Cardiac Resynchronization Therapy (CRT) Reduces Hospitalizations, and CRT + an Implantable Defibrillator (CRT-D) Reduces Mortality in Chronic Heart Failure: Preliminary Results of the COMPANION Trial

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Disclosures: Drs. Bristow, Saxon, Boehmer, Kass, and Feldman are consultants to Guidant (sponsor); Mr. DeVries is an employee of Guidant ; Dr. White is under contract to Guidant; Dr. DiCarlo is an employee of Pfizer

COMPANION

COMParison of MedicAl Therapy, PaciNg, and DefibrillatION in Heart Failure

Evolution of COMPANION
1999 - 2003

- Ability to Resynchronize
- Heart Failure Community -
  - Affect on M & M
- New Vision for Devices
- Do Mechanics Influence Outcomes/Remodeling?

- Trial Design
- Steering Committee DSMB/CRO
- Investment
- Commitment of Investigators & Sponsor

COMPANION Background

- Heart failure affects more than 5.5 million people annually in the U.S.
- Standard therapy improves symptoms and delays progressive remodeling by targeting:
  - Neurohormonal activation
  - Volume overload
- Approximately 30% of heart failure patients have disynchronous cardiac function secondary to conduction system delay

COMPANION: *Background*

- In the 25-30% of advanced HF patients with QRS widening, CRT improves contractile function and reverses remodeling, the 2 pathophysiological components of the DCM phenotype
- In ischemic cardiomyopathy with and without heart failure ICD therapy reduces mortality (MADIT-II)
- There are no appropriately powered clinical trials that have prospectively investigated the effect of CRT or CRT-D on major clinical endpoints, including mortality or mortality + hospitalization, in a heart failure population

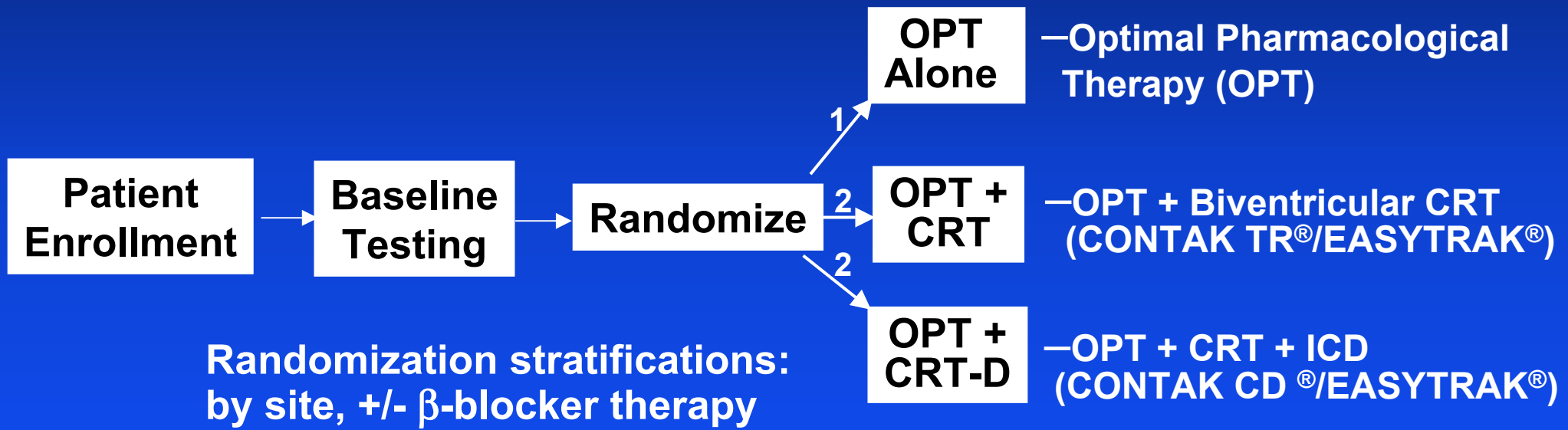
COMPANION: *Primary Hypotheses*

In patients with advanced heart failure and QRS widening, when used in conjunction with optimal pharmacological therapy

- **Biventricular cardiac resynchronization therapy (CRT) alone decreases combined all-cause mortality and all-cause hospitalization**
- **Biventricular CRT combined with cardioverter-defibrillator therapy (CRT-D) decreases combined all-cause mortality and all-cause hospitalization**

COMPANION: *Study Design*

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



Randomization stratifications: by site, +/- β-blocker therapy

Target Time to Implant ≤2 days from randomization

COMPANION: *Endpoints*

- **Primary**

  Time to death or hospitalization (both all cause)

  - **definition of hospitalization: all-cause except elective admit for CRT or CRT-D; also includes treatment of decompensated HF with vasoactive drugs for a period of >4 hours, in an urgent care setting**

- **Secondary**

  All cause mortality, cardiac morbidity, maximal exercise (substudy), other

- **Tertiary**

  Submaximal exercise, QOL, other

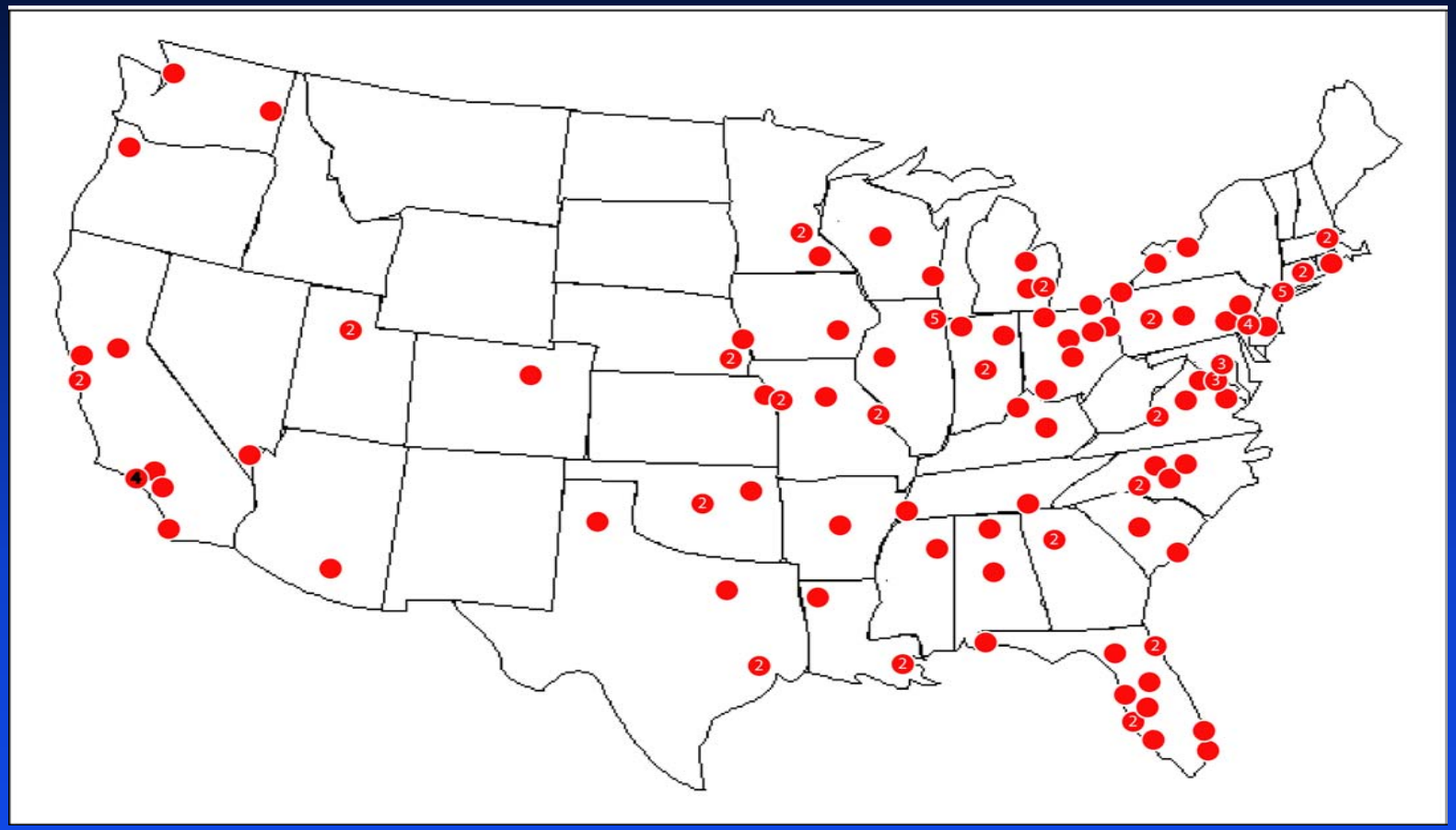
COMPANION:
Key Inclusion Criteria

- NYHA Class III or IV
- NSR, QRS ≥120 ms, PR interval >150ms
- LVEF ≤35%, LVEDD ≥60 mm
- Optimal pharmacological therapy
  - Beta blocker (for at least 3 months)
  - Diuretic, ACEI/ARB, Spironolactone (1 month); +/- Dig
- Hx of HF hospitalization (or Rx equivalent) <12 months, >1 month prior to enrollment

COMPANION: *Biostatistical Plan*

- Intention to treat, outcomes/safety data collection begins with randomization; open-label (ethical reasons)
- Alpha allocation: OPT vs. CRT = .02; OPT vs. CRT-D = .03
- Sample size assumptions and calculations:
  - ***primary endpoint***: 12 month event rate of 40% in OPT arm, 25% reduction in either device arm would require 2200 patients followed for ≥12 month (would translate to 1000 primary events), **power = >90%**
  - ***mortality (secondary endpoint)***: 12 month event rate of 24% in the OPT arm, 25% reduction in either device arm; **power = 80%**

COMPANION: *Study Sites*



The numbers within the red dot indicate the number of centers in that particular region

128 U.S. Centers, Avg 12 patients enrolled/center

COMPANION: *Sequential Monitoring and Trial Termination*

- First patient randomized January 24, 2000
- On 11/18/02 DSMB informed the Steering Committee (SC) that:
  - the trial was projected to have reached the target # of primary endpoints (~1000), median f/u = 16 mos
  - pre-specified efficacy monitoring boundaries had been nearly reached or crossed for the primary endpoint (CRT and CRT-D arms), as well as for mortality (CRT-D)
- As recommended by the DSMB, the SC stopped enrollment on that day, and all efficacy follow-up on 12/1/02

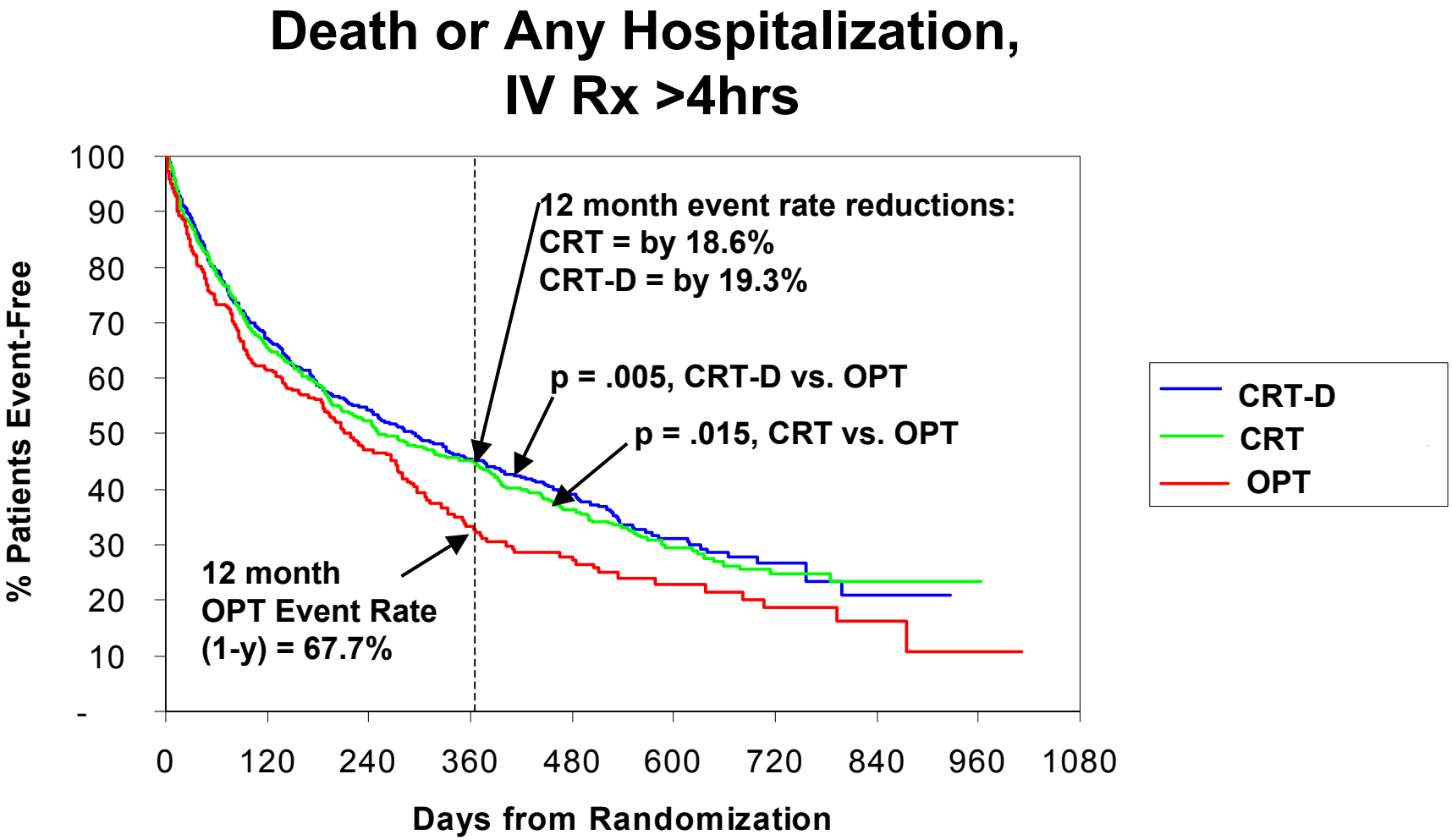
COMPANION: *Data Analysis*

- **Primary Analysis**
  - includes follow-up of all study withdrawals, using re-consent to capture events in patients who had withdrawn consent; process requires new IRB approval and is incomplete as of 3/31/03
  - endpoint adjudication process also incomplete
- **Analysis for ACC presentation 3/31/03**
  - preliminary, based on data from Nov 2002 DSMB mtg
  - all patients/events censored at date of withdrawal
  - differential withdrawal, ↑ in OPT group creates potential for bias, due to different lengths of f/u
  - endpoints are from CRFs, unadjudicated
  - all p values are nominal
- ***Despite these caveats, we believe that the results presented today are likely an accurate representation of the COMPANION final outcomes***

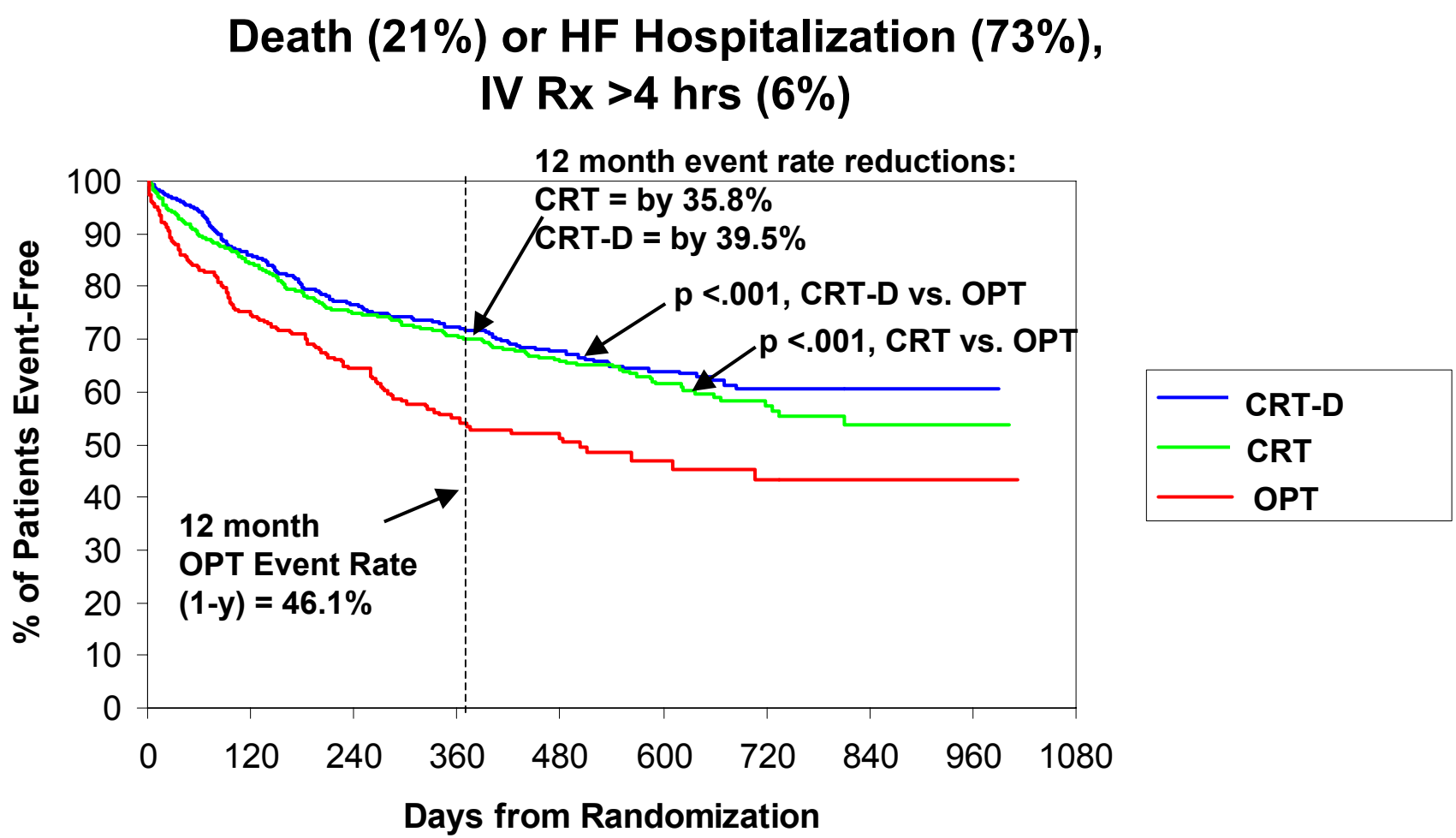
COMPANION: *Selected Baseline Characteristics (total randomized n = 1520)*

Parameter	A. OPT n = 308	B. CRT n = 617	C. CRT-D n = 595	p values, A/B, A/C
Age (years)	67	65	66	0.12, 0.14
Male gender (%)	69	67	67	0.70, 0.73
NYHA Class III (%)	82	87	86	.047, 0.12
Duration of HF (Mos)	4.9	4.8	4.4	0.97, 0.44
LVEF (%)	22.8	22.0	22.5	0.08, 0.47
QRS duration (ms)	156	159	159	0.17, 0.11
Ischemic CMY (%)	59	54	55	0.16, 0.23
LBBB (%)	70	69	73	0.84, 0.23
RBBB (%)	9	12	10	0.10, 0.48
ACEI (%) (or ARB)	69 (89)	70 (89)	68 (90)	0.75. 0.90 0.93, 0.66
Beta Blocker (%)	66	68	68	0.54, 0.69
Spironolactone (%)	55	53	55	0.69, 0.94

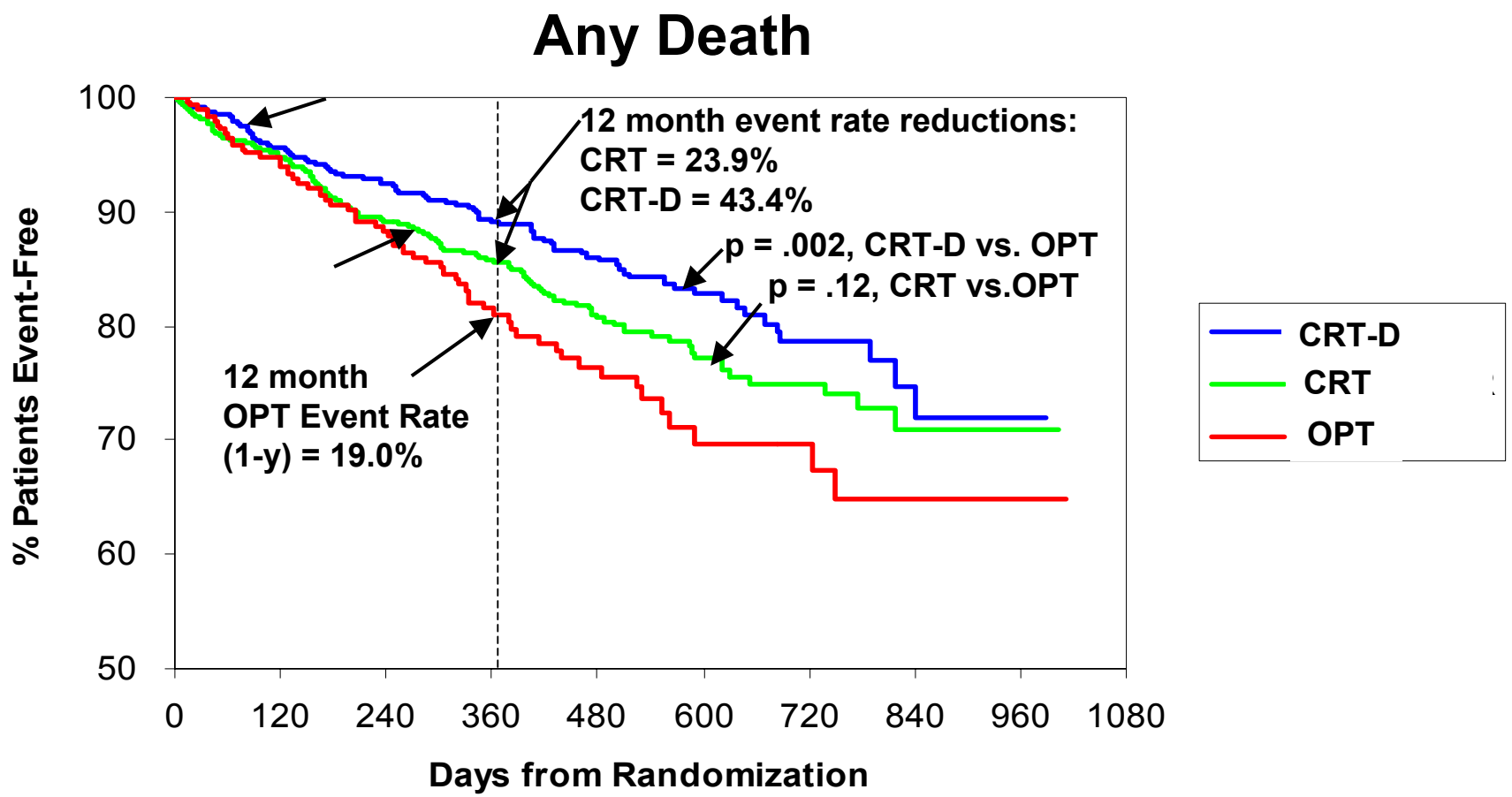
COMPANION: *Primary Endpoint*



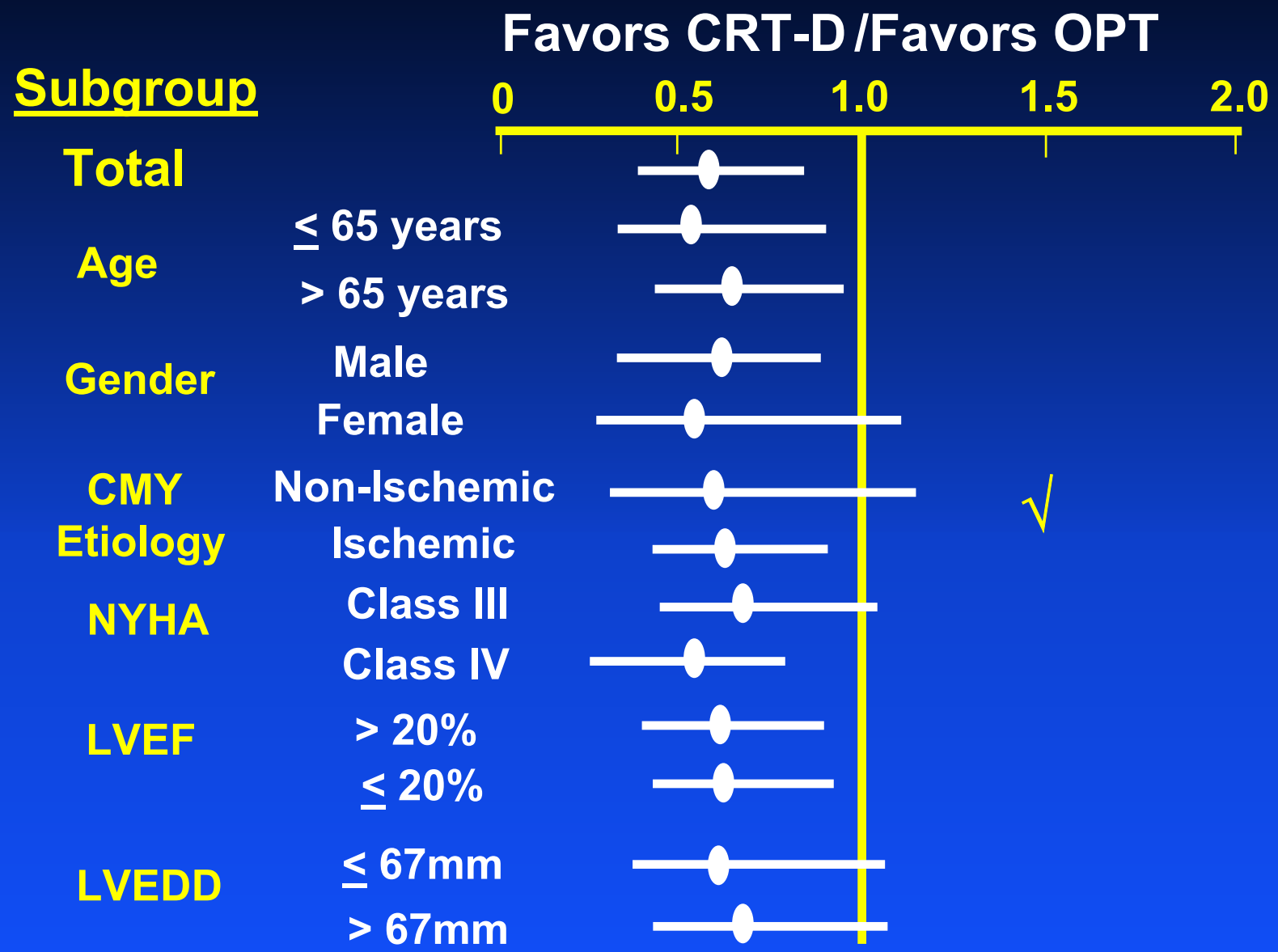
COMPANION: *Death or HF Hospitalization (% of composite ep)*



COMPANION: *Secondary Endpoint of All-Cause Mortality*



Subgroup Hazard Ratios (CRT-D vs. OPT), Mortality



ACC Late-Breaker 3/31/03 Preliminary Results

COMPANION:
Implant Data and Adverse Events

Parameter	OPT	OPT + CRT	OPT + CRT-D
Implant Success (%) Median Time to Implant (Days)	–	88.3 2.0	92.0 2.0
Total Implant Time (min±SD)†	–	200 ±116	213 ±131
Total overall AEs (% of total patients)	74	89*	87*
Moderate or Severe overall AEs (% of total patients)	55	58	60
Moderate or Severe Device AEs (% of total patients)	1.0	9.7* 2 deaths	7.6* 2 deaths
30 day crude mortality (%), from randomization or {implantation}	1.0 {–}	1.8 {2.1}	0.9 {0.7}

†, after 7/1/01; *, p < .05 vs. OPT

COMPANION:
Summary of Major Outcomes

- Reduction in the combined endpoints of death + all-cause, CV or HF hospitalizations was due to CRT, since CRT and CRT-D resulted in similar effect sizes
- CRT was associated with a trend for reduction in mortality (24% reduction in the 12 month rate)
- The addition of an ICD to CRT increased the mortality reduction, resulting in a highly significant decrease in mortality (43% reduction in the 12 month rate)
- No obvious difference in mortality benefit of CRT-D in ischemic vs. nonischemic CMY
- Complications of device therapy were acceptable

COMPANION: *Firsts*

- 1st trial of CRT or CRT-D to use mortality + morbidity as primary endpoint; first to demonstrate reduction in M&M by CRT or CRT-D, mortality by CRT-D in a general HF population
- 1st trial to measure effects of CRT and CRT-D
- 1st CRT trial to measure efficacy from time of randomization (ITT)
- 1st HF trial to use total hospitalizations in PEP
- 1st HF Trial to be conducted on a background of ACEI, β-blockade, spironolactone
- 1st HF trial to use an historical HF hospitalization as an inclusion criterion

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