

**Comparison of Medical Therapy, Pacing,
and Defibrillation in Heart Failure
(COMPANION)**

**FDA Circulatory Systems Panel Meeting
July 28, 2004**

Guidant Panel Attendees

John P. Boehmer, MD -- Steering Committee

- Milton Hershey Medical Center

Michael R. Bristow, MD, Ph.D -- Co-Chair, Steering Committee

- University of Colorado Health Sciences Center

Peter E. Carson, MD -- Chair, Morbidity and Mortality Committee

- Washington DC VA Medical Center

David L. DeMets, Ph.D -- Statistical Data Analysis Center

- University of Wisconsin Medical School

Arthur M. Feldman, MD, Ph.D -- Co-Chair, Steering Committee

- Jefferson Medical College

Leslie A. Saxon, MD -- Steering Committee

- University of Southern California Medical Center

Jonathan S. Steinberg, MD -- Morbidity and Mortality Committee

- St. Luke's Roosevelt Hospital

Agenda and Presenters

- **Background and Study Overview**
Arthur M. Feldman, MD, Ph.D
- **Data Handling and Adjudication Process**
Peter E. Carson, MD
- **Effectiveness Results**
Michael R. Bristow, MD, Ph.D
- **Study Withdrawals and Censoring**
David L. DeMets, Ph.D
- **Safety and Conclusions**
Leslie A. Saxon, MD

Background and Study Overview

Arthur Feldman, MD, Ph.D

Introduction

- **Heart failure is a progressive disease syndrome characterized by high morbidity and mortality**
- **In some cases, heart failure may be associated with prolonged conduction resulting in a dyssynchronous contraction and further impairment of myocardial function**
- **Pharmacologic therapies for treating heart failure have been established through major, randomized trials, and have evolved over time**
- **Electrical stimulation of both ventricles (cardiac resynchronization therapy) helps restore ventricular synchrony and improves myocardial function**

Drug Trials for Advanced HF

Trial (Back-ground Rx)	12 month Control group mortality	Active Rx	Sample Size	Relative Reduction (%)
BEST (ACEI +)	17%	Bucindolol (β-blocker)	2708	↓ 10%
RALES (ACEI +)	24%	Spiro- lactone (Aldo ant.)	1663	↓ 25%
COPERNICUS (ACEI +)	18%	Carvedilol (β-blocker)	2289	↓ 35%

Each trial conducted with best pharmacological background therapy

Cardiac Resynchronization Therapy (CRT)

- CRT devices are specifically designed to restore ventricular synchrony in patients already receiving optimal drug therapy
- Terminology
 - “CRT-P” describes a device with biventricular pacing only
 - “CRT-D” describes a device with both biventricular pacing and defibrillation capability
 - “CRT” generically describes the therapy independent of the device

Indications for Use

Indications

Guidant Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are indicated for patients with moderate to severe heart failure (NYHA III/IV) who remain symptomatic despite stable, optimal heart failure drug therapy, and have left ventricular dysfunction (EF \leq 35%) and QRS duration \geq 120 ms.

Outcomes

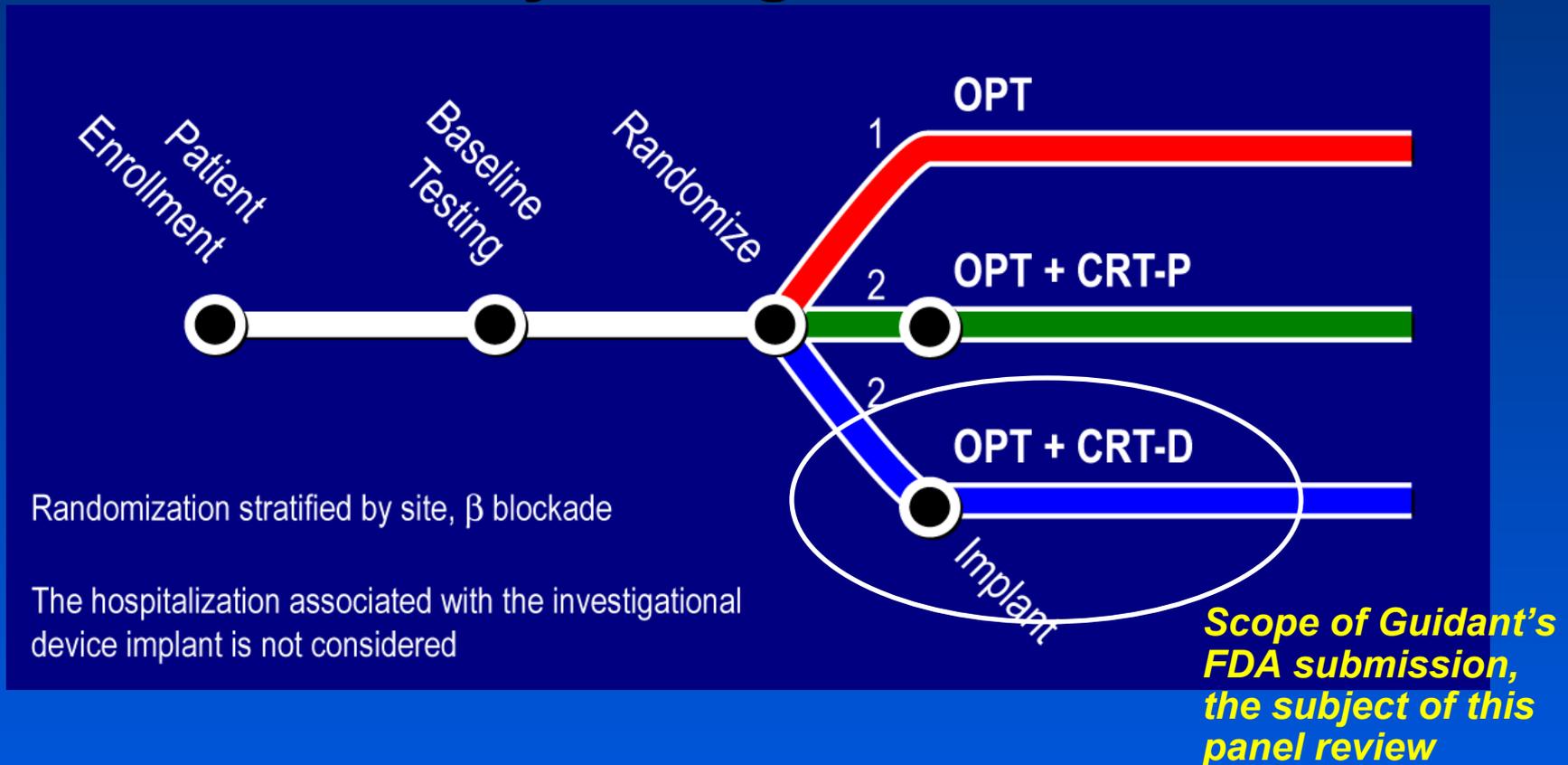
Guidant Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) have demonstrated the following outcomes in the indicated population specified above:

- **Reduction in risk of all-cause mortality or first all-cause hospitalization**
Note: Hospitalization is defined as administration of IV inotropes or vasoactive drugs > 4 hours (outpatient or inpatient), or admission to a hospital that includes or extends beyond a calendar date change.
- **Reduction in risk of all-cause mortality**
- **Reduction of heart failure symptoms (previously established)**

COMPANION Study Rationale

- **COMPANION was designed to determine if CRT-P or CRT-D results in a significant reduction of a composite of time to first all-cause hospitalization or all-cause mortality when compared to OPT alone**
- **There have been no appropriately powered clinical trials that have prospectively investigated the effect of CRT on mortality or hospitalization**
- **Investigation of these endpoints is necessary to understand the role of this new therapy for the treatment of heart failure**

Study Design Overview



- The **CRT-P/CRT-D** device impact is measured 'on top of' OPT

Primary Endpoint

- **Composite of time to first all-cause hospitalization or all-cause mortality event**
 - **Analyzed as time to first event as measured from the randomization visit**
 - **Analysis by intention-to-treat**

Secondary Endpoints

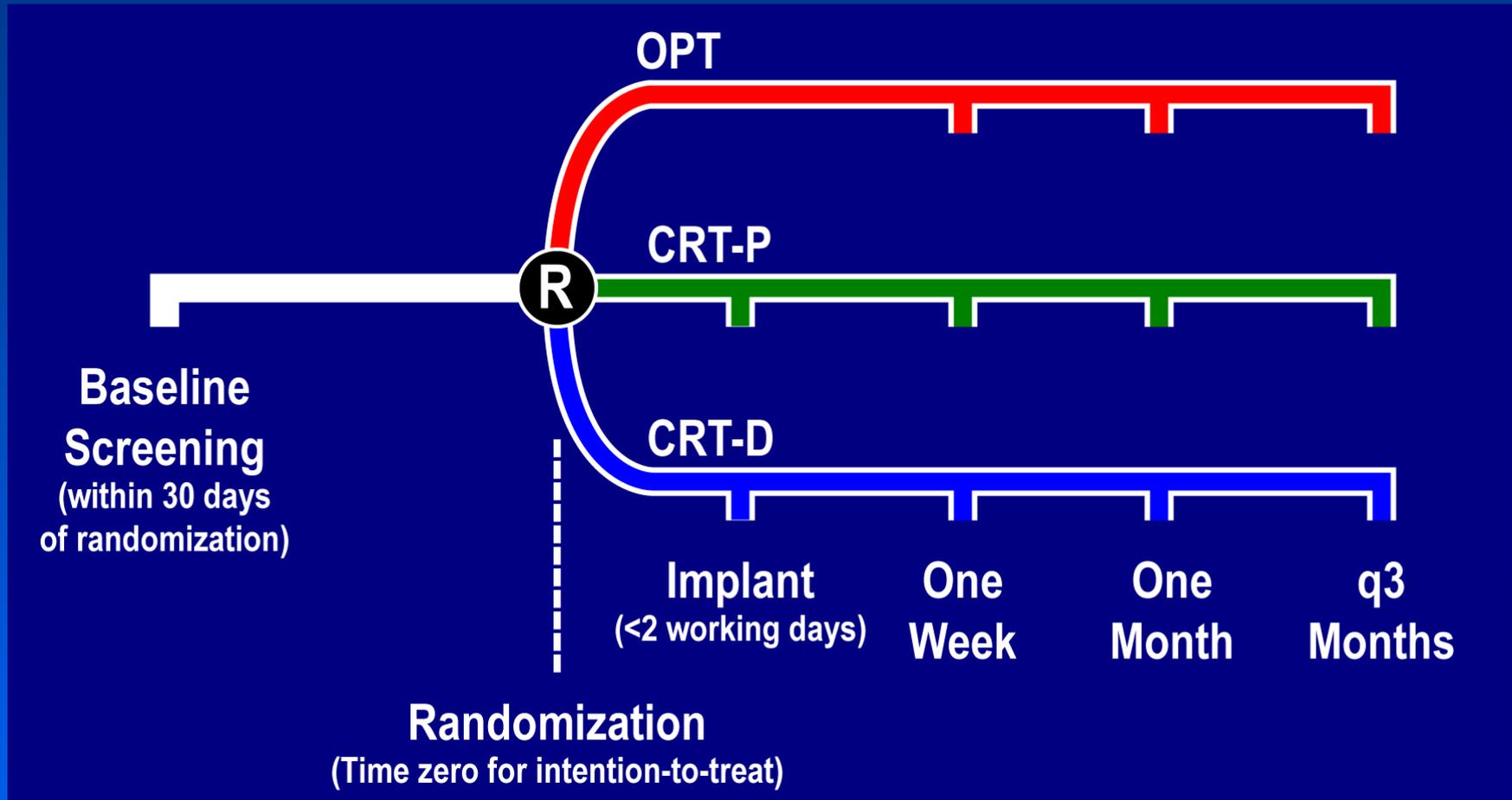
- **All-cause mortality (highest order)**
 - Analysis by intention-to-treat
 - Analyzed as time to first event as measured from the randomization visit
- **Cardiac morbidity**
 - Analysis by intention-to-treat

Main Entry Criteria

- **NYHA Class III or IV**
- **Optimal pharmacologic therapy, defined as:**
 - **Loop diuretics**
 - **Beta blockers (stable dose > 3 months)**
 - **ACE inhibitors or ARBs (stable dose > 1 month)**
 - **Spironolactone (stable dose > 1 month)**
- **LVEF \leq 35%, LVEDD \geq 60 mm**
- **QRS \geq 120 ms and PR > 150 ms**
- **HF hospitalization, or equivalent, between 1 and 12 months prior to enrollment**
- **No indication for a pacemaker or ICD**

Study Design

Patients randomized 1:2:2 to the following three arms:



Randomization stratified by site and by beta blocker use

Statistical Assumptions

- **Powered to detect a 25% reduction in 12 month event rates in each device arm vs. OPT for both primary and secondary (all-cause mortality) endpoints**
 - **Alpha allocation: $\alpha=0.02$ for CRT-P vs. OPT and $\alpha=0.03$ for CRT-D vs. OPT**
 - **Primary: 40% 12 month event rate assumed in OPT arm, power>90%**
 - **Secondary (all-cause mortality): 24% 12 month event rate assumed in OPT arm, power=80%**

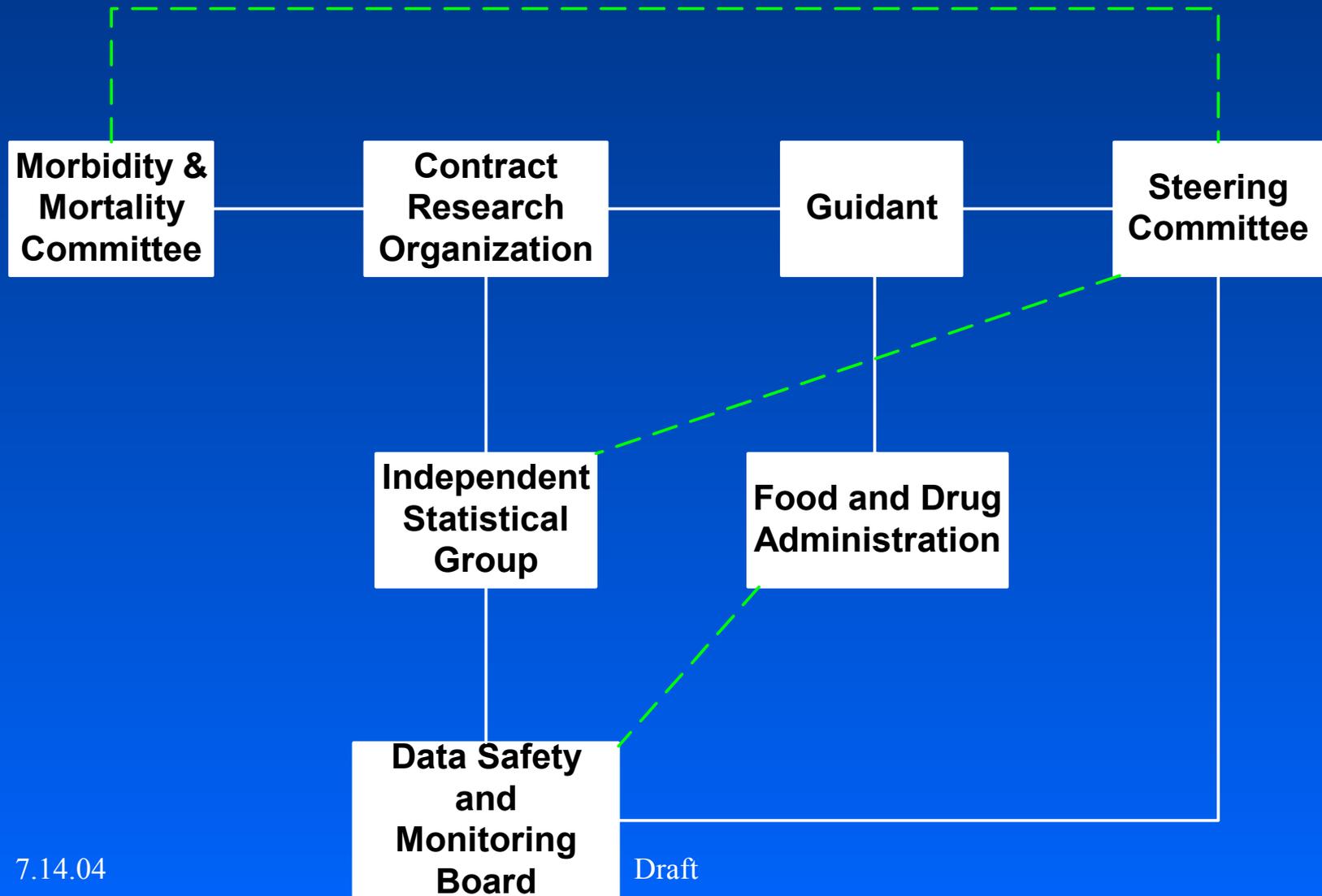
Statistical Assumptions (cont.)

- **Event driven trial with a target number of 1000 first events to detect the 25% reduction for the primary endpoint**
- **Sequential monitoring of primary and secondary (all-cause mortality) endpoint events was performed by the DSMB every six months**

Study Management

- **Steering Committee**
 - Provided overall guidance and leadership of study
- **Morbidity and Mortality (MM) Committee**
 - Reviewed and adjudicated hospitalizations
- **Data and Safety Monitoring Board (DSMB)**
 - Reviewed study outcomes at prescribed intervals
- **Independent Statistical Group**
 - Provided statistical support and guidance
- **Contract Research Organization**
 - Administrated study and acted as clearinghouse for CRFs and study monitoring

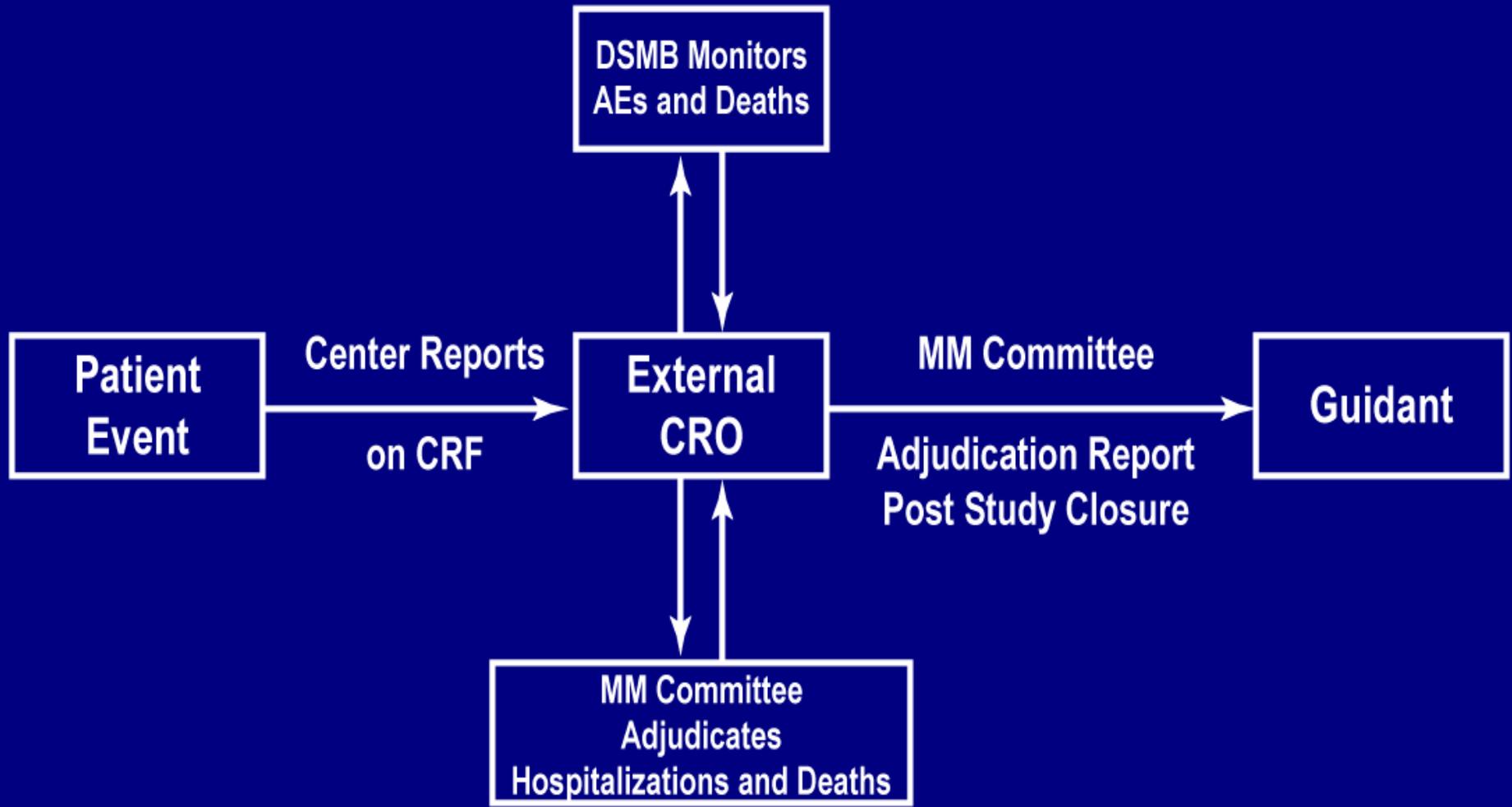
Study Management Relationships



Data Handling and Adjudication Process

Peter Carson, MD

Data and Adjudication Process Flow



MM Committee Adjudication Process

- **CRO collated clinical summary and event information from investigational centers**
 - Hospitalizations involving a calendar date change
 - Outpatient IV inotrope for > 4 hours
 - Deaths
- **Primary and secondary reviewer assigned to each event**
 - Pt ID, randomization arm, physician, center, and device identification removed from documents
 - However complete blinding could not be done, because committee was charged to adjudicate events in relation to device cause
 - Vote taken for each adjudication
- **Process documented with meeting minutes**

**Note: AE's not adjudicated by committee
Reported by center, reviewed by CRO**

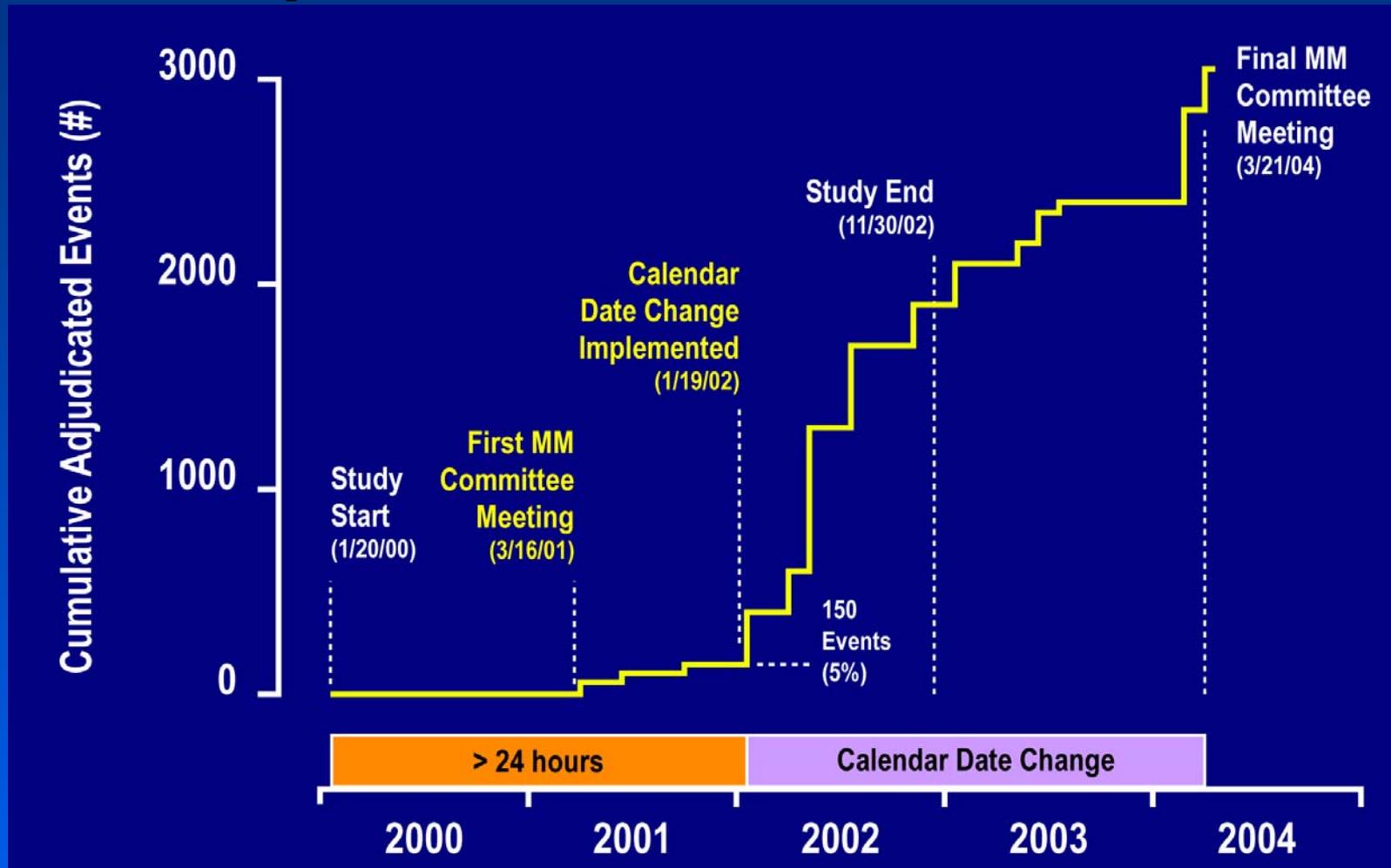
Defining Hospitalization

- **Defining hospitalization events should be:**
 - Consistently applied across multiple institutions
 - Uniformly documented in a way practical to measure
 - Similar to those used in other heart failure studies
- **MM Committee used investigational plan early in adjudication process as guidance for defining hospitalization as part of its charter**
 - **Morbidity and Mortality committee produced MOP with definitions of hospitalizations and deaths that was in place prior to first adjudication meeting**
- **Consistent with the protocol, hospitalizations associated with implant or reattempts were not considered a primary endpoint event**
 - **Implant hospitalizations for device implant for OPT patients were only considered events if admission was due to worsening heart failure or arrhythmic condition**

Hospitalization Definition

- **Definition per protocol:**
 - Admission to a hospital for any reason. Additionally, emergency room visits (or unscheduled office visits) that result in treatment with intravenous (IV) inotropes or vasoactive drugs
- **Definition was later clarified by MM committee:**
 - Admissions greater than 24 hours for any reason; later documented as a hospitalization resulting in a calendar date change
 - Administration of intravenous inotropes or vasoactive infusions for greater than 4 hours
- **This conservative definition is consistent with other recent HF studies, such as MERIT HF and VAL-HeFT**

Implementation of Definition



Calendar date change definition implemented early in process
All prior events were readjudicated

All-Cause Mortality

Adjudicated as:

- **Sudden, unexpected**
 - Observed or unobserved, but assumed to be instantaneous due to the clinical setting
 - With or without worsening HF
- **Pump failure**
 - Progressive deterioration or recurrent hospitalization
- **Ischemic**
- **Other Cardiac**
- **Vascular**
- **Non-cardiac**

All-Cause Mortality (cont)

Adjudicated as:

- Operative relationship
 - Pre-, peri-, post-operative
- Procedure related
- Device-related

Cardiac Morbidity History

- No precedent for reporting cardiac morbidity in HF device trials, hence, definition unique to the COMPANION study
- Intent was to provide more specific assessment of cardiac morbidity connected with a HF hospitalization treatment effect
- Designed as an index to encompass significant events that could happen to a HF patient; including serious device related hospitalization
- Pre-identified approach is one method to look at cardiac morbidity

Cardiac Morbidity

- **Defined in COMPANION protocol as the occurrence of the following events:**
 - **Hospitalization for acute decompensation of HF**
 - **Worsening HF resulting in use of intravenous vasoactive or inotropic therapy exceeding four hours**
 - **Mechanical respiratory or cardiac support**
 - **Any cardiac surgery, including heart transplant**
 - **Resuscitated cardiac arrest or sustained ventricular tachycardia requiring intervention**
 - **Hospitalization that results in death from cardiac causes**
 - **Significant device-related events resulting in:**
 - **Permanent disability**
 - **Hospitalization for pending death or permanent disability**

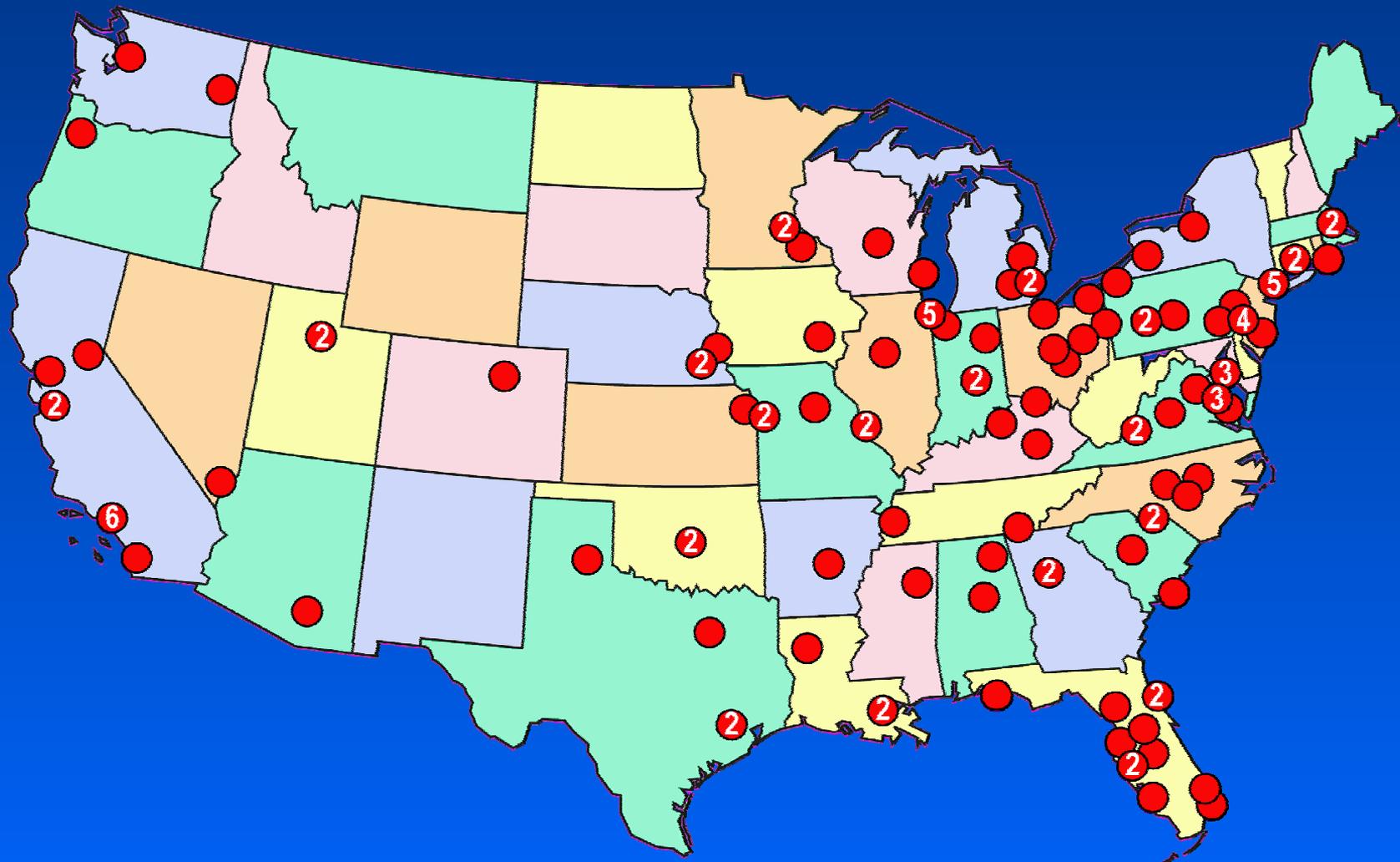
Effectiveness Results

Michael Bristow, MD, PhD

Trial Termination

- **The DSMB recommended to the Steering Committee on November 18, 2002 that enrollment be stopped due to:**
 - **Target number (n=1000) of primary endpoint (PEP) events had likely been reached, actual number reviewed (n= 950), final number (n=1020)**
 - **Effectiveness boundaries for primary endpoint and mortality had been crossed (CRT-D)**
- **The Steering Committee stopped enrollment (n=1520 randomized) on November 18, 2002 and established study data cutoff date through November 30, 2002**

Study Sites



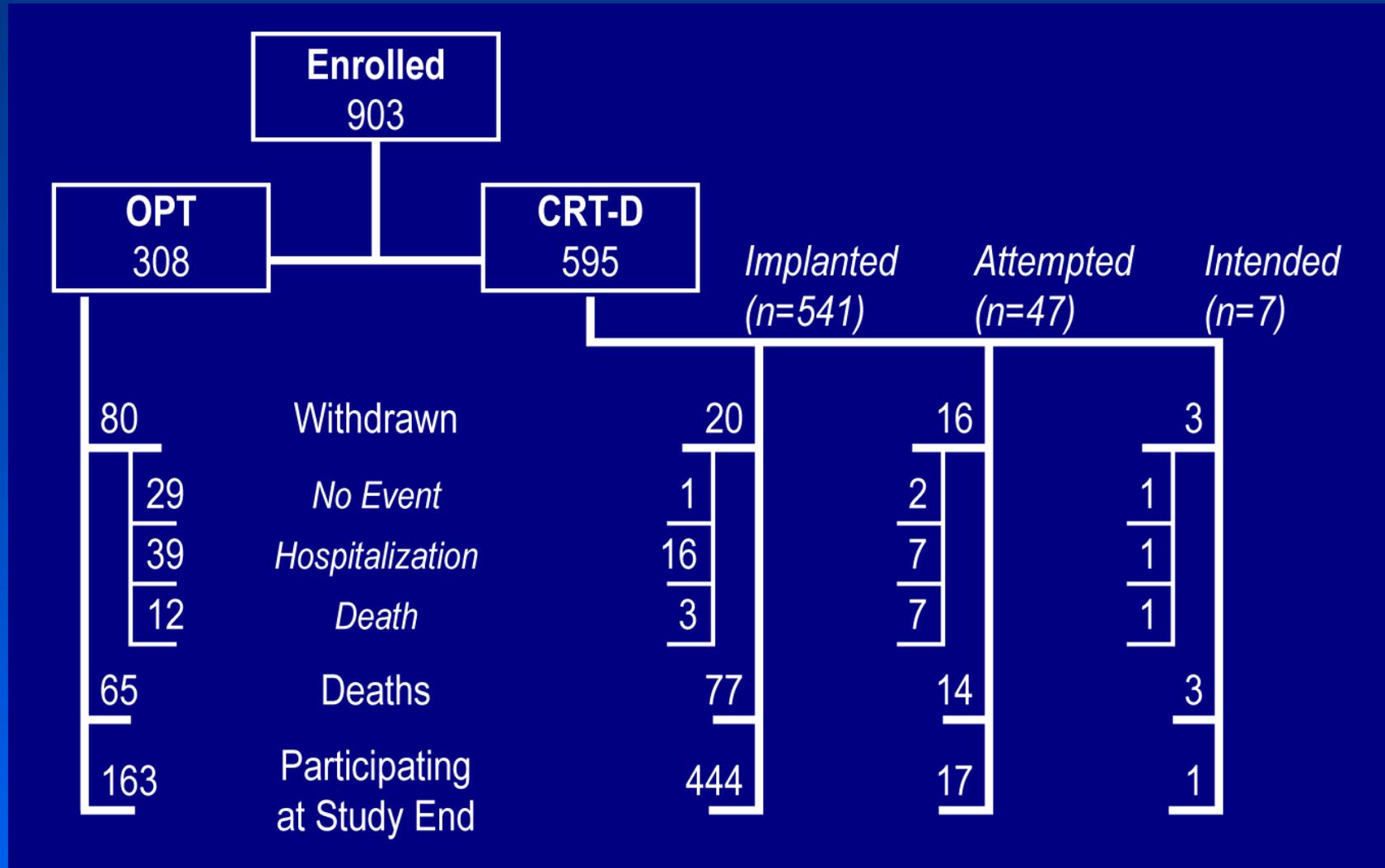
Demographics and Medical History (n=903)

Parameter	OPT n = 308	CRT-D n = 595	p values, OPT/CRT-D
Age (years)	68	66	0.14
Male gender (%)	69	67	0.73
NYHA Class III (%)	82	86	0.12
Duration of HF (Yrs)	3.6	3.5	0.43
LVEF (%)	22	22	0.47
LVEDD (mm)	67	67	0.73
Heart Rate (bpm)	72	72	0.37
Systolic BP (mm Hg)	112	112	0.76
Diastolic BP (mm Hg)	64	68	0.14

Demographics and Medical History (cont)

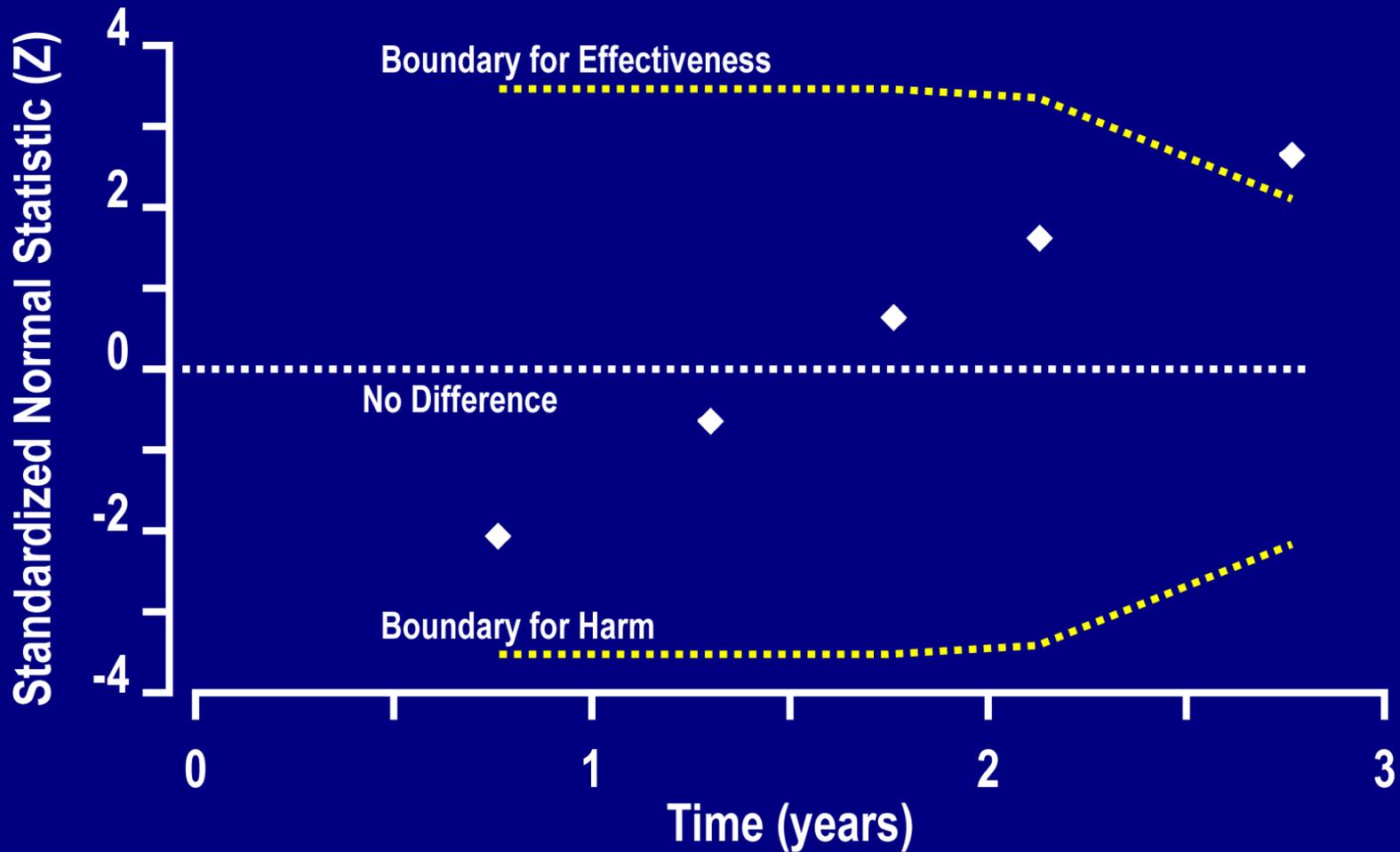
Parameter	OPT n = 308	CRT-D n = 595	p values, OPT/CRT-D
Six minute walk (m)	244	258	0.59
PR interval (ms)	202	206	0.28
QRS duration (ms)	158	160	0.10
Ischemic CMY (%)	59	55	0.23
Diabetes (%)	45	41	0.27
LBBB (%)	70	73	0.32
RBBB (%)	9	10	0.48
ACEI (%)	69	69	0.90
(ACEI or ARB)	(89)	(90)	(0.66)
Beta Blocker (%)	66	68	0.68
Loop Diuretic (%)	94	97	0.12
Spirolactone (%)	55	55	0.94

Patient Disposition

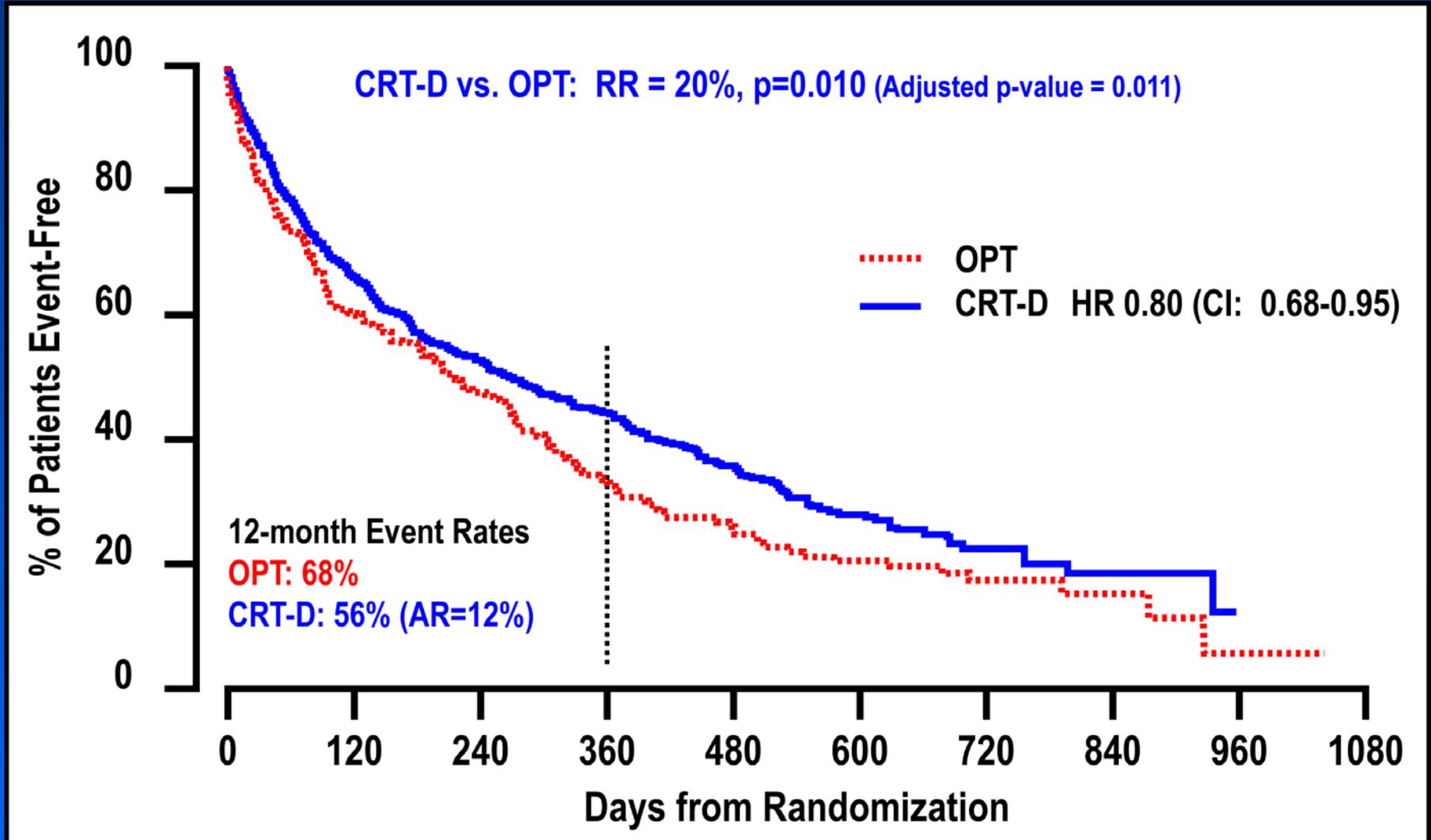


Analysis is by intention-to-treat; patients analyzed within randomization group regardless of whether or not device was implanted

Primary Endpoint: Sequential Monitoring



Primary Endpoint: All-cause Mortality or All-cause Hospitalization

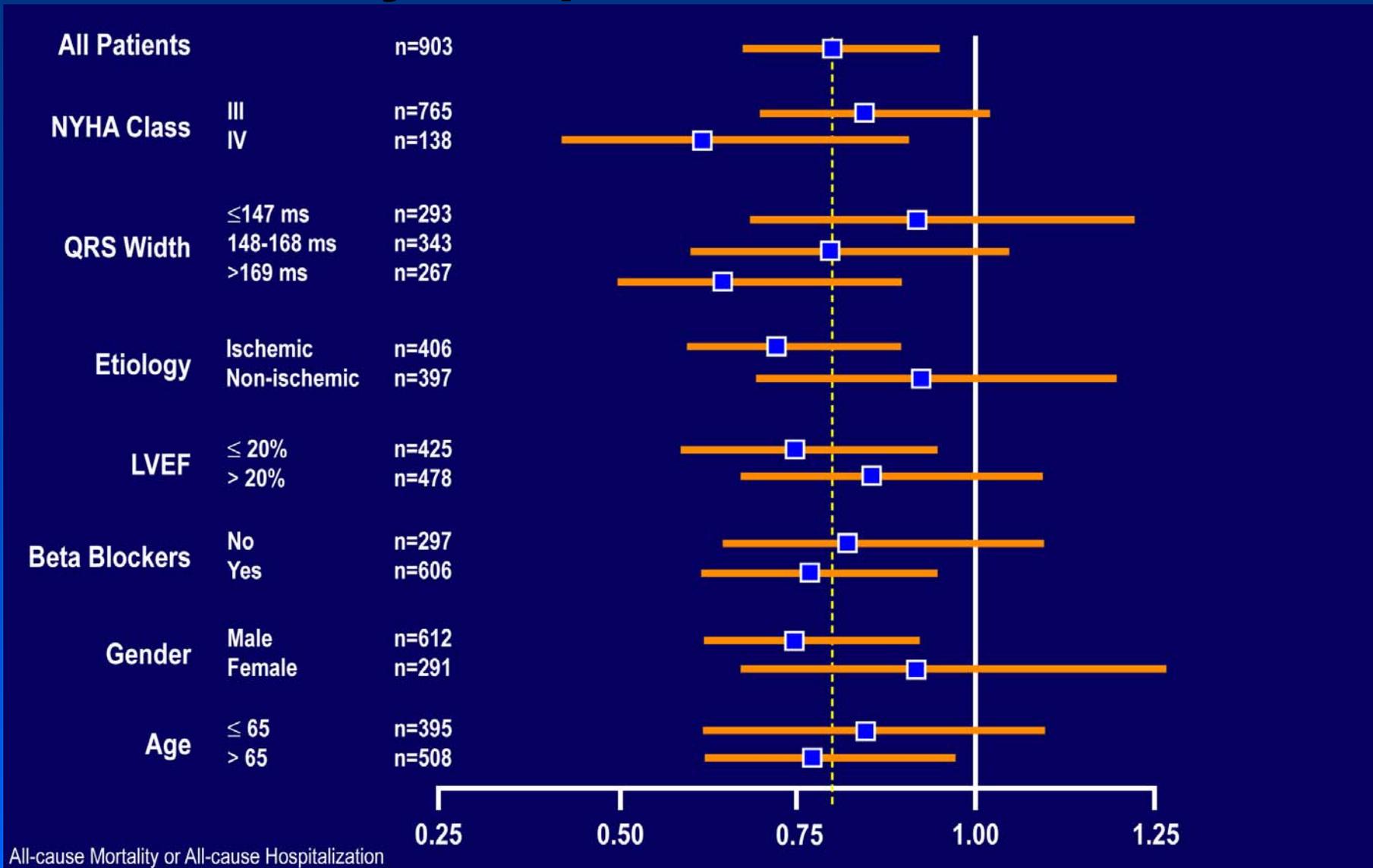


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RR = Relative Reduction, AR = Absolute Reduction

Primary Endpoint: Hazard Ratios

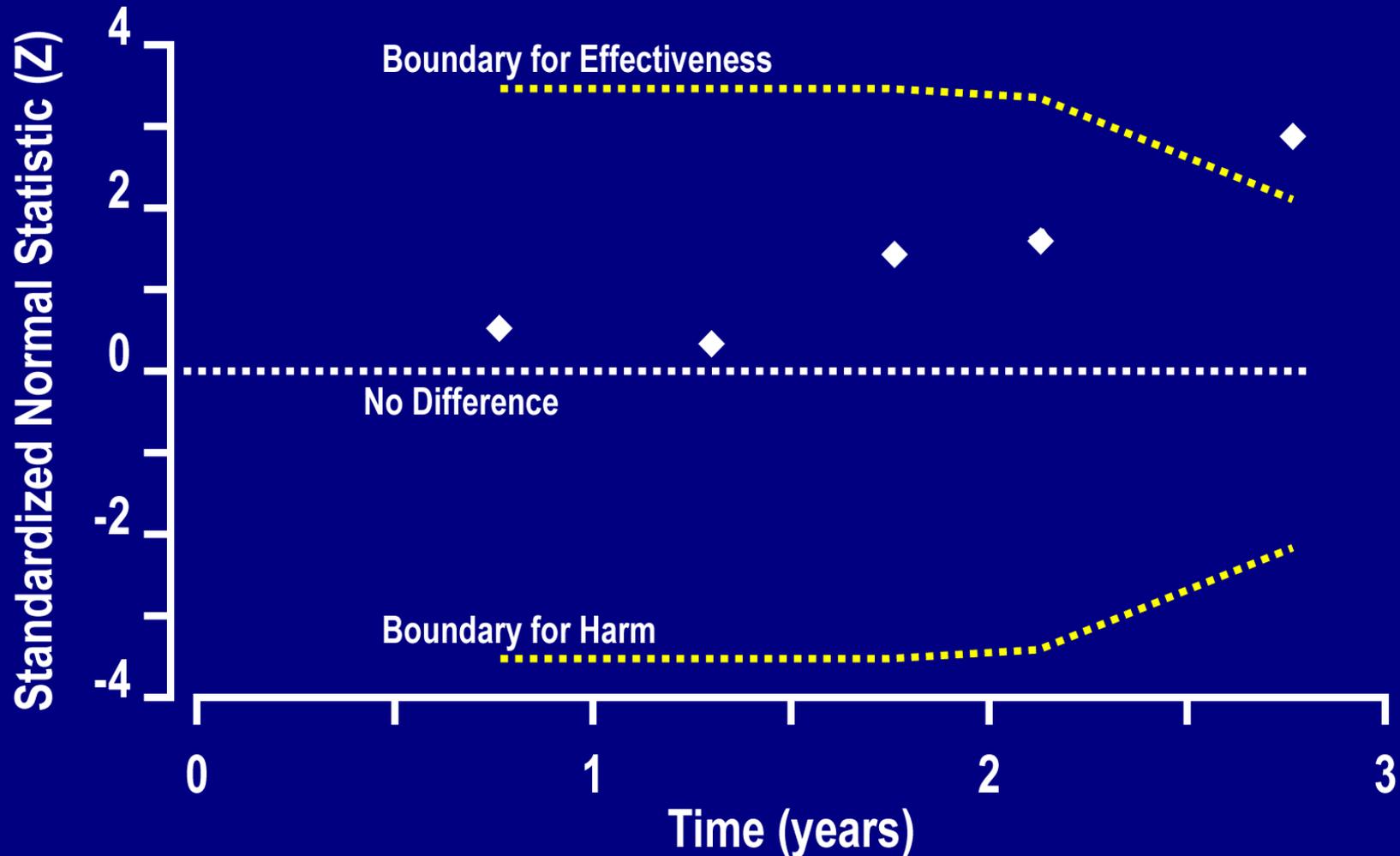


All-cause Mortality or All-cause Hospitalization

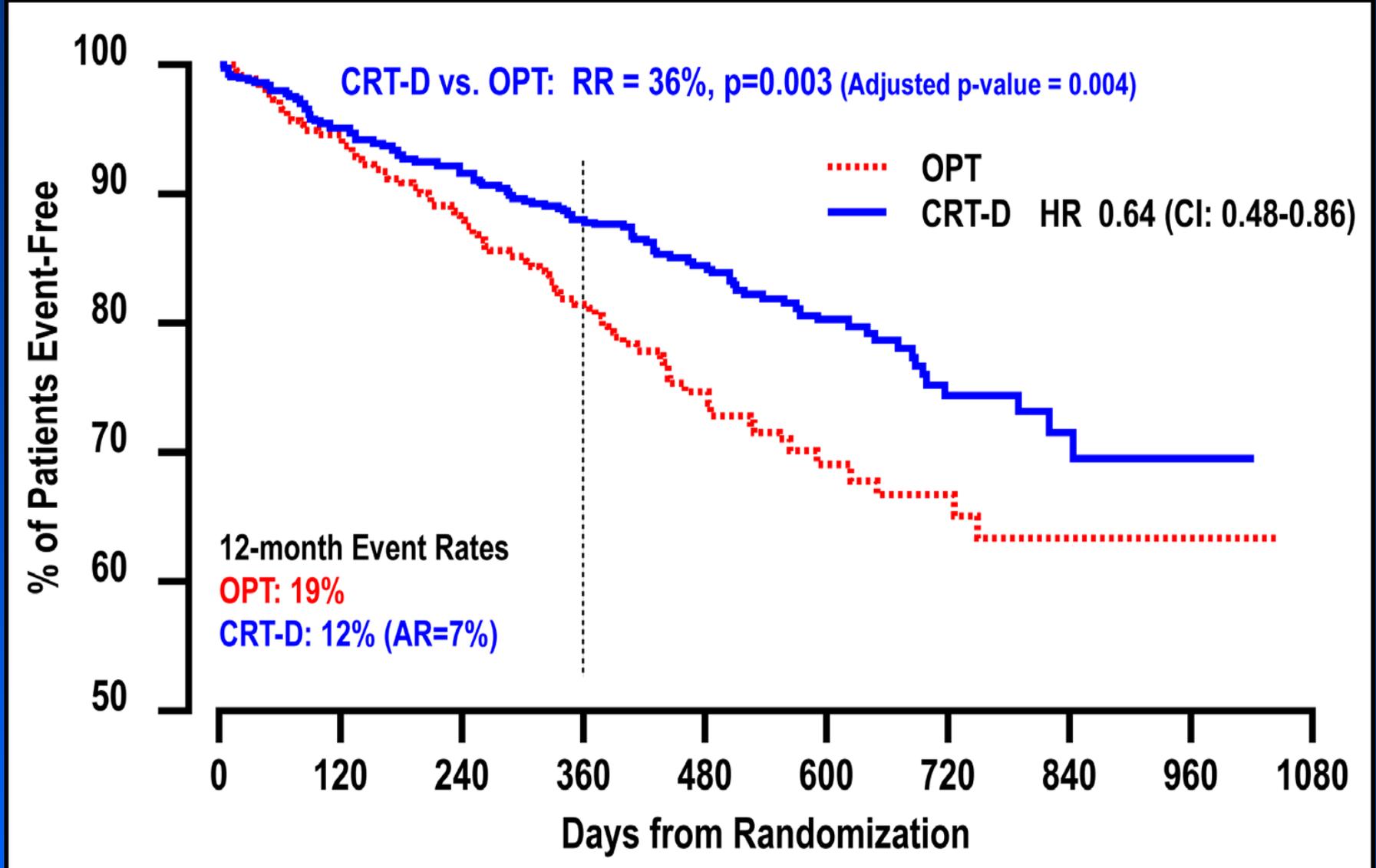
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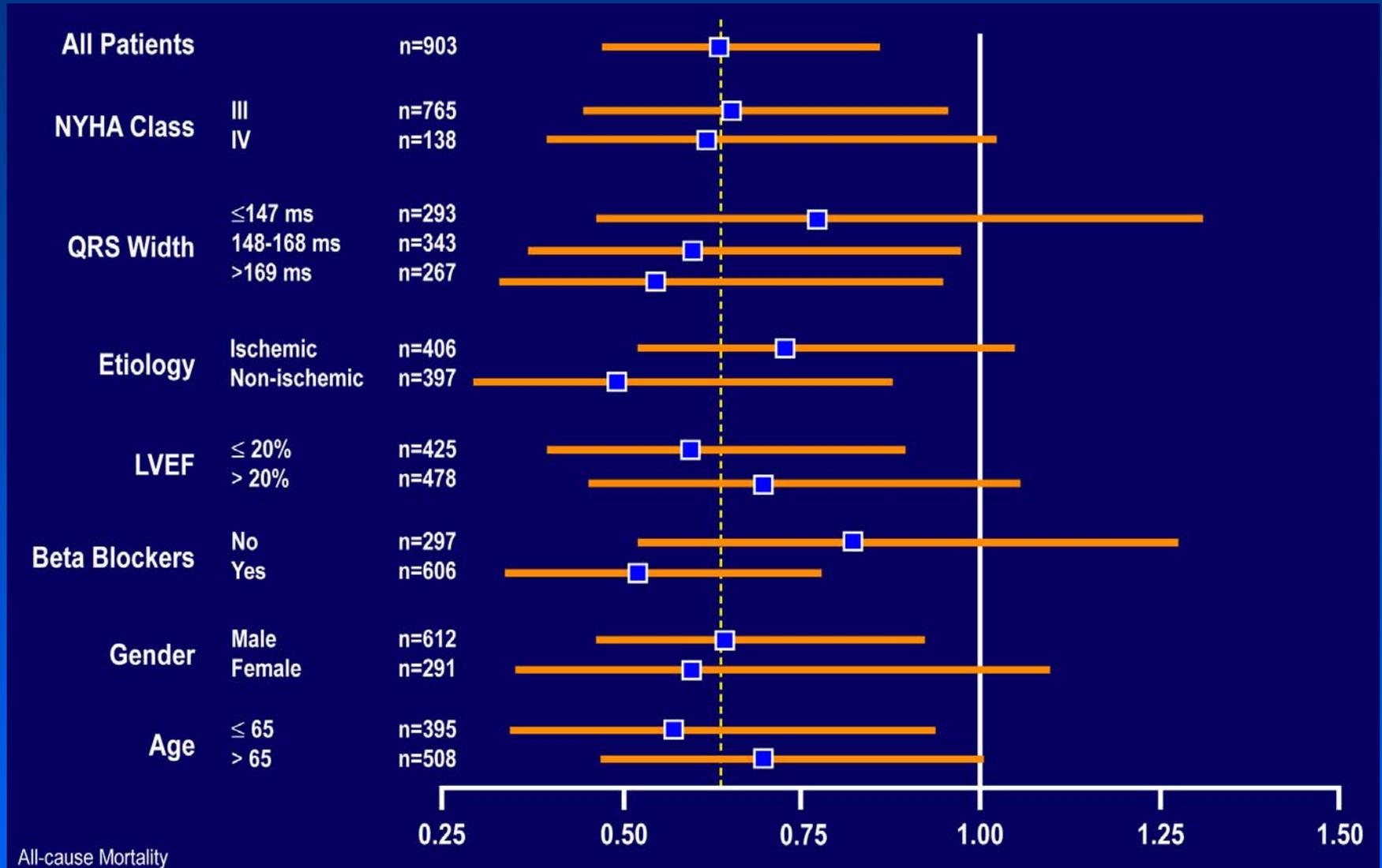
Secondary Endpoint of All-cause Mortality: Sequential Monitoring



Secondary Endpoint of All-cause Mortality



Hazard Ratio: All-cause Mortality



All-cause Mortality

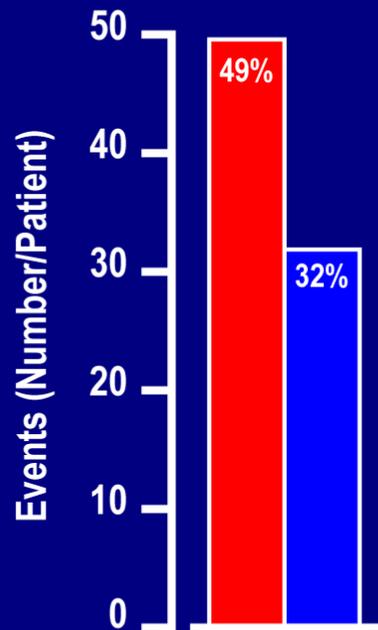
All-cause Mortality Breakdown by Cause of Death

Cause of Death	OPT Arm n = 308	CRT-D n = 595	Total n = 903
Cardiac	58 (18.8%)	76 (12.8%)	134 (14.8%)
Pump Failure	34 (11.0%)	52 (8.7%)	86 (9.5%)
Sudden Death	18 (5.8%)	17 (2.9%)	35 (3.9%)
Vascular	0	3 (0.5%)	3 (0.3%)
Non-cardiac	11 (3.6%)	21 (3.5%)	32 (3.5%)
Unknown/ Unclassified	8 (2.6%)	5 (0.8%)	13 (1.4%)
Total	77 (25.0%)	105 (17.6%)	182 (20.2%)

Secondary Endpoint of Cardiac Morbidity

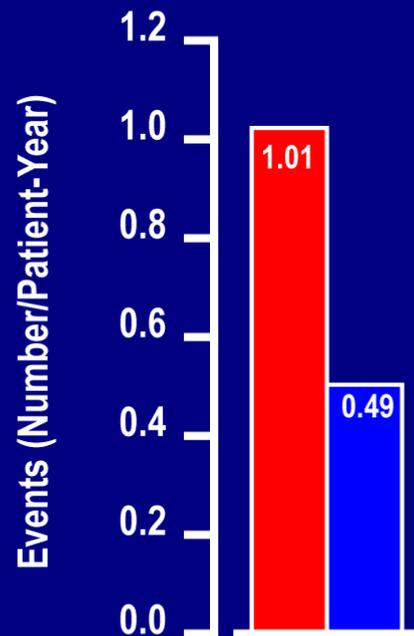
Event Rate (Per Patient)

35% reduction



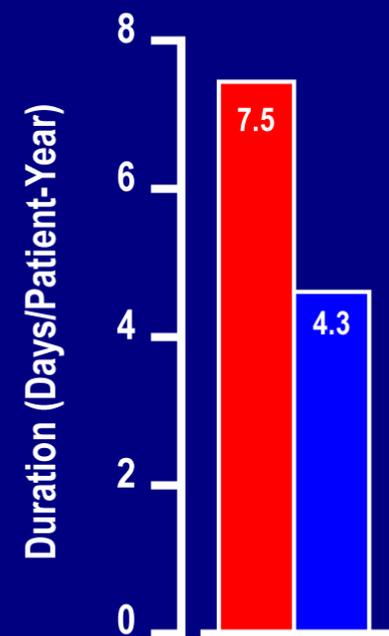
Event Rate (Per Patient Year)

51% reduction



Event Duration

43% reduction

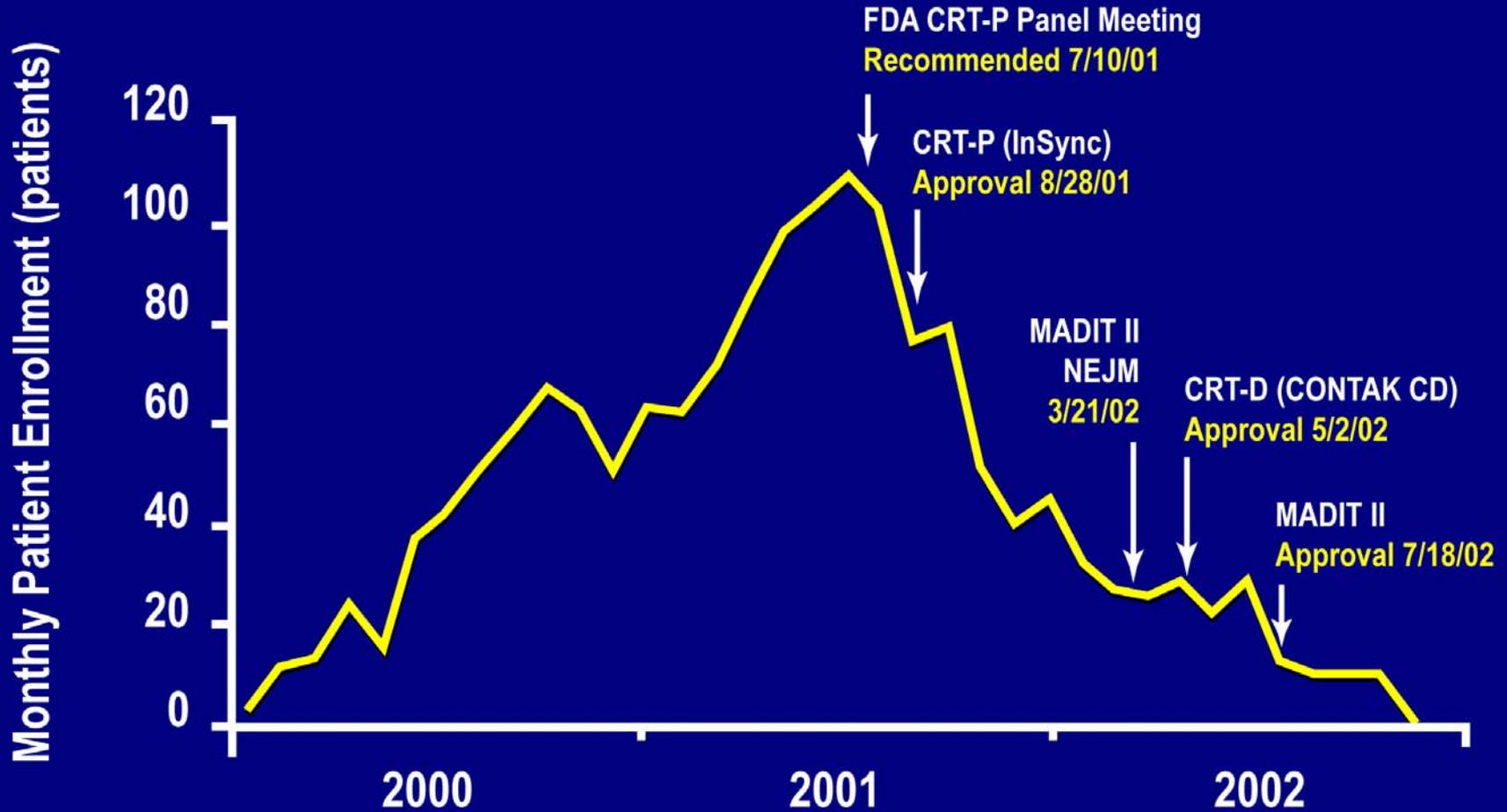


■ OPT (n=308) ■ CRT-D (n=595)

Challenges in Conducting COMPANION

- **Contemporaneous device therapies approved while study in progress**
 - CRT-P
 - CRT-D
 - ICD expanded indications
- **Availability of these therapies affected ability to:**
 - Enroll new patients
 - Retain existing patients in the OPT group

Influence of Device Availability on Enrollment



Response to Commercial Availability of CRT

- **CRT device approval while COMPANION was in progress influenced clinical equipoise**
 - **Investigators faced with a difficult choice of treating OPT patients with CRT or maintaining them in study**
- **Steering Committee recommended**
 - **Maintaining OPT patients in study unless worsening HF required CRT**
 - **Investigators were asked to consult with Steering Committee prior to implanting a CRT device**
- **Rate of withdrawals increased after CRT available**

Consequences of Withdrawal Rate

- Preliminary data analysis indicated disproportionate withdrawal rate initially observed without prior PEP; OPT=13%, CRT-D=2%
- The study was based on an intention-to-treat analysis; due diligence required accounting for as many patients as possible
- The independent statistician recommended to the Steering Committee to obtain vital status and hospitalization status on all withdrawn patients
- Reconsent process targeted patients that had withdrawn prior to 11/30/02 without experiencing a primary endpoint

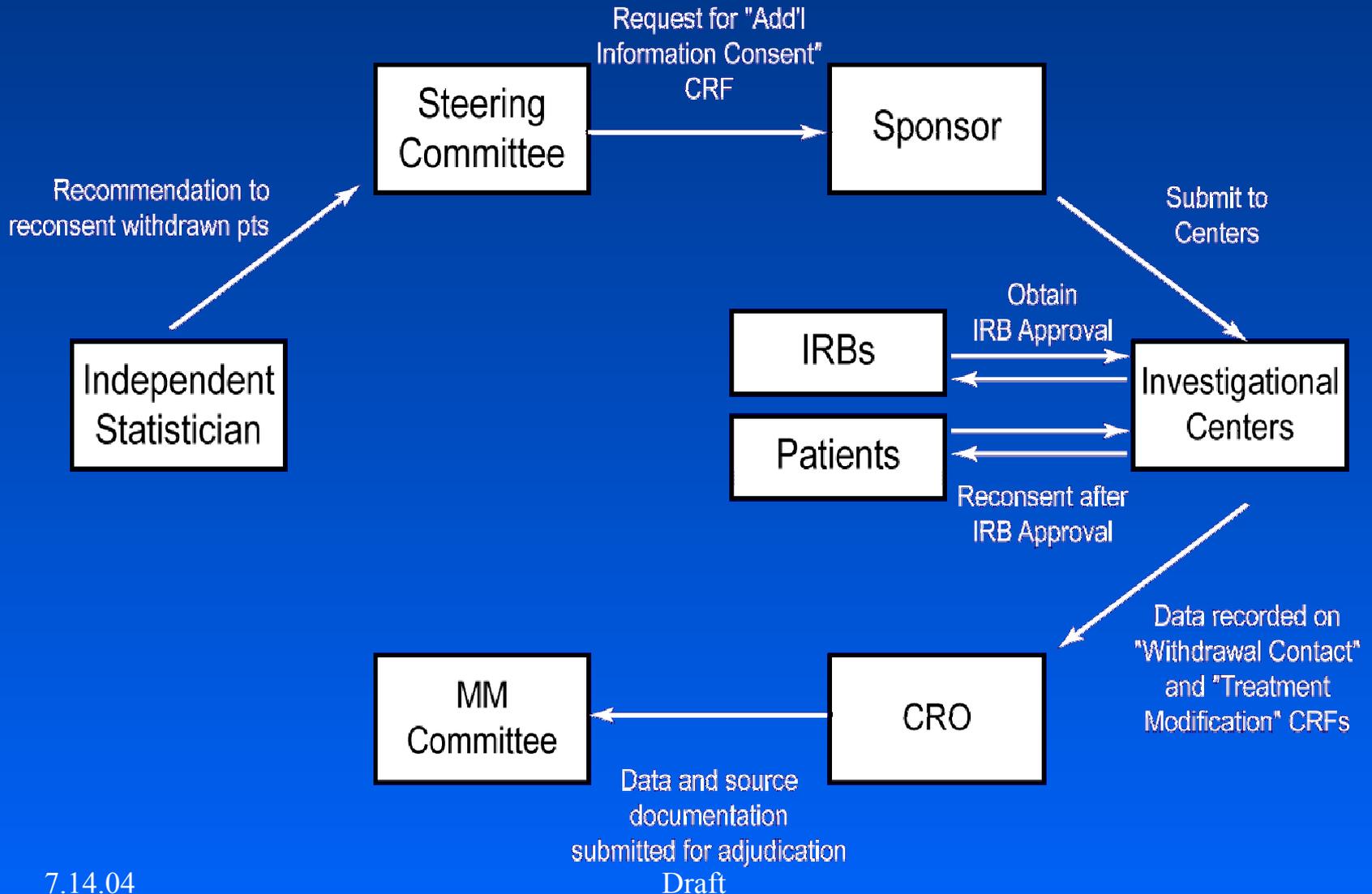
Study Withdrawals and Reconsent

David DeMets, Ph.D

Rationale

- **Study integrity may be affected by withdrawal**
- **Intention-to-treat analysis dictates diligence in obtaining outcome data on patients once they are randomized**
- **Recommendation made to Steering Committee to approach withdrawn patients who had not yet experienced a PEP event and reconsent them to improve completeness of data set**

Reconsent Process



Reconsent Process (cont.)

- **IRB approval was required before any medical records were reviewed or patients and/or legal representatives were contacted**
- **All data was collected on “Withdrawal Contact” CRF and “Treatment Modification” CRF**
- **Events collect via the “Withdrawal Contact” and “Treatment Modification” CRF’s was accompanied by source documentation for adjudication by the Morbidity and Mortality committee**

MM Committee Adjudication Post-withdrawal

- **Withdrawn patients in all study arms were considered**
- **58 patients did not have a PEP prior to withdrawal**
 - **Consent, hospitalization and/or death information was collected by investigative centers on 42 pts**
 - **PEP status unknown on remaining 16 patients**

Results of Reconsent Process

- **Data collection completed on patients withdrawn on or before November 30, 2002; primary endpoint status known for OPT=91%, CRT-D=99%**
- **Data collection completed on patients withdrawn on or before November 30, 2002; vital status known for OPT=96%, CRT-D=99% for the secondary endpoint of all-cause mortality**

Summary

- **Efforts to determine outcomes in withdrawn patients were necessary to preserve intention-to-treat analysis**
- **Obtaining consent and including post-withdrawal data in results helps maintain study integrity**

Safety of CRT-D, and Study Conclusions

Leslie A. Saxon, MD

Safety

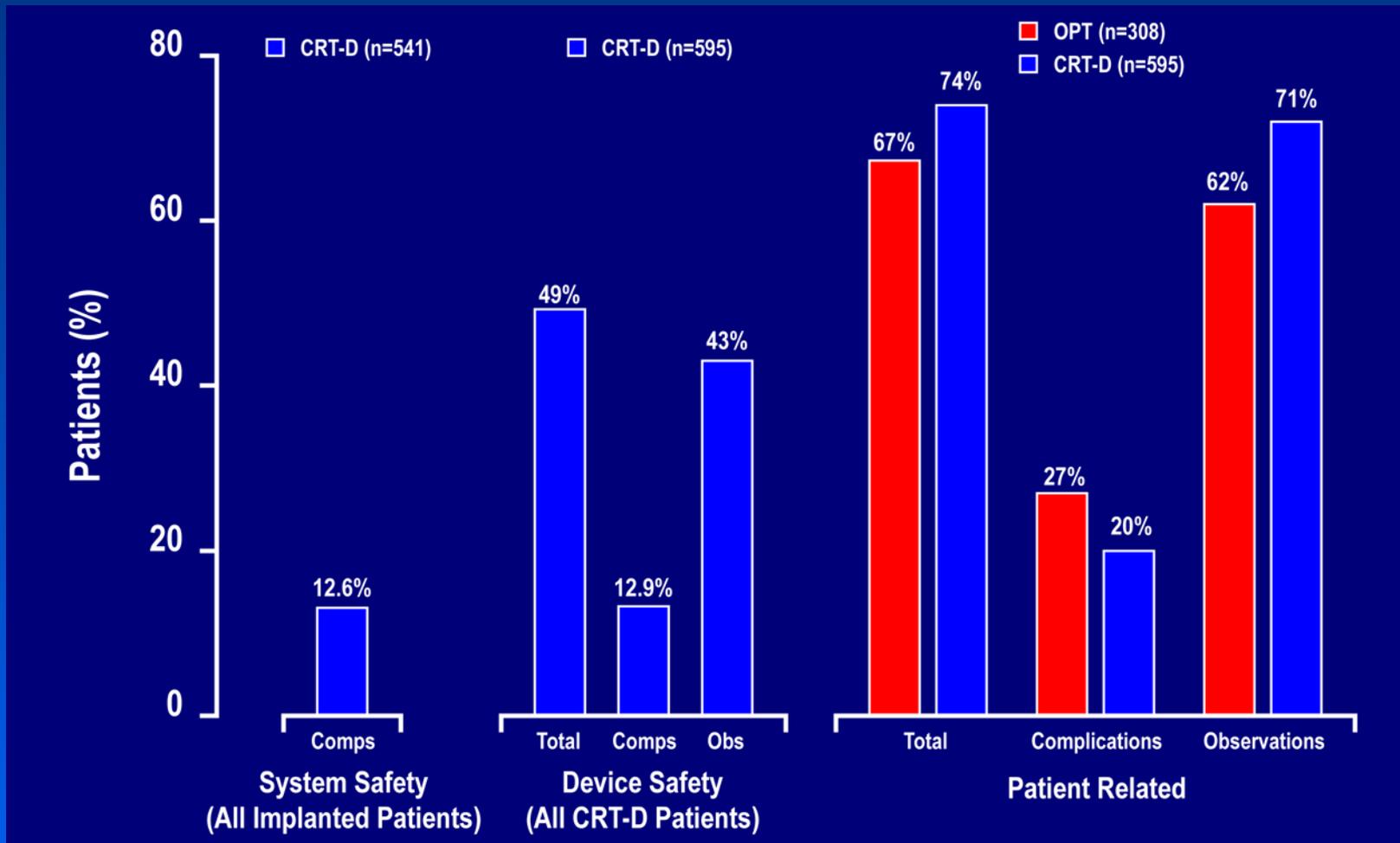
Background

- The CONTAK CD device (CRT-D) and EASYTRAK lead have been approved in a patient population with current indications for both CRT and an ICD (CONTAK CD study)
 - This includes patients with MADIT II criteria (approx. 40% of COMPANION patient population)
- The RENEWAL TR (CRT-P) device and EASYTRAK lead have been approved in a patient population with indications for CRT
- This analysis provides the safety profile of the CONTAK CD in patients indicated for CRT but who do not have a conventional ICD indication

Adverse Event Reporting

- Centers were required to report all adverse events, whether they were related to the device or not
- Complications were defined as adverse events resulting in:
 - Invasive intervention to correct
 - Permanent loss of device function
 - Death or permanent disability
- Observations were defined as adverse events that were resolved non-invasively and were generally transient or reversible

Adverse Event Categories

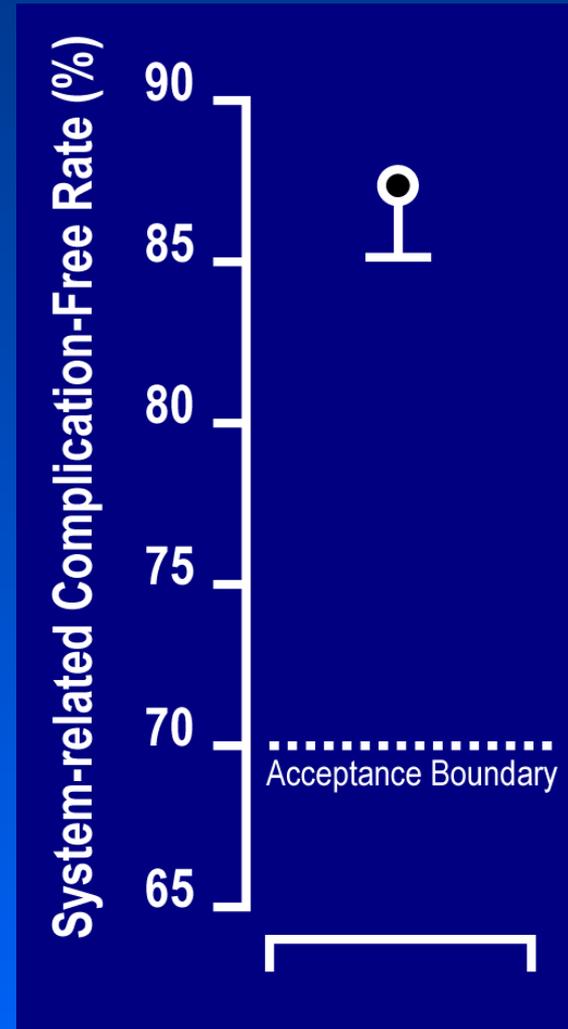


System Safety

- **System safety evaluated using complication-free rate (CFR) employed for previous CRT devices**
 - **CONTAK CD, MIRACLE, MIRACLE ICD**
- **System safety defined as:**
 - **Number of patients free from any system-related complication within six months of implant**
 - **Includes all components of the implanted system, whether investigational or not**
- **Lower boundary of 95% confidence interval of the device-related CFR was to be greater than 70% (Benchmark used in previous CRT trials)**

System Safety Results

- System-related complications were observed in 68/541 patients (12.6%)
- Events $\geq 1\%$ in frequency include:
 - Loss of LV capture, 25 pts (4.6%)
 - Loss of RA capture, 9 pts (1.7%)
 - Phrenic stimulation, 8 pts (1.5%)
- System-related complication-free rate = 87.4%, 95% LB = 85.1%
- System complication-free rates consistent with currently accepted rates for CRT



System Related Adverse Events (n=541)

Adverse Events Occurring within Six Months in $\geq 1\%$ of Patients

Event Description	Patients	Intervention		Loss of Therapy
		Reprogram	Invasive	
Phrenic nerve/diaphragm stimulation	59 (10.9%)	51 (9.4%)	7 (1.3%)	1 (0.2%)
Loss of LV capture/elevated threshold	36 (6.1%)	11 (1.9%)	22 (4.1%)	3 (0.2%)
Inappropriate shock (SVT)	23 (3.9%)	23 (3.9%)	0 (0%)	0 (0%)
Multiple counting - tachy	17 (3.1%)	15 (2.8%)	1 (0.2%)	1 (0.2%)
Loss of RA capture//elevated threshold	12 (2.0%)	3 (0.5%)	9 (1.5%)	0 (0%)
Inappropriate shock (oversensing)	11 (1.8%)	11 (1.8%)	0 (0%)	0 (0%)
Loss of RV capture/elevated threshold	8 (1.5%)	3 (0.6%)	5 (0.9%)	0 (0%)
Pacemaker mediated tachycardia	7 (1.0%)	7 (1.0%)	0 (0%)	0 (0%)

Procedure Related Adverse Events (n=595)

Adverse Events Occurring in $\geq 1\%$ of Patients

Event Description	Patients	Intervention		Loss of Therapy	Death/ Perm Dis
		Noninvasive	Invasive		
Post-surgical wound discomfort	62 (10.4%)	62 (10.4%)	0 (0%)	0 (0%)	0 (0%)
Hematoma	31 (5.2%)	29 (4.9%)	2 (0.3%)	0 (0%)	0 (0%)
Coronary venous trauma	23 (3.9%)	18 (3.0%)	5 (0.8%)	0 (0%)	0 (0%)
Pocket Infection	17 (3.1%)	14 (2.8%)	1 (0.2%)	2 (0.2%)	0 (0%)
Pneumothorax	10 (2.0%)	4 (0.5%)	6 (1.5%)	0 (0%)	0 (0%)
Hypotension	11 (1.8%)	11 (1.8%)	0 (0%)	0 (0%)	1 (0.2%)
Physical trauma	8 (1.3%)	8 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Heart block	7 (1.2%)	5 (0.8%)	1 (0.2%)	0 (0%)	1 (0.2%)
Physiologic reaction	6 (1.0%) ^{Draft}	6 (1.0%)	0 (0%)	0 (0%)	0 (0%)

Comparison of COMPANION Results to other Mortality Trials in Advanced HF

Trial (Back-ground Rx)	12 month Control group mortality	Active Rx	Sample Size	Relative Reduction (%)
BEST (ACEI +)	17%	Bucindolol (β-blocker)	2708	↓ 10%
RALES (ACEI +)	24%	Spiro- lactone (Aldo ant.)	1663	↓ 25%
COPERNICUS (ACEI +)	18%	Carvedilol (β-blocker)	2289	↓ 35%
COMPANION (ACEI, β-bl, SPL +)	19%	CRT-D	1520	↓ 36%

Overall Conclusions

- **When added to optimal pharmacological therapy in patients with moderate to severe heart failure, left ventricular dysfunction, and ventricular dyssynchrony:**
 - **Time to all-cause mortality or all-cause hospitalization was significantly reduced by CRT-D (HR=0.80, p=0.010)**
 - **All-cause mortality was significantly reduced by CRT-D (HR=0.64, p=0.003)**
- **All COMPANION endpoints for CRT-D have been met**
- **CRT-D is safe for use in this patient population, with a safety profile similar to the results of prior CRT studies**