TWO YEARS AFTER MADIT CRT TRIAL

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Declaration of advisory board participation, educational honoraria and congress support from Medtronic, Boston Scientific, St Jude, Biotronik and Spectranetics

Studies → Guidelines (NICE)

Low ejection fraction, already on optimal pharma. treatment ? ➡

MADIT I
MUSTT
CASH
…

MADIT II

COMPANION

SCD-HeFT

CARE-HF

MADIT-CRT?

1990 … 2002 2003 2004 2005 2006 2008 2009

Previous ACC/AHA ICDs Guidelines

ESC updated HF guidelines

ACC/AHA updated guidelines

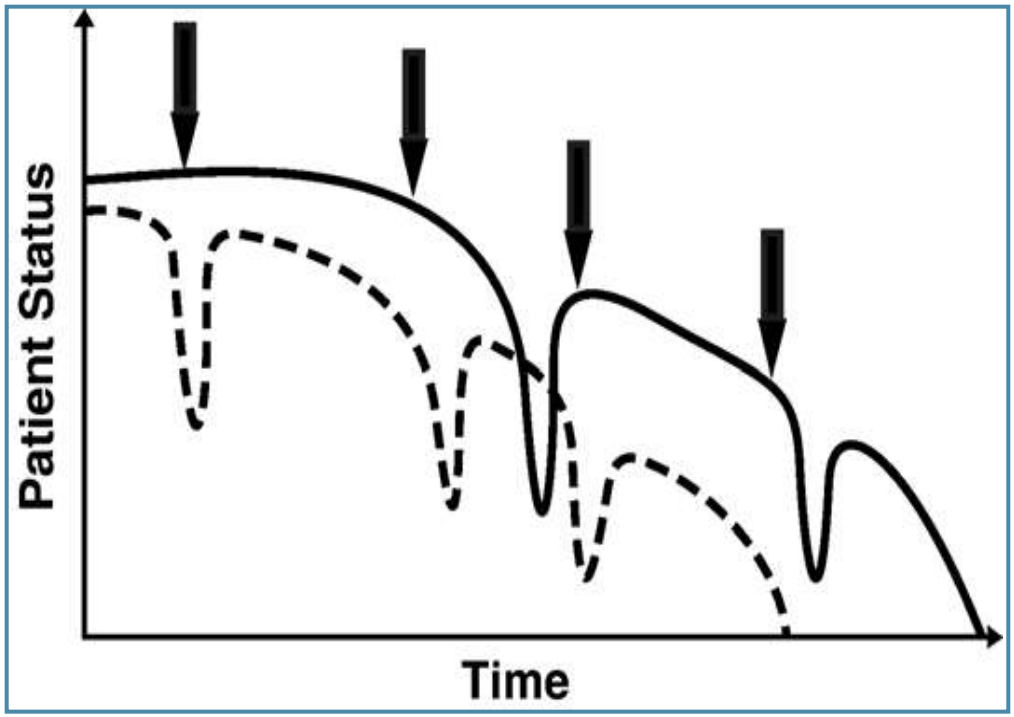
New worldwide SCD guidelines

AHA/ACC/ HRS device guidelines

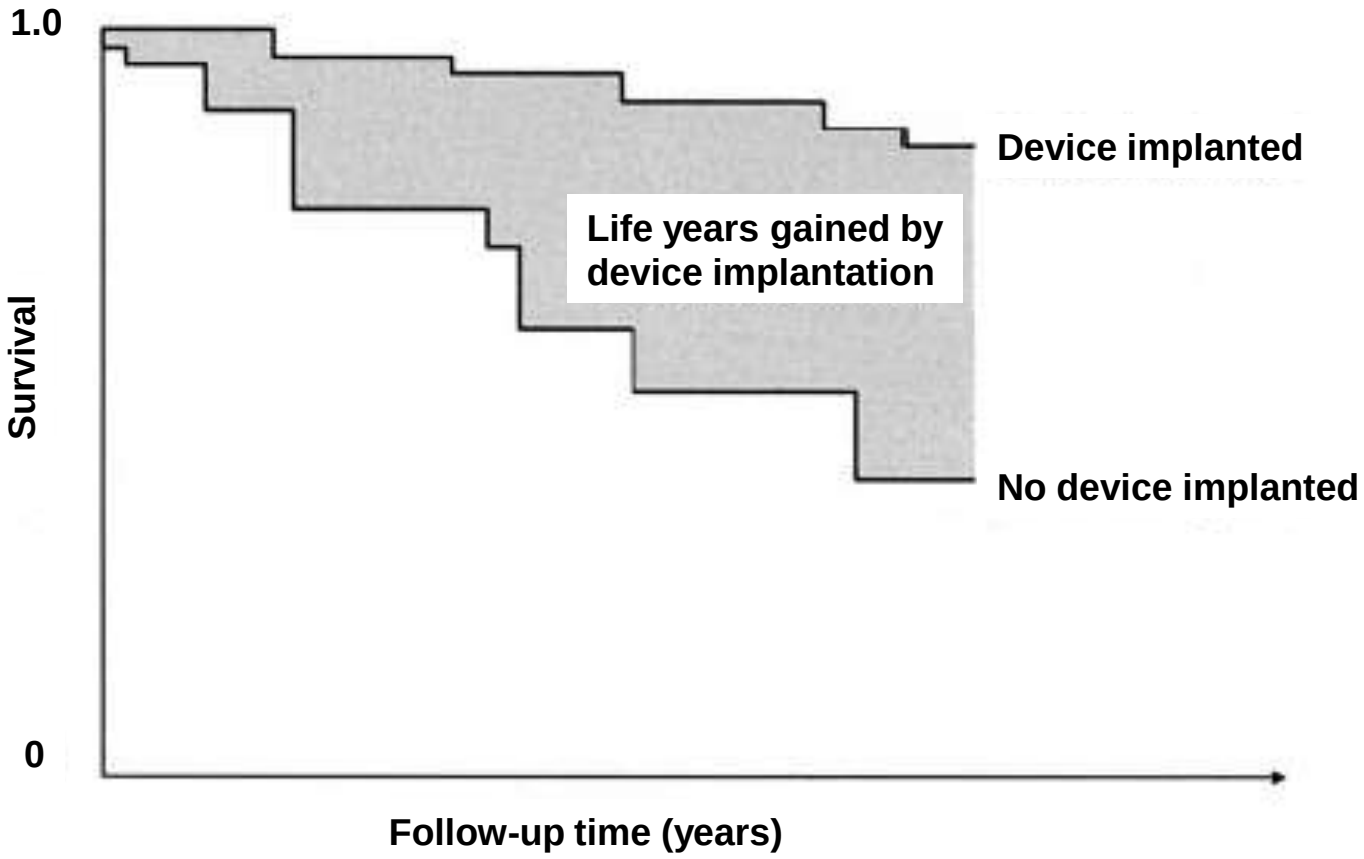
2008 ESC HF guidelines

Heart Failure Diagnosis
Anticipate worsening of Heart Failure

- **Cumulative effect of recurrent acute heart failure events leads to progressive decline in cardiac function**



“ICD benefit (life-years gained) increases dramatically with follow-up time”

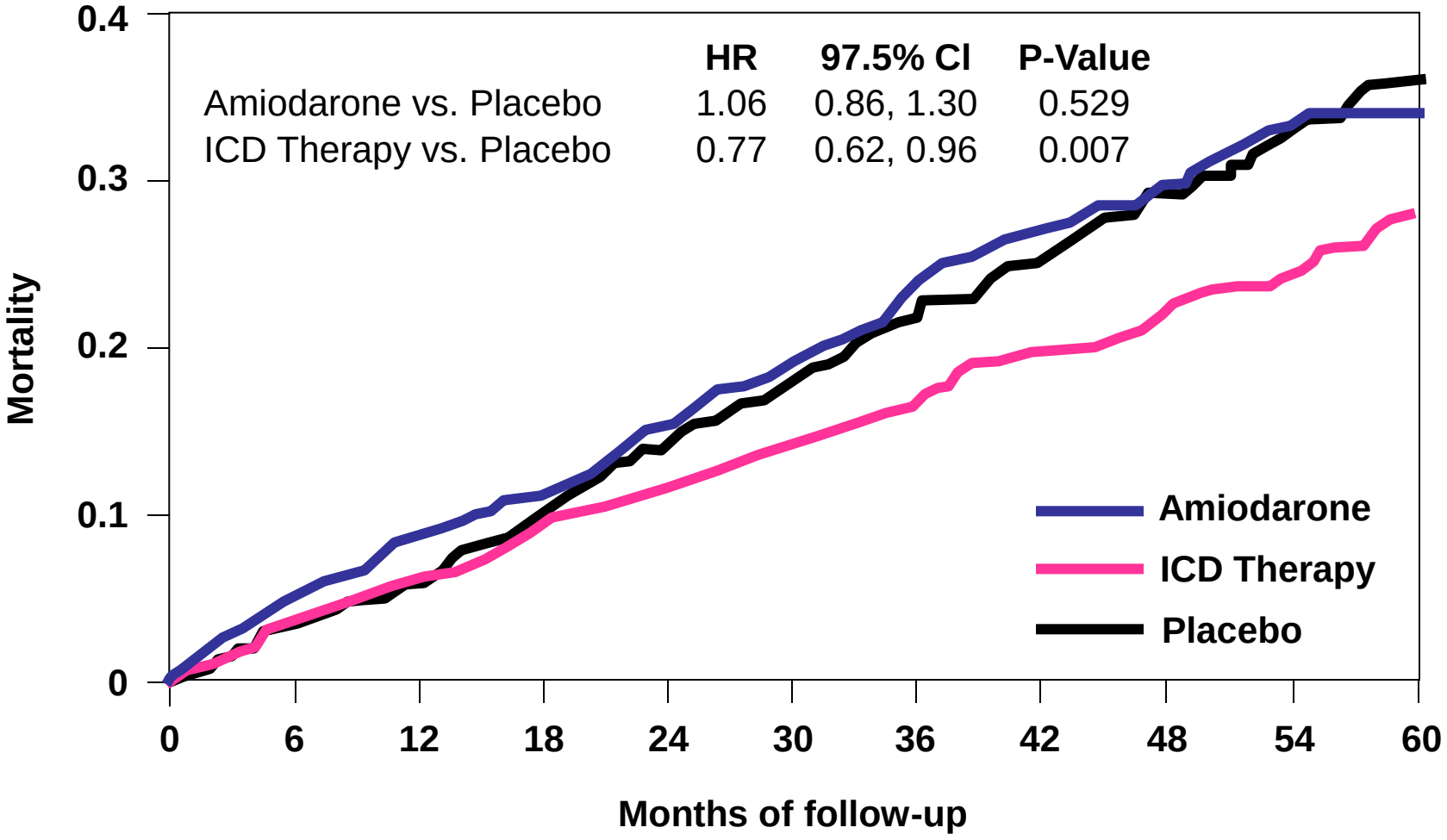


Salukhe, Circulation 2004

SCD-HeFT Inclusion Criteria

- Symptomatic CHF (NYHA class II and III) due to ischaemic or nonischaemic dilated cardiomyopathy
- LVEF $\leq$ 35%
- > 18 years of age; no upper age limitation
- CHF $\geq$ 3 months
- Appropriate dose of ACE I and Beta Blocker therapy, if tolerated, for at least 1 month prior to randomization

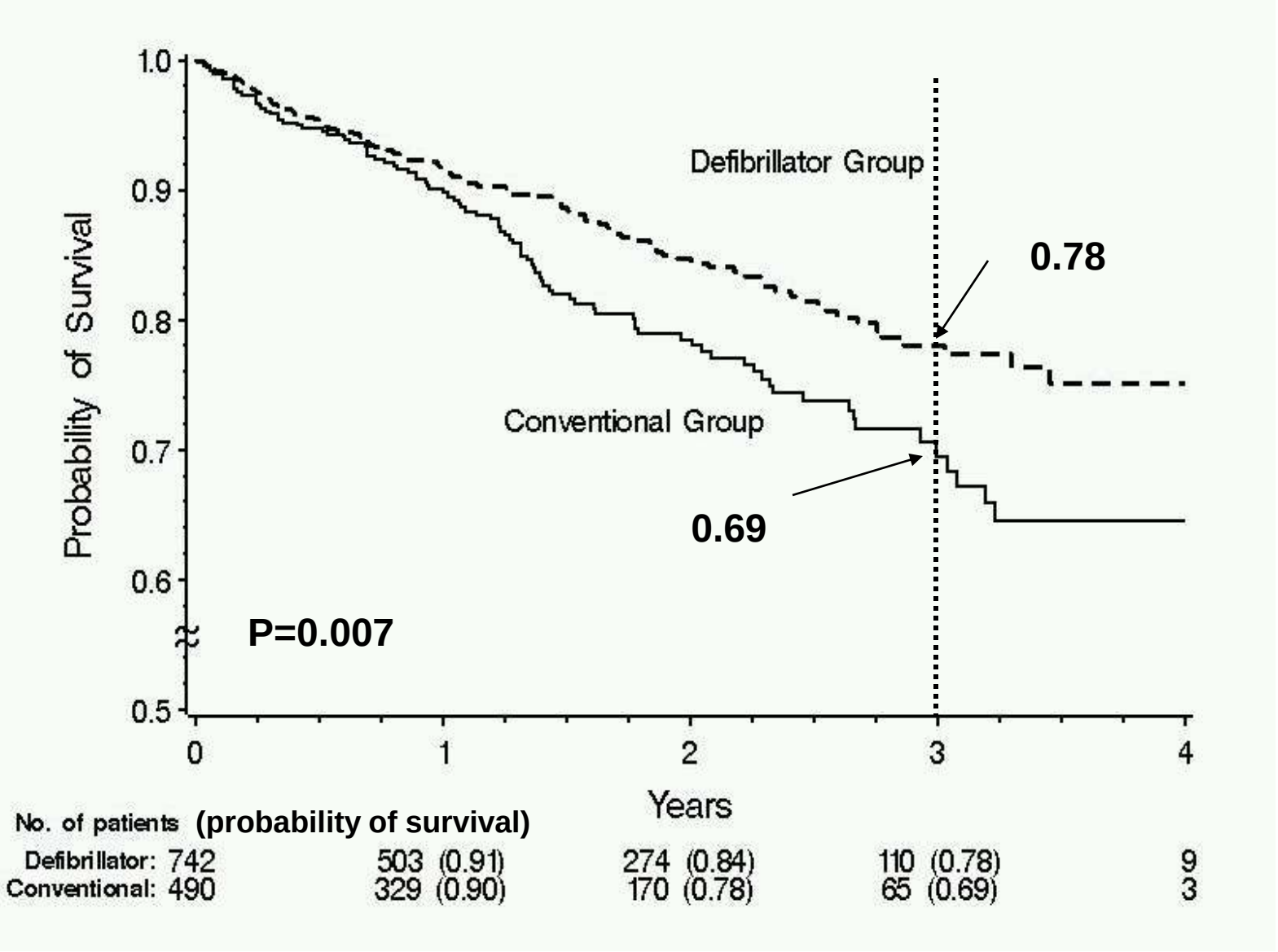
Mortality by Intention-to-Treat



MADIT-II: Eligibility

- Chronic CAD with prior MI
- EF≤0.30
- No requirement for NSVT or EPS
- No upper age limitation

Kaplan-Meier Survival by Treatment Group



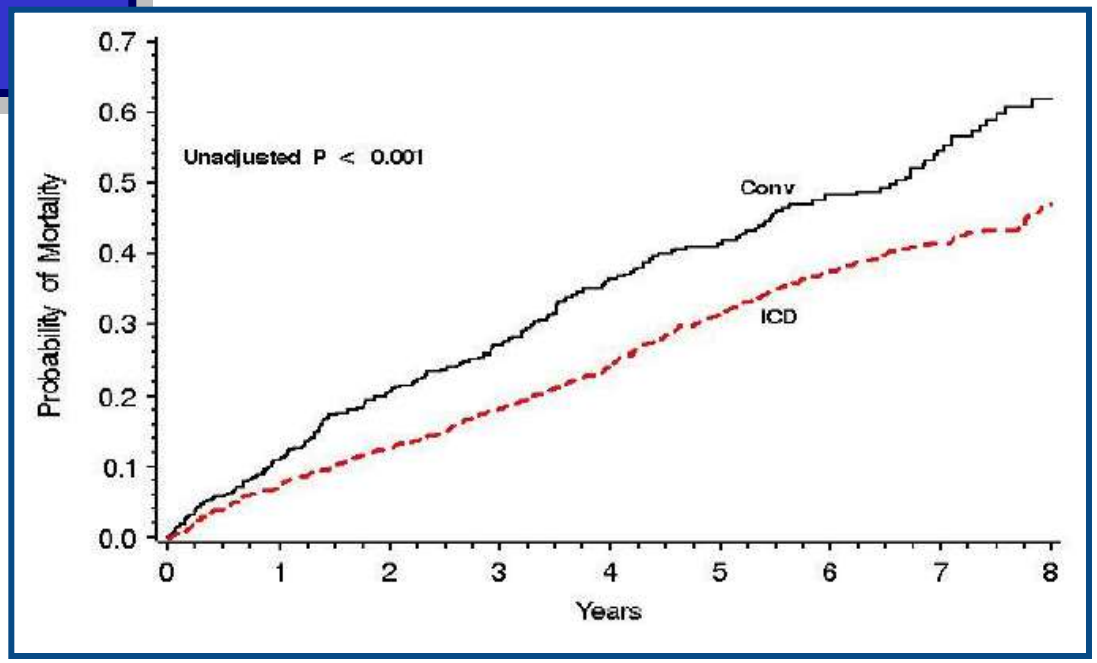
MADIT-II 8y FU

Clinical Question

Is MADIT II Survival benefit with ICD sustained long-term?[1]

NNT=6:1

1 life is saved every 6 patient who received an ICD.
Significant improvement over the 2 years data (N=17:1)

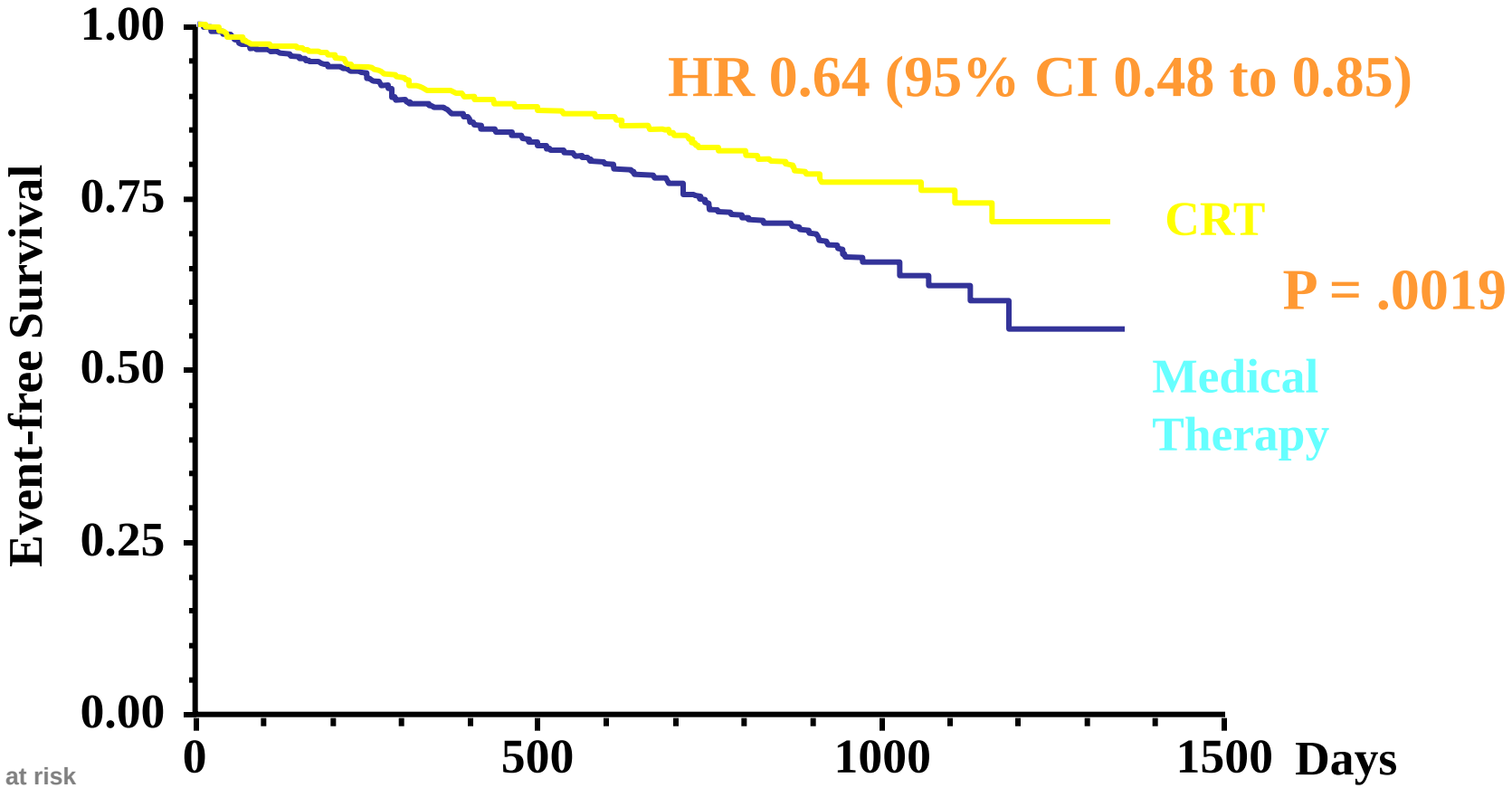


* I. Goldenberg, MD, HRS 2009 (Preliminary data)

CARE-HF Inclusion & Exclusion Criteria

- Heart failure for at least 6 weeks requiring loop diuretics
- Currently in NYHA class III/IV
- A high standard of pharmacological therapy
- LV systolic dysfunction and dilation
  - EF ≤35%; EDD ≥30mm/height in metres
- QRS ≥120 ms
  - Dyssynchrony confirmed by echo if QRS 120-149 ms
    - Aortic pre-ejection delay >140 ms
    - Interventricular mechanical delay >40 ms
    - Delayed activation of postero-lateral LV wall
- Patients with AF or requiring pacing excluded

All-Cause Mortality

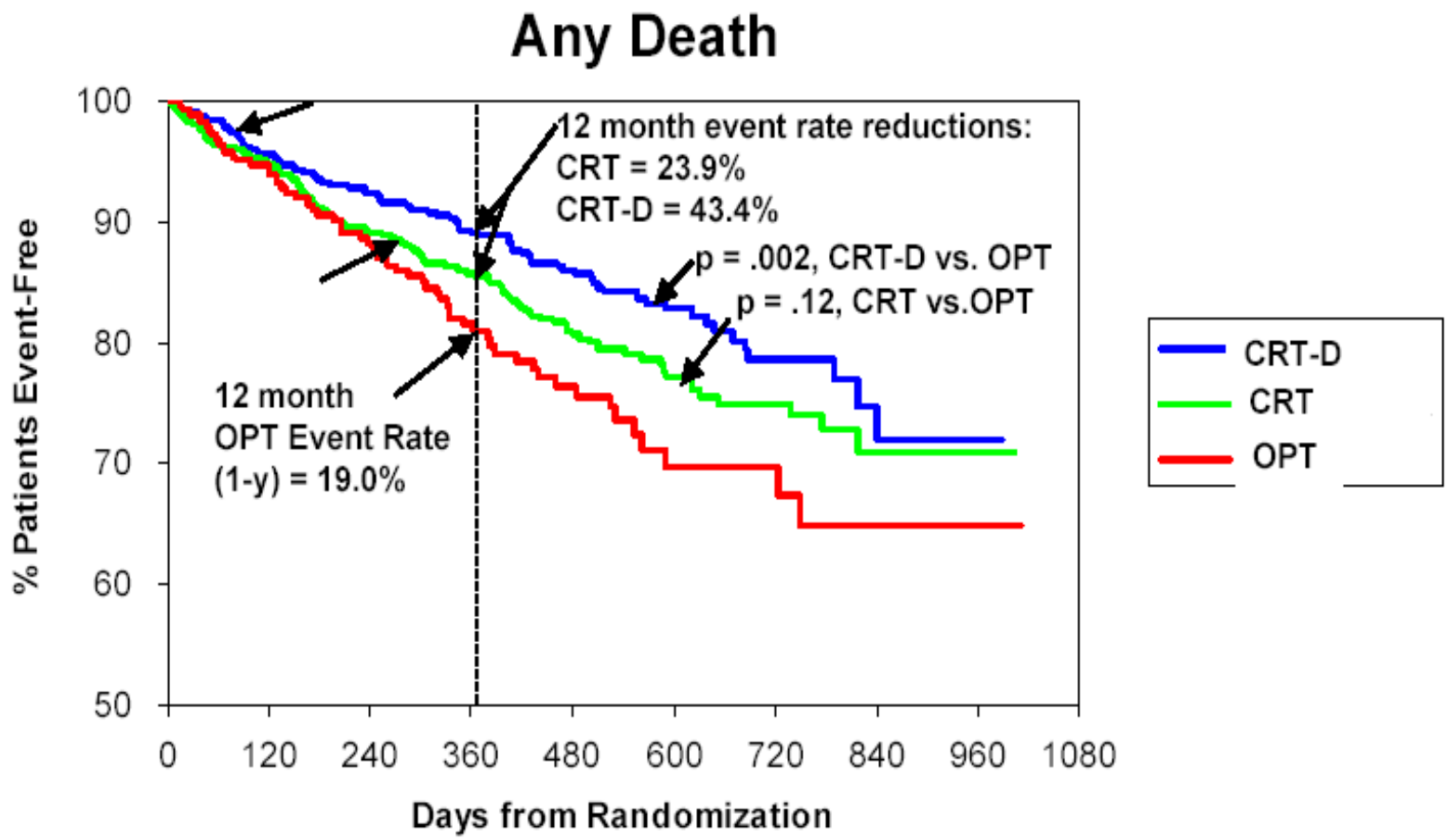


Number at risk						
CRT	409	376	351	213	89	8
Medical Therapy	404	365	321	192	71	5

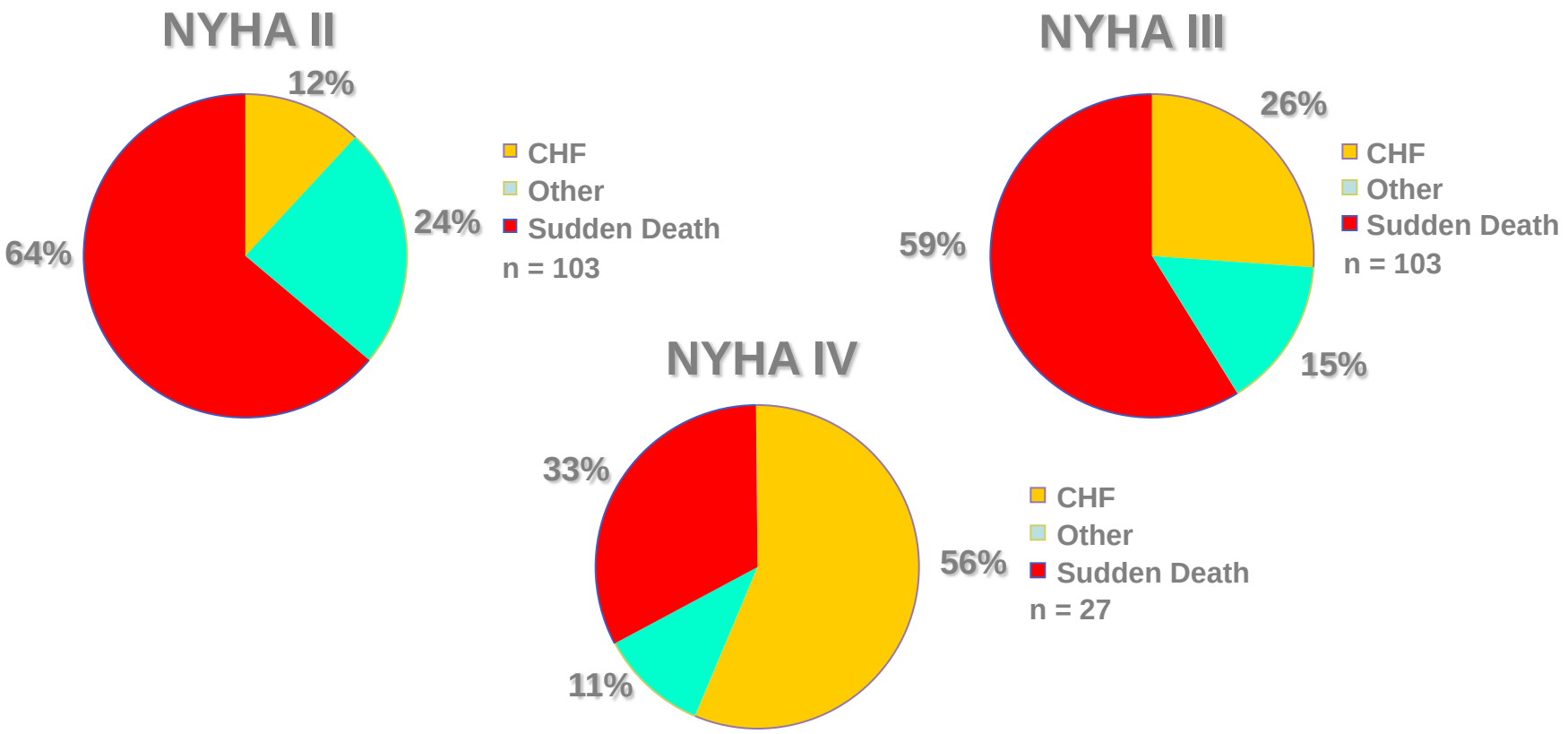
COMPANION: *Key Inclusion Criteria*

- 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: *Secondary Endpoint of All-Cause Mortality*



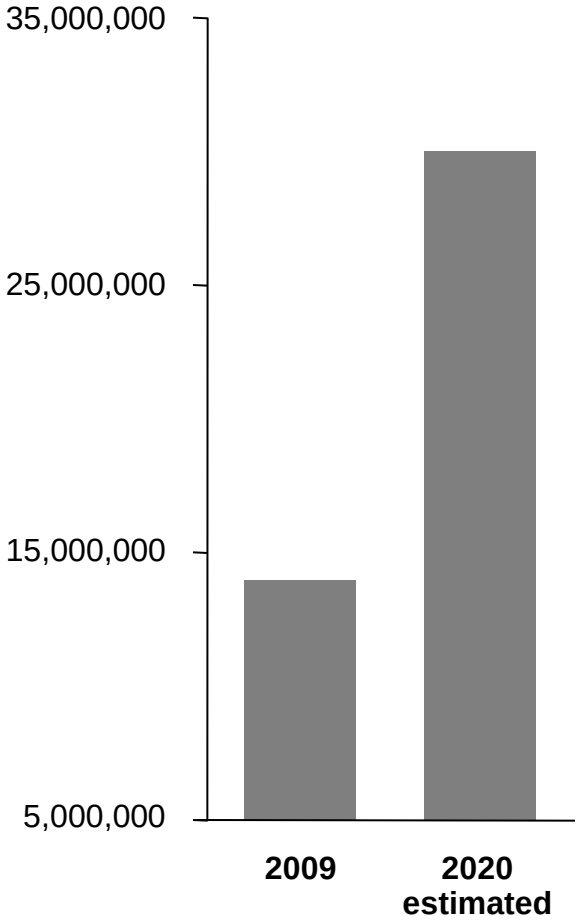
Sudden Death accounts for ~ 50 of mortality in advanced heart failure



MERIT-HF. Lancet. 1999;353:2001-07.

Heart Failure prevalence will more than double in the next 10 years

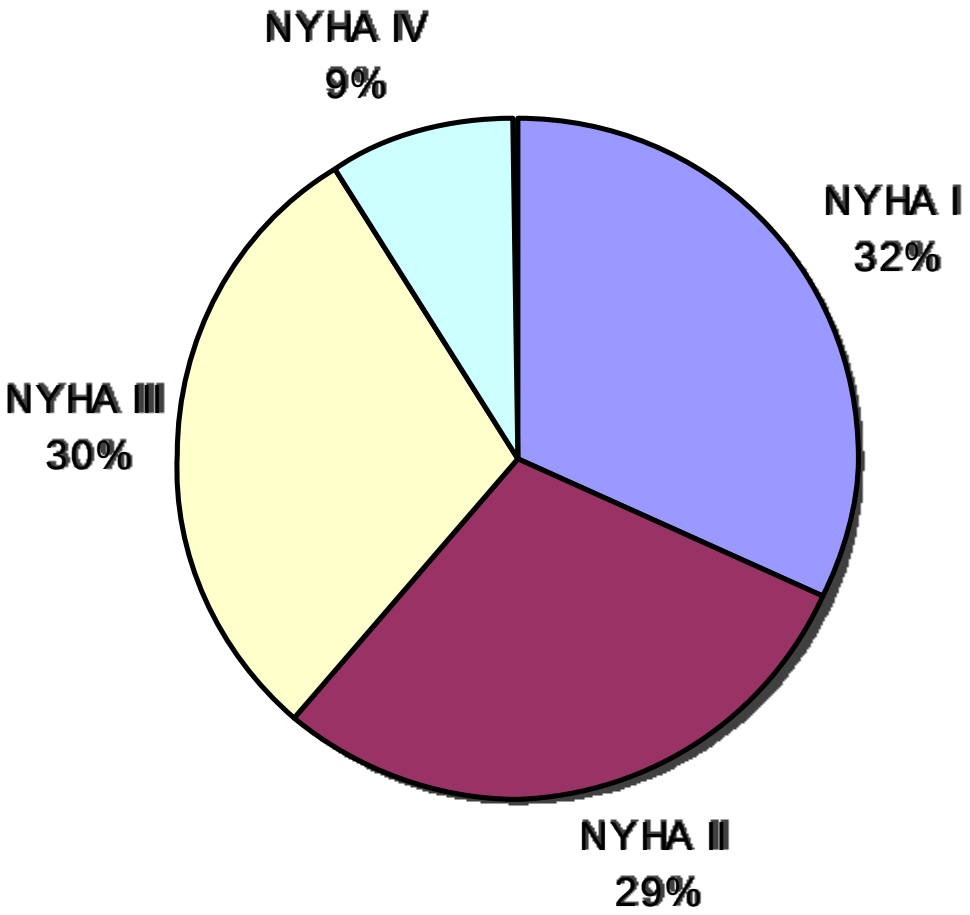
Heart Failure prevalence



- The number of people suffering from HF in Europe *is expected to increase 114% between 2009 and 2020*
- Admission to hospital with HF *has more than doubled* in the last 20 years
- The European healthcare systems will face a challenge in caring for the increased prevalence of HF

[1] SHAPE: Study Group on Heart Failure Perception and Awareness in Europe, www.heartfailure-europe.com

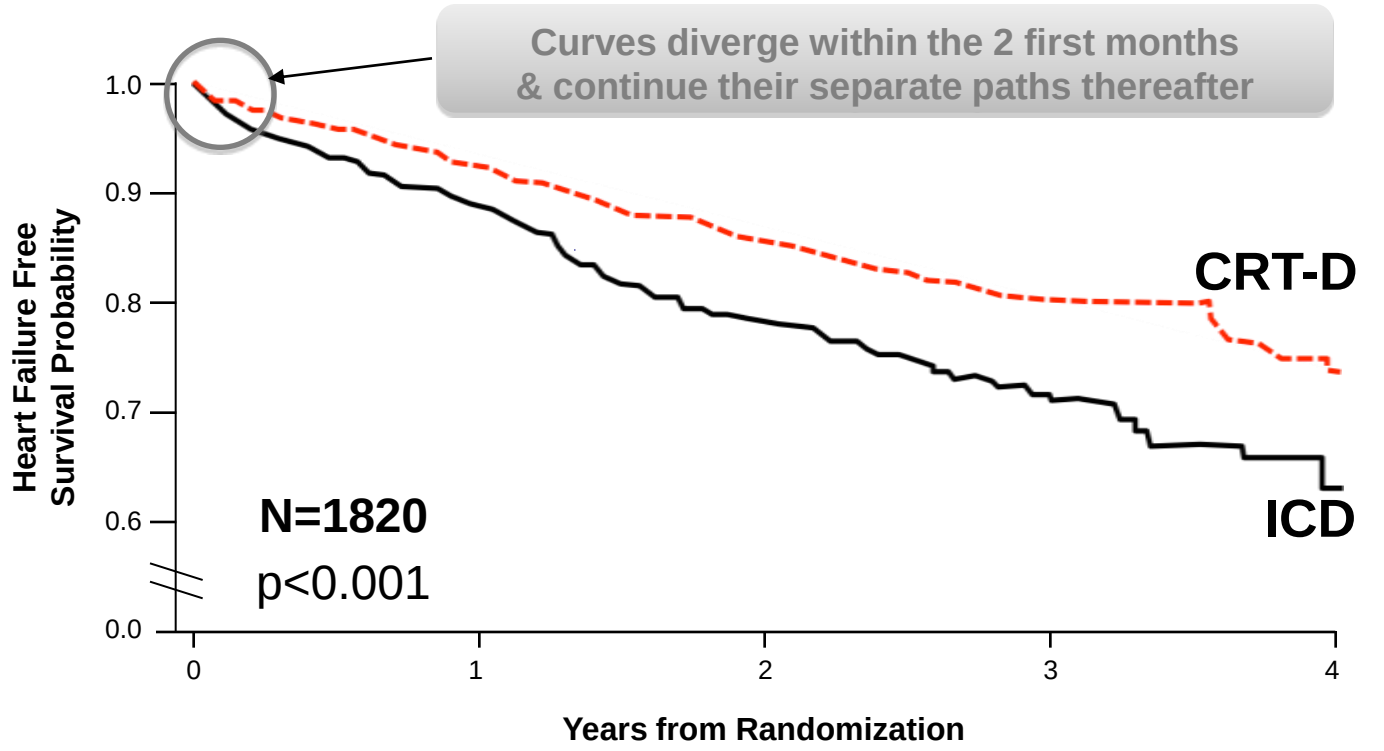
UK: > 60% of patients in NYHA I-II



Diller PM, et al. Congestive heart failure due to diastolic or systolic dysfunction. Frequency and patient characteristics in an ambulatory setting. Archives of Family Medicine. 1999;8(5):414-420.

MADIT-CRT: Results Primary Endpoint (1)

Kaplan-Meier Estimate of Heart Failure Free Survival Probability

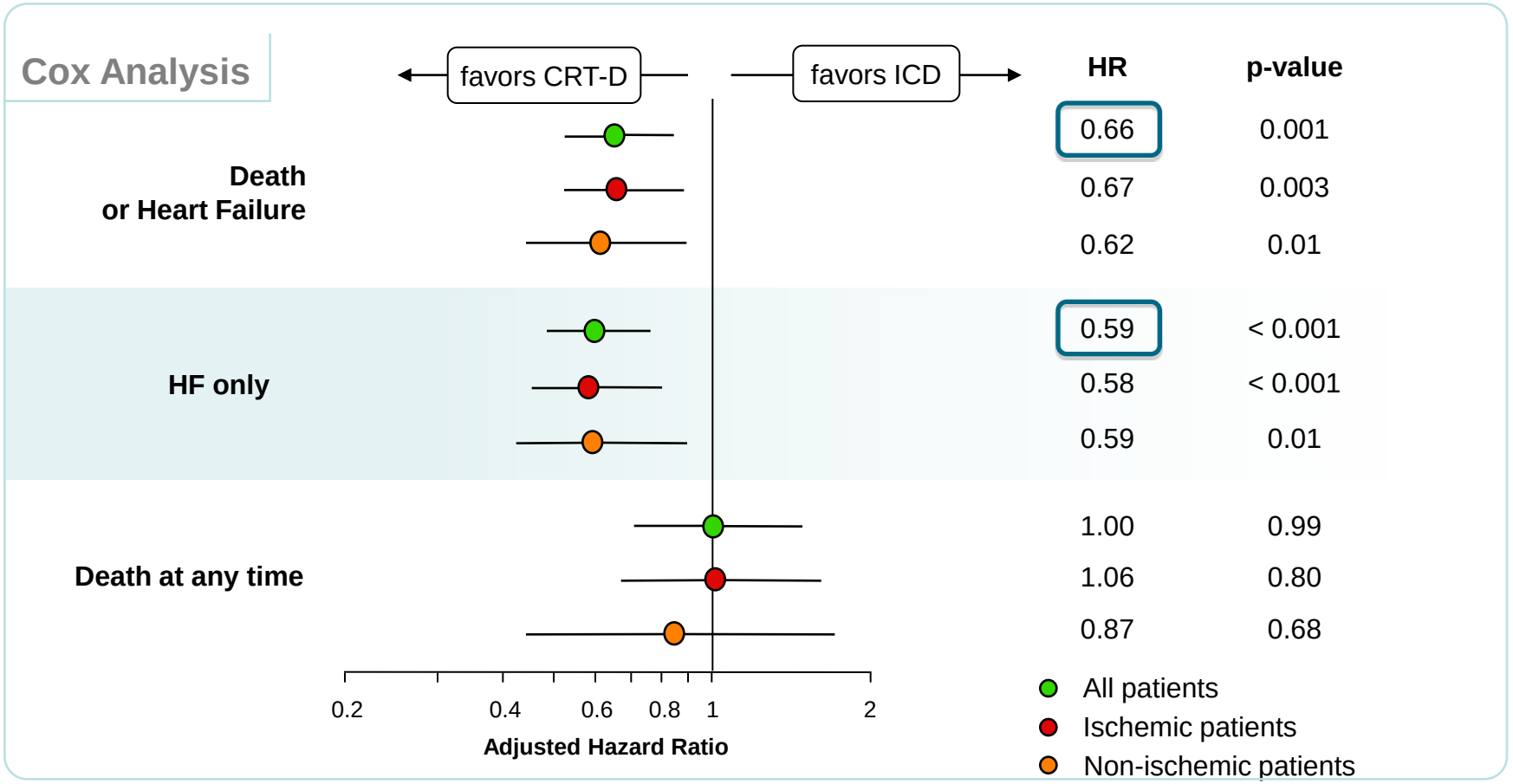


Patients at risk					
ICD-only	731 (1.00)	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT-D	1089 (1.00)	965 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

MADIT-CRT: Results Primary Endpoint (2)

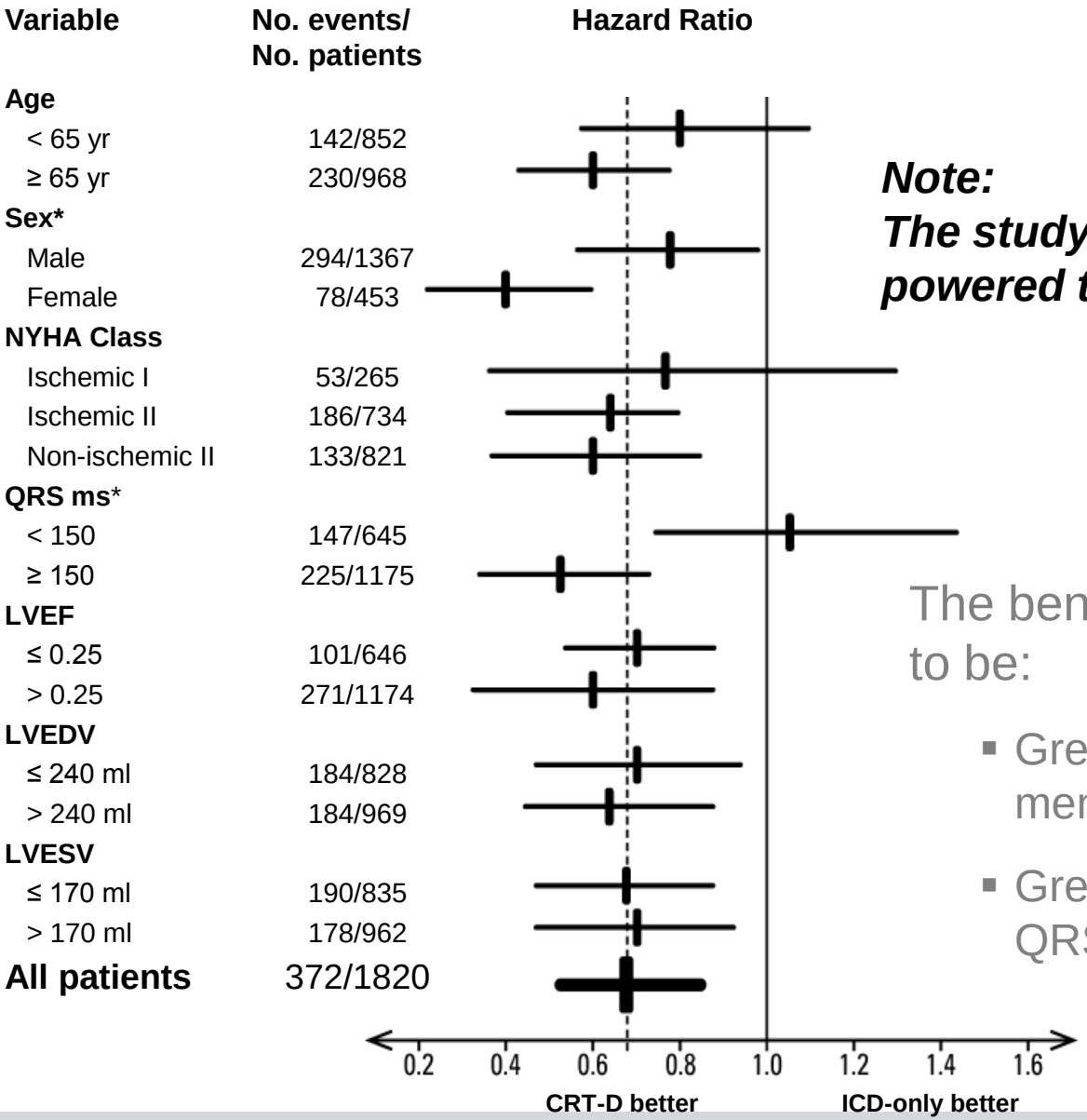
34% reduction in the risk of all-cause mortality or first HF event

- Benefit driven by **41% reduction** in the risk of heart failure events
- **Similar benefit** for ischemic and non-ischemic patient



Moss AJ, Hall WJ, Cannom DS, Klein H et al. New Engl J Med. 2009, 361:1329-1338

MADIT-CRT: Sub-group Analyses



Note:
The study was not statistically powered to evaluate subgroups

The benefit of CRT-D appeared to be:

- Greater in women that in men
- Greater in patients with wider QRS duration

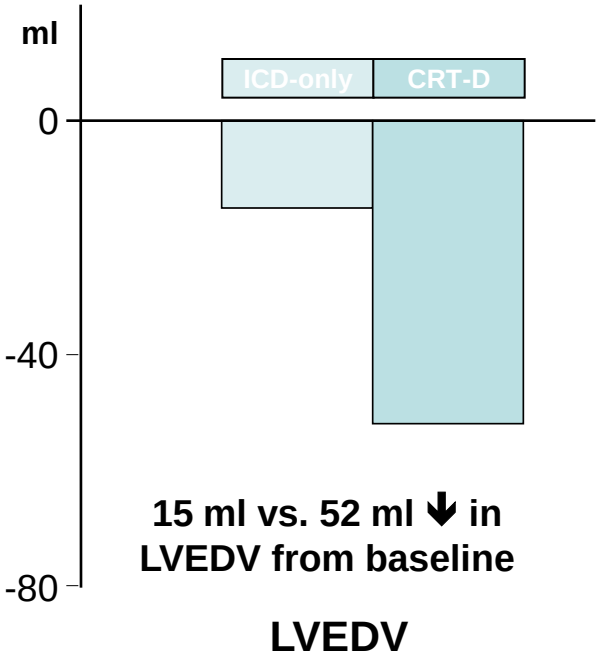
Moss AJ, Hall WJ, Cannom DS, Klein H et al. New Engl J Med. 2009, 361:1329-1338

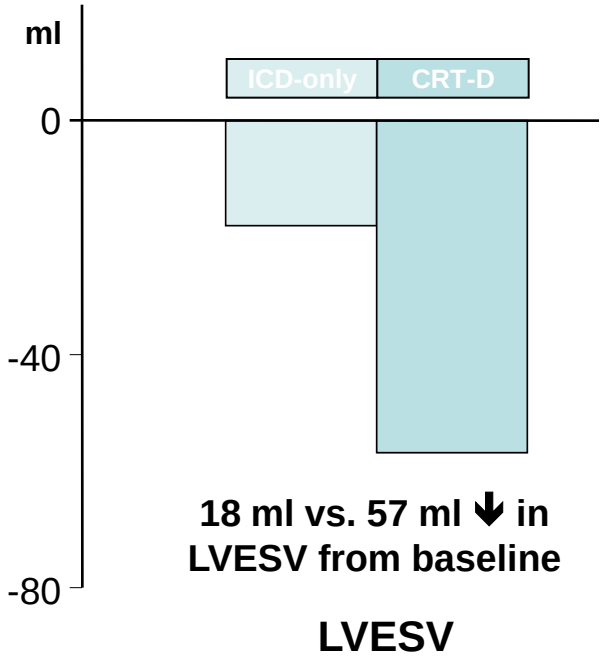
MADIT-CRT: Left Ventricular Volumes

CRT-D reduced left ventricular volumes greater than ICD

LVEDV	ICD	CRT-D
N	620	746
Baseline (ml)	251 ± 65	245 ± 60
Absolute Δ (ml)	-15	-52
p-value	< 0.001	

LVESV	ICD	CRT-D
N	620	746
Baseline (ml)	179 ± 53	175 ± 48
Absolute Δ (ml)	-18	-57
p-value	< 0.001	



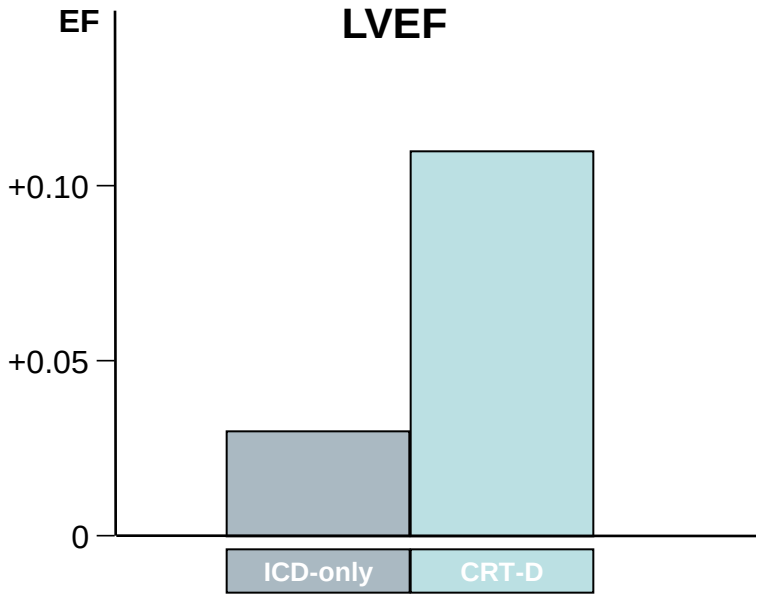


Moss AJ, Hall WJ, Cannom DS, Klein H et al. New Engl J Med. 2009, 361:1329-1338

MADIT-CRT: Left Ventricular Ejection Fraction

CRT-D increased LVEF greater than ICD

LVEF	ICD	CRT-D
N	620	746
Baseline (%)	24 ± 5	24 ± 5
Absolute Δ (%)	3	11
p-value	< 0.001	



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different ways to consider the economic impact of a technology to the healthcare system

NNT
"Number Needed To Treat"

- Number Needed to Treat to achieve one additional positive outcome
- The lower the NNT the better because it means fewer patients needed to be treated to reap a benefit
- NNT is measured at a specific point in time
- Number Needed To Treat (NNT) = 1 / Absolute Risk Reduction (ARR)

COST

Examples:

- Cost per day
- Total cost to healthcare system
- Total cost to hospital budget

COST EFFECTIVENESS ANALYSIS

- Ratio between the cost of a health-related intervention and the benefit it produces
- Benefit may be measured in life-years saved or quality-adjusted life years (QALY)
- Generally accepted benchmarks for therapeutic interventions[1]:
  - €40,000 per QALY in Europe
  - $50,000 per QALY to $100,000 per QALY in the US

1- Feldman AM, de Lissovoy G, Bristow MR, et al. Cost-effectiveness of cardiac resynchronization therapy in the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. JACC, 2005 Dec 20; 46 (12): 2311-21

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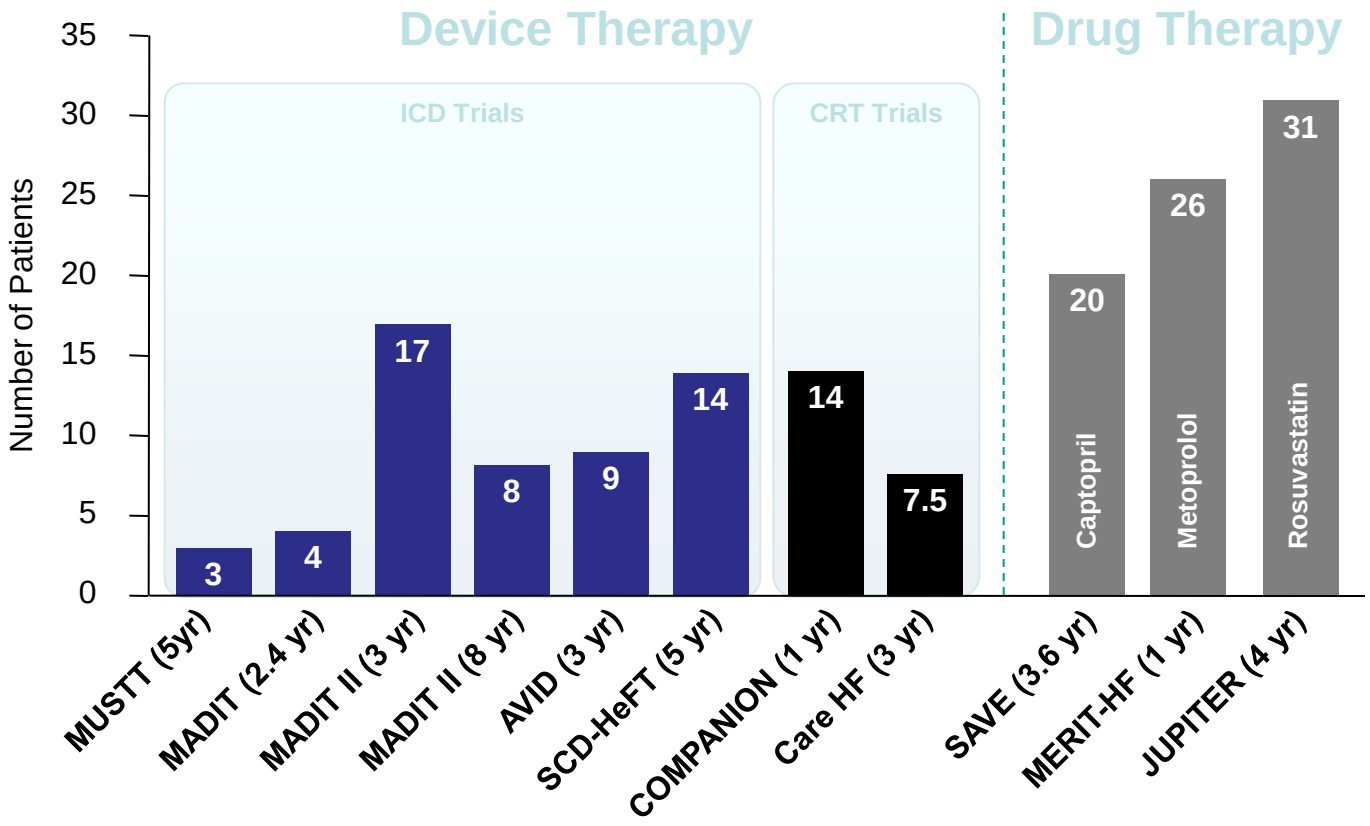
Number Needed to Treat (NNT) with ICD, CRT-P or CRT-D is significantly lower than drug therapy



Note: patient populations and therapeutic goals not the same for all trials. NNT is a function of the length of time horizon. See notes section for sources.

NNT "markedly decreases" with time

	Number Needed to Treat to gain 1 Life-		
	1 Year	2 Years	3 Years
TRIAL	10	3.3	1.7
Wever et al.[1]	9	3.3	2.0
MADIT[2]	21	8	4.6
AVID[3]	123	24	11
CIDS[4]	133	17	8
MADIT II[5]	133	11	5.6
CASH[6]	15	4.4	2.5
Schläpfer et al.[7]	15	4.7	2.5
MUSTT[8]			

Source: Salukhe et al. Ci

[1]Wever EFC, Hauer, RN

[2] Moss AJ, Hall, WJ, Can
Investigaros. *N Engl J Me*

[3] The Antiarrhythmics Ve

N Engl J Med. 1997; 337: 1576-1583

95: 91: 2195-2203.

mplantation Trial (MADIT)

rrhythmias.

[4]Connolly SJ, Gent M, Roberts RS, et al. Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation.* 2000; 101:1297-1302.

[5]Moss, AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defbrillator in patients with myocardial infarction and reduced ejection fraction: the Multicenter Automated Defibrillator implantation Trial II (MADIT II) Investigators. *N Eng J Med.* 2002: 346: 887-883

[6]Kuck K-H, Cappato R, Siebels J, et al. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hambrug (CASH). *Circulation.* 2000; 102: 748-754

[7]Schläpfer, J, Rapp F, Kappenberger L, et al. Electrophysiological guided amiodarone therapy versus the implantable cardioverter-defibrillator for sustained ventricular tachyarrhythmias after myocardial infarction. *J Am Coll Cardiology* 2002;39:1813-1819.

[8] Buxton, AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of suddent death in patients with coronary artery disease: the Multicenter Unsustained Tachycardia Trial (MUSTT) Investigators. *N Engl J Med.* 1999; 341: 1882-1890

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Cost of Device

- ICD £5-12,000
- CRTP £3-6,000
- CRTD £11-18,000

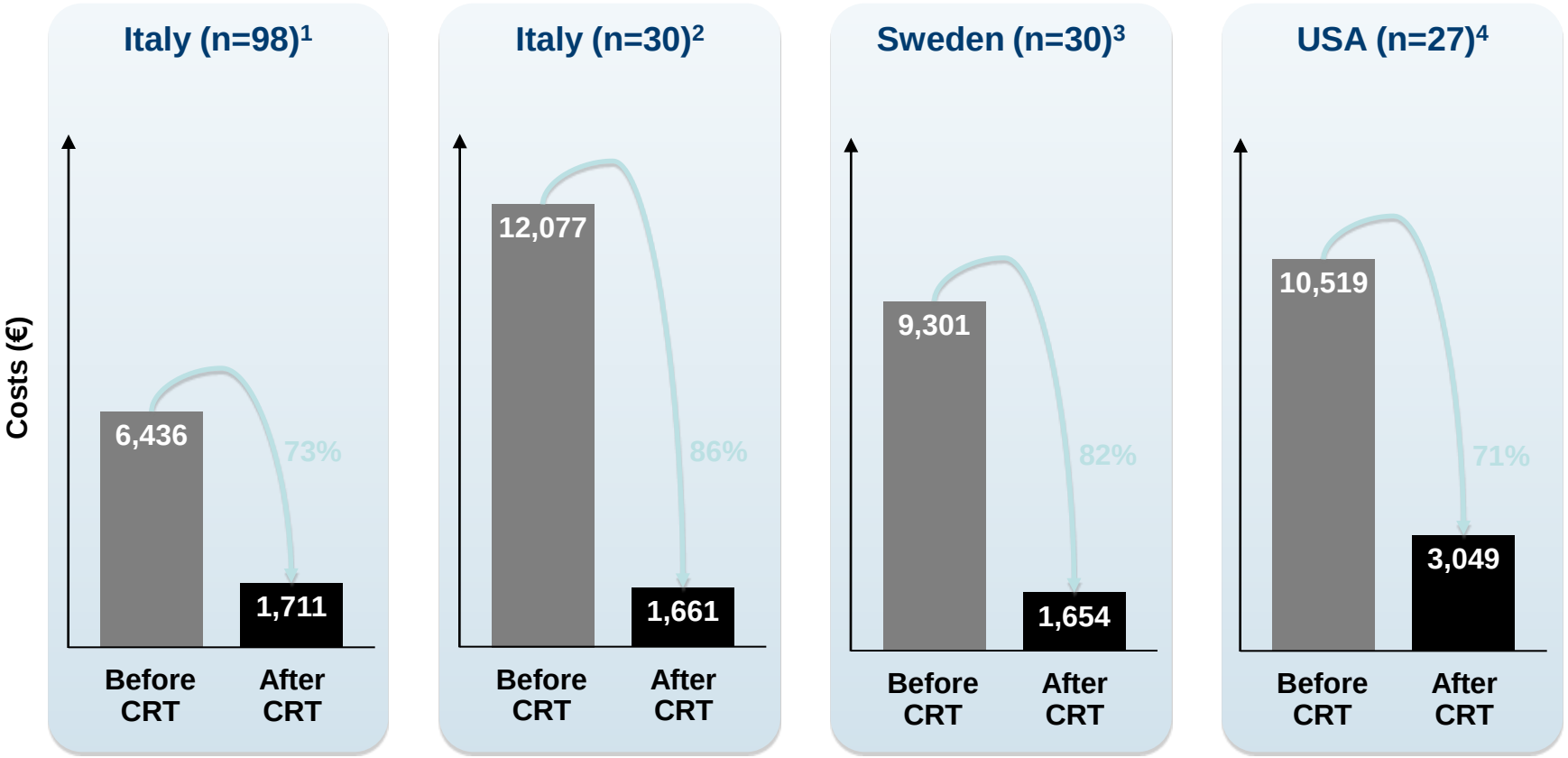
CRTD vs ICD hidden costs

Adverse events	CRTD	ICD	Excess
Pneumothorax	1.7%	0.8%	0.9%
Infection	1.1%	0.7%	0.4%
Haematoma	3.3%	2.5%	0.8%
CS diss / eff	0.5%		0.5%
LV lead repos	4%		4%

Total 6.6%

Costs offset by significant reduction in hospitalisation

CRT reduces HF hospitalization annual costs by up to 86%



1. Bocchiardo M. et al., XXXV ANMCO Congress, Florence, 2004. | 2. Curnis A. et al., Pharmacoeconomics 2003; 5:11-22. | 3. Braunschweig F. et al., Eur J Heart Fail 2001; 2:399-406.
4. Dixon L. et al., Europace 2004; 6:586-9.

Cost per QALY is the most common way to evaluate technologies and interventions

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***Studies presented are for indicated patient populations**

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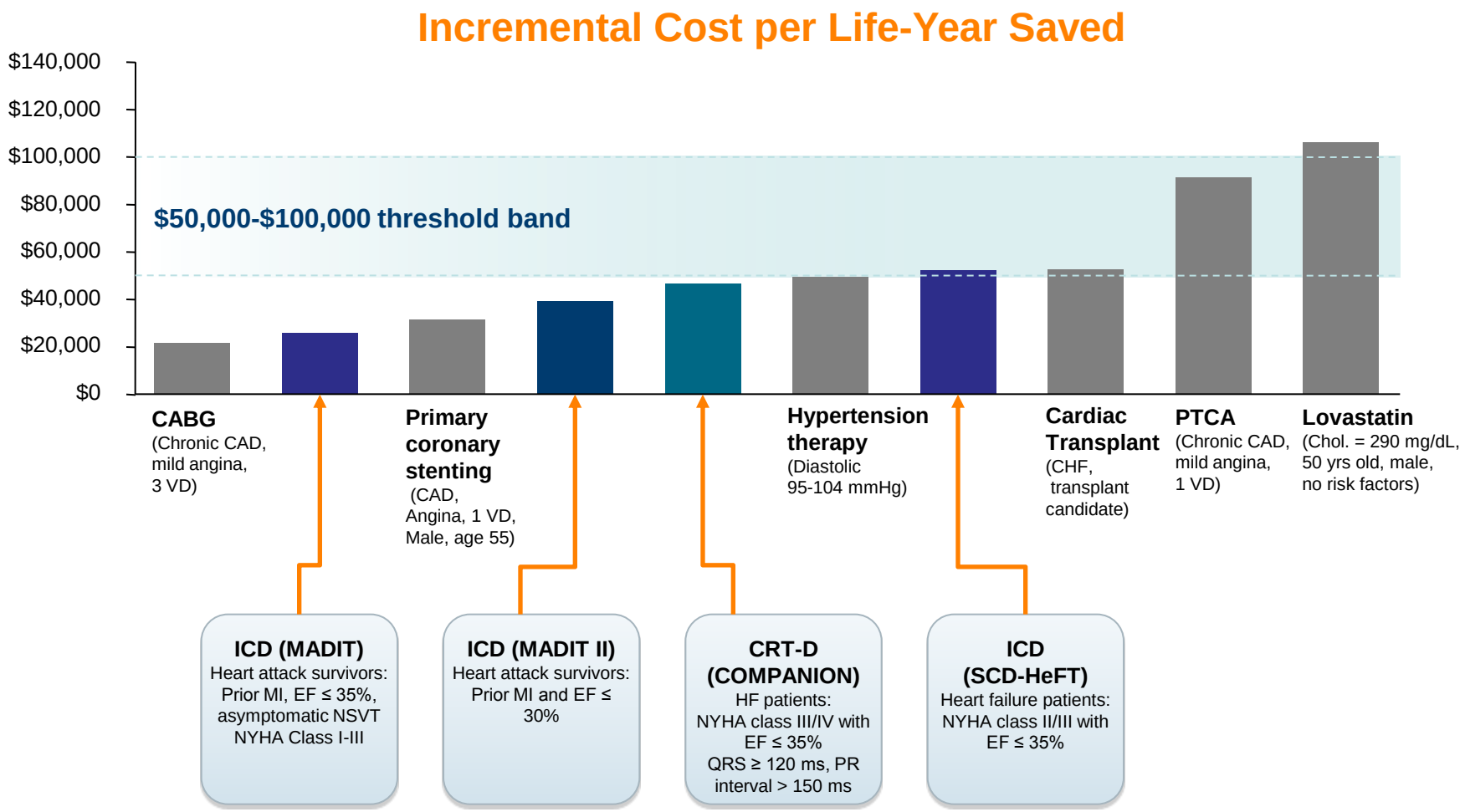
Cost effectiveness of ICD/CRT-D is comparable to that of other cardiac interventions…

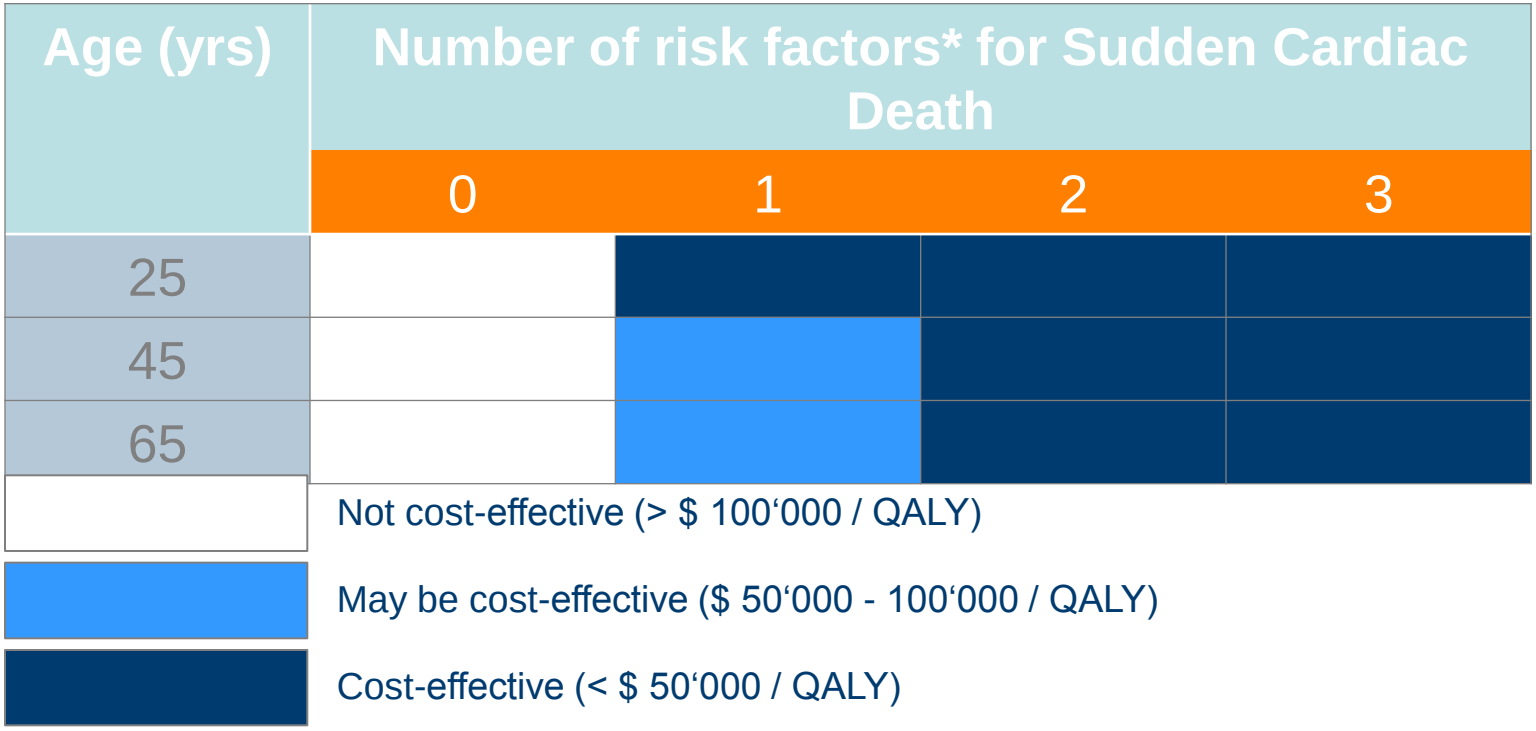


Stanton M. Circulation. 2000; 101:1067-1074

Feldman AM, de Lissovoy G, Bristow MR, et al. Cost-effectiveness of cardiac resynchronization therapy in the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. JACC, 2005 Dec 20; 46 (12): 2311-21

Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. N Engl. J Med. 2005 Oct 6; 353(14): 1471-8

Cost effectiveness of prophylactic ICD therapy depends on number of risk factors for SCD and age



***Risk factors**: *Family history of premature SCD, history of unexplained syncope, nonsustained ventricular tachycardia, abnormal blood pressure response to exercise*

You et al. , *Life expectancy gains and cost-effectiveness of implantable cardioverter/defibrillators for the primary prevention of sudden cardiac death in patients with hypertrophic cardiomyopathy.* Am Heart J 2007;154:899-907.

Conclusion

- ICD - clinical + cost effectiveness with increasing risk of SCD
- CRTP - clinical + cost effectiveness with symptomatic HF
- CRTD vs CRTP - clinical + cost effectiveness if symptomatic HF and long FU
- CRTD vs ICD - possible cost benefit with longer FU and some risk stratification