

***ICDs for Prevention of Sudden Cardiac Death in
Non-ischemic Cardiomyopathy -
Could the DANISH Trial Change the Guidelines?***

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Disclosures

- **Research Grants**
 - *NHLBI*
 - *Amgen*
 - *Novartis*
 - *Pfizer*
 - *Alnylam*
- **Consultant**
 - *Novartis*
 - *Amgen*
 - *Merck*





Last week....36 yo male returns to clinic

- business professional travels frequently for work, married, active with 2 small children at home
- May 2013 admitted with new diagnosis of ADHF
 - ? viral syndrome, progressive dyspnea/cough/mild edema, CXR - cardiomegaly, pulmonary congestion
 - TTE: LVEF < 15%, LVIDD 7.2 cm
 - CMR: LVEF 10-15%, Stress perfusion nl, no scar
 - Discharged on Lisinopril, Carvedilol

3



Last week.... 36 yo male returns to clinic

- August 2013 - NYHA FC I
 - TTE: LVEF 27%, LVIDD 6.8 cm
 - Lisinopril 40, Carvedilol CR 40 mg,
 - spironolactone 12.5 mg started/stopped due to rash
- January 2014 – NYHA FC I
 - TTE: LVEF 48%, LVIDD 6.5 cm, GLS -14%
- January 2015 – NYHA FC I
- January 2016 – NYHA FC I-II
 - TTE: LVEF 40%, LVIDD 7.3 cm, GLS – 12%

4





Last week.... 36 yo male returns to clinic

- October 2016 - NYHA FC I
 - Unexpected weight loss (25lb), increase urination
 - DM diagnosed - Hgb A1c 13.5%
 - Metformin/Linagliptin started – Hgb A1c 6.7%
- February 2017 – NYHA FC II, weight stable
 - “occasional fatigue when he pushes it”
 - BP: 112/62; HR 57; PE noncontributory
 - TTE: LVEF 32%, LVIDD 7.3 cm, GLS -13%

Should I send him for an ICD? Risk stratify him – if so how? Do nothing?

5



ICDs for Prevention of SCD in NICM

- What is the risk of SCD in NICM?
 - How does it compare to Ischemic CM?
 - Medical therapy implications?
- What do we know about ICDs in NICM?
 - Secondary Prevention
 - Primary Prevention
 - Risk Stratification
- What do the ESC Guidelines 2016 tell us?
- DANISH results – *ESC Rome 2016, L. Kober et al.*
- Putting it together

6

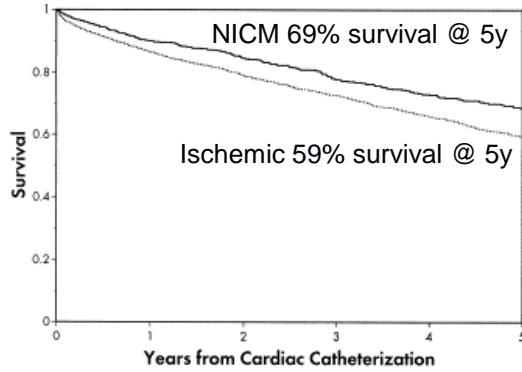




Survival in HF Differs by Etiology

Duke Cath Lab Database

Bart, JACC 1997;30:1002



- SOLVD: had found equivalent survival
- CHF-STAT: 71% vs 72% survival @ 2y for ICM/NCM
- SCD-HeFT: 57% vs 72% survival @ 5y for ICM/NCM



Beta-Blockers: Similar Benefits in NCM

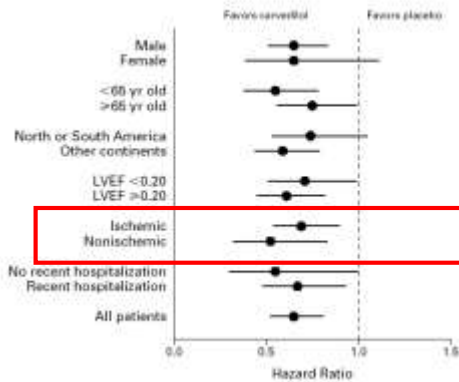


Table 4. Randomized Trials of Beta-Blockade in Patients With Nonischemic Cardiomyopathy: Effect of Beta-Blockade on Mortality

Study (ref. no.)	Deaths/Sample Size		Total Death [OR (95% CI)]*
	Beta-Blocker	Control	
Anderson et al. (14)	5/25	6/25	0.79 (0.23-3.0)
CIBIS (33)	17/140	20/151	0.58 (0.30-1.1)
Engelbrecht et al. (17)	5/8	2/16	0.68 (0.07-11)
MDC (44)	23/194	21/189	1.08 (0.57-2.0)
Morris et al. (41)	0/20	0/20	1.00 (0.02-53)
Olson et al. (40)	0/21	0/20	0.87 (0.02-46)
Packer et al. (32)†	8/562	14/208	0.35 (0.15-0.87)
Pollock et al. (38)	0/7	0/5	0.68 (0.01-42)
Woodley et al. (42)	0/13	0/9	0.68 (0.01-38)
Total	55/793	72/643	0.69 (0.47-0.99)

Meta-analysis
 NICM Placebo: BBL
 HR for ACM = 0.69

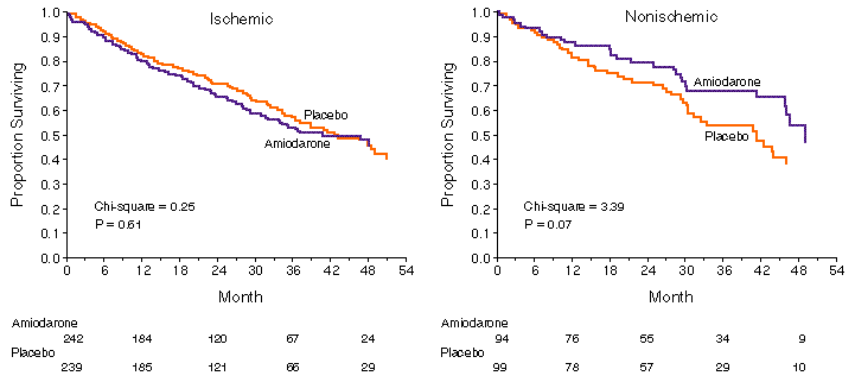
Heidenreich, JACC 1997;30:27

Packer, NEJM 2001;344:1651





Amiodarone: Differential Effect in NICM?



Singh, NEJM 1995;333:77



RCT's of ICD's Enrolling Patients with NICM

TRIAL	INCLUSION	DESIGN	N	Hazard Ratio (overall)
AVID 1993	EF<40%, VT/VF	ICD/Amio	193/1016	0.62, p<0.02
CASH 1987	Cardiac arrest	ICD/AAD	35/288	0.76, p=NS
CIDS 1990	VT/VF	ICD/Amio	77/659	0.8, p=NS
CAT 1991	DCM, EF<30%	ICD/med rx	104/104	No difference
AMIOVIRT 1996	DCM, EF<35%, NSVT	ICD/Amio	103/103	No difference
DEFINITE 1998	NICMP, CHF, EF<35%	ICD/med rx	458/458	0.66, p=0.06
SCD-HeFT 1997	CHF, EF<35%	ICD/Amio/Placebo	792/1692	0.73, NS
COMPANION 2000	EF<35%, CHF, wide QRS	CRT-D vs. CRT vs. med	842/1520	0.50, p<0.05

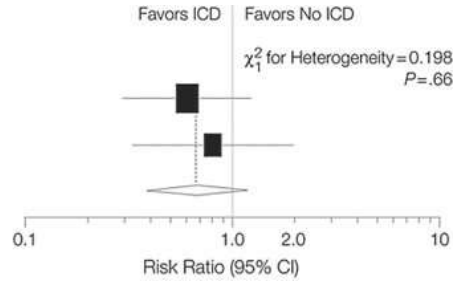
Desai JAMA 2004; 292:2874





NICM: Secondary Prevention ICD

Study	Years of Enrollment	No. of Patients	Risk Ratio (95% CI)
AVID ¹	1993-1997	193	0.6 (0.29-1.33)
CIDS ²	1990-1997	63	0.8 (0.33-2.00)
Combined		256	0.69 (0.39-1.24)



ICD vs Control 31% RRR

Desai JAMA 2004; 292:2874



Primary Prevention Trials

Characteristic	CAT	AMIOVIRT	DEFINITE	SCD-HeFT'	COMPANION**
#Pts. Randomized	104	103	458	1676	903
# NICM (%)	104 (100%)	103 (100%)	458 (100%)	792 (47.3%)	397 (44.0%)
Follow-Up (Mos)	66 ± 26.4	24 ± 14.4	26 ± 4	45.5	14.8-16.5
Patients					
Age, mean, y	52	59	58	60	67
% Male	80%	70%	71%	77%	67%
NYHA III/IV	34.6%	20%	21%	30%	85.6%
Duration of CHF	3 months	3.2 yrs	2.8 yrs	24.5 months	3.5 yrs
LVEF (%)	0.24 ± 0.07	0.23 ± 0.09	0.21 ± 0.14	25.0 ± 0.05	0.22
Meds (baseline)					
Beta-blocker	3.8%	51.5%	84.0%	69%	68%
ACE-ARB	96.2%	85%	96.7%	96%	89%
Design	ICD vs. Med Rx	ICD vs. Amio	ICD vs. Med RX	ICD vs. Amio vs. Placebo	Optimal Med Rx vs. CRT vs. CRT-D
1-yr Mortality (control)	3.7%	10%	7%	7.2%	19%

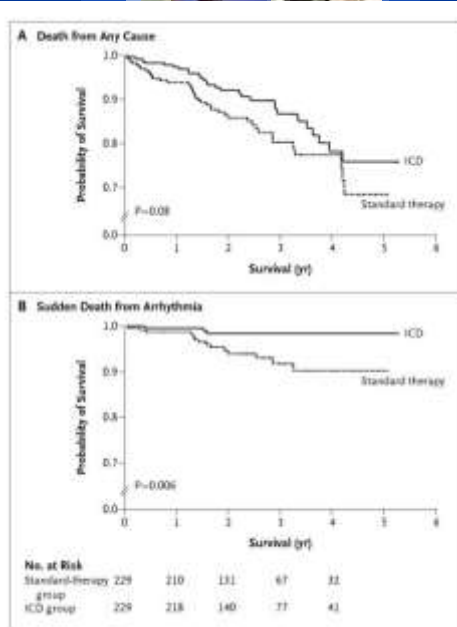
Desai JAMA 2004; 292:2874



DEFINITE

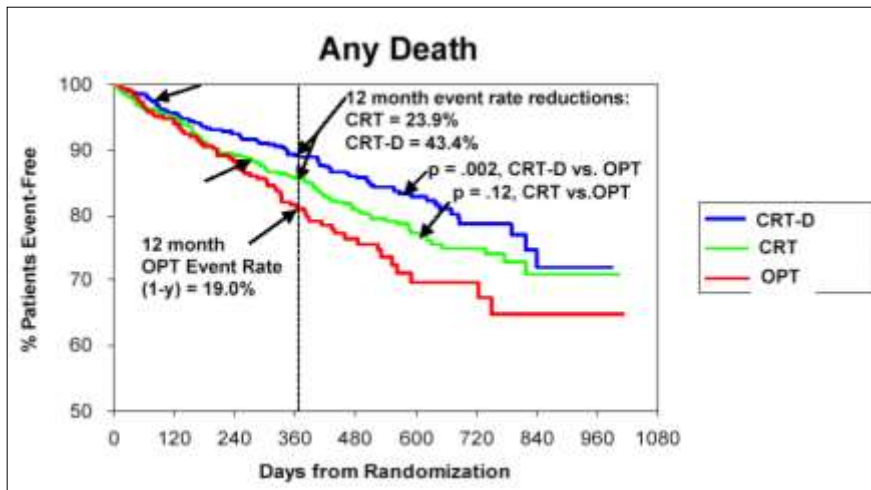
Total Mortality

Sudden Death Mortality



Kadish, N Engl J Med 2004;350:2151

COMPANION: Total Mortality



Bristow, N Engl J Med 2004





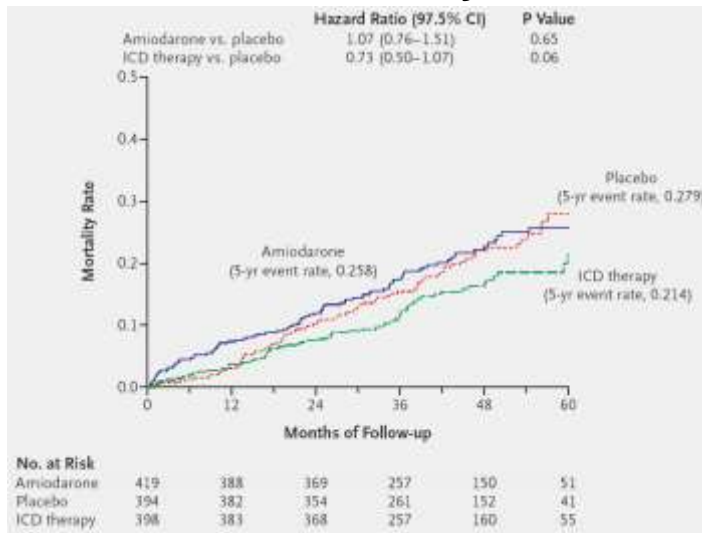
COMPANION: Total Mortality

Variable	No. of Patients			Hazard Ratio for Death from Any Cause
	Pharmacologic therapy (n=308)	Pacemaker (n=617)	Pacemaker-defibrillator (n=617)	
<i>Bristow, N Engl J Med 2004</i>				
Age				
≤65 yr	123	272	272	
>65 yr	185	345	323	
Sex				
Male	211	415	401	
Female	97	202	194	
Cardiomyopathy				
Ischemic	181	331	325	0.73
Nonischemic	127	285	270	0.50

Bristow, N Engl J Med 2004



SCD-HeFT Total Mortality: Nonischemic

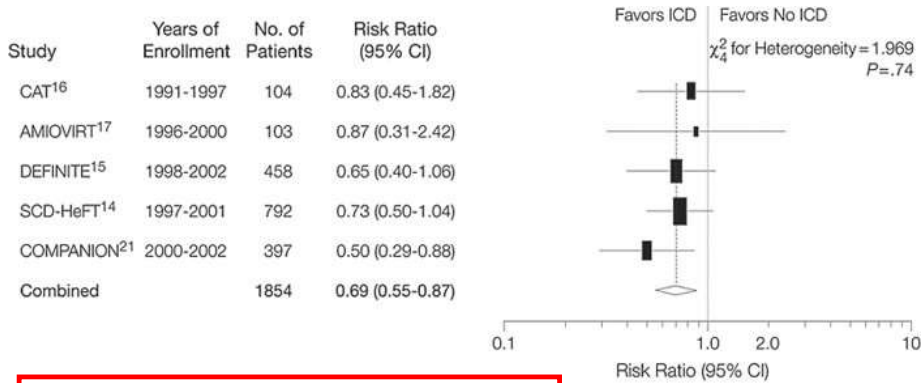


Bardy G et al. NEJM 2005; 352:225





NICM: Primary Prevention ICD



ICD vs Control 31% RRR

Desai A et al. JAMA 2004



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Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure

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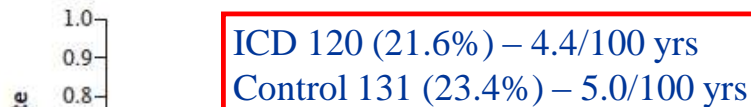
DANISH: Study Details

- 1116 randomized (556 ICD v 560 Control)
- Age, median – 64 years
- Female – 27%
- HF Duration, median – 20 months
- NYHA FC II/III – 97%
- CRT – 58% (in both groups)
- ACEi/ARB – 97%
- Beta Blockers – 92%
- MRA – 58%
- Amiodarone – 9%

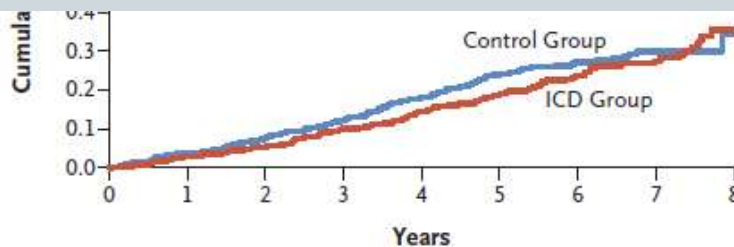


DANISH: All Cause Mortality

Death from Any Cause



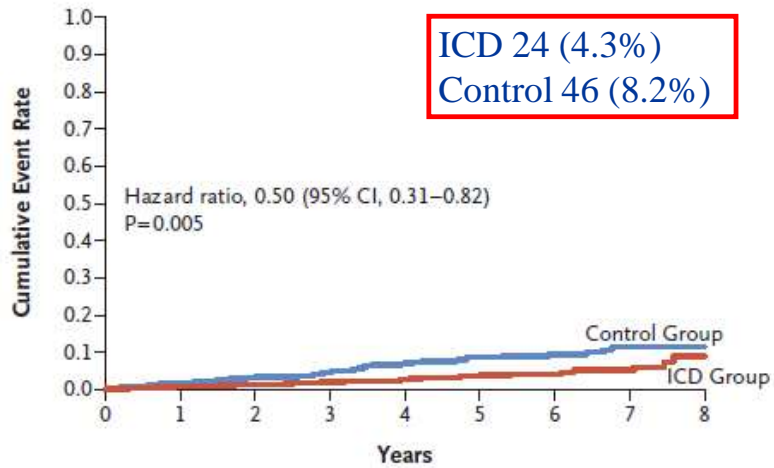
In this trial, prophylactic ICD implantation in patients with symptomatic systolic heart failure not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care.



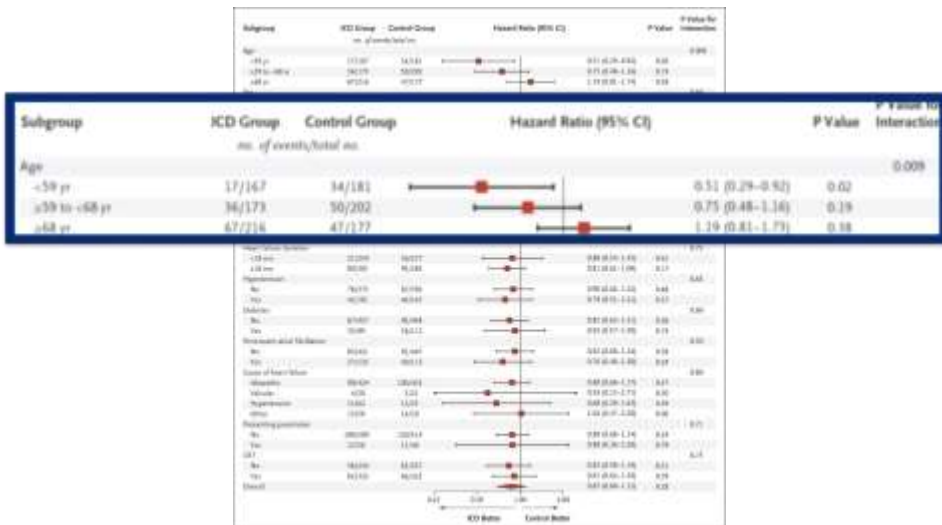


DANISH: Sudden Cardiac Death

Sudden Cardiac Death

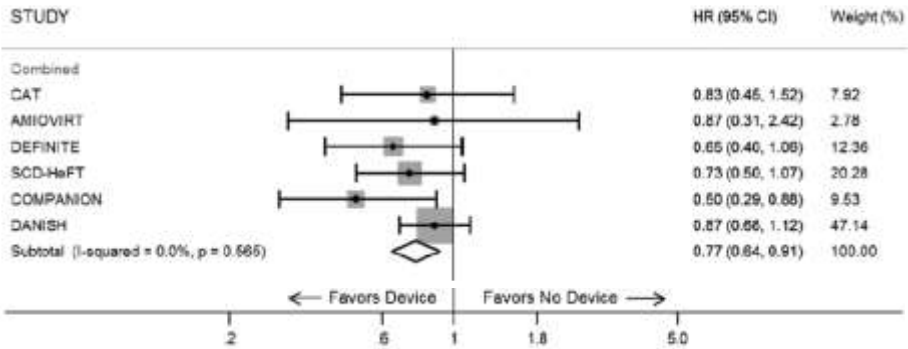


DANISH: Pre-specified Subgroups





ICD for NICM: *Updated Meta-Analyses*



ICD vs Control 23% RRR



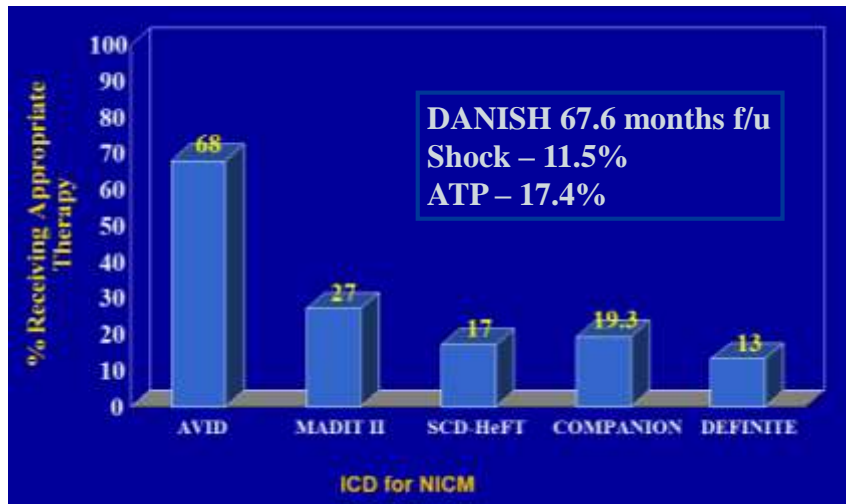
DANISH: What did we (re)learn? What next?

- Medical therapy optimization critical
- CRT may be sufficient alone
 - ICD decision likely to be driven by additional cost/risk
- ICD effect is likely marginal if broadly applied
- Age discrimination?
 - Subgroup analysis results
 - Non Cardiovascular mortality was 31%
- Back to the drawing board
 - EF has known poor sensitivity/specificity
 - Need for better risk stratification models





Appropriate ICD Therapy Infrequent at 2 years



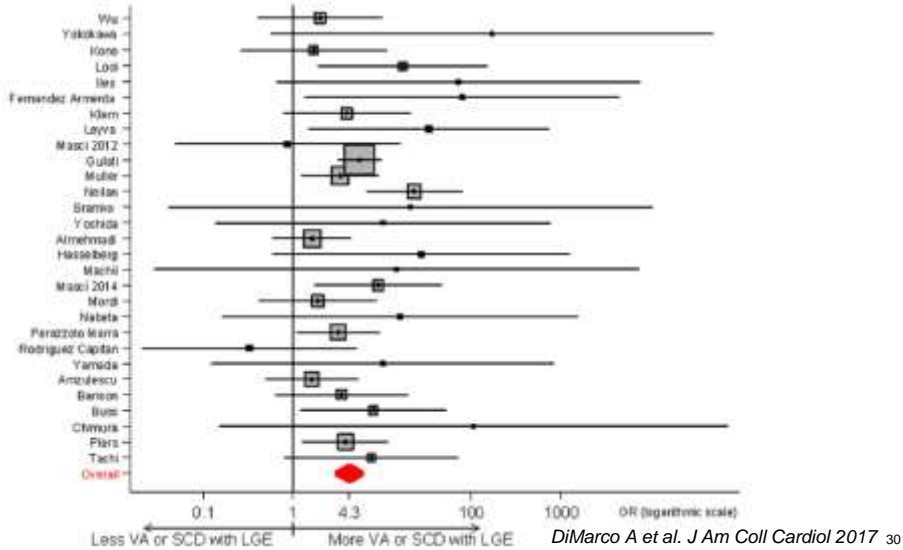
ICD Risk Stratification in NICM: A Field of Failure

- NYHA Class
- Patient's sex
- Duration of cardiomyopathy
- Invasive EP: programmed ventricular stimulation
- Noninvasive risk stratifiers
 - QRSD
 - NSVT
 - TWA
 - SAECD
 - BRS, HRV
 - Turbulence
 - QT dispersion

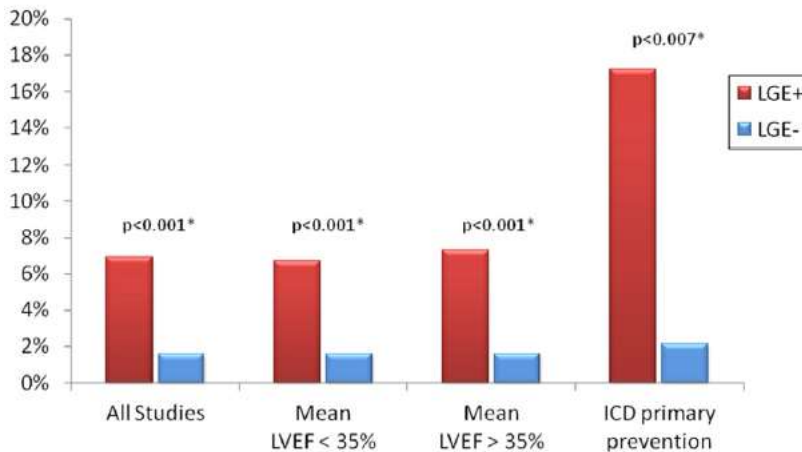




CMR LGE: Is it the answer?



Annual Rate of SCD/VA by LGE Status





2016 ESC HF Guidelines: ICDs pre-DANISH

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:		
<ul style="list-style-type: none"> • IHD (unless they have had an MI in the prior 40 days – see below). 	I	A
<ul style="list-style-type: none"> • 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

Ponikowski P et al. Eur Heart J 2016 32



Last week....36 yo male returns to clinic

- business professional travels frequently for work, married, active with 2 small children at home
- **Risk stratify further – repeat CMR for LGE**
- **EP Consultation to Discuss ICD risks/benefits**
- **Reassurance and continue current medications/close follow-up**





Summary

- The best way to minimize SCD in NICM population
 - *Aggressively start and titrate GDMT to goal doses*
- EP device therapy post-DANISH
 - *CRT should be considered for all appropriate candidates*
 - *ICD has marginal additive benefits broadly applied but it still likely has a role*
 - *Moreso in the young*
- Need more, larger strategy studies to evaluate CMR LGE based decision-making
- We need to talk more often and frankly to our patients, individualize decision making