

Sudden Cardiac Death

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Caesaria - 2004

SCA Background

Sudden Cardiac Arrest (SCA) Statistics

- One of the most common causes of death in developed countries:

	Incidence (cases/year)	Survival
Worldwide	3,000,000 ¹	<1%
U.S.	450,000 ²	5%
W. Europe	400,000 ³	<5%

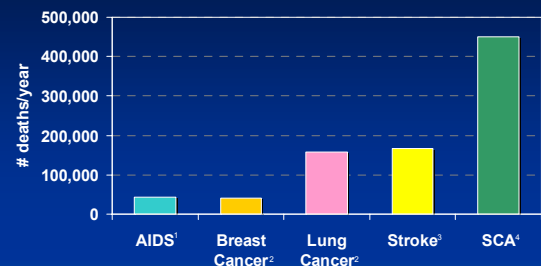
- High recurrence rate

¹ Myerberg RJ, Castellanos A. Cardiac Arrest and Sudden Cardiac Death. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 5th Ed. New York: WB Saunders. 1997: 742-779.

² *Circulation*. 2001; 104: 2158-2163.

³ Vreede-Swagemakers JJ et al. *J Am Coll Cardiol* 1997; 30: 1500-1505.

Magnitude of SCA in the U.S.



SCA claims more lives each year than these other diseases combined.

¹ U.S. Census Bureau, *Statistical Abstract of the United States* 2001.

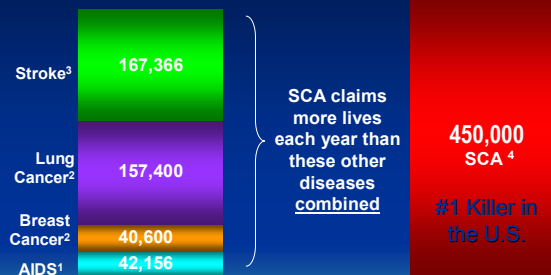
² American Cancer Society, Inc., *Surveillance Research, Cancer Facts and Figures* 2001.

³ 2002 Heart and Stroke Statistical Update, American Heart Association.

⁴ *Circulation*. 2001; 104: 2158-2163.

SCA Risk Factors

Magnitude of SCA in the US



SCA claims more lives each year than these other diseases combined

#1 Killer in the U.S.

¹ U.S. Census Bureau, *Statistical Abstract of the United States* 2001.

² American Cancer Society, Inc., *Surveillance Research, Cancer Facts and Figures* 2001.

³ 2002 Heart and Stroke Statistical Update, American Heart Association.

⁴ *Circulation* 2001; 104: 2158-2163.

Risk Factors for SCA

- Previous Myocardial Infarction (MI)
- Heart Failure and/or decreased LVEF
- Previous Sudden Cardiac Arrest Event
- Prior Episode of Ventricular Tachyarrhythmia (VT)
- Coronary Artery Disease (CAD)
- Hypertrophic Cardiomyopathy (HCM)
- Long QT, Short QT, Brugada Syndromes

A combination of these risk factors further increases the risk of SCA

Previous Myocardial Infarction

- A previous MI can be identified in as many as 75% of SCA patients.
- A previous MI raises the one-year risk of SCA by 5% as a single risk factor.
- The five-year risk of SCA for patients with a previous MI, non-sustained VT, and a LVEF ≤ 0.40 is 24%.

¹ Myerburg RJ. *Heart Disease, A textbook of Cardiovascular Medicine*, 5th ed, Vol 1. Philadelphia: WB Saunders Co, 1997:ch 24.

² De Vreede-Swagemakers JJ. *J Am Coll Cardiol*. 1997;30:1500-1505.

³ Shen WK. *Mayo Clin Proc*. 1991;66:950-962.

⁴ Buxton AE. *N Engl J Med*. 2000;342:1937-40.

Heart Failure and/or Decreased LV Function

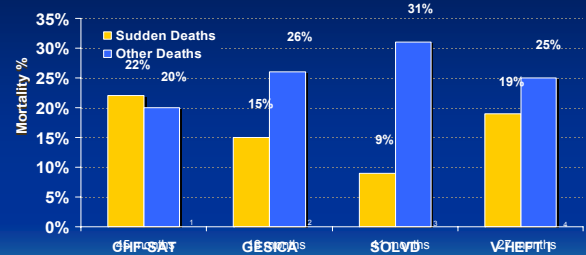
- About one-half of all deaths in heart failure patients are characterized as sudden due to arrhythmias.
- The risk of SCA increases as left ventricular function deteriorates (low LVEF).
- Unexplained syncope has predicted SCA in patients in functional NYHA Class II - IV.

¹ Myerburg RJ. *Heart Disease, A Textbook of Cardiovascular Medicine*, 5th ed, Vol 1. Philadelphia: WB Saunders Co, 1997:ch 24.

² Middlekauff HR. *J Am Coll Cardiol*. 1993;21:110-116.

³ Stevenson WE. *Circulation*. 1993;88:2953-2961.

Mortality in Placebo Arms of CHF Trials



¹ Singh, SN. *N Engl J Med*. 1995.

² Bonell, H, C. *Lancet*. 1984.

³ SOLVD Investigators. *N Engl J Med*. 1991.

⁴ Goldman, S. *Circulation*. 1993.

CHF Magnitude in the US

- \approx 5 million have CHF (prevalence)¹
- \approx 550,000 new cases annually (incidence)¹
- HF most common cardiovascular discharge in elderly patients²
- 25% probability of dying over 2.5 years³
 - 50% of these deaths occur suddenly

¹ AHA. *Heart and Stroke Statistical Update*. 2004.

² NHLBI. *CHF Data Fact Sheet*. September 1996.

³ Sweeney MO. *PACE* 2001;24:871-886.

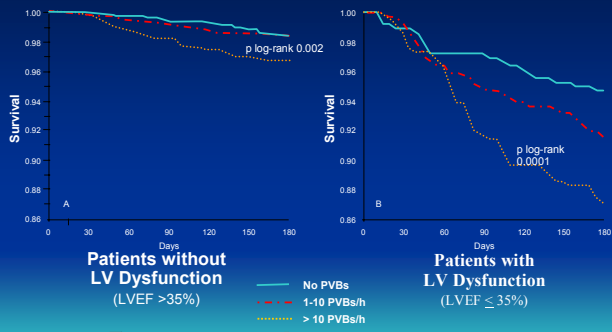
Relationship of SCD and Left Ventricular Dysfunction

- Reduced left ventricular ejection fraction (LVEF) remains **the single most important risk factor** for overall mortality and sudden cardiac death.¹
- Increased risk is measurable at ejection fractions above 30 percent, but an ejection fraction equal to or less than 30 percent is the single most powerful independent predictor for SCD.²

¹ Prior SG, Allot E, Blomstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur Heart J*. Vol. 22: 16; August 2001.

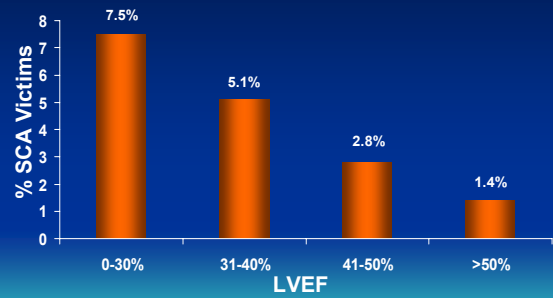
² Myerburg RJ, Castellanos A. Cardiac Arrest and Sudden Cardiac Death, in Braunwald E, Zipes DP, Libby P. *Heart Disease, A textbook of Cardiovascular Medicine*, 6th ed, 2001. W.B. Saunders, Co., p. 895.

Risk of Sudden Death: Data from GISSI-2 Trial



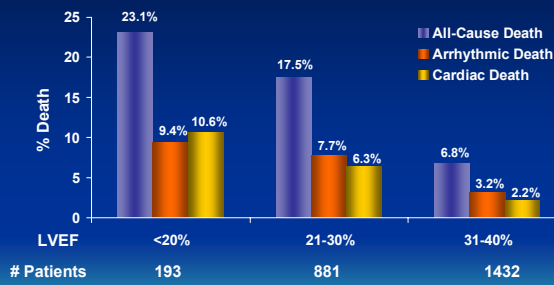
Maggioli AP. Circulation. 1993;87:312-322.

LVEF and SCA Incidence



Vreede-Swagemakers JJ. J Am Coll Cardiol. 1997;30:1500-1505.

Type of Death and LVEF

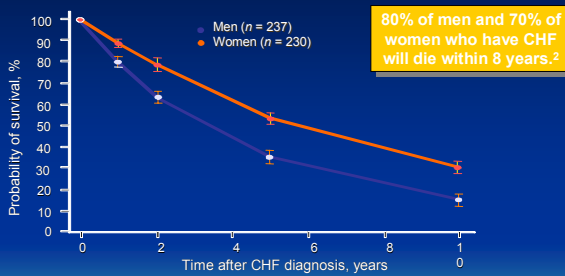


Yap Y. Heart. 2000;83:55.

In people diagnosed with CHF, sudden cardiac death occurs at **6-9 times** the rate of the general population.¹

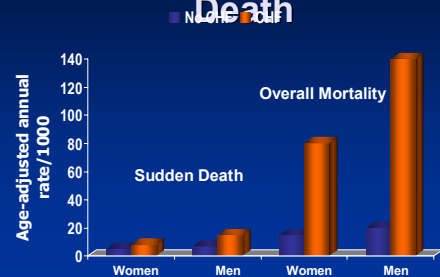
¹ American Heart Association. Heart and Stroke Statistical 2003 Update. Dallas, Tex.: American Heart Association; 2002.

CHF Patients Survival Results¹



¹ Framingham Heart Study (1948 - 1988) in Atlas of Heart Diseases.
² American Heart Association. Heart Disease and Stroke Statistics - 2003 Update.

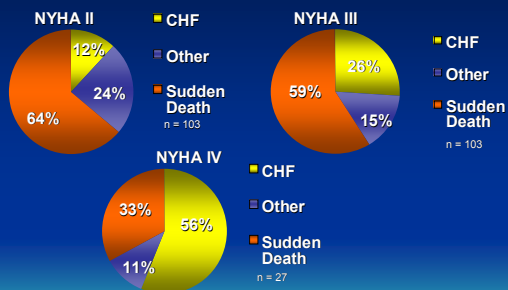
CHF and Sudden Cardiac Death



CHF Predicts increased sudden death and overall mortality. During a 39-year follow-up of subjects in the Framingham heart Study, the presence of CHF significantly increased sudden death and overall mortality in both men and women.¹

¹ Redrawn from Kannel WB, Wilson PWF, D'Agostino RB, Cobb J. Sudden coronary death in women. Am Heart J 1998 Aug; 136: 205-212

Severity of Heart Failure Modes of Death



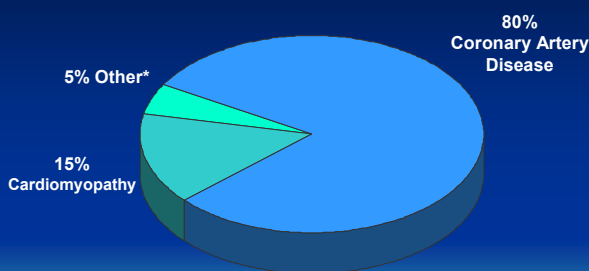
MERIT-HF Study Group. Effect of Metoprolol CRXL in chronic heart failure: Metoprolol CRXL randomized intervention trial in congestive heart failure (MERIT-HF). *LANCET*. 1999;353:2001-07.

SCD in Heart Failure ^{1, 2}

- Despite improvements in medical therapy, symptomatic HF still confers a 20-25% risk of pre-mature death in the first 2.5 yrs after diagnosis.
- ≈ 50% of these premature deaths are SCD (VT/VF)

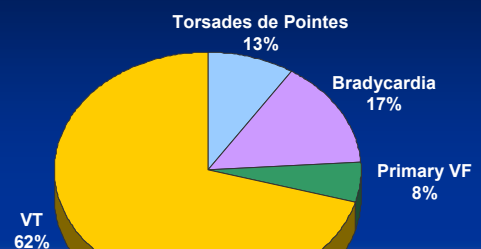
¹ Bardy G. The Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT) in Woosley RL, Singh S. *Arrhythmia Treatment and Therapy*. Copyright 2000 by Marcel Dekker, Inc. pp. 323-342.
² Sweeney MO. *PACE* 2001;24:871-888.

Underlying Causes of Fatal Arrhythmias



Adapted from Heikkinen et al. *N Engl J Med*, Vol. 345, No. 20, 2001.
 * Ion-channel abnormalities, valvular or congenital heart disease, other causes

Underlying Arrhythmias of SCA



Adapted from Bayés de Luna A. *Am Heart J*. 1989;117:151-159.

Conclusions on SCA

- Post-MI patients with a low left ventricular ejection fraction are at risk for SCA.
- SCA can be prevented if high-risk patients are identified and referred to an Electrophysiologist (EP).

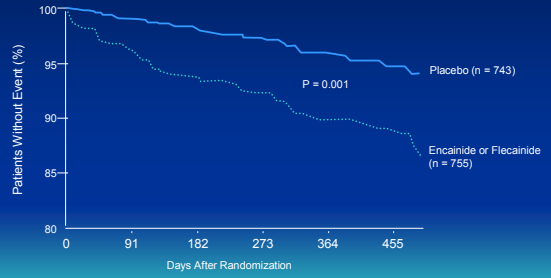
PREVENTION OF SCD

Overview of Antiarrhythmic Drug and ICD Trials

Antiarrhythmic Drug Trials

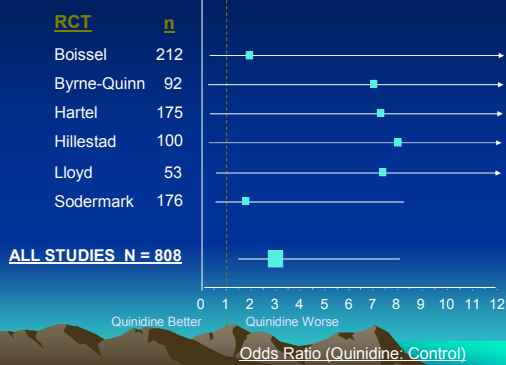
ICD Trials

CAST 1 – Prognosis of Post-MI Patients



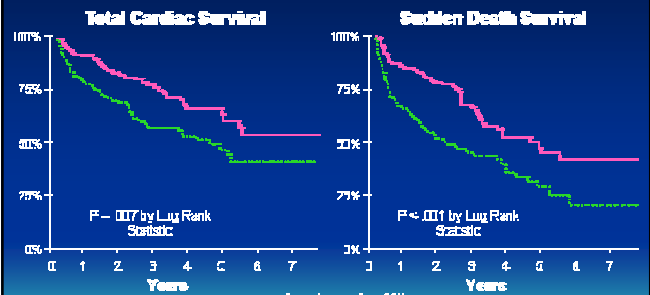
Echt DS. *N Engl J Med.* 1991;324:781-788.

Odds Ratio for Total Mortality - Quinidine vs Control



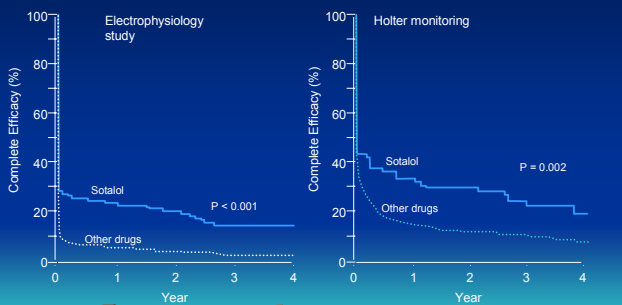
Coplen SE. *Circulation.* 1990;82:1106-1116.

CASCADE Survival



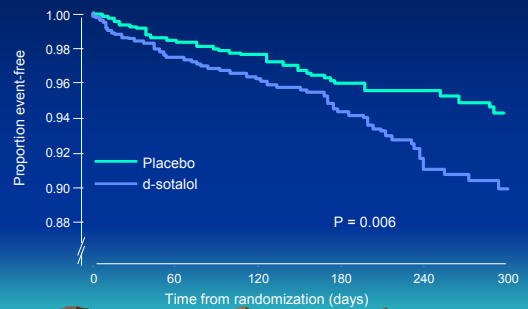
CASCADE Investigators. *Am J Cardiol.* 1992;72:208-207.

ESVEM Results



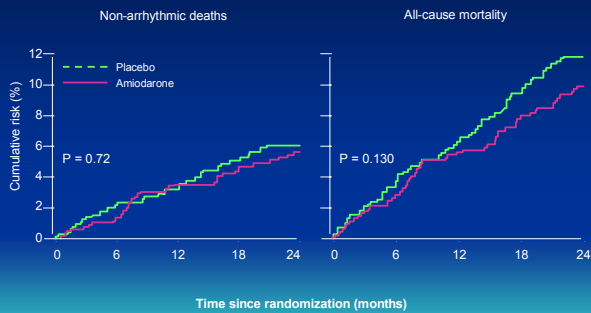
Mason JW. *N Engl J Med.* 1993;320(7):452-458.

SWORD – Survival with d-sotalol vs. Placebo



Waldo AL. *Lancet.* 1996;348:7-12.

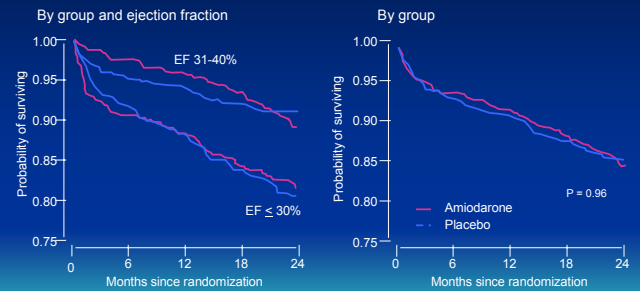
CAMIAT Results



Carmé JA. Lancet. 1997;349:675-682.

EMIAT Results

All Cause Mortality



Julian DG. Lancet. 1997;349:667-674.

Summary of EMAIT / CAMIAT

- Amiodarone shows a slight improvement in mortality.
- The benefit of amiodarone may be greater in the non-ischemic group but may not be sufficient to adequately protect patients from SCD.

Coman, J. Sudden Cardiac Death: Therapy in Evolution. October 2001.

New Class III AA Drugs

- ALIVE studies - There was no difference in all-cause mortality between **Azimilide** and placebo in both the high-risk group (hazard ratio [HR] =0.95, p=NS) and the entire at risk group (HR=1.0, p=NS).
- DIAMOND Studies (Post MI & CHF) – **Dofelide** has no effect on mortality when compared to placebo.

Summary of Drug Trials

At present, regardless of underlying heart disease, currently used specific AA drugs **do not improve survival**. Furthermore, some of them are **harmful**.

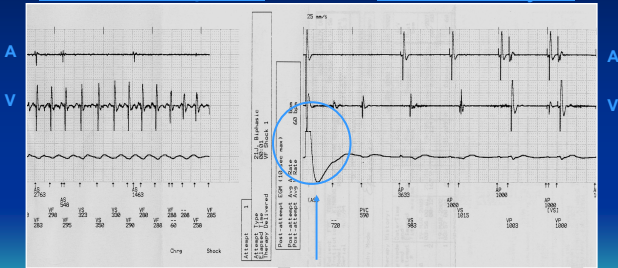
Antiarrhythmic Drug Trials

ICD Trials

ICD Discharge

Ventricular Tachycardia

Paced/Sinus Rhythm



Primary Prevention

Secondary Prevention

AVID

Inclusion Criteria

- VF
- VT with syncope
- VT without syncope, but with hemodynamic compromise, in patients with LVEF < 40%.

AVID

Size and Scope of Study

- Multicenter, prospective, randomized, unblinded.
- 4621 patients qualified.
- 1016 patients randomized to ICD or antiarrhythmic drugs (amiodarone or sotalol).
- Primary endpoint: all-cause mortality .

N Engl J Med. 1997;337(22):1576-83

AVID

Results:

- Reduction in mortality for ICD patients compared to patients managed with Class III antiarrhythmic drugs:
- One year 39%
- Two years 27%
- Three years 31%
- (Hazard ratio = 0.62, $P < 0.02$)

Conclusion:

- The ICD was superior to antiarrhythmic drug therapy in prolonging survival among AVID patients.

N Engl J Med. 1997;337(22):1576-83

CIDS

- Secondary prevention trial.
- Purpose: To compare implantable cardioverter defibrillator (ICD) therapy vs. amiodarone in patients with prior cardiac arrest or hemodynamically unstable VT.
- ICD arm = 328 patients; Amiodarone arm = 331 patients.
- 30% of ICD group and 22% of amio groups crossed over.

Circulation 2000; 101: 1297-1302.

CASH

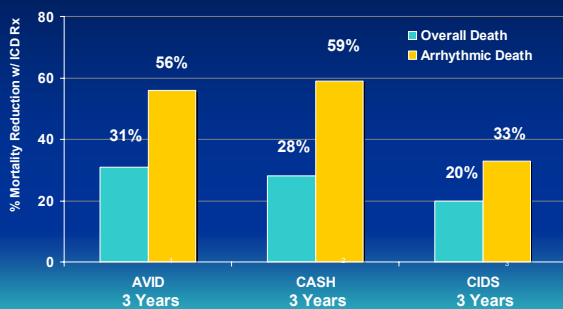
- Patients resuscitated from cardiac arrest.
- 4 groups of treatment, 100 patients each.
- Randomization to: ICD, Amiodarone, Sotalol & Propafenone.
- Propafenone discontinued because of increased mortality.

Secondary Prevention ICD Trials Results

	ICD	AA	Total Mortality Reduction
AVID¹	507	509	31%
CASH²	99	199	28%
CIDS³	378	331	19.6% NS

1 The AVID Investigators. N Engl J Med. 1997;337:1576-83.
2 Kuck K. Circ. 2000;102:748-54.
3 Connolly S. Circ. 2000;101:1297-1302.

Secondary Prevention Trials: Reduction in Mortality with ICD Therapy



1 The AVID Investigators. N Engl J Med. 1997;337:1576-83.
2 Kuck K. Circ. 2000;102:748-54.
3 Connolly S. Circ. 2000;101:1297-1302.

Primary Prevention

Secondary Prevention

CABG-Patch Trial Design

- Primary prevention trial
- Hypothesis: Prophylactic ICD implantation will improve the survival of patients:
 - Receiving CABG surgery
 - Having an EF < 36%
 - Having a positive signal averaged ECG
- 900 patients enrolled
- Used epicardial ICD lead systems

New Engl J Med. 1997; 337:1569-1575

CABG-Patch Trial Results

- Terminated early.
- Prophylactic ICD implantation did not appear to improve survival in patients with CAD, LV dysfunction, and abnormal SAECG who undergo elective CABG.
- Effect of coronary revascularization may exceed effect of ICD implantation in a patient population whose control group has a lower mortality than MADIT or AVID.
- Sustained ventricular arrhythmias appear to be a more specific marker than abnormal SAECG in identifying patients at risk for SCD.

New Engl J Med. 1997; 337:1569-1575

Clinical Trials of ICD Therapy in Post-MI Patients

ICD Clinical Trials in Post-MI Patients

MADIT

Multicenter Automatic Defibrillator Implantation Trial
Moss AJ. *N Engl J Med*. 1996;335:1933-40.

MUSTT

Multicenter Unsustained Tachycardia Trial
Buxton AE. *N Engl J Med*. 1999;341:1882-90.

MADIT-II

Multicenter Automatic Defibrillator Implantation Trial-II
Moss AJ. *N Engl J Med*. 2002;346:877-83.

MADIT Multicenter Automatic Defibrillator Implantation Trial

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

MADIT Hypothesis

In patients with a previous MI and LV dysfunction, prophylactic therapy with an ICD can improve survival versus treatment with conventional medical therapy.

Moss AJ. *N Engl J Med*. 1996;335:1933-1940.

MADIT Endpoints

Primary:

- Total mortality

Secondary:

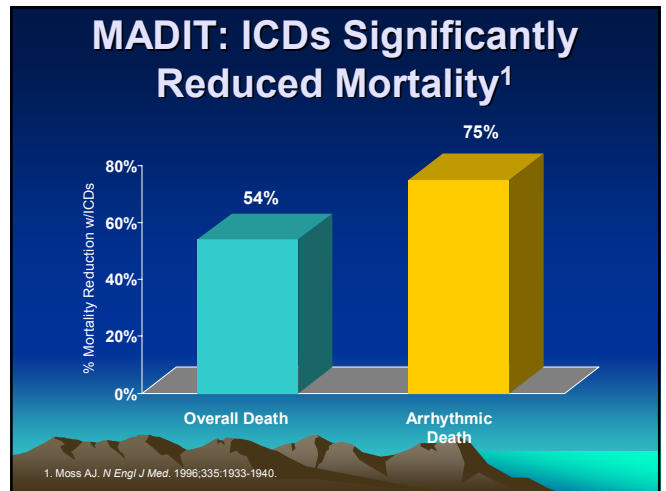
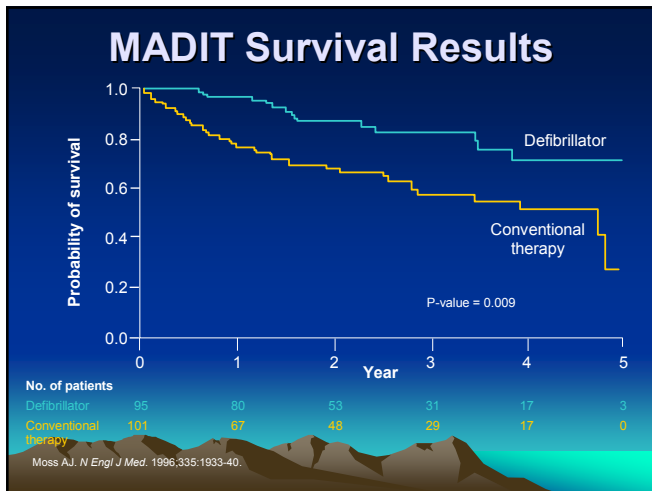
- Arrhythmic mortality
- Costs and cost effectiveness

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

MADIT Inclusion Criteria

- Q-Wave MI \geq 3 weeks
- Asymptomatic, unsustained VT
- LVEF \leq 35%
- Inducible, non-suppressible VT on EP testing w/procainamide
- NYHA Class I-III
- Age 25-80
- No requirement for revascularization

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



MADIT Conclusion

In post-MI patients at a high risk for VT, **prophylactic therapy with an implanted defibrillator reduced overall mortality by 54% and arrhythmic mortality by 75%** compared with conventional medical therapy.

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

MUSTT

Multicenter UnSustained Tachycardia Trial

Buxton AE. *N Engl J Med.* 1999;341:1882-90

MUSTT Hypothesis

Antiarrhythmic (AA) therapy guided by EP testing can reduce the risk of arrhythmic death and cardiac arrest in patients with:

- CAD
- EF \leq 0.40
- Asymptomatic nonsustained VT (> 3 beats, < 30 sec, rate > 100 bpm)

Buxton AE. *N Engl J Med.* 1999;341:1882-90

MUSTT Inclusion Criteria

- CAD
- LVEF \leq 0.40
- Asymptomatic, unsustained VT
- Inducible VT on EP testing

Buxton AE. *N Engl J Med.* 1999;341:1882-90

MUSTT Endpoints

Primary:

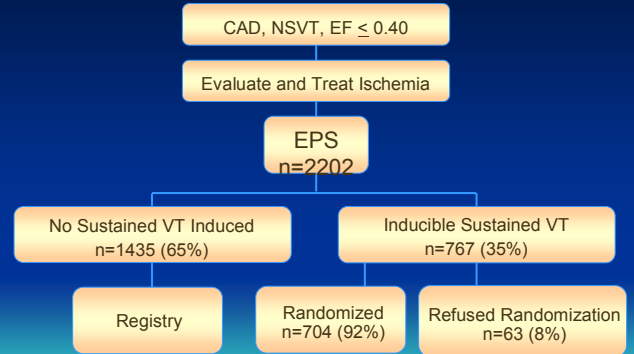
- Arrhythmic death or cardiac arrest

Secondary:

- Total mortality
- Cardiac mortality
- Spontaneous, sustained VT

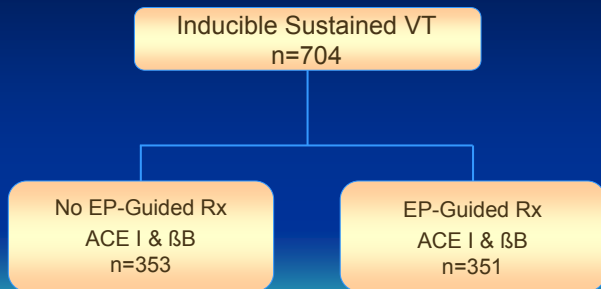
Buxton AE. *N Engl J Med.* 1999;341:1882-90

MUSTT Initial Protocol



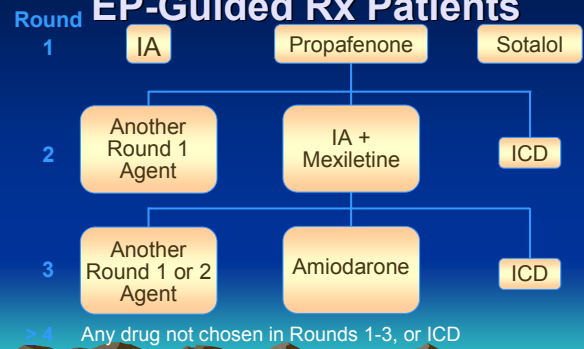
Buxton AE. *N Engl J Med.* 1999;341:1882-90.
Buxton AE. *N Engl J Med.* 2000; 342: 1937-40.

MUSTT Protocol Randomized Treatment Groups



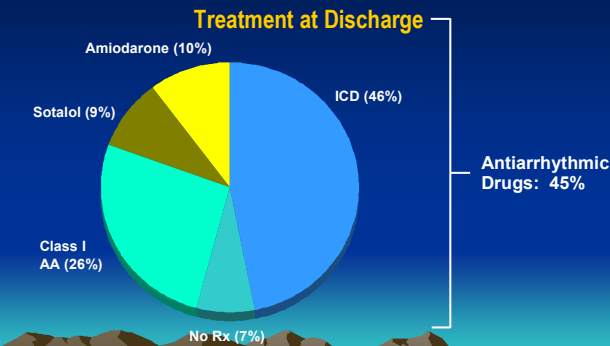
Buxton AE. *N Engl J Med.* 1999;341:1882-90.

MUSTT Protocol EP-Guided Rx Patients



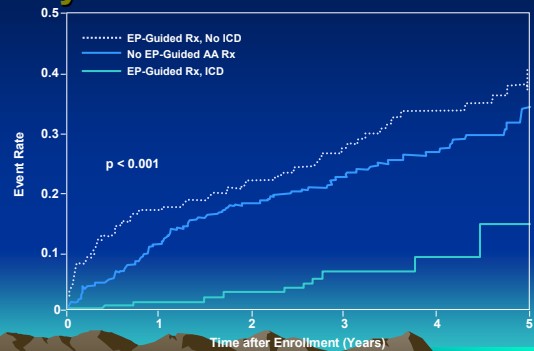
Buxton AE. *N Engl J Med.* 1999;341:1882-90.

MUSTT EP-Guided Rx Patients



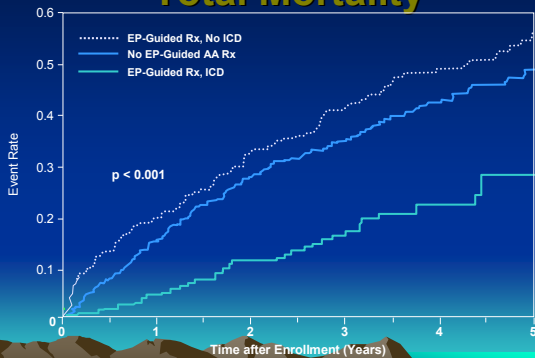
Buxton AE. *N Engl J Med.* 1999;341:1882-90.

MUSTT Randomized Patient Results: Arrhythmic Death or Cardiac Arrest



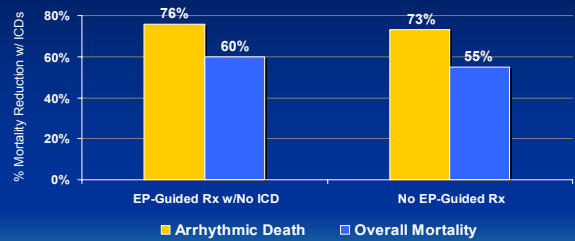
Buxton AE. *N Engl J Med.* 1999;341:1882-90.

MUSTT Randomized Patient Results: Total Mortality



Buxton AE. *N Engl J Med.* 1999;341:1882-90.

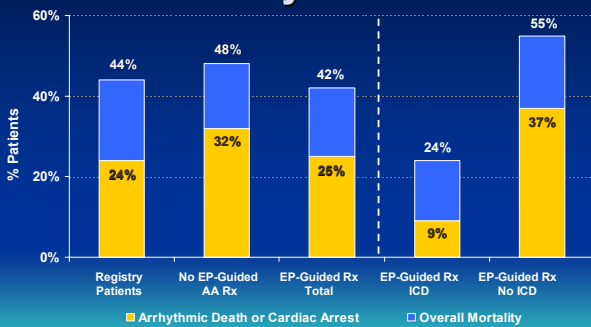
MUSTT: ICDs Significantly Reduce Mortality



* $P < 0.001$ for adjusted estimates of relative risk for each end point. Adjusted estimates were made from all available clinical and prognostic factors.

Buxton AE. *N Engl J Med.* 1999;341:1882-90.

MUSTT Patient Results Mortality/5 Years



Buxton AE. *N Engl J Med.* 1999;341:1882-90.
Buxton AE. *N Engl J Med.* 2000;342:1937-45.

MUSTT Conclusions

For post-MI patients with $EF \leq 40\%$, and asymptomatic NSVT:

- 44% death rate in Registry Patients (non-inducible VT)
- ICD therapy significantly reduced the incidence of death in the patients with inducible VT:
 - Arrhythmic death or cardiac arrest (73% – 76% reduction)
 - Overall mortality (55% – 60% reduction)
- EP-guided pharmacologic antiarrhythmic therapy provides no survival benefit

Buxton AE. *N Engl J Med.* 1999;341:1882-90.
Buxton AE. *N Engl J Med.* 2000;342:1937-45.

MADIT II

Multicenter Automatic Defibrillator Implantation Trial - II

Moss AJ. *N Engl J Med.* 2002;346:877-83.

MADIT-II Hypothesis

ICD therapy is able to reduce overall mortality assuming:

- Mortality in control = 19%
- Mortality in ICD = 11.8%
- 38% reduction in mortality at 2 years

Moss AJ. *N Engl J Med.* 2002;346:877-83.

MADIT-II Inclusion Criteria

- Q-wave MI \geq 4 weeks
- LVEF \leq 0.30
- \geq 21 years of age; no upper age limitation
- No requirement for NSVT or EPS

Moss AJ. *N Engl J Med.* 2002;346:877-83.

MADIT-II Endpoints

Primary:

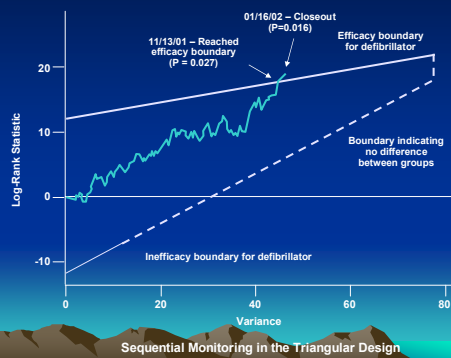
- All cause mortality (intention-to-treat analysis)

Secondary:

- Predictability of ICD discharge based on VT inducibility at EPS
- Usefulness of SAECG, HRV, TWA in predicting mortality or ICD discharge
- Cost-effectiveness
- Quality of life

Moss AJ. *Ann Noninvasive Electrocardiol.* 1999;4:83-91.

MADIT-II Statistical Analysis Triangular Sequential Design



Moss AJ. *N Engl J Med.* 2002;346:877-83.

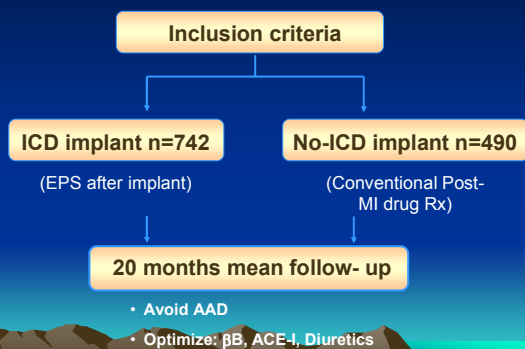
MADIT-II Treatment Arms

Randomized 1,232 patients using a 3:2 ratio (ICD: non-ICD):

- 742 patients: ICD + conventional post-MI Rx
- 490 patients: Conventional post-MI Rx

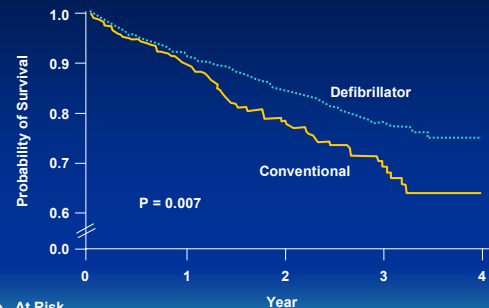
Moss AJ. *N Engl J Med.* 2002;346:877-83.

MADIT-II Protocol



Moss AJ. *N Engl J Med.* 2002;346:877-83.

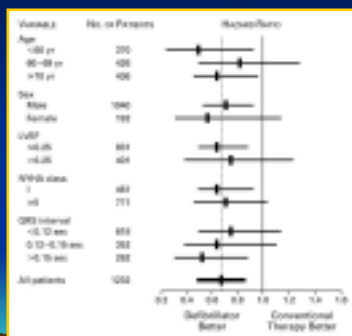
MADIT-II Survival Results



No. At Risk	Year 0	Year 1	Year 2	Year 3	Year 4
Defibrillator	742	502 (0.91)	274 (0.94)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

Moss AJ. *N Engl J Med.* 2002;346:877-83.

MADIT-II Survival Results – Subgroup Analyses



Moss AJ. *N Engl J Med.* 2002;346:877-83.

MADIT-II Conclusions

For post-MI patients with LVEF \leq 30%:

- ICD therapy significantly reduced the incidence of overall mortality by 31%
- ICD therapy provided significant benefit among patients who were on optimal drug therapies.

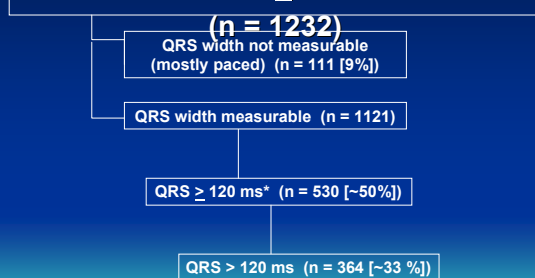
Moss AJ. *N Engl J Med.* 2002;346:877-83.

MADIT II QRS width sub-study

Noninvasive ECG Parameters in Multivariate Cox Model for Predicting Total Mortality in MADIT II Patients Randomized to Conventional Therapy

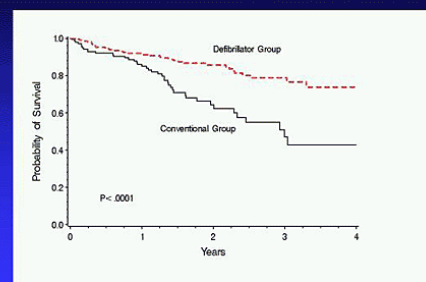
Variable	HR	(95% CI)	P value
Age \geq 65 years	1.47	(0.86-2.52)	0.164
NYHA \geq II	2.00	(1.20-3.34)	0.008
BUN > 25	1.94	(1.17-3.21)	0.010
No BB use	1.57	(0.94-2.66)	0.089
A. Fib.	2.36	(1.14-4.89)	0.021
QRS > 0.12 sec	1.90	(1.14-3.14)	0.013

CAD (\geq 1 month after acute MI), LVEF \leq 30%



* 3 ECG divisions

Survival in Defibrillator Group and Conventional Treatment Group in 364 MADIT II Patients with QRS > 0.12 sec (excluding paced patients).

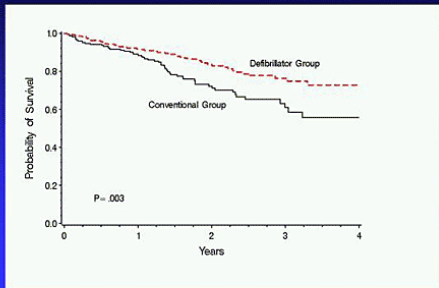


	Mortality 2-yr	3-yr
Conv	36%	53%
ICD	14%	21%

HR=0.37 (p=0.016) \rightarrow 63% reduction in mortality

Zareba. NASPE 2002

Survival in Defibrillator Group and Conventional Treatment Group in 530 MADIT II Patients with QRS ≥ 0.12 sec (excluding paced patients).



	Mortality 2-yr	Mortality 3-yr
Conv	27%	39%
ICD	17%	24%

HR=0.51 (p=0.070) \rightarrow 49% reduction in mortality

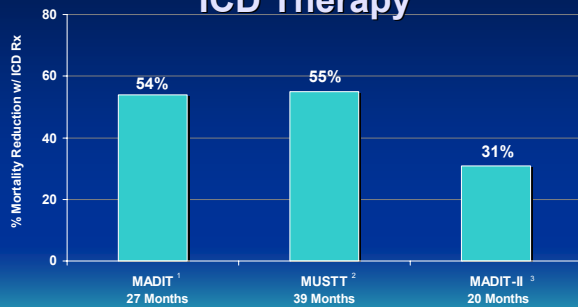
Zareba. NASPE 2002

Primary findings

ICD group had mortality reductions, depending on QRS width:

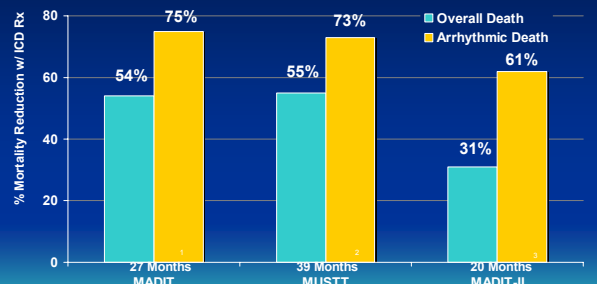
- > 120 ms (33%): 63% lower mortality when compared to conventionally treated patients (HR = 0.37, P=0.016).
- ≥ 120 ms (50%): 49% lower mortality when compared to conventionally treated patients (HR = 0.51, P=0.07).

Primary Prevention Post-MI Trials: Reduction in Overall Mortality with ICD Therapy



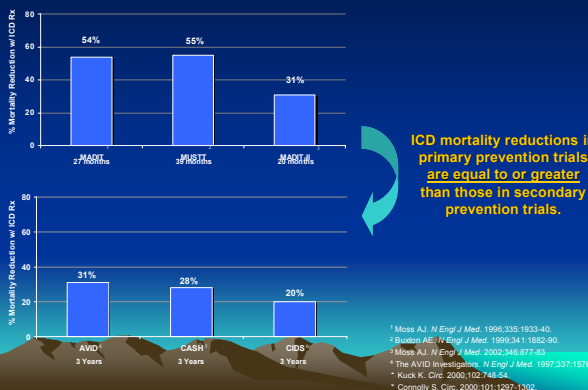
¹ Moss AJ. *N Engl J Med.* 1996;335:1933-40.
² Buxton AE. *N Engl J Med.* 1999;341:1882-90.
³ Moss AF. *N Engl J Med.* 2002;346:877-83.

Primary Prevention Post-MI Trials: Reduction in Mortality with ICD Therapy



¹ Moss AJ. *N Engl J Med.* 1996;335:1933-40.
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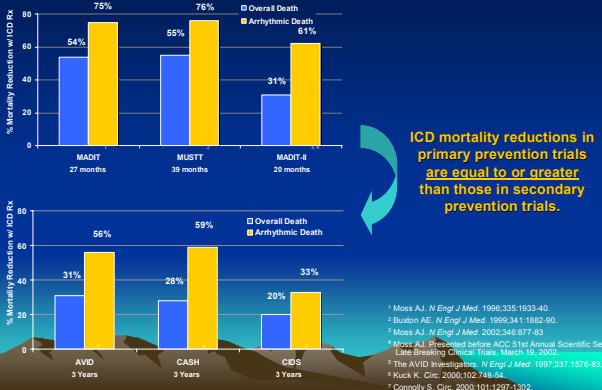
Reductions in Overall Mortality with ICD Therapy



ICD mortality reductions in primary prevention trials are equal to or greater than those in secondary prevention trials.

¹ Moss AJ. *N Engl J Med.* 1996;335:1933-40.
² Buxton AE. *N Engl J Med.* 1999;341:1882-90.
³ Moss AJ. *N Engl J Med.* 2002;346:877-83.
⁴ The AVID Investigators. *N Engl J Med.* 1997;337:1576-83.
⁵ Kuck K. *Circ.* 2000;102:748-54.
⁶ Connolly S. *Circ.* 2000;101:1297-1302.

Reductions in Mortality with ICD Therapy



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² Buxton AE. *N Engl J Med.* 1999;341:1882-90.
³ Moss AJ. *N Engl J Med.* 2002;346:877-83.
⁴ Moss AJ. Presented before ACC 51st Annual Scientific Sessions, Late Breaking Clinical Trials, March 19, 2002.
⁵ The AVID Investigators. *N Engl J Med.* 1997;337:1576-83.
⁶ Kuck K. *Circ.* 2000;102:748-54.
⁷ Connolly S. *Circ.* 2000;101:1297-1302.

The **D**efibrillator in **A**cute **M**ycocardial **I**nfarction **T**rial (DINAMIT)

Inclusion Criteria

- Occurrence of MI 6 to 40 days prior to enrollment
- Left ventricular ejection fraction (LVEF) $\leq 35\%$
- Signs of impaired cardiac autonomic modulation
 - Depressed standard deviation of sinus RR intervals ≤ 70 ms
 - Elevated heart rate (mean RR interval ≤ 750 ms)

Methods

- Patients were screened at 73 centers in 10 countries. Of the 1016 patients who met entry criteria, 674 (66%) agreed to enrollment and were randomized to either OMT plus ICD therapy (n = 332) or OMT alone (control, n = 342).

Conclusions on Post-MI ICD Trials

- Stable (1 month) Post-MI patients with LV dysfunction are at an increased risk of SCA.
- ICD therapy in these patients results in significant reductions in overall mortality (31-55%) over antiarrhythmics or conventional therapy.

Conclusions on Post-MI ICD Trials

- ICD mortality reductions in stable post-MI patients (primary prevention) are equal to or greater than the mortality reductions achieved in VT/VF trials (secondary prevention).

How the Various Clinical Trials Supported the ICD Indications...

Significance of Secondary Prevention Clinical Trials

AVID,
CASH,
CIDS

CIDS and
AVID
Registry
Sub-
studies

1998 ACC/AHA Class I Indications for ICD Therapy:

1. Cardiac arrest due to VF or VT not due to a transient or reversible cause.
2. Spontaneous sustained VT.
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study when drug therapy is ineffective, not tolerated, or not preferred.

Gregoratos G. *Circulation*. 1998;97:1325-35.

Significance of MADIT-II

MADIT-II represents a broader patient group for ICD therapy:

Patients with previous myocardial infarction (≥ 4 weeks) and with low left-ventricular ejection fraction ($\leq 30\%$).

Significance of Post-MI Clinical Trials

• MADIT
• MUSTT

1998 ACC/AHA Class I Indications for ICD Therapy:

4. Nonsustained VT with coronary disease, prior MI, LV dysfunction, and inducible VF or sustained VT at EP study that is not suppressible by a Class I antiarrhythmic drug.

Class IIb Indications:

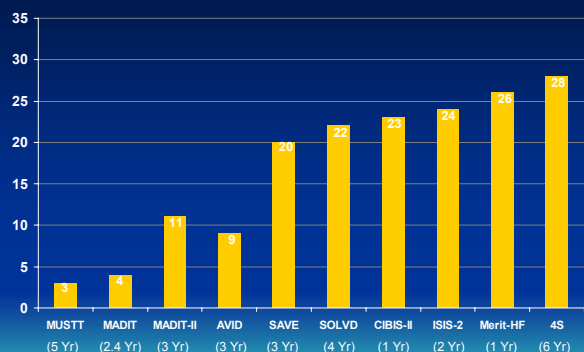
4. Nonsustained VT with CAD, prior MI, and LV dysfunction, and inducible sustained VT or VF at EP study.

Gregoratos G. *Circulation*. 1998;97:1325-35.

Goals After Myocardial Infarction

- Reducing the risk of another heart attack
 - Antithrombotic therapy
 - ACE inhibitors
 - Beta-blockers
 - Statins
- Reducing the risk of heart failure
 - Aldosterone antagonists
 - ACE inhibitors
 - Beta-blockers
- Reducing the risk of sudden cardiac death
 - Medications: are they enough?
 - ICD therapy

Number Needed to Treat to Save One Life



Recent Clinical ICD Trials in CHF Patients, including Non Ischemic



Sponsored by
The National Heart, Lung, & Blood
Institute

Funding Provided by
Medtronic, Inc., & Wyeth

Key Trial Question:

Will Amiodarone and/or an ICD improve survival compared to placebo in patients with NYHA Class II and III CHF and reduced left ventricular ejection fraction ($\leq 35\%$) without a history of sustained VT or VF?

Bardy GH. Chapter Excerpt from *Arrhythmia Treatment and Therapy*. Woosley RL, Singh SN, editors. Marcel Dekker, 1st edition. 2000:323-42.

SCD-HeFT Inclusion Criteria

- Symptomatic CHF (NYHA class II and III) due to ischemic or nonischemic dilated cardiomyopathy
- LVEF $\leq 35\%$
- ≥ 18 years of age; no upper age limitation
- CHF ≥ 3 months
- ACE I and Beta Blocker therapy if tolerated

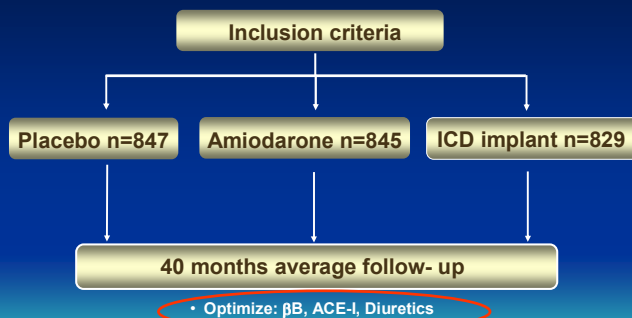
Bardy GH. Chapter Excerpt from *Arrhythmia Treatment and Therapy*. Woosley RL, Singh SN, editors. Marcel Dekker, 1st edition. 2000:323-42.

SCD-HeFT Endpoints

- **Primary**
 - To compare all cause mortality after 2.5 years of follow-up (Power: 90% to detect 25% benefit)
- **Secondary**
 - Mortality – Ischemic, Non-Ischemic, Class II, III,
 - Cause-Specific Death
 - HF Morbidity & Mortality
 - Consistency of treatment effects across sub groups defined by other variables – age, gender, EF, Hx of MI, time of MI, QRS width
 - Quality of Life
 - Cost of Care & Cost Effectiveness

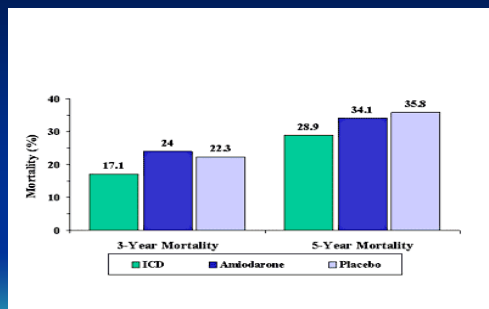
Bardy GH. Chapter Excerpt from *Arrhythmia Treatment and Therapy*. Woosley RL, Singh SN, editors. Marcel Dekker, 1st edition. 2000:323-42.

SCD-HeFT Protocol



Bardy GH. Chapter Excerpt from *Arrhythmia Treatment and Therapy*. Woosley RL, Singh SN, editors. Marcel Dekker, 1st edition. 2000:323-42.
SCD-HeFT Investigators Meeting, August 2001, data from most recent follow-up

SCD-HeFT Results



SCD-HeFT Results

Measurement	ICD n=	Amiodarone n=	Placebo
Three-year mortality	17.1%	24%	22.3%
Five-year mortality by ITT	28.9%	34.1%	36.1%
Total deaths at study end (n=666)	22% (n=182)	28% (n=240)	29% (n=244)

SCD-Heft Subgroups

Measurement	ICD vs. placebo	Amiodarone vs. Placebo
Mortality in all patients	.77 HR (p=.007) (23% decreased risk)	1.06 (p=.529) (6% increased risk)
NYHA Class II	.54 (46% decreased risk)	.85 (15% decreased risk)
NYHA Class III	1.16 (16% increased risk)	1.44 (44% increased risk)
Non-ischemic patients	.73 (27% decreased risk)	1.07 (7% increased risk)
Ischemic patients	.79 (21% decreased risk)	1.05 (5% increased risk)
QRS <120	.84	1.06
QRS ≥120	.67	1.05

Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial.

Study Design

- A total of 458 patients with LV dysfunction (ejection fraction [EF] ≤ 35%) and non-ischemic dilated cardiomyopathy were randomized to either standard oral medical therapy (n = 229) or standard oral medical therapy plus ICD implantation (n = 229). Patients were randomized at 48 centers in the United States and Israel between July 1998 and May 2003.

Inclusion criteria

- Age 21-80 years
- Non-ischemic cardiomyopathy with LVEF ≤ 35%
- Symptomatic heart failure
- Documented nonsustained ventricular tachycardia (VT) or an average of 10 PVCs/hour on Holter monitor

Outcomes

- Patients were followed for a mean of 26 ± 4 months. A total of 56 deaths occurred in the study (prespecified); 33 in the standard therapy arm and 23 deaths in the ICD arm. Arrhythmic death accounted for 33% of deaths that occurred in the therapy arm and 13% of deaths that occurred in the ICD arm (Figure 1).

Conclusions

- Patients with non-ischemic cardiomyopathy, severe LV dysfunction, and an arrhythmia marker have an annual mortality of only 6% to 7% when treated with ACE inhibitors and beta-blockers.
- On drug therapy, arrhythmic SCD accounts for only one third of all deaths, a lower proportion than expected.
- ICD implantation reduced arrhythmic death.
- ICD implantation tended to reduce all-cause mortality. The absolute mortality benefit was 5.7% at 2 years. **The relative risk reduction was 34% ($P = .06$).**

COMPANION

Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure

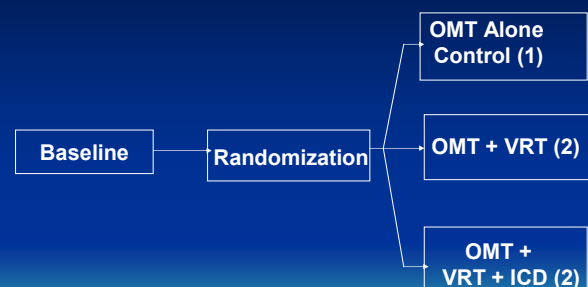
COMPANION Trial

- The trial enrolled a total of 1520 patients with advanced heart failure (NYHA functional class III/IV), a QRS interval of > 120 msec, PR interval > 150 msec, and a left ventricular ejection fraction (LVEF) $\leq 35\%$;

COMPANION Endpoints

- Primary
 - All-cause mortality and hospitalizations
- Secondary
 - Cardiac morbidity
 - All-cause mortality
 - Exercise performance sub-study

COMPANION Study Design

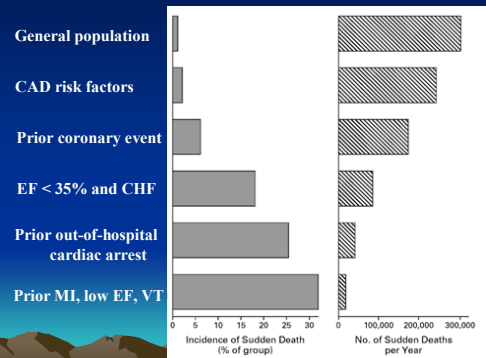


COMPANION TRIAL RESULTS

Risk Reduction in Primary and Secondary Endpoints

12-Month Outcomes	Reduction Compared With OPT				
	OPT (n = 30)	CRT (n = 617)	P	CRT-D (n = 595)	P
Primary endpoint*	68%	19%	0.014	20%	0.01
Secondary endpoint†	19%	24.00%	0.059	36%	0.003
Combined death from and hospitalization for:					
Cardiovascular causes	60%	25%	0.002	28%	< .001
Heart failure	45%	34%	0.002	40%	< .001

Patients at risk for sudden cardiac death



Huikiri et al, NEJM 2001