 (0.3)	2.13 (0.39, 11.70)
History of CHF: no	28/4960 (0.6)	16/4920 (0.3)	1.74 (0.94, 3.22)
Heparin only	21/3838 (0.5)	12/3799 (0.3)	1.74 (0.85, 3.53)
Angiomax only	6/1021 (0.6)	6/1055 (0.6)	1.03 (0.33, 3.21)
Femoral	27/4052 (0.7)	17/4012 (0.4)	1.58 (0.86, 2.90)
Radial	5/1411 (0.4)	3/1444 (0.2)	1.71 (0.41, 7.16)
# Vessels = 1	26/4545 (0.6)	15/4604 (0.3)	1.76 (0.93, 3.33)
# Vessels ≥2	6/878 (0.7)	5/817 (0.6)	1.12 (0.34, 3.68)

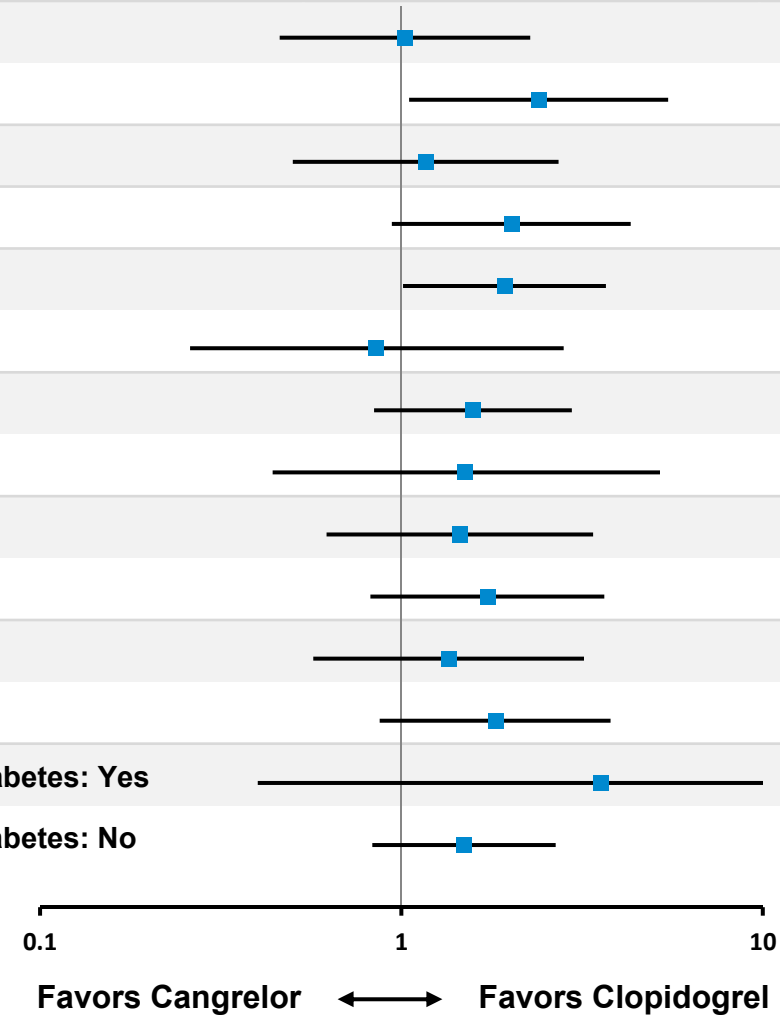
Figure 6: Forest Plot for 48 Hour Non-CABG GUSTO Severe/Moderate Bleeding by Subgroup (Safety Population) (4 of 4)



	Cangrelor	Clopidogrel	OR [95% CI]
Drug-Eluting Stent	14/3061 (0.5)	11/3020 (0.4)	1.26 (0.57, 2.77)
Bare Metal Stent	18/2468 (0.7)	9/2507 (0.4)	2.04 (0.91, 4.55)
Aspirin ≤100 mg	9/2722 (0.3)	5/2693 (0.2)	1.78 (0.60, 5.33)
Aspirin >100 mg	19/2125 (0.9)	14/2163 (0.6)	1.38 (0.69, 2.77)
Load before PCI: Yes	15/3460 (0.4)	12/3442 (0.3)	1.24 (0.58, 2.66)
Load before PCI: No	15/1982 (0.8)	7/1997 (0.4)	2.17 (0.88, 5.33)
Infusion ≤129 minutes	20/2864 (0.7)	12/2820 (0.4)	1.65 (0.80, 3.37)
Infusion >129 minutes	12/2659 (0.5)	8/2697 (0.3)	1.52 (0.62, 3.73)
Peri Proc GPI	5/153 (3.3)	5/229 (2.2)	1.51 (0.43, 5.32)
No Peri Proc GPI	27/5376 (0.5)	15/5297 (0.3)	1.78 (0.94, 3.35)

48 hour Non-CABG GUSTO Severe/Moderate Bleeding by Subgroup

C-PHOENIX (Safety Population)



	Cangrelor	Clopidogrel	OR [95% CI]
Male	12/3946 (0.3)	12/4018 (0.3)	1.02 (0.46, 2.27)
Female	20/1583 (1.3)	8/1509 (0.5)	2.40 (1.05, 5.47)
Age ≥ 75	12/1025 (1.2)	10/996 (1.0)	1.17 (0.50, 2.72)
Age < 75	20/4504 (0.4)	10/4531 (0.2)	2.02 (0.94, 4.31)
Race: White	27/5188 (0.5)	14/5175 (0.3)	1.93 (1.01, 3.68)
Race: Non-white	5/338 (1.5)	6/345 (1.7)	0.85 (0.26, 2.81)
Weight ≥ 60	25/5210 (0.5)	16/5255 (0.3)	1.58 (0.84, 2.96)
Weight < 60	7/319 (2.2)	4/272 (1.5)	1.50 (0.44, 5.19)
United States	13/2062 (0.6)	9/2062 (0.4)	1.45 (0.62, 3.39)
Rest of World	19/3467 (0.5)	11/3465 (0.3)	1.73 (0.82, 3.64)
Diabetes: yes	12/1535 (0.8)	9/1547 (0.6)	1.35 (0.57, 3.20)
Diabetes: no	20/3986 (0.5)	11/3972 (0.3)	1.82 (0.87, 3.79)
Insulin-Dependent Diabetes: Yes	4/461 (0.9)	1/408 (0.2)	3.56 (0.40, 32.00)
Insulin-Dependent Diabetes: No	28/5068 (0.6)	19/5119 (0.4)	1.49 (0.83, 2.67)

Table 1: Primary Efficacy Endpoint (Death/MI/IDR) at 48 Hours in C-PCI and C-PLATFORM (mITT Population)

Death/MI/IDR	Cangrelor	Clopidogrel	OR (95% CI)	p-value
C-PCI	308/4335 (7.1)	293/4312 (6.8)	1.05 (0.89, 1.24)	0.5709
C-Platform	185/2654 (7.0)	210/2641 (8.0)	0.87 (0.71, 1.07)	0.1746

IDR=ischemia driven revascularization; MI=myocardial infarction

Table 2: Bleeding in C-PCI and C-PLATFORM POOL

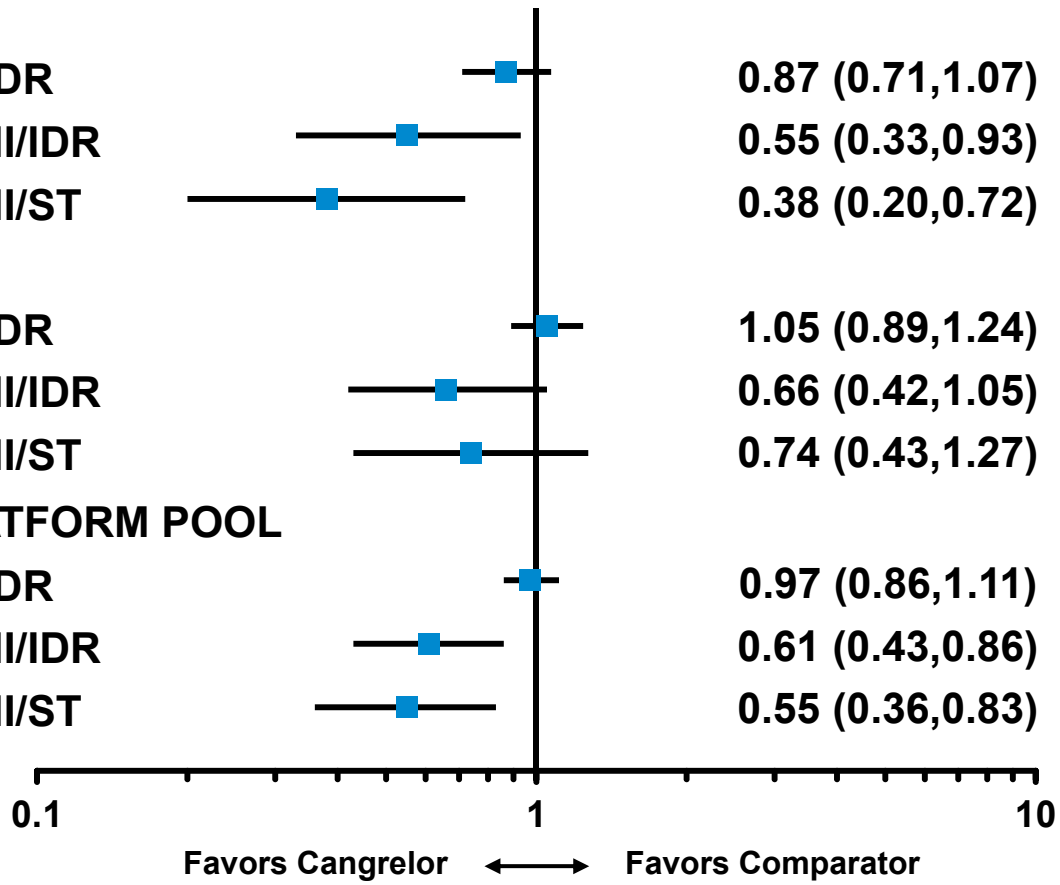
	Cangrelor	Clopidogrel	OR (95% CI)
All GUSTO Bleeding			
GPI - No	952/5636 (16.9)	694/5597 (12.4)	1.44 (1.29, 1.60)
GPI - Yes	388/1396 (27.8)	401/1414 (28.4)	0.97 (0.82, 1.15)
GUSTO Moderate/Severe			
GPI - No	52/5636 (0.9)	32/5597 (0.6)	1.62 (1.04, 2.52)
GPI - Yes	20/1396 (1.4)	28/1414 (2.0)	0.72 (0.40, 1.28)
TIMI Major/Minor			
GPI - No	47/5636 (0.8)	32/5597 (0.6)	1.46 (0.93, 2.30)
GPI - Yes	34/1396 (2.4)	32/1414 (2.3)	1.08 (0.66, 1.76)
ACUITY Major			
GPI - No	223/5636 (4.0)	137/5597 (2.4)	1.64 (1.32, 2.04)
GPI - Yes	73/1396 (5.2)	74/1414 (5.2)	1.00 (0.72, 1.39)

GPI=glycoprotein inhibitor; GUSTO=Global Use of Strategies to Open Occluded Arteries; TIMI=Thrombolysis in Myocardial Infarction

Efficacy Findings

C-PCI, C-PLATFORM and C-PCI & C-PLATFORM Pool (mITT)

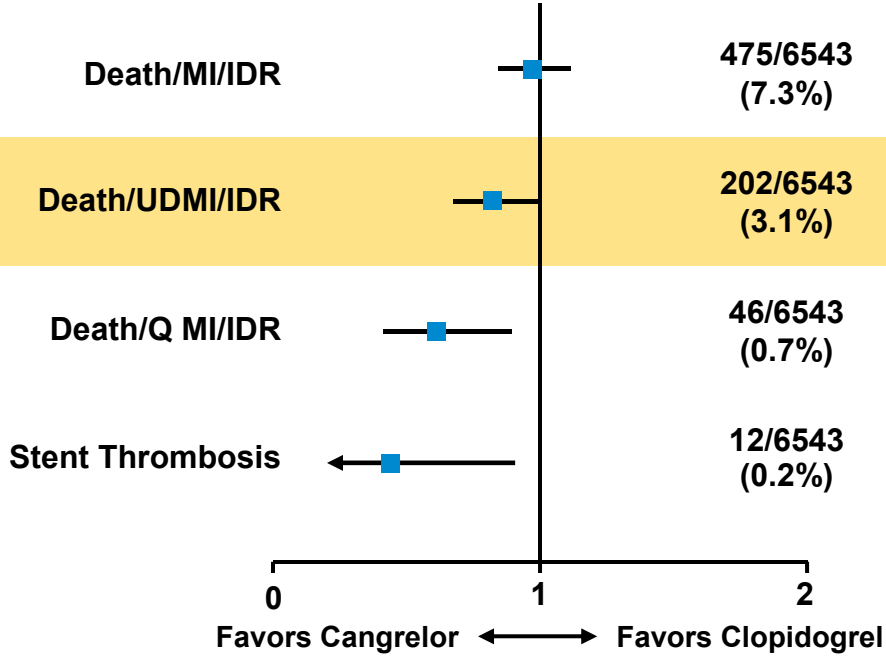
48-hour Events	Odd Ratio (95% CI)	P value
C-PLATFORM		
Death/MI/IDR	0.87 (0.71,1.07)	0.1746
Death/Q-MI/IDR	0.55 (0.33,0.93)	0.0243
Death/Q-MI/ST	0.38 (0.20,0.72)	0.0029
C-PCI*		
Death/MI/IDR	1.05 (0.89,1.24)	0.5709
Death/Q-MI/IDR	0.66 (0.42,1.05)	0.0801
Death/Q-MI/ST	0.74 (0.43,1.27)	0.2681
C-PCI & C-PLATFORM POOL		
Death/MI/IDR	0.97 (0.86,1.11)	0.6793
Death/Q-MI/IDR	0.61 (0.43,0.86)	0.0049
Death/Q-MI/ST	0.55 (0.36,0.83)	0.0040



*PCI study results include STEMI population

UDMI Analysis
CHAMPION PCI/PLATFORM Pooled

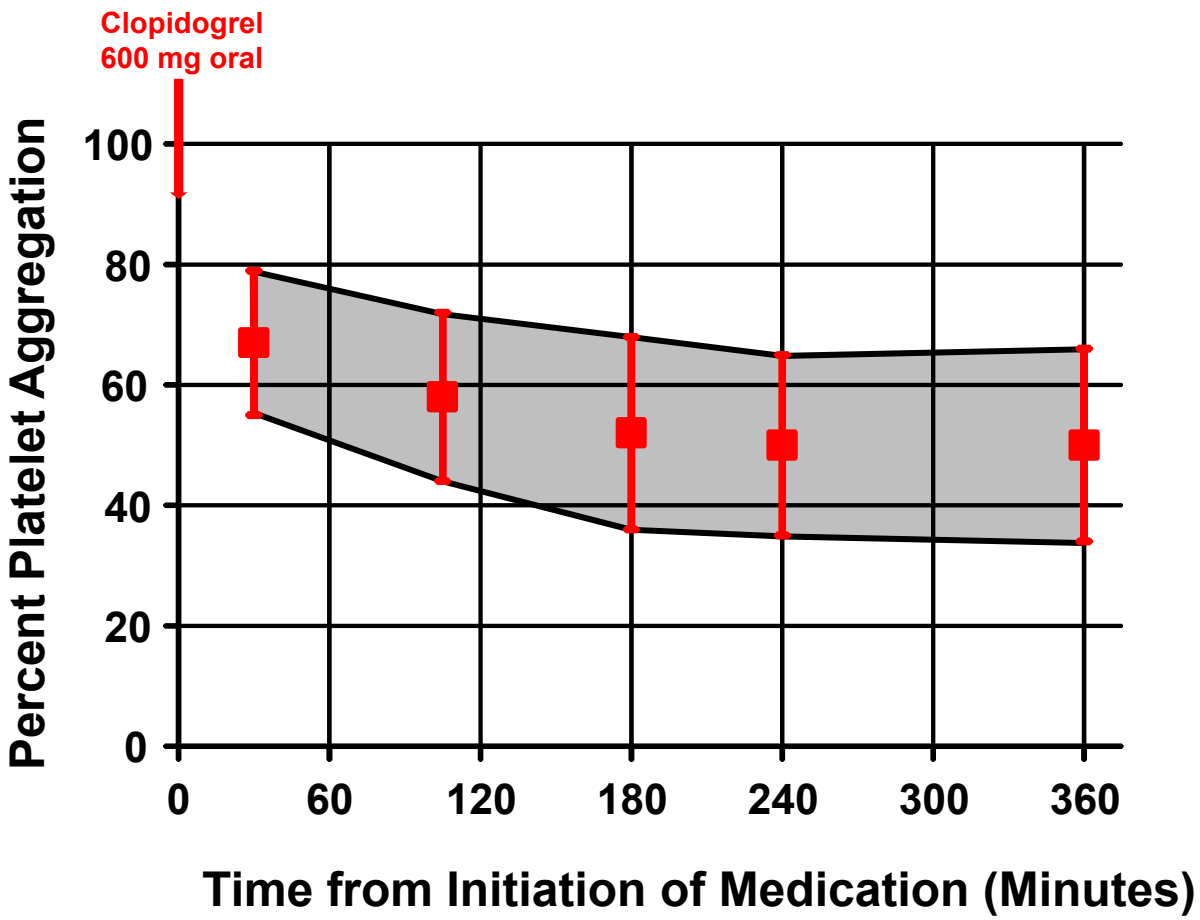
- Post-hoc pooled analysis modeled after UDMI
  - Baseline normal subset | CEC adjudicated CKMB MI
  - Baseline abnormal subset | QMI
- Significant treatment effect observed at 48h



	Risk ratio ± 95% CI	Cangrelor n/N (%)	Clopidogrel n/N (%)	RR (95% CI)	P value
Death/MI/IDR		475/6543 (7.3%)	486/6506 (7.5%)	0.97 (0.86,1.10)	0.646
Death/UDMI/IDR		202/6543 (3.1%)	244/6506 (3.8%)	0.82 (0.68,0.99)	0.037
Death/Q MI/IDR		46/6543 (0.7%)	75/6506 (1.2%)	0.61 (0.42,0.88)	0.008
Stent Thrombosis		12/6543 (0.2%)	27/6506 (0.4%)	0.44 (0.22,0.87)	0.018

EF-625

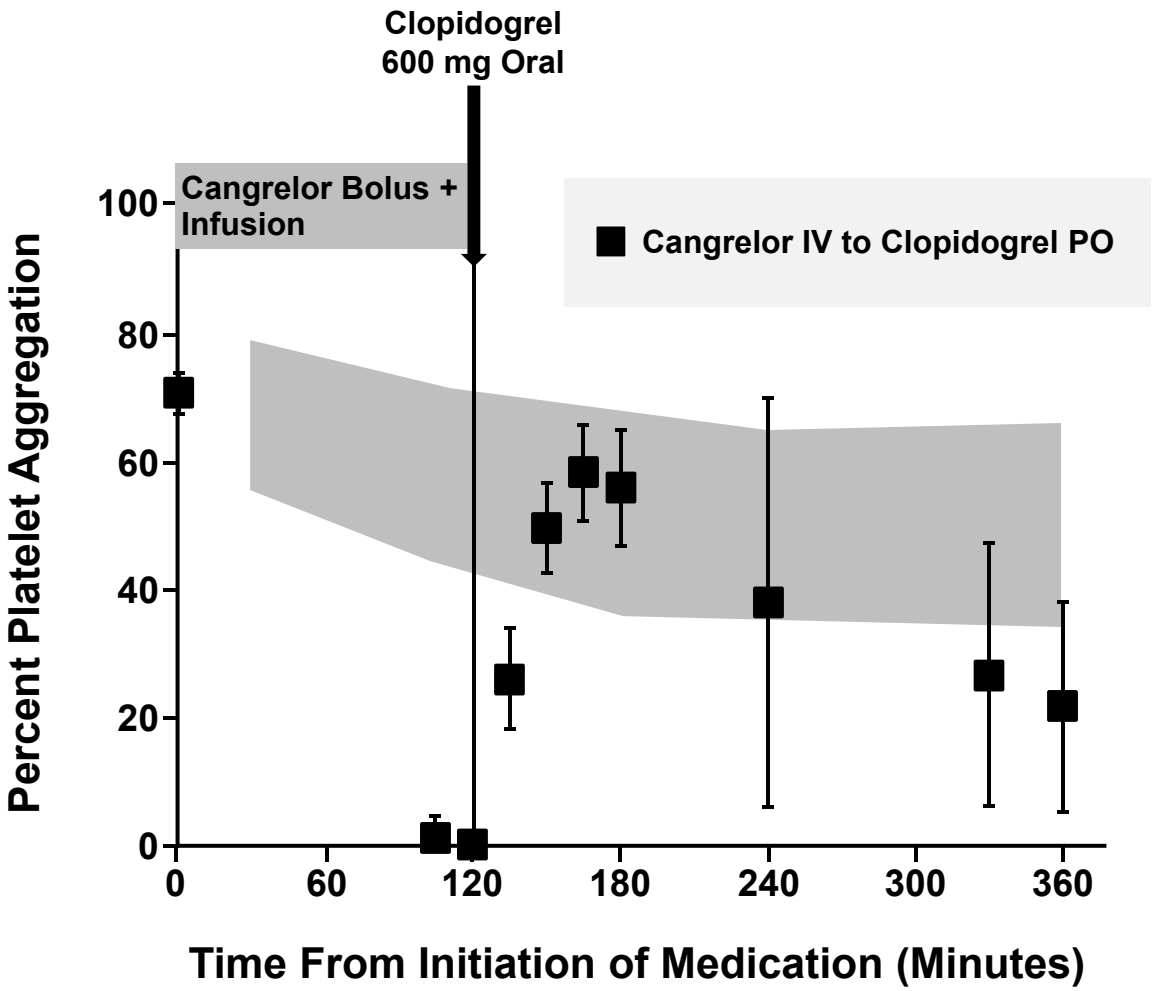
Time Course of Clopidogrel Onset



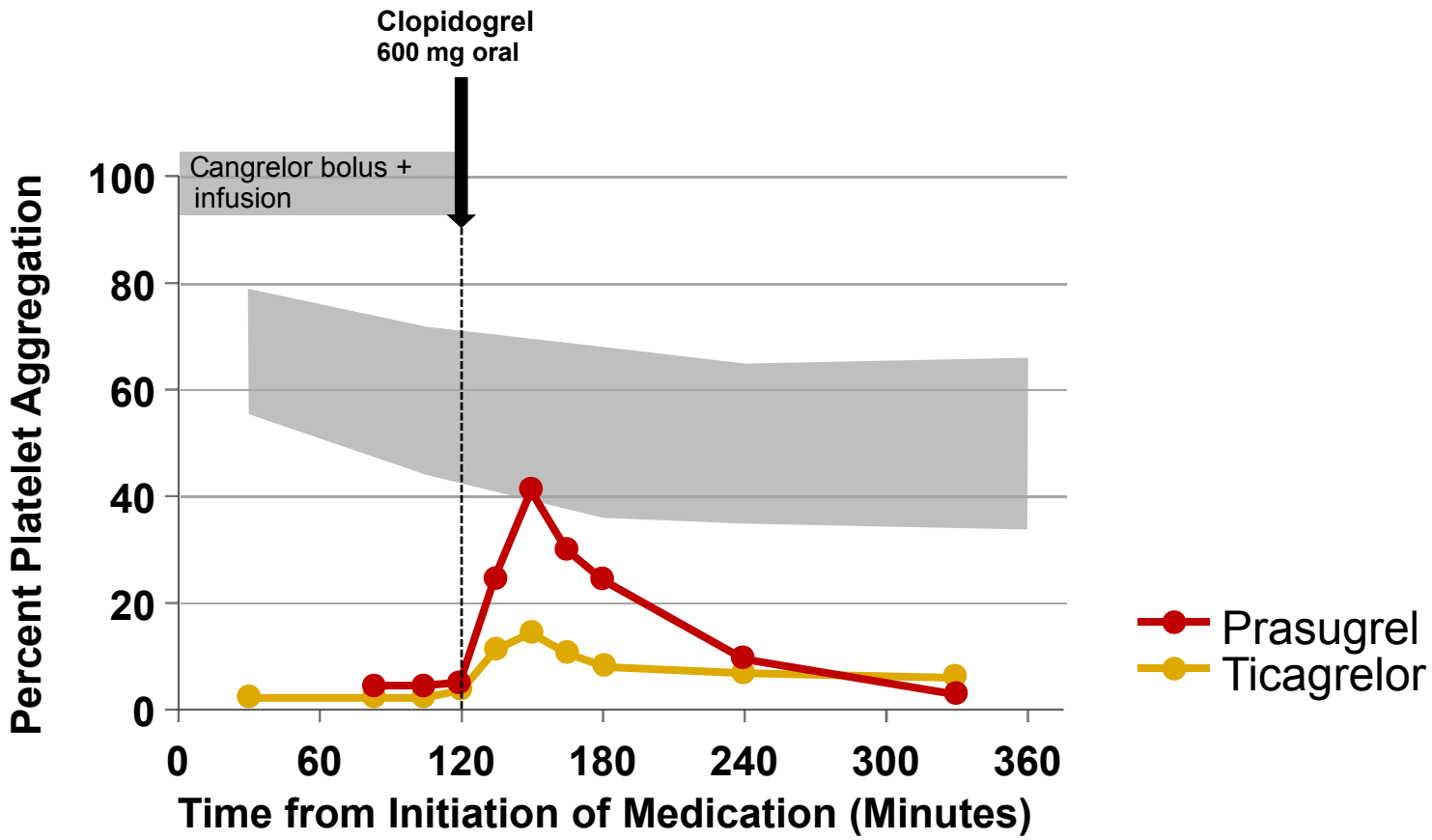
Platelet Aggregation (%) Ex Vivo in Response to 20 μM ADP After Clopidogrel 600 Mg Administered for PCI

Adapted from Hochholzer et al. 2005

Transition Regimens: Cangrelor to Oral



Platelet Aggregation During Transition From Cangrelor to Prasugrel or Ticagrelor

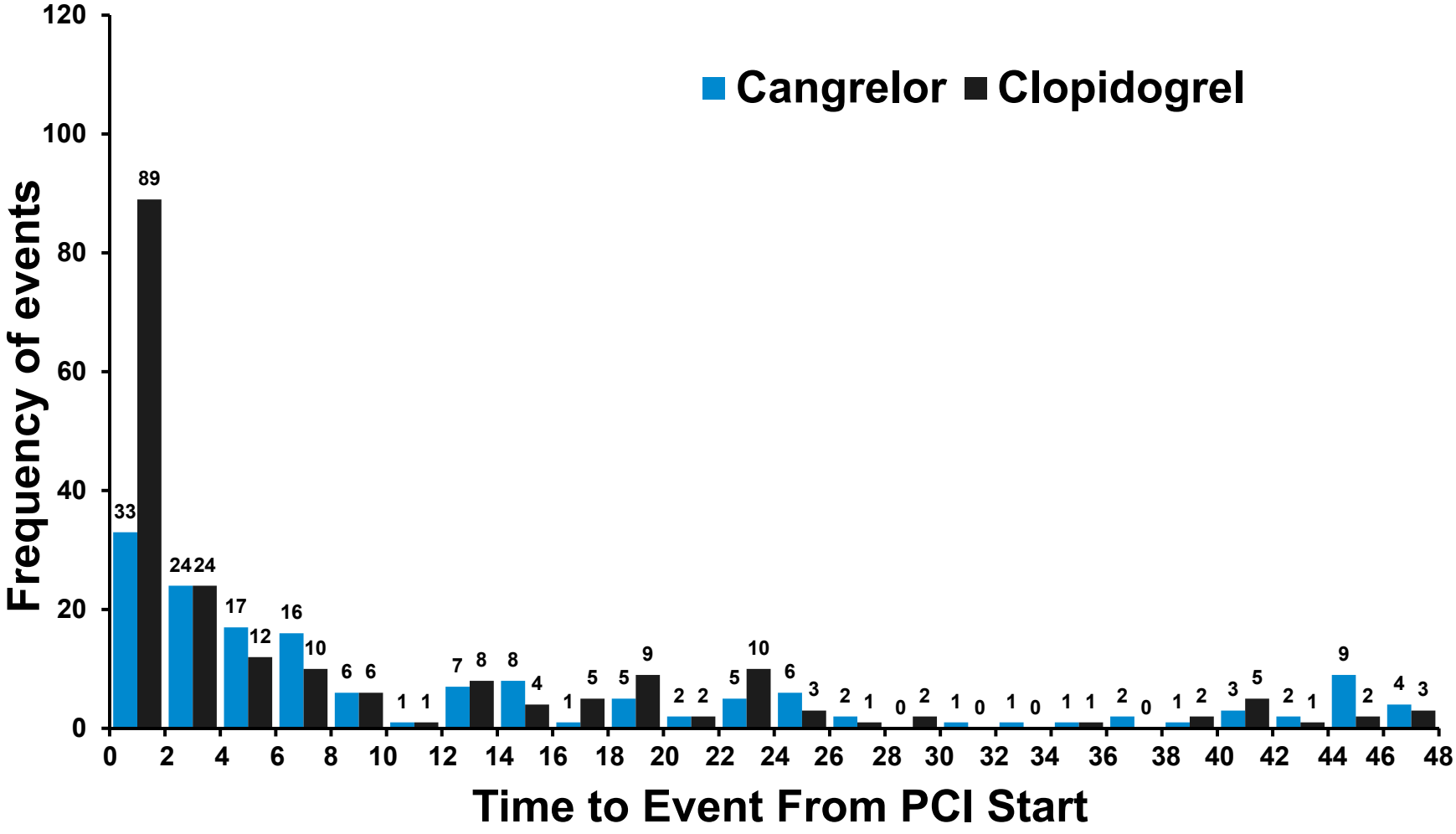


Data are from MDCO-CAN-12-0. Platelet Aggregation (%) Ex Vivo in Response to 20 μM ADP with Cangrelor Bolus (30 μg) Followed by an Infusion for 2 Hours (4 μg/kg/h) and then by Clopidogrel 600 mg Given Orally; N=3

For reference, range of platelet aggregation following oral dose of clopidogrel 600 mg given at time-0 from Hochholzer et al [2005] is shown as grey area

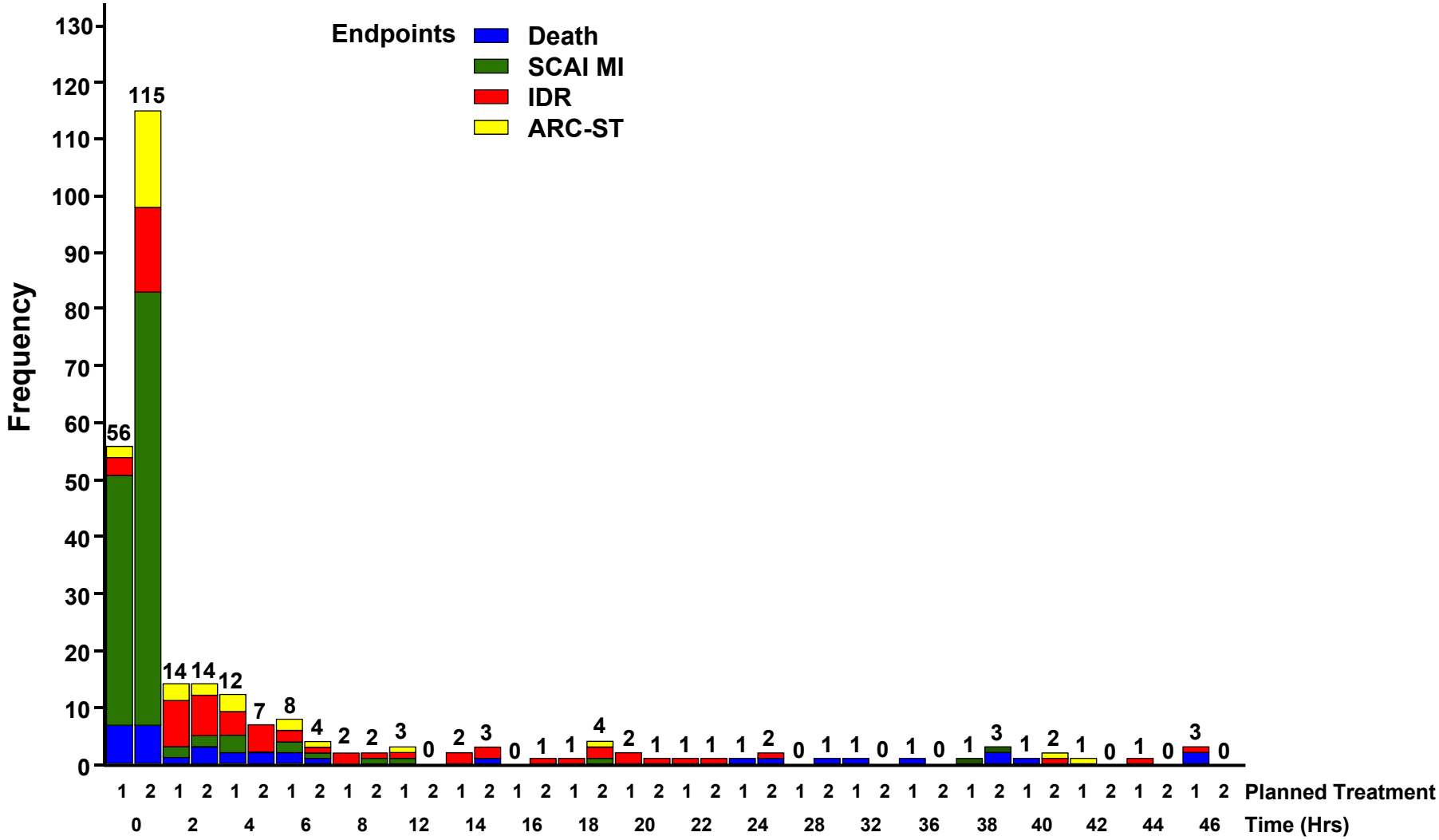
Time to Site-Reported Death/MI/IDR/ARC-ST from PCI Start

C-PHOENIX (mITT)

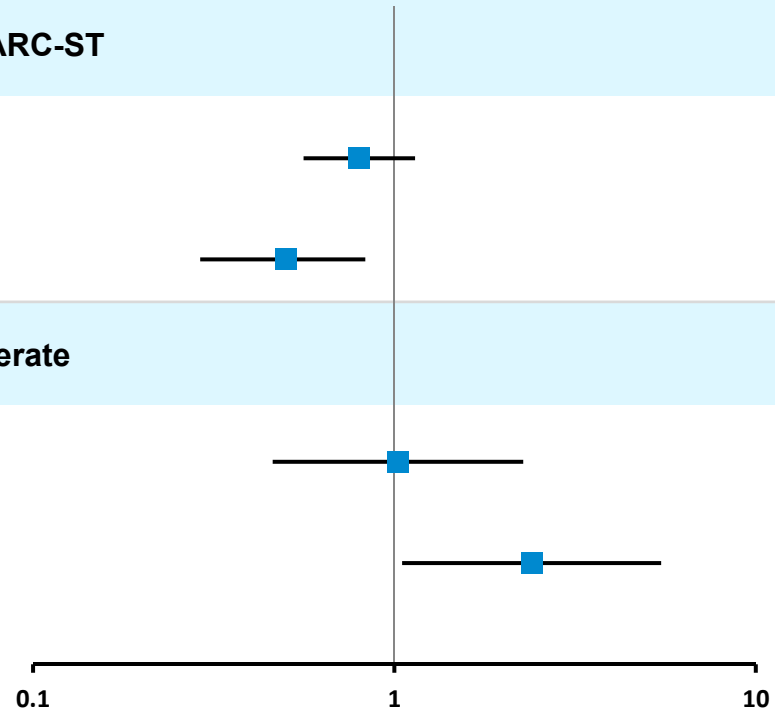


EF-638

Multiple Events - Death/SCAI MI/IDR/ARC-ST Time to Event from PCI Start C-PHOENIX (mITT)



Gender Subgroup
C-PHOENIX (mITT and Safety Population)

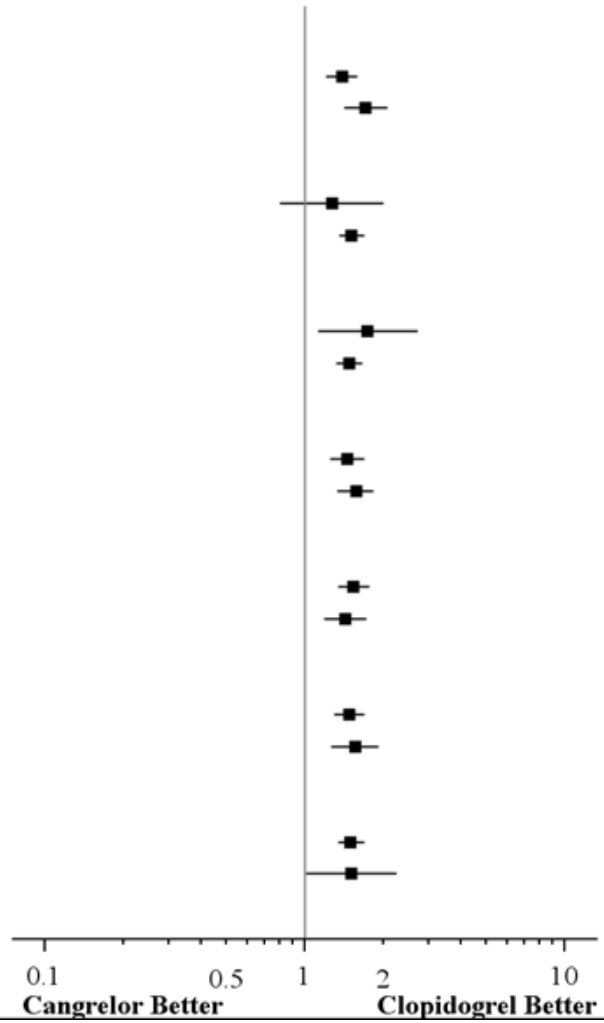


	Cangrelor	Clopidogrel	OR (95% CI)
Death/SCAI MI/IDR/ARC-ST			
Male	57/3913 (1.5)	72/3976 (1.8)	0.80 (0.56,1.14)
Female	22/1557 (1.4)	42/1493 (2.8)	0.50 (0.29, 0.83)
GUSTO Severe/Moderate			
Male	12/3946 (0.3)	12/4018 (0.3)	1.02 (0.46, 2.27)
Female	20/1583 (1.3)	8/1509 (0.5)	2.40 (1.05, 5.47)

Forest Plot for 48 Hour Non-CABG Any Bleeding

Safety Population

	Cangrelor	Clopidogrel	OR (95% CI)
Gender			
Male	517/ 3946 (13.1)	394/ 4018 (9.8)	1.39 (1.21,1.59)
Female	340/ 1583 (21.5)	208/ 1509 (13.8)	1.71 (1.42,2.07)
Race=White			
No	46/ 338 (13.6)	38/ 345 (11.0)	1.27 (0.80,2.01)
Yes	810/ 5188 (15.6)	564/ 5175 (10.9)	1.51 (1.35,1.70)
Weight>=60			
No	67/ 319 (21.0)	36/ 272 (13.2)	1.74 (1.12,2.71)
Yes	790/ 5210 (15.2)	566/ 5255 (10.8)	1.48 (1.32,1.66)
US			
No	423/ 3467 (12.2)	302/ 3465 (8.7)	1.46 (1.25,1.70)
Yes	434/ 2062 (21.0)	300/ 2062 (14.5)	1.57 (1.33,1.84)
Biomarker			
Normal	559/ 3540 (15.8)	375/ 3458 (10.8)	1.54 (1.34,1.77)
Abnormal	297/ 1983 (15.0)	226/ 2064 (10.9)	1.43 (1.19,1.72)
Diabetes			
No	610/ 3986 (15.3)	431/ 3972 (10.9)	1.48 (1.30,1.69)
Yes	246/ 1535 (16.0)	169/ 1547 (10.9)	1.56 (1.26,1.92)
Ins. Dep. Diabetes			
No	786/ 5068 (15.5)	558/ 5119 (10.9)	1.50 (1.34,1.69)
Yes	71/ 461 (15.4)	44/ 408 (10.8)	1.51 (1.01,2.25)



Summary of Updated GUSTO, TIMI, and ACUITY Data

C-PHOENIX

	Cangrelor N=5529 n (%)	Clopidogrel N=5527 n (%)	Cangrelor vs Clopidogrel OR (95% CI)
Non-CABG-related bleeds	857 (15.5)	602 (10.9)	1.50 (1.34, 1.68)
GUSTO			
Severe or moderate	32 (0.6)	20 (0.4)	1.60 (0.92, 2.81)
Severe	11 (0.2)	6 (0.1)	1.83 (0.68, 4.96)
Moderate	21 (0.4)	14 (0.3)	1.50 (0.76, 2.96)
TIMI			
Major or minor	45 (0.8)	17 (0.3)	2.66 (1.52, 4.65)
Major	12 (0.2)	6 (0.1)	2.00 (0.75, 5.34)
Minor	33 (0.6)	11 (0.2)	3.01 (1.52, 5.96)
ACUITY			
Major	249 (4.5)	145 (2.6)	1.75 (1.42, 2.16)
Minor	608 (11.1)	457 (8.3)	1.38 (1.21, 1.57)

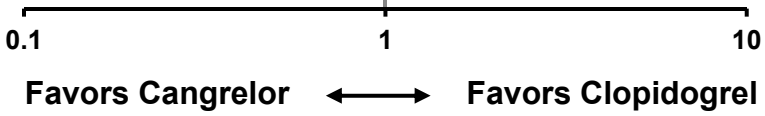
mITT and ITT

Endpoint	mITT OR (95% CI)	ITT OR (95% CI)
Death/MI/IDR/ST 48 Hours	0.78 (0.66, 0.93)	0.79 (0.67, 0.93)
Death/MI 48 Hours	0.80 (0.67, 0.96)	0.80 (0.67, 0.96)
Site MI 48 Hours	0.72 (0.52, 1.01)	0.72 (0.52, 1.01)
Site Death/MI 48 Hours	0.74 (0.55, 1.01)	0.72 (0.52, 1.01)
Death/MI 30 Days	0.86 (0.73, 1.01)	0.86 (0.73, 1.02)

Protocol-Defined and Supplemental Primary Efficacy Endpoints at 48 Hours

C-PHOENIX (mITT Population)

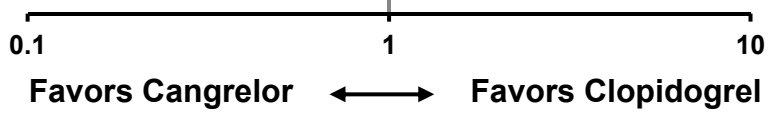
	Cangrelor N=5472 n (%)	Clopidogrel N=5470 n (%)	OR (95% CI)	P-value
Protocol-defined Primary Endpoint				
Death/MI/IDR/ST[1]	257 (4.7)	322 (5.9)	0.78 (0.66, 0.93)	0.005
Death	18 (0.3)	18 (0.3)	1.00 (0.52, 1.92)	0.100
MI	207 (3.8)	255 (4.7)	0.80 (0.67, 0.97)	0.022
IDR	28 (0.5)	38 (0.7)	0.74 (0.45, 1.20)	0.217
ST	46 (0.8)	74(1.4)	0.62 (0.43, 0.90)	0.010
Supplemental and Sensitivity Analysis				
Death/MI/IDR/ARC-ST	230 (4.2)	286 (5.2)	0.80 (0.67, 0.95)	0.012
Death/SCAI MI/IDR/ARC-ST	79 (1.4)	114 (2.1)	0.69 (0.52, 0.92)	0.011
Death/MI (CK-MB ≥ 10X ULN)/IDR/ARC-ST	77 (1.4)	111 (2.0)	0.69 (0.51, 0.92)	0.012
Death/MI(clinical)/IDR/ARC-ST	86 (1.6)	130 (2.4)	0.66 (0.50, 0.86)	0.003
Death/IDR/ARC-ST	43 (0.8)	54 (1.0)	0.79 (0.53, 1.19)	0.262
Death/MI	220 (4.0)	272 (5.0)	0.80 (0.67, 0.96)	0.016
Site Death/MI/IDR/ST	96 (1.8)	121 (2.2)	0.79 (0.60, 1.03)	0.086



Protocol-Defined and Sensitivity Analyses of Primary Efficacy Endpoints at 48 Hours

C-PHOENIX (ITT)

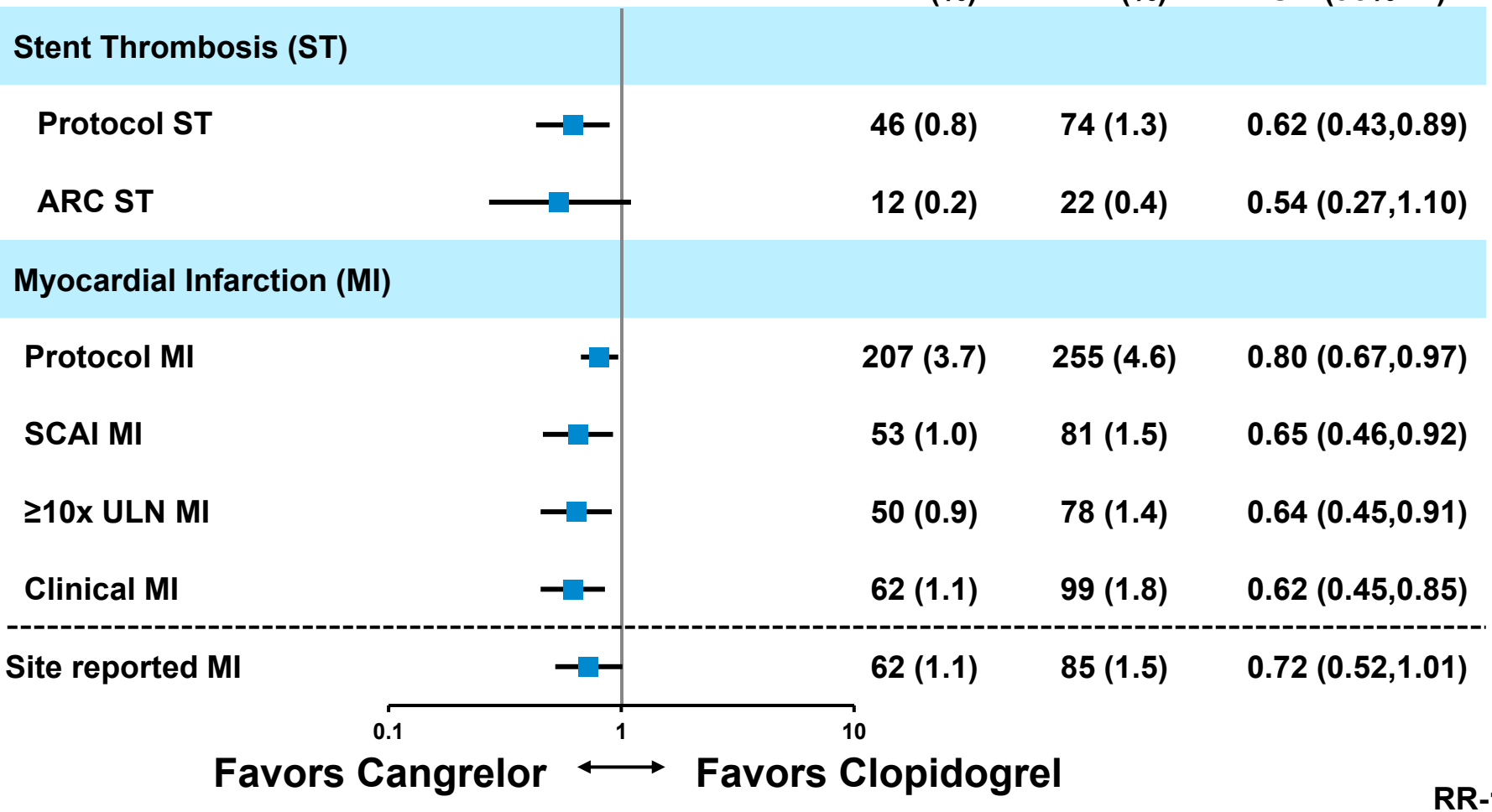
	Cangrelor N=5573 n (%)	Clopidogrel N=5561 n (%)	OR (95% CI)
Protocol-defined Primary Endpoint			
Death/MI/IDR/ST	260 (4.7)	325 (5.8)	0.79 (0.67,0.93)
Death	20 (0.4)	21 (0.4)	0.95 (0.51,1.75)
MI	207 (3.7)	255 (4.6)	0.80 (0.67,0.97)
IDR	29 (0.5)	38 (0.7)	0.76 (0.47,1.23)
ST	46 (0.8)	74(1.3)	0.62 (0.44,0.89)
Sensitivity Analyses			
Death/MI/IDR/ARC-ST	233 (4.2)	289 (5.2)	0.80 (0.67,0.95)
Death/SCAI MI/IDR/ARC-ST	82 (1.5)	117 (2.1)	0.69 (0.52,0.92)
Death/MI(≥ 10X ULN)/IDR/ARC-ST	80 (1.4)	114 (2.0)	0.70 (0.52,0.93)
Death/Clinical MI/IDR/ARC-ST	89 (1.6)	133 (2.4)	0.66 (0.51,0.87)
Death/IDR/ARC-ST	46 (0.8)	57 (1.0)	0.80 (0.54,1.19)
Death/MI	222 (4.0)	275 (4.9)	0.80 (0.67, 0.96)
Site Death/MI/IDR/ST	103 (1.8)	125 (2.2)	0.82 (0.63, 1.07)



Sensitivity Analyses of the ST and MI Endpoints at 48 Hours

PHOENIX (ITT)

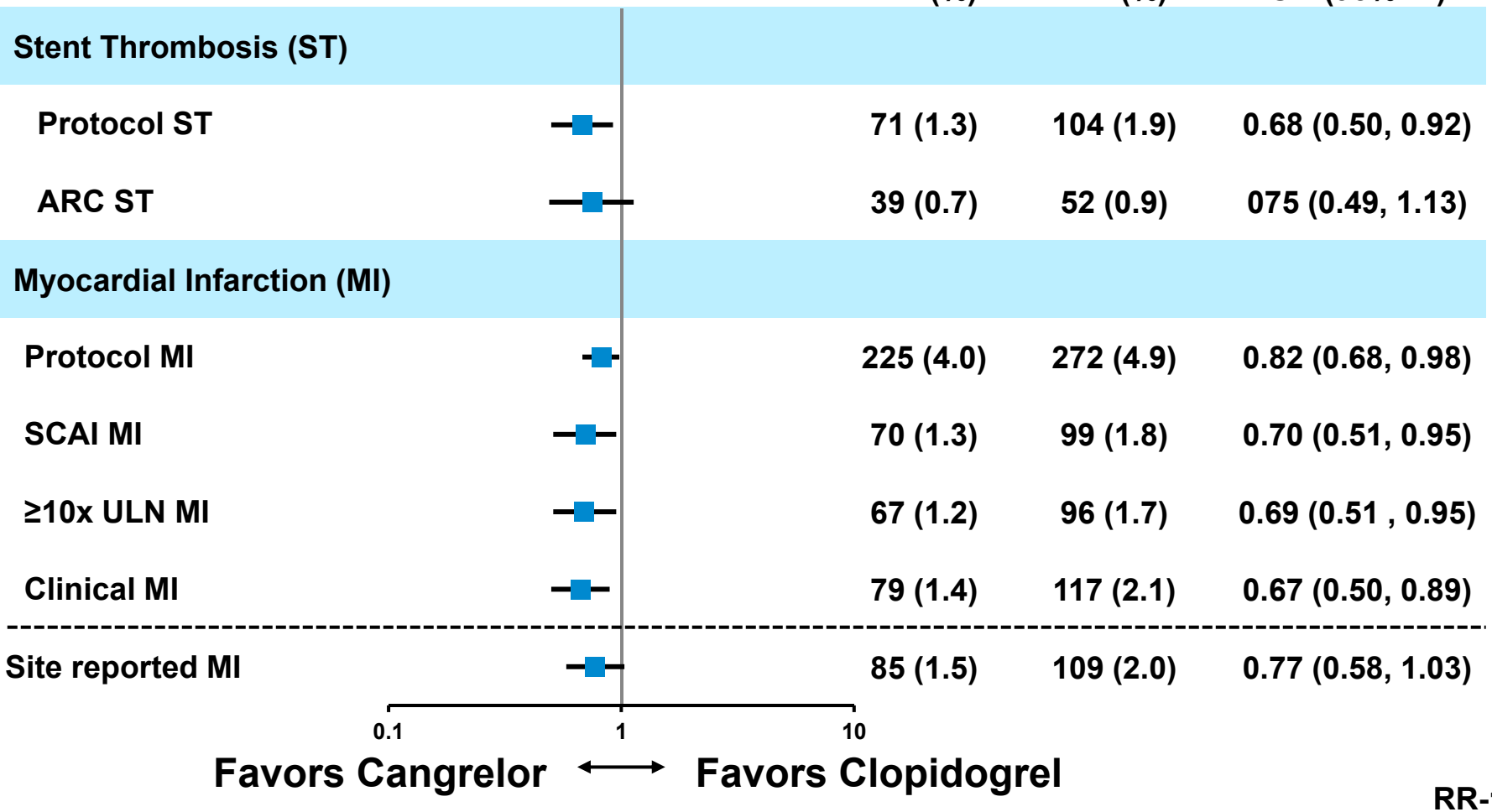
	Cangrelor N=5573 n/N (%)	Clopidogrel N=5561 n/N (%)	OR (95% CI)
Stent Thrombosis (ST)			
Protocol ST	46 (0.8)	74 (1.3)	0.62 (0.43,0.89)
ARC ST	12 (0.2)	22 (0.4)	0.54 (0.27,1.10)
Myocardial Infarction (MI)			
Protocol MI	207 (3.7)	255 (4.6)	0.80 (0.67,0.97)
SCAI MI	53 (1.0)	81 (1.5)	0.65 (0.46,0.92)
≥10x ULN MI	50 (0.9)	78 (1.4)	0.64 (0.45,0.91)
Clinical MI	62 (1.1)	99 (1.8)	0.62 (0.45,0.85)
Site reported MI	62 (1.1)	85 (1.5)	0.72 (0.52,1.01)



Sensitivity Analyses of the ST and MI Endpoints at 30 Days

PHOENIX (ITT)

	Cangrelor N=5564 n/N (%)	Clopidogrel N=5545 n/N (%)	OR (95% CI)
Stent Thrombosis (ST)			
Protocol ST	71 (1.3)	104 (1.9)	0.68 (0.50, 0.92)
ARC ST	39 (0.7)	52 (0.9)	075 (0.49, 1.13)
Myocardial Infarction (MI)			
Protocol MI	225 (4.0)	272 (4.9)	0.82 (0.68, 0.98)
SCAI MI	70 (1.3)	99 (1.8)	0.70 (0.51, 0.95)
≥10x ULN MI	67 (1.2)	96 (1.7)	0.69 (0.51 , 0.95)
Clinical MI	79 (1.4)	117 (2.1)	0.67 (0.50, 0.89)
Site reported MI	85 (1.5)	109 (2.0)	0.77 (0.58, 1.03)



mITT and ITT

Endpoint	mITT			ITT		
	Cangrelor n (%)	Clopidogrel n (%)	OR (95% CI)	Cangrelor n (%)	Clopidogrel n (%)	OR (95% CI)
Death/MI/IDR/ST 48 Hours	257 (4.7)	322 (5.9)	0.78 (0.66, 0.93)	260 (4.7)	325 (5.8)	0.79 (0.67, 0.93)
Death/MI 48 Hours	220 (4.0)	272 (5.0)	0.80 (0.67, 0.96)	222 (4.0)	275 (4.9)	0.80 (0.67, 0.96)
Site MI 48 Hours	60 (1.1)	83 (1.5)	0.72 (0.52, 1.01)	62 (1.1)	85 (1.5)	0.72 (0.52, 1.01)
Site Death/MI 48 Hours	73 (1.3)	98 (1.8)	0.74 (0.55, 1.01)	77 (1.4)	102 (1.8)	0.72 (0.52, 1.01)
Death/MI 30 Days	274 (5.0)	316 (5.8)	0.86 (0.73, 1.01)	278 (5.0)	319 (5.8)	0.86 (0.73, 1.02)

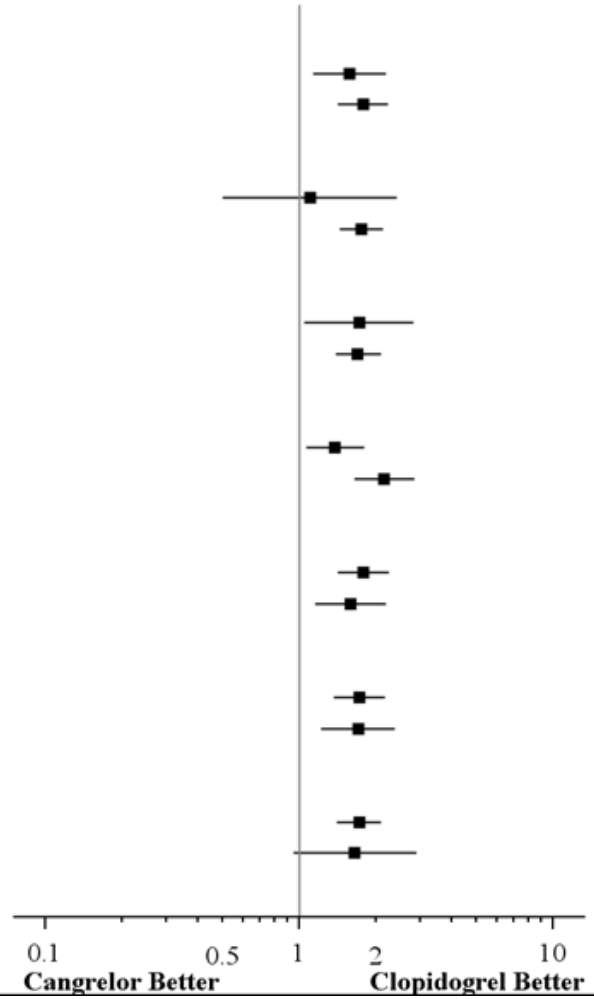
mITT and ITT at 48 Hours

Endpoint	mITT			ITT		
	Cangrelor n (%)	Clopidogrel n (%)	OR (95% CI)	Cangrelor n (%)	Clopidogrel n (%)	OR (95% CI)
Death/MI/IDR/ST	257 (4.7)	322 (5.9)	0.78 (0.66, 0.93)	260 (4.7)	325 (5.8)	0.79 (0.67, 0.93)
Death/MI	220 (4.0)	272 (5.0)	0.80 (0.67, 0.96)	222 (4.0)	275 (4.9)	0.80 (0.67, 0.96)
Death	18 (0.3)	18 (0.3)	1.00 (0.52, 1.92)	20 (0.4)	21 (0.4)	0.95 (0.51, 1.75)
SCAI MI	53 (1.0)	81 (1.5)	0.65 (0.46, 0.92)	53 (1.0)	81 (1.5)	0.65 (0.46, 0.92)
Death/SCAI MI	66 (1.2)	98 (1.8)	0.67 (0.49, 0.92)	68 (1.2)	101 (1.8)	0.67 (0.49, 0.91)
Site MI	60 (1.1)	83 (1.5)	0.72 (0.52, 1.01)	62 (1.1)	85 (1.5)	0.72 (0.52, 1.01)
Site Death/MI	73 (1.3)	98 (1.8)	0.74 (0.55, 1.01)	77 (1.4)	102 (1.8)	0.72 (0.52, 1.01)

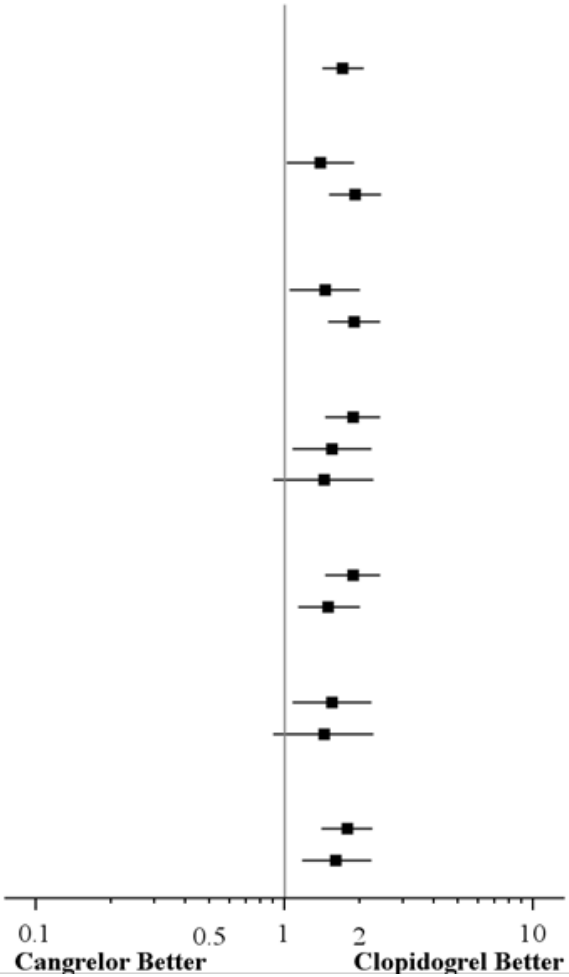
Female Forest Plot for 48 Hour Non-CABG Any Bleeding

C-Phoenix (Safety Population)

	Cangrelor	Clopidogrel	OR (95% CI)
Age>=65			
No	100/ 596 (16.8)	66/ 582 (11.3)	1.58 (1.13,2.20)
Yes	240/ 987 (24.3)	142/ 927 (15.3)	1.78 (1.41,2.24)
Race=White			
No	14/ 108 (13.0)	14/ 117 (12.0)	1.10 (0.50,2.42)
Yes	326/ 1474 (22.1)	194/ 1390 (14.0)	1.75 (1.44,2.13)
Weight>=60			
No	56/ 236 (23.7)	30/ 196 (15.3)	1.72 (1.05,2.81)
Yes	284/ 1347 (21.1)	178/ 1313 (13.6)	1.70 (1.39,2.09)
US			
No	149/ 949 (15.7)	107/ 901 (11.9)	1.38 (1.06,1.81)
Yes	191/ 634 (30.1)	101/ 608 (16.6)	2.16 (1.65,2.84)
Biomarker			
Normal	229/ 1046 (21.9)	133/ 983 (13.5)	1.79 (1.42,2.26)
Abnormal	111/ 536 (20.7)	74/ 524 (14.1)	1.59 (1.15,2.19)
Diabetes			
No	233/ 1066 (21.9)	140/ 1003 (14.0)	1.72 (1.37,2.17)
Yes	107/ 516 (20.7)	67/ 504 (13.3)	1.71 (1.22,2.38)
Ins. Dep. Diabetes			
No	300/ 1406 (21.3)	184/ 1349 (13.6)	1.72 (1.40,2.10)
Yes	40/ 177 (22.6)	24/ 160 (15.0)	1.65 (0.95,2.89)



Female Forest Plot for 48 Hour Non-CABG Any Bleeding

C-Phoenix (Safety Population)

	Cangrelor	Clopidogrel	OR (95% CI)
Overall	340/ 1583 (21.5)	208/ 1509 (13.8)	1.71 (1.42,2.07)
Strat Factor 1: Patient Status			
Abnormal	119/ 563 (21.1)	81/ 501 (16.2)	1.39 (1.02,1.90)
Normal	221/ 1020 (21.7)	127/ 1008 (12.6)	1.92 (1.51,2.44)
Strat Factor 2: Clopidogrel dose*			
300 mg	113/ 409 (27.6)	84/ 402 (20.9)	1.45 (1.05,2.00)
600 mg	227/ 1174 (19.3)	124/ 1107 (11.2)	1.90 (1.50,2.41)
IVRS Patient Type			
Stable Angina	196/ 917 (21.4)	114/ 904 (12.6)	1.88 (1.46,2.42)
NSTE-ACS	90/ 428 (21.0)	56/ 381 (14.7)	1.55 (1.07,2.23)
STEMI	54/ 238 (22.7)	38/ 224 (17.0)	1.44 (0.90,2.28)
IVRS SA vs ACS			
SA	196/ 917 (21.4)	114/ 904 (12.6)	1.88 (1.46,2.42)
ACS	144/ 666 (21.6)	94/ 605 (15.5)	1.50 (1.13,2.00)
IVRS NSTE-ACS vs STEMI			
NSTE-ACS	90/ 428 (21.0)	56/ 381 (14.7)	1.55 (1.07,2.23)
STEMI	54/ 238 (22.7)	38/ 224 (17.0)	1.44 (0.90,2.28)
Age>=75			
No	222/ 1147 (19.4)	130/ 1092 (11.9)	1.78 (1.40,2.25)
Yes	118/ 436 (27.1)	78/ 417 (18.7)	1.61 (1.17,2.23)