Primary prophylactic ICD in patients with non-ischaemic dilated cardiomyopathy – State-of-the-Art

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What do guidelines tell us?

2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

Recommendations	Class	Level
ICD therapy is recommended to reduce SCD in patients with symptomatic HF (NYHA class II–III) and LVEF ≤35% after ≥3 months of optimal medical therapy who are expected to survive for at least 1 year with good functional status:		
• Ischaemic aetiology (at least 6 weeks after myocardial infarction).	I	A
• Non-ischaemic aetiology.	I	B

Priori SG, et al. *Eur Heart J* 2015;36:2793-2867

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Primary prevention ICD trials in patients with non-ischaemic dilated cardiomyopathy (1)

Characteristic	CAT (2002)	AMIOVIRT (2003)	DEFINITE (2004)	SCD-HeFT (2004/2005)	COMPANION (2004)
No. randomized	104	103	458	(ICD vs. placebo) 1676	(CRT-D vs. medical) 903
No. (%) with NICM	104 (100)	103 (100)	458 (100)	792 (47.3)	397 (44.0)
Duration of FU mean (SD), mo	66 (26.4)	24 (14.4)	26 (4)	45.5	Range, 14.8-16.5
Age, mean (SD), y	52 (11)	59 (11.5)	58	60	67
Male, % (No.)	80 (83)	70 (72)	71 (326)	77 (1291)	68 (611)
NYHA III/IV, % (No.)	35.6 (36)	20 (21)	21 (96)	30 (503)	100 (903)
Duration of CHF, mean	3 mon	3.2 y	2.8 y	24.5 mo	3.5 y
LVEF, mean (SD), %	24 (7)	23 (9)	21 (14)	25 (5)	22
β-Blocker at baseline, % (No.)	3.8 (4)	51.5 (53)	84.9 (389)	69 (1156)	67 (608)
ACE-I/ARB at baseline, % (No.)	96.2 (100)	85 (88)	96.7 (443)	96 (1609)	89 (810)

Modif. from Desai AS, et al. *JAMA* 2004;292:2874-9

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Primary prevention ICD trials in patients with non-ischaemic dilated cardiomyopathy (2)

Characteristic	CAT (2002)	AMIOVIRT (2003)	DEFINITE (2004)	SCD-HeFT (2004/2005)	COMPANION (2004)
Design	ICD vs pharmacologic	ICD vs amiodarone	ICD vs pharmacologic	ICD vs amiodarone vs placebo	Pharmacologic vs CRT vs CRT-D
Primary endpoint	Total mortality	Total mortality	Total mortality	Total mortality	Total mortality/all-cause rehospitalization
Control 1-y mortality, % (No./total)	3.7 (2/54)	10 (5/52)	6.2 (14/259)	7.2 (NR)	19 (59/308)
ICD type, % (No.) Transvenous	100 (50)	100 (51)	100 (259)	100 (NR)	100 (595)
Internal validity FU, %	100	100	100	NR	>95
Crossovers to ICD, % (No.)	NR	15.4 (8)	10 (23)	NR	26 (80)†
Intent-to-treat	Yes	Yes	Yes	Yes	Yes
Events committee	NR	Blinded	Blinded	NR	Blinded

NR, not reported; †Rate of withdrawal from medical therapy reported as crossover rate

Modif. from Desai AS, et al. *JAMA* 2004;292:2874-9

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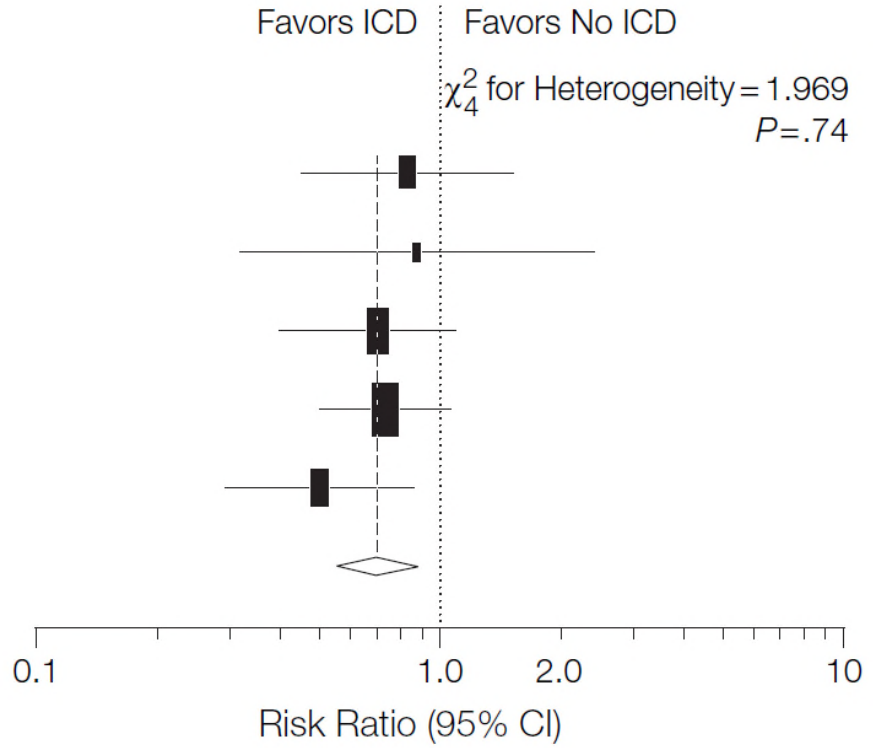
Concerns about ICD trials in patients with non-ischaemic cardiomyopathy

- Small to medium sized trials with neutral outcomes (CAT, AMIOVIRT, DEFINITE)
- Subgroup analyses of larger trials (SCD-HeFT, COMPANION)
- Heterogeneous trial designs and populations
- No added benefits of ICD implantation in patients with CRT reported
- Medical therapy improved sinces these landmark trials

All-Cause mortality among patients with non-ischaemic dilated cardiomyopathy randomized to ICD or CRT-D vs medical therapy in primary prevention

Study	Years of Enrollment	No. of Patients	Risk Ratio (95% CI)
CAT[16]	1991-1997	104	0.83 (0.45-1.82)
AMIOVIRT[17]	1996-2000	103	0.87 (0.31-2.42)
DEFINITE[15]	1998-2002	458	0.65 (0.40-1.06)
SCD-HeFT[14]	1997-2001	792	0.73 (0.50-1.04)
COMPANION[21]	2000-2002	397	0.50 (0.29-0.88)
Combined		1854	0.69 (0.55-0.87)



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Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure

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The DANISH Study – inclusion criteria

- Clinical heart failure
- Documented non-ischaemic aetiology
- Optimal medical treatment
- NYHA functional class II and III (class IV if planned CRT)
- Left ventricular ejection fraction ≤35%[1]
- NT-proBNP >200 pg/ml (23.6 pmol/l)[1]

[1]measured after maximum achievable drug target levels, which were the guideline-specified levels whenever possible

Køber L, et al. *N Engl J Med* 2016;375:1221-30

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The DANISH Study – endpoints/outcomes

- Primary endpoint
  - All-cause mortality
- Secondary endpoints
  - Cardiovascular mortality
  - Sudden cardiac death
  - Resuscitated cardiac arrest or sustained VT
  - Change in QoL from baseline

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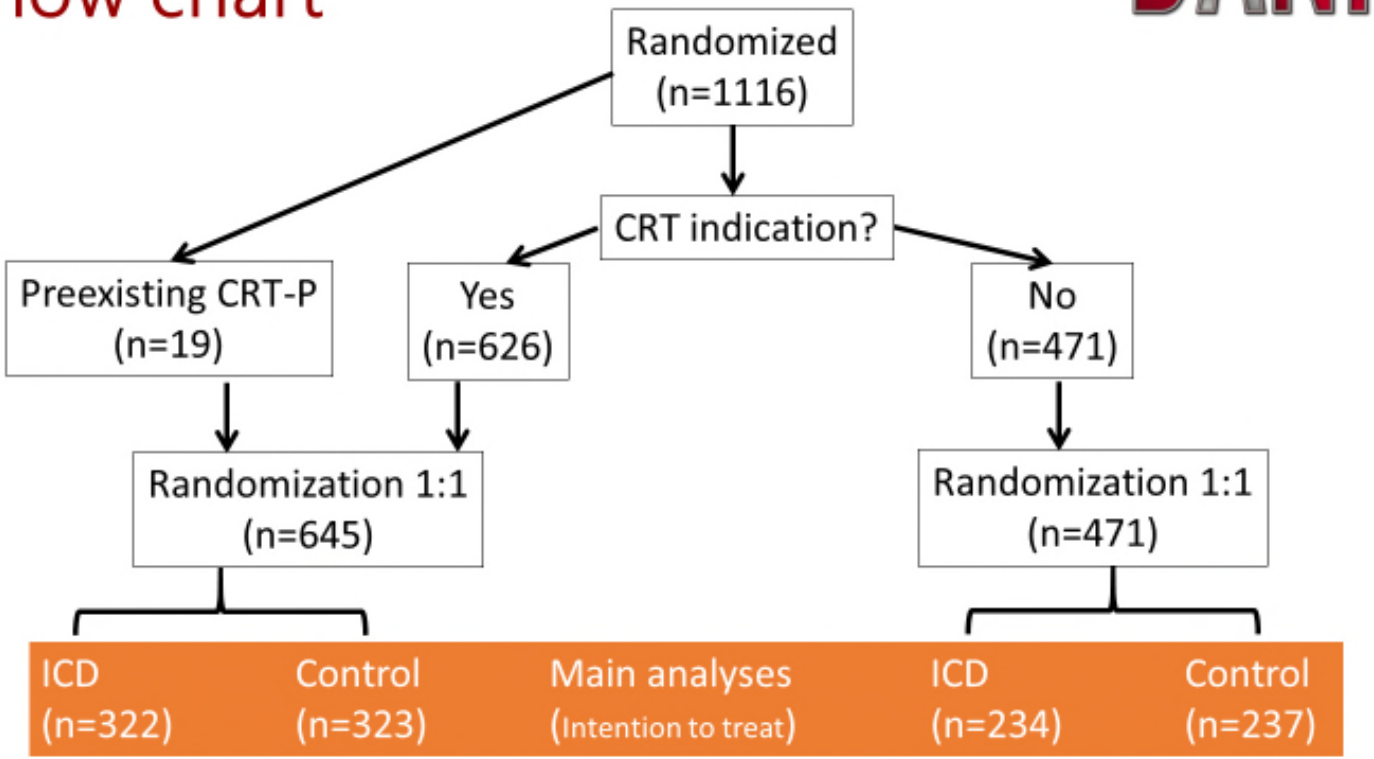
The DANISH Study – Enrollment and randomization

DANISH

Flow chart



ESC Congress Rome, Abstract No. 1220, 28 August 2016

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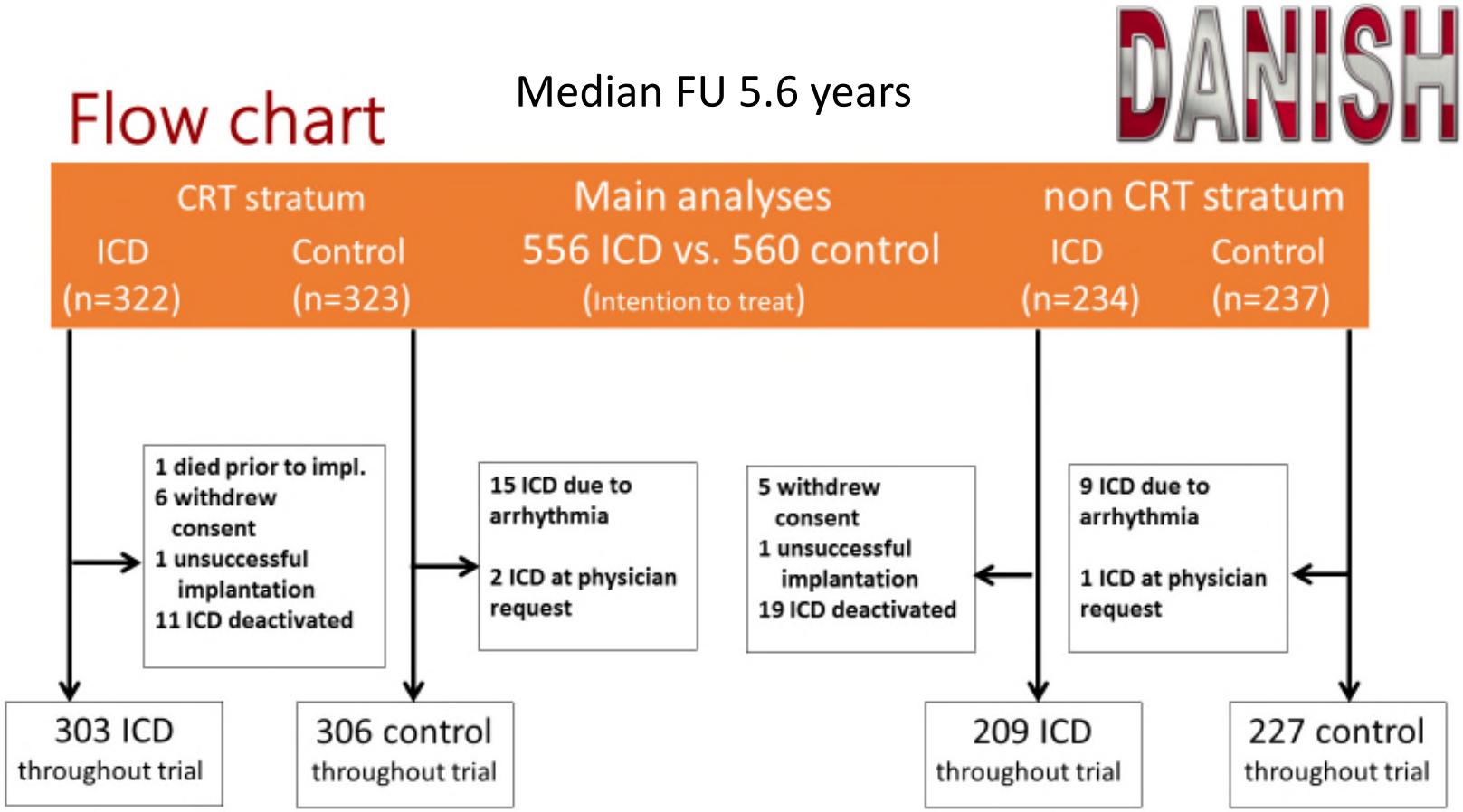
The DANISH Study – Enrollment and randomization

Median FU 5.6 years



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The DANISH Study – baseline characteristics

	ICD (N=556)	Control (N=560)
Age (years)	64 (56-72)	63 (56-70)
Female gender – no. (%)	151 (27)	156 (28)
NT-proBNP (pg/ml)	1244 (616-2321)	1110 (547-2166)
LVEF (%)	25 (20-30)	25 (20-30)
eGFR (ml/min/1.73 m2)	74 (58-91)	73 (58-92)
NYHA II – no. (%)	297 (53)	300 (54)
NYHA III – no. (%)	252 (45)	253 (45)
NYHA IV – no. (%)	7 (1)	7 (1)
Duration of HF (months)	20 (8-72)	18 (8-50)
BMI (kg/m^2)	26.8 (23.9-30.5)	26.8 (23.8-30.1)

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The DANISH Study – baseline characteristics

	ICD (N=556)	Control (N=560)
Hypertension – no. (%)	181 (33)	167 (30)
Diabetes – no. (%)	99 (18)	112 (20)
Permanent AF – no. (%)	135 (24)	113 (20)
Aetiology - no. (%)		
Idiopathic	424 (76)	425 (76)
Hpt, valvular, other	132 (24)	135 (24)
Medications – no. (%)		
ACE-I or ARB	533 (96)	544 (97)
Beta-blocker	509 (92)	517 (92)
MRA	326 (59)	320 (57)
Amiodarone	34 (6)	32 (6)
Planned CRT – no. (%)	322 (58)	323 (58)

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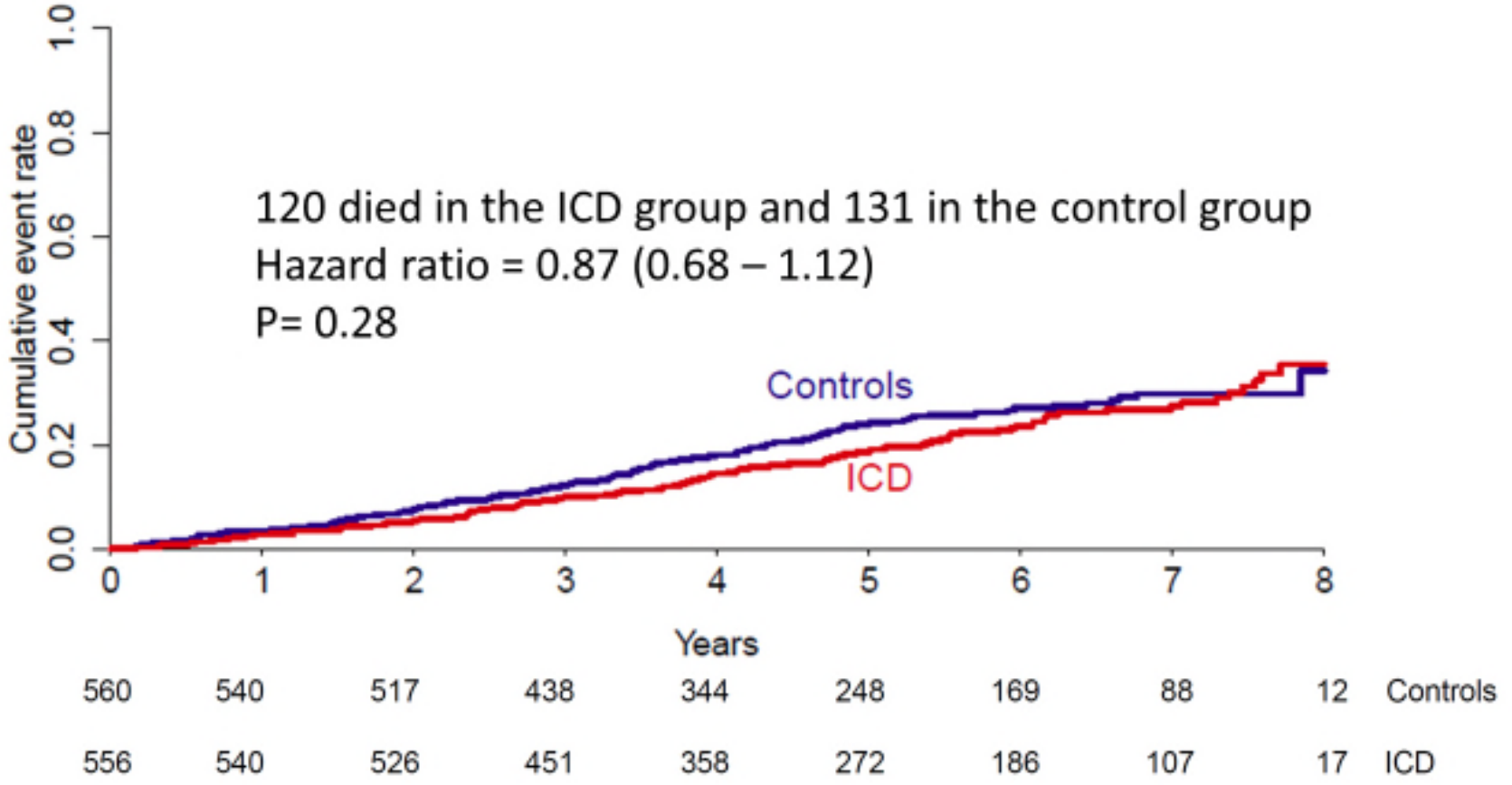
The DANISH Study – Primary outcome: all-cause mortality



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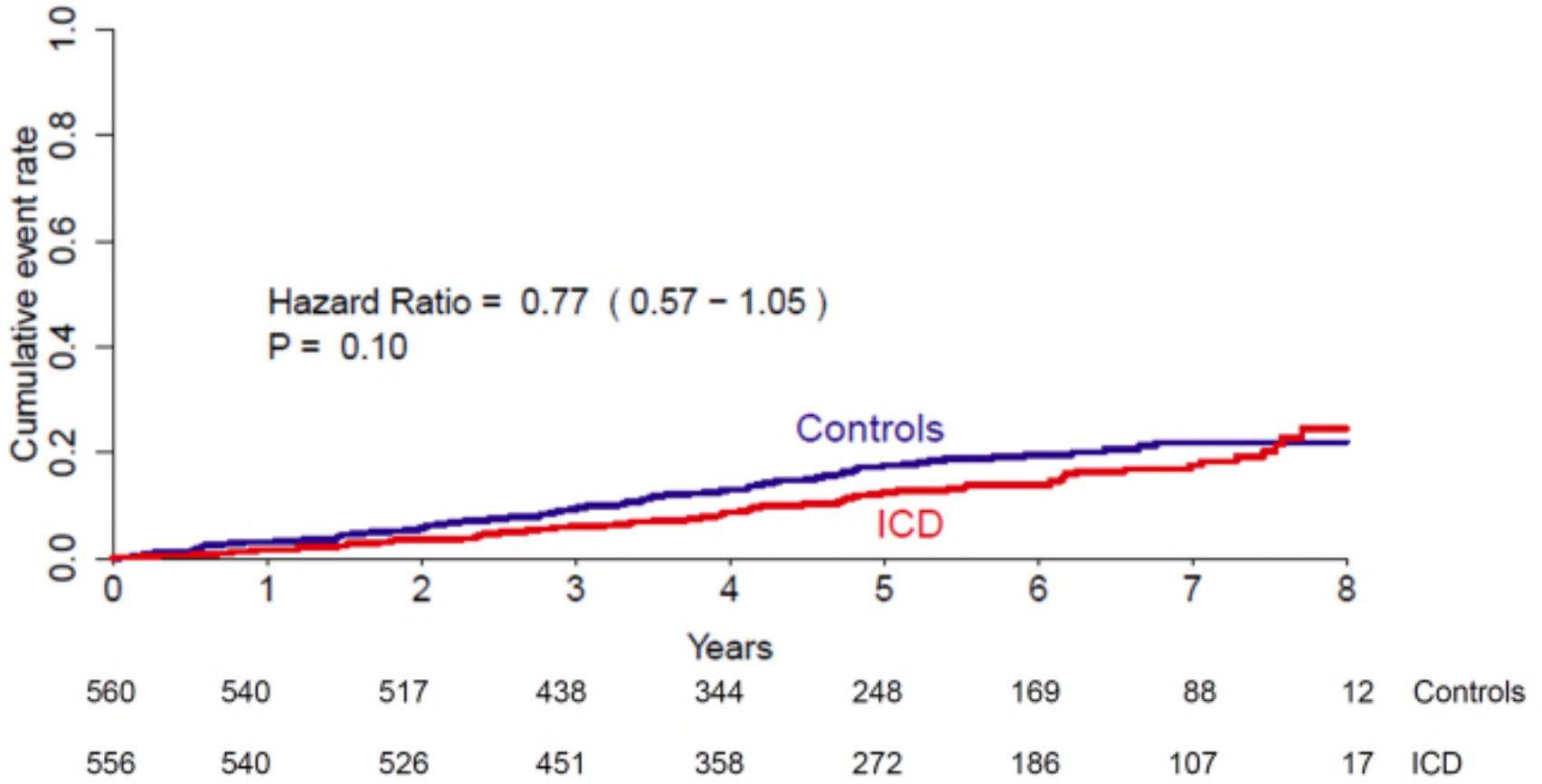
The DANISH Study – Secondary outcome: cardiovascular mortality



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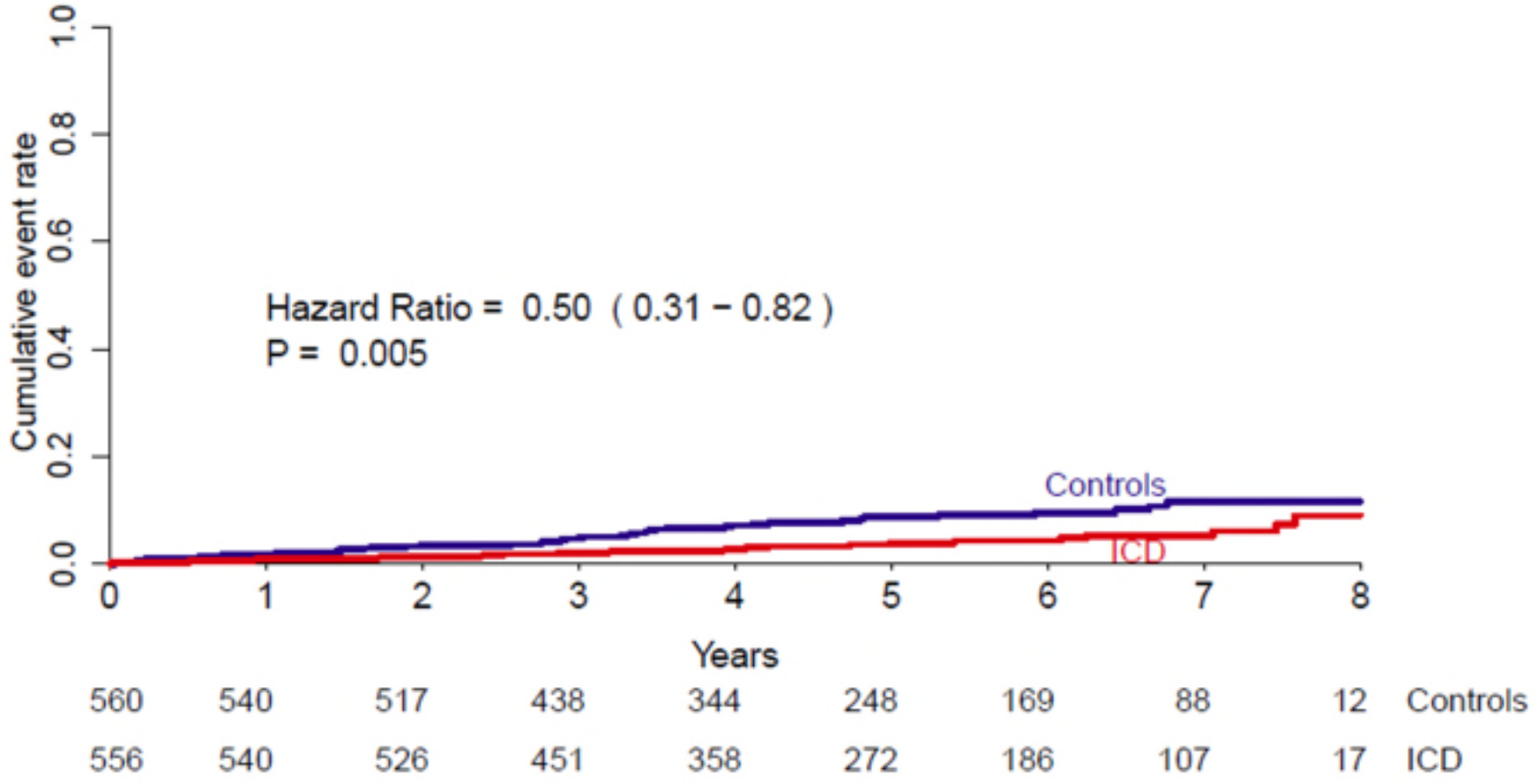
The DANISH Study – Secondary outcome: sudden cardiac death



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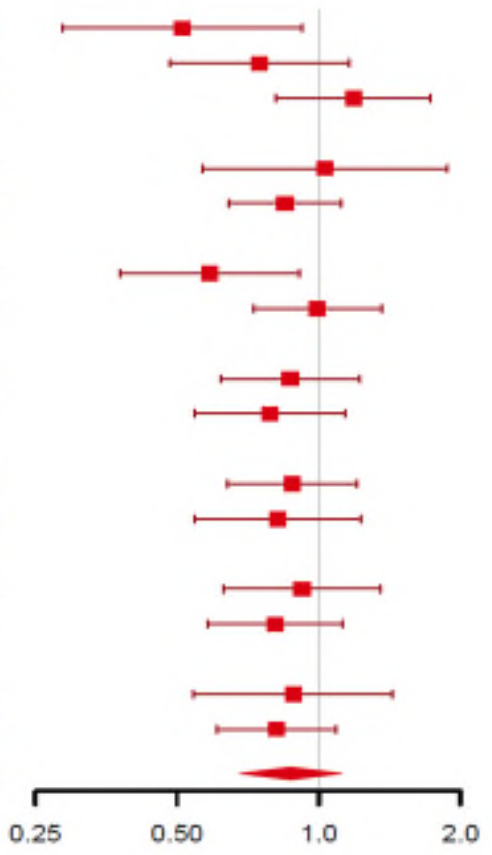
The DANISH Study – subgroup analysis: all-cause mortality

Subgroup	ICD	Control	HR	P value	P value
Age					**0.009**
<59 years	17/167	34/181	0.51 (0.29–0.92)	0.02	
≥59 – <68 years	36/173	50/202	0.75 (0.48–1.16)	0.19	
≥68 years	67/216	47/177	1.19 (0.81–1.72)	0.38	
Gender					**0.66**
Women	22/151	23/156	1.03 (0.57–1.87)	0.92	
Men	98/405	108/404	0.85 (0.64–1.12)	0.24	
NT–proBNP					**0.06**
<1177 pg/mL	32/266	74/268	0.59 (0.38–0.91)	0.02	
≥1177 pg/mL	57/292	88/290	0.99 (0.73–1.36)	0.96	
LV ejection fraction					**0.69**
<25%	70/264	65/242	0.87 (0.62–1.22)	0.42	
≥25%	50/292	66/318	0.79 (0.54–1.14)	0.21	
eGFR					**0.86**
<73 mL/min/1.73m²	75/272	80/278	0.88 (0.64–1.21)	0.42	
≥73 mL/min/1.73m²	45/283	50/280	0.82 (0.55–1.23)	0.33	
NYHA functional class					**0.71**
II	52/297	54/300	0.92 (0.63–1.35)	0.68	
III–IV	68/259	77/260	0.81 (0.58–1.13)	0.21	
Heart failure duration					**0.73**
<18 months	31/254	36/277	0.88 (0.54–1.43)	0.61	
≥18 months	89/301	95/283	0.81 (0.61–1.09)	0.17	
Overall			**0.87 (0.68–1.12)**	**0.28**	



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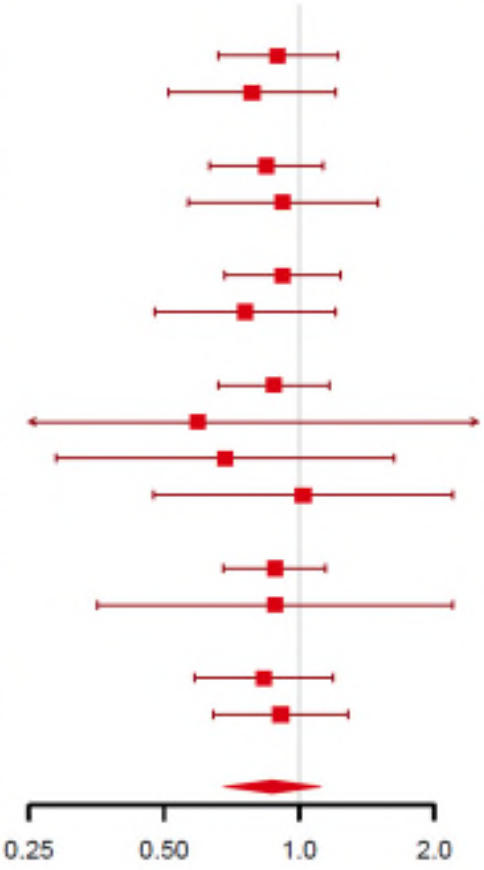
The DANISH Study – subgroup analysis: all-cause mortality

Subgroup	ICD	Control	HR	P value	P value
Hypertension					0.63
No	78/375	87/392	0.90 (0.66–1.22)	0.48	
Yes	42/181	44/167	0.79 (0.51–1.21)	0.27	
Diabetes					0.60
No	87/457	95/448	0.85 (0.63–1.31)	0.26	
Yes	33/99	36/112	0.92 (0.57–1.50)	0.74	
Permanent atrial fibr.					0.30
No	83/421	91/447	0.92 (0.68–1.24)	0.58	
Yes	37/135	40/113	0.76 (0.48–1.20)	0.24	
Aetiology					0.80
Idiopathic	90/424	100/425	0.88 (0.66–1.17)	0.37	
Valvular	4/20	5/21	0.59 (0.13–2.71)	0.50	
Hypertension	13/62	12/55	0.68 (0.29–1.63)	0.39	
Other	13/50	14/59	1.02 (0.47–2.20)	0.96	
Pre–existing CRT–P or PM					0.71
No	108/500	120/514	0.88 (0.68–1.14)	0.34	
Yes	12/56	11/46	0.88 (0.36–2.20)	0.79	
CRT					0.73
No	58/234	65/237	0.83 (0.58–1.19)	0.31	
Yes	62/322	66/323	0.91 (0.64–1.29)	0.59	
Overall			**0.87 (0.68–1.12)**	**0.28**	



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The DANISH Study – outcomes and adverse events

Outcome	ICD Group† (N=556)	Control Group† (N=560)	Hazard Ratio (95% CI)	P Value
	no. of patients/total no. (%)			
Death from any cause	120 (21.6)	131 (23.4)	0.87 (0.68–1.12)	0.28
Cardiovascular death	77 (13.8)	95 (17.0)	0.77 (0.57–1.05)	0.10
Sudden cardiac death	24 (4.3)	46 (8.2)	0.50 (0.31–0.82)	0.005
Other cardiovascular death	53 (9.5)	49 (8.8)	1.03 (0.70–1.52)	0.89
Noncardiovascular death	43 (7.7)	36 (6.4)	1.12 (0.72–1.76)	0.60
Resuscitated cardiac arrest or sustained VT	26 (4.7)	25 (4.5)	1.03 (0.59–1.79)	0.91
Cardiac arrest	11 (2.0)	14 (2.5)	0.79 (0.36–1.75)	0.56
Sustained VT requiring medical intervention or electrical conversion	16 (2.9)	14 (2.5)	1.12 (0.54–2.30)	0.76
			Odds Ratio (95% CI)	
Device infection	27 (4.9)	20 (3.6)	1.38 (0.73–2.63)	0.29
CRT‡	15/322 (4.7)	18/323 (5.6)	0.83 (0.38–1.78)	0.60
No CRT‡	12/234 (5.1)	2/237 (0.8)	6.35 (1.38–58.87)	0.006
Serious device infection§	15 (2.7)	13 (2.3)	1.17 (0.51–2.69)	0.69
CRT‡	9/322 (2.8)	11/323 (3.4)	0.82 (0.29–2.20)	0.65
No CRT‡	6/234 (2.6)	2/237 (0.8)	3.09 (0.54–31.56)	0.24
Bleeding requiring intervention	1 (0.2)	0	—	—
Pneumothorax	11 (2.0)	6 (1.1)	1.86 (0.68–5.08)	0.22
Inappropriate shocks	33 (5.9)	0	—	—

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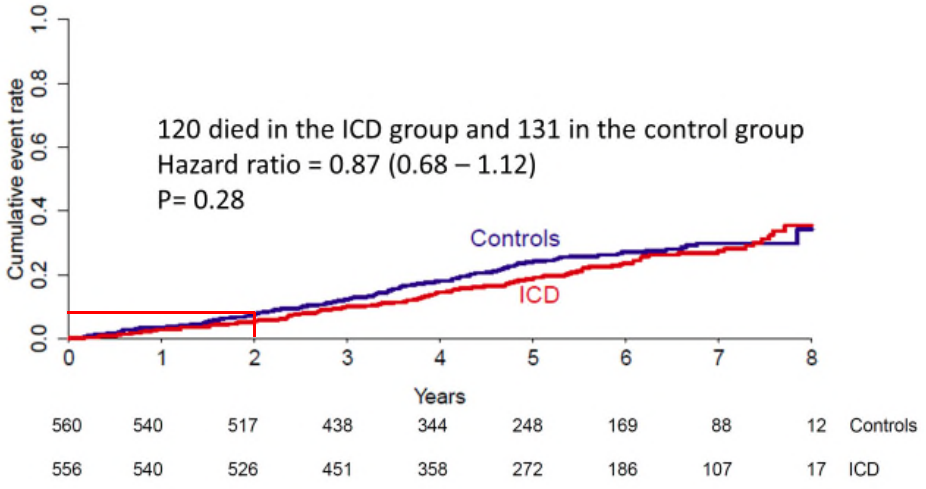
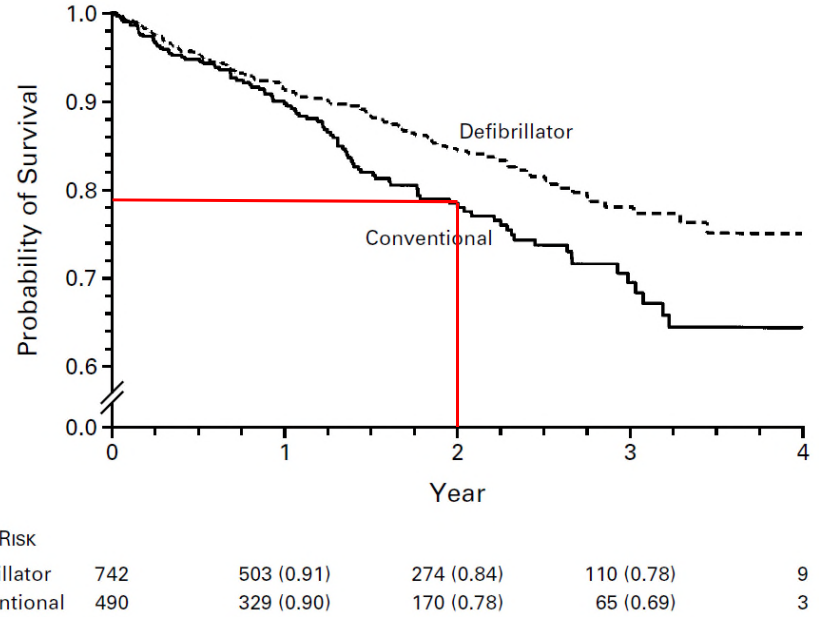
All-cause mortality in DANISH and MADIT II





	DANISH	MADIT II
ACE-I or ARB (%)	96 (ICD)/97 (control)	68 (ICD)/72 (control)
Beta-blocker (%)	92 (both groups)	70 (both groups)
MRA (%)	59 (ICD)/57 (control)	NR
CRT (%)	58 (both groups)	N/A

Køber L, et al. *N Engl J Med* 2016;375:1221-30
Moss AJ, et al. *N Engl J Med* 2002;346:877-83

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DANISH – implications for clinical practice

- The absolute benefit of ICDs in typical and well-treated heart failure patients without ischaemic heart disease might be small.
  - Younger patients might benefit most.
- The ICD – not for every patient with non-ischaemic heart failure.
- ICDs should be targeted to those patients, who remain at high absolute risk for SCD despite optimal medical and device (CRT) therapy, as
  - ICDs are expensive
  - ICDs are not without adverse effects (infections, inappropriate shocks)
- But: How can we identify those high-risk patients?