

Device Therapy for Heart Failure Patients with Reduced Ejection Fraction

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Relevant Financial Relationship Disclosure Statement

*Device Therapy for Heart Failure Patients with Reduced
Ejection Fraction: Liviu Klein, MD, MS*

I **will** discuss off label use and/or investigational use of devices.

The following relevant financial relationships exist related to this presentation:

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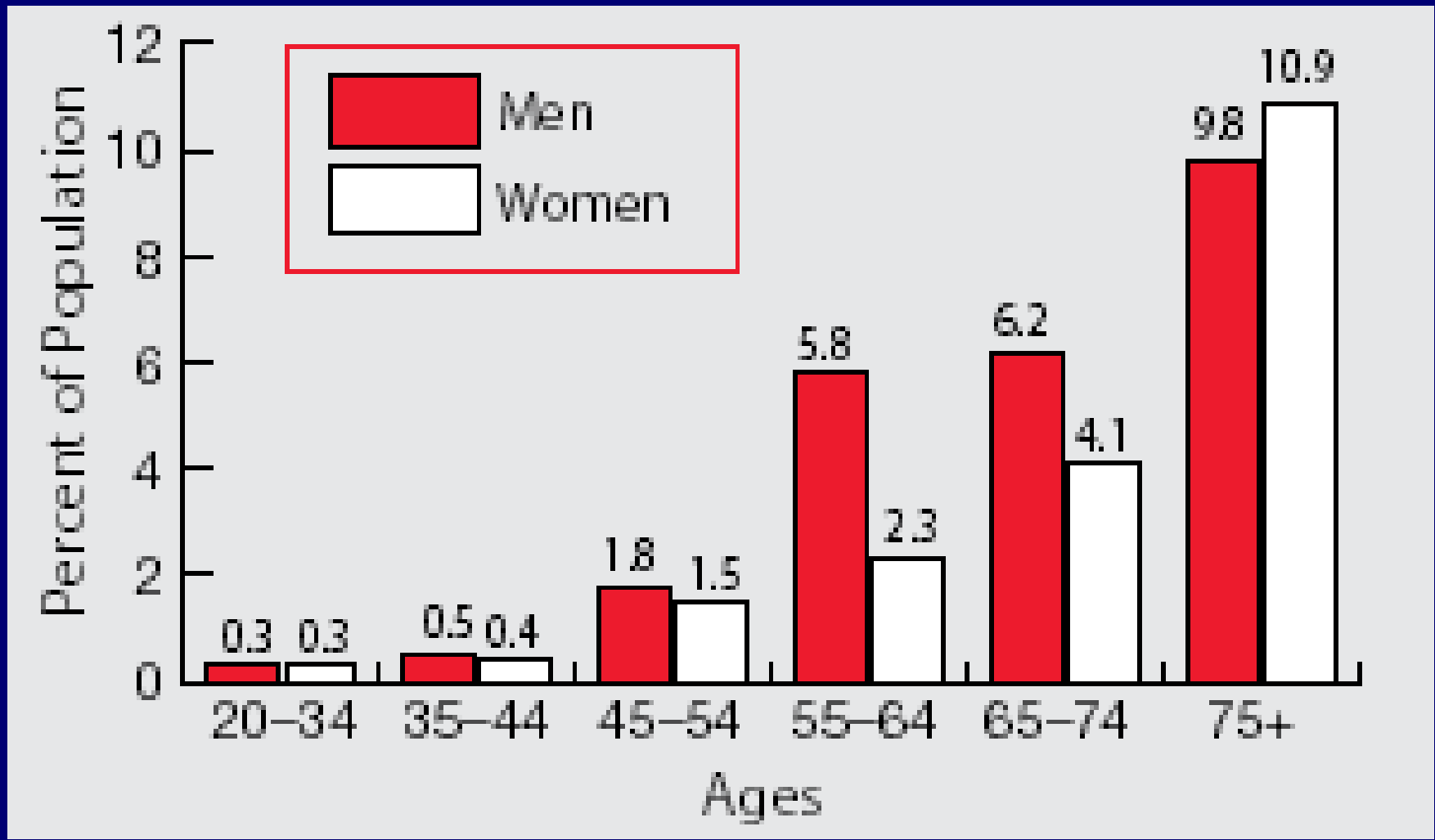
Heart Failure Definition

- A complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.
- Cardinal manifestations are dyspnea and fatigue (which may limit exercise tolerance), and fluid retention (which may lead to pulmonary congestion and peripheral edema).
- Both abnormalities can impair the functional capacity and quality of life of affected individuals, but they do not necessarily dominate the clinical picture at the same time.



Hunt SA et al. Circulation. 2009; 119: e391-e479.

Prevalence of Heart Failure



Lloyd-Jones DM et al. *Circulation*. 2009; 119: e21-181.

Temporal Changes in Incidence

Table 1. Temporal Trends in the Age-Adjusted Incidence of Heart Failure

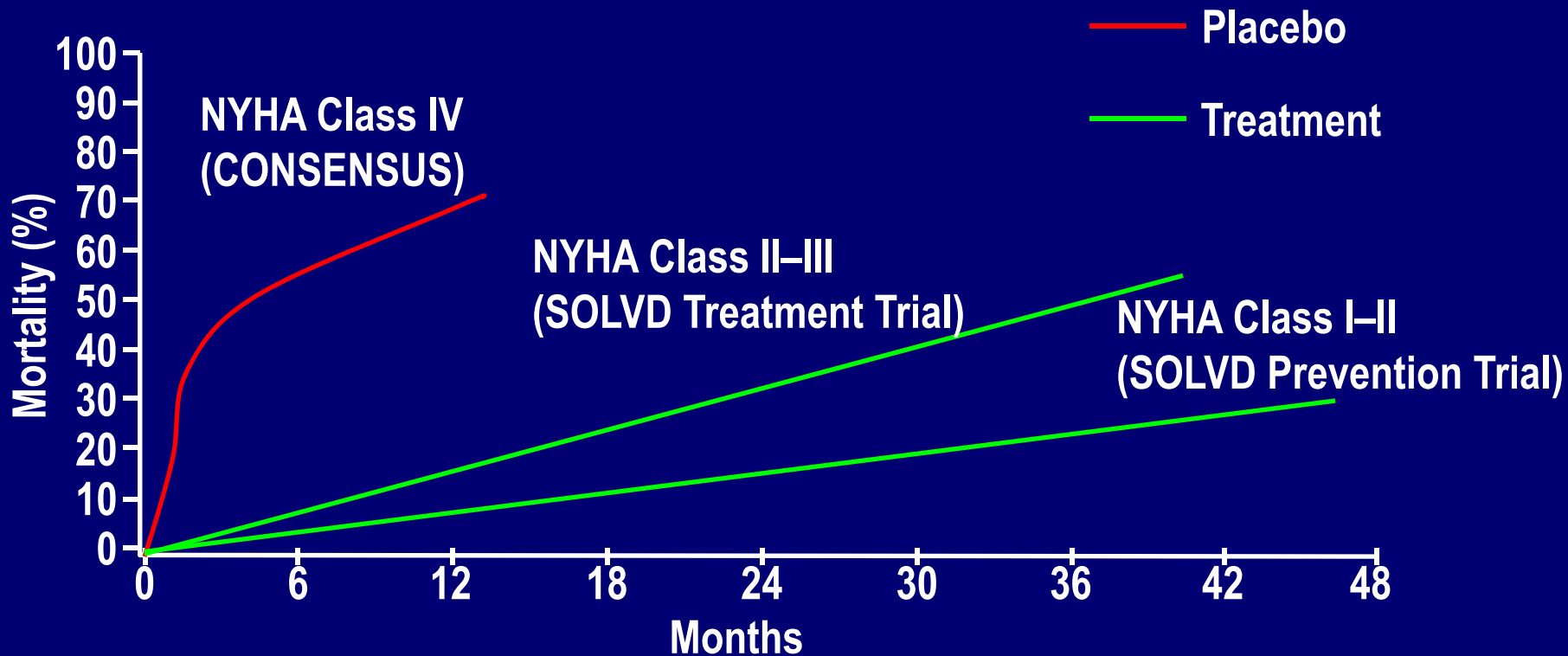
	1979-1984	1985-1990	1991-1995	1996-2000
Men				
Incidence per 100 000 (95% CI)	360 (323-396)	390 (354-425)	375 (340-409)	383 (351-415)
RR (95% CI)	1.00	1.07 (0.94-1.22)	1.01 (0.88-1.15)	1.04 (0.92-1.18)
Women				
Incidence per 100 000 (95% CI)	284 (260-307)	292 (270-315)	260 (238-282)	315 (292-338)
RR (95% CI)	1.00	1.04 (0.93-1.16)	0.93 (0.83-1.05)	1.11 (1.00-1.24)

Abbreviations: CI, confidence interval; RR, relative risk.



Roger VL et al. JAMA. 2004; 292: 344-351.

Survival according to NYHA Class



CONSENSUS Trial Study Group. *N Engl J Med.* 1987; 316: 1429-1435.

The SOLVD Investigators. *N Engl J Med.* 1991; 325: 293-298.

The SOLVD Investigators. *N Engl J Med.* 1992; 327: 685-690.



Trends in Heart Failure Mortality

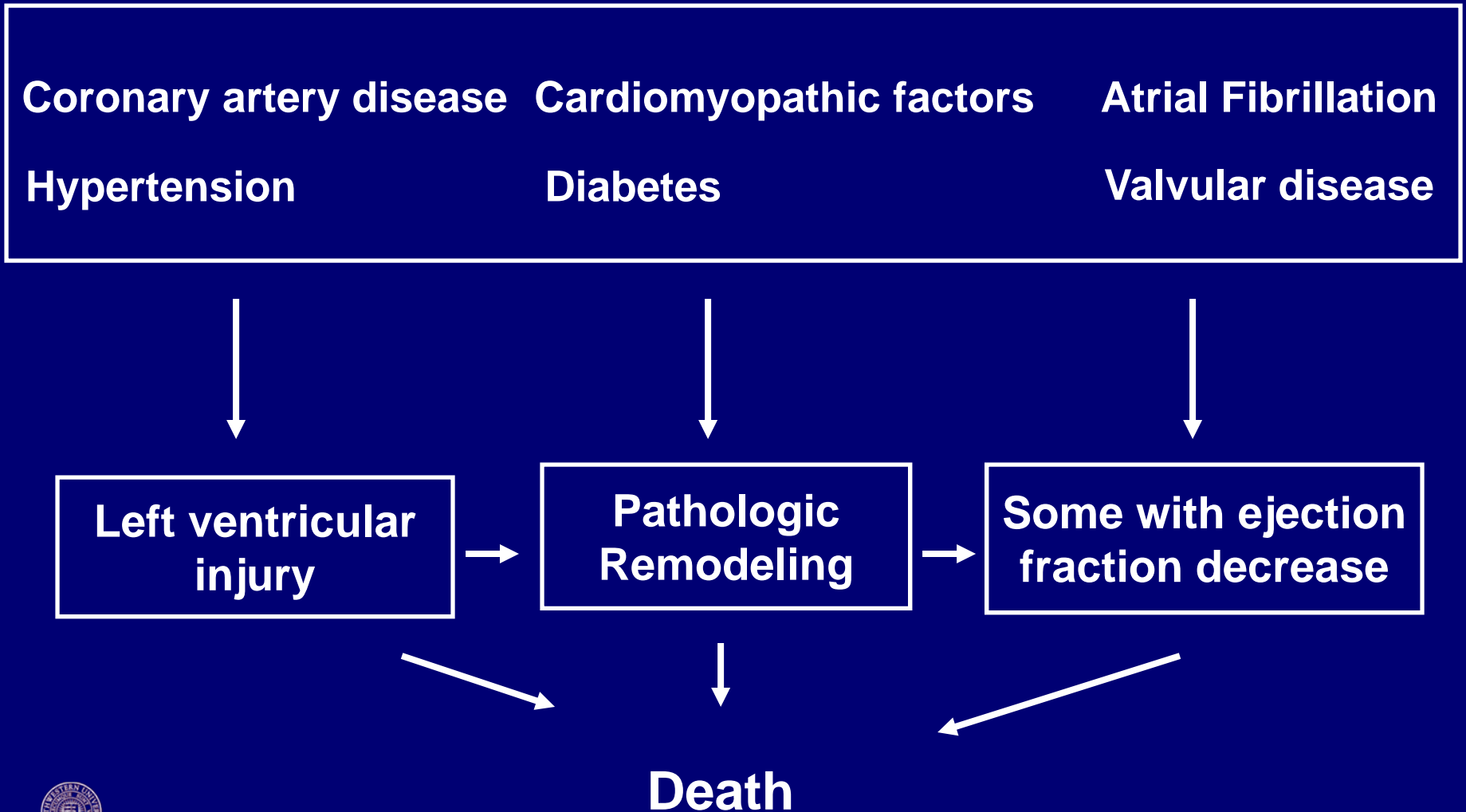
Table 4. Relative Risk for Death After Onset of Heart Failure Defined by the Framingham Criteria

Age, y	Relative Risk (95% Confidence Interval)			
	1979-1984	1985-1990	1991-1995	1996-2000
Men				
60	1.00	0.84 (0.69-1.02)	0.63 (0.50-0.80)	0.48 (0.36-0.64)
70	1.00	0.84 (0.73-0.97)	0.74 (0.63-0.88)	0.59 (0.49-0.71)
80	1.00	0.85 (0.72-1.00)	0.88 (0.75-1.04)	0.72 (0.61-0.87)
Women				
60	1.00	0.80 (0.63-1.03)	0.95 (0.73-1.24)	0.67 (0.48-0.92)
70	1.00	0.91 (0.77-1.06)	0.99 (0.83-1.18)	0.79 (0.64-0.98)
80	1.00	1.02 (0.90-1.15)	1.03 (0.90-1.17)	0.94 (0.82-1.09)



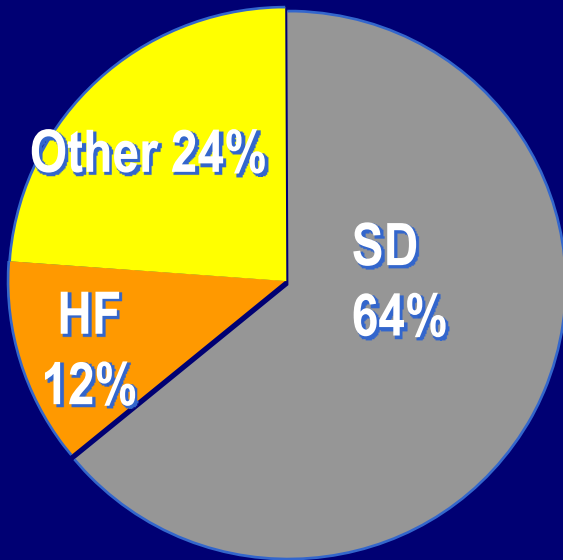
Roger VL et al. JAMA. 2004; 292: 344-351.

Progression of Heart Failure

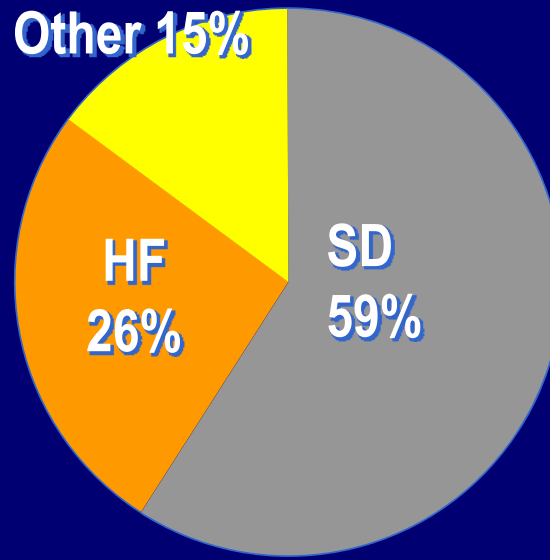


Mode of Death by NYHA Class

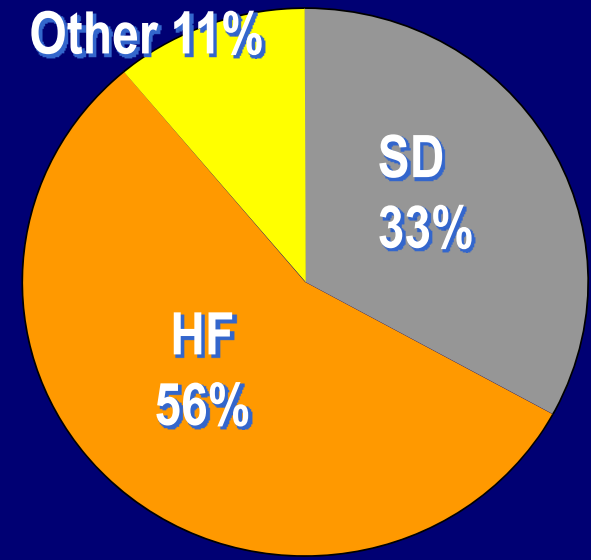
NYHA II



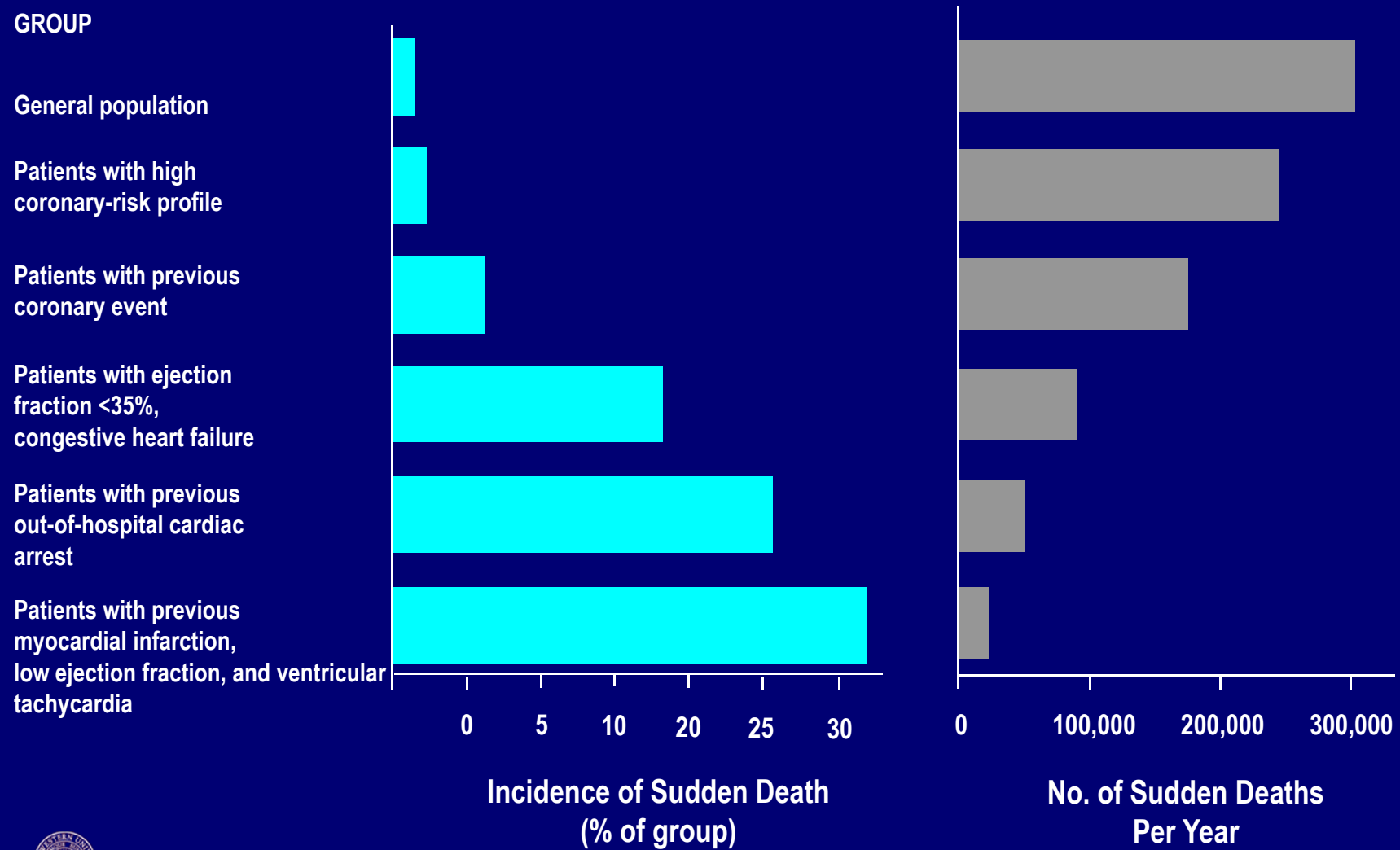
NYHA III



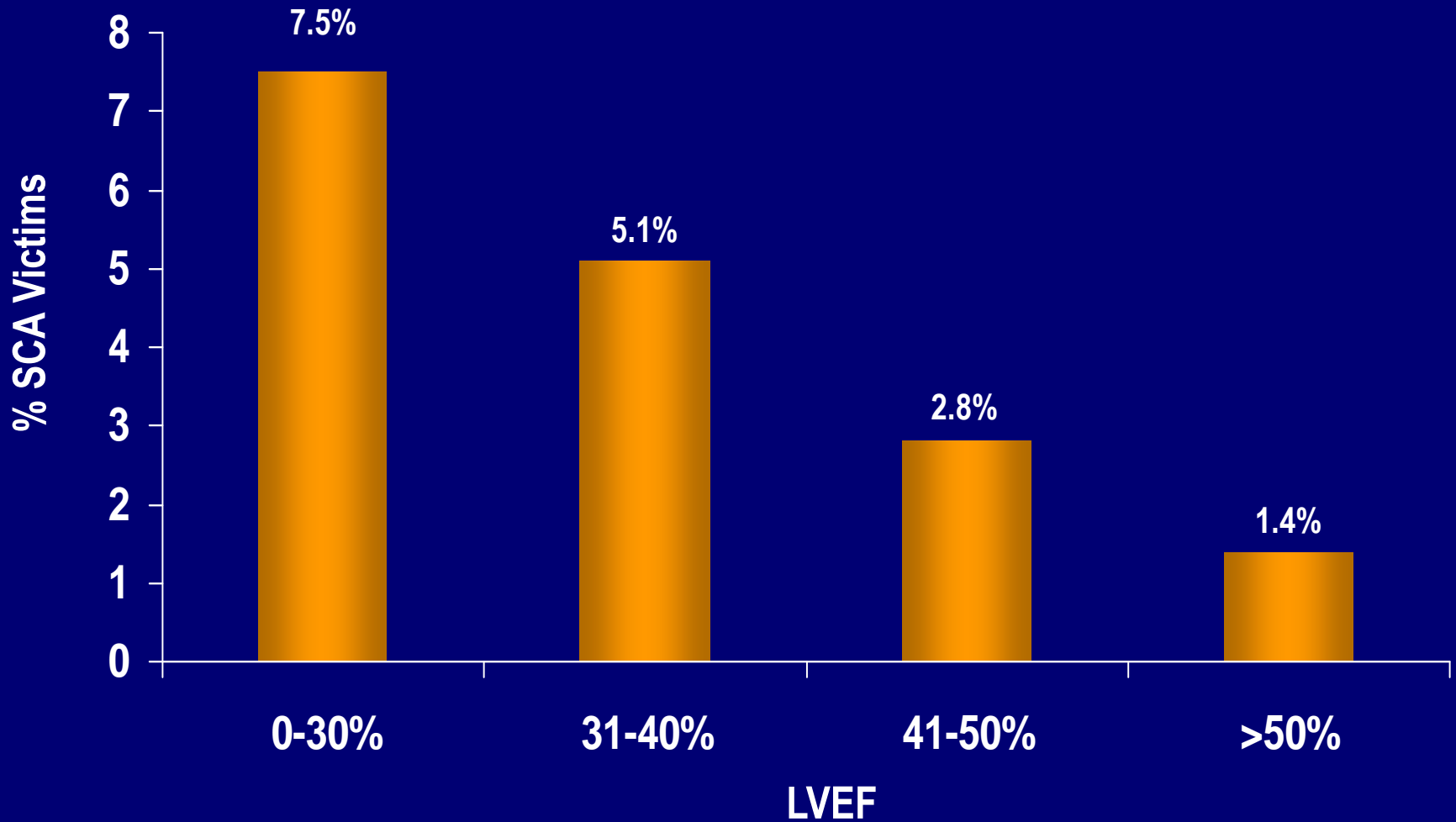
NYHA IV



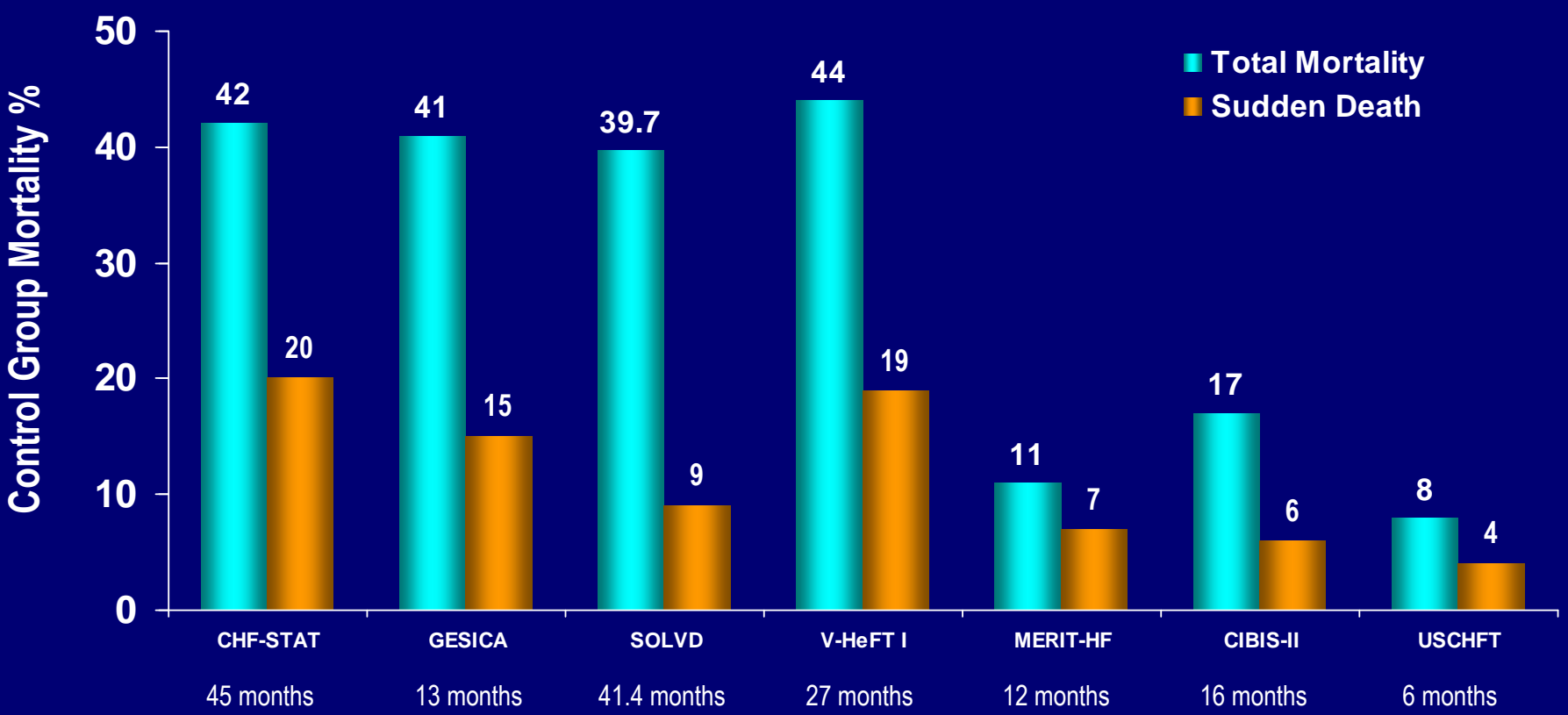
Sudden Death in Specific Populations



Impact of LVEF on Sudden Death



Sudden Death Rates in Heart Failure



Sudden Death in Heart Failure Trials

Study	HF Class	Control (n)	Treatment (n)	Total Mortality Reduction w/Treatment	SCD % of Total Death in Control Arm	SCD % of Total Death in Treatment Arm
MERIT-HF ¹ (Metoprolol)	II, III, IV	2001	1990	34%	60%	54%
BEST ² (Bucindolol)	III, IV	1354	1354	10%	45%	44%
CIBIS-II ³ (Bisoprolol)	III, IV	1320	1327	34%	36%	31%
CARVEDILOL (US) ⁴	II, III, IV	398	696	65%	48%	54%
RALES ⁵	III, IV	841	882	30%	28%	29%

¹ MERIT-HF Investigators. *Lancet*. 1999;353:2001-2007.

⁴ Packer M. *N Engl J Med*. 1996;334:1349-1355.

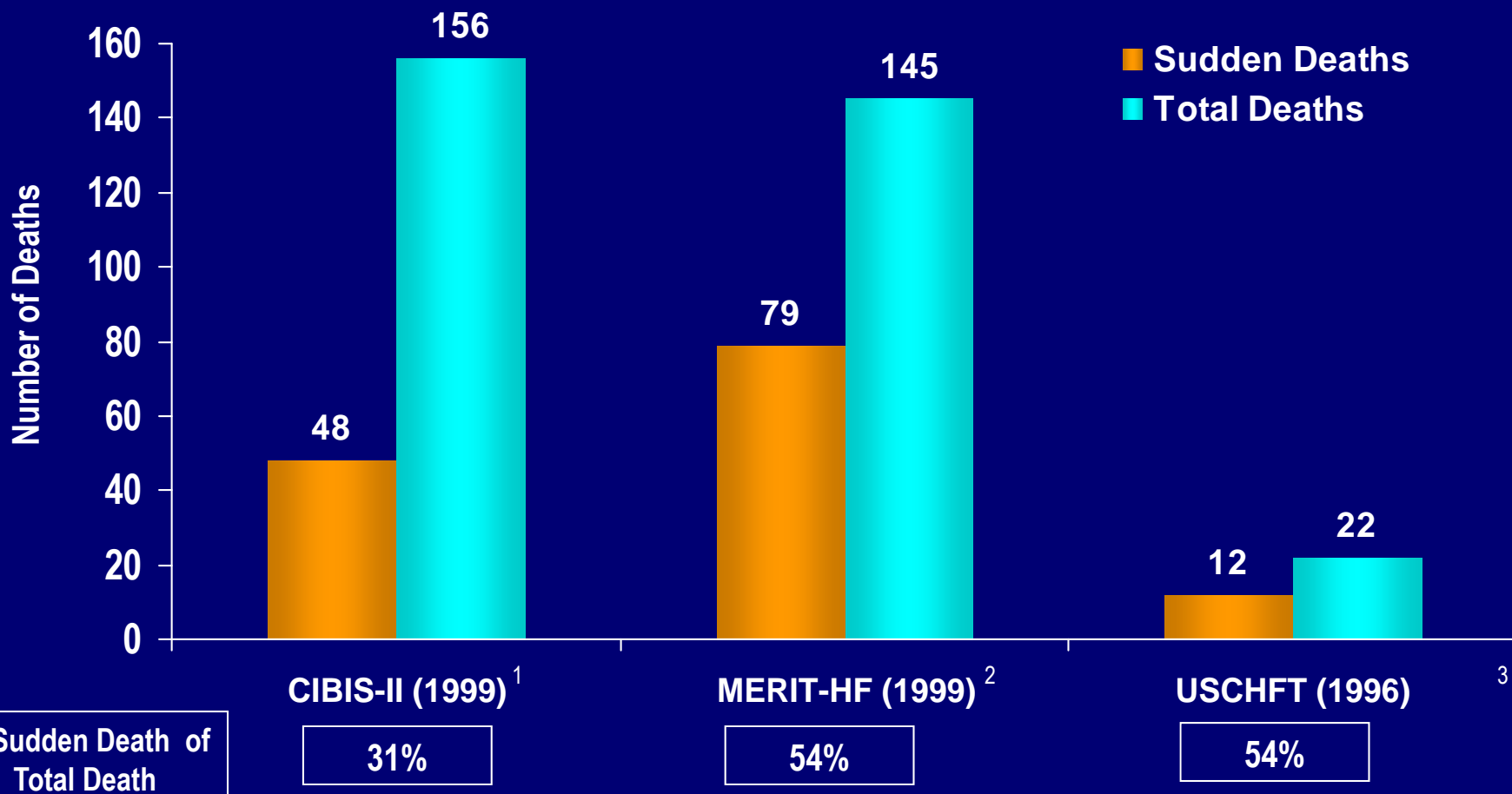
² BEST Investigators. *N Engl J Med*. 2001;344:1659-1667.

⁵ Pitt B. *N Engl J Med*. 1999;341:709-717.

³ CIBIS-II Investigators. *Lancet*. 1999;353:9-13.



Residual Risk of Sudden Death in Heart Failure Trials



¹ CIBIS-II Investigators. *Lancet*. 1999;353:9-13.

² MERIT-HF Study Group. *Lancet*. 1999;353:2001-2007.

³ Packer M. *N Engl J Med*. 1996;334:349-355.



ICD, CRT-D, CRT-P Clinical Trials Heart Failure Patients

SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial)

DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation)

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

CARE-HF (Cardiac Resynchronization in Heart Failure Study)



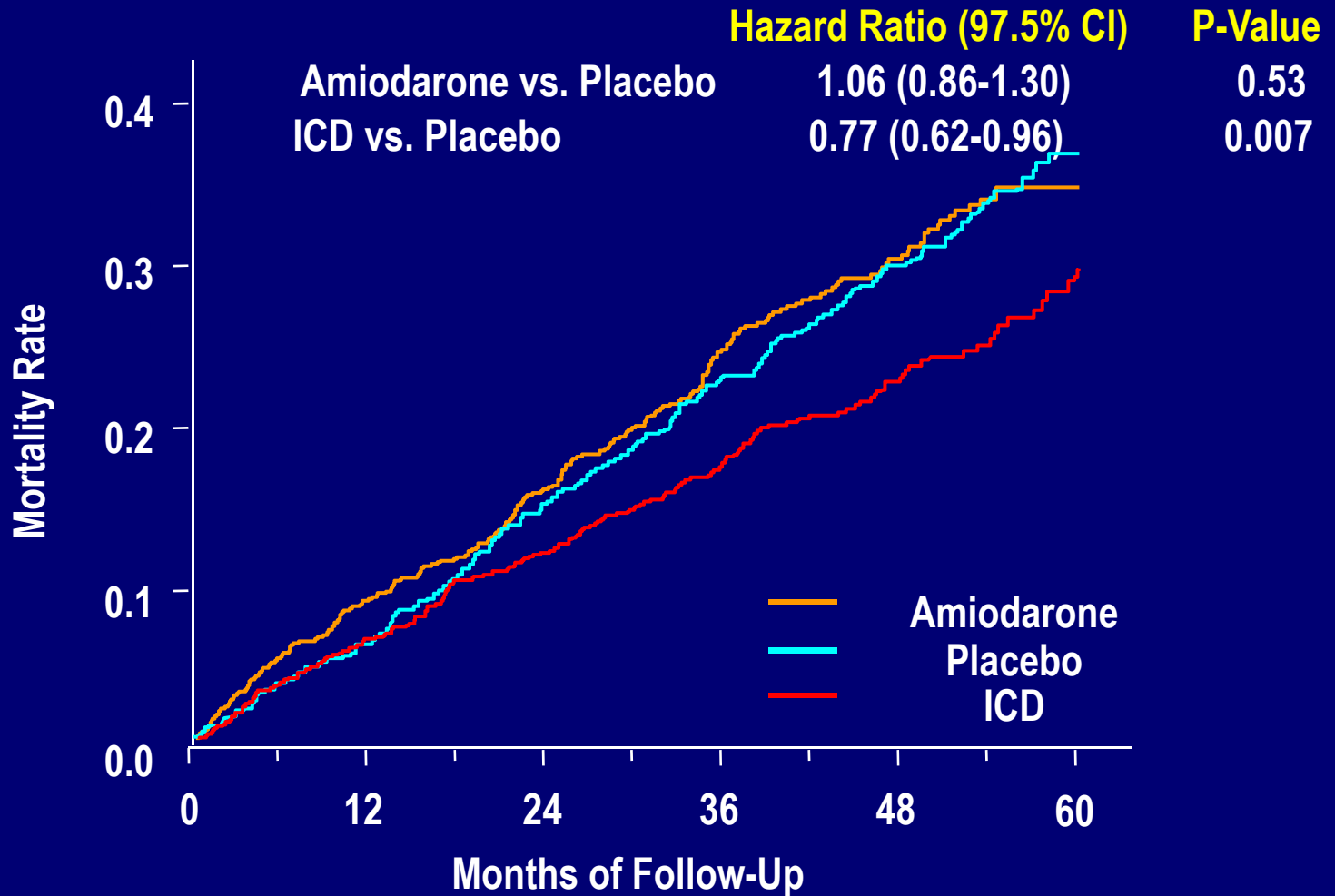
SCD-HeFT Inclusion Criteria

- Symptomatic CHF (NYHA Class II and III) due to ischemic or non-ischemic dilated cardiomyopathy
- LVEF $\leq 35\%$
- ≥ 18 years of age; no upper age limitation
- CHF ≥ 3 months
- On optimal medical therapy for ≥ 3 months
 - Appropriate dose of ACE-I
 - Beta blocker, if tolerated



Bardy GH. N Engl J Med. 2005;352:225-237.

SCD-HeFT All Cause Mortality



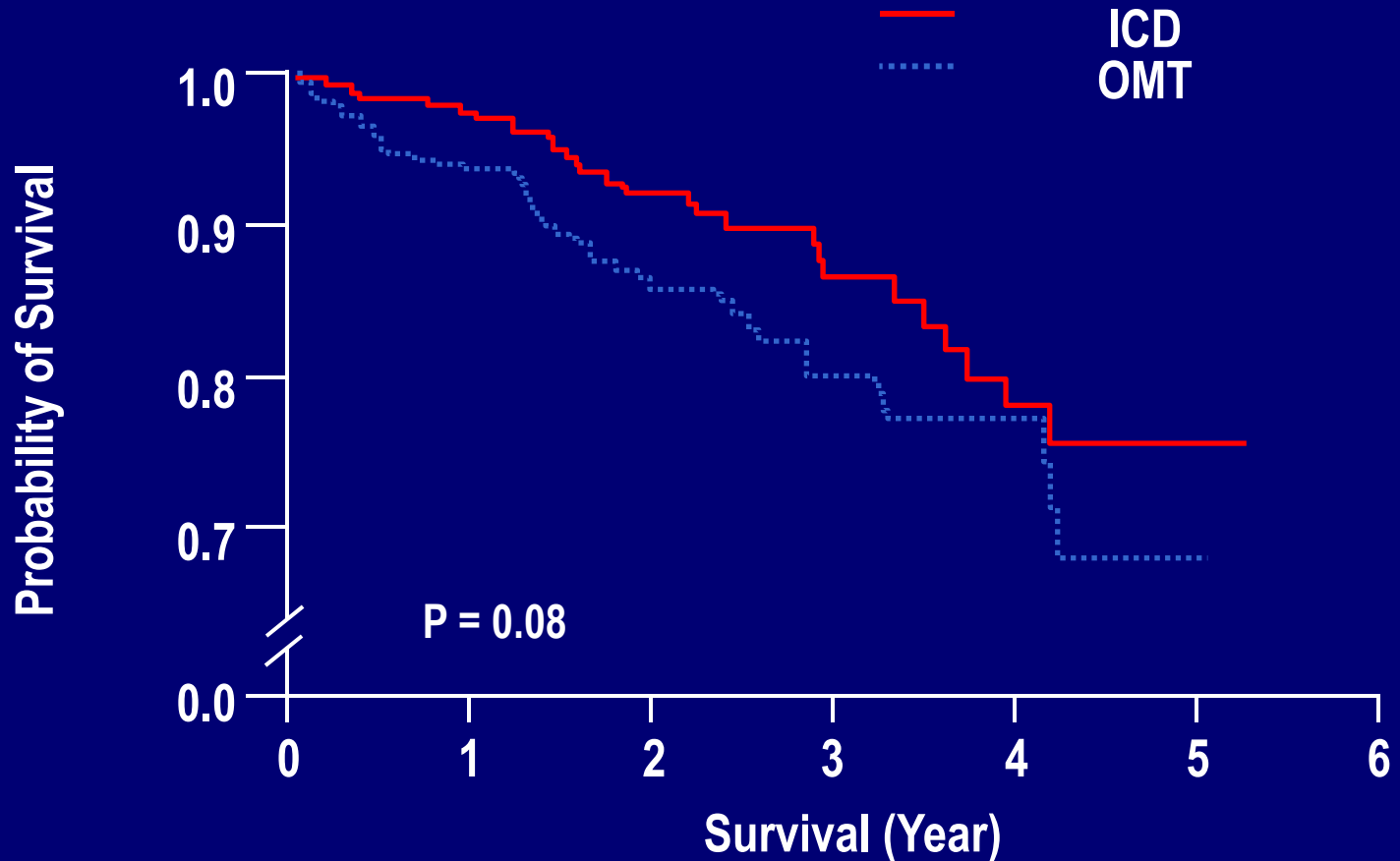
Bardy GH. *N Engl J Med.* 2005;352:225-237.

DEFINITE Inclusion Criteria

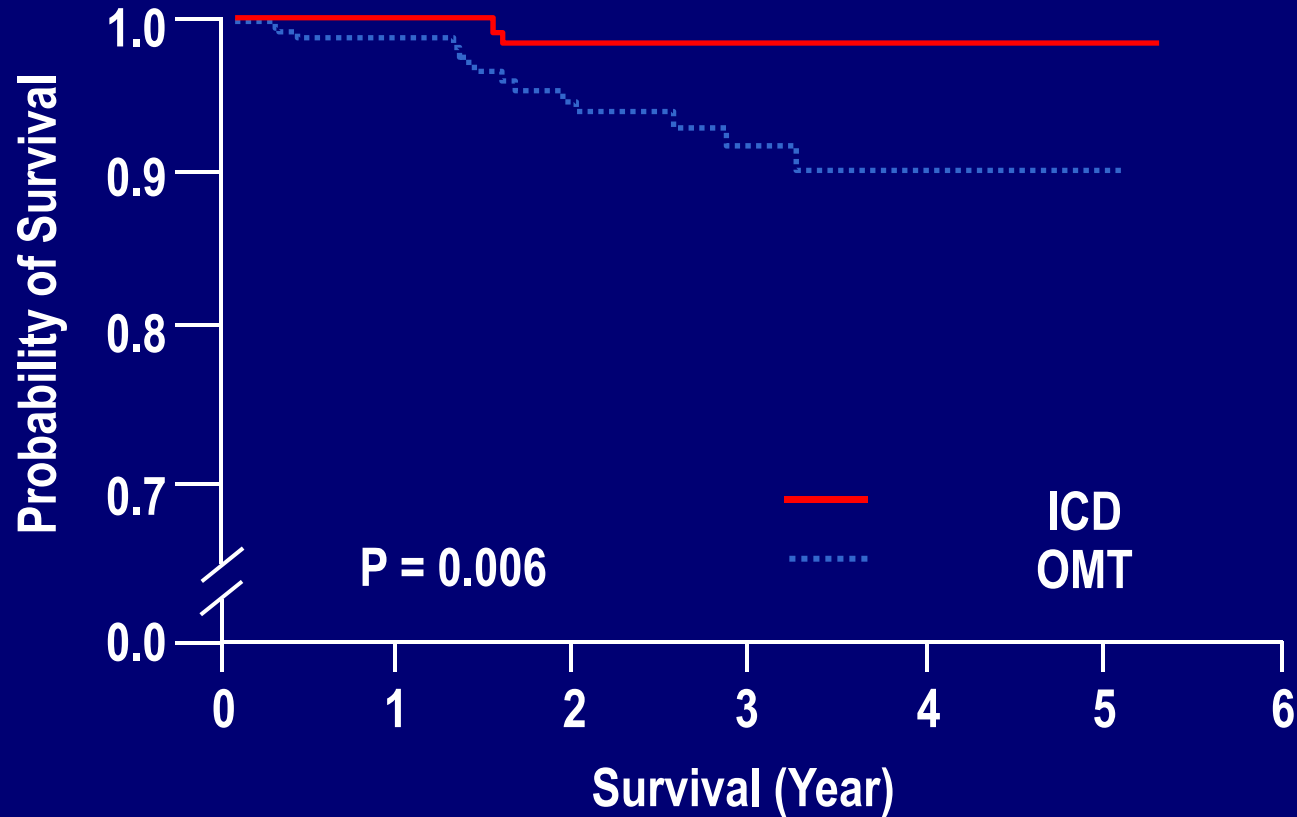
- Non-ischemic cardiomyopathy
- LVEF \leq 35%
- Asymptomatic NSVT
- NYHA Class I, II, or III
- Hx of symptomatic HF



DEFINITE All Cause Mortality



DEFINITE Sudden Death Rate

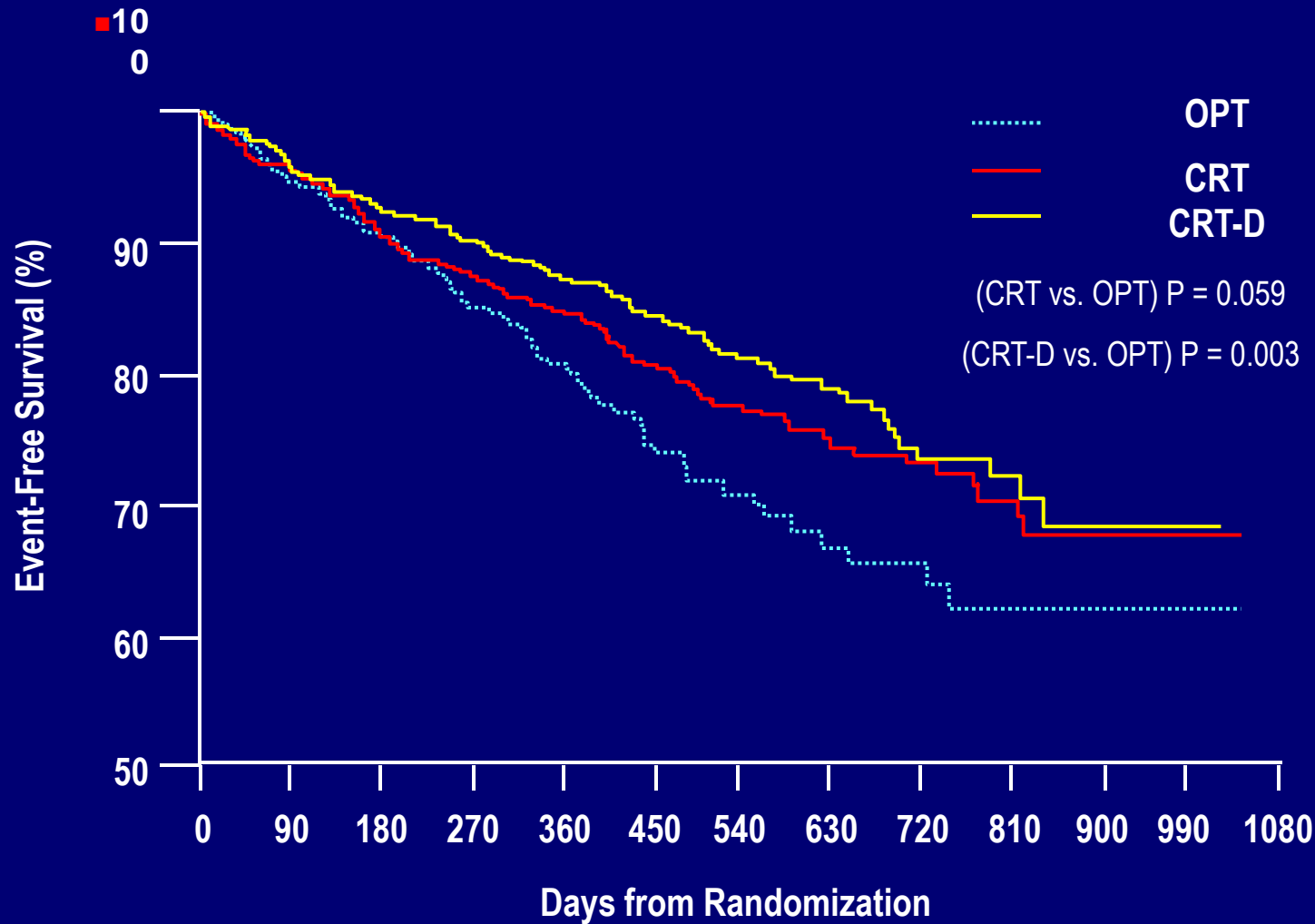


COMPANION Study Design

- Prospective randomized study
- 1520 patients randomized 1:2:2 to three arms:
 - 308 Optimal Pharmacological Therapy (OPT) alone
 - 617 OPT + CRT
 - 595 OPT + CRT-D
- Median follow-up: 11.9 - 16.2 months



COMPANION All-Cause Mortality



COMPANION All Cause Mortality

	Hazard Ratio (95% CI)	P-Value	Reduction in Events
CRT vs. OPT	0.76 (0.58 - 1.01)	0.059	24%
CRT-D vs. OPT	0.64 (0.48 - 0.86)	0.003	36%



CARE-HF Inclusion Criteria

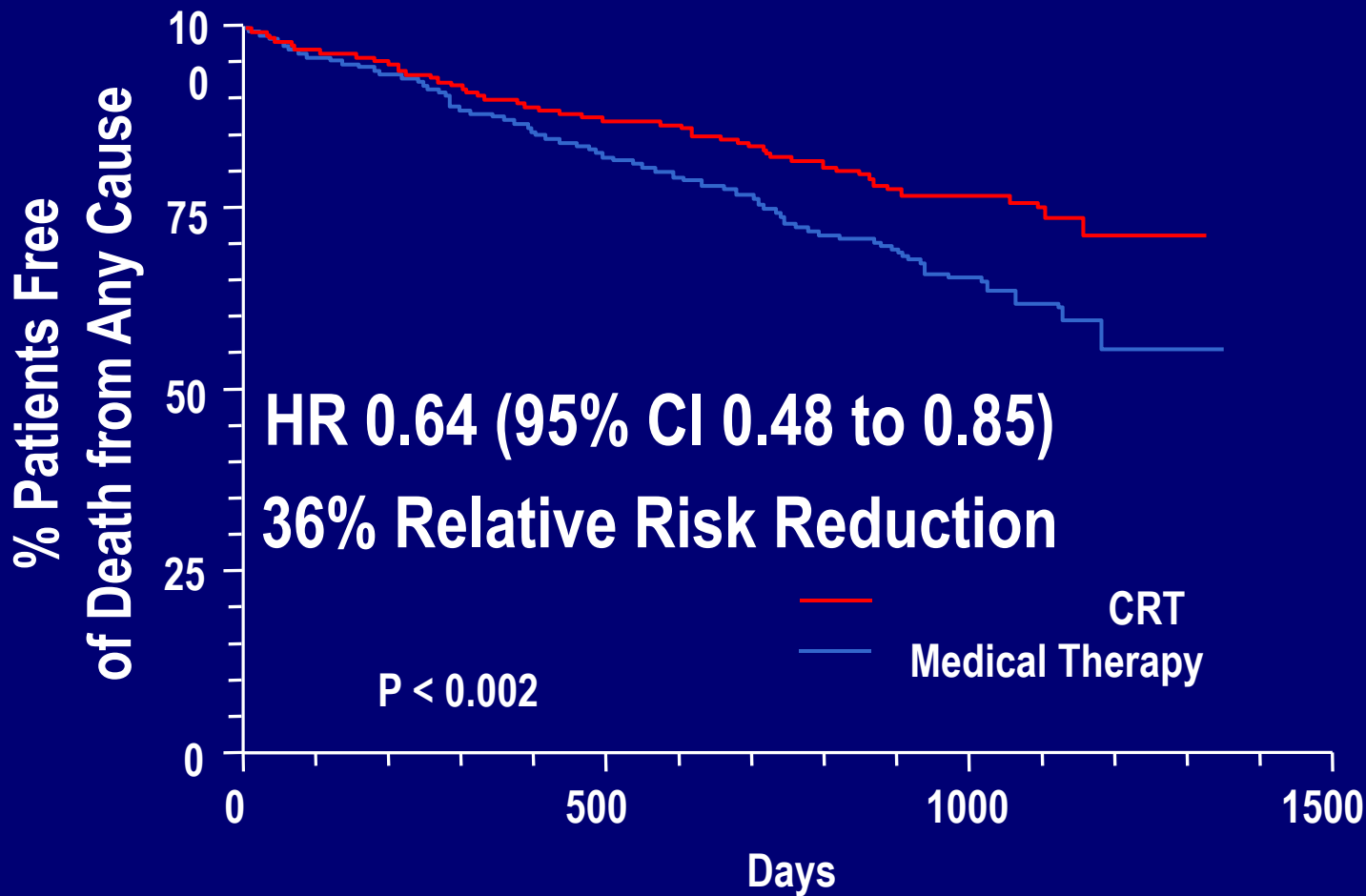
- Heart failure ≥ 6 weeks
- NYHA Class III, IV
- LVEF $\leq 35\%$
- Left ventricular end-diastolic dimension > 30 mm
- Cardiac dyssynchrony as indicated (QRS ≥ 120 ms*)
- Optimal Medical Therapy (OMT)

Patients with QRS 120-149 ms were required to meet echocardiographic evidence for ventricular dyssynchrony including aortic pre-ejection delay ≥ 140 ms, interventricular mechanical delay ≥ 40 ms, delayed activation of posterolateral LV-wall.



Cleland JGF. N Engl J Med. 2005;352:1539-1549.

CARE-HF All Cause Mortality



2009 Heart Failure Guideline Update

Stage B:

- ICD Therapy (Class IIa)
- ICD Therapy (Class IIb)

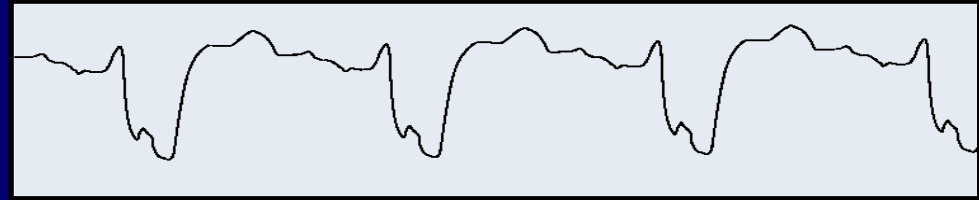
Stage C:

- ICD Therapy (Class I)
- ICD Therapy (Class IIa)
- Cardiac Resynchronization Therapy (Class I)



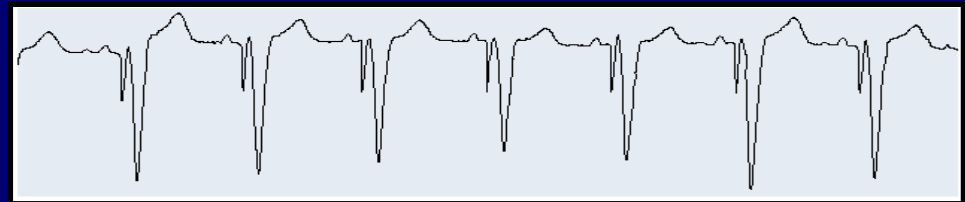
Ventricular Dysynchrony and Cardiac Resynchronization

- Ventricular Dysynchrony



- **Electrical:** Inter- or Intraventricular conduction delays typically manifested as left bundle branch block
- **Structural:** disruption of myocardial collagen matrix impairing electrical conduction and mechanical efficiency
- **Mechanical:** Regional wall motion abnormalities with increased workload and stress—compromising ventricular mechanics

- Cardiac Resynchronization

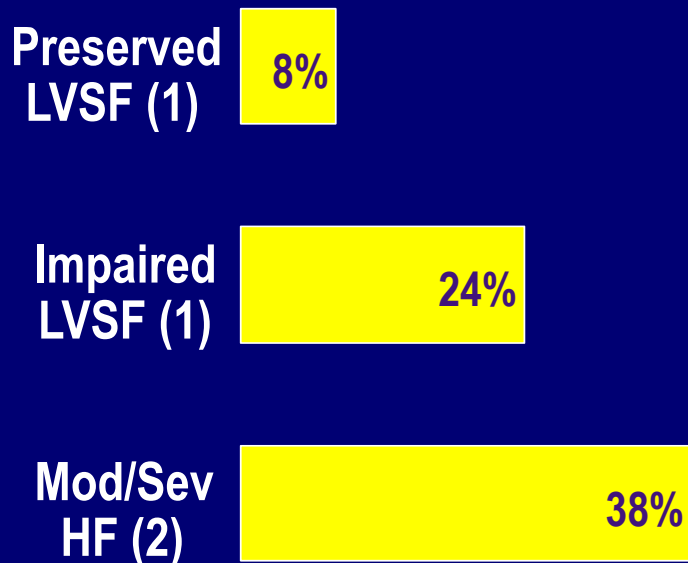


- Therapeutic intent of atrial synchronized biventricular pacing
 - Modification of interventricular, intraventricular, and atrial-ventricular activation sequences in patients with ventricular dysynchrony
 - Complement to optimal medical therapy

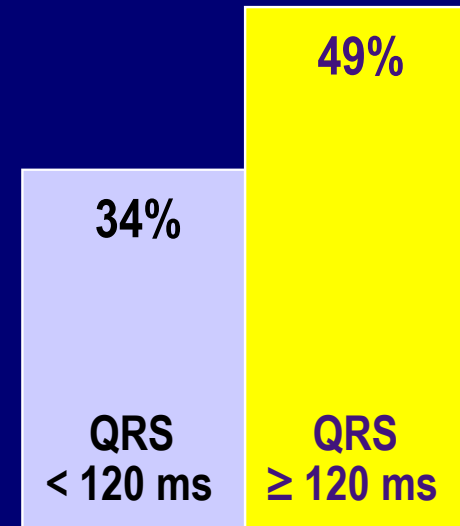


Prevalence and Prognosis of Ventricular Dyssynchrony

LBBB More Prevalent with Impaired LV Systolic Function



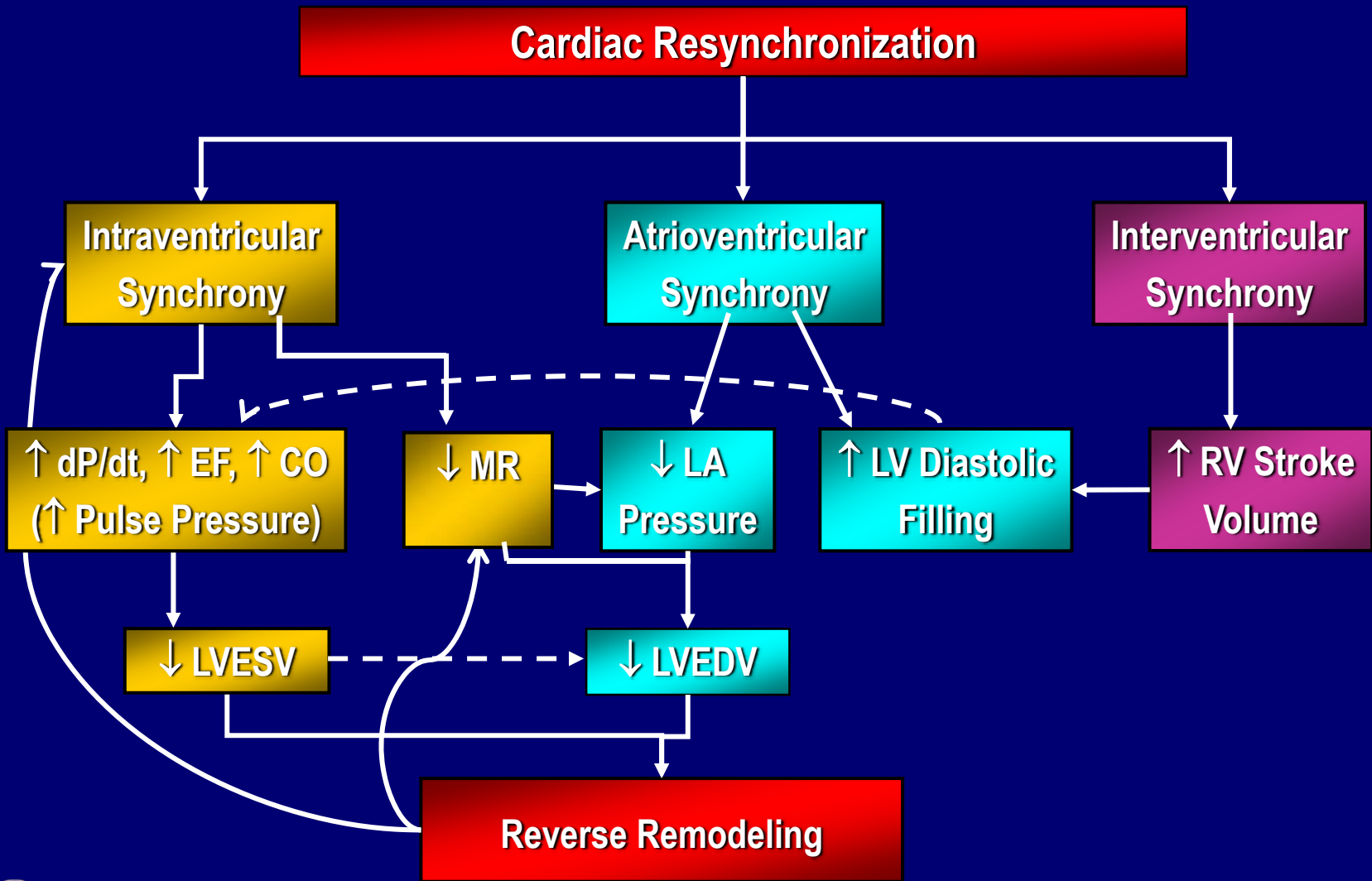
Increased All-Cause Mortality with Wide QRS at 45 Months (3)



1. Masoudi, et al. *JACC*. 2003;41:217-223.
2. Aaronson, et al. *Circulation*. 1997;95:2660-2667.
3. Iuliano, et al. *AHJ*. 2002;143:1085-1091.



CRT Proposed Mechanisms



CRT Improves QoL and NYHA Class

	QoL	NYHA
PATH-CHF ¹ (n=41)	+	+
InSync (Europe) ² (n=103)	+	+
InSync ICD (Europe) ³ (n=84)	+	+
MUSTIC ⁴ (n=67)	+	
MIRACLE ⁵ (n=453)	+	+
MIRACLE ICD ⁶ (n=364)	+	+

¹ Auricchio A et al. *J Am Coll Cardiol* 2002;39:2026-2033

² Gras D et al. *Eur J Heart Failure* 2002;4:311-320

³ Kuhlkamp V. *JACC* 2002;39:790-797

⁴ Linde C et al. *J Am Coll Cardiol* 2002;40:111-118

⁵ Abraham W et al. *N Engl J Med*. 2002;346:1845-1853

⁶ Leon A. *HRS Scientific Sessions* 2002.



CRT Improves Exercise Capacity

	6 Min Walk	Peak VO ₂	Exercise Time
PATH-CHF ¹ (n=41)	+	+	
InSync (Europe) ² (n=103)	+		
InSync ICD (Europe) ³ (n=84)	+		
MUSTIC ⁴ (n=67)	+	↔	
MIRACLE ⁵ (n=453)	+	+	+
MIRACLE ICD ⁶ (n=364)	↔	+	+

¹ Auricchio A et al. *J Am Coll Cardiol* 2002;39:2026-2033

⁴ Linde C et al. *J Am Coll Cardiol* 2002;40:111-118

² Gras D et al. *Eur J Heart Failure* 2002;4:311-320

⁵ Abraham W et al. *N Engl J Med*. 2002;346:1845-1853

³ Kuhlkamp V. *JACC* 2002;39:790-797

⁶ Leon A. *HRS Scientific Sessions* 2002.



CRT Improves Cardiac Function

	LVEF	MR	Other
PATH-CHF ¹ (n=41)			+ LVEDP + LV dP/dt _{max}
InSync (Europe) ² (n=103)	+		+ Filling Time
InSync ICD (Europe) ³ (n=84)	+		+ Filling Time
MUSTIC ⁴ (n=67)	↔	↔	↔ LVEDD, LVESD ↔ Filling Time
MIRACLE ⁵ (n=453)	+	+	+ LVEDD, + LVEDV, LVESV
MIRACLE ICD ⁶ (n=362)	↔	+	+ LVESV, + LVEDV

¹ Auricchio A et al. *J Am Coll Cardiol* 2002;39:2026-2033

⁴ Linde C et al. *J Am Coll Cardiol* 2002;40:111-118

² Gras D et al. *Eur J Heart Failure* 2002;4:311-320

⁵ Abraham W et al. *N Engl J Med*. 2002;346:1845-1853

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⁶ Leon A. *HRS Scientific Sessions* 2002.



CRT Clinical Trials

<u>Trial</u>	<u># Pts</u>	<u>Trial</u>	<u>Outcome</u>
MUSTIC	131	NYHA III EF<35% QRS>150	Improved 6m walk, pV02 QoL; reduced hospitalizations
MIRACLE	453	NYHA III-IV EF<35% QRS>130	Improved 6m walk, pV02 QoL; reduced hospitalizations
CONTAK CD	490	NYHA II-IV EF<35% QRS>120	Composite end-point of all-cause mortality, HF hospitalization or VT/VF therapy <u>not</u> met
COMPANION	1120	NYHA III-IV EF<35% QRS>120	Reduced all-cause mortality and hospitalization
CARE-HF	813	NYHA III-IV EF<35% QRS>120	Reduced all-cause mortality and hospitalization



Develop Patient Care Pathways

- Some clinics have developed patient care pathways to find patients at risk of SCA
- At-risk patients are referred for further evaluation to an electrophysiologist for treatment decisions



