Super-responders for ICD primary preventions

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- **ISSUE OF PATIENT SELECTION**
  : more sudden cardiac death risks

- **ISSUE OF ICD PROGRAMMING**
  : less ICD shock

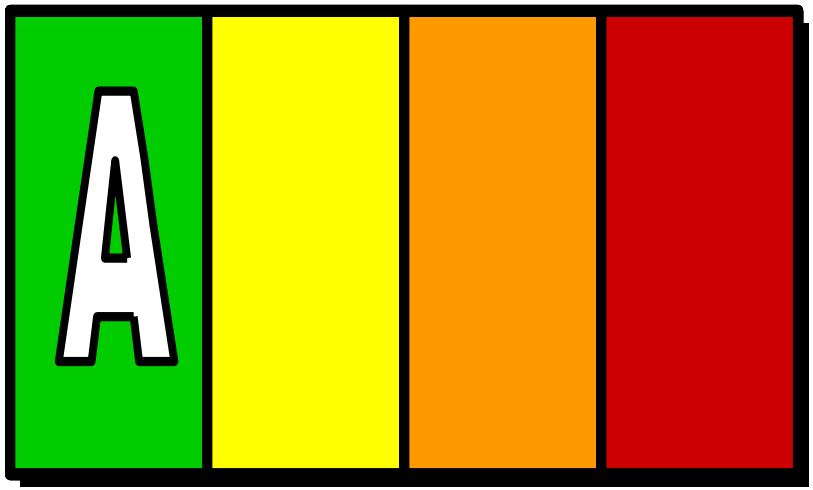
ISSUE OF PATIENT SELECTION

(ICD USE FOR PRIMARY PREVENTION OF SCD)

- In 2008, a joint task force of the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Heart Rhythm Society (HRS) in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Cardiac Pacemakers and Antiarrhythmia Devices updated the 2002 guidelines for device-based therapy

ACC/AHA Guideline Recommendations for Primary Prevention ICD Therapy

I IIa IIb III



Jessup M et al. J Am Coll Cardiol 2009;53
Epstein AE et al. Circulation. 2008;117

Class I Recommendations

ICD therapy is indicated in patients*:

Level of Evidence: A

- With LVEF ≤ 35% due to prior MI who are at least 40 days post-MI and are in NYHA Functional Class II or III
- With LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF ≤ 30%, and are in NYHA Functional Class I
- Who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes

Level of Evidence: B

- With nonischemic DCM who have an LVEF ≤ 35% and who are in NYHA Functional Class II or III
- With nonsustained VT due to prior MI, LVEF < 40%, and inducible VF or sustained VT at electrophysiological study
- With structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable
- With syncope of undetermined origin with clinically relevant,

* Assuming patients are on chronic, optimal medical therapy and have a reasonable expectation of survival with good functional status for > 1 year.

ICDs for Primary Prevention

Eligible Population for 1° Prevention ICD

1996 **2013**

ICD Indication Expansion for Primary Prevention

Ischemic CMP

MADIT
MADIT II
CABG Patch
MUSTT
SCD-HeFT
DINAMIT
IRIS

Non-ischemic CMP

CAT and AMIOVIRT
SCD-HeFT
DEFINITE

MADIT I: ICDs Prevent Death in Ischemic LVSD

Enrollment criteria:

- NYHA functional class I-III
- Prior myocardial infarction
- LVEF $\leq$0.35
- Documented asymptomatic non-sustained VT
- Inducible, non-suppressible ventricular tachyarrhythmia on EP study (on procainamide)
- 196 patients enrolled

Results:

- 54% relative reduction (23% absolute reduction) in the risk of death from all causes

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

Evolution of studies

STUDY	YEAR	POPULATION	OUTCOME	RR/ARR
MUSTT (EPS vs. no AAR)	1999	•CAD •LVEF ≤0.40 •NSVT •Inducible VT	•Death (arrhythmic) •Cardiac arrest	0.24 (0.13-0.45)* ARR 19.5%
MADIT-II	2002	•Prior MI •LVEF ≤0.30 •NYHA I-III •No EPS required	•Death (any)	0.69 (0.51-0.93) ARR: 5.4%
SCD-HeFT	2005	•NYHA II-III HF •LVEF ≤0.35 •Includes non-ischemic	•Death (any)	0.77 (0.62-0.96) ARR: 7.2%

Buxton AE et al. NEJM 1999;341:1882-1890.
Moss AJ et al. NEJM 2002;346:877-83.
Bardy GH et a. NEJM 2005;352:225-37.

MADIT II Trial

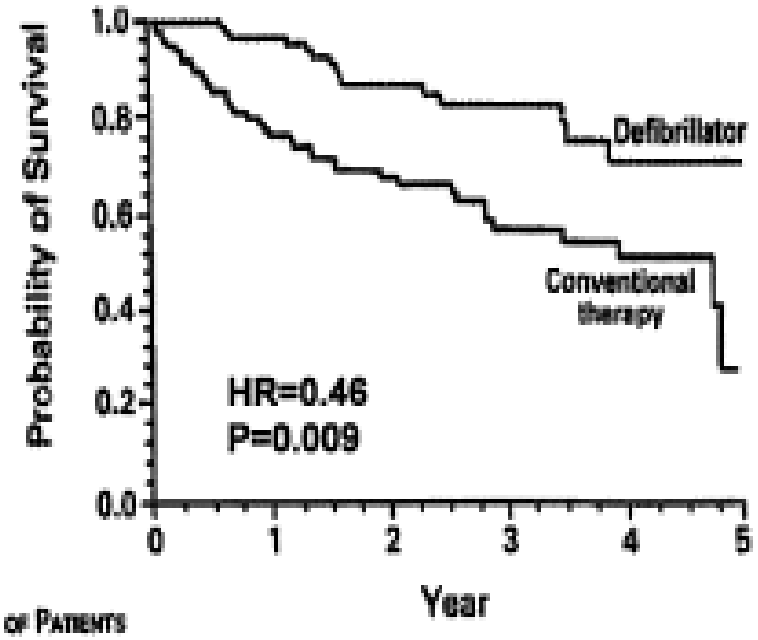
Enrollment criteria:

- NYHA functional class I-III
- Myocardial infarction at least 30 days prior to enrollment
- LVEF $\leq$0.30
- 1232 patients enrolled

Results:

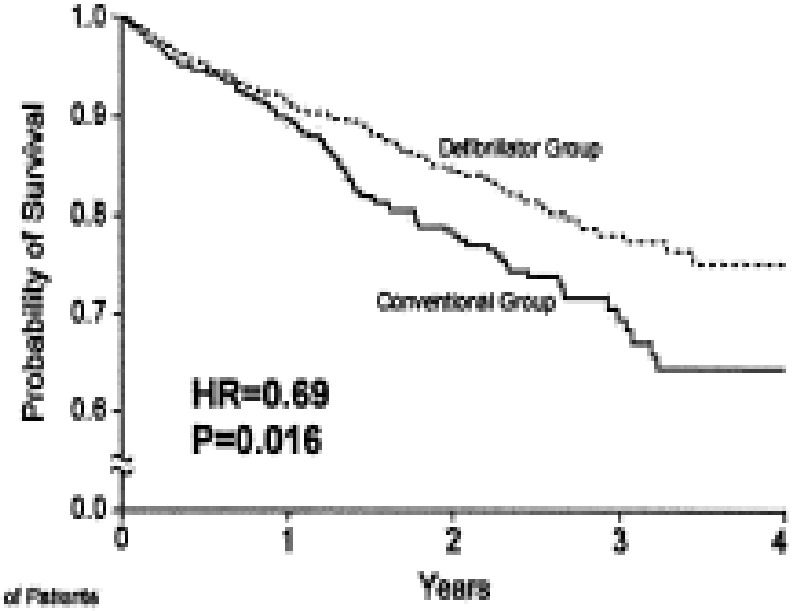
- 31% relative reduction (5.4% absolute reduction) in the risk of death from all causes

MADIT-I (1996)



No. of Patients						
Defibrillator	95	80	53	31	17	3
Conventional therapy	101	67	48	29	17	0

MADIT-II (2002)



No. of Patients					
Defibrillator	742	503	273	110	9
Conventional	490	329	170	65	3

SCD-HeFT study

Enrollment criteria:

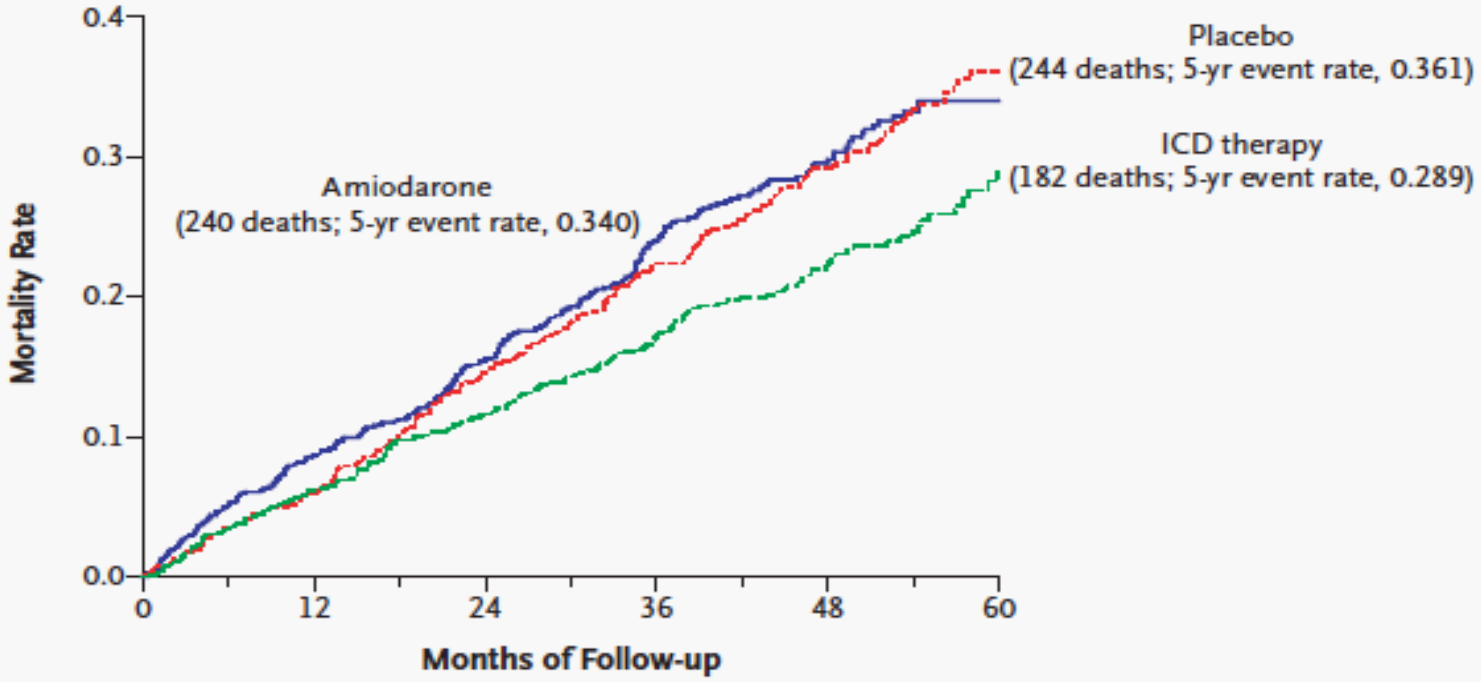
- NYHA functional class II-III
- Chronic, stable CHF with LVEF $\leq$0.35
- 2521 patients enrolled

Results:

- 23% relative risk reduction in the risk of death from all causes

Results

	Hazard Ratio (97.5% CI)	P Value
Amiodarone vs. placebo	1.06 (0.86–1.30)	0.53
ICD therapy vs. placebo	0.77 (0.62–0.96)	0.007



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

Defibrillation in Acute Myocardial Infarction Trial (DINAMIT)

Enrollment criteria:

- Age 18-80
- Recent MI (6 to 40 days), and low heart rate variability or high resting heart rate

  (Needed to have impaired autonomic dysfunction)
- LVEF $\leq$0.35
- 653 patients enrolled

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

DINAMIT: RESULTS

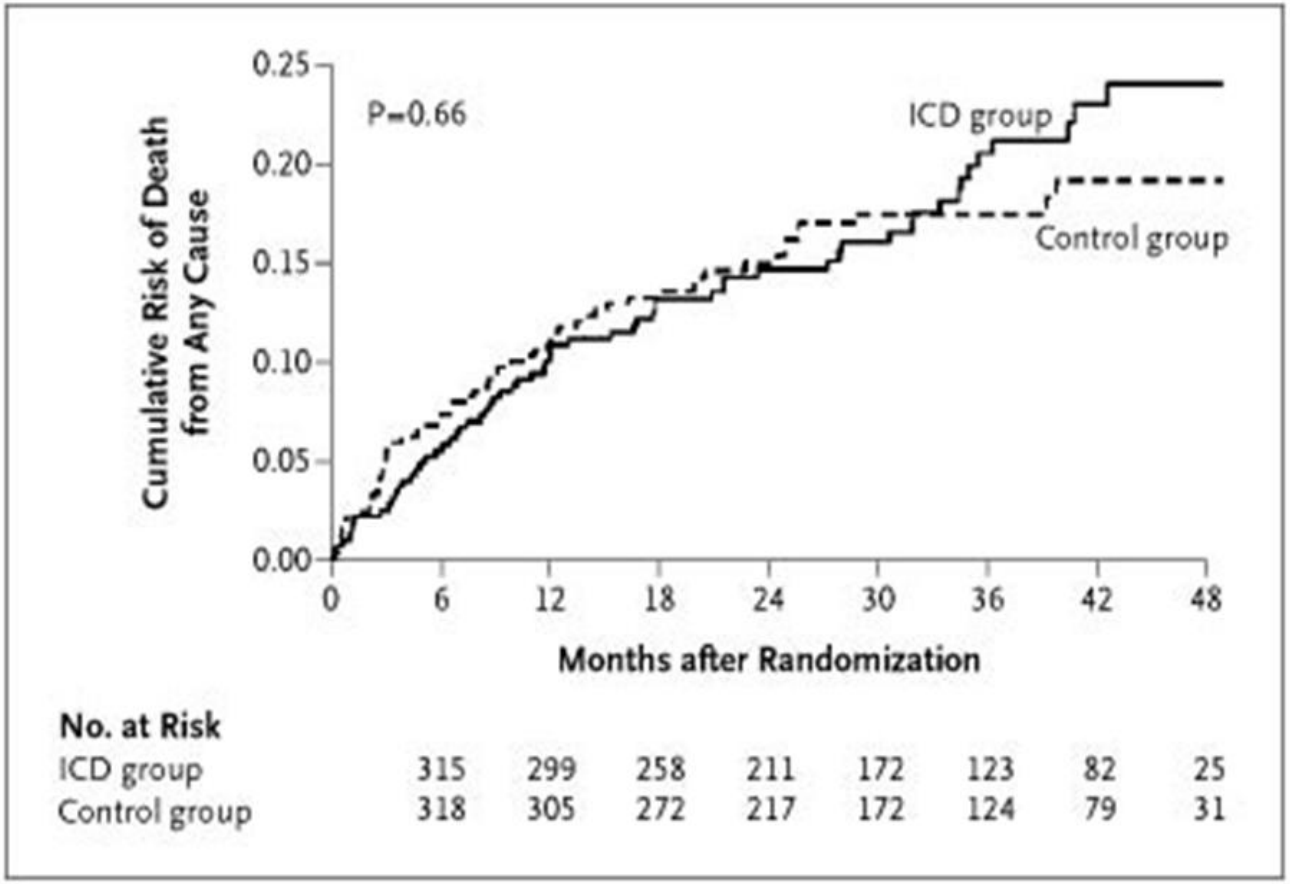
► 332 pts in ICD group and 342 in No ICD group

Table 2. Mortality Rates.*

Cause of Death	ICD Group		Control Group		Hazard Ratio (95% CI)†	P Value‡
	No. of Deaths	Rate %/yr	No. of Deaths	Rate %/yr		
Any cause	62	7.5	58	6.9	1.08 (0.76–1.55)	0.66
Arrhythmia	12	1.5	29	3.5	0.42 (0.22–0.83)	0.009
Nonarrhythmic causes	50	6.1	29	3.5	1.75 (1.11–2.76)	0.02
Cardiac, nonarrhythmic	34	4.1	20	2.4	1.72 (0.99–2.99)	0.05
Vascular, noncardiac	5	0.6	3	0.4	1.69 (0.40–7.06)	0.47
Nonvascular	11	1.3	6	0.7	1.85 (0.68–5.01)	0.22

* The data were analyzed with use of the Cox model. ICD denotes implantable cardioverter–defibrillator, and CI confidence interval.
† Hazard ratios are for the ICD group as compared with the control group.
‡ P values are two-sided.

Results


Cumulative Risk of Death from Any Cause
0.25
0.20
0.15
0.10
0.05
0.00
P=0.66
ICD group
Control group
0
6
12
18
24
30
36
42
48
Months after Randomization
No. at Risk
ICD group 315 299 258 211 172 123 82 25
Control group 318 305 272 217 172 124 79 31

DINAMIT Conclusions

- “Prophylactic ICD therapy does not reduce overall mortality in high-risk patients who have recently had a myocardial infarction”
- “Although ICD therapy was associated with a reduction in the rate of death due to arrhythmia, that was offset by an increase in the rate of death from nonarrhythmic causes”
- Helped in framing the guideline that ICD should not be placed until at least 40 days after an MI

IRIS study

- European Investigator initiated study
- Defibrillator Implantation Early after Myocardial Infarction

N Engl J Med 2006;651:1427-36.

IRIS study

- Inclusion Criteria
  - enrolled 5 to 31 days after the event
  - a reduced left ventricular ejection fraction (≤40%)
  - heart rate of 90 or more beats per minute on the first available electrocardiogram (ECG) : critreion 1
  - nonsustained ventricular tachycardia (≥150 beats per minute) during Holter monitoring : criterion 2

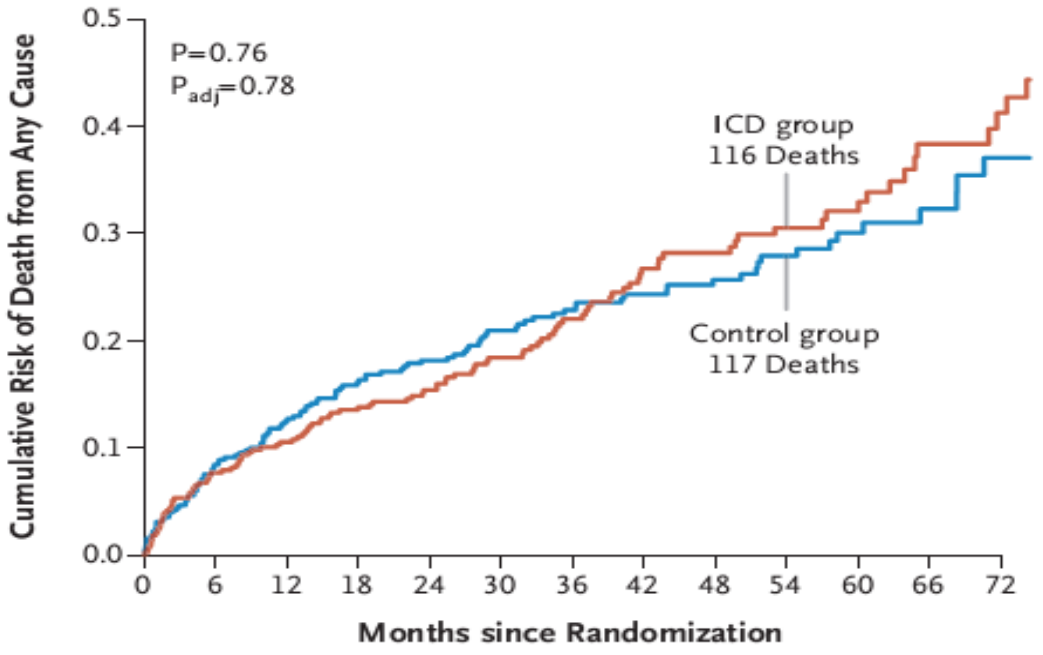
IRIS Results

Table 2. Causes of Death in the Study Groups.*

Cause of Death	ICD Group	Control Group	Subdistribution Hazard Ratio	Unadjusted P Value
	no./total no. (%)			
All patients				
Any cause	116/445 (26.1)	117/453 (25.8)	1.04	0.76
Sudden cardiac death	27/445 (6.1)	60/453 (13.2)	0.55	0.049
Nonsudden cardiac death	68/445 (15.3)	39/453 (8.6)	1.92	0.001
Noncardiac death	21/445 (4.7)	18/453 (4.0)	1.23	0.51
Patients meeting criterion 1 only				
Any cause	78/299 (26.1)	82/303 (27.1)	1.02	0.91
Sudden cardiac death	20/299 (6.7)	45/303 (14.9)	0.46	0.003
Nonsudden cardiac death	44/299 (14.7)	27/303 (8.9)	1.80	0.02
Noncardiac death	14/299 (4.7)	10/303 (3.3)	1.52	0.32
Patients meeting criterion 2 only				
Any cause	21/99 (21.2)	20/109 (18.3)	1.16	0.63
Sudden cardiac death	3/99 (3.0)	7/109 (6.4)	0.46	0.25
Nonsudden cardiac death	13/99 (13.1)	6/109 (5.5)	2.58	0.06
Noncardiac death	5/99 (5.1)	7/109 (6.4)	0.74	0.60
Patients meeting criteria 1 and 2				
Any cause	17/47 (36.2)	15/41 (36.6)	0.84	0.62
Sudden cardiac death	4/47 (8.5)	8/41 (19.5)	0.36	0.08
Nonsudden cardiac death	11/47 (23.4)	6/41 (14.6)	1.53	0.39
Noncardiac death	2/47 (4.3)	1/41 (2.4)	1.50	0.72

* The data include all deaths during a follow-up period of up to 106 months (average, 37). ICD denotes implantable car-

IRIS Results



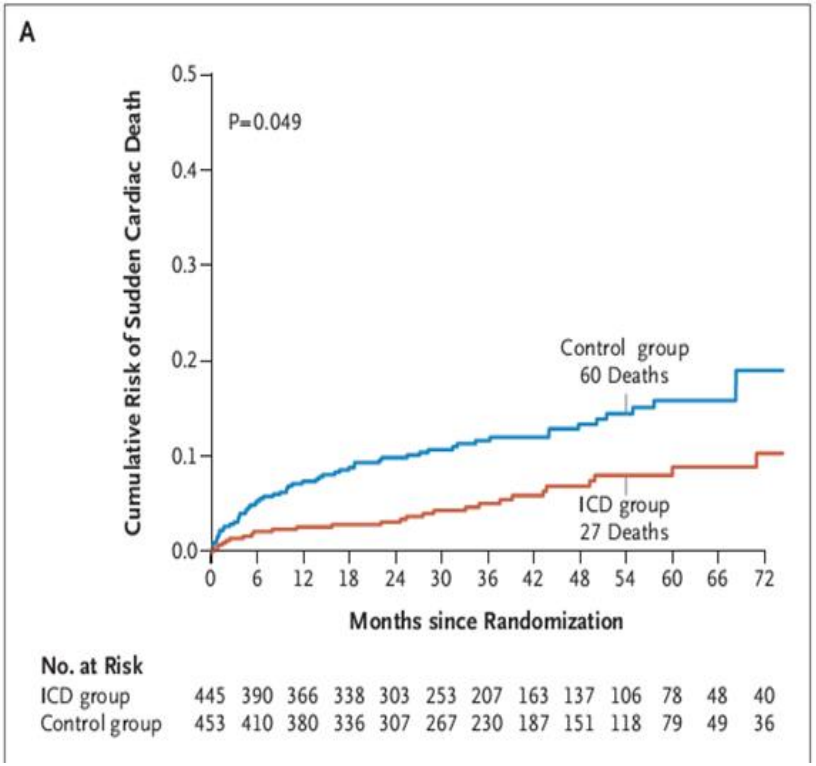
No. at Risk													
ICD group	445	390	366	338	303	253	207	163	137	106	78	48	40
Control group	453	410	380	336	307	267	230	187	151	118	79	49	36

Figure 1. Cumulative Risk of Death from Any Cause According to Study Group.

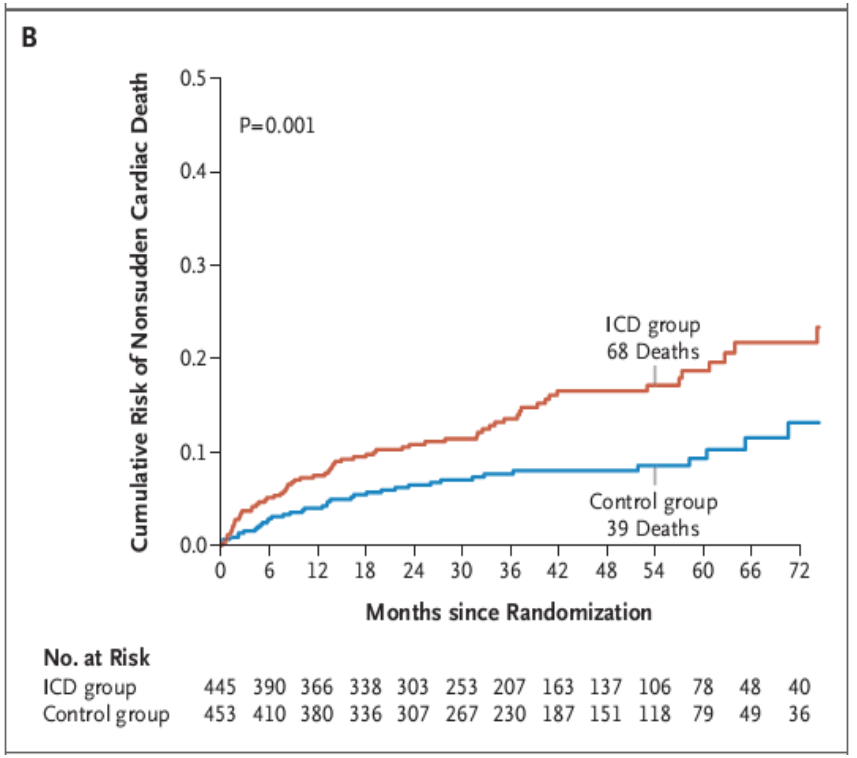
At the close of the study, definitive information about vital status was available for 897 patients. One patient was lost to follow-up. For patients who withdrew their consent, data were censored at the time of withdrawal. ICD denotes implantable cardioverter–defibrillator.

IRIS Results

Sudden cardiac death



Non-sudden cardiac death



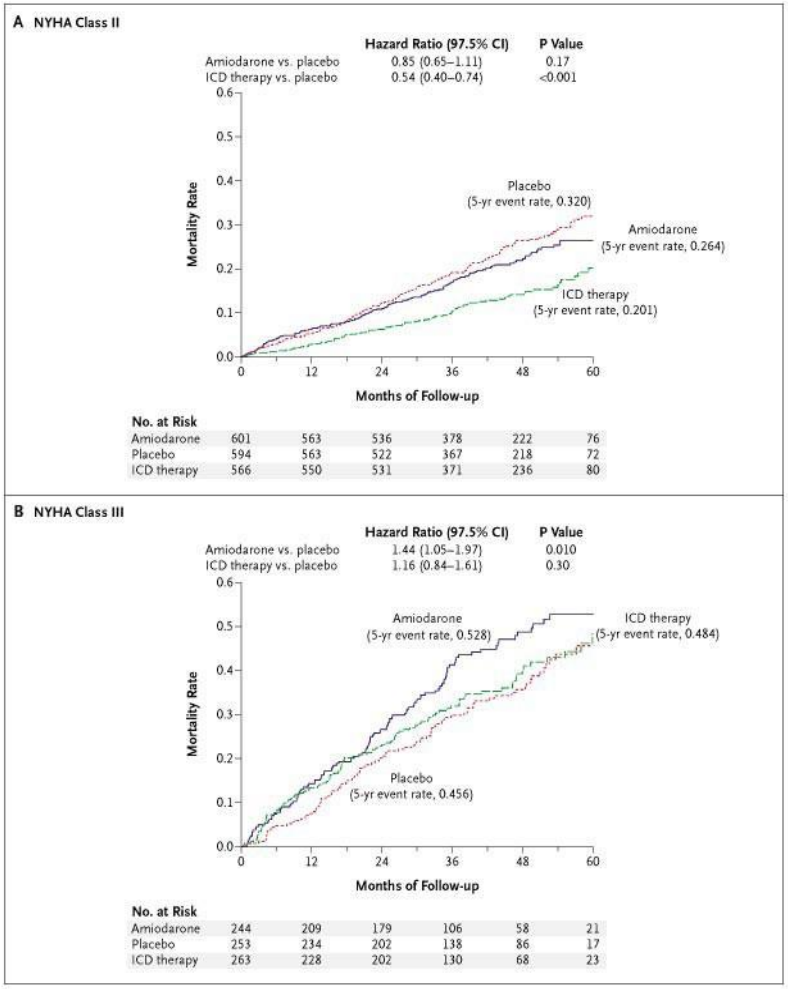
Heart failure and ICD Benefit

MADIT II

	HR	P Value
Overall ICD vs non-ICD	0.74	0.01
By HF status at trial closure		
No HF (ICD vs non-ICD)	0.52	0.002
HF (NYHA ≥ 2)	0.87	0.34

Goldenberg HRS 2009

SCD-Heft



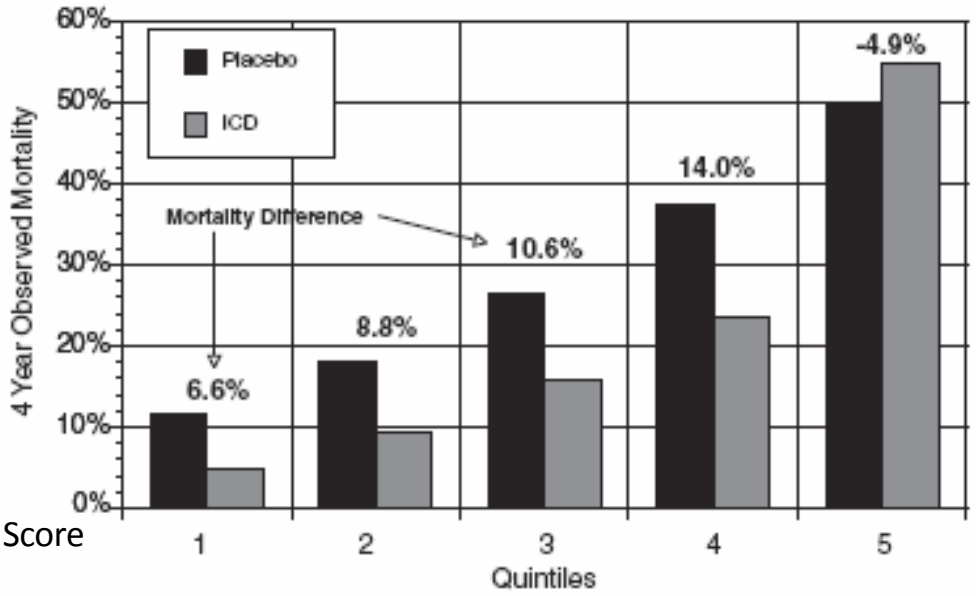
Bardy et al NEJM 2005 352:225

SCD-HeFT sub-group study by SHFM

- SHFM(Seattle Heart Failure Model)
  - validated risk prediction model based on routinely collected clinical variables
  - age, gender, ischemic origin, systolic blood pressure, ejection fraction, medication use (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, statin, and daily diuretic dose, allopurinol), serum sodium, total cholesterol, hemoglobin, percent lymphocytes, and uric acid

Circulation. 2009; 120:835-842.

Risk stratification in SCDHeft



Seattle Heart Failure Score

NNT*:	15.2	11.4	9.7	7.1	N/A

*: NNT for 1yr added life over 4yrs F/U

Levi et al Circulation 2009 120:835

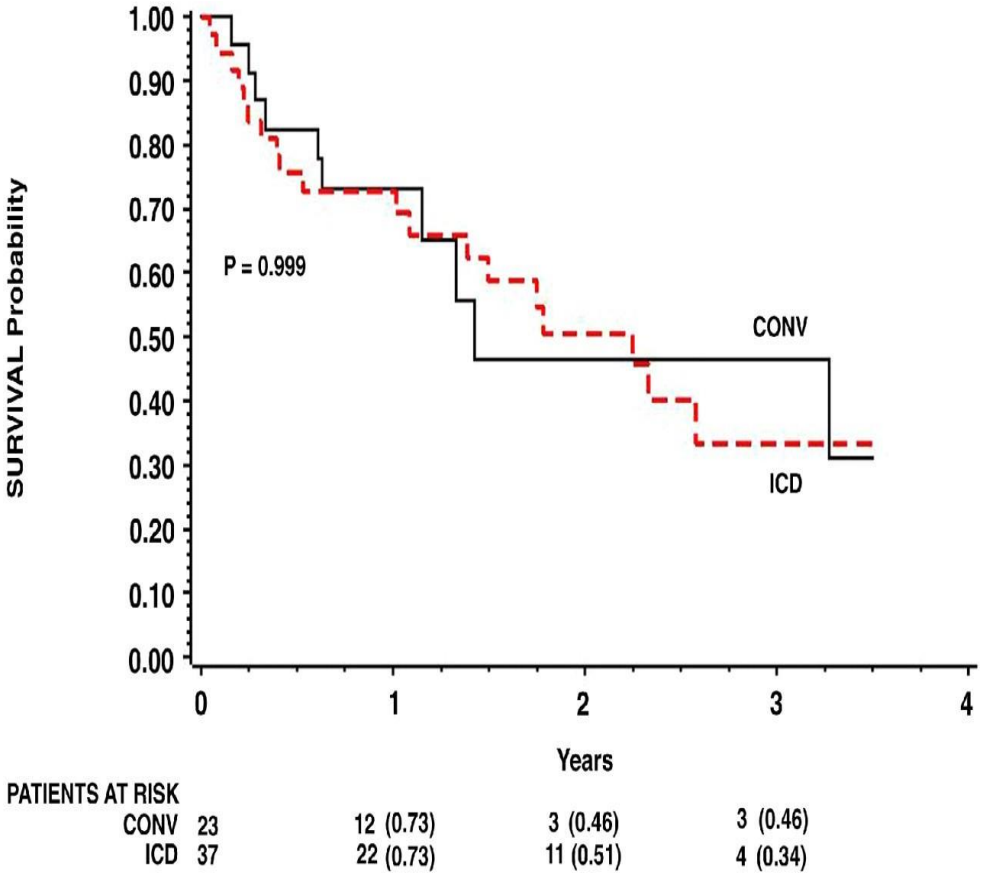
MADIT II sub-group study

Very high risk

- Cr > 2.5 mg/dl
- Urea > 50 mg/dl
- Renal disease

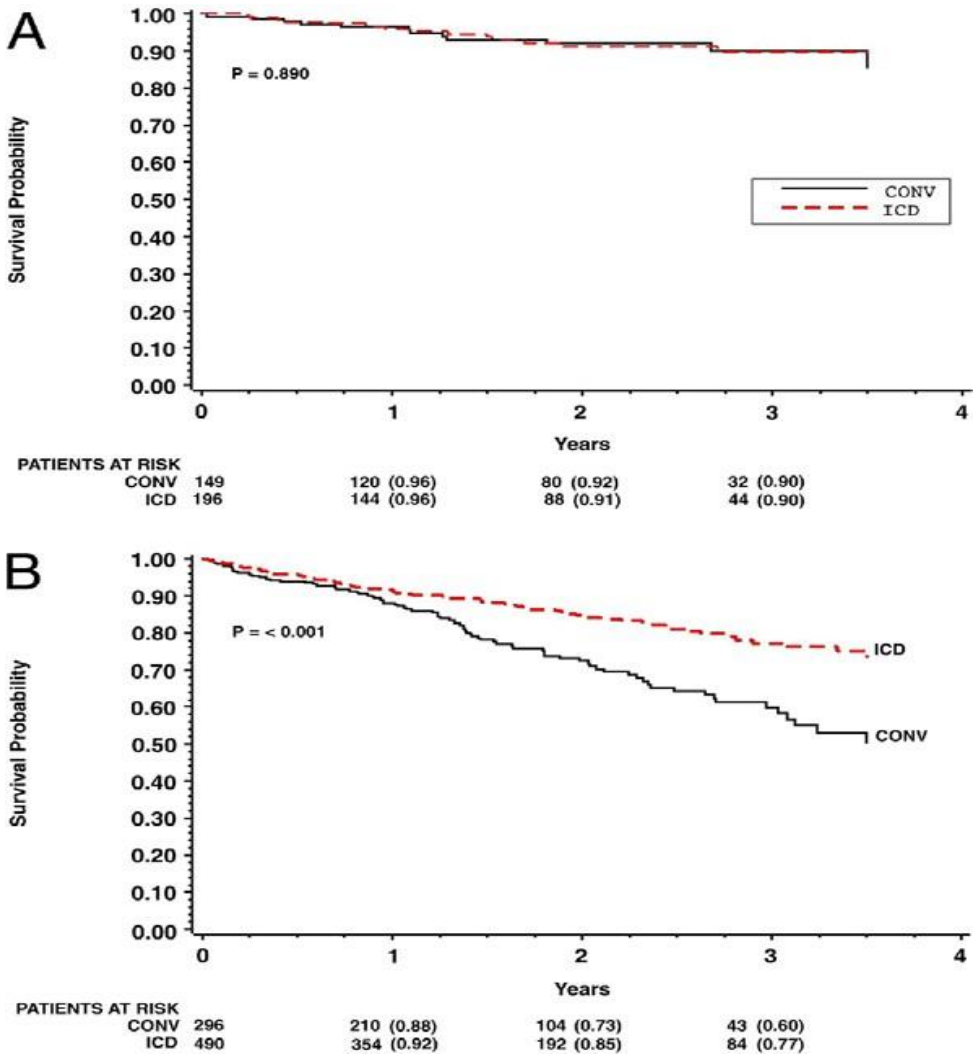
Others :Risk Score

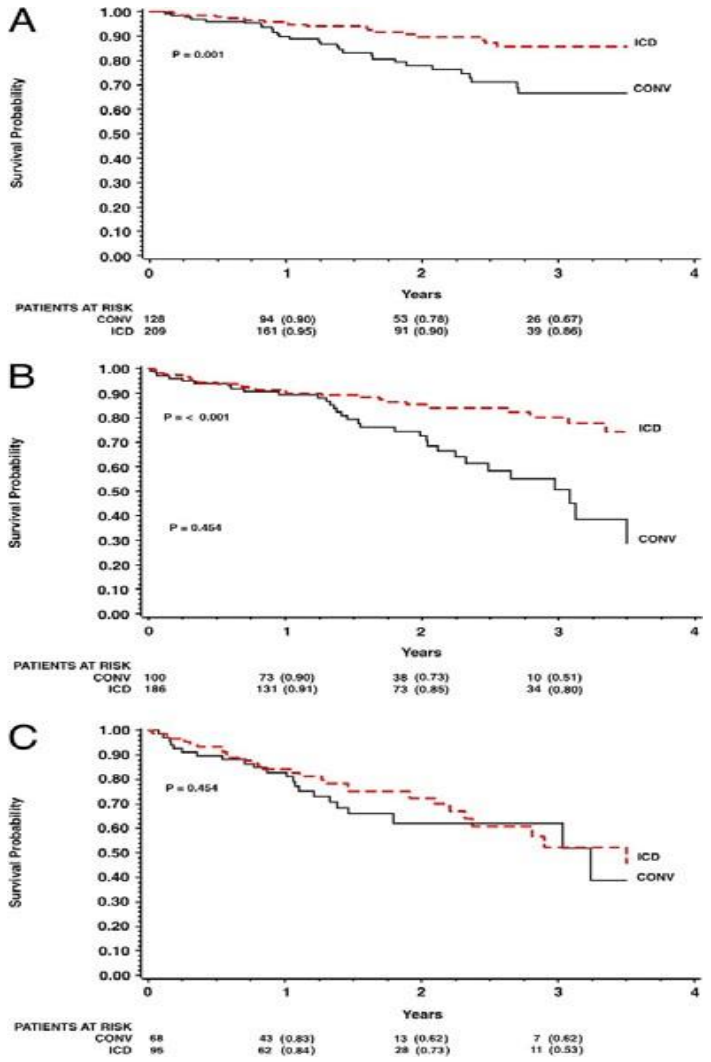
- NYHA >2
- Age >70
- Urea > 26 mg/dl
- QRS >120ms
- A Fib



Goldenberg et al JACC 2008 51:288-296

Survival by risk score





Goldenberg et al JACC 2008 51:288-296

Issue of patient selection

- ICD is not beneficial for very high risk patient due to more non-sudden cardiac death in ICD group

* Assuming patients are on chronic, optimal medical therapy and have a reasonable expectation of survival with good functional status for > 1 year.

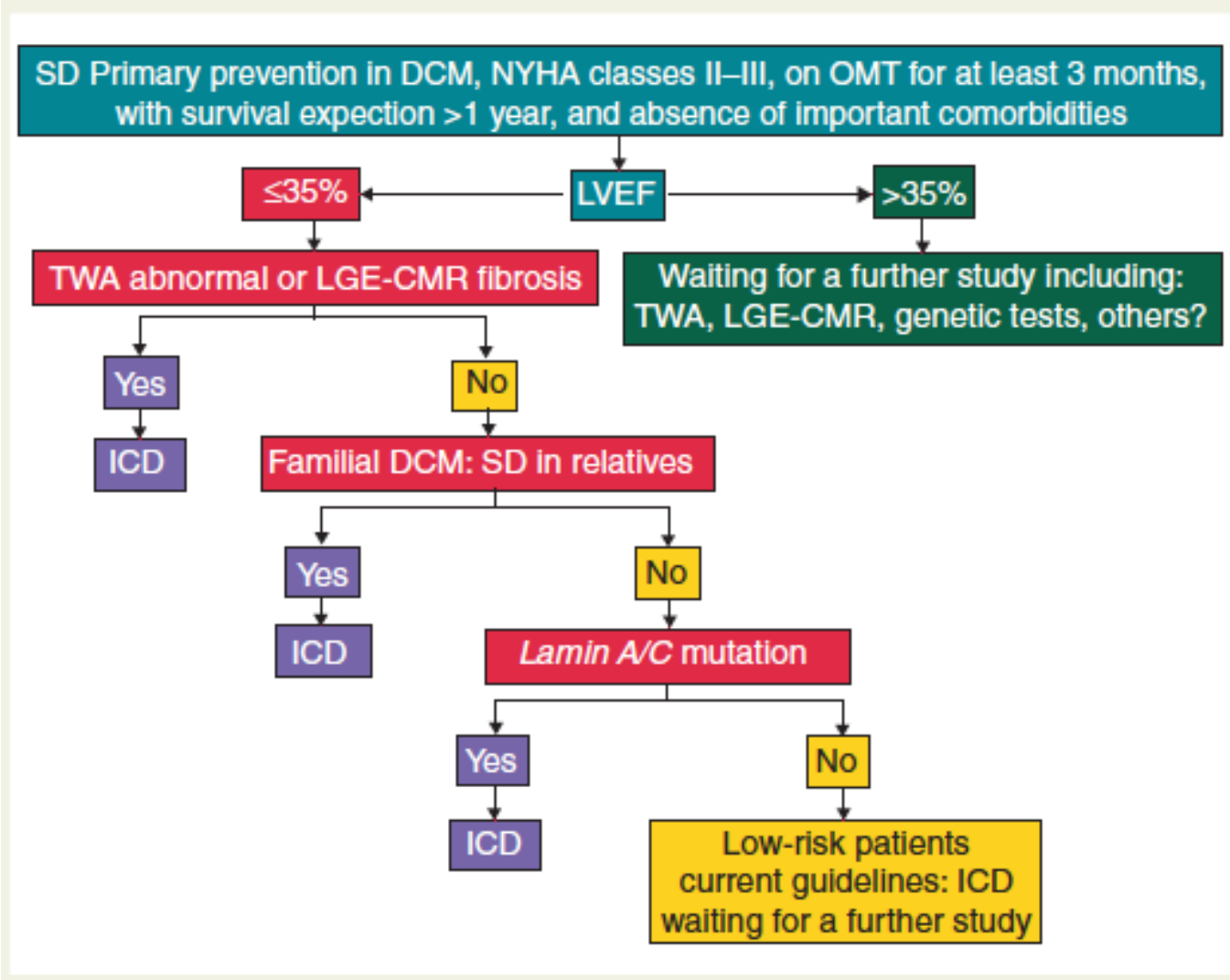
Primary prevention in non-ischemic DCM

Table 2 Randomized controlled trials on ICD primary prevention in DCM patients[3,38–40]

Study	Inclusion criteria	DCM pts (*n*)	Treatment	Mean FU m.	Hazard ratio	*P*-value
Cat[38] 2002	LVEF ≤ 30%, NYHA II–III	104	OMT vs. ICD	66	–	0.55
AMIOVIRT[39] 2003	LVEF ≤ 35%; NSVT; NYHA I–III	103	A vs. ICD	24	–	0.80
DEFINITE[40] 2004	LVEF ≤ 35%; NSVT; PVE; NYHA I–III	458	OMT vs. ICD	29	95% CI 0.65 (0.40–1.06)	0.08
SCD-HeFT DCM subgroup[3] 2005	LVEF ≤ 35%; NYHA II–III	1211	OMT vs. OMT + A vs. OMT + ICD	45.5[a]	97.5% CI 0.73 (0.50–1.07)	0.06

Europace 2013 15:1693-1701

Decision making algorithm in DCM patients



Europace 2013 15:1693-1701

Effectiveness of Implantable Cardioverter Defibrillators for Primary Prevention of Sudden Cardiac Death in Subgroups

- To examine ICD effectiveness for primary prevention of SCD across subgroups by **sex, age, New York Heart Association class, left ventricular ejection fraction, heart failure, left bundle branch block, QRS interval, time since myocardial infarction, blood urea nitrogen level, and diabetes**

- 27 articles described 10 randomized and 4 nonrandomized comparative studies of ICD versus no ICD treatment

Ann Intern Med. 2014;160(2):111-121

Results

- All 10 randomized and 4 nonrandomized studies provided consistent and precise findings of a statistically significant **benefit of ICD** to reduce all-cause mortality rates

- The 10 studies that conducted subgroup analyses did not support a statistical difference in the benefit of ICD for all-cause mortality across subgroups on the basis of **age, sex, race or ethnicity, NYHA class, LVEF, heart failure, LBBB, QRS interval, heart disease, time since MI, previous coronary revascularization, time since coronary revascularization**

Supplement Figure 2. Random-Effects Model Meta-analysis of ICD vs. No ICD for All-Cause Mortality

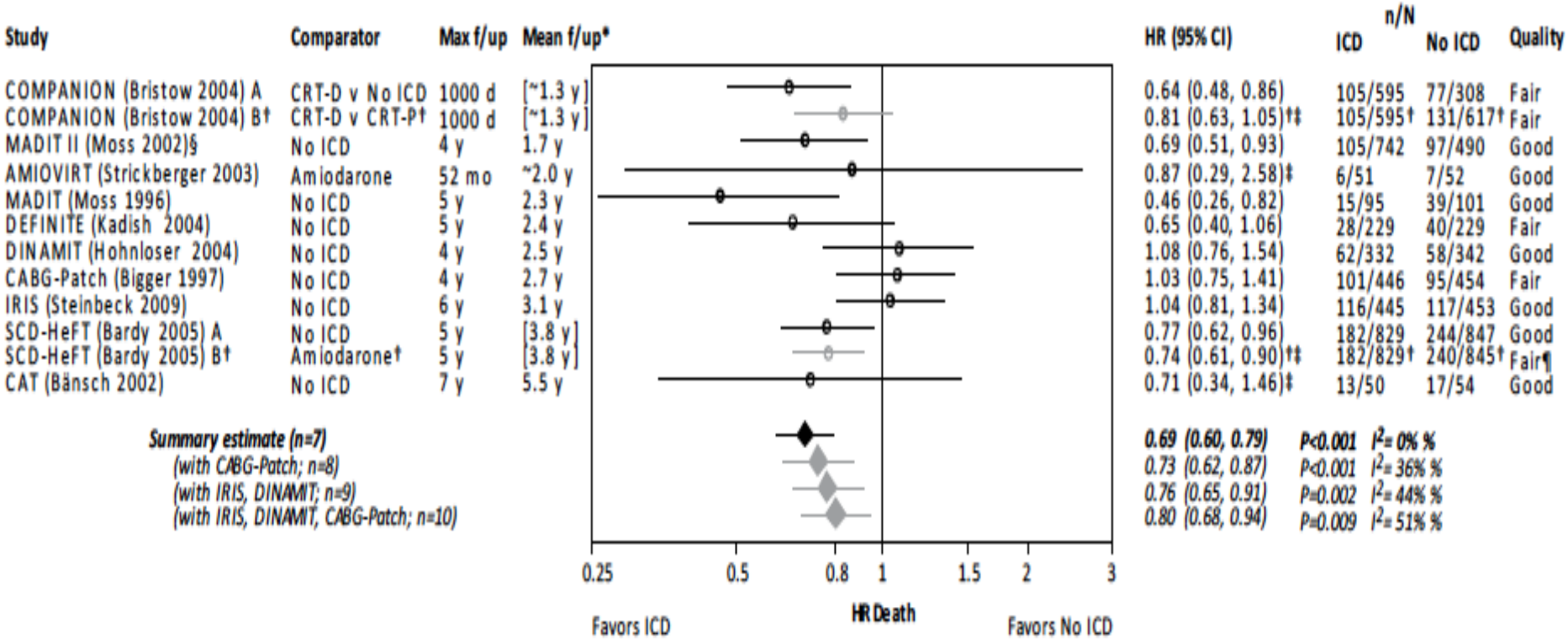


Figure 1. **Men vs. women: RORs of implantable cardioverter defibrillators vs. no implantable cardioverter defibrillators for all-cause mortality.**

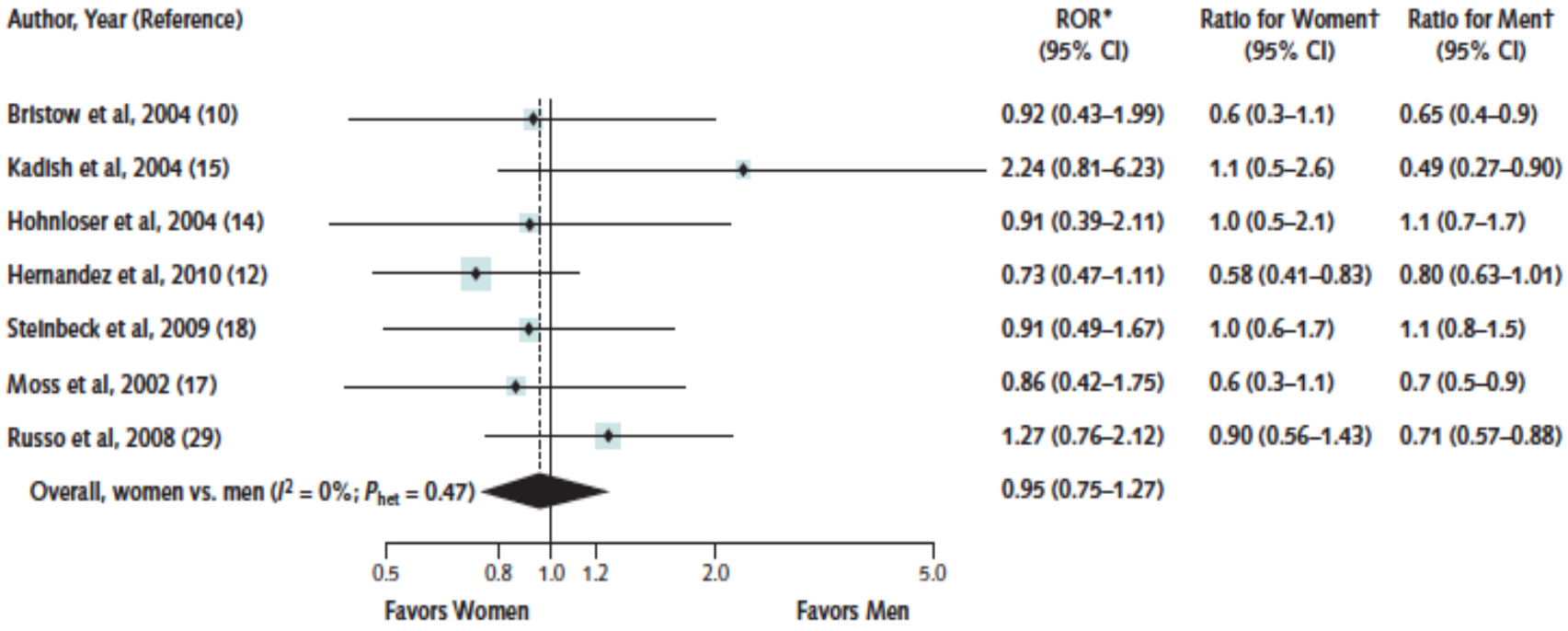
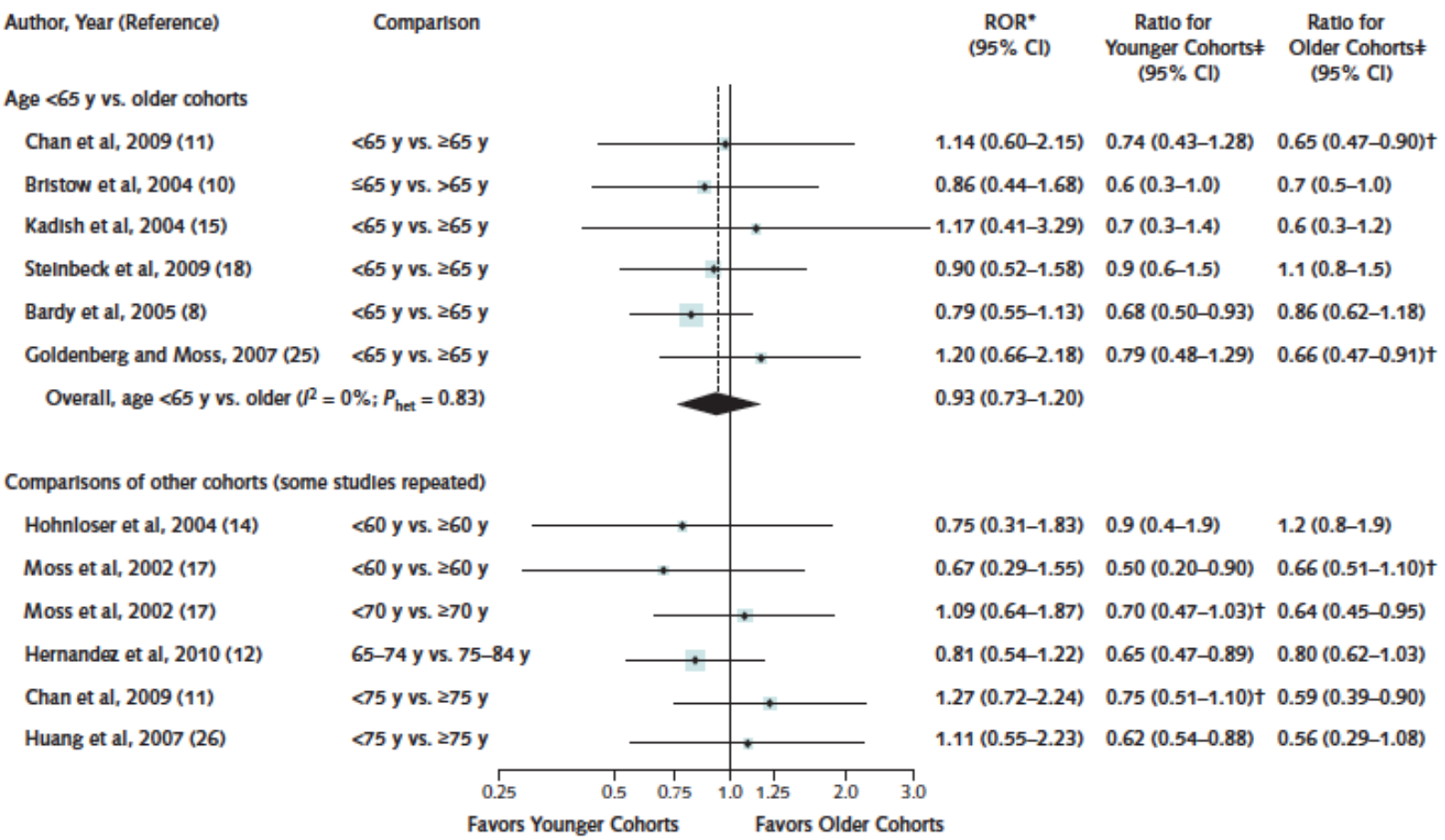


Figure 2. **Younger vs. older subgroups: RORs of implantable cardioverter defibrillators vs. no implantable cardioverter defibrillators for all-cause mortality.**



Summary

- Implantable cardioverter defibrillator therapy for primary prevention of SCD versus no ICD therapy shows benefit with regard to mortality and SCD

- Weak evidence for all-cause mortality in subgroups of sex, age, and QRS interval does not show differences

- Exploring about potentially predicting marker in non-ischemic DCM patients

- ICD is not beneficial for very high risk patient due to more non-sudden cardiac death in ICD group

Can we select more effectively?

- Heart rate variability
- T-Wave alternans
- QRS fractionation
- Genetic analysis
- Time dependent profiling