Sudden Cardiac Death Prevention Trials

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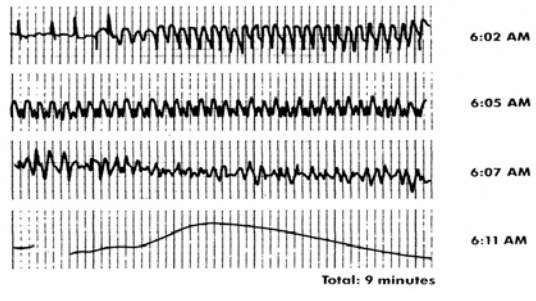
Important Epidemiological Concepts

- **Relative Risk reduction is a *population effect***
- **Absolute Risk reduction is a Individual effect**

Definitions

- **Sudden Cardiac Death (SCD): is defined as unexpected death that occurs immediately or within one hour of an abrupt change from a stable clinical state**
- **SCD Primary Prevention: Therapy that attempts to reduce mortality in patient at risk for SCD but no prior event**
- **SCD Secondary Prevention: Therapy that attempts to reduce mortality in patient with Aborted SCD, HD unstable VT or VT in a setting of structural heart disease**

Sudden Death Is Frequently Due To Ventricular Tachycardia Degenerating To Ventricular Fibrillation



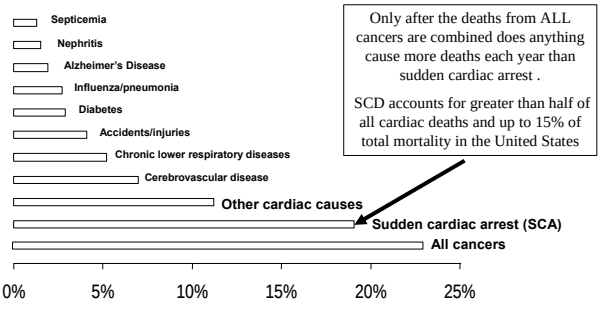
Incidence of SCD in Specific Populations and Annual SCD Numbers

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

Magnitude of the Problem

- **U.S. estimates of sudden cardiac death 300,000-350,000 derived figure from the 70s**
- **National center for disease statistics in 2001 estimated a total of 456,000 SCD**
- **Oregon/Seattle 2002/4 <200,000**

Magnitude of the Problem



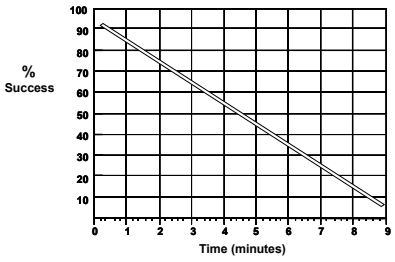
Only after the deaths from ALL cancers are combined does anything cause more deaths each year than sudden cardiac arrest .

SCD accounts for greater than half of all cardiac deaths and up to 15% of total mortality in the United States

National Vital Statistics Report, Vol 49 (11), Oct. 12, 2001

Urgency of Sudden Cardiac Arrest

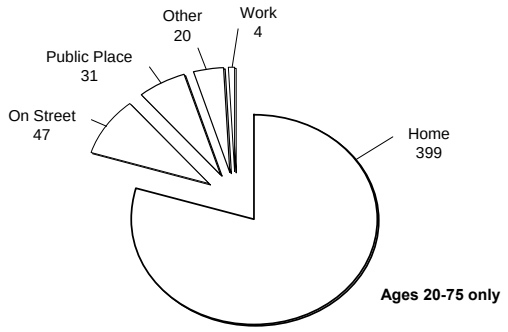
Resuscitation Success vs. Time



Chance of success reduced 7-10% every minute

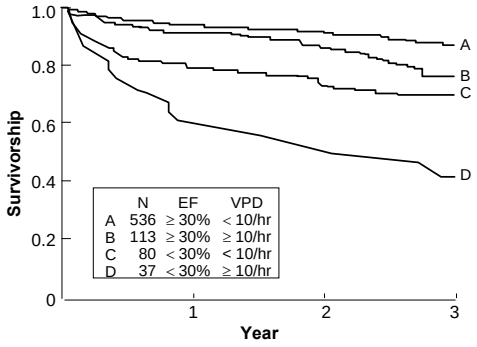
Adapted from text: Cummins RO, 1998. *Annals of Emergency Medicine*. 18:1269-1275.

Out of Hospital Cardiac Arrest
Site of Cardiac Arrest - The Maastricht Study



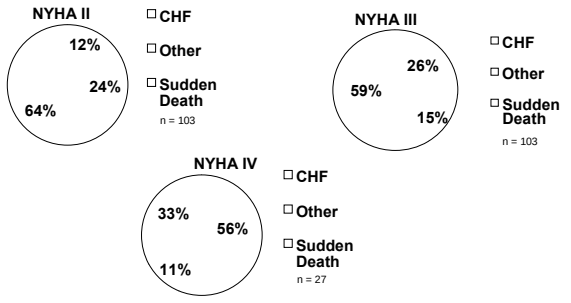
Vreede-Swagemakers et al. JACC 1997;30:1500-5.

Survival After Acute MI: Who is at Risk?



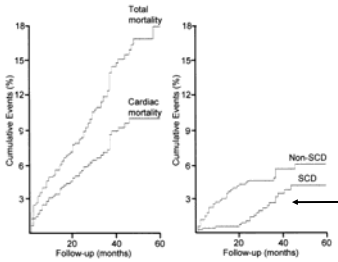
Bigger JT. Am J Cardiology. 1986;57:12B.

Severity of Heart Failure
Modes of Death



LANCET. 1999;353:2001-07.

Time Dependence of Mortality Risk Post-MI:
Prediction of Sudden Cardiac Death After Myocardial Infarction in the Beta-Blocking Era



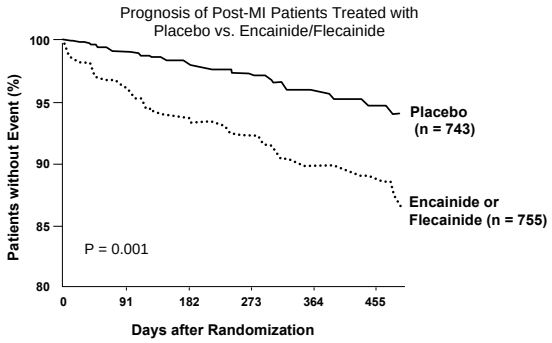
- **700 post-MI patients; ~95% on beta blockers 2 years after discharge.**
- **The epidemiologic pattern of SCD was different from that reported in previous studies.**
  - ✓ Arrhythmia events or SCDs did not concentrate early after the index event, but most of them occurred more than 18 months post-MI.

Huikuri H, et al. J Am Coll Cardiol 2003; 42: 652-8.

Pharmacological SCD Primary Prevention Trials

	Post-MI Patients	Heart Failure Patients
Antiarrhythmic Drugs	CAST BASIS *CAMIAT* PAT *EMIAT* SSSD *SWORD* DIAMOND-MI	*GESICA* *CHF-STAT* *DIAMOND-CHF*
Beta-Blockers	BHAT CAPRICORN	CIBIS-II USCHFT *MERIT* COMET COPERNICUS
ACE Inhibitors	SAVE SMILE TRACE	SOLVD
Aldosterone Receptor Blockades		*RALES* *EPHESUS*

CAST-I



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

CAST-I

Objective:

- ✓ **Evaluate the effectiveness of Class IC AA drugs (Encainide and Flecainide) (n = 755) compared to placebo (n = 743) in post-MI patients.**

Inclusion Criteria:

- ✓ **MI within 6 days to 2 years, and**
- ✓ **LVEF > 40% if recruited > 90 days post-MI or ≤ 55% if recruited within 90 days post-MI, and**
- ✓ **> 6 PVCs per hour but no VT > 15 beats or > 120 bpm, and**
- ✓ **PVCs suppressible with Encainide or Flecainide**

Class IC AA Drug Results:

- ✓ **Caused excessive mortality compared to placebo. The study was stopped early.**

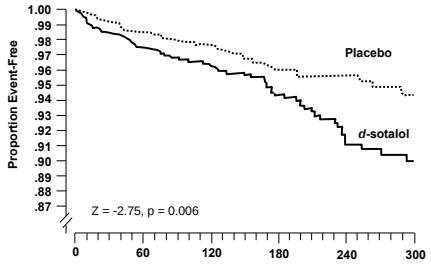
Echt DS. *N Engl J Med.* 1991;324:781-788.

EMIAT and CAMIAT Trials

Factor	EMIAT[1]	CAMIAT[2]
Protocol	Amiodarone vs. placebo	Amiodarone vs. placebo
Patient characteristics	Poor LV function (LVEF ≤ 40%)	Frequent ventricular ectopic activity (VEA; ≥ 10 VPDs/hr)
Recruitment	5-21 days post-MI	6-45 days post-MI
Risk reduction of arrhythmic death at 24 months	35% (p = 0.05)	48.5% (p = 0.016)
Overall mortality at 24 months	No difference	No difference

[1] Julian DG. *Lancet.* 1997;349:667-674. [2] Cairns JA. *Lancet.* 1997;349:675-682.

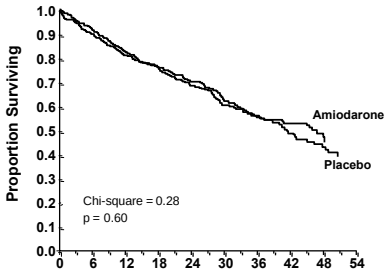
Pharmacological SCD Primary Prevention Trials SWORD Survival Results



Patients at Risk					
Placebo	1,572	1,170	874	551	330
d-sotalol	1,549	1,150	844	544	323

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

CHF-STAT Survival Results



Amiodarone	336	260	175	101	33
Placebo	338	263	178	95	39

Singh SW. *N Engl J Med.* 1995;333:77-82.

CHF-STAT

Objective:

- ✓ **Evaluate the effectiveness of amiodarone (n = 336) versus placebo (n = 338) in heart failure patients**
- ✓ **NYHA Class II, III, or IV, and**
- ✓ **EF ≤ 40%, and**
- ✓ **> 10 PVCs/hour**

Singh SW. *N Engl J Med.* 1995;333:77-82.

MERIT-HF

Objective and Inclusion Criteria:

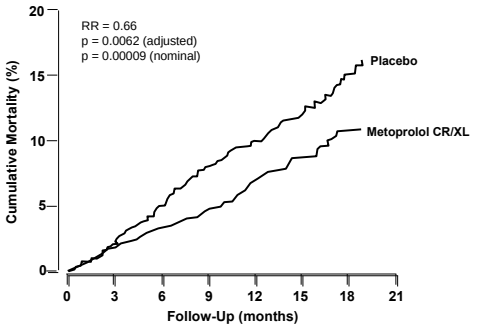
- ✓ **Evaluate the effectiveness of Metoprolol | CR/XL (n = 1,900) compared to placebo (n = 2,001) in heart failure patients**
- ✓ **NYHA II, III, or IV, and**
- ✓ **LVEF ≤ 40%**

Results:

- ✓ **Reduced overall mortality by 34% (7.2% vs. 11%) (p = 0.0062)**
- ✓ **Reduced SCD by 41% (4% vs. 6.6%) (p = 0.0002)**
- ✓ **Reduced deaths from worsening heart failure by 49% (p = 0.0023)**

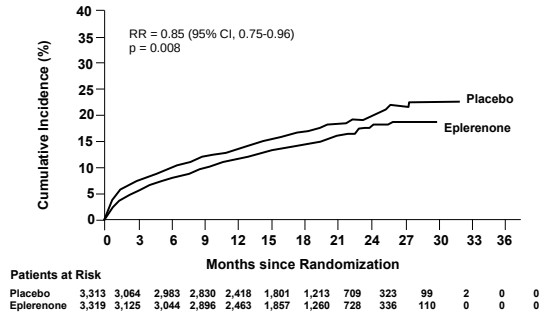
MERIT-HF Study Group. *Lancet.* 1999;333:2001-2007.

MERIT-HF Overall Mortality Results



MERIT-HF Study Group. *Lancet.* 1999;333:2001-2007.

EPHESUS Overall Mortality Results



Patients at Risk

Placebo	3,313	3,064	2,983	2,830	2,418	1,801	1,213	709	323	99	2	0	0
Eplerenone	3,319	3,125	3,044	2,896	2,463	1,857	1,260	728	336	110	0	0	0

Pitt B. *N Engl J Med.* 2003;348:1309-1321.

EPHESUS

Objective:

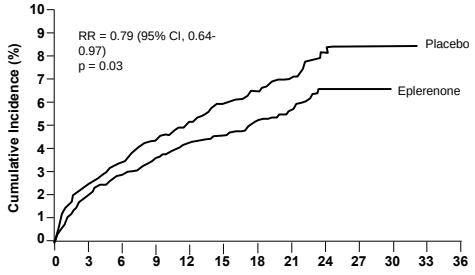
- ✓ **Evaluate the effectiveness of Eplerenone (n = 3,313) to placebo (n = 3,319) in acute MI patients with left ventricular dysfunction and heart failure**
- ✓ **Acute MI (3-17 days), and**
- ✓ **LVEF ≤ 40%, and**
- ✓ **Evidence of heart failure**

Eplerenone Results:

- ✓ **Reduced overall mortality by 15% (p = 0.008)**
- ✓ **Reduced SCD by 21% (p = 0.03)**
- ✓ **Reduced the risk of CV death or CV hospitalization by 13% (p = 0.002)**

Pitt B. *N Engl J Med.* 2003;348:1309-1321.

EPHESUS Sudden Cardiac Death Results

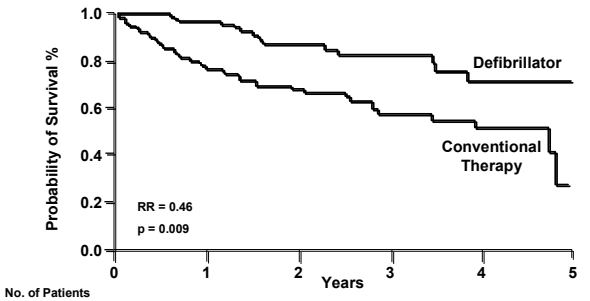


Patients at Risk

Eplerenone	3,319	3,125	3,044	2,896	2,463	1,857	1,260	728	336	110	0	0	0
Placebo	3,313	3,064	2,983	2,830	2,418	1,801	1,213	709	323	99	2	0	0

Pitt B. *N Engl J Med.* 2003;348:1309-1321.

MADIT Survival Results



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

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

Major Implantable Cardioverter-Defibrillator Trials for Primary Prevention of Sudden Cardiac Death

Trial	Year	Patients (n)	LVEF	Additional Study Features	Hazard Ratio*	95% CI	p
MADIT I	1996	196	≤ 35%	NSVT and EP+	0.46	(0.26-0.82)	p=0.009
MADIT II	2002	1232	≤ 30%	Prior MI	0.69	(0.51-0.93)	p=0.016
CABG-Patch	1997	900	≤ 36%	+SAECG and CABG	1.07	(0.81-1.42)	p=0.63
DEFINITE	2004	485	≤ 35%	NICM, PVCs or NSVT	0.65	(0.40-1.06)	p=0.08
DINAMIT	2004	674	≤ 35%	6-40 days post-MI and Impaired HRV	1.08	(0.76-1.55)	p=0.66
SCD-HeFT	2006	1676	≤ 35%	Prior MI of NICM	0.77	(0.62-0.96)	p=0.007

CI indicates Confidence Interval, NS = Not statistically significant, NSVT = nonsustained ventricular tachycardia, SAECG = signal-averaged electrocardiogram.
Epstein A, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. J Am Coll Cardiol 2008; 51:e1–62. Table 5. MODIFIED

Primary Prevention Trials

MADIT

Objective:

- **Evaluate the effectiveness of ICD therapy (n = 99) versus conventional therapy (n = 101) in high risk MI patients**

Inclusion Criteria:

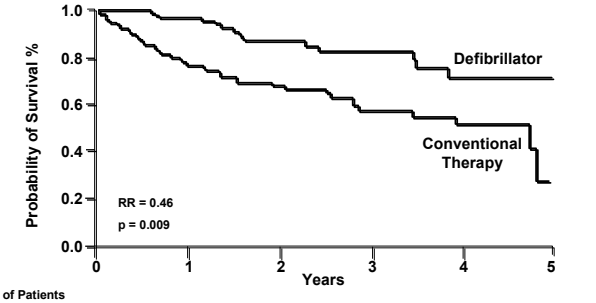
- **Q-wave MI > 3 weeks, and**
- **Asymptomatic NSVT, and**
- **LVEF < 35%, and**
- **Inducible VT, but not suppressible on EPS, and**
- **NYHA Class I-III**

ICD Results:

- **Reduced overall mortality by 54% (p = 0.009)**
- **Reduced arrhythmic mortality by 75%**

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

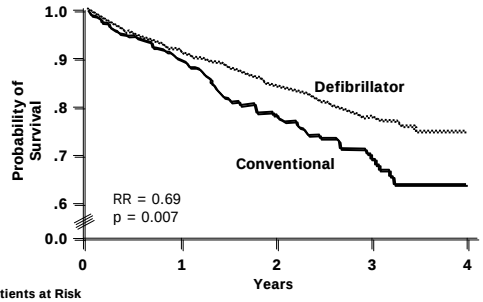
MADIT Survival Results



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

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

MADIT-II Survival Results



Patients at Risk					
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;346:877-883.

MADIT-II

Objective:

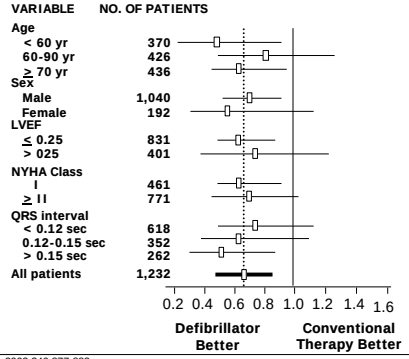
- **Evaluate the effectiveness of ICD therapy (n = 742) compared to conventional therapy (n = 490) in high-risk post-MI patients**
- **Post-MI ≥ 4 weeks, and**
- **LVEF ≤ 30%**

ICD Results:

- **Reduced overall mortality by 31% (p = 0.007)[1]**
- **Reduced arrhythmic death by 61%[2]**

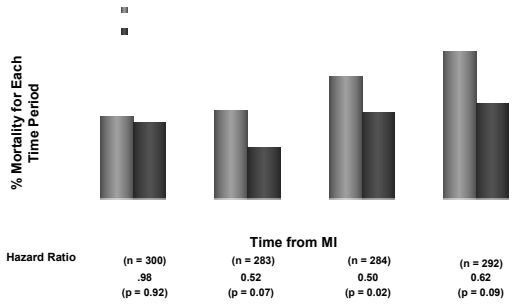
[1] Moss AJ. *N Engl J Med.* 2002;346:877-883
[2] Moss AJ. Presented before ACC 51st Annual Scientific Sessions, Late Breaking Clinical Trials, March 19, 2002.

MADIT-II
Survival Results – Sub-Group Analyses



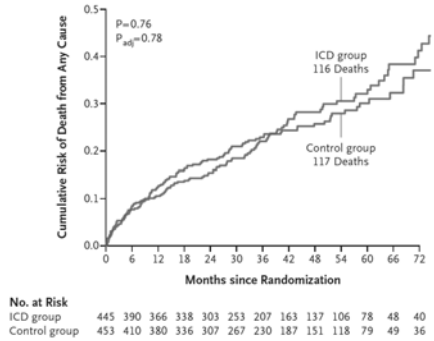
Moss AJ. *N Engl J Med.* 2002;346:877-883.

Relation of Time from MI to ICD Benefit in the MADIT-II Trial



Wilber, D. *Circulation*. 2004;109:1082-1084.

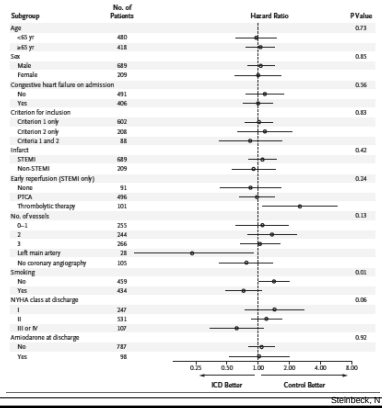
Cumulative Risk of Death from Any Cause According to Study Group



Steinbeck, N Engl J Med 2009;361:1427-36

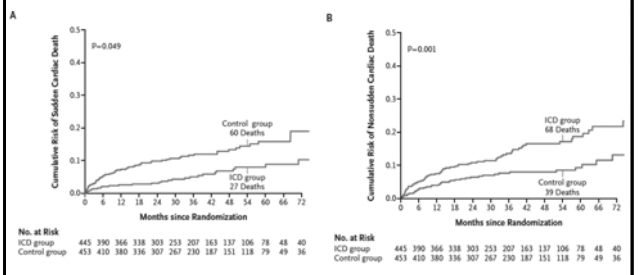
ICD Post Immediate Myocardial Infarction

Hazard Ratios for Death from Any Cause in Selected Subgroups of Patients



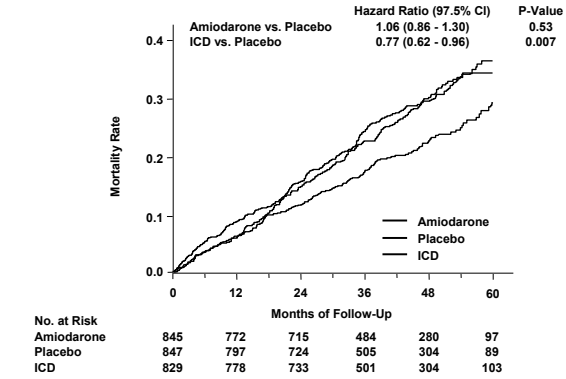
Steinbeck, N Engl J Med 2009;361:1427-36

Cumulative Risk of Cardiac Death, According to Study Group



Steinbeck, N Engl J Med 2009;361:1427-36

SCD-HeFT Mortality Rate Overall Results

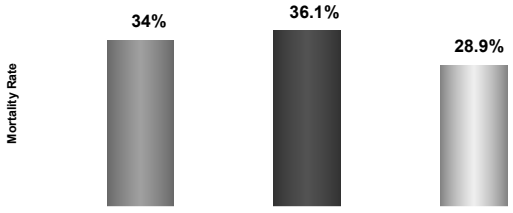


Bardy GH. *N Engl J Med.* 2005;352:225-237.

SCD-HeFT Sudden Cardiac Death in Heart Failure Trial

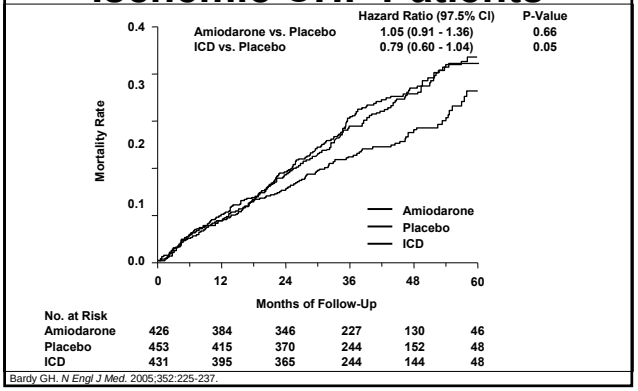
- **Determine if amiodarone or ICD will decrease the risk of death from any cause in patients with mild-to-moderate heart failure (Class II and III).**
- **Maximally treated CHF for ≥ 3 months with a LVEF of ≥ .35**

SCD-HeFT 5-Year Mortality Rate Overall Results



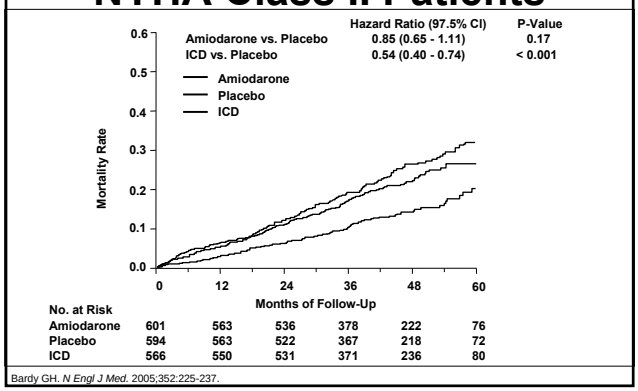
Bardy GH. *N Engl J Med.* 2005;352:225-237.

SCD-HeFT Mortality Rate Ischemic CHF Patients



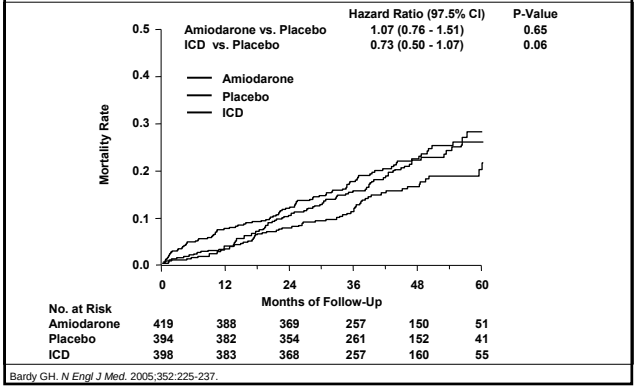
Bardy GH. *N Engl J Med.* 2005;352:225-237.

SCD-HeFT Mortality Rate NYHA Class II Patients



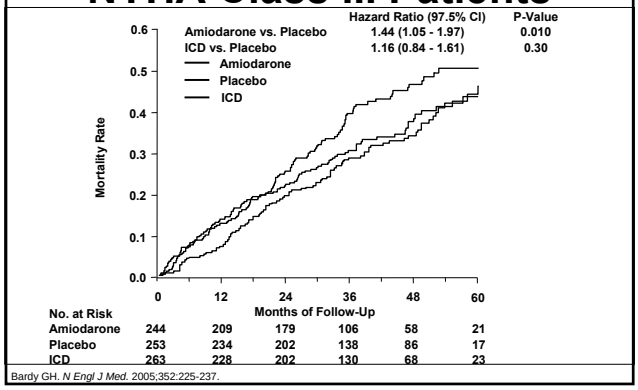
Bardy GH. *N Engl J Med.* 2005;352:225-237.

SCD-HeFT Mortality Rate Non-Ischemic CHF Patients



Bardy GH. *N Engl J Med.* 2005;352:225-237.

SCD-HeFT Mortality Rate NYHA Class III Patients



Bardy GH. *N Engl J Med.* 2005;352:225-237.

MUSTT

Objective:

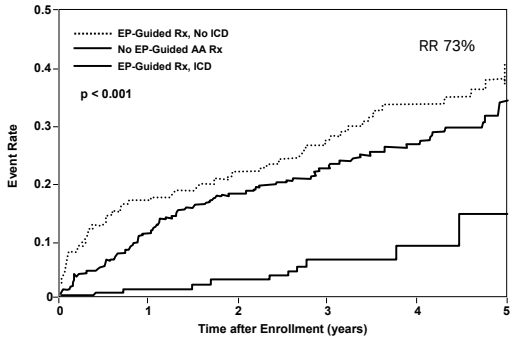
- **Evaluate if AA therapy guided by EP testing could reduce arrhythmic death and overall mortality in high-risk post-MI patients**

Inclusion Criteria:

- **CAD, and**
- **LVEF < 40%, and**
- **Asymptomatic NSVT, and**
- **Inducible VT on EP testing**

Buxton AE. *N Engl J Med*. 1999;341:1882-1890.

MUSTT Randomized Patient Results: Arrhythmic Death or Cardiac Arrest



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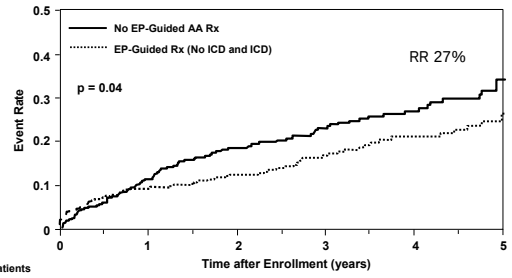
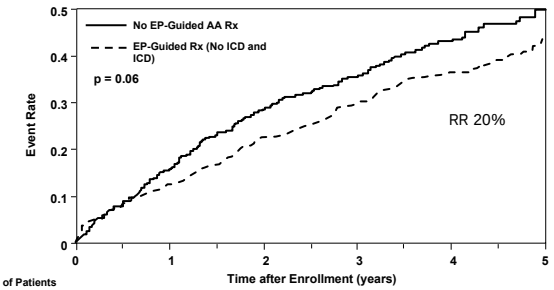


No. of Patients						
No EP-Guided AA Rx	353	290	242	178	118	67
EP-Guided Rx	351	301	265	199	119	68

Buxton AE. *N Engl J Med*. 1999;341:1882-1890.

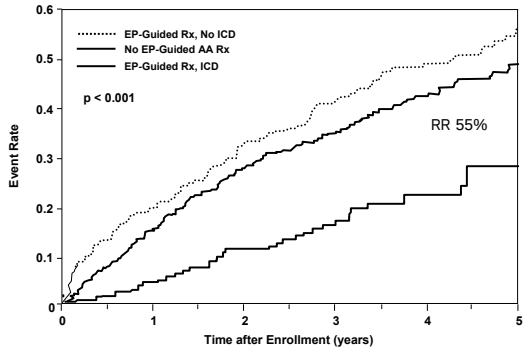
MUSTT Randomized Patient Results: Overall Mortality



No. of Patients						
No EP-Guided AA Rx	353	290	242	178	122	67
EP-Guided Rx	351	301	265	199	121	68

Buxton AE. *N Engl J Med*. 1999;341:1882-1890.

MUSTT Randomized Patient Results: Overall Mortality



Buxton AE. *N Engl J Med*. 1999;341:1882-1890.

Major Implantable Cardioverter-Defibrillator Secondary Prevention Trials for

Trial	Year	Patients (n)	LVEF	Additional Study Features	Hazard Ratio*	95% CI	p
AVID	1997	1016	Prior cardiac arrest	NA	0.62	(0.43-0.82)	NS
CASH†	2000	191	Prior cardiac arrest	NA	0.766	‡	1-sided p=0.081
CIDS	2000	659	Prior cardiac arrest, syncope	NA	0.82	(0.60-1.1)	NS

* Hazard ratios for death from any cause in the ICD group compared with the non-ICD group. Includes only ICD and amiodarone patients from CASH.
‡CI Upper Bound 1.112 CI indicates Confidence Interval, NS = Not statistically significant, NSVT = nonsustained ventricular tachycardia, SAECG = signal-averaged electrocardiogram.

Epstein A, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. J Am Coll Cardiol 2008; 51:e1–62. Table 5. MODIFIED

Secondary Prevention Trial

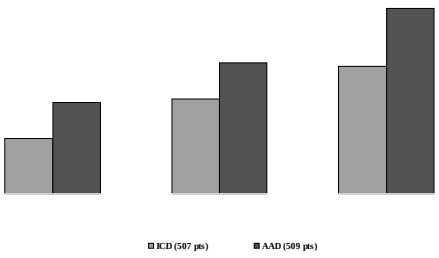
AVID (1993-1997)

Antiarrhythmics Versus Implantable Defibrillators

- **Objective - Determine the impact of ICDs and AADs on all-cause mortality**
- **Inclusion - Candidates who had a cardiac arrest due to VF, VT w/ syncope, or sustained VT without syncope and EF < 40% with one of the following:**
  - ✓ **Systolic BP of < 80 mmHg, chest pain, near syncope, or acute CHF**

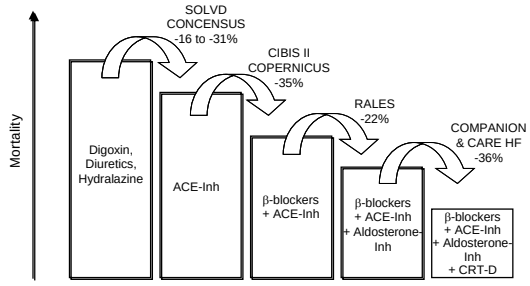
Cardiac Electrophysiology Review 2, 8-10, 1998

AVID
All-cause Mortality Percentage



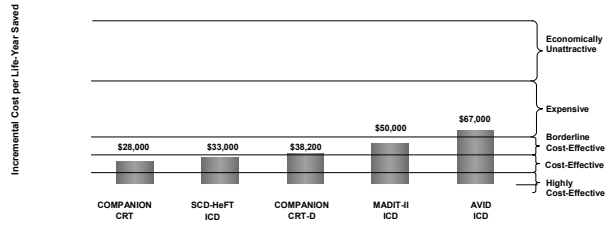
Cardiac Electrophysiology Review 2, 8-10, 1998

Add-on Therapy In Heart Failure



K. Ellenbogen JACC 2005;46:2199 –203

Incremental Cost-Effectiveness ICD, CRT, and CRT-D Therapies



Conclusions

- **Defibrillators have shown conclusively to reduced sudden cardiac death and total mortality in primary and secondary prevention trials**
- **Antiarrhythmic drugs in general do not improve survival, even though in some cases prevent SCD. In some cases it may increases mortality**

Conclusions

- Ace-inhibitors, Beta-blockers, Aldosterone receptor blockers all are all associated with improve survival
- Defibrillators improve survival in high risk groups. The benefit is additive to medical therapy (which should be initiated and maximize prior to implantation)

Indications for ICD Therapy

2008 ACC/AHA/ESC Guidelines

The Future

- Appropriate device selection
  - Single/Dual Chamber Vs. Bi-V
- Improved patient selection
  - Pt's clinical characteristics
  - EPS/MTWA/SAECG/MRIs/Genetic testing
- Lower cost defibrillators
- Leadless defibrillators

Implantable Cardioverter-Defibrillators

ICD therapy is indicated in patients who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes.

ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable.

ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study.

All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.

Implantable Cardioverter-Defibrillators

ICD therapy is indicated in patients with LVEF less than 35% due to prior MI who are at least 40 days post-MI and are in NYHA functional Class II or III.

ICD therapy is indicated in patients with nonischemic DCM who have an LVEF less than or equal to 35% and who are in NYHA functional Class II or III.

ICD therapy is indicated in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than 30%, and are in NYHA functional Class I.

ICD therapy is indicated in patients with nonsustained VT due to prior MI, LVEF less than 40%, and inducible VF or sustained VT at electrophysiological study.

All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.

Implantable Cardioverter-Defibrillators

ICD implantation is reasonable for nonhospitalized patients awaiting transplantation.

ICD implantation is reasonable for patients with Brugada syndrome who have had syncope.

ICD implantation is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest.

ICD implantation is reasonable for patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving beta blockers.

ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease.

All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.

Implantable Cardioverter-Defibrillators

ICD implantation is reasonable for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM.

ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function.

ICD implantation is reasonable for patients with HCM who have 1 or more major† risk factors for SCD.

ICD implantation is reasonable for the prevention of SCD in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) who have 1 or more risk factors for SCD.

ICD implantation is reasonable to reduce SCD in patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta blockers.

All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.

Implantable Cardioverter-Defibrillators

ICD therapy may be considered in patients with nonischemic heart disease who have an LVEF of less than or equal to 35% and who are in NYHA functional Class I.

ICD therapy may be considered for patients with long-QT syndrome and risk factors for SCD.

ICD therapy may be considered in patients with syncope and advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed to define a cause.

ICD therapy may be considered in patients with a familial cardiomyopathy associated with sudden death.

ICD therapy may be considered in patients with LV noncompaction.

Implantable Cardioverter-Defibrillators

ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the Class I, IIa, and IIb recommendations above.

ICD therapy is not indicated for patients with incessant VT or VF.

ICD therapy is not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up.

ICD therapy is not indicated for NYHA Class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or cardiac resynchronization therapy defibrillators (CRT-D).

All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.

ICDs in Pediatric Patients and Patients With Congenital Heart Disease

ICD implantation is indicated in the survivor of cardiac arrest after evaluation to define the cause of the event and exclusion of any reversible causes.

ICD implantation is indicated for patients with symptomatic sustained VT in association with congenital heart disease who have undergone hemodynamic and electrophysiological evaluation. Catheter ablation or surgical repair may offer possible alternatives in carefully selected patients.

All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.

Implantable Cardioverter-Defibrillators

ICD therapy is not indicated for syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease.

ICD therapy is not indicated when VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, RV or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease).

ICD therapy is not indicated for patients with ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma).

All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.

ICDs in Pediatric Patients and Patients With Congenital Heart Disease

ICD implantation is reasonable for patients with congenital heart disease with recurrent syncope of undetermined origin in the presence of either ventricular dysfunction or inducible ventricular arrhythmias at electrophysiological study.

ICD implantation may be considered for patients with recurrent syncope associated with complex congenital heart disease and advanced systemic ventricular dysfunction when thorough invasive and noninvasive investigations have failed to define a cause.

All Class III recommendations found in Section 3 of the full-text guidelines, "Indications for Implantable Cardioverter-Defibrillator Therapy," apply to pediatric patients and patients with congenital heart disease, and ICD implantation is not indicated in these patient populations.

All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.