An Introduction to Cardiac Resynchronization Therapy
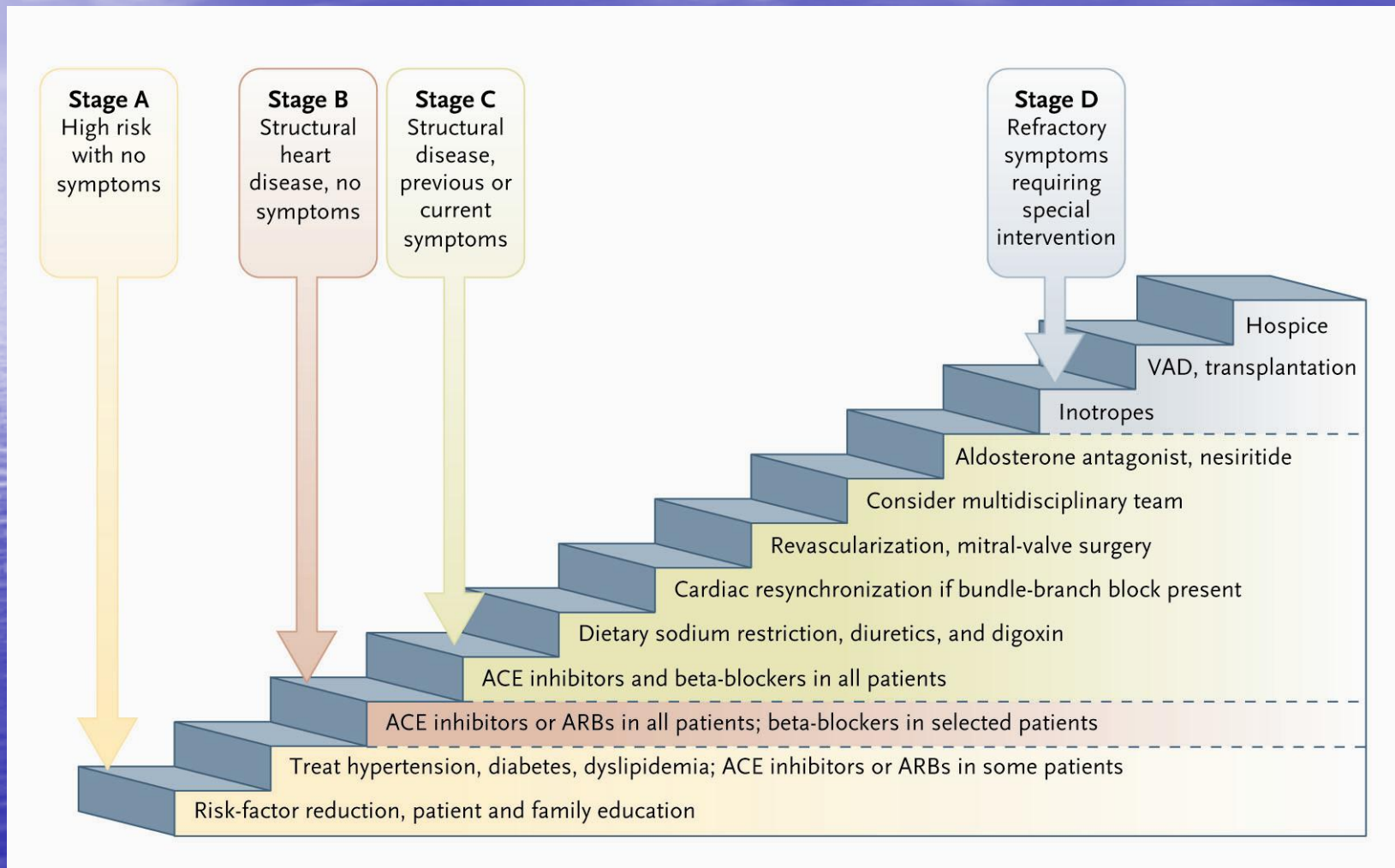
Kevin Wolfe MD

September 21, 2018

Conflicts of Interest

- None

The Spectrum of Heart Failure

Stage A High risk with no symptoms

Stage B Structural heart disease, no symptoms

Stage C Structural disease, previous or current symptoms

Stage D Refractory symptoms requiring special intervention

Hospice

VAD, transplantation

Inotropes

Aldosterone antagonist, nesiritide

Consider multidisciplinary team

Revascularization, mitral-valve surgery

Cardiac resynchronization if bundle-branch block present

Dietary sodium restriction, diuretics, and digoxin

ACE inhibitors and beta-blockers in all patients

ACE inhibitors or ARBs in all patients; beta-blockers in selected patients

Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs in some patients

Risk-factor reduction, patient and family education

Recommendations for pharmacological therapy for management of stage C HF*r*EF

| Recommendations	COR	LOE
Diuretics		
Diuretics are recommended in patients with HF*r*EF with fluid retention	I	C
ACE inhibitors		
ACE inhibitors are recommended for all patients with HF*r*EF	I	A
ARBs		
ARBs are recommended in patients with HF*r*EF who are ACE inhibitor intolerant	I	A
ARBs are reasonable as alternatives to ACE inhibitors as first-line therapy in HF*r*EF	IIa	A
Addition of an ARB may be considered in persistently symptomatic patients with HF*r*EF on GDMT	IIb	A
Routine *combined* use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful	III: Harm	C
Beta blockers		
Use of 1 of the 3 beta blockers proven to reduce mortality is recommended for all stable patients	I	A
Aldosterone receptor antagonists		
Aldosterone receptor antagonists are recommended in patients with NYHA class II-IV who have LVEF ≤35 percent	I	A
Aldosterone receptor antagonists are recommended in patients following an acute MI who have LVEF ≤40 percent with symptoms of HF or DM	I	B
Inappropriate use of aldosterone receptor antagonists may be harmful	III: Harm	B
Hydralazine and isosorbide dinitrate		
The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA class III-IV HF*r*EF on GDMT	I	A
A combination of hydralazine and isosorbide dinitrate can be useful in patients with HF*r*EF who cannot be given ACE inhibitors or ARBs	IIa	B
Digoxin		
Digoxin can be beneficial in patients with HF*r*EF	IIa	B

Magnitude of Benefit

Demonstrated benefits of guideline-recommended heart failure therapies

Guideline-recommended therapy	Relative risk reductions in pivotal randomized clinical trial(s) (%)	Number needed to treat for mortality benefit (standardized to 12 m)	
Angiotensin converting enzyme inhibitor OR angiotensin II receptor blocker	17	77	
Beta-blocker therapy (carvedilol, bisoprolol, extended release metoprolol succinate)	34	28	
Aldosterone antagonist	30	18	
Hydralazine plus nitrate	43	21	
Cardiac resynchronization therapy	36	24	
Implantable cardioverter-defibrillator	23	70	

Original figure modified for this publication. Fonarow GC, Yancy CW, Hernandez AF, et al. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. Am Heart J 2011;

Prevalence Of LBBB

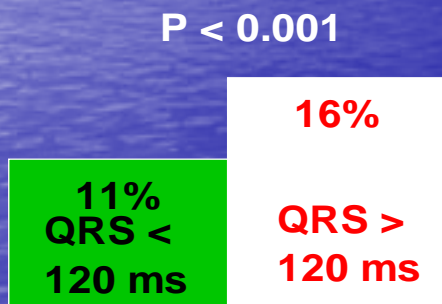**Left Bundle Branch Block More Prevalent
with Impaired LV Systolic Function**

Preserved LVSF (1)	8%
Impaired LVSF (1)	24%
Moderate/Severe HF (2)	38%
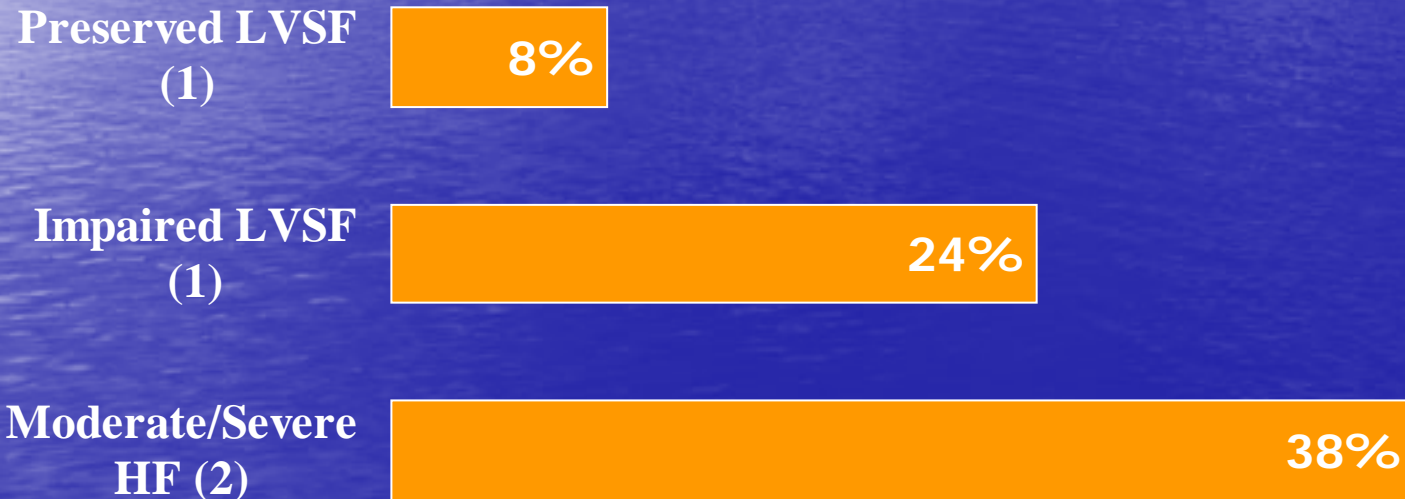
Adverse Cardiac Mechanical Consequences of Conduction Problems in Systolic Heart Failure

	Mechanical effects	Electrical causes
Inappropriate AV timing	Inadequate LV filling due to improper AV interval	First degree AV block Interatrial conduction delay
Interventricular dyssynchrony	RV-LV competition in filling and ejection	BBB IVCD
Intraventricular dyssynchrony	Lack of coordinated LV contraction and relaxation	BBB IVCD

Abbreviations: AV = Atrioventricular, BBB = Bundle branch block, IVCD = Intraventricular conduction delay, LV = Left ventricular, RV = Right ventricular.

Prognosis with Ventricular Dyssynchrony

Long-term (45 Mo) Survival

1 Year Survival

P < 0.001

16%

11%
QRS <
120 ms

QRS >
120 ms

P < 0.001

49%

34%

QRS <
120 ms

QRS ≥
120 ms

Baldasseroni S, et al. *Eur Heart J* 2002;23:1692-98
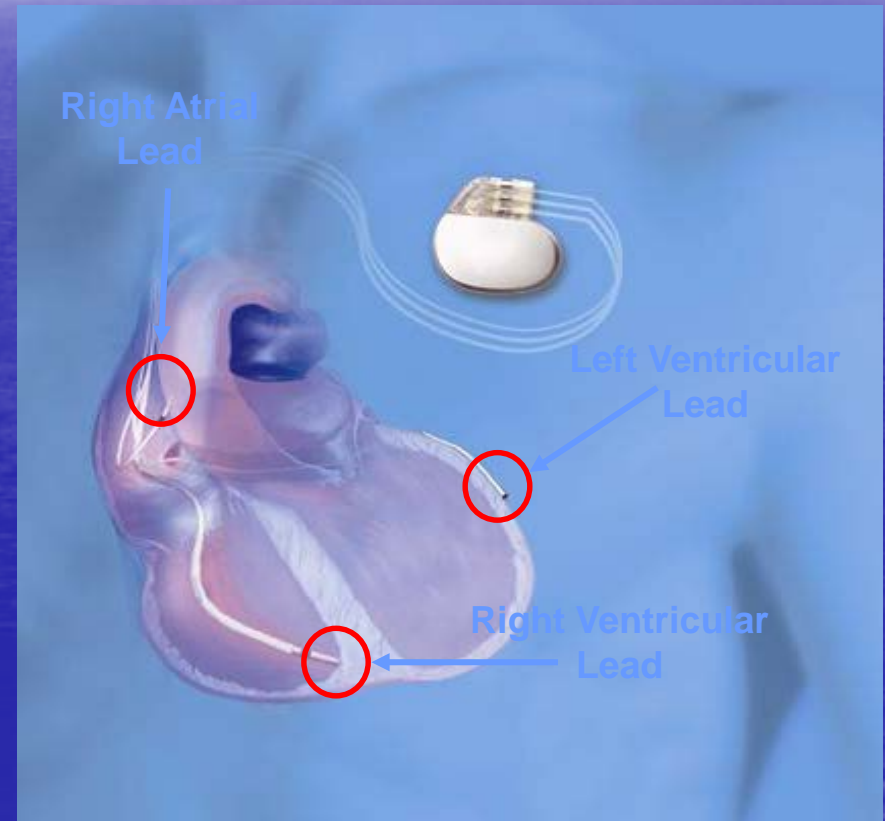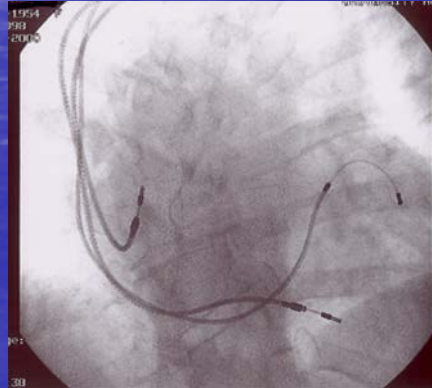N=5,517
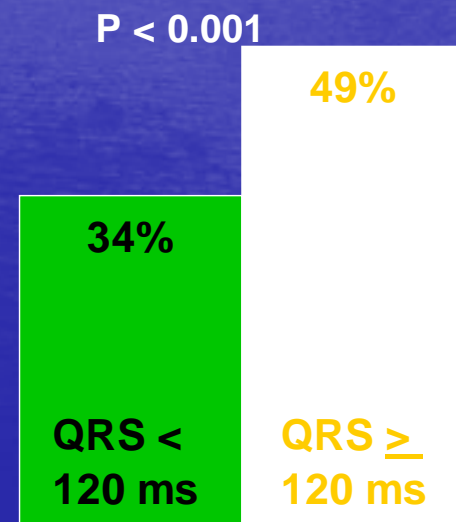
Iuliano et al. AHJ 2002;143:1085-91
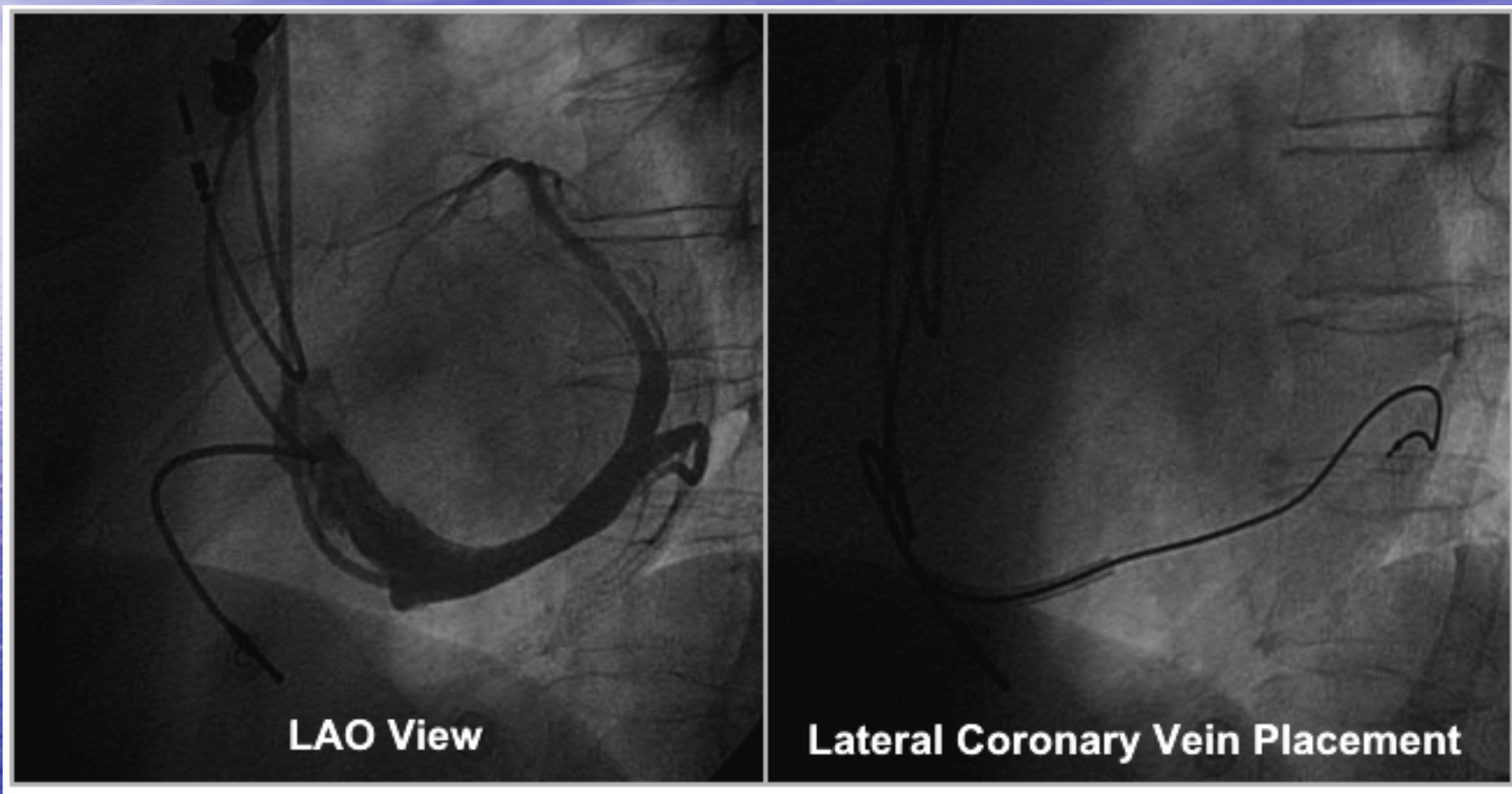N=669

Achieving Cardiac Resynchronization

GOAL: ATRIAL SYNCHRONOUS BIVENTRICULAR PACING

TRANSVENOUS APPROACH FOR LEFT VENTRICULAR LEAD VIA CORONARY SINUS
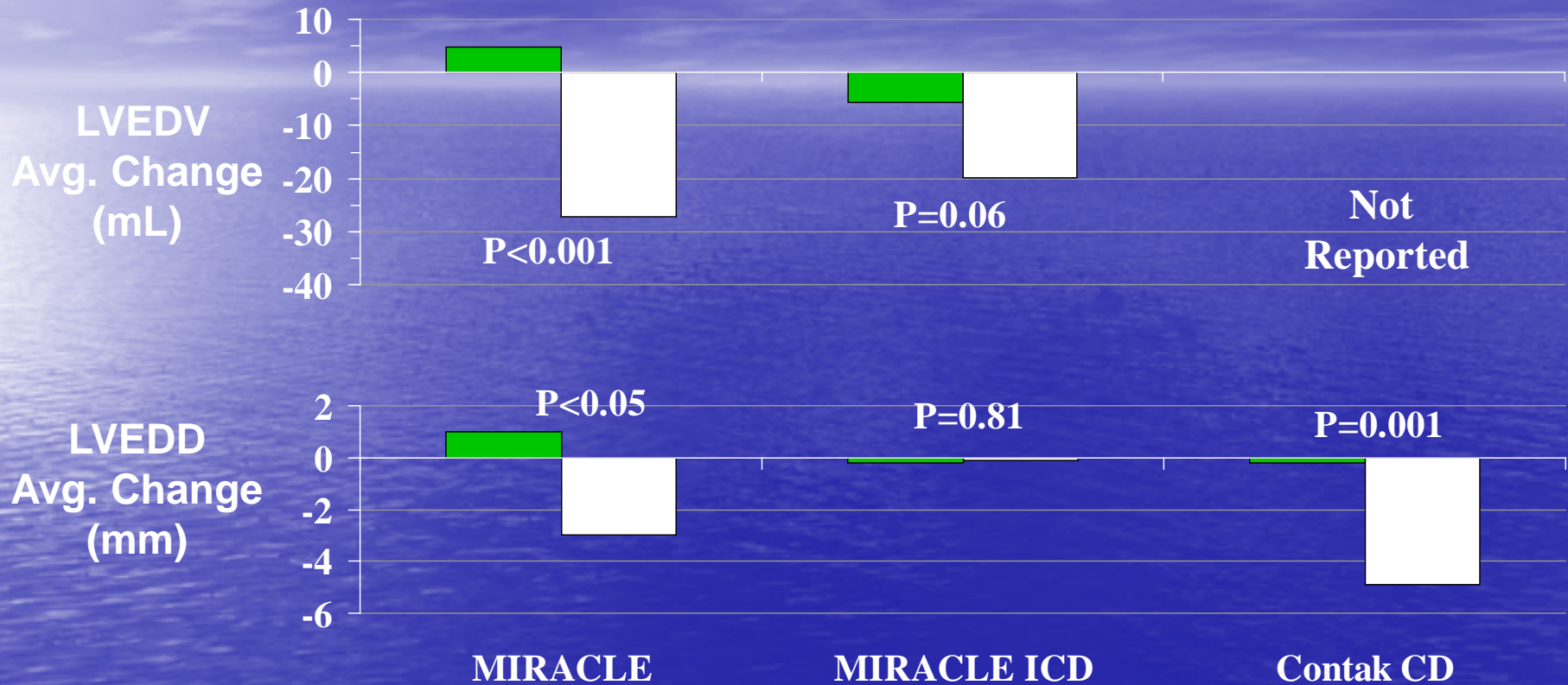
BACK-UP EPICARDIAL APPROACH

Right Atrial Lead

Left Ventricular Lead

Right Ventricular Lead

Doug Smith:

EASYTRAK lead system

LAO View   **Lateral Coronary Vein Placement**

CRT Effect on LV Structure at 6 Months in Moderate to Severe Heart Failure

LVEDV Avg. Change (mL)

10
0
-10
-20
-30
-40

P<0.001

P=0.06

Not Reported

LVEDD Avg. Change (mm)

2
0
-2
-4
-6

P<0.05

P=0.81

P=0.001

MIRACLE   MIRACLE ICD   Contak CD

■ Control ■ CRT

Data sources: MIRACLE: *Circulation* 2003;107:1985-1990
MIRACLE ICD:*JAMA* 2003;289:2685-2694
Contak CD: *J Am Coll Cardiol* 2003;2003;42:1454-1459

CRT Improves Exercise Capacity in Moderate to Severe Heart Failure
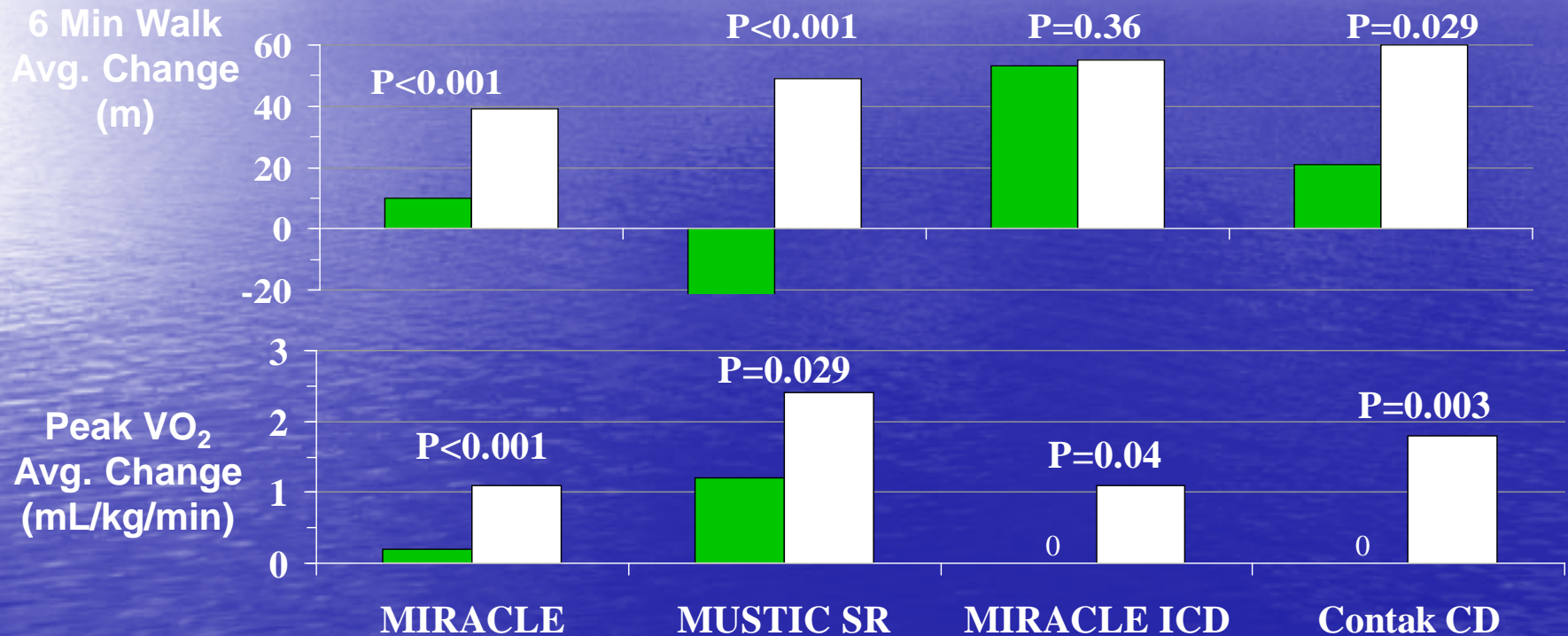
6 Min Walk Avg. Change (m)

P<0.001   P<0.001   P<0.001   P=0.36   P=0.029

60
40
20
0
-20

Peak VO$_2$ Avg. Change (mL/kg/min)

3
2
1
0

P<0.001   P=0.029   P=0.04   P=0.003

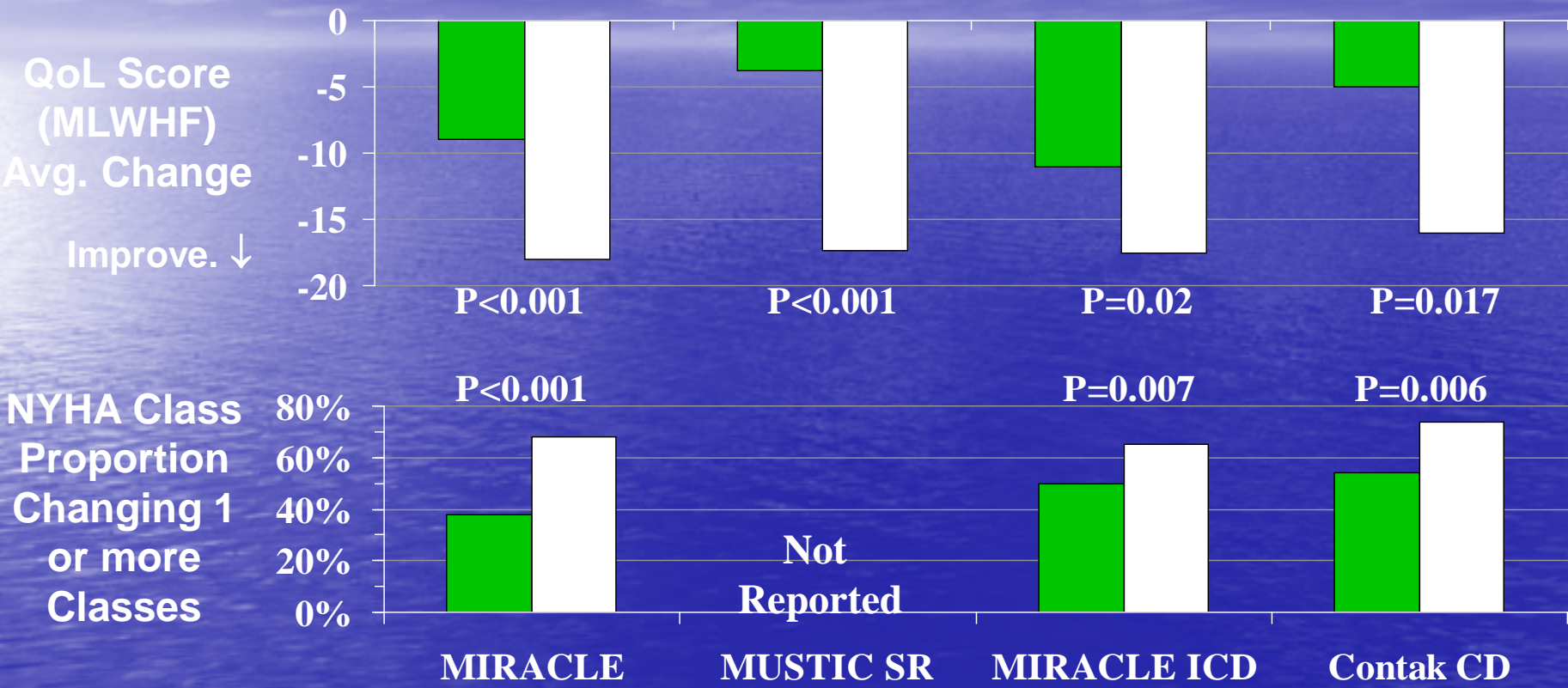MIRACLE   MUSTIC SR   MIRACLE ICD   Contak CD

Data sources:
MIRACLE: *Circulation* 2003;107:1985-90
MUSTIC SR: NEJM 2001;344:873-80
MIRACLE ICD:*JAMA* 2003;289:2685-94
Contak CD: *J Am Coll Cardiol* 2003;2003;42:1454-59

■ Control ■ CRT

CRT Improves Quality of Life & Functional Capacity in Moderate to Severe Heart Failure

QoL Score (MLWHF) Avg. Change

Improve. ↓

NYHA Class Proportion Changing 1 or more Classes

Data sources:
MIRACLE: *Circulation* 2003;107:1985-90
MUSTIC SR: NEJM 2001;344:873-80
MIRACLE ICD:*JAMA* 2003;289:2685-94
Contak CD: *J Am Coll Cardiol* 2003;2003;42:1454-59

COMPANION: *Key Eligibility 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); +/- digoxin

- Hx of HF hospitalization (or Rx equivalent)

  <12 months, >1 month prior to enrollment

- No bradycardiac or tachyarrhythmic device indication at the time of enrollment
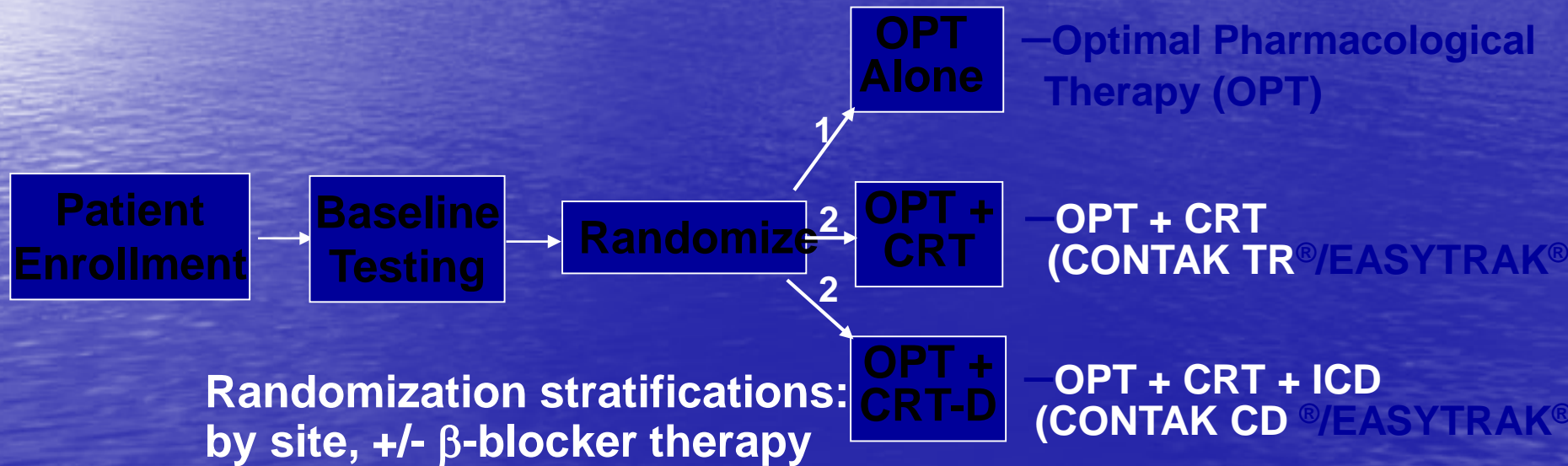
COMPANION: *Endpoints*

- Primary Endpoint:

  – Composite of time to first all-cause mortality or all-cause hospitalization analyzed from randomization

    - Hospital emergency or outpatient (unscheduled) administration of IV inotropes or vasoactive drugs for more than 4 hours were considered a hospitalization primary endpoint

COMPANION (COmparison of Medical Therapy, Pacing, ANd DefibrillatION in Heart Failure):
Study Design

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

Patient Enrollment → **Baseline Testing** → **Randomize**

- 1 → **OPT Alone** —**Optimal Pharmacological Therapy (OPT)**
- 2 → **OPT + CRT** —**OPT + CRT (CONTAK TR®/EASYTRAK®**
- 2 → **OPT + CRT-D** —**OPT + CRT + ICD (CONTAK CD ®/EASYTRAK®**

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

**Target Time to Implant ≤2 days from randomization**

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

Parameter	OPT n = 308	CRT n = 617	CRT-D n = 595	p values, OPT/CRT, OPT/CRT-D
Age (years)	68	67	66	0.12, 0.14
Male gender (%)	69	67	67	0.70, 0.73
NYHA Class III (%)	82	87	86	0.05, 0.12
Duration of HF (Yrs)	3.6	3.7	3.5	0.88, 0.43
LVEF (%)	22	20	22	0.08, 0.47
QRS duration (ms)	158	160	160	0.17, 0.10
Ischemic CMY (%)	59	54	55	0.14, 0.23
LBBB (%)	70	69	73	0.84, 0.32
RBBB (%)	9	12	10	0.10, 0.48
ACEI (%) (or ARB)	69 (89)	70 (89)	69 (90)	0.75. 0.90 (0.93, 0.66)
Beta Blocker (%)	66	68	68	0.54, 0.68
Spironolactone (%)	55	53	55	0.69, 0.94

COMPANION: *Primary Endpoint*
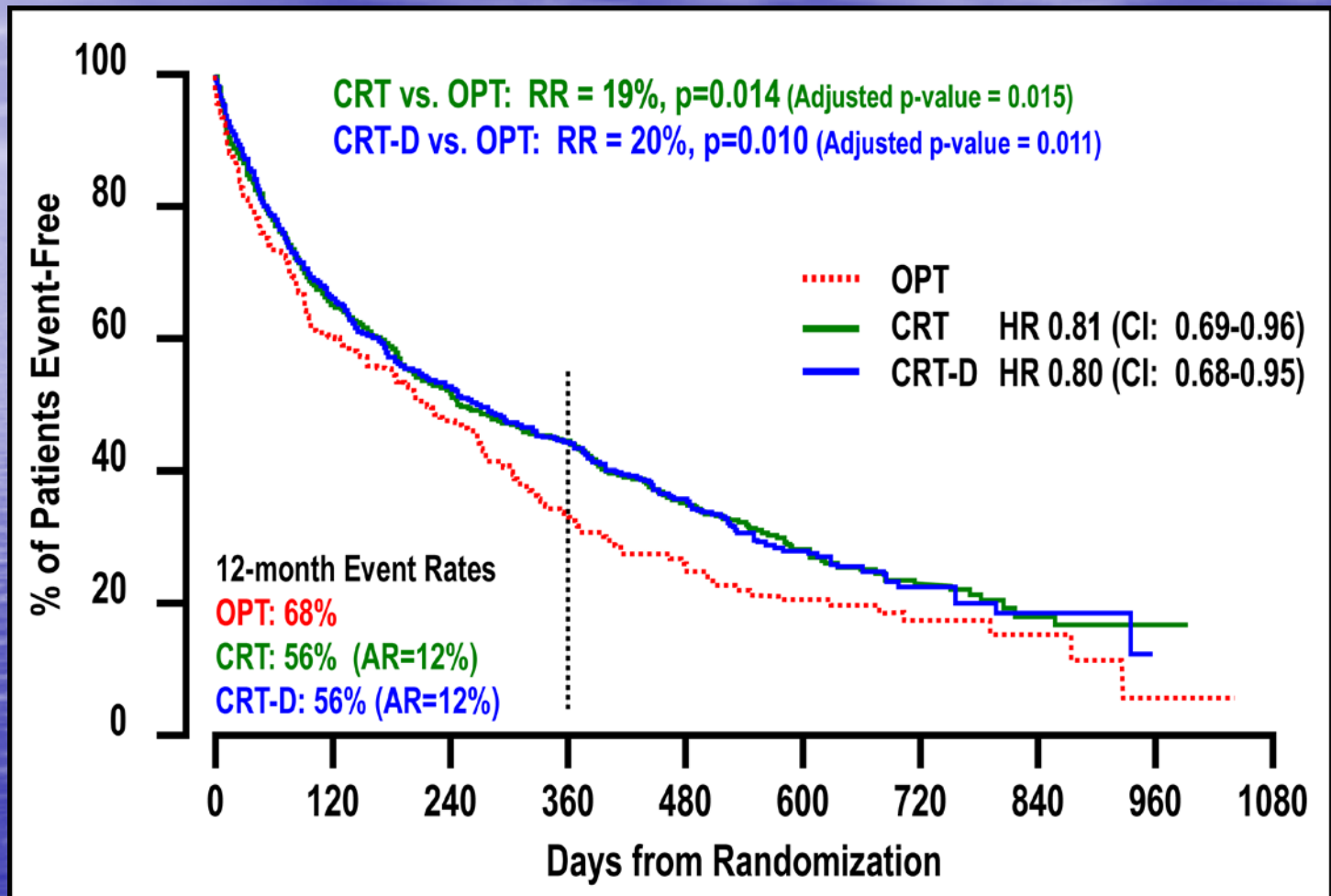
COMPANION: *Secondary Endpoint of All-Cause Mortality*
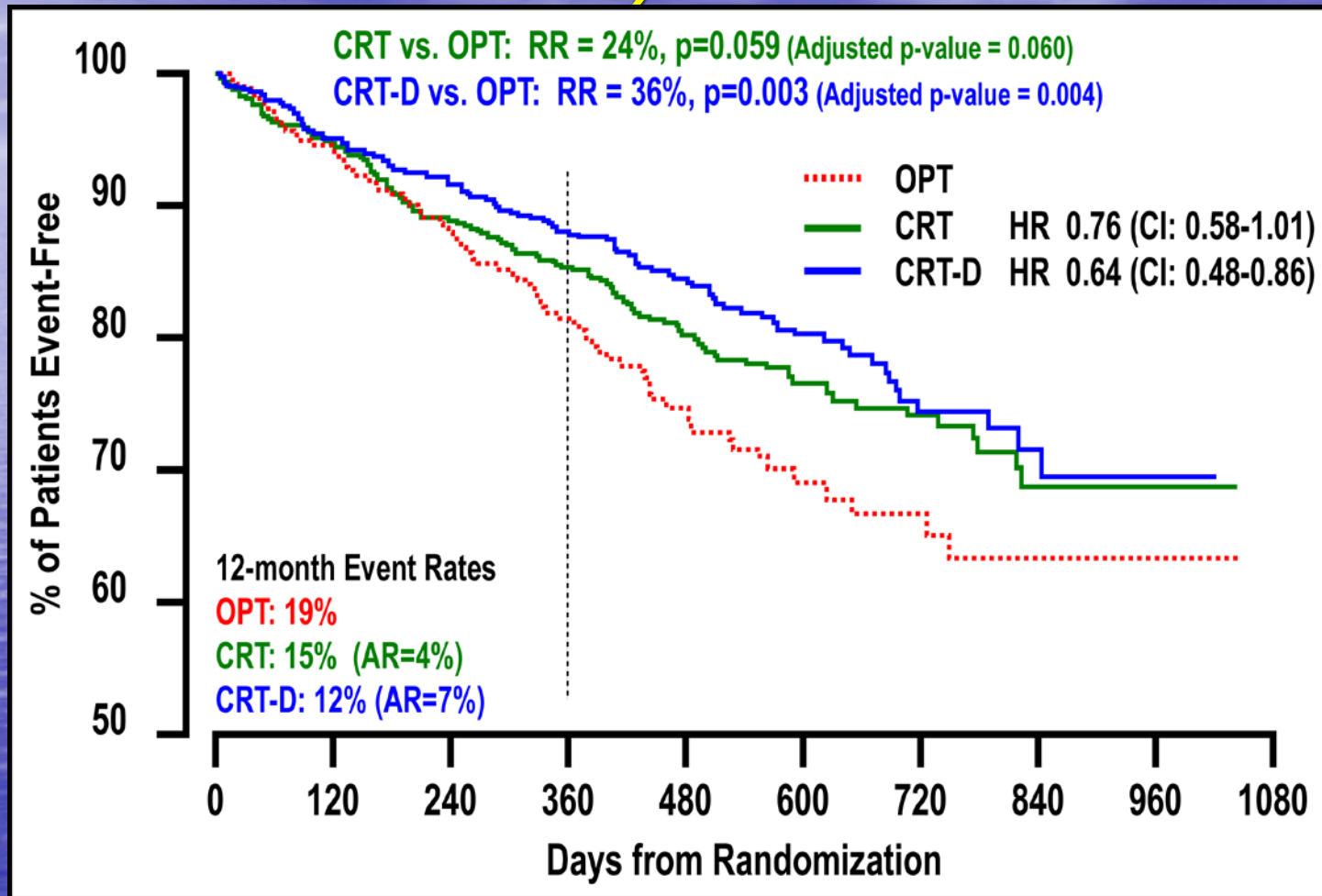
Different Math

- At 2 years 77 of 308 patients on OPT died(25%) , 105 of 595 patients with CRT-D died (17.6%)
- Absolute reduction in mortality of 7.4% or 3.7%/year
- 60 % of patients improved one NYHA category

CONCLUSIONS

When added to optimal pharmacological therapy in patients with moderate-severe LV dysfunction, NYHA Class III or IV symptoms and QRS lengthening:

- **CRT or CRT-D reduces mortality + hospitalizations**

- **CRT-D reduces mortality**
  - **2/3 of the effect size can be attributed to CRT**

CCS Guidelines 2017

RECOMMENDATION

58. We recommend CRT for patients in sinus rhythm with NYHA class II, III, or ambulatory class IV HF despite optimal medical therapy, a LVEF ≤ 35%, and QRS duration ≥ 130 ms with left bundle branch block (LBBB) (Strong Recommendation; High-Quality Evidence).

59. We suggest that CRT may be considered for patients in sinus rhythm with NYHA class II, III, or ambulatory class IV HF despite optimal medical therapy, a LVEF ≤ 35%, and QRS duration ≥ 150 ms with non-LBBB (Weak Recommendation; Low-Quality Evidence).

CCS Guidelines 2017

RECOMMENDATION

60. We suggest that CRT may be considered for patients in permanent AF who can expect to achieve close to 100% pacing and are otherwise suitable for this therapy (Weak Recommendation; Low-Quality Evidence).

CCS Guidelines

RECOMMENDATION

61. We suggest that CRT might be considered for patients who require chronic right ventricular (RV) pacing in the setting of HF symptoms and reduced LVEF (Weak Recommendation; Moderate-Quality Evidence).

62. We recommend CRT not be used for patients with QRS < 130 ms, irrespective of HF symptoms, LVEF, or the presence or absence of mechanical dyssynchrony shown on current imaging techniques (Strong Recommendation; Moderate-Quality Evidence).

63. We recommend the addition of ICD therapy be considered for patients referred for CRT who meet primary ICD requirements (Strong Recommendation; High-Quality Evidence).

Values and preferences. These recommendations place a value on the benefit of CRT in patient groups included in the landmark RCTs and high-quality systematic reviews, and less value on post hoc subgroup analyses from clinical trials. On the basis of the available evidence, there is insufficient evidence to recommend CRT in patients with NYHA class I status or in hospitalized NYHA class IV patients. Patients with a QRS duration ≥ 150 ms are universally more likely to benefit from CRT than patients with less QRS prolongation. CRT pacemaker therapy should also be considered in patients who are not candidates for ICD therapy such as those with a limited life expectancy because of significant comorbidities, and in patients who decline to receive an ICD.

Conclusions

- Cardiac resynchronization therapy reduces hospitalizations and mortality in selected heart failure patients

- CRT-P is very likely close to CRT-D in effectiveness

- Symptomatic response rates are approximately 70 % across all the trials