ADVANCES IN CARDIAC ARRHYTHMIAS
and
GREAT INNOVATIONS IN CARDIOLOGY

XXIX GIORNATE CARDIOLOGICHE TORINESI – 27th October 2017

The ICD in nonischemic cardiomyopathy: should we change our practice?

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SCD Epidemiology in Heart Failure (HF)

- **In the pre-implantable cardioverter defibrillator (ICD) era SCD accounted for ≈ 1/3 of all deaths in the HF population**

The CONSENSUS Trial Study Group *N Engl J Med 1987*; 316:1429-1435
Pitt B et al. *N Engl J Med 1999*; 341:709-717

- **From 30% to 50% of all SCD events occur in a patient with known reduced left ventricular ejection fraction (LVEF)**

Chugh SS et al. *Prog Cardiovasc Dis 2008*; 51:213-228
Stecker EC et al. *J Am Coll Cardiol 2006*; 47:1161-1166

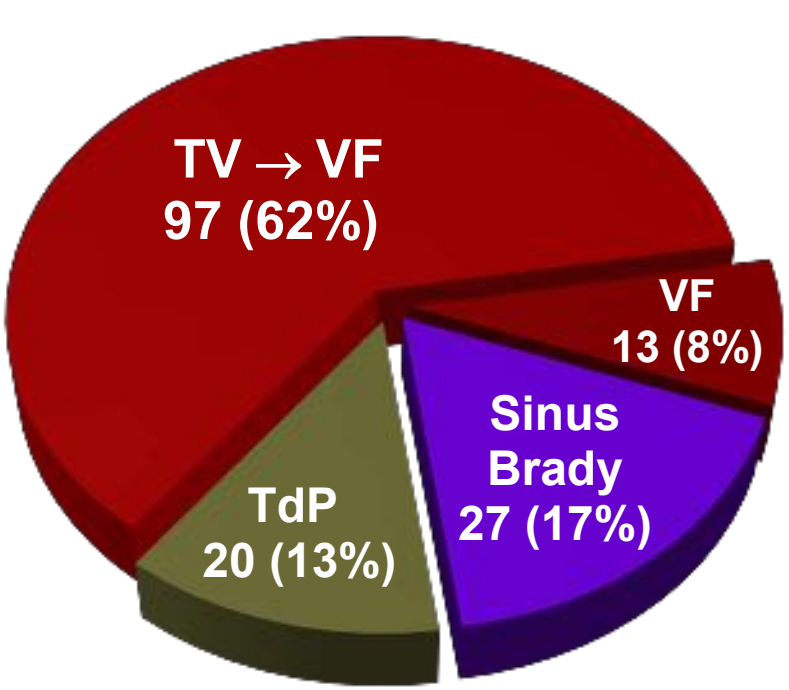
- **HF is one of the greatest risk factors for out-of-hospital cardiac arrest**

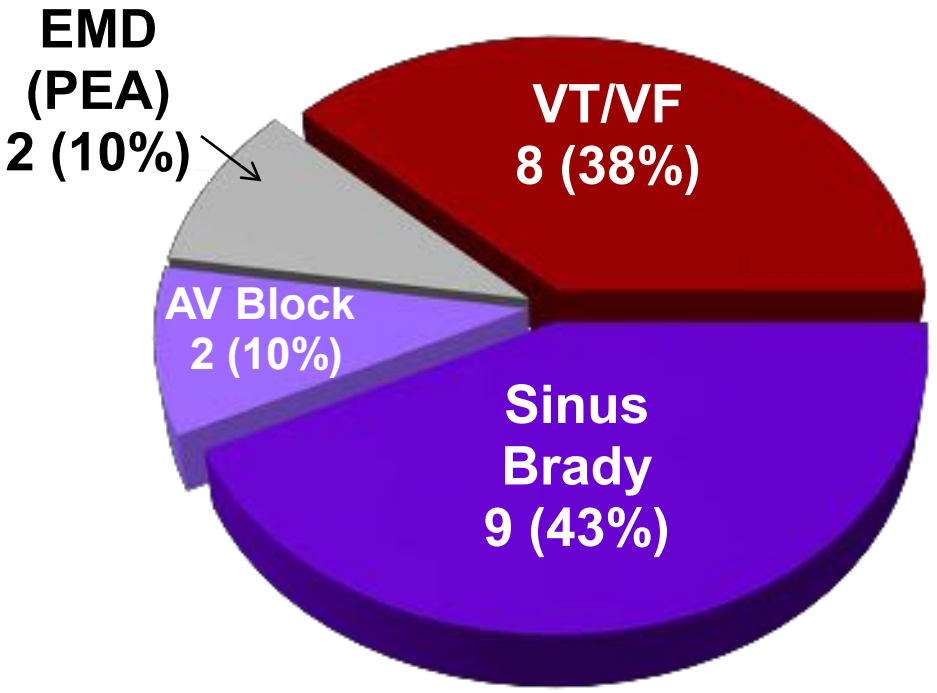
Rea TD et al. *Am J Cardiol 2004*; 93:1455-1460

Diverse Mechanisms of Unexpected SCD

157 patients with and without structural heart disease died while wearing Holter ECG

20 HF patients hospitalized with NYHA III/IV, severe LVSD experiencing cardiac arrest





Bayes de Luna A. et al. *Am Heart J* 1989; 117:151-159

Luu M. et al. *Circulation* 1989; 80:1675-1680

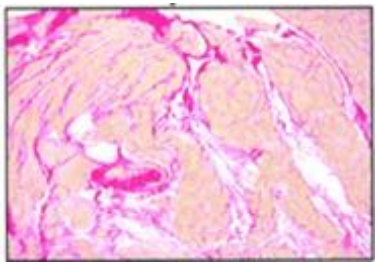
Pathophysiology of SCD in HF

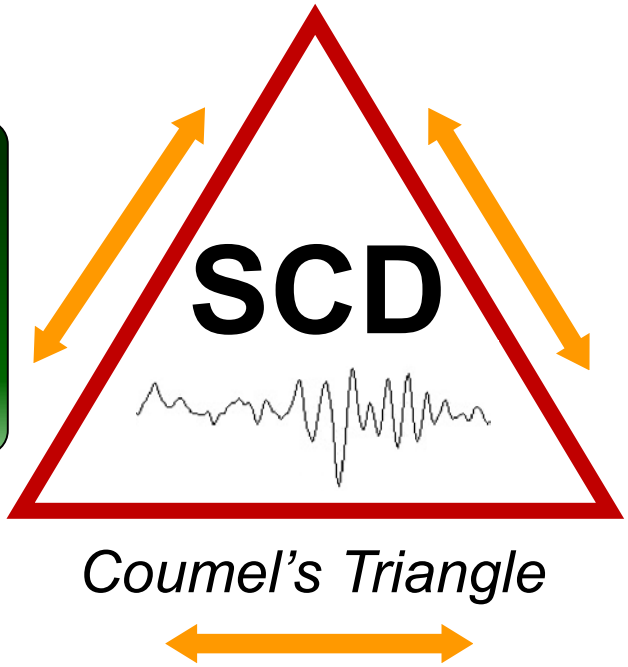
Modulating Factors

↑ Sympathetic Activation
↓ Parasympathetic Tone

Hypertrophy
LV Dilatation
LV Remodelling
Scar formation/Fibrosis
Conduction Abnormalit.

Substrate





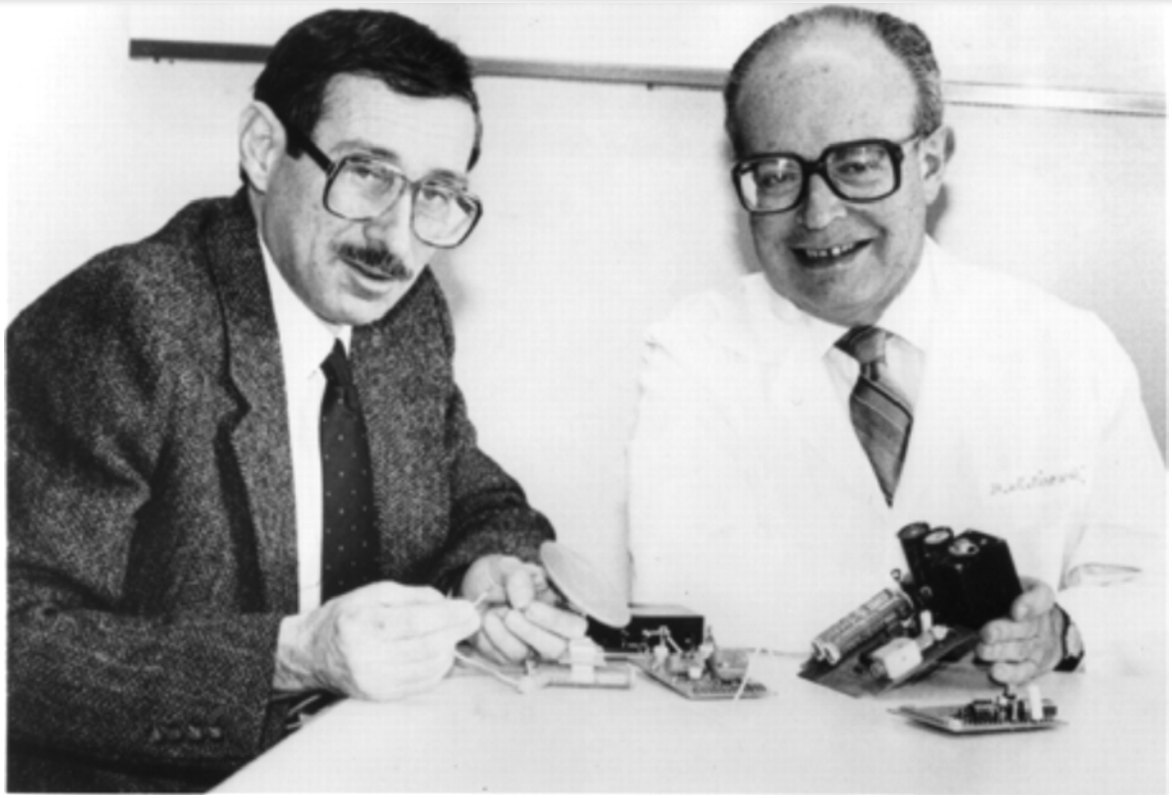
Coumel's Triangle

PVCs and VTs
Electrolyte Imbalances
Myocardial Ischaemia
Haemodynamic Changes

Triggers

ICD and SCD Prevention

First Human Implant February 1980
John Hopkins Hospital, Baltimore, MD, USA



Drs Morton Mower (left) and Michel Mirowski (right) with their first prototype of an automatic defibrillator

ICDs and Secondary SCD Prevention

	AVID (1997)	CIDS (2000)	CASH (2000)
Inclusion Criteria	- Resuscitated from VF - VT with syncope - VT with LVEF<40% and hemodynamic compromise (near syncope, angina, or heart failure)	- Resuscitated from VF-VT - VT with syncope - VT > 150 bpm with LVEF <35% and syncope or angina - Unmonitored syncope with spontaneous or inducible VT	- Resuscitated SCD with documented sustained ventricular arrhythmias
Patients, n	1016	659	288
Mean age, y	65 y	64 y	58 y
Mean LVEF, %	31	33	46
Follow-up, months	18	36	57
Drug in control grp	Amiodarone 85% Sotalol 15%	Amiodarone	Amiodarone 49% Metoprolol 51%
Other features	79% men 81% CAD 50% heart failure	85% men 80% CAD 50% heart failure	80% men 73% CAD 10% without SHD

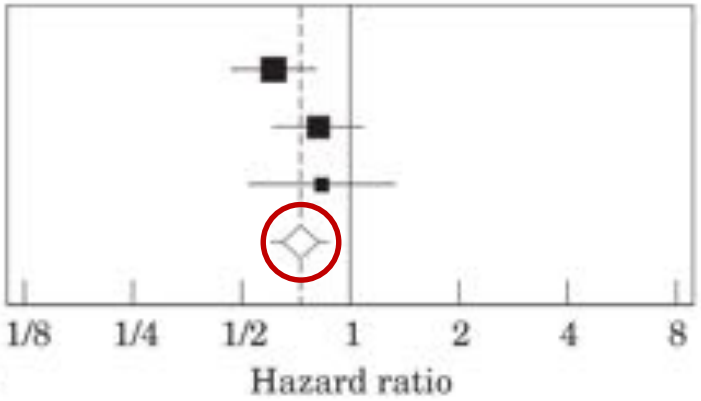
ICDs and Secondary SCD Prevention

Total mortality

Name	n	Events	HR	95% CI
AVID	1016	80	0·62	0·47, 0·81
CIDS	659	83	0·82	0·61, 1·10
CASH	191	37	0·83	0·52, 1·33
Fixed effects HR = 0·72				95% = 0·60, 0·87

Test for association (U = 11·77 on 1 df) $P = 0·00060$

Test for heterogeneity (Q = 2·37 on 2 df) $P = 0·30550$

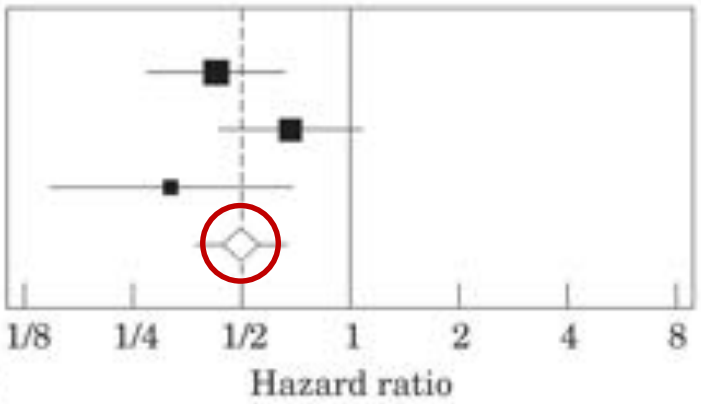


Arrhythmic mortality

Name	n	Events	HR	95% CI
AVID	1016	24	0·43	0·27, 0·66
CIDS	659	30	0·68	0·43, 1·08
CASH	191	7	0·32	0·15, 0·69
Fixed effects HR = 0·50				95% = 0·37, 0·67

Test for association (U = 21·73 on 1 df) $P = 0·00000$

Test for heterogeneity (Q = 3·57 on 2 df) $P = 0·16807$



Connolly S. et al. *Eur Heart J 2000*; 21:2071-8

ICDs and Secondary SCD Prevention

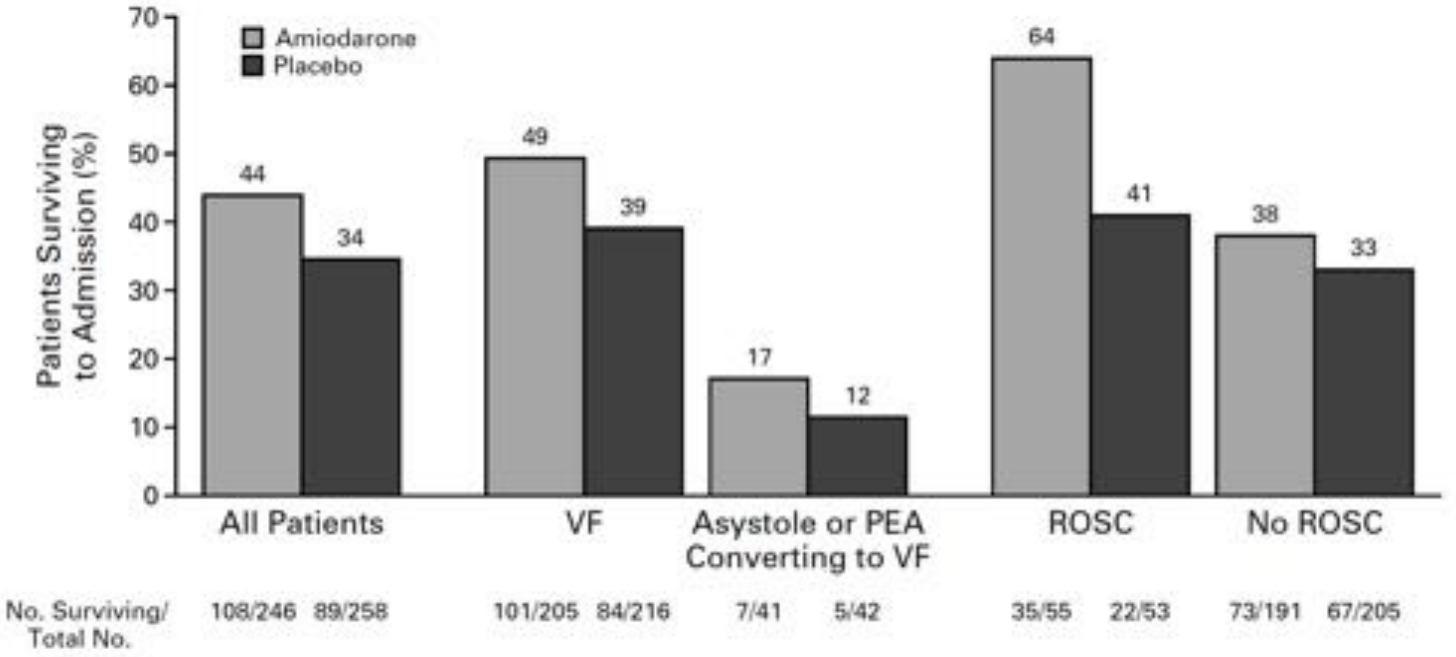
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Recommendations
Secondary Prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for > 1 year with good functional status

Class	Level
I	A

Eur Heart J 2016; 37(27):2129-200

Survival and QoL after Resuscitation



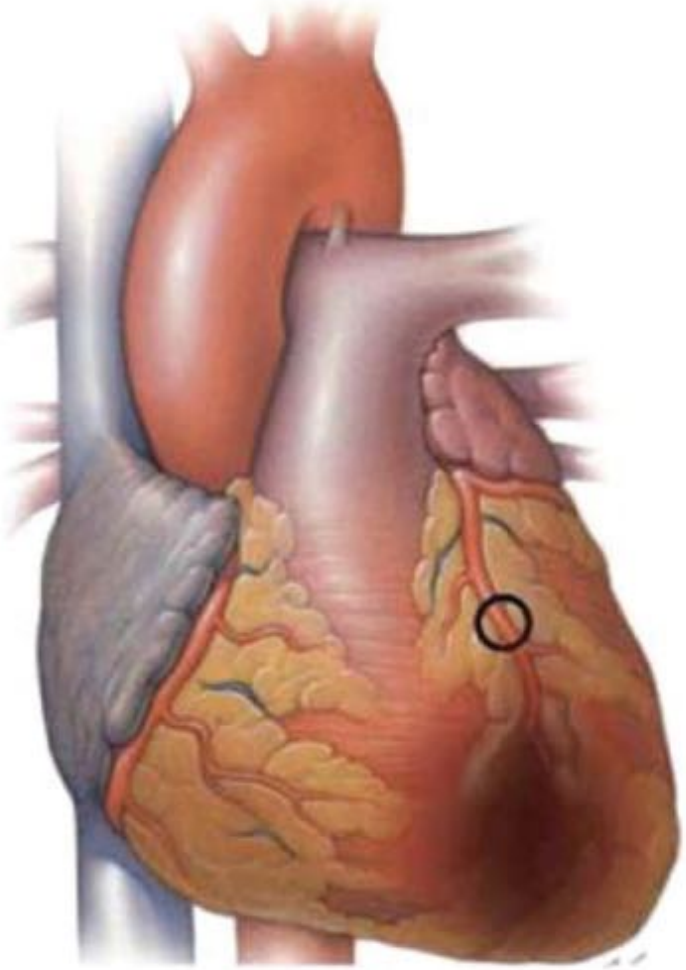
- 44% (amiodarone) vs. 34% (placebo) of patients reached the hospital alive after VF/CPR
- Only 13% (67 of 504) pts. were dismissed alive
- Only 6.9% (35 of 504) could lead an independent life after VF/CRP

Kudenchuk PJ, et al. *N Engl J Med* 1999; 341:871-8

ICDs and Primary SCD Prevention

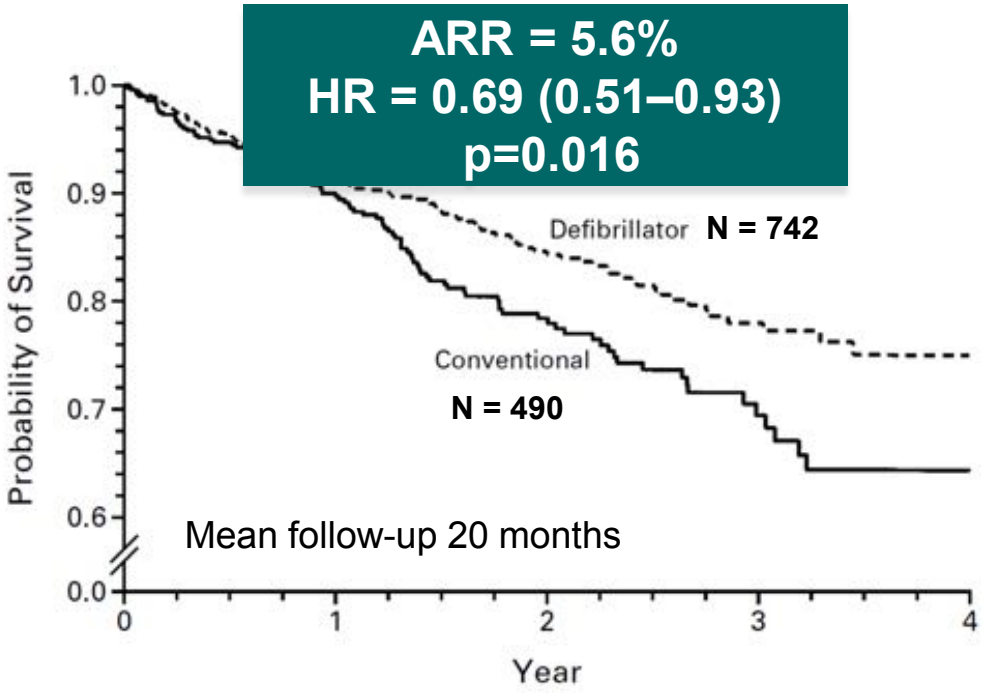
Study		Patients (n)	Inclusion criteria	Therapy	Hazard ratio	95% CI	P value
AMIOVIRT	Amiodarone versus Implantable Cardioverter-Defibrillator	103	NYHA I-III, DCM, asymptomatic NSVT, LVEF ≤0.35	ICD vs. amiodarone	0.87	0.31–2.42	NS
CABG-Patch	Coronary Artery Bypass Graft Patch trial	900	Scheduled for CABG, LVEF ≤0.35, positive SAECG	ICD vs. standard medical therapy	1.07[a]	0.81–1.42	NS
CAT	Cardiomyopathy Trial	104	NYHA II or III, DCM≤9 months, LVEF ≤0.30	ICD vs. standard medical therapy	0.83	0.45–1.82	NS
DEFINITE	Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation	458	DCM, LVEF ≤0.35, PVCs, or NSVT	ICD vs. standard medical therapy	0.65[a] 0.20[b]	0.40–1.06 0.06–0.71	0.08 0.006
DINAMIT	Defibrillator in Acute Myocardial Infarction Trial	674	Recent MI, LVEF ≤0.35, impaired cardiac autonomic function	ICD vs. standard medical therapy	1.08[a] 0.42[b]	0.76–1.55 0.22–0.83	NS 0.009
IRIS	Immediate Risk Stratification Improves Survival	898	Recent MI, LVEF ≤0.40, or NSVT	ICD vs. standard medical therapy	1.04	0.81–1.35	NS
MADIT	Multicenter Automatic Defibrillator Implantation Trial	196	NYHA I–III, prior MI, LVEF ≤0.35, NSVT, and positive EPS	ICD vs. standard medical therapy	0.46[b]	0.26–0.82	0.009
MADIT-II	Multicenter Automatic Defibrillator Implantation Trial-II	1232	Prior MI, LVEF ≤0.30	ICD vs. standard medical therapy	0.69[a]	0.51–0.93	0.016
MUSTT	Multicenter Unsustained Tachycardia Trial	351[c]	CAD, LVEF ≤0.40, NSVT, and positive EPS	ICD vs. conventional antiarrhythmic therapy	0.40[a] 0.24[b]	0.27–0.59 0.13–0.45	<0.001 <0.001
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial	1676[d]	NYHA II or III, LVEF ≤0.35, ischaemic and nonischaemic cardiomyopathy	ICD plus standard medical therapy vs. placebo plus standard medical therapy	0.77[a]	0.62–0.96	0.007

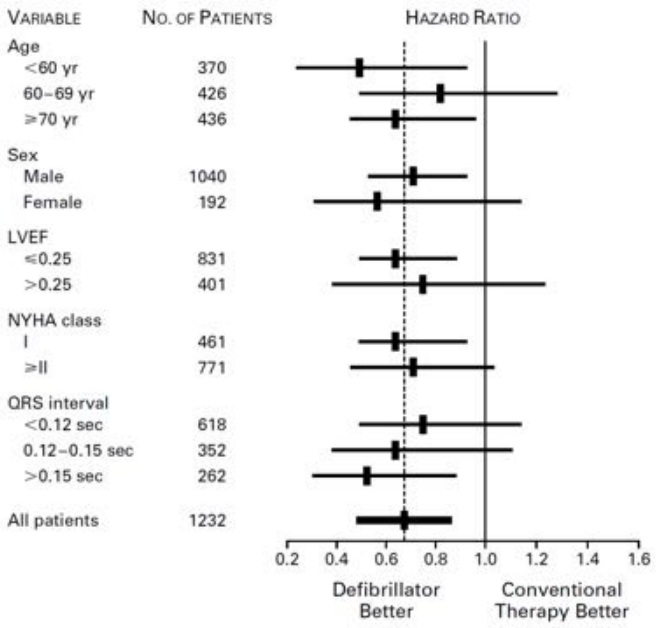
ICDs and Primary SCD Prevention in Ischaemic Cardiomyopathy



MADIT II (1997-2001)

- ≥ 1 months after myocardial infarction
- LVEF ≤ 30% + multiple / repetitive PVCs on Holter
- EP study not required
- Inclusion of 1232 patients between 7/1997 – 11/2001





Moss A, et al. *N Engl J Med* 2002; 346:877-884

ICDs and Primary SCD Prevention

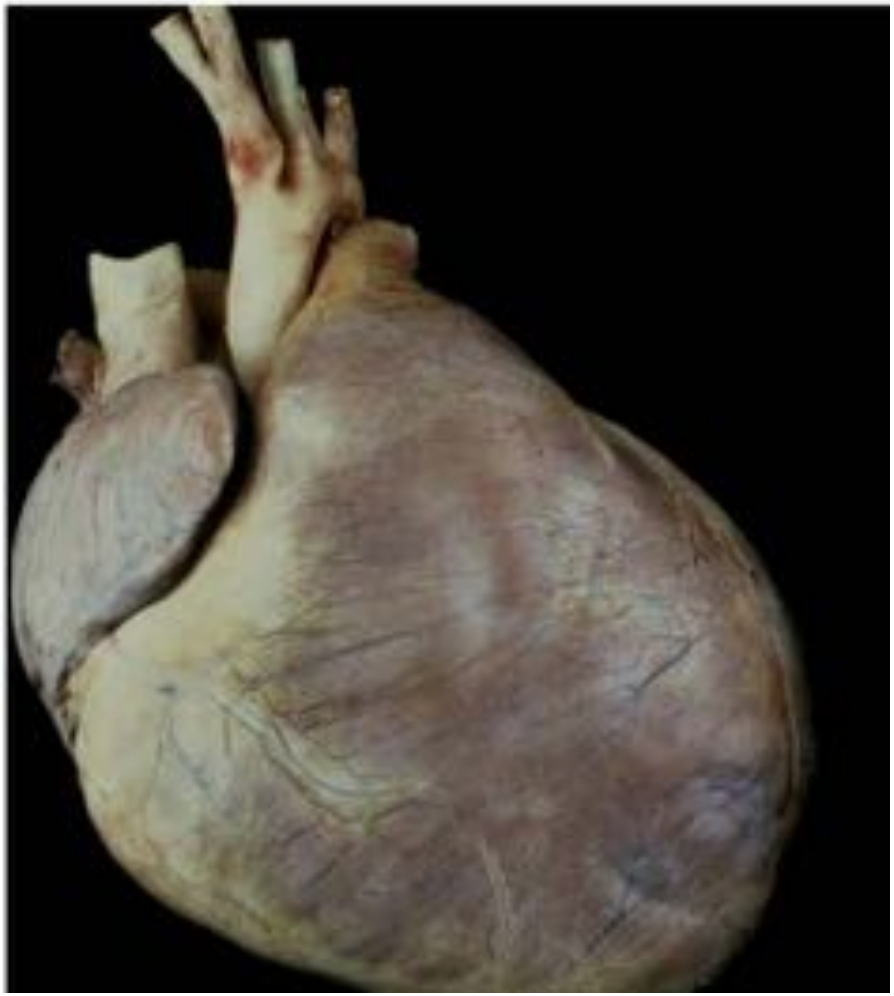
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Recommendations
Primary Prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II-III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than one year with good funnctional status, and they have: • IHD (unless they have an MI in the prior 40 days)

Class	Level
I	A

Eur Heart J 2016; 37(27):2129-200

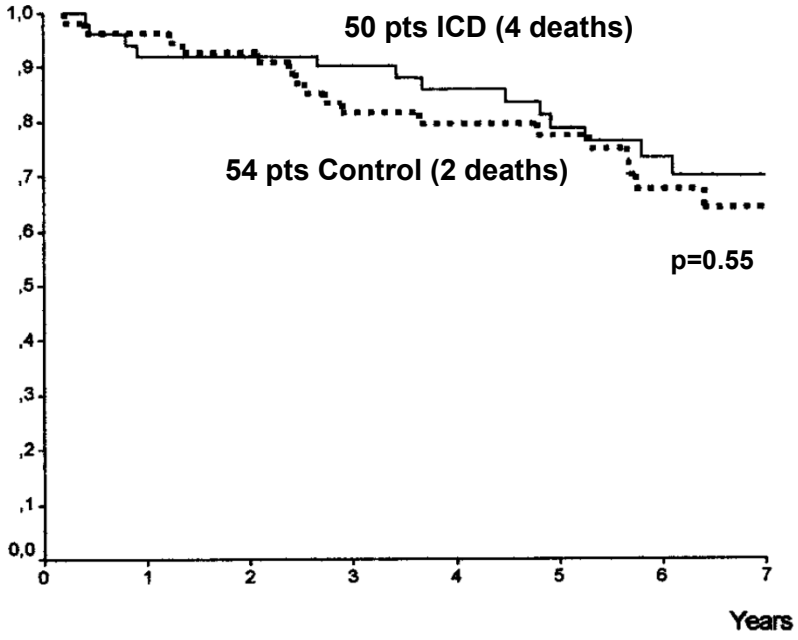
ICDs and Primary SCD Prevention in Nonischaemic Cardiomyopathy



ICD in Nonischaemic Cardiomyopathy
First Randomized Controlled Trials

Cardiomyopathy Trial (CAT)

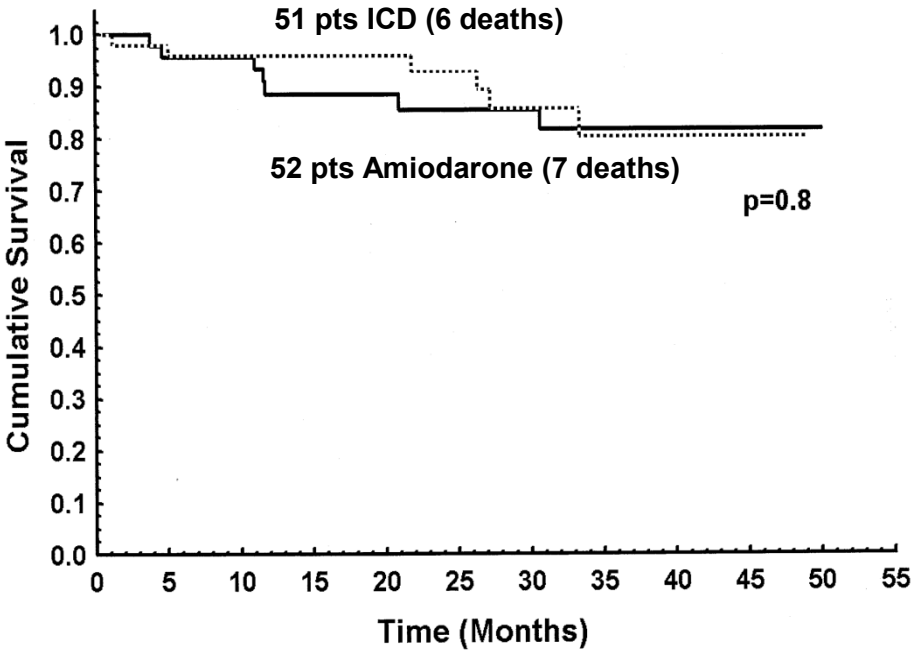
- **104** patients, LVEF<30%
- Recent (<9 mo) onset DCM
- ACE-I 96%, β-blocker 4%



Bansch D. et al. *Circulation* 2002; 105:1453-1458

Amio vs. ICD (AMIOVIRT)

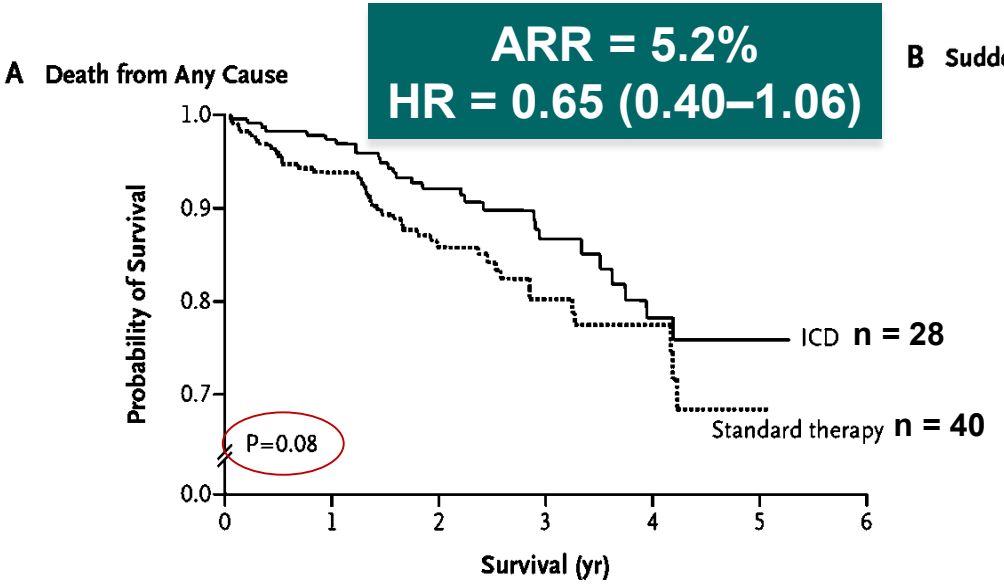
- **103** patients, LVEF<35%
- Non-ischaemic DCM + NSVT
- ACE-I 86%, β-blocker 52%

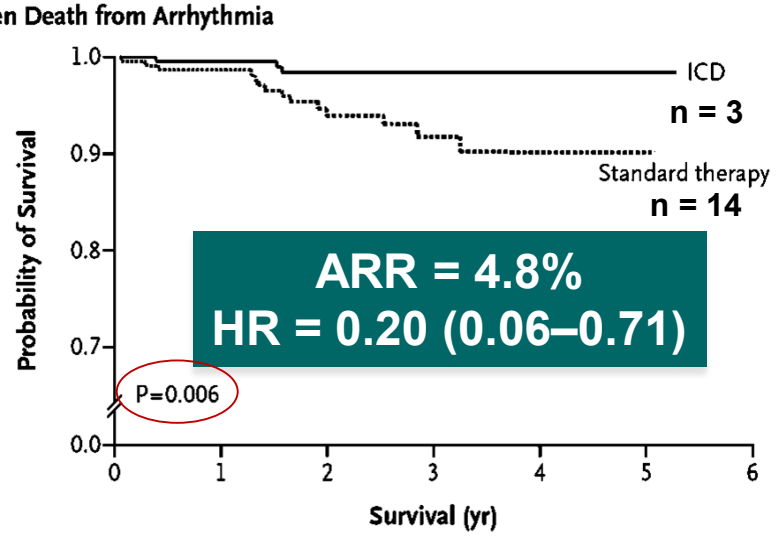


Strickberger AS. et al. *J Am Coll Cardiol* 2003; 41:1707–12

DEFINITE Trial (2004)

- Non-ischaemic cardiomyopathy, LVEF < 36%, NYHA I–III
- nsVT (3-15 cycles >120 bpm) or >10 PVCs/h (Ø EP Study)
- ICD (229 pts.) *vs.* Standard treatment (229 pts.)
- 86% pts. on ACE-I and 85% pts. on β-blocker

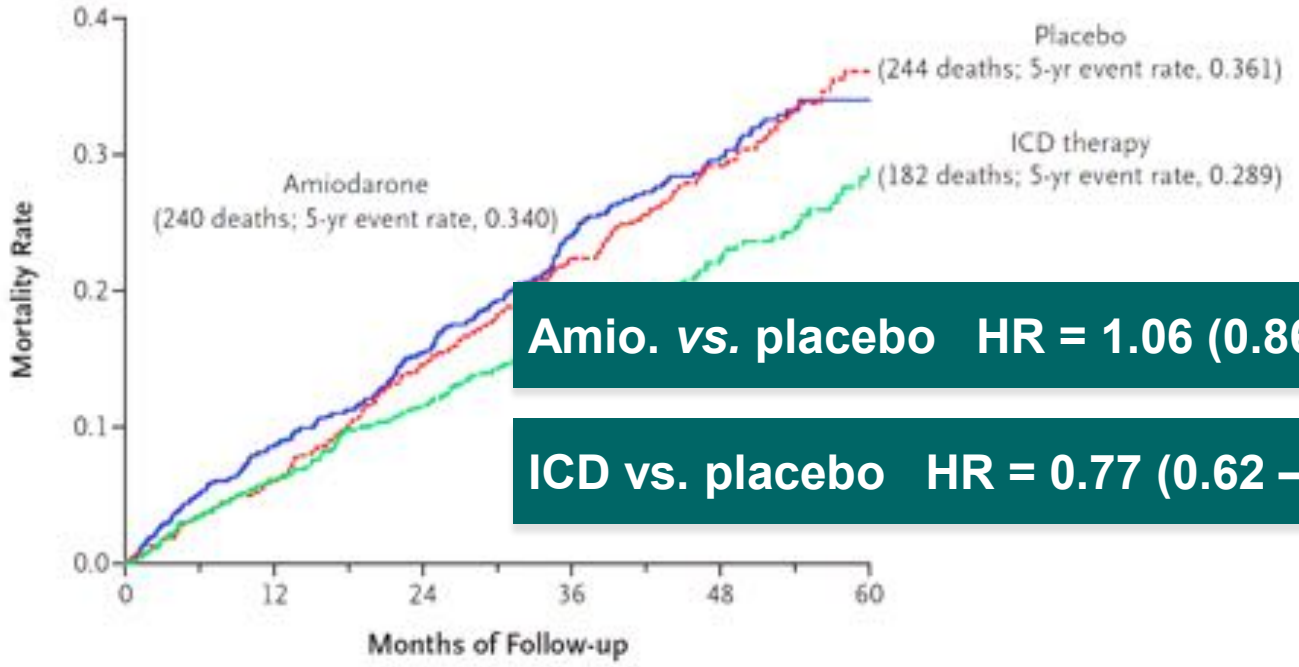




Kadish N, et al. *N Engl J Med* 2004; 350:2151-58

SCD-HeFT Trial (2005)

- **2521** patients with any cardiomyopathy (ICM + NICM)
- LVEF ≤ 35%, NYHA II – III
- 96% pts. on ACE-I / ARB and 69% pts. on β-blocker



No. at Risk						
Amiodarone	845	772	715	484	280	97
Placebo	847	797	724	505	304	89
ICD therapy	829	778	733	501	304	103

Amio. *vs.* placebo HR = 1.06 (0.86 – 1.30) p=0.53

ICD vs. placebo HR = 0.77 (0.62 – 0.96) p=0.007

Bardy G, et al. *N Engl J Med* 2005; 352:225-37

ICDs and Primary SCD Prevention

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Recommendations
Primary Prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II-III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than one year with good funnctional status, and they have: • DCM (Dilated Cardiomyopathy)

Class	Level
I	B

Eur Heart J 2016; 37(27):2129-200

Primary Prophylactic ICD in Nonischaemic Cardiomyopathy

- Based on small to medium sized trials with neutral outcomes and subgroup analysis of larger trials
- Medical therapy has improved since the landmark ICD trials

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 29, 2016 VOL. 375 NO. 13

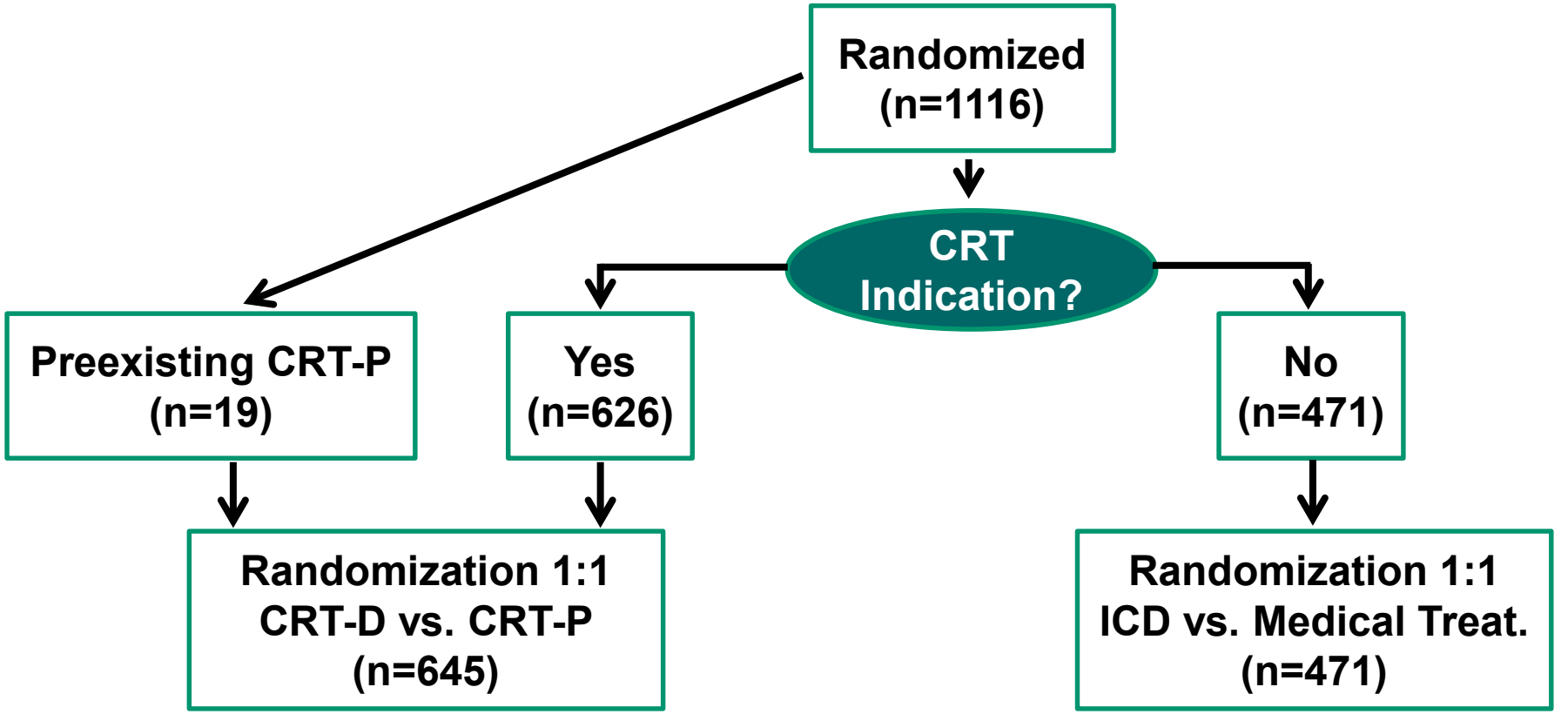
Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure

Lars Køber, M.D., D.M.Sc., Jens J. Thune, M.D., Ph.D., Jens C. Nielsen, M.D., D.M.Sc., Jens Haarbo, M.D., D.M.Sc., Lars Videbæk, M.D., Ph.D., Eva Korup, M.D., Ph.D., Gunnar Jensen, M.D., Ph.D., Per Hildebrandt, M.D., D.M.Sc., Flemming H. Steffensen, M.D., Niels E. Bruun, M.D., D.M.Sc., Hans Eiskjær, M.D., D.M.Sc., Axel Brandes, M.D., Anna M. Thøgersen, M.D., Ph.D., Finn Gustafsson, M.D., D.M.Sc., Kenneth Egstrup, M.D., D.M.Sc., Regitze Videbæk, M.D., Christian Hassager, M.D., D.M.Sc., Jesper H. Svendsen, M.D., D.M.Sc., Dan E. Høfsten, M.D., Ph.D., Christian Torp-Pedersen, M.D., D.M.Sc., and Steen Pehrson, M.D., D.M.Sc., for the DANISH Investigators*

1116 HF patients NYHA II-III (IV if planned CRT), LVEF ≤35% with non-ischaemic aetiology

N Engl J Med 2016; 375(13) 1221-1230

Danish Trial – Study Overview



CRT Stratum	
CRT-D	CRT-P
N = 322	N = 323

Non-CRT Stratum	
ICD	Medical Trt
N = 234	N = 237

N Engl J Med 2016; 375(13) 1221-1230

Danish Trial – Study Overview

Means of exclusion of ischemic cause of heart failure — no. (%)		
Catheterization	533 (96)	541 (97)
Cause of heart failure — no. (%)		
Idiopathic	424 (76)	425 (76)
Valvular	20 (4)	21 (4)
Hypertension	62 (11)	55 (10)
Other	50 (9)	59 (11)
Medications — no. (%)		
ACE inhibitor or ARB	533 (96)	544 (97)
Beta-blocker	509 (92)	517 (92)
Mineralocorticoid-receptor antagonist	326 (59)	320 (57)
Amiodarone	34 (6)	32 (6)
CRT — no. (%)	322 (58)	323 (58)

N Engl J Med 2016; 375(13) 1221-1230

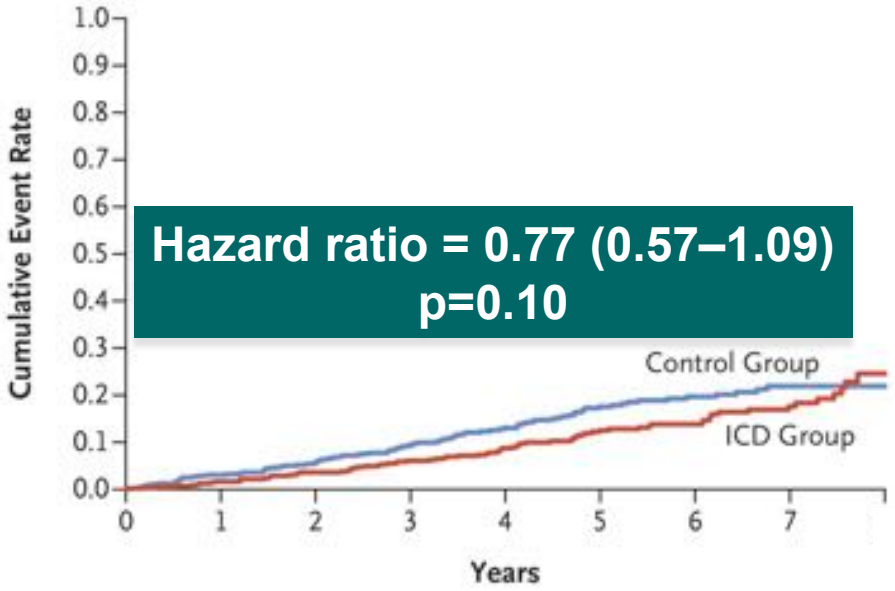
Danish Trial – Primary Outcome

- At a median of 67.6 months, there was no significant difference in mortality between the two groups

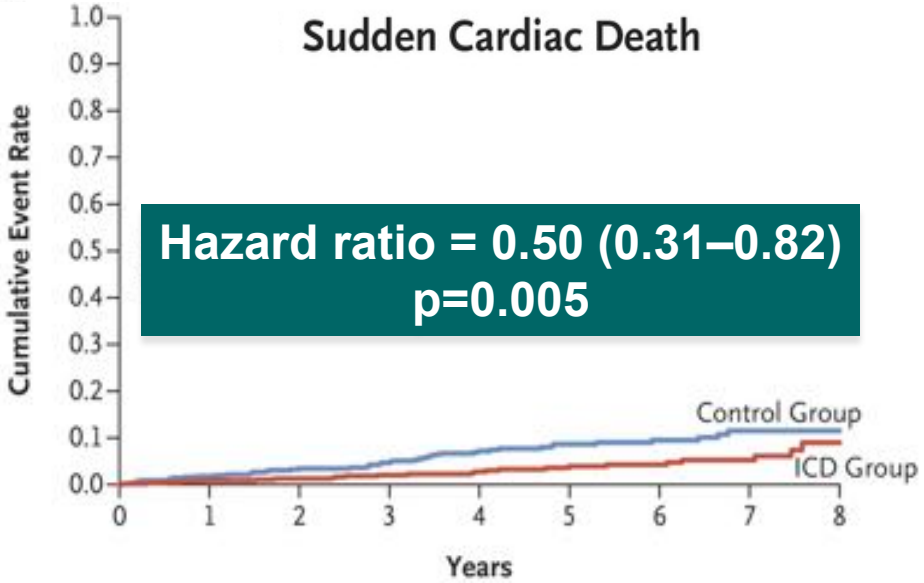
Hazard ratio = 0.87 (0.68–1.12)
p=0.28

N Engl J Med 2016; 375(13) 1221-1230

Danish Trial – Secondary Outcome



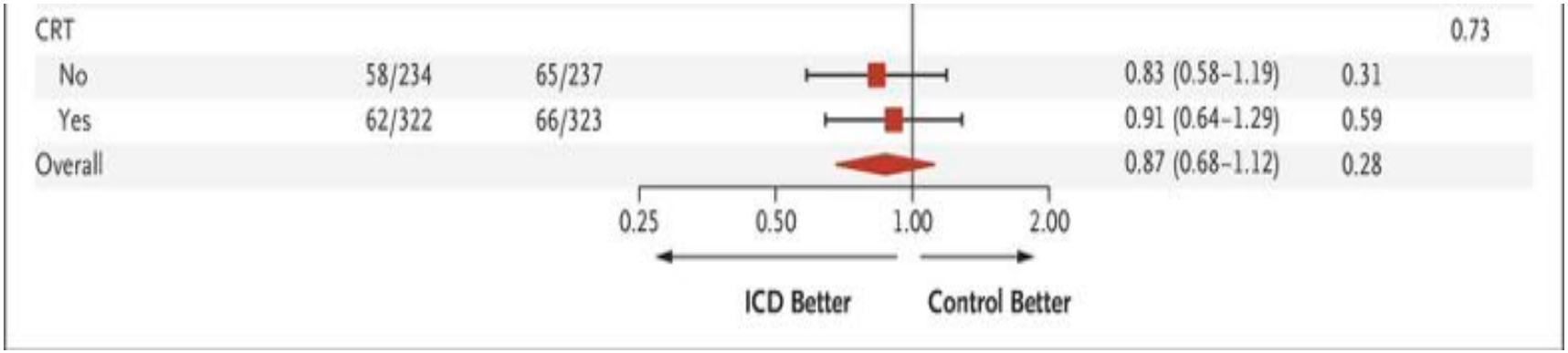
Hazard ratio = 0.77 (0.57–1.09)
p=0.10



Hazard ratio = 0.50 (0.31–0.82)
p=0.005

N Engl J Med 2016; 375(13) 1221-1230

Danish Trial – Interaction with Age



N Engl J Med 2016; 375(13) 1221-1230

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

The ICD in Heart Failure — Time for a Rethink?

John J.V. McMurray, M.D.

Most ICD recipients never experience ICD therapy

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

Risk stratification and prediction of SCD

"Prediction is very difficult, especially about the future"

Niels Bohr (1885-1962)

Nonsustained VTs and risk of SCD in HF

Non-sustained ventricular tachycardia as a predictor of sudden cardiac death in patients with left ventricular dysfunction: A meta-analysis

Marcos R. de Sousa [a,b,*], Carlos A. Morillo [c], Fábio T. Rabelo [b], Antônio M. Nogueira Filho [d], Antonio L.P. Ribeiro [a,b]

Predictors of Appropriate Implantable Cardioverter Defibrillator (ICD) Therapy in Primary Prevention Patients with Ischemic and Nonischemic Cardiomyopathy

ATUL VERMA, M.D., BRADLEY SARAK, B.Sc., ALEXANDER J. KAPLAN, B.Sc., RICHARD OOSTHUIZEN, B.Sc., MARIANNE BEARDSALL, R.N. M.S.N.,

Increased SCD risk in patients with Non-sustained VT

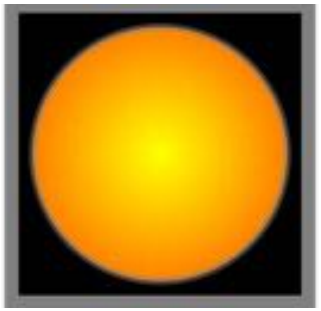
Circulation

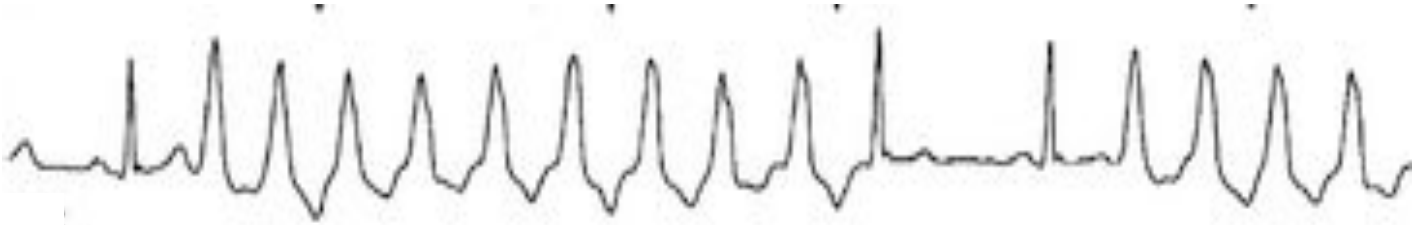
Nonsustained Ventricular Tachycardia in Severe Heart Failure

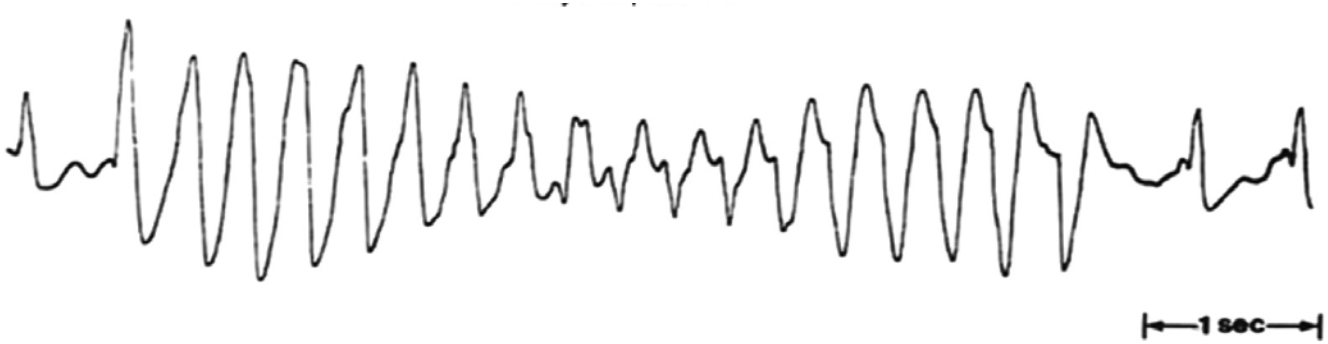
Independent Marker of Increased Mortality due to Sudden Death

Hernan C. Doval, Daniel R. Nul, Hugo O. Grancelli, Sergio D. Varini, Saul Soifer, Gianni Corrado, Sergio Dubner, Omar Scapin and Sergio V.

Not All Nonsustained VTs Are Created Equal







How Can Optimization of Medical Treatment Avoid Unnecessary Implantable Cardioverter-Defibrillator Implantations in Patients With Idiopathic Dilated Cardiomyopathy Presenting With "SCD-HeFT Criteria?"

Baseline Evaluation

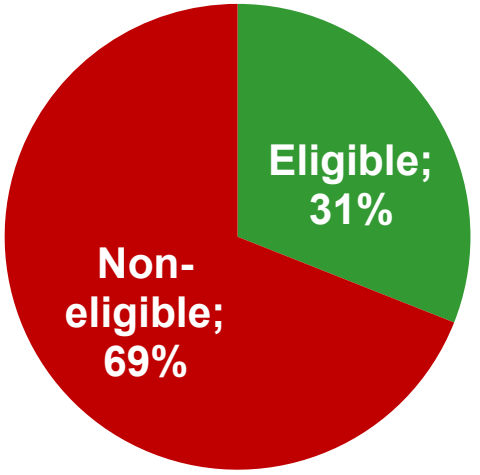
3-9 months Re-evaluation

Eligible for ICD
162 pts
β-blockers 0%
ACE-I 41%

3 pts (2%)
NYHA IV

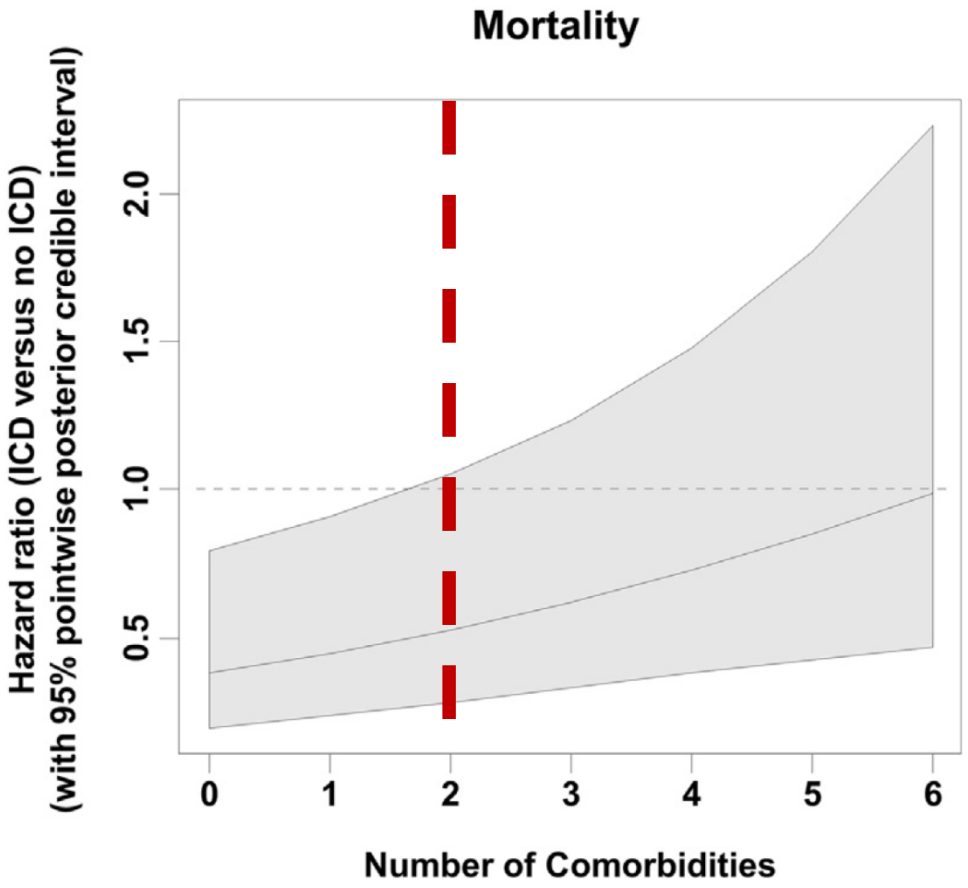
Eligible for ICD
50 pts (31%)
β-block 85%, ACE-I 94%

Non-eligible for ICD
109 pts (67%)
β-block 90%, ACE-I 95%



Adapted from Zecchin M, et al. *Am J Cardiol* 2012; 109:729-735

Impact of Comorbidities on ICD Benefit

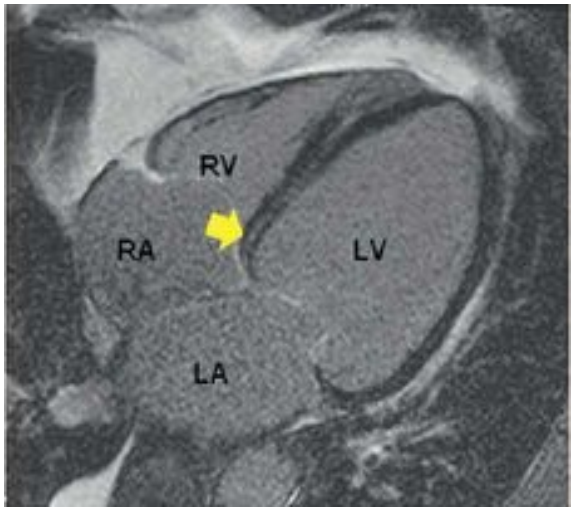


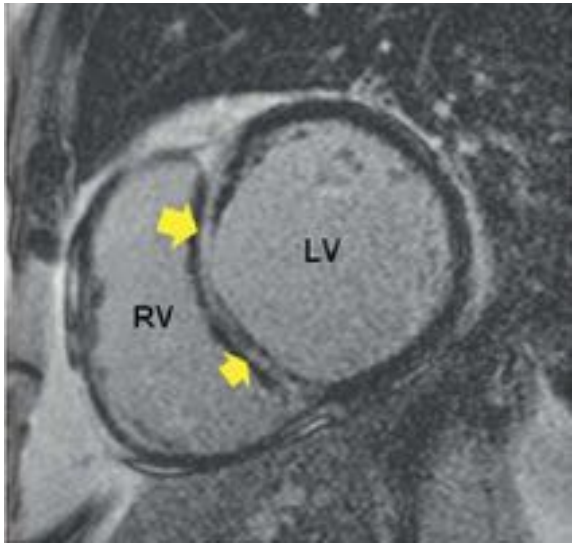
1. Smoking
2. Diabetes
3. Ischaemic Heart Disease
4. Peripheral Vascular Dis.
5. Atrial Fibrillation
6. eGFR <60 ml/min
7. COPD

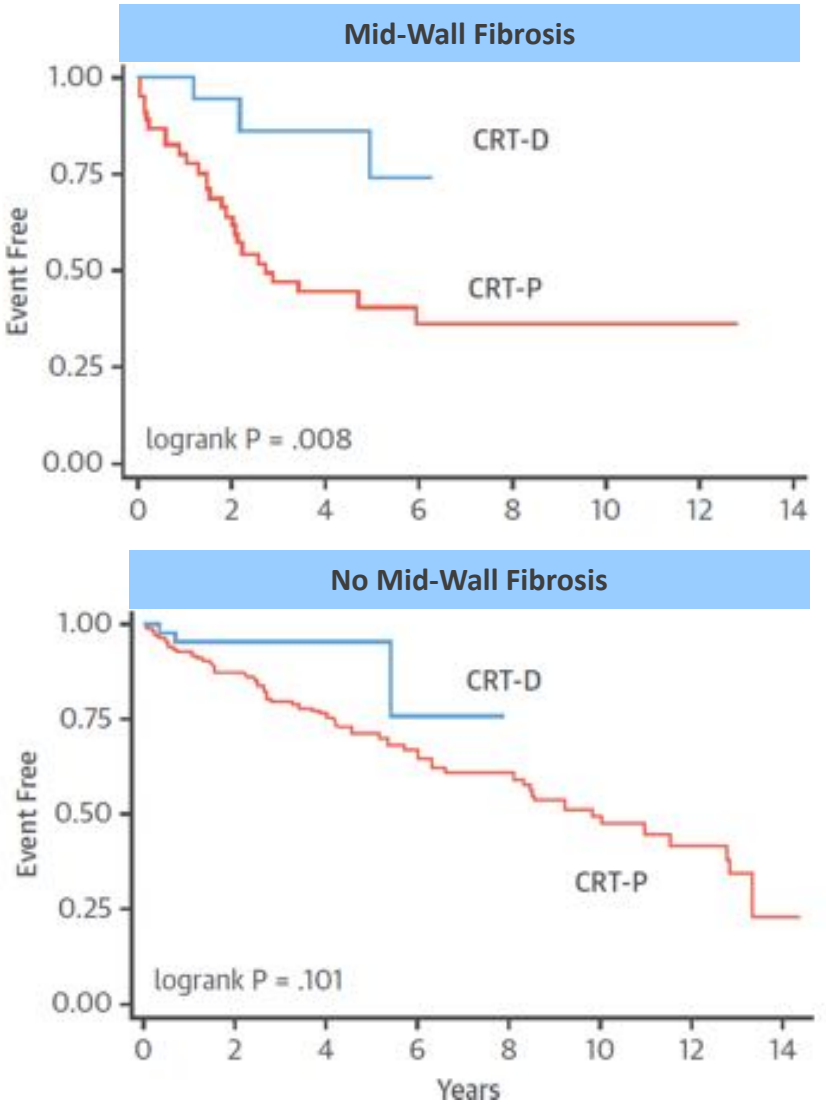
CONCLUSIONS Patients with extensive comorbid medical illnesses may experience less benefit from primary prevention ICDs than those with less comorbidity; implantation should be carefully considered in sick patients. Further study of ICDs in medically complex patients is warranted.

Steinberg BA. *J Am Coll Cardiol HF* 2014; 2:623-9

Role of Left Ventricular Midwall Fibrosis







Leyva F. *J Am Coll Cardiol* 2017; 70:1216-1227

Take Home Messages

The role of ICD in treatment of Ventricular Arrhythmias and prevention of SCD among patients with HF and reduced LVEF is established

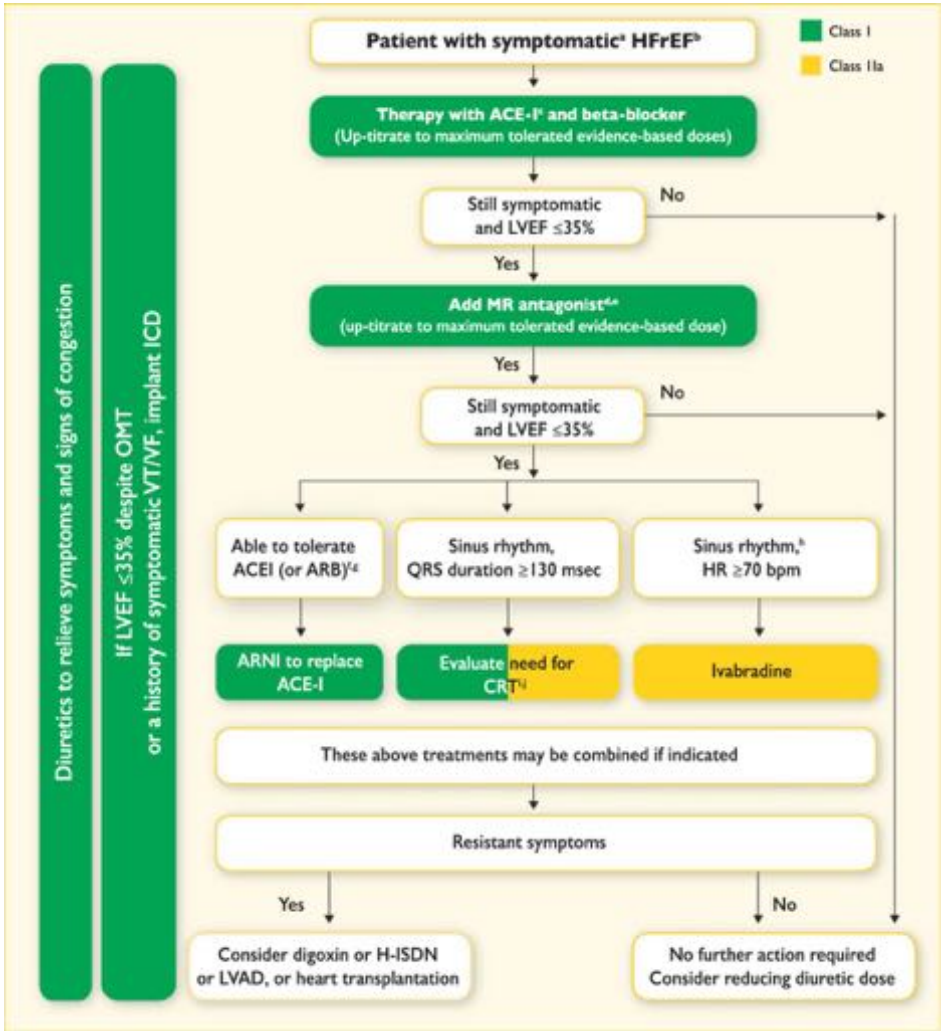
HOWEVER

- **Evidence for nonischaemic CMP are less robust**
- **Optimized medical therapy is mandatory**
- **Risk stratification before implantation is crucial**
- **Comorbidities/fibrosis may influence ICD benefit**


Thank you for your attention!

HF-REF Treatment Algorithm 2016

Treatment for patients with symptomatic HF-REF (NYHA II-IV)



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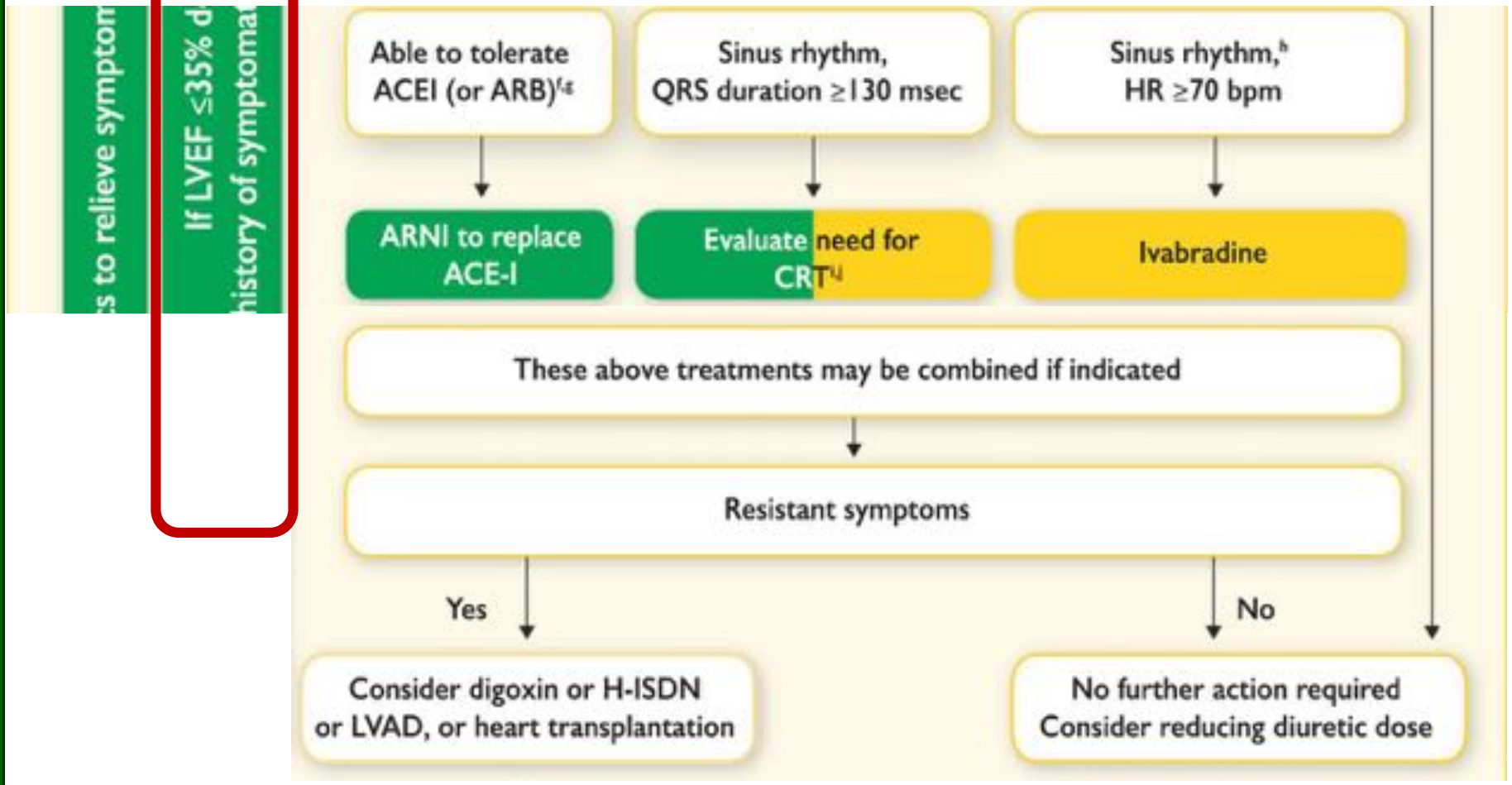
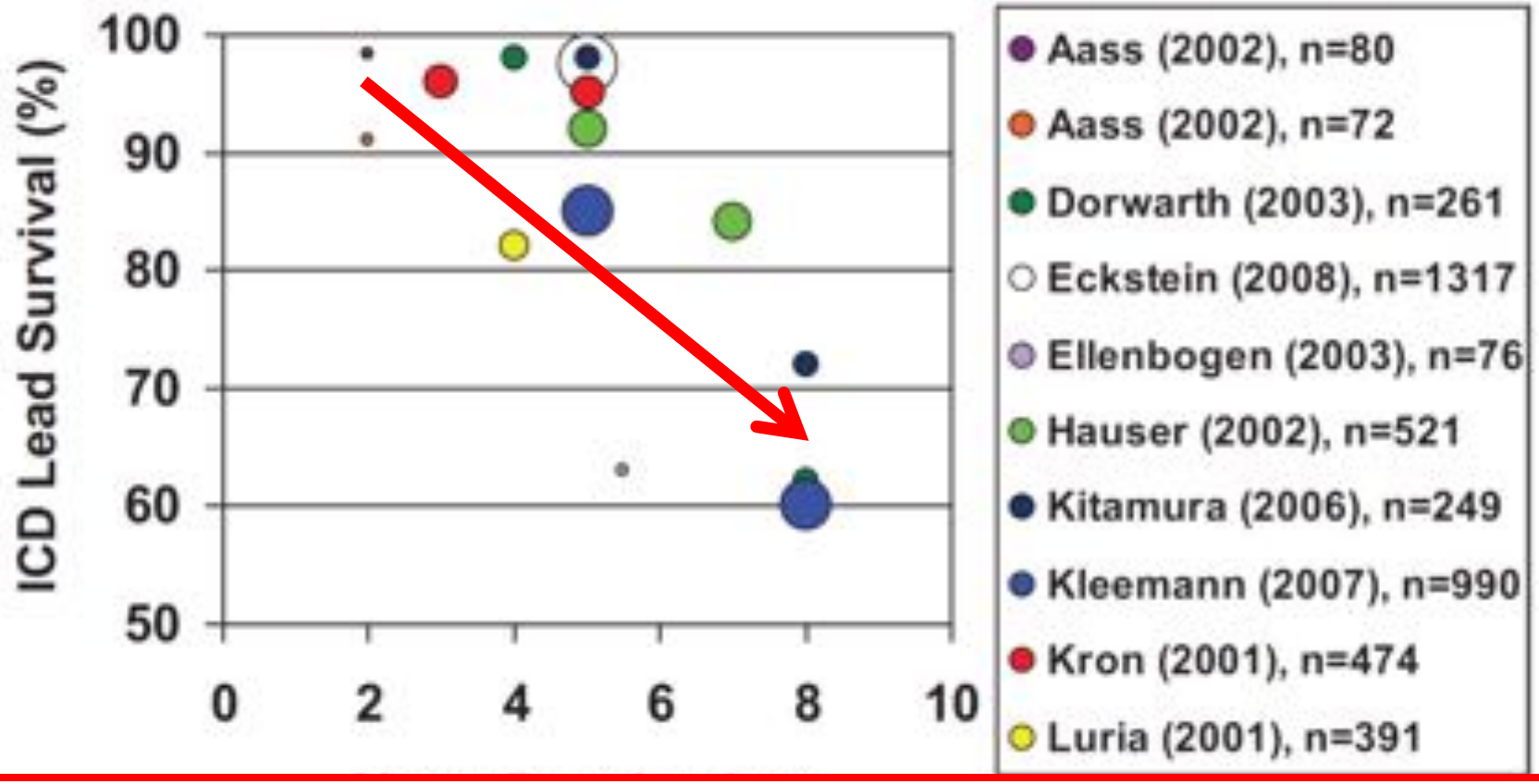
Eur Heart J 2016; 37(27):2129-200

Nonpharmacological Treatments in Selected Patients



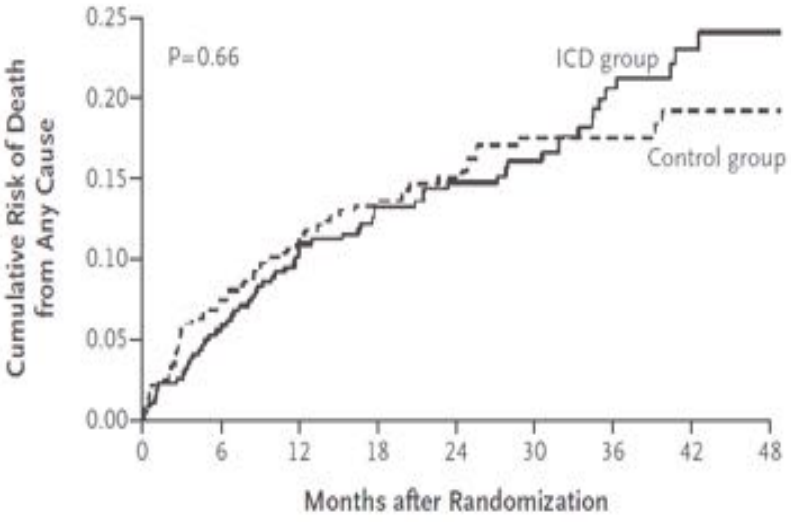
Eur Heart J 2016; 37(27):2129-200

ICD Lead Performance



≈ 20-30% ICD transvenous lead fail by 10 yrs

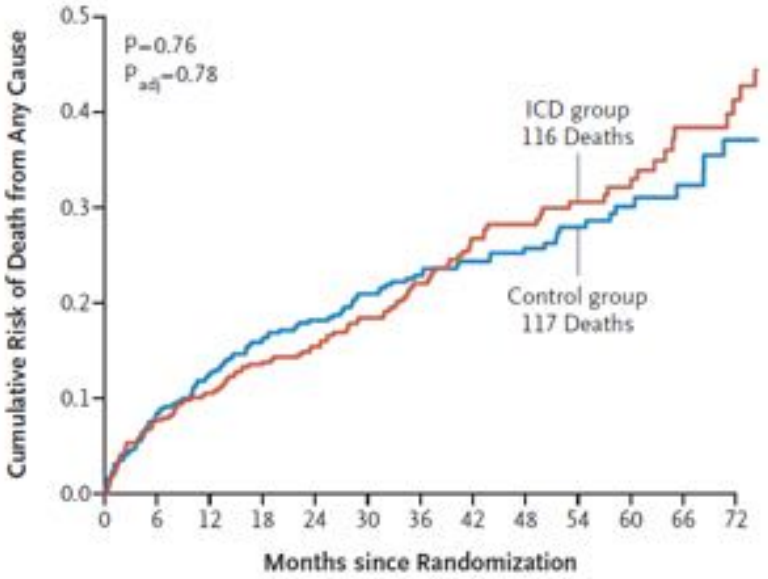
ICDs and Primary SCD Prevention
2016 ESC Heart Failure GLs



No. at Risk

ICD group	315	299	258	211	172	123	82	25
Control group	318	305	272	217	172	124	79	31

DINAMIT N Engl J Med 2004;351:2481-8.



No. at Risk

ICD group	445	390	366	338	303	253	207	163	137	106	78	48	40
Control group	453	410	380	336	307	267	230	187	151	118	79	49	36

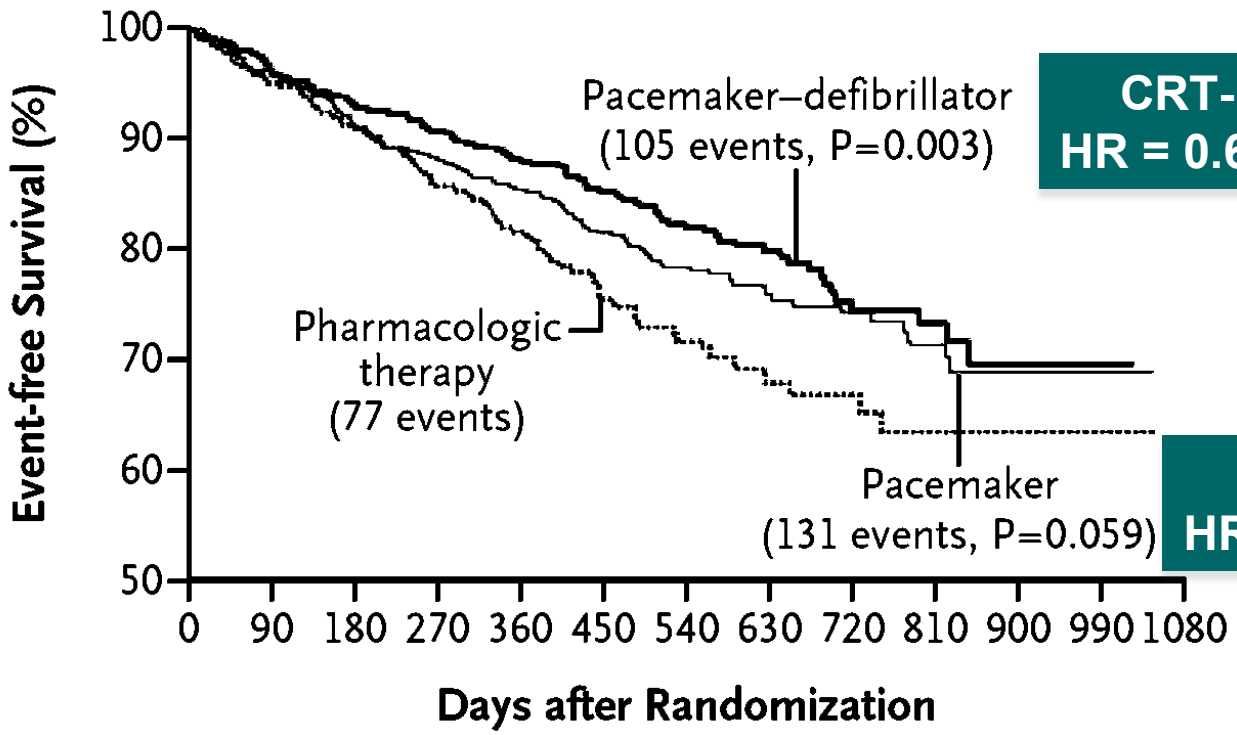
IRIS N Engl J Med 2009;361:1427-36

ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis.	III	A

Eur Heart J 2016; 37(27):2129-200

COMPANION Trial (2005)

- 1520 patients with any cardiomyopathy (ICM + NICM)
- LVEF ≤ 35%, NYHA III – IV, QRS ≥ 120 msec
- 89% pts. on ACE-I / ARB and 67% pts. on β-blocker



CRT-D *vs.* Drugs
HR = 0.64 (0.48 – 0.86)

CRT-P *vs.* Drugs
HR = 0.76 (0.58 – 1.01)

Bristow N, et al. *N Engl J Med* 2005; 352:225-37