Training course:
All About Clinical Trials

ICD trials

Frieder Braunschweig
Professor, Director of Arrhythmia, heart failure and congenital heart disease
Karolinska University Hospital

ESC Working Group Cardiovascular Pharmacotherapy

Sudden Cardiac Death

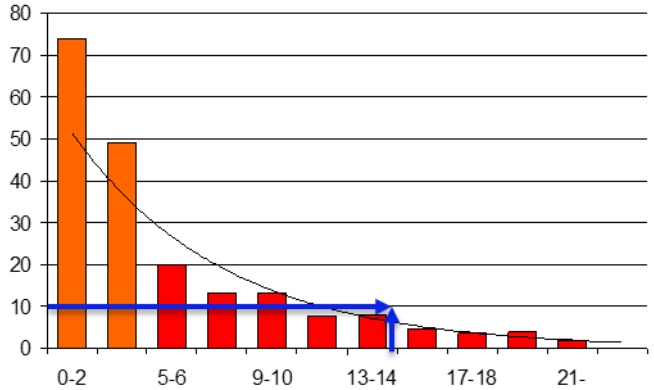
4 to 5 million sudden death/year worldwide

Ca: 400.000/year in Europe

Ca: 1000/d

Ca: 10.000/year in Sweden

Mortality: 90%



Time to defibrillation:

chance of survival decreases

by 10% for every minute

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ICD history

1969:	**First experimental model**
1969:	**First transvenous defibrillation**
1975:	**First animal implant**
1980:	**First human implant**
1981:	**Addition of Cardioversion**
1985:	**FDA approval**
1988:	**First programmable ICD implanted in a human**

Michel Mirowski, M.D.
1924-1990
Johns Hopkins University
School of Medicine

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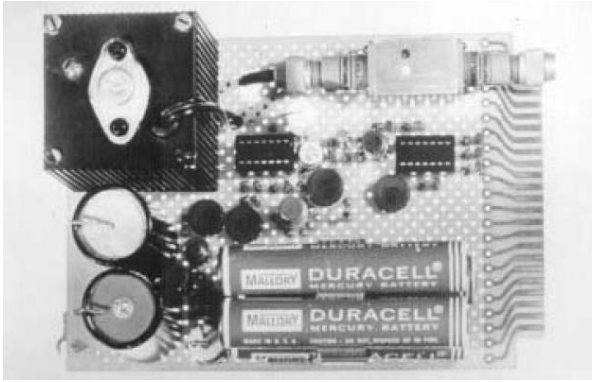
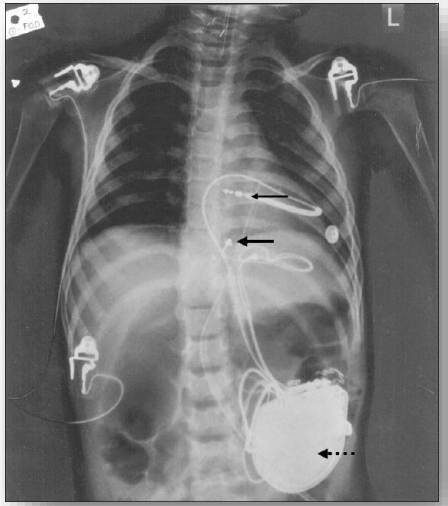
ICD history





Courtesy, Boston Scientific

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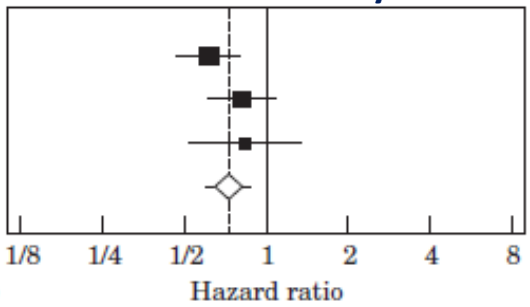
Secondary prevention: meta-analysis

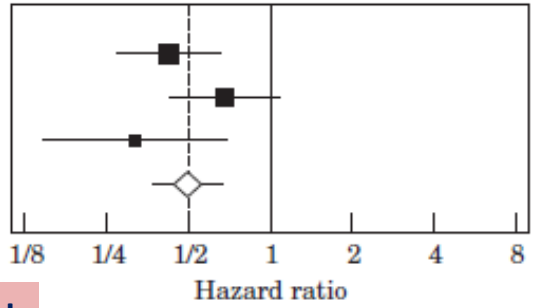
Name	n	Events	HR	95% CI
AVID	1016	80	0·62	0·47, 0·81
CIDS	659	83	0·82	0·61, 1·10
CASH	191	37	0·83	0·52, 1·33
Fixed effects			HR = 0·72	95% = 0·60, 0·87

Total 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

Arrhythmic mortality



ICD prolonged life by 4.4 months over 6y FU
No significant benefit with LVEF >35%

Conolly et al, Eur Heart J (2000) 21, 2071–2078

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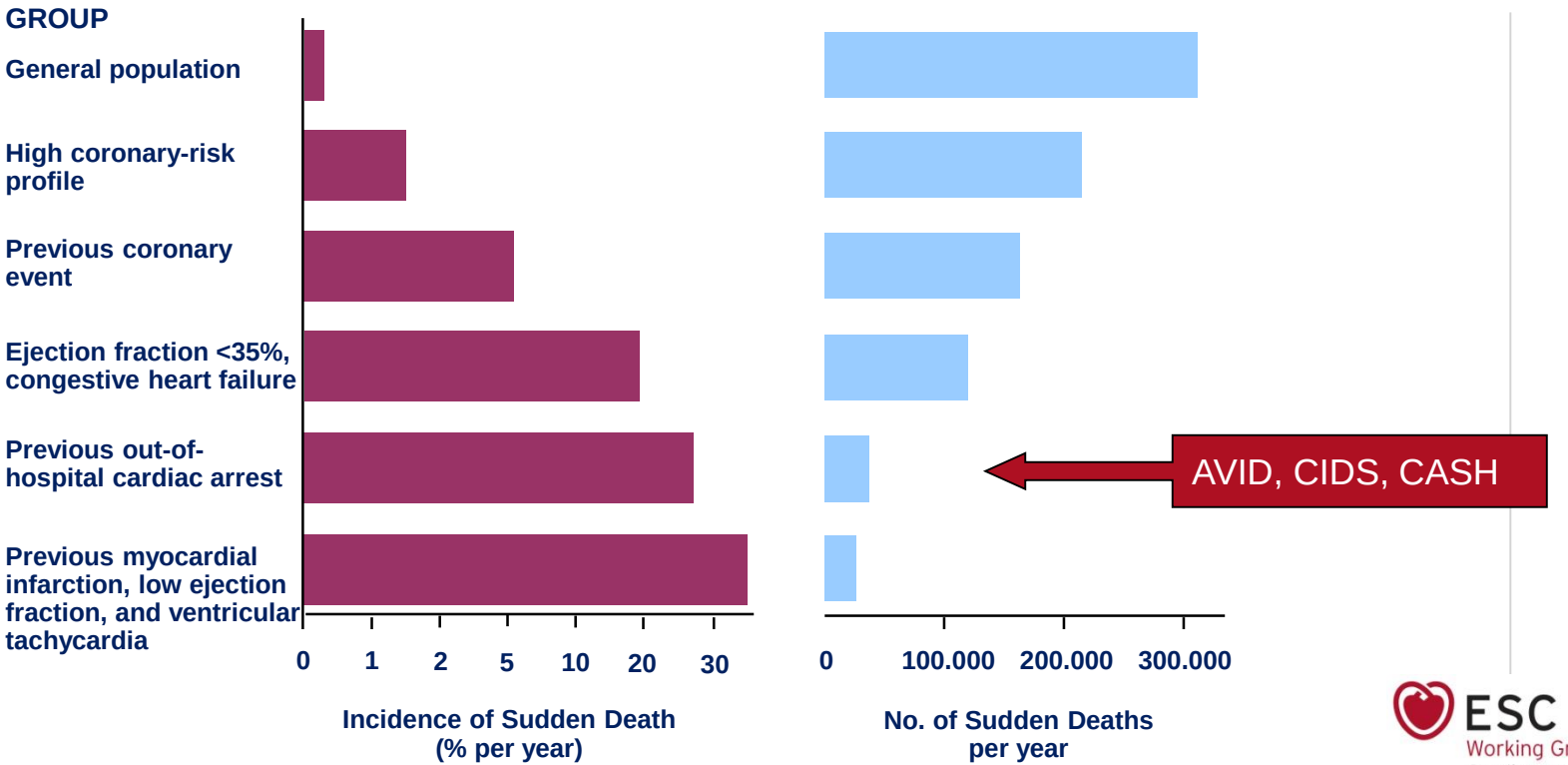
Incidence of SCD in Specific Populations



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Myerburg RJ. Circulation.1998;97:1514-1521.

Primary prevention: MADIT

The Multicenter Automatic Defibrillator Implantation Trial

NYHA I/II/III
prior MI
LVEF ≤ 35%

↓

Holter: asymptomatic,
non-sustained VT

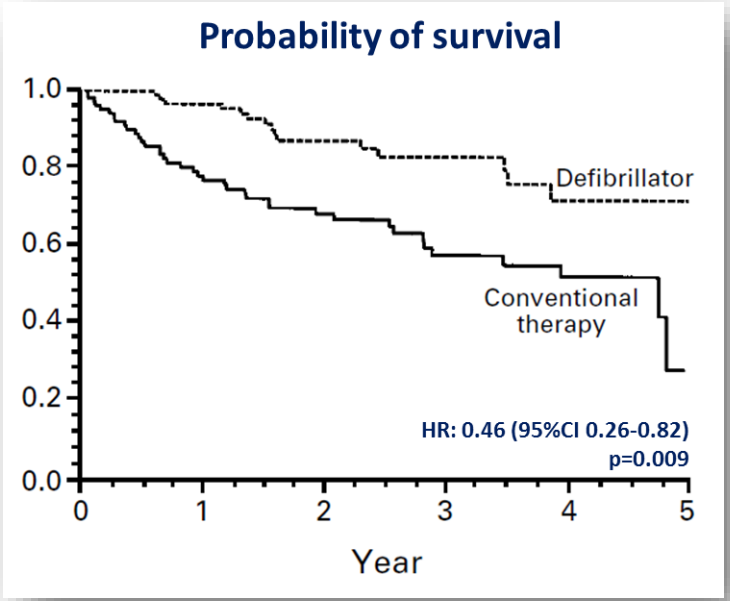
↓

EPS: inducible VT,
non-suppressible by drugs
(n=196)

↓

Conventional
medical therapy
(74% amiodarone)
(n=101)

ICD
(n=95)



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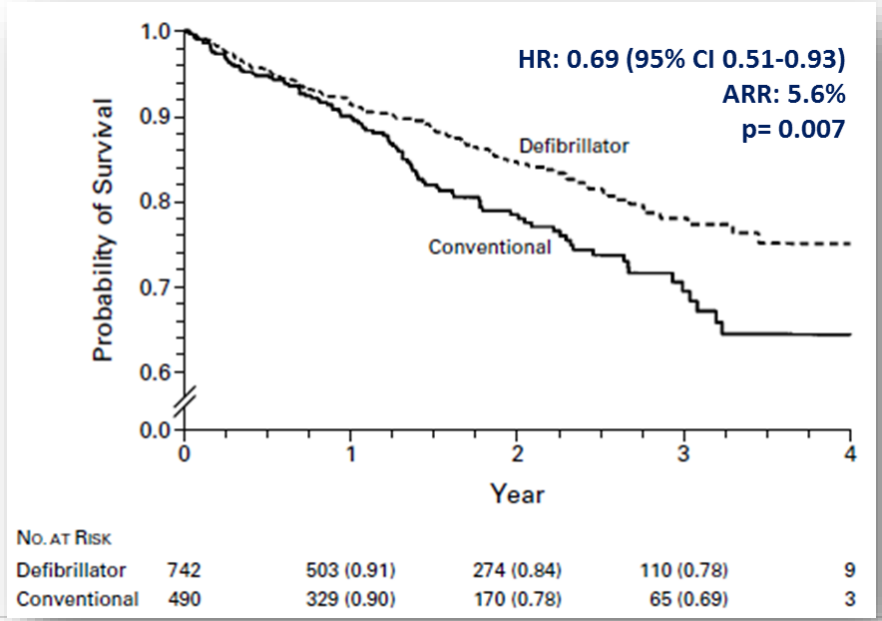
Moss et al N Engl J Med 1996;335:1933-40.

Primary prevention: MADIT II

The Multicenter Automatic Defibrillator Implantation Trial II

1) Prior MI (>1 month); 2) EF ≤ 30%

(no requirement of previous arrhythmia event or inducibility on EPS)



Moss et al. N Engl J Med 2002;346:877-83.

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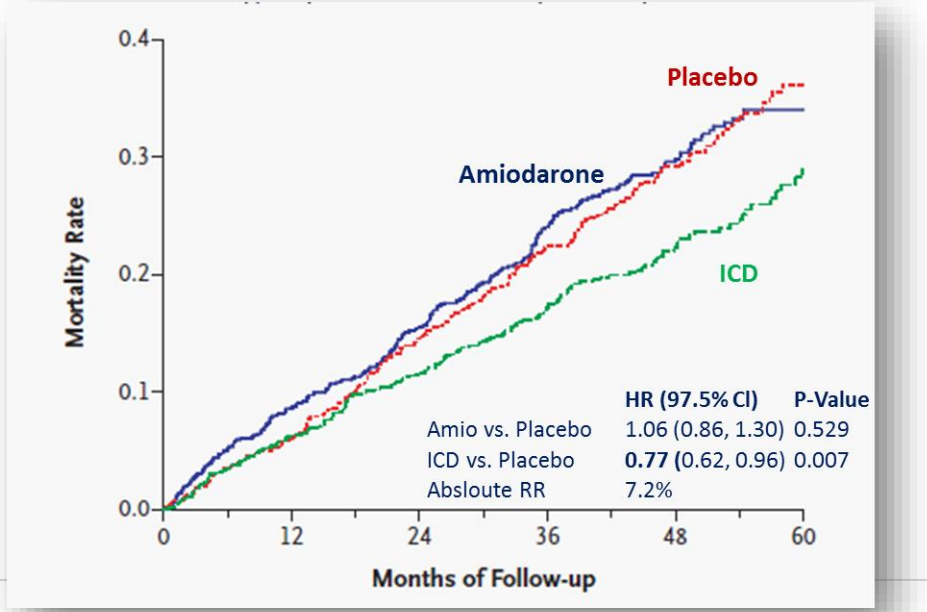
Primary prevention: SCD-HeFT

Sudden Cardiac Death in Heart Failure Trial

Ischemic *and* non-ischemic CMP

N=2.521; NYHA II-III, LVEF ≤ 35%, optimal medical therapy



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

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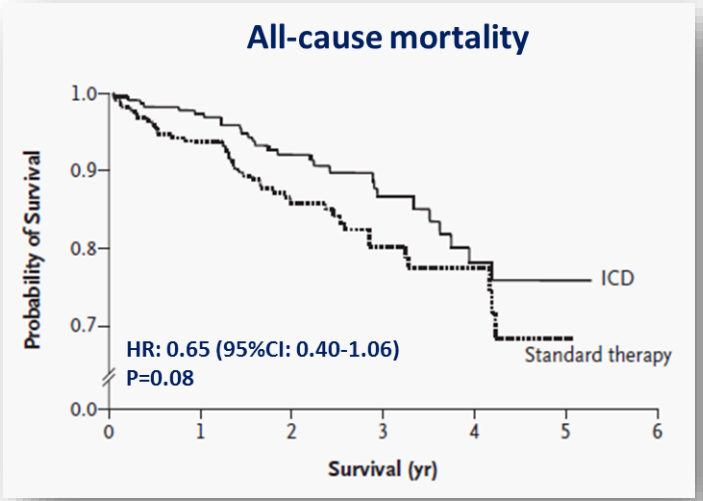
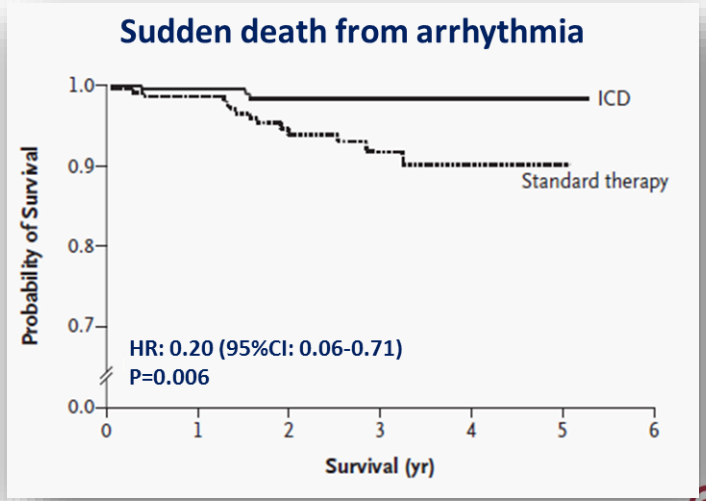
Primary prevention(DCM): DEFINITE

Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation

N=458; non-ischemic DCM; LVEF ≤ 35%, PVC or NSVT[1]

([1]: 3 to 15 beats at ≥ 120 bpm *or* ≥ 10 PVC/hour on Holter)





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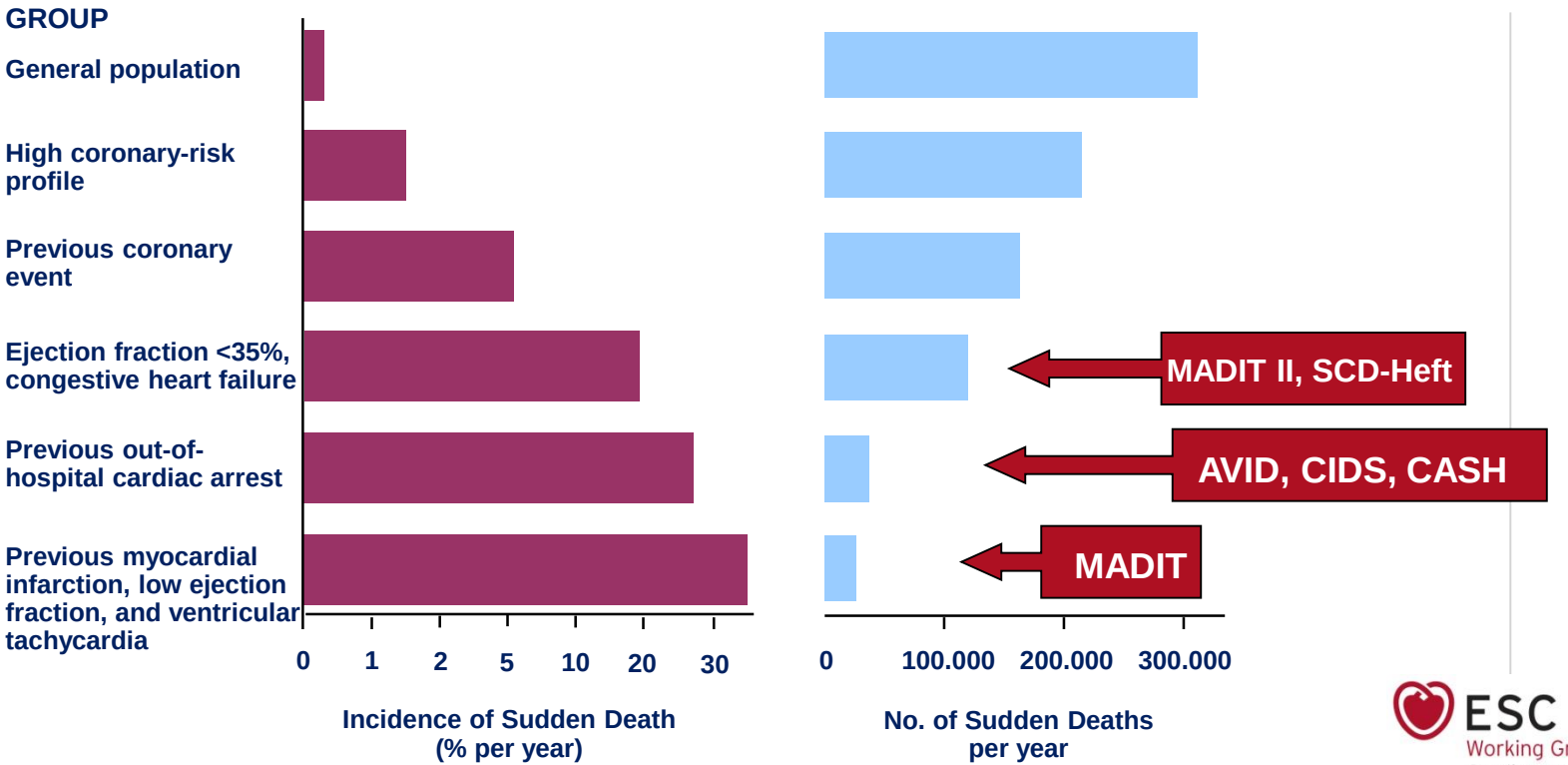
Kadish et al , N Engl J Med 2004;350:2151-8.

Incidence of SCD in Specific Populations



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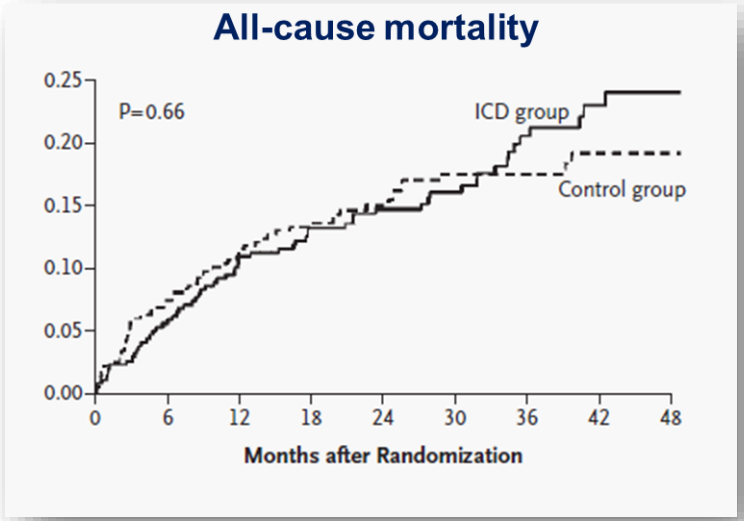
Myerburg RJ. Circulation.1998;97:1514-1521.

Primary prevention: post MI patients

DINAMIT

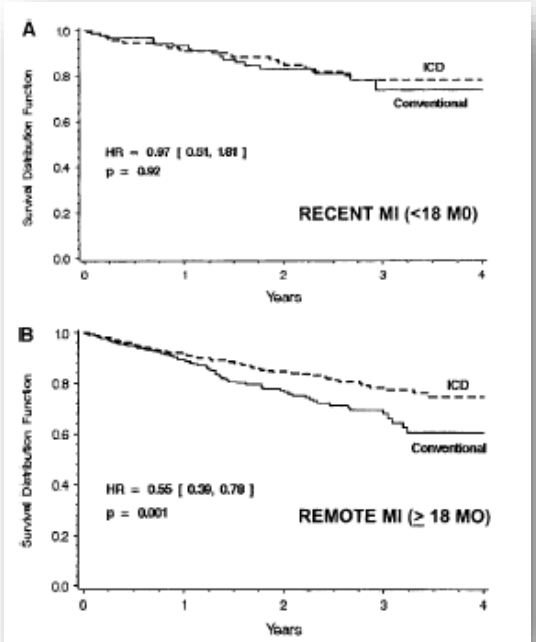
The Defibrillator in Acute Myocardial Infarction Trial

N=674: 6 to 40 days after MI;
LVEF≤35%, depressed HRV



Hohnloser et al; N Engl J Med 2004;351:2481-8.

MADIT II



Wilber et al; Circulation. 2004;109:1082-1084

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ESC HF guidelines 2016: ICD

Recommendations for implantable cardioverter-defibrillator in patients with heart failure

Recommendations	Class [a]	Level [b]
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.	I	A
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 functional status, and they have:		
IHD (unless they have had an MI in the prior 40 days)	I	A
DCM	I	B
ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis.	III	A
ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a ventricular assist device, or cardiac transplantation.	III	C
Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals and the patient's needs and clinical status may have changed.	IIa	B
A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device.	IIb	C

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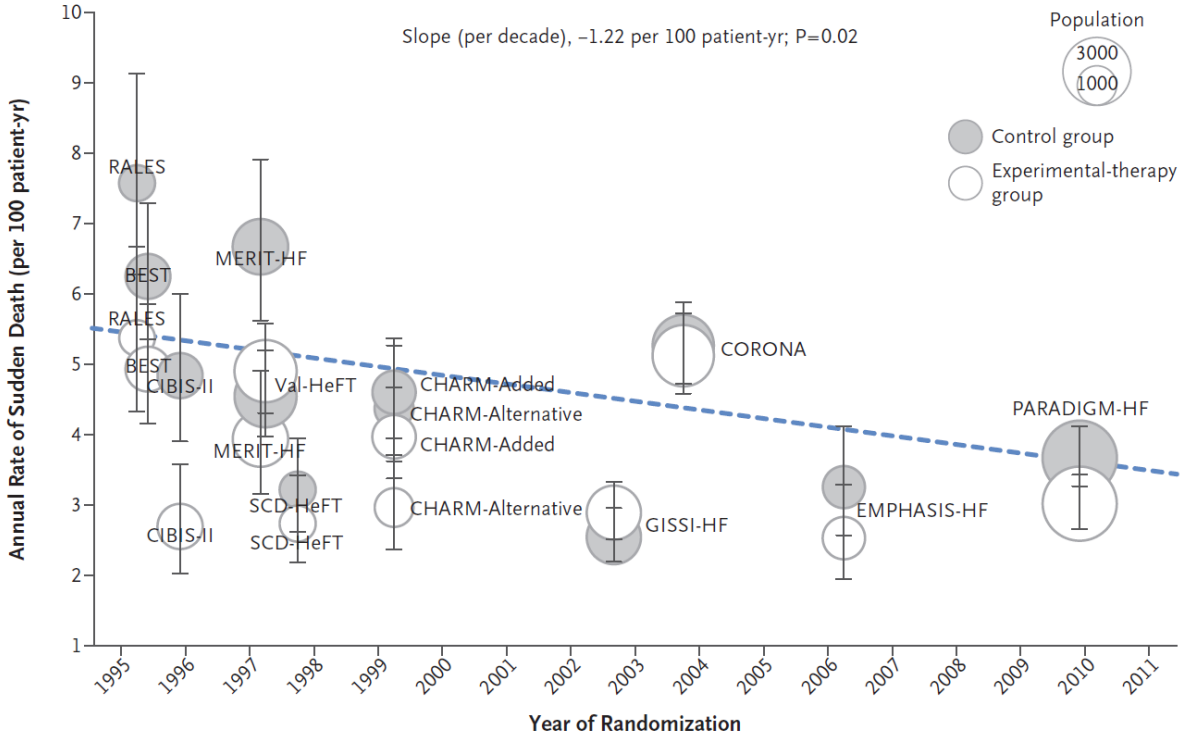
Sudden Cardiac Death: risk reduction



Shen et al, N Engl J Med 2017; 377:41-51

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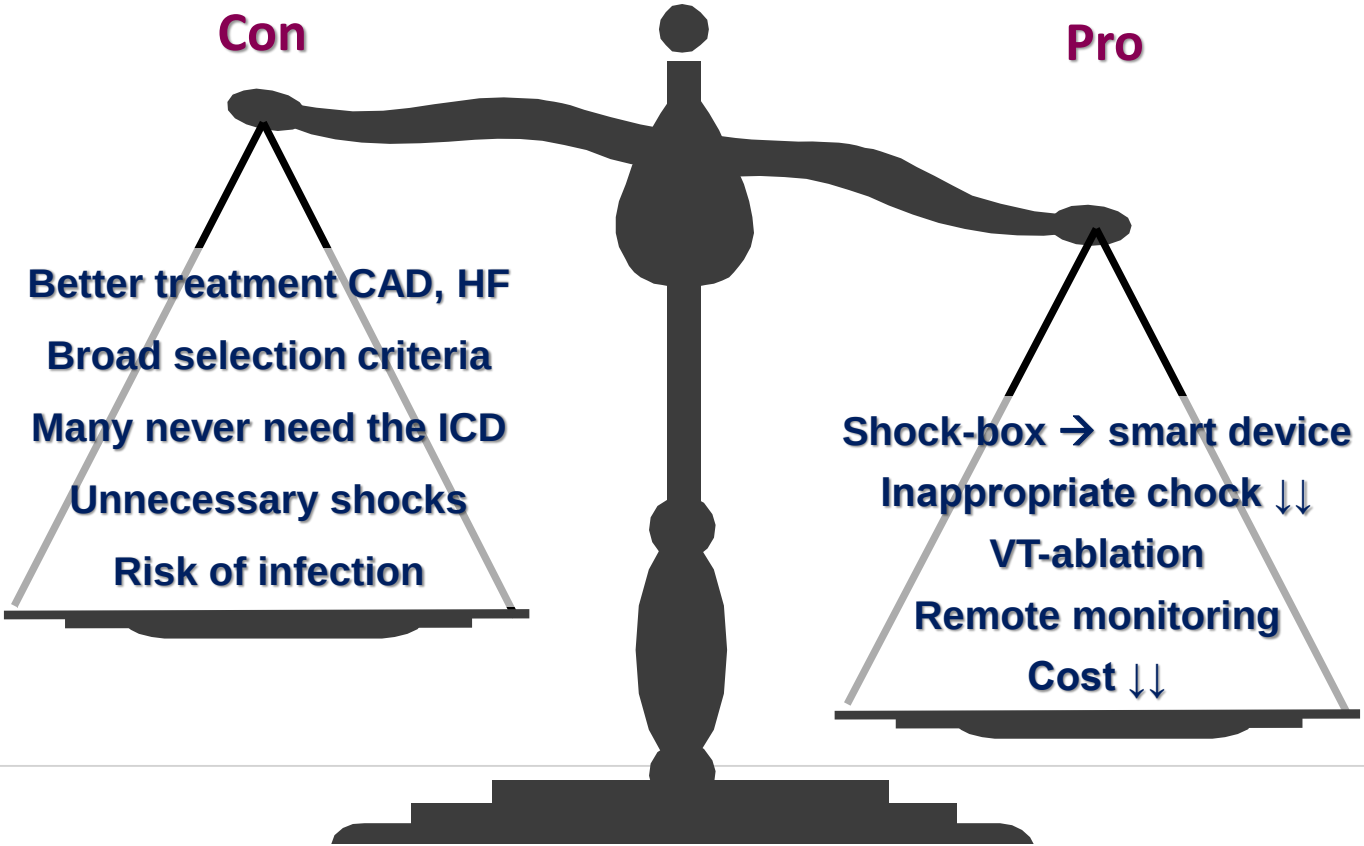
Primary prophylactic ICD: pros and cons



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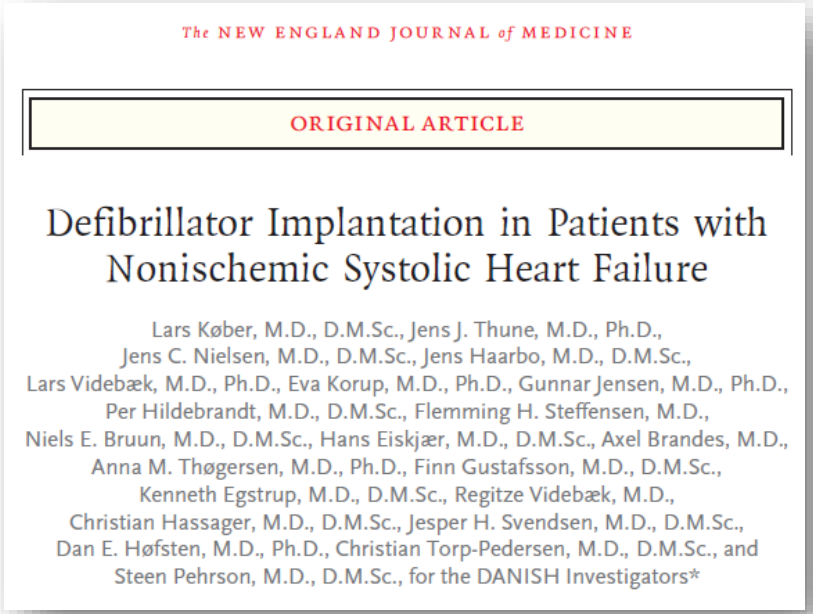

Inclusion

- Symptomatic HF
- LVEF ≤35%
- **No CAD** (angio, CT, SPECT)
- Optimal medical treatment (CRT allowed)

Recruitment

- February 2008 to June 2014

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DANISH - patient characteristics

			ICD (n = 556)	Control (n = 560)
Median age		*(IQR) - yr*	64 *(56–72)*	63 *(56–70)*
Female sex		*no. (%)*	151 *(27)*	156 *(28)*
QRS duration		*(IQR) - ms*	146 *(114–166)*	145 *(110–164)*
LVEF		*(IQR) - %*	25 *(20–30)*	25 *(20–30)*
NYHA	II	*no. (%)*	297 *(53)*	300 *(54)*
	III		252 *(45)*	253 *(45)*
	IV		7 *(1)*	7 *(1)*
Permanent AF		*no. (%)*	135 *(24)*	113 *(20)*
ACE-I or ARB		*no. (%)*	533 *(96)*	544 *(97)*
Beta-blocker		*no. (%)*	509 *(92)*	517 *(92)*
MRA		*no. (%)*	326 *(59)*	320 *(57)*
Amiodarone		*no. (%)*	34 *(6)*	32 *(6)*
CRT		*no. (%)*	322 *(58)*	323 *(58)*

Kober et al , N Engl J Med 2016; 375:1221-1230

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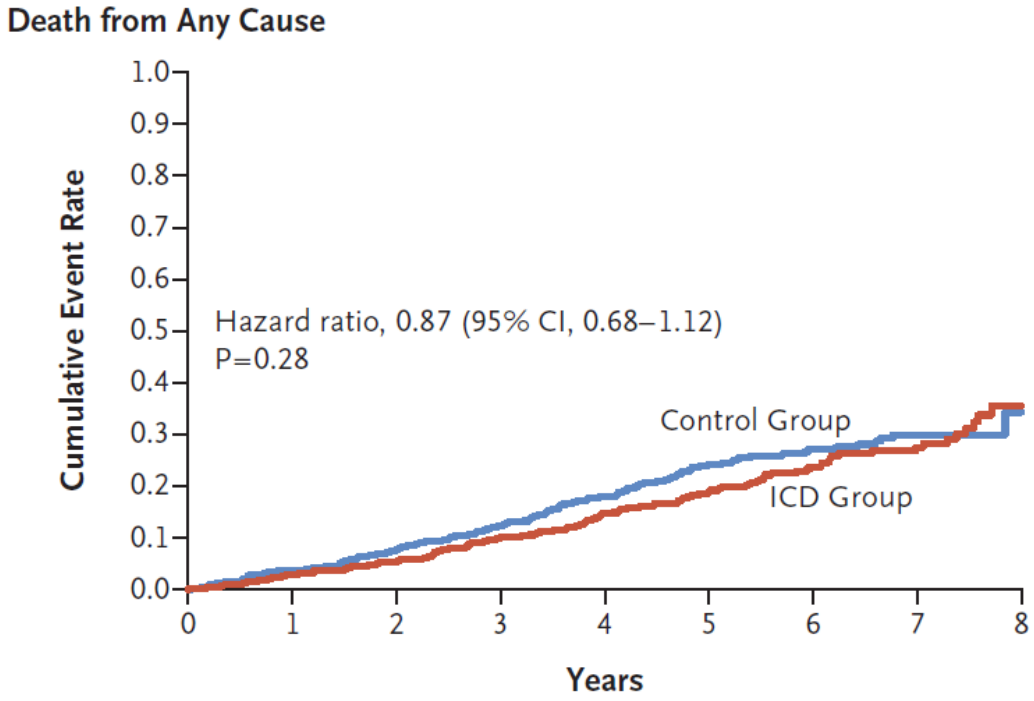
DANISH – primary outcome



Median follow-up: 67.6 months

Kober et al , N Engl J Med 2016; 375:1221-1230

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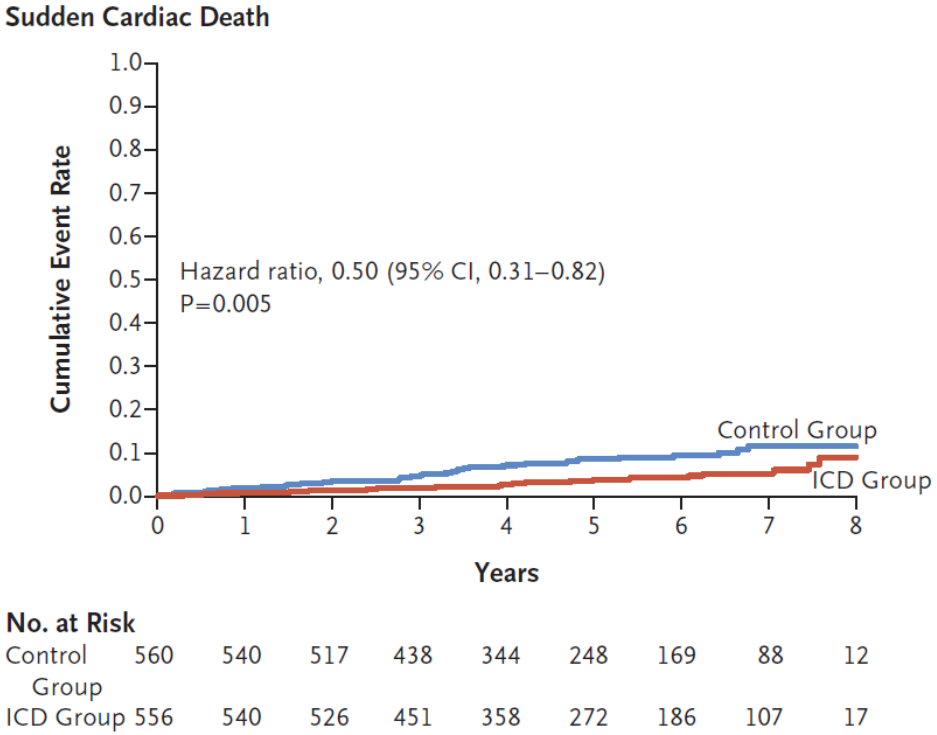
DANISH – secondary outcome



Kober et al , N Engl J Med 2016; 375:1221-1230

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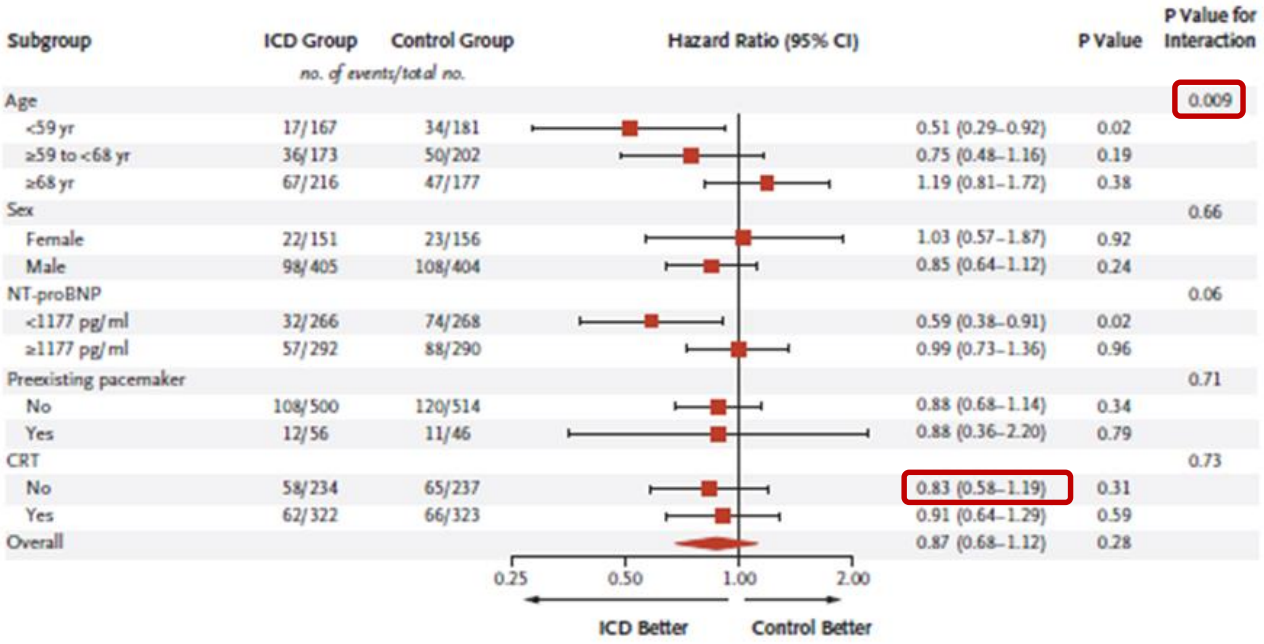
DANISH - subgroups



Subgroup	ICD Group	Control Group	Hazard Ratio (95% CI)	P Value	P Value for Interaction
	no. of events/total no.				
Age					0.009
<59 yr	17/167	34/181	0.51 (0.29–0.92)	0.02	
≥59 to <68 yr	36/173	50/202	0.75 (0.48–1.16)	0.19	
≥68 yr	67/216	47/177	1.19 (0.81–1.72)	0.38	
Sex					0.66
Female	22/151	23/156	1.03 (0.57–1.87)	0.92	
Male	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	
Preexisting pacemaker					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	

Kober et al , N Engl J Med 2016; 375:1221-1230

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Association between implantable cardioverter-defibrillator use for primary prevention and mortality: a prospective propensity-score matched study.

Benedikt Schrage, Lars H. Lund, Alicia Uijl, Lina Benson, Stefan Blankenberg, Marcus Ståhlberg, Ulf Dahlström, Frieder Braunschweig and Gianluigi Savarese

Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

University Heart Centre Hamburg, Dept of General and Interventional Cardiology, Hamburg, Germany.

SwedeHF
Heart Failure Registry

ESC
Working Group
Cardiovascular
Pharmacotherapy

Study population

- **≥18 years, clinician judged HF**
- **Enrolled Swede-HF between 2000 and 2016**
- **Linked with National Patient Registry/Cause of Death Registry**

- **Inclusion criteria in accordance with ESC 2016 HF guidelines:**
  - EF <40% (which is a categorized variable in SwedeHF, i.e. <30%, 30-39%, 40-49%, and ≥50%).
  - HF duration ≥3 months
  - NYHA class ≥II
  - No missing data on ICD use

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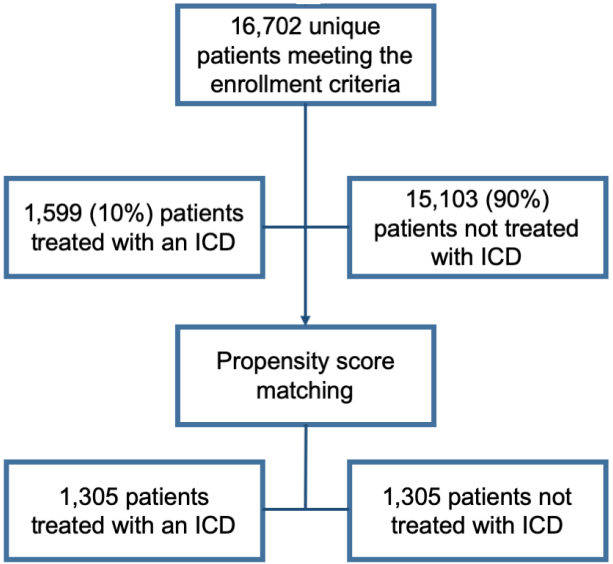
Schrage et al, Circulation. 2019;140:1530–1539

Overall cohort



Propensity scores for ICD were calculated based on 31 clinically relevant variables. Patients were matched 1:1 based on their propensity score to compare ICD recipients vs. non-recipients.

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Schrage et al, Circulation. 2019;140:1530–1539

Baseline characteristics, matched cohort

	ICD patients (N=1,305)	Matched controls (N=1,305)	SD
Age (years)	68 (±11)	68 (±13)	1.0%
Female sex	228 (17.5%)	216 (16.6%)	2.4%
Ejection fraction <30%	842 (64.5%)	861 (66.0%)	3.1%
NYHA class III	653 (50.1%)	670 (51.4%)	2.7%
Ischaemic heart disease	997 (76.4%)	1,007 (77.2%)	1.8%
Atrial fibrillation	758 (58.1%)	770 (59.0%)	1.9%
Anaemia	420 (33.5%)	438 (34.4%)	1.8%
Diabetes mellitus	423 (32.4%)	426 (32.6%)	0.5%
Valvular heart disease	349 (26.7%)	345 (26.4%)	0.7%
CRT	449 (34.4%)	427 (32.7%)	3.6%
Beta-blocker	1,257 (96.6%)	1,254 (96.2%)	2.4%
RAS inhibitors	1,236 (99.8%)	1,209 (99.8%)	3.7%
MRA	703 (54.2%)	699 (53.7%)	1.5%

SD: absolute standard difference

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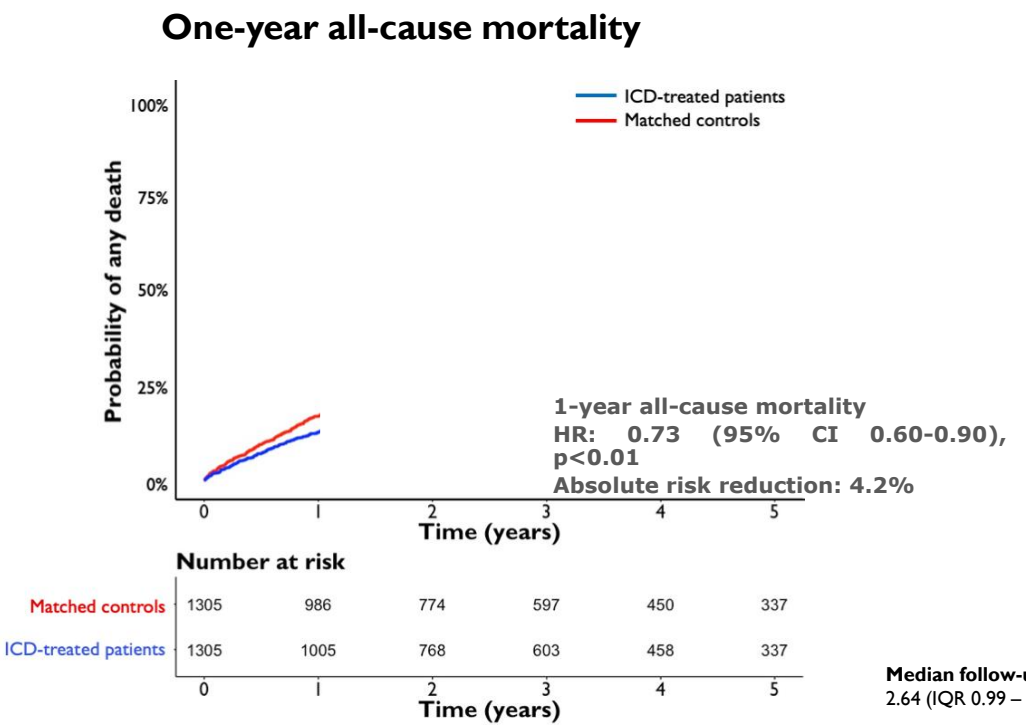
Schrage et al, Circulation. 2019;140:1530–1539

Primary outcome



Median follow-up:
2.64 (IQR 0.99 – 5.00) years

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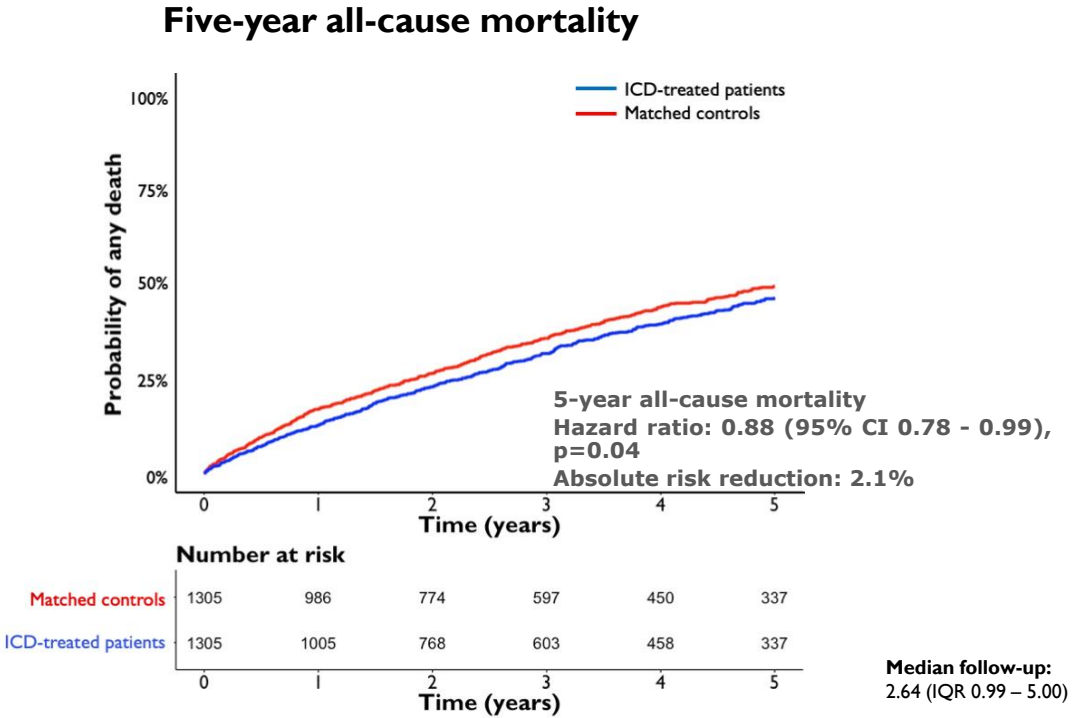
Schrage et al, Circulation. 2019;140:1530–1539

Primary outcome



Median follow-up:
2.64 (IQR 0.99 – 5.00) years

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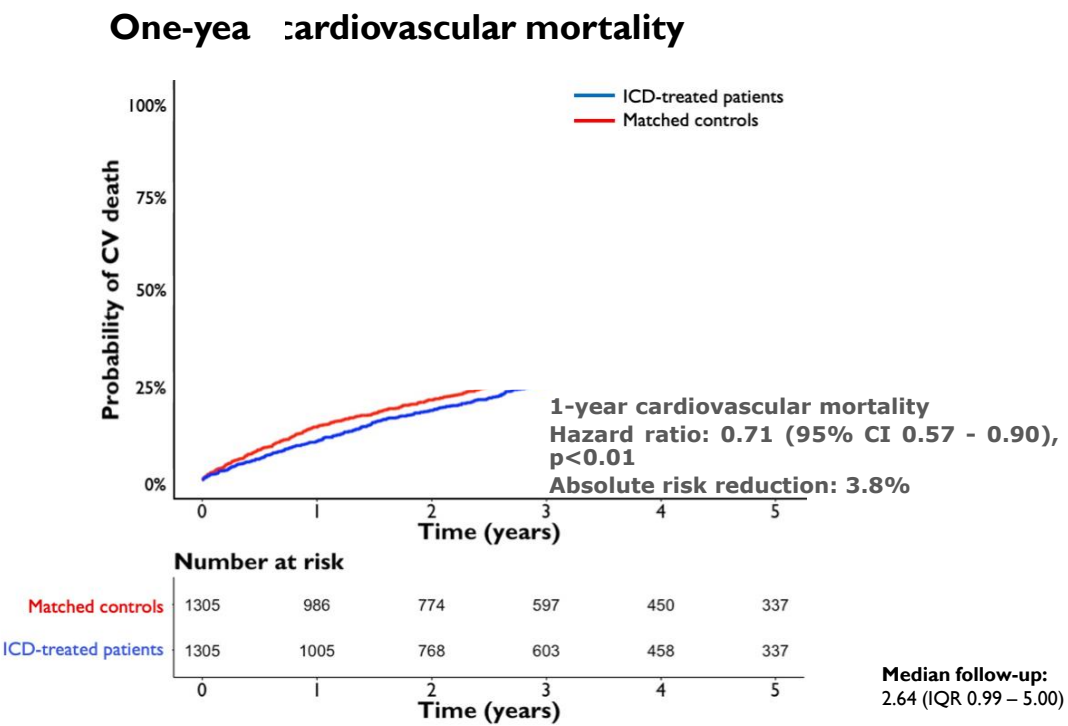
Schrage et al, Circulation. 2019;140:1530–1539

Secondary outcome



Median follow-up:
2.64 (IQR 0.99 – 5.00) years

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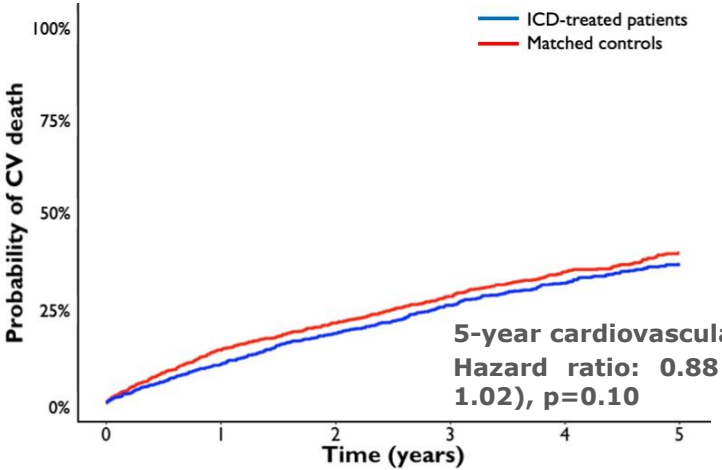
Schrage et al, Circulation. 2019;140:1530–1539

Secondary outcome

Five-year cardiovascular mortality



Median follow-up:
2.64 (IQR 0.99 – 5.00) years

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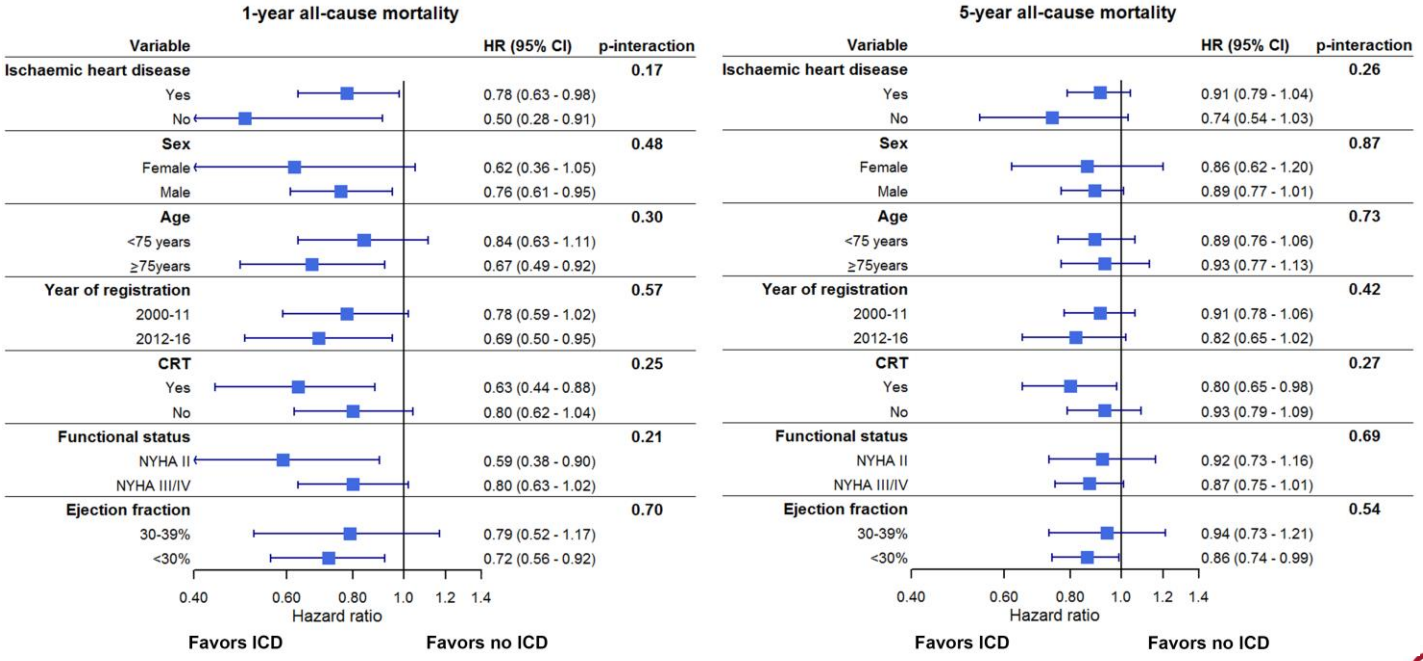
Schrage et al, Circulation. 2019;140:1530–1539

Subgroup analyses



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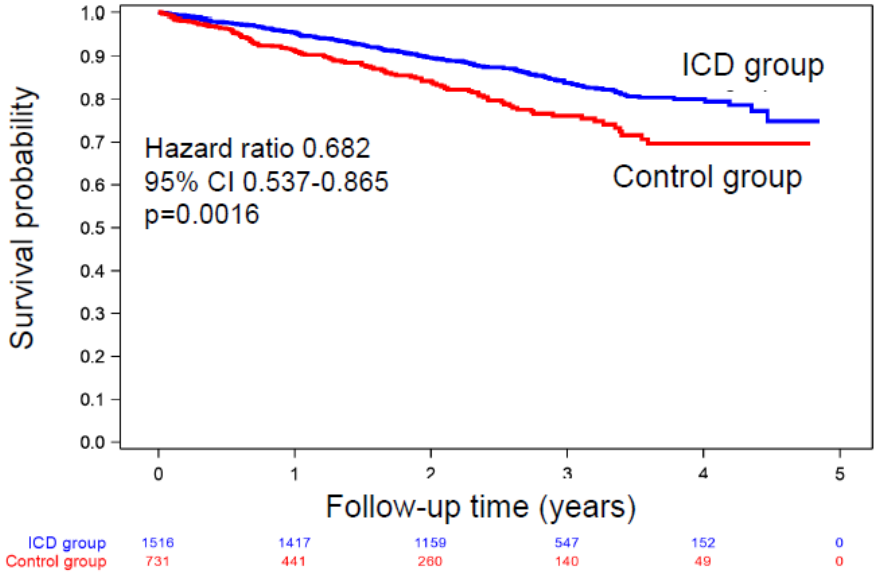
Schrage et al, Circulation. 2019;140:1530–1539

EU-CERT-ICD

EU-CERT-ICD

All-cause mortality: ICD vs. control group



Zabel et al, ESC 2019

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EU-CERT-ICD

EU-CERT-ICD

Adjusted hazard ratios for comparison of mortality ICD vs. no-ICD (multivariate predictors), and sensitivity analyses (propensity score techniques)

Model	n	Events	p-value	HR ICD vs. control	95% CI	
Unadjusted Strata by region	2247	342	0.0016	**0.682**	0.537	0.865
Adjusted by mortality predictors	2154	326	0.0140	**0.731**	0.569	0.938
Propensity score as covariate	2221	334	0.0029	**0.675**	0.521	0.874
Strata by propensity score quintiles	2221	334	0.0016	**0.667**	0.519	0.858
Propensity score matching (2:1)	1776	259	<.0001	**0.587**	0.451	0.763

CI confidence interval, HR hazard ratio

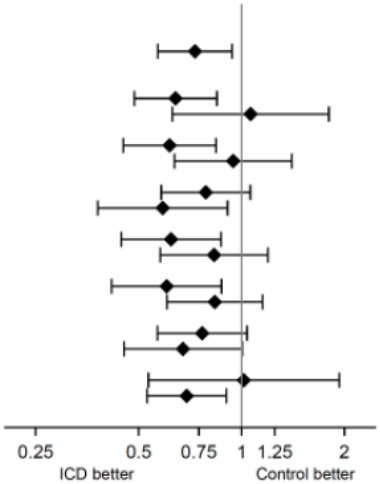
Zabel et al, ESC 2019

EU-CERT-ICD

EU-CERT-ICD

Mortality hazard ratios (adjusted by multivariate risk score) for selected subgroups

	ICD Events / N (%)		Control Events / N (%)		Hazard ratio (95% CI)	p	$p_{interaction}$
Overall	223/1470	(15.2)	103/684	(15.1)	0.731 (0.569, 0.938)	0.0140	
Age							0.0902
<75 years	168/1270	(13.2)	78/560	(13.9)	0.641 (0.486, 0.847)	0.0017	
≥75 years	55/200	(27.5)	25/124	(20.2)	1.063 (0.628, 1.800)	0.8206	
Diabetes							0.0887
no	136/1030	(13.2)	66/474	(13.9)	0.616 (0.451, 0.842)	0.0024	
yes	87/440	(19.8)	37/210	(17.6)	0.945 (0.637, 1.403)	0.7797	
Disease							0.2727
ICM	170/1014	(16.8)	66/387	(17.1)	0.786 (0.582, 1.061)	0.1162	
DCM	53/456	(11.6)	37/297	(12.5)	0.588 (0.380, 0.910)	0.0172	
Mortality predictors							0.1416
lower risk groups	110/1171	(9.4)	56/552	(10.1)	0.622 (0.445, 0.870)	0.0055	
highest risk group	113/299	(37.8)	47/132	(35.6)	0.831 (0.578, 1.195)	0.3173	
NYHA							0.1816
classes I or II	97/926	(10.5)	44/382	(11.5)	0.604 (0.417, 0.874)	0.0075	
classes III or IV	126/544	(23.2)	59/302	(19.5)	0.835 (0.605, 1.153)	0.2739	
Region							0.6136
eastern	119/616	(19.3)	69/460	(15.0)	0.767 (0.567, 1.038)	0.0853	
non-eastern	104/854	(12.2)	34/224	(15.2)	0.674 (0.453, 1.004)	0.0521	
Sex							0.2717
female	33/269	(12.3)	14/124	(11.3)	1.015 (0.534, 1.931)	0.9631	
male	190/1201	(15.8)	89/560	(15.9)	0.691 (0.529, 0.903)	0.0067	



ESC Congress Paris 2019 World Congress of Cardiology

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Zabel et al, ESC 2019

Summary

Guideline recommendations for primary prophylactic ICD are broad and based on outdated trials.

However, 2 recent non-randomized studies confirmed ICD effectiveness in contemporary patient groups.

Still there is need to further narrowing selection criteria to reduce unnecessary ICD implantation and to identify high-risk patients not fulfilling current guideline criteria.

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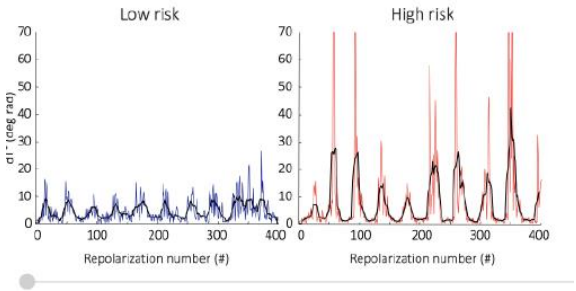
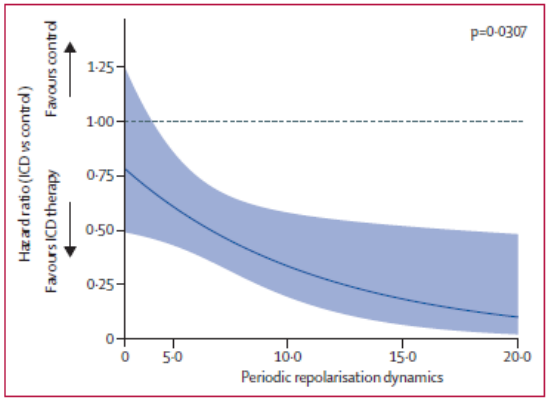
Prediction of mortality benefit based on periodic repolarisation dynamics in patients undergoing prophylactic implantation of a defibrillator: a prospective, controlled, multicentre cohort study

Axel Bauer, Mathias Klemm, Konstantinos D Rizas, Wolfgang Hamm, Lukas von Stülpnagel, Michael Dommasch, Alexander Steger, Andrezej Lubinski, Panagiota Flevari, Markus Harden, Tim Friede, Stefan Kääb, Bela Merkely, Christian Sticherling, Rik Willems, Heikki Huikuri, Marek Malik, Georg Schmidt, Markus Zabel*, and the EU-CERT-ICD investigators†*





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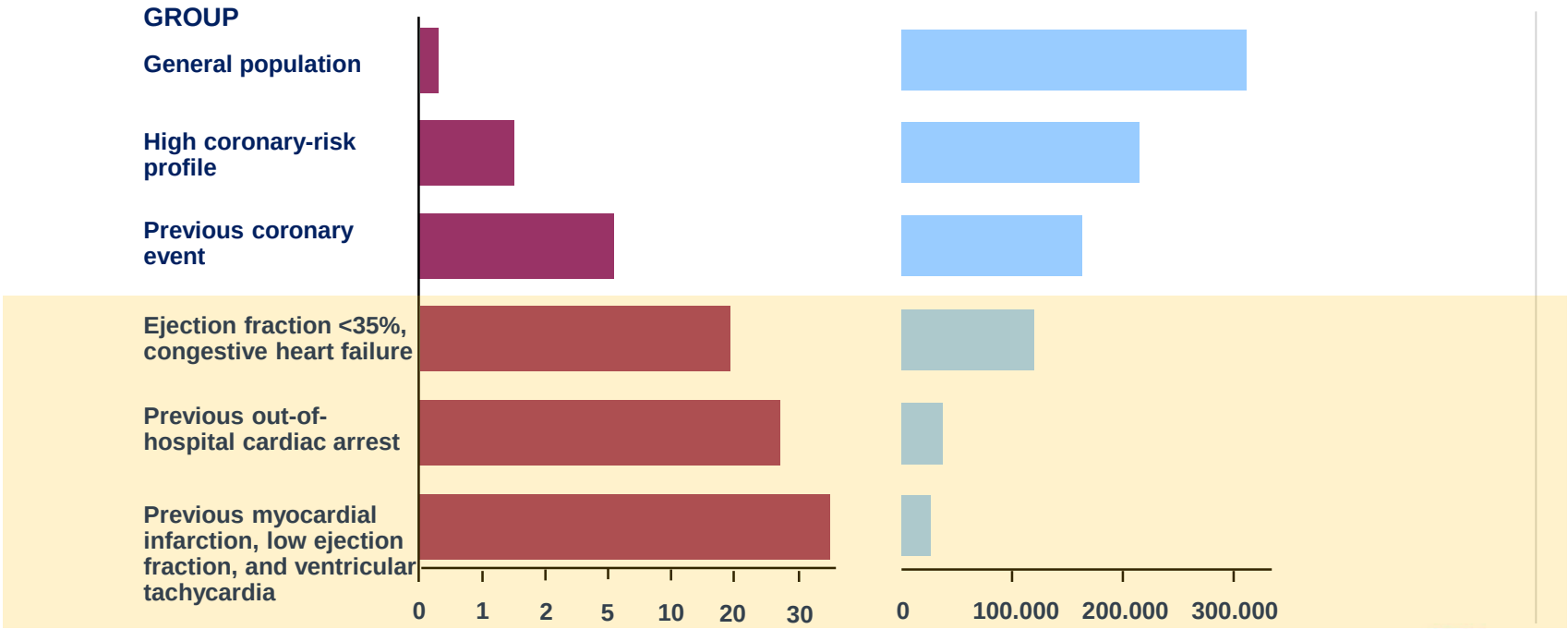
Bauer et al Lancet 2019; 394: 1344–51

Incidence of SCD in Specific Populations



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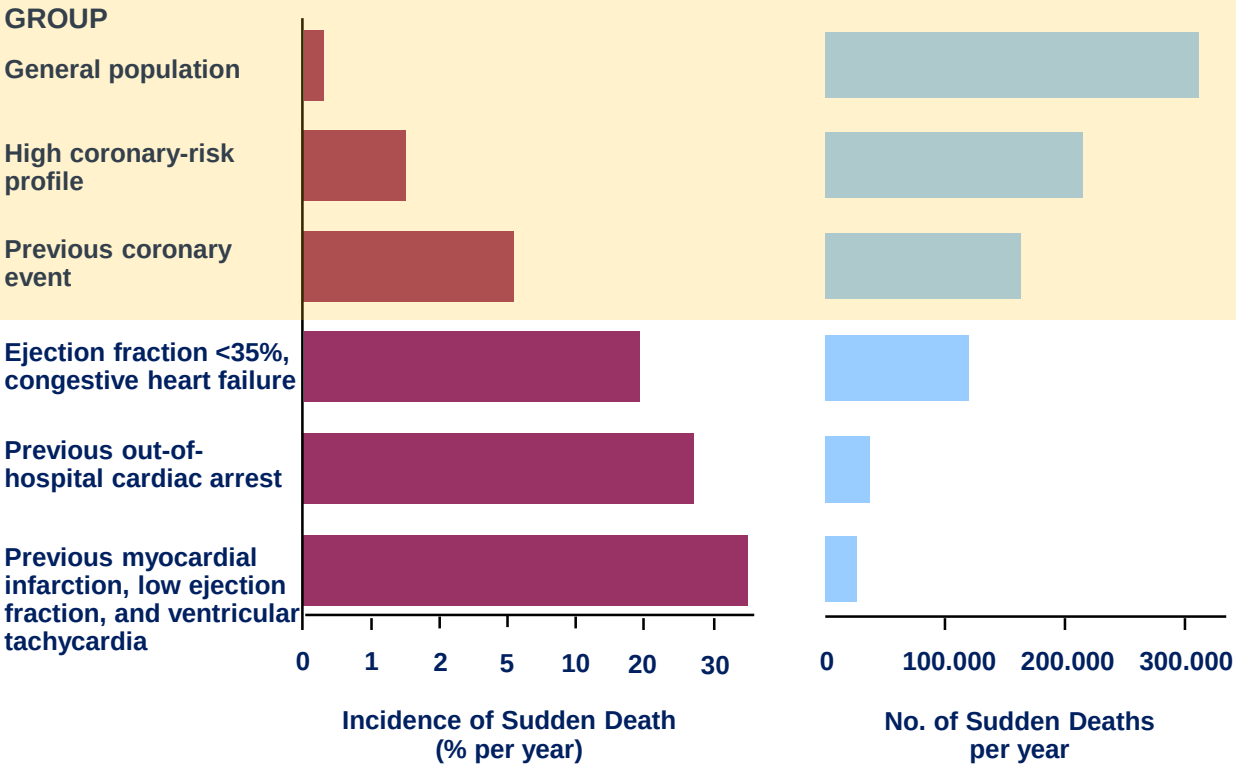
Myerburg RJ. Circulation.1998;97:1514-1521.

Incidence of SCD in Specific Populations



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Myerburg RJ. Circulation.1998;97:1514-1521.

Personalized SCD risk prediction

H2020 BHC-25: **Technical annex**

PROFID: Implementation of personalised risk score for sudden cardiac death in post-infarct patients

Heart Center Leipzig

Helios