



UNIVERSITÀ DEGLI STUDI DI TORINO



Primary prevention of sudden cardiac death in nonischemic cardiomyopathy: indication to cardiac defibrillator

Pro

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Osp Padre A. Micone, Genova

Conflitto di interessi : nessuno



Total mortality at 5 yrs

70% in the 80s -> 20-30% at present

Sudden cardiac death

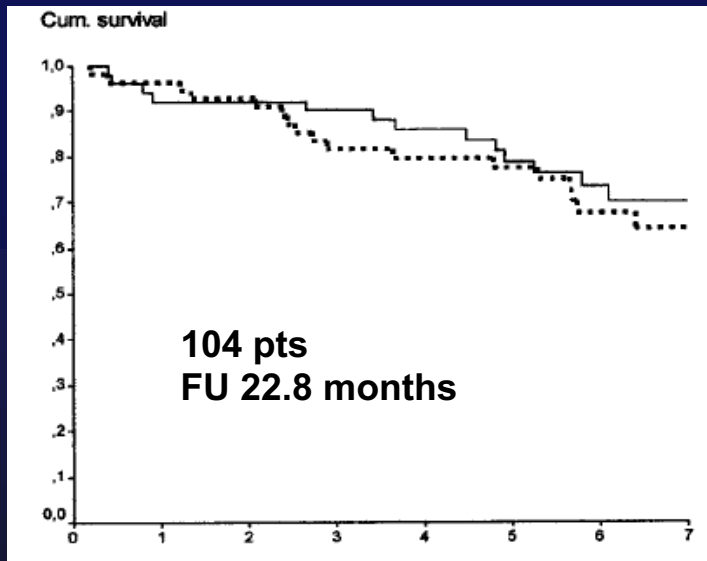
30% of total mortality

2-3% annual rate

involves many working people

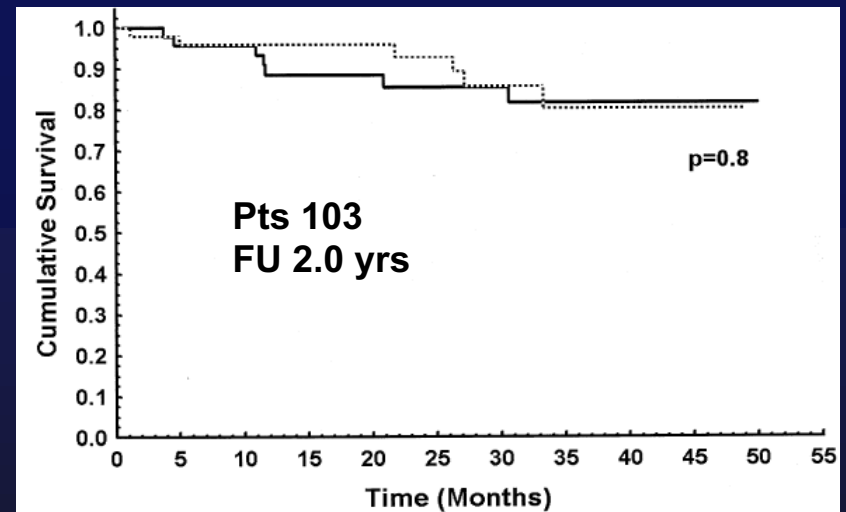
ICD in nonischemic cardiomyopathy

Primary Prevention of Sudden Cardiac Death in Idiopathic Dilated Cardiomyopathy The Cardiomyopathy Trial (CAT)



Bansch D Circulation 2002;105:1453

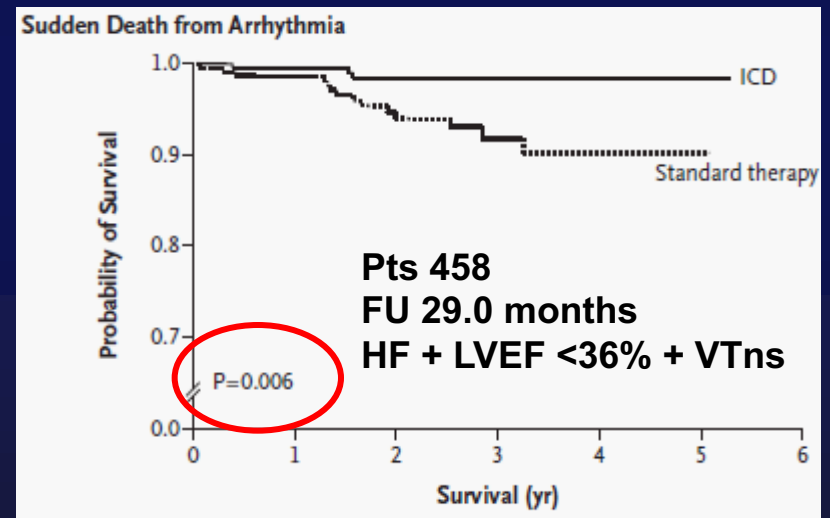
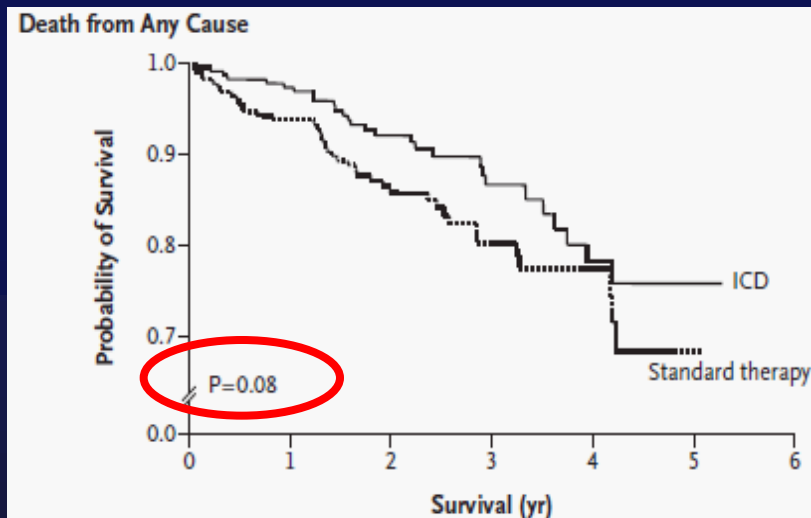
Amiodarone Versus ICD Therapy: Randomized Trial in Patients With Nonischemic Dilated CMP and Asymptomatic nsVentricular Tachycardia: AMIOVIRT



Strikberger SA JACC 2003;41:1707

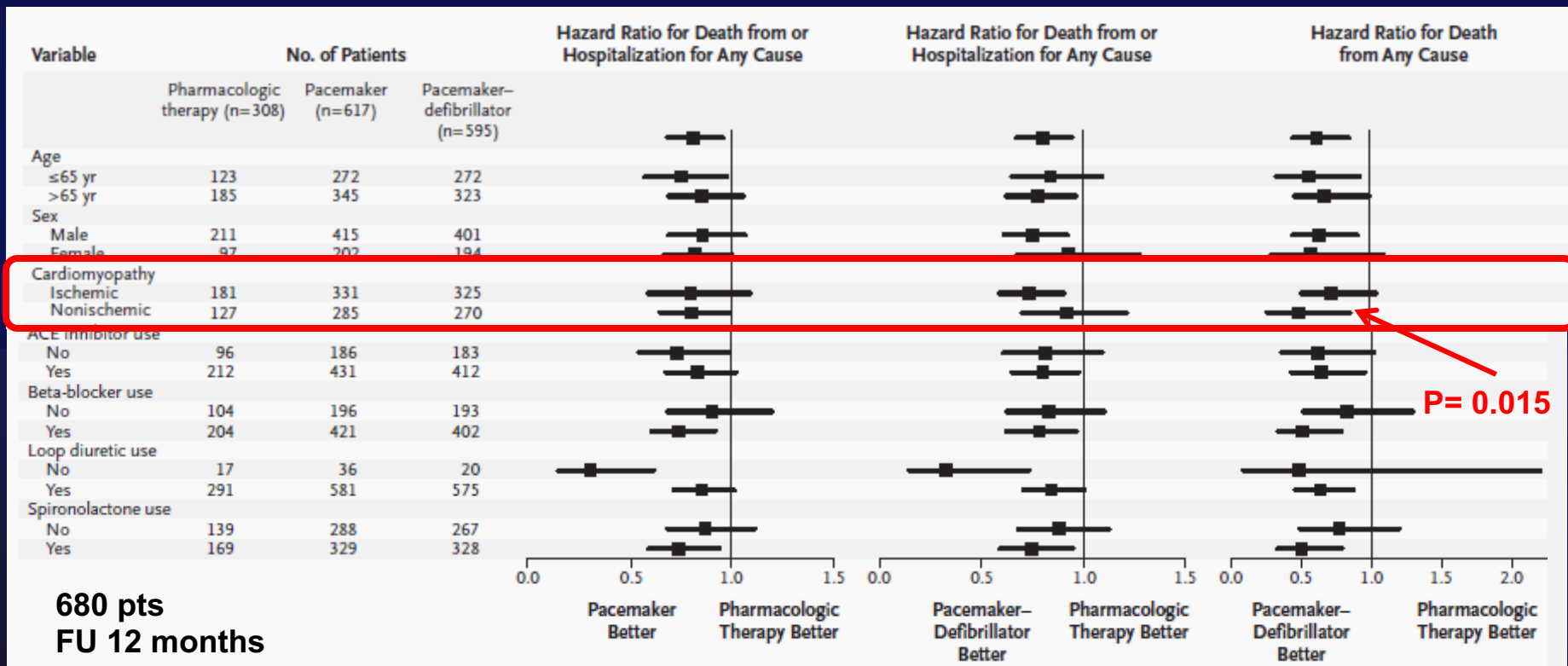
ICD in nonischemic cardiomyopathy

Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy



ICD in nonischemic cardiomyopathy

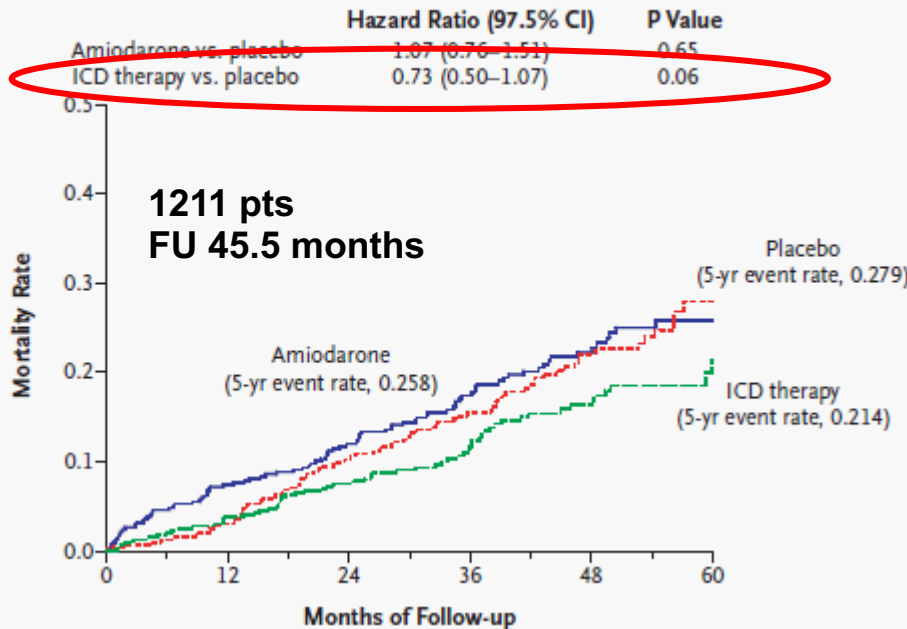
Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure



ICD in nonischemic cardiomyopathy

Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure

Nonischemic CHF

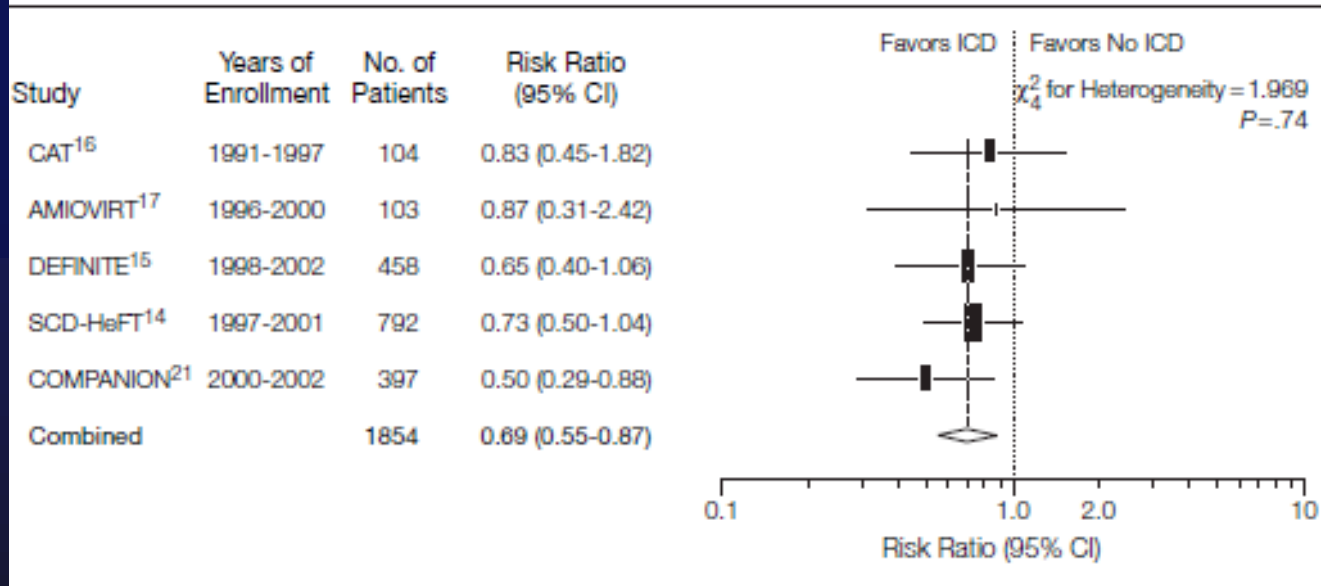


no data
on
sudden
cardiac death

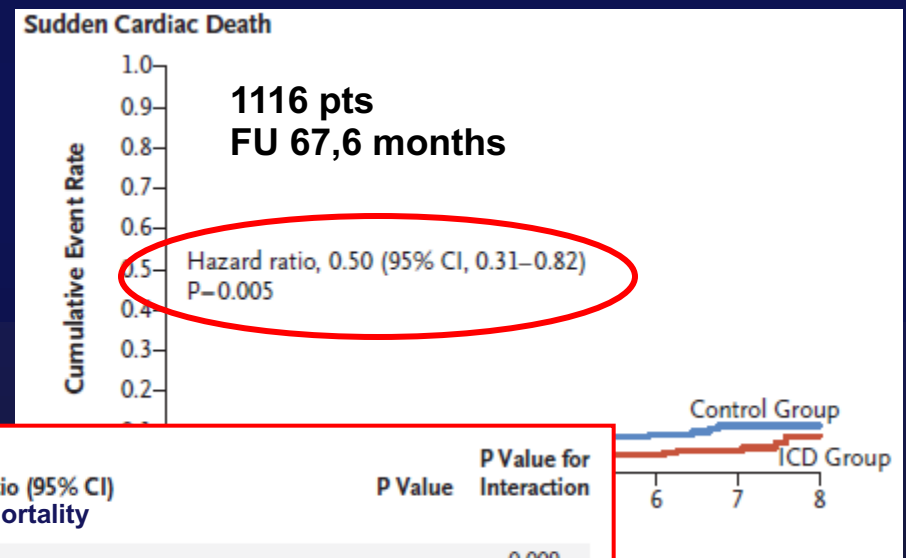
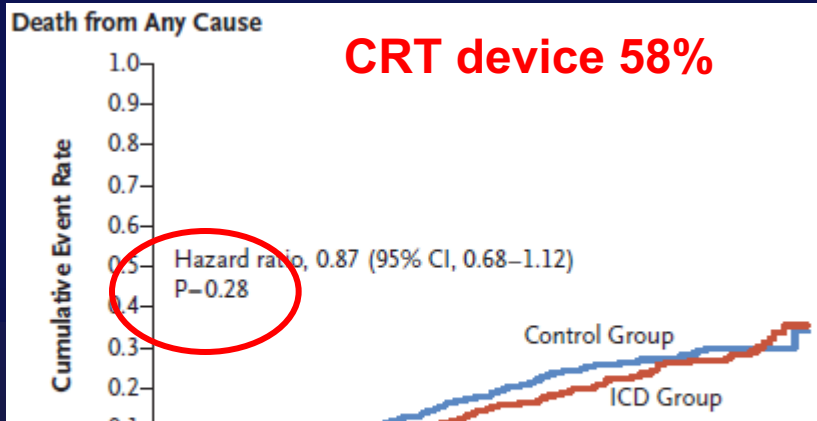
ICD in nonischemic cardiomyopathy

Metaanalisi

All-Cause Mortality Among Patients With NICM Randomized to ICD or CRT-D vs Medical Therapy in Primary Prevention



Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure



Subgroup	ICD Group no. of events/total no.	Control Group no. of events/total no.	Hazard Ratio (95% CI) Total mortality	P Value	P Value for Interaction
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 (0.81–1.73)	0.38	

ICD in nonischemic cardiomyopathy

Metaanalisi

Barakat AF

Barakat A

Study

CAT

AMIOVIRT

DEFINITE

SCD-HeFT

DANISH

Overall (I-squared = 0.0%, p = 0.565)

NOTE: Weights are from random effects analysis

ICD is associated with lower all-cause mortality

Study Year

AMIOVIRT 2006

DEFINITE 2006

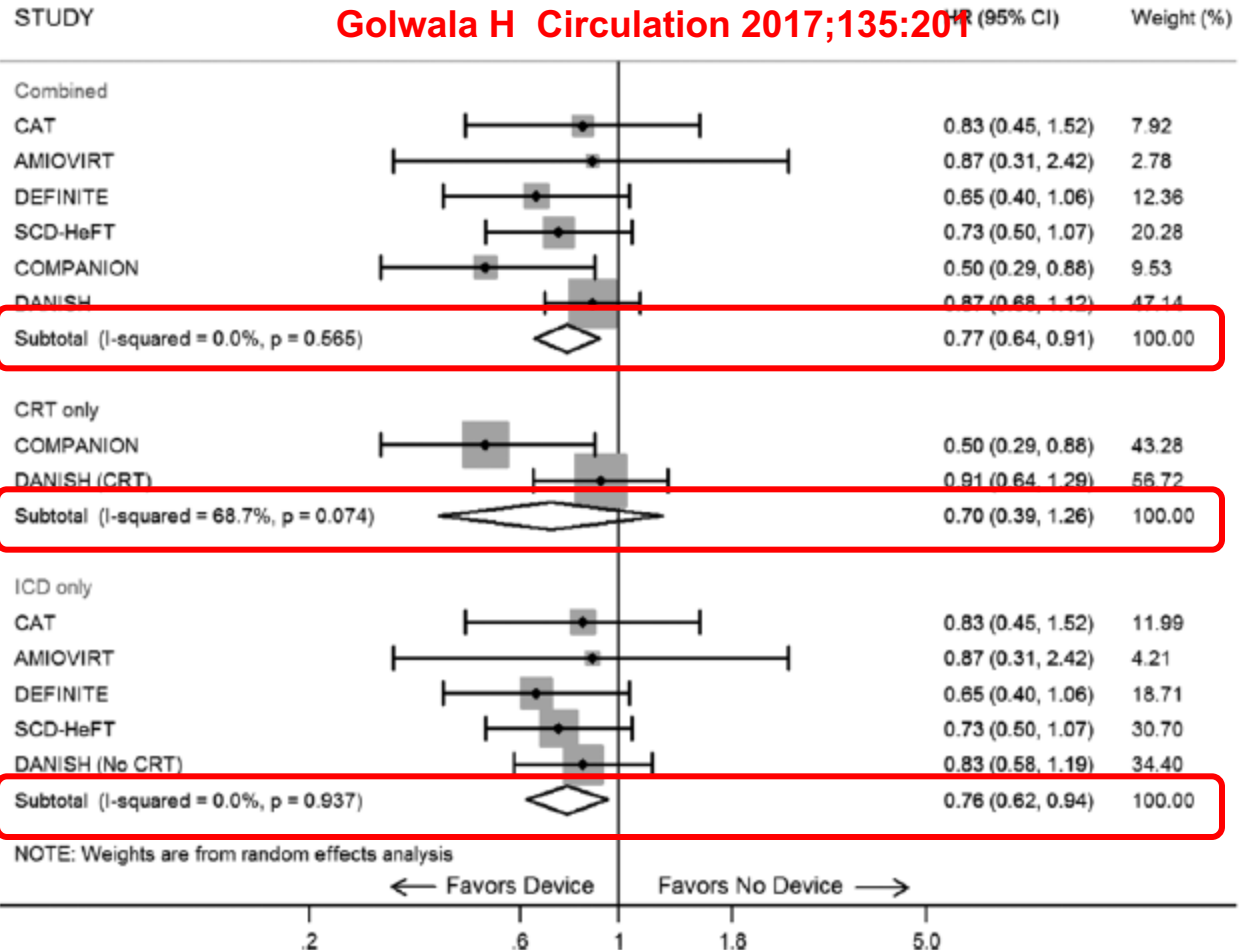
DANISH 2011

Overall (I-squared = 0.0%, p = 0.565)

NOTE: Weights are from random effects analysis

ICD is associated with lower all-cause mortality

Golwala H Circulation 2017;135:201



Guidelines

An ICD is recommended in patients with DCM, symptomatic HF (NYHA class II–III) and an ejection fraction $\leq 35\%$ despite ≥ 3 months of treatment with optimal pharmacological therapy who are expected to survive for > 1 year with good functional status.	I	B
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Recommendations for Primary Prevention of SCD in Patients With NICM		
COR	LOE	Recommendations
I	A	1. In patients with NICM, HF with NYHA class II–III symptoms and an LVEF of 35% or less, despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected (1-6).

Prognostic stratification for SD

Noninvasive Arrhythmia Risk Stratification in Idiopathic Dilated Cardiomyopathy

Results of the Marburg Cardiomyopathy Study

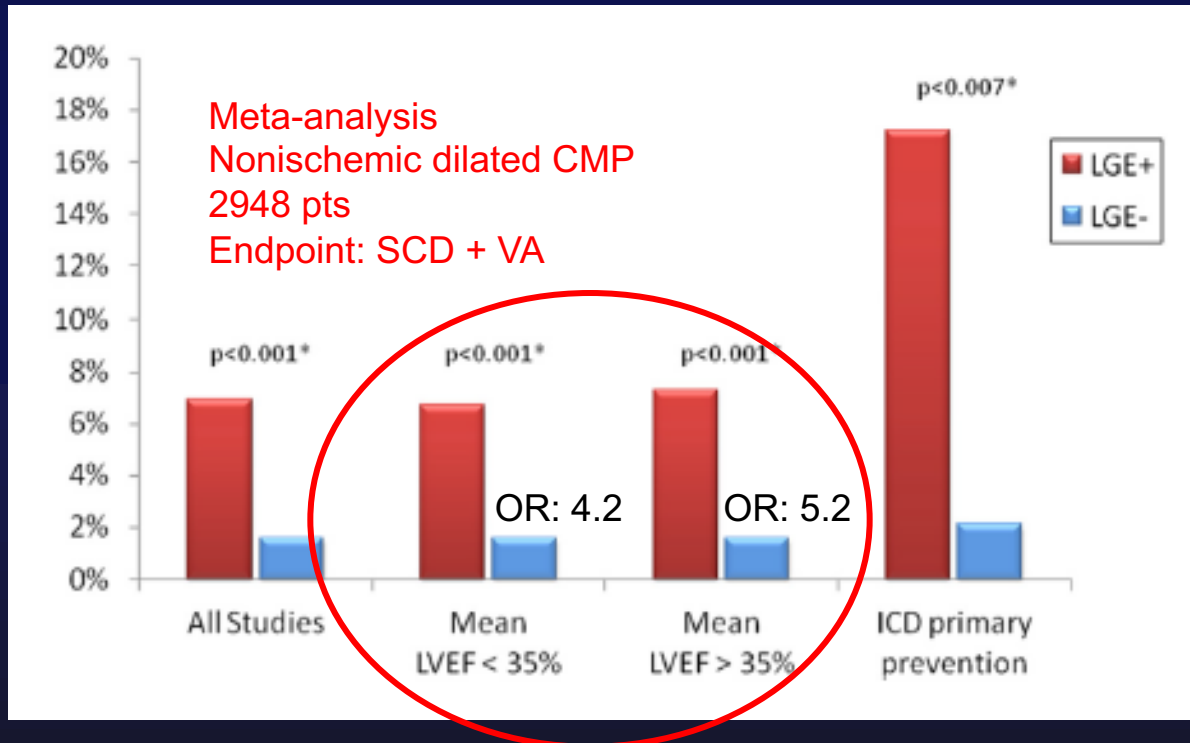
Conclusions—Reduced LV ejection fraction and lack of β -blocker use are important arrhythmia risk predictors in IDC, whereas signal-averaged ECG, baroreflex sensitivity, heart rate variability, and T-wave alternans do not seem to be helpful for arrhythmia risk stratification. These findings have important implications for the design of future studies evaluating prophylactic implantable cardioverter-defibrillator therapy in IDC. (*Circulation*. 2003;108:2883-2891.)

Prognostic stratification for SD

Meta-Analytic Summaries of Test Performance by Predictor Category

Predictor	Studies	Events/n (%)	Calculated 3-Yr Event Rate (%)	Prev. (%)	Sens. (%)	Spec. (%)	PPA (%)	NPA (%)	RR (95% CI)	OR (95% CI)	p Value
Autonomic											
BRS	2	48/359 (13.4)	17.0	52.9	64.6	48.9	16.3	89.9	1.80 (0.63–5.16)	1.98 (0.60–6.59)	0.23
HRT	3	66/434 (15.2)	18.6	32.3	47.0	70.4	22.1	88.1	2.12 (0.77–5.83)	2.57 (0.64–10.36)	0.16
HRV	4	83/630 (13.2)	15.6	43.1	55.4	58.8	16.9	89.7	1.52 (0.84–2.75)	1.72 (0.80–3.73)	0.13
Functional											
LV											
LV											
Arrhy											
EP											
NS											
Techniques incorporating functional parameters, depolarization abnormalities, repolarization abnormalities, and arrhythmic markers provide only modest risk stratification for sudden cardiac death in patients with nonischemic dilated cardiomyopathy. It is likely that combinations of tests will be required to optimize risk											
Depolarization											
QRS/LBBB	10	262/1,797 (14.6)	14.7	35.7	45.4	65.9	18.5	87.6	1.43 (1.11–1.83)	1.51 (1.13–2.01)	0.010
SAECG	10	152/1,119 (13.6)	19.9	36.9	51.3	65.4	18.9	89.5	1.84 (1.18–2.88)	2.11 (1.18–3.78)	0.017
Frag. QRS	2	65/652 (10.0)	11.8	25.6	61.5	78.4	24.0	94.8	5.16 (3.17–8.41)	6.73 (3.85–11.76)	<0.001
Repolarization											
QRS-T	1	97/455 (21.3)	25.0	62.2	74.2	41.1	25.4	85.5	1.75* (1.16–2.65)	2.01* (1.22–3.31)	0.006*
TWA	12	177/1,631 (10.9)	15.8	66.8	91.0	36.2	14.8	97.0	3.25 (2.04–5.16)	4.66 (2.55–8.53)	<0.001

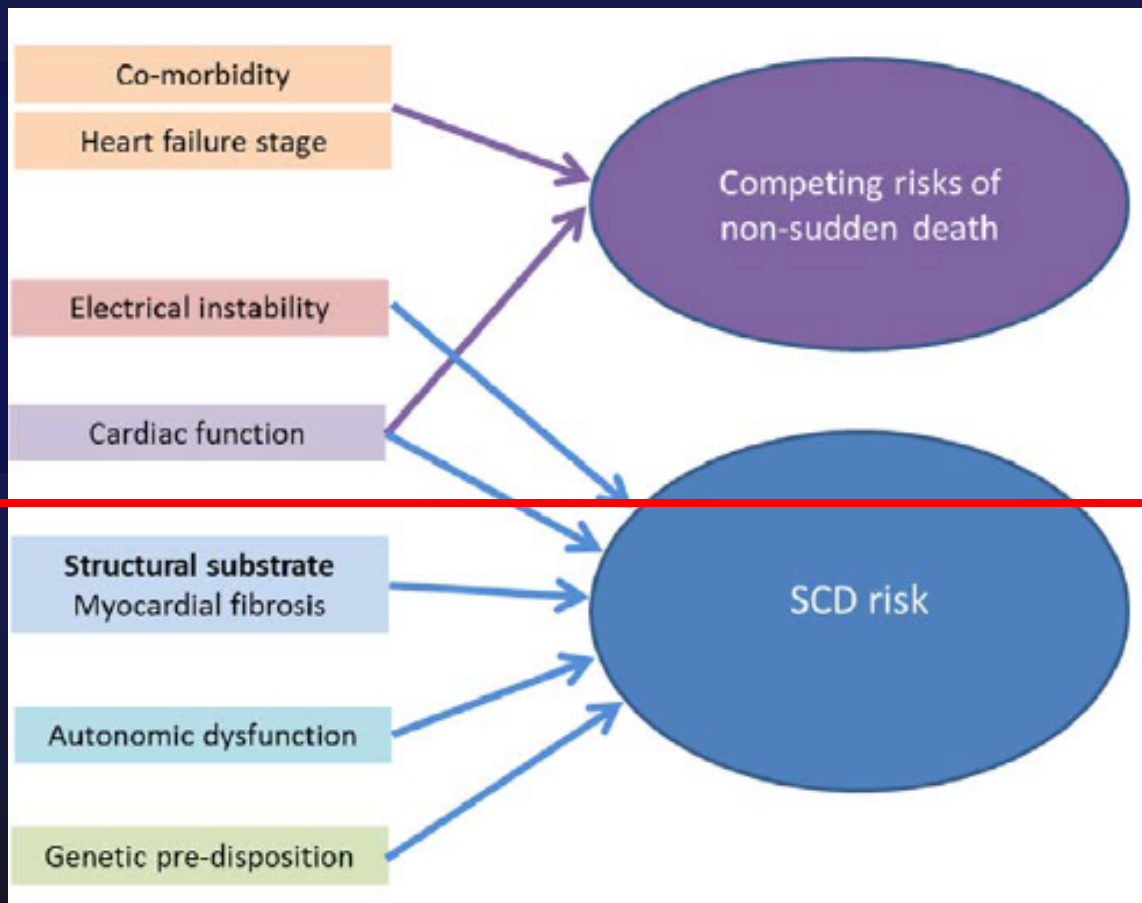
Prognostic stratification for SD



Limitations

- Observational studies
- Differing inclusion criteria for enrollment of subjects
- Nonrandomized studies to confirm that pts with LGE+ benefit from ICD
- Lackig data on predictive accuracy

Prognostic stratification for SD



Nonischemic CMP definition

Dilated cardiomyopathy

Left ventricular or biventricular systolic dysfunction and dilatation that are not explained by abnormal loading conditions or coronary artery disease.

Coronary artery disease should be excluded in patients more than 35 years of age, or before 35 years if there are significant personal coronary artery disease (CAD) risk factors or a family history of early CAD.

SD and coronary artery disease

class II or III. Coronary artery disease (coronary stenosis >70%) had to be excluded by angiography. Patients with a history of prior

CAT Study Circulation 2002;105:1453

absence of clinically significant coronary artery disease as the cause of the cardiomyopathy was confirmed by coronary angiography or by a negative stress imaging study. Patients were excluded if they

DEFINITE Study NEJM 2004;350:2151

of a myocardial infarction. Nonischemic CHF was defined as left ventricular systolic dysfunction without marked stenosis.

SCD-HeFT NEJM 2005;352:225

able. Patients could be included even if they had one or two coronary arteries with stenoses, if the extent of coronary artery disease was not considered to be sufficient to account for the reduced left ventricular systolic function. Patients

DANISH Study NEJM 2016;375:1221

SD and coronary artery disease

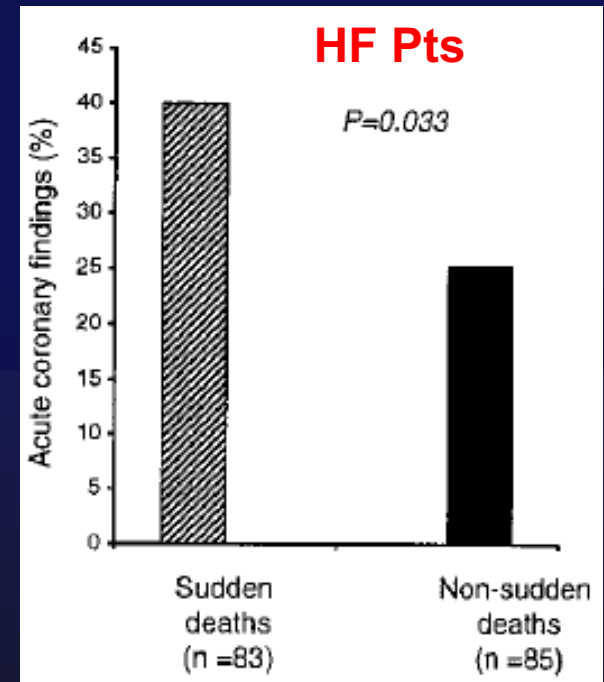
Although patients enrolled in these studies must not have an overt ischemic heart disease they can show some degree of coronary stenoses < 50%-75% up to 2 vessels

Thus the enrolled patients may be at increased risk of acute coronary attacks which in turn may result in VT-VF

SD and acute coronary attacks

638 pts resuscitated from cardiac arrest

Complete revascularization, <i>n</i> (%)	181 (47)
DES, <i>n</i> (%)	46 (14)
Local success, <i>n</i> (%)	349 (89)
Target vessel	
RCA	88 (22)
LM	21 (5)
LAD	206 (52)
LCx	79 (20)
Thrombectomy, <i>n</i> (%)	55 (9)
Stent length (mean ± SD)	18.4 ± 6.0
Stent diameter (mean ± SD)	3.1 ± 0.5
Acute occlusion	205 (52)
Chronic total occlusion	29 (7)



SD and acute coronary attacks

UNFORTUNATELY ACUTE ISCHEMIC ATTACKS
CANNOT BE PREDICTED

Dynamic Risk profiling

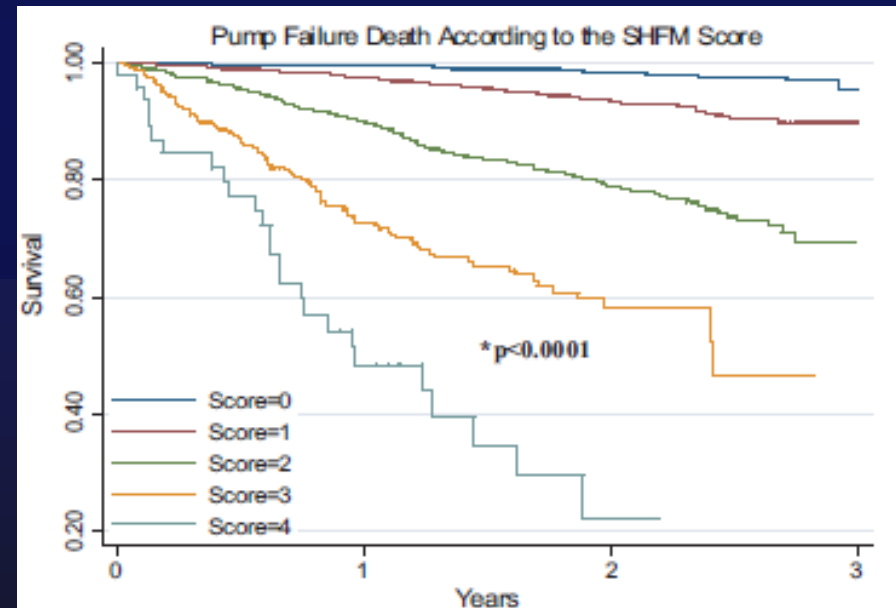
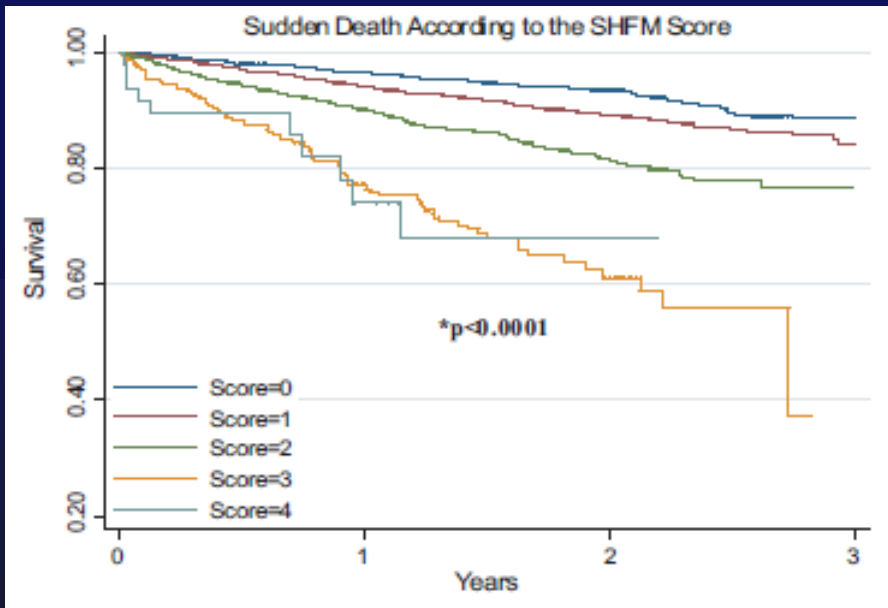
- ventricular remodelling
- comorbidity evolution
- temporal variation in risk
- unknown frequency of risk assessment

Conclusion

- 1) ICD implantation in nonischemic cardiomyopathy patients is effective in reducing total and SD mortality
- 2) ICD implantation is strongly indicated in agreement with guidelines
- 3) Accurate identification of patients with a high probability of dying of both non cardiac causes and non SD is needed
- 4) Younger people with fewer competing risk factors should be favorite

Comorbidity/Heart failure stage and SCD

Prediction of Mode of Death in Heart Failure The Seattle Heart Failure Model



ICD in nonischemic cardiomyopathy

	CAT ¹²	AMIOVIRT ¹³		DEFINITE ¹⁴		SCD-HeFT ⁵				COMPANION ⁶		DANISH ⁷	
Mean follow-up duration (months)	66	29		26		45.5				Range 14.8-16.5 months		67.6	
Location	Germany	USA		USA		USA, Australia, and New Zealand				USA		Denmark	
Control	MT	AMIO		MT		MT/MT +AMIO				MT/MT+ CRT		MT	
Participants	104	103		458		792				397		1116	
Participants with NICM No. (%)	104 (100)	103 (100)		458 (100)		1210 (48)				397 (44)		1116 (100)	
Patients (n)		ICD (50)	Control (54)	ICD (51)	Control (52)	ICD (229)	Control (229)	ICD (829)	Control (845/847)	ICD (617)	Control (308/595)	ICD (556)	Control (560)
Age-mean (years)		52	52	58	60	58	58	60.1	60.4/59.7	67	68/66	64	63

Appropriate ICD therapy

5% over 1 year in SCD-HeFT

18% over 3 years in DEFINITE

12% over 5 years in DANISH

Average 2.5-6 therapies/years

ICD in nonischemic cardiomyopathy

Microvolt TWA (cardiomiopatia non ischemica)

446 NICMP pts		No. of Events		Rate* (95% CI)		p Value	NPV† (95% CI)		PPV‡ (95% CI)	
End Point		Abnormal TWA Test	Normal TWA Test	Abnormal TWA Test	Normal TWA Test		12 months	18 months	12 months	18 months
Arrhythmic death + life-threatening arrhythmia		20	2	4.5 (2.9-7.0)	0.8 (0.2-3.3)	5.53 (1.29-23.65) 0.004	99.3% (96.4-100)	98.6% (95.2-99.8)	4.9 (2.7-8.1)	7.0 (4.3-10.7)

Salerno J ALPHA Study JACC 2007;50:1896

Metaanalysis 6200 NICMP pts								
Predictor	Studies	Sens. (%)	Spec. (%)	PPA (%)	NPA (%)	RR (95% CI)	OR (95% CI)	p Value
Repolarization								
QRS-T	1	74.2	41.1	25.4	85.5	1.75* (1.16-2.65)	2.01* (1.22-3.31)	0.006*
TWA	12	91.0	36.2	14.8	97.0	3.25 (2.04-5.16)	4.66 (2.55-8.53)	<0.001

Goldberger JJ JACC 2014;63:1879

Fibrosi alla RMN

Metaanalisi, 1105 pz, FEVS mediana $\leq 36\%$

Summary estimates	Relative risk (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Patient no.	Events	No. of studies
All	4.33 (2.98–6.29)	1.98 (1.66–2.37)	0.33 (0.24–0.46)	1063	201	11
Subgroups:						
CAD patients only	4.63 (2.48–8.67)	2.01 (1.66–2.44)	0.28 (0.16–0.50)	262	67	4
NICM patients only	3.79 (1.20–11.94)	2.10 (1.60–2.75)	0.46 (0.18–1.20)	227	23	3
Core scar as predictor	3.82 (2.49–6.66)	1.83 (1.57–2.13)	0.40 (0.25–0.64)	188	80	5
Grey zone as predictor	5.94 (2.82–12.52)	2.37 (1.45–3.87)	0.24 (0.13–0.44)	459	86	4
Only appropriate ICD therapy as primary endpoint	6.22 (2.41–16.05)	2.54 (1.73–3.71)	0.27 (0.14–0.52)	294	55	4

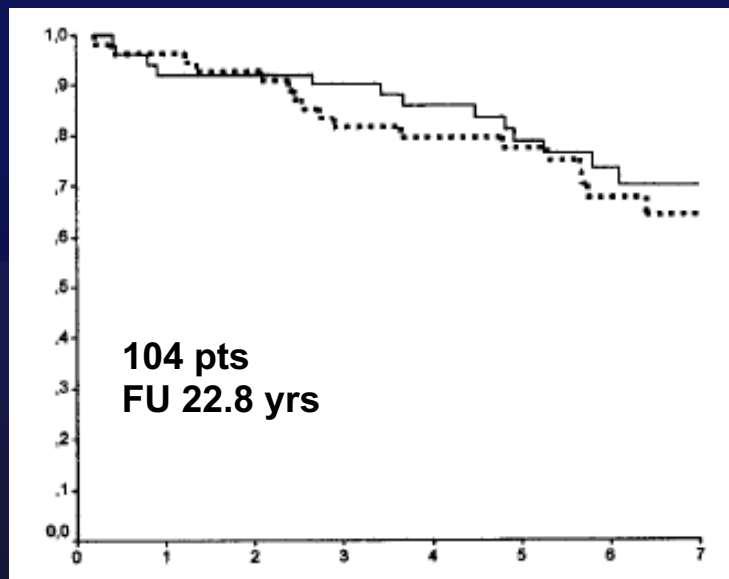
ICD in nonischemic cardiomyopathy

Table 2. Univariable Relation of Baseline Characteristics With Mortality **1991 pts with HF and LVEF < 40%**

Characteristics	Chi-Square	p Value	Hazard Ratio
Age (10 yr increments)	143.3	0.0001	1.400
Men	7.0	0.0081	1.201
Race: white	1.0	0.3106	1.078
Ejection fraction (5 U increments)	24.3	0.0001	0.907
Mitral regurgitation	14.5	0.0001	1.163
Vascular disease (PVD, CRV, bruits)	28.1	0.0001	1.446
Hx hypertension	5.4	0.0203	1.167
NYHA functional class	9.7	0.0019	1.137
Diabetes	27.4	0.0001	1.424
Hx angina	5.9	0.0150	1.183
Hx revascularization	0.1	0.8206	0.983
Valvular disease	20.2	0.0001	1.338
Ischemia variable			
Ischemic	54.7	0.0001	1.755
Number diseased vessels	98.0	0.0001	1.295
CAD index (per 10 U)	87.0	0.0001	1.111

ICD in nonischemic cardiomyopathy

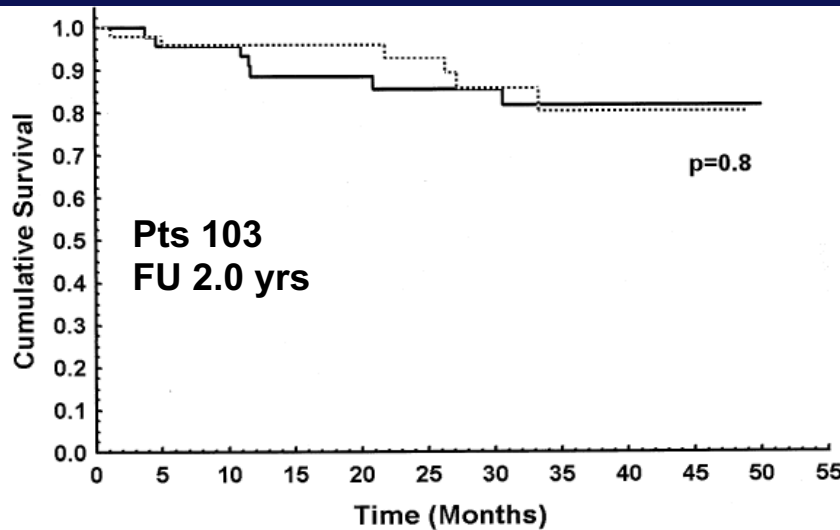
Primary Prevention of Sudden Cardiac Death in Idiopathic Dilated Cardiomyopathy The Cardiomyopathy Trial (CAT)



End Point	Incidence at 1 y
All-cause mortality	
ICD	4 (8.0)
Control	2 (3.7)
Sudden death	
ICD	0
Control	0
Cardiac death	
ICD	4 (8.0)
Control	1 (1.9)
Heart transplantation	
ICD	2 (4.0)
Control	1 (1.9)

ICD in nonischemic cardiomyopathy

Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients With Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia—AMIOVIRT



	Amiodarone	ICD	p Value
n	52	51	—
# Deaths (%)	7 (13.5)	6 (11.8)	0.8
# Cardiac deaths (%)	5 (71)	4 (67)	0.9
# SCD (%)	2 (40)	1 (25)	0.7
# Non SCD (%)	3 (60)	3 (75)	0.7
# Noncardiac (%)	2 (29)	2 (33)	0.9
# Cardiac transplant (%)	2 (4)	1 (2)	0.8

SD and statin assumption

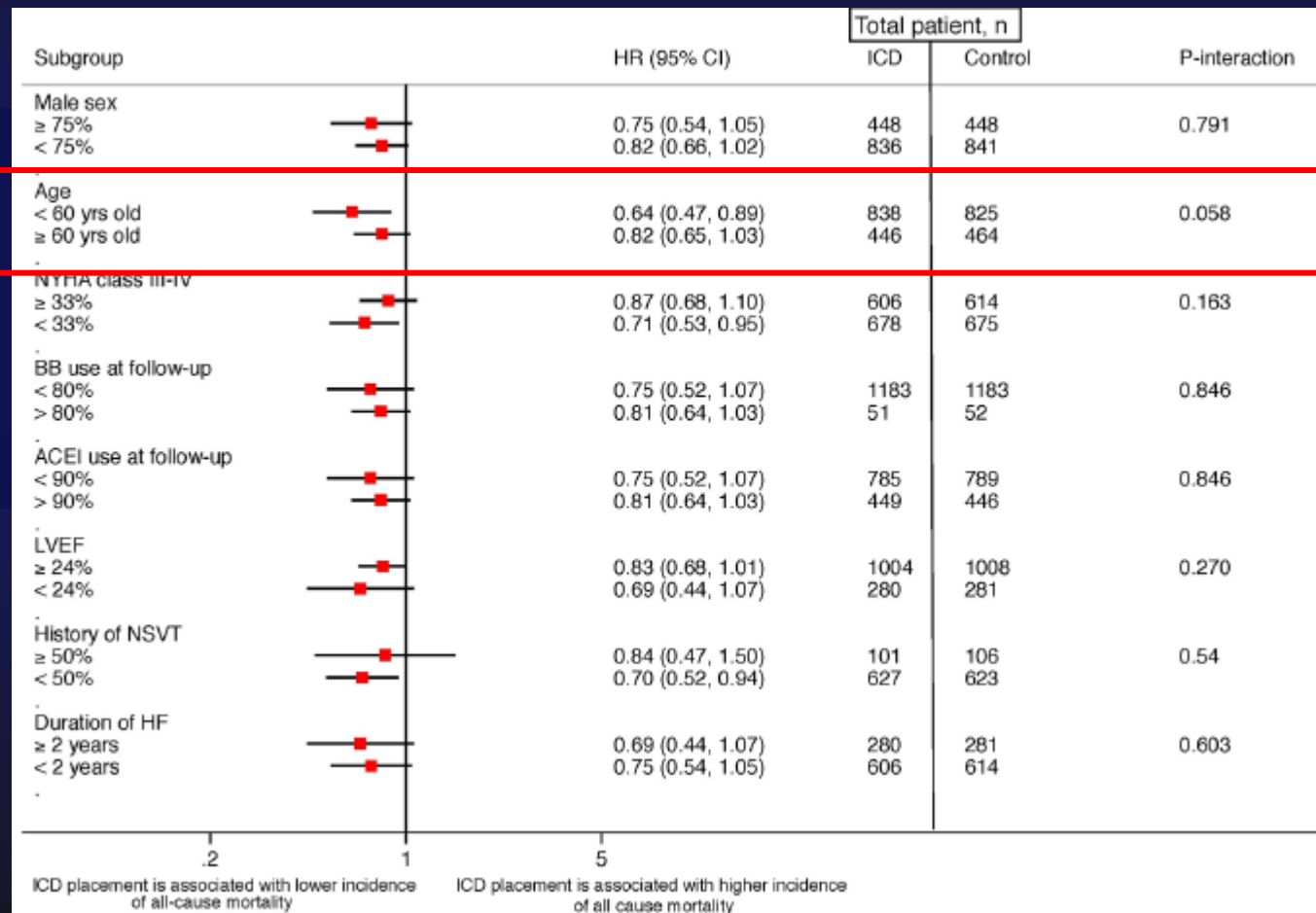
DEFINITE Study	Not Treated With Statins	Treated With Statins	p Value
n	348	110	
Age (yrs)	57.7 ± 13.3	60.1 ± 11.5	0.09
Gender (female)	103 (29.6%)	29 (26.4%)	0.51
Randomized to ICD	172 (49.4%)	57 (51.8%)	0.66
Current smokers	45 (12.9%)	14 (12.7%)	0.96
Ever smokers	151 (43.4%)	42 (38.2%)	0.34
DM	73 (21.0%)	32 (29.1%)	0.08
HTN	41 (11.8%)	8 (7.3%)	0.18
LVEF (%)	21.4 ± 6.0	21.3 ± 6.0	0.95
QRS duration (ms)	114.7 ± 29.2	116.12 ± 26.9	0.64
NYHA class I	74 (21.3%)	25 (22.7%)	0.75
NYHA class II	196 (56.3%)	67 (60.9%)	0.40
NYHA class III	78 (22.4%)	18 (16.4%)	0.17
CHF duration >1 yr	166 (47.7%)	57 (51.8%)	0.45
Beta-blocker	292 (83.9%)	97 (88.2%)	0.28
ACE inhibitor/ARB	333 (95.7%)	102 (92.7%)	0.22
Aspirin	122 (35.1%)	37 (33.6%)	0.79
Arrhythmic sudden death	18 (5.2%)	1 (0.9%)	0.04
Total mortality	64 (18.4%)	5 (4.5%)	<0.001

Statin use was associated with reduced mortality in both ischemic and nonischemic cardiomyopathy from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)

Nonischemic cardiomyopathy
(0.67 [0.47-0.96])

Dickinson MG Am Heart J 2007;153:573

ICD in nonischemic cardiomyopathy



ICD in nonischemic cardiomyopathy

Studies performed on small numbers of pts
for a study population characterized
by a low rate of SD

Significant differences in heart failure therapy
(betablockers, ACEI, statins, etc.)

Different follow up periods