Randomized Controlled Trials in EP: Now We Have Some Data

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Internal Medicine Grand Rounds

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Richard L. Page, MD has disclosed financial interests or other relationships with commercial concerns related directly or indirectly with this program. Dr. Page will be discussing off-label uses in his presentation.

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Introduction

Sudden cardiac death accounts for approximately 250,000 deaths annually in the United States. Patients at the highest risk, such as those who already have survived a cardiac arrest, clearly have benefited by the development of the implantable cardioverter-defibrillator (ICD). Those without evidence of cardiac disease may sustain sudden death, and will benefit from the implementation of public access defibrillation with the automated external defibrillator (AED) [1,2], as shown in figure 1 [3]. Even with full deployment of AEDs for public access defibrillation, up to 80% will remain unprotected since only 16-20% of arrests occur in public places.[4] The challenge remains to identify patients at greatest risk and treat prophylactically to avoid the first, and potentially fatal, manifestation of cardiac disease.

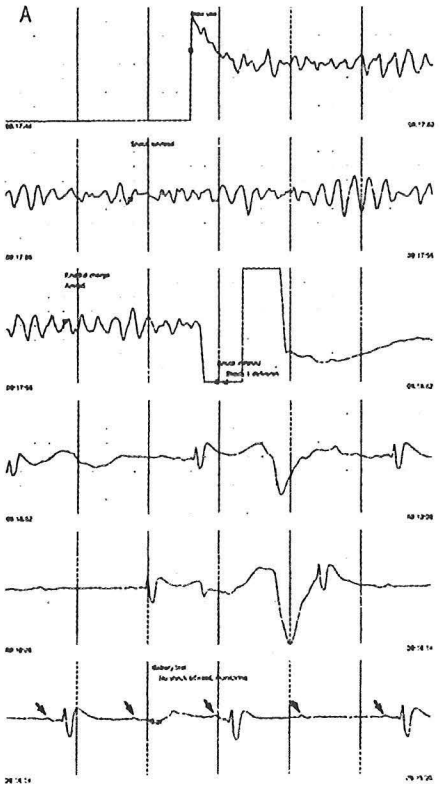

Figure 1. Example of AED delivery of a shock to terminate ventricular fibrillation aboard a commercial aircraft. Note that the shock converts VF after 12 seconds, to sinus with 2:1 conduction. After 10 minutes, the patient was awake, and in atrial fibrillation. He has survived long-term, and has an implantable cardioverter-defibrillator.[3]

Risk of sudden death: whom should we treat?

As above, up to 250,000 Americans die suddenly each year. However, the risk of sudden death for each citizen is relatively small (about 0.1% per adult per year). Through risk stratification, higher-risk individuals can be identified, although the absolute numbers of patients to benefit become smaller. Thus, risk stratification occurs at the expense of losing the potential of treating the larger population that may die suddenly despite not

previously manifesting risk. Myerberg [5] has emphasized this point very well in his work, as shown in figure 2.

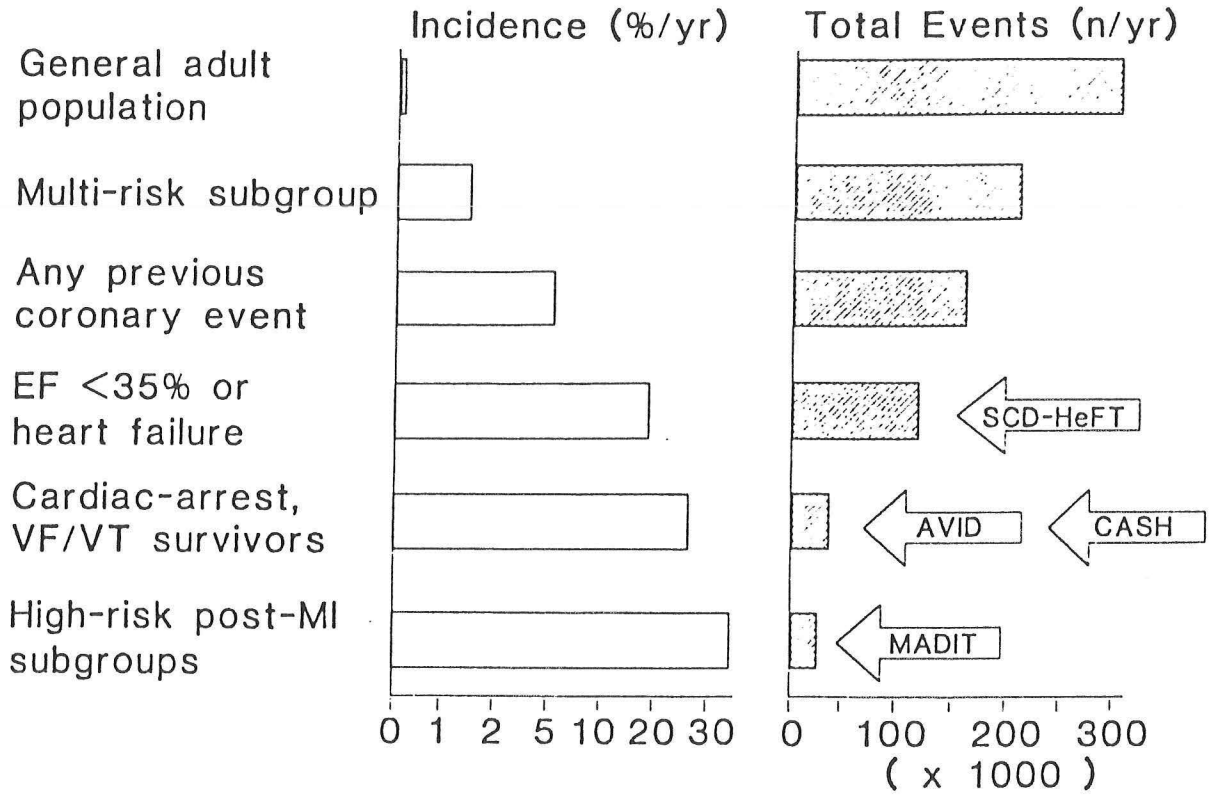

Figure 2. The highest risk patients comprise a minority of the absolute number of sudden deaths, while most deaths occur in patients who have relatively low individual risk.[5] Trials are defined later in this paper.

Prior myocardial infarction (MI) conveys significant risk when it results in impairment of left ventricular function. Although there is minor increased risk when the ejection fraction is >40%, risk increases markedly below 40%, and below 30% the ejection fraction becomes the single most powerful predictor of mortality.

A further important predictor of mortality in patients post-MI is ventricular ectopy. Although premature ventricular contractions (PVCs) are not of significance in asymptomatic patients with structurally normal hearts, PVC counts of 10 or more per hour are independently associated with increased risk of sudden death and reduced survival.[6] The combination of depressed ejection fraction and ventricular ectopy results in further risk, as shown in Figure 3. Nonsustained ventricular tachycardia (VT) has also been associated with increased mortality, although in recent studies this has not been shown to be a predictor independent of PVCs. The high risk associated with the

combination of reduced ejection fraction and high-grade ventricular ectopy in patients with prior MI led to the "PVC hypothesis" that suppression of ectopy in high-risk patients would reduce mortality. This theory was rejected after the results of CAST were published, as described later in this paper.[7]

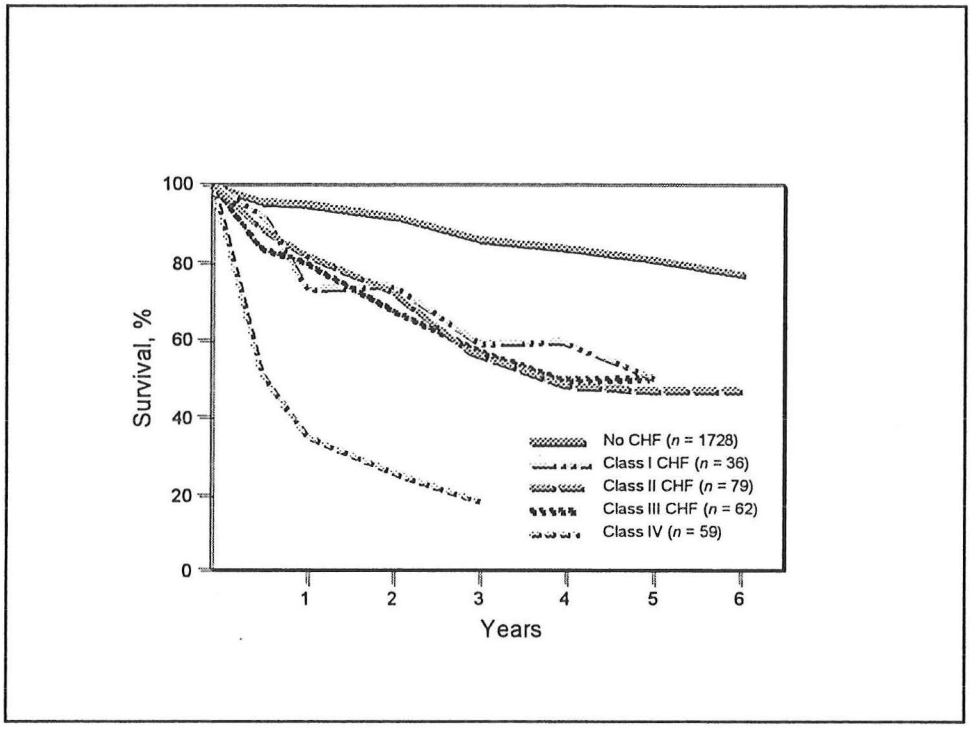

Figure 3. Survival post myocardial infarction, showing the additive risk of depressed ejection fraction and ventricular ectopy.[6]

Among the highest risk patients are those who already have experienced a potentially lethal arrhythmia. Patients with a history of coronary artery disease who survived sudden death have the highest risk in the first 6 months following the event (11.2% over 6 months); this risk falls to 3.3% every six months for the following year and a half. Thereafter, the risk is reduced, with estimated mortality of 1.6% per year. [8] The high risk of death in patients who have already manifested potentially lethal arrhythmias led to development of secondary prevention trials. Our group summarized the trials as of 1999.[9] Others recently published a summary of survival trials with device therapy.[10] In this paper I will highlight the most important information for treating patients at risk of sudden death.

Secondary prevention: Treatment of patients who have already survived a potentially lethal arrhythmia.

In the pre-ICD era, secondary prevention focused on antiarrhythmic drug treatment. The choice of therapy was accomplished by evaluating the effect of the drug on either the occurrence of ventricular ectopy[11] or on the inducibility of a sustained ventricular arrhythmia with programmed electrical stimulation. Early reports suggested that therapy guided by suppression of inducible VT resulted in a favorable prognosis, although placebo-controlled trials were not performed. The Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) study compared the strategy of Holter-guided versus invasive EP-guided drug therapy in patients who had electrocardiographically documented sustained ventricular tachycardia or fibrillation (lasting 15 seconds or more), resuscitation from cardiac arrest, or syncope (with inducible VT).[12,13] In order to be enrolled in the study, patients had to demonstrate both frequent PVCs on Holter and inducible VT at EP study; this generated a very select group. Holter-guided and EP-guided therapy were equivalent in terms of prognosis, although Holter-guided therapy was more likely to find "effective" therapy. Figure 4 shows the similar survival among patients in the two treatment groups. In comparison with other antiarrhythmic agents, sotalol was the most effective agent, but amiodarone was not studied. A further problem with this study was the high recurrence rate, with over 40% experiencing recurrent arrhythmia within 2 years.

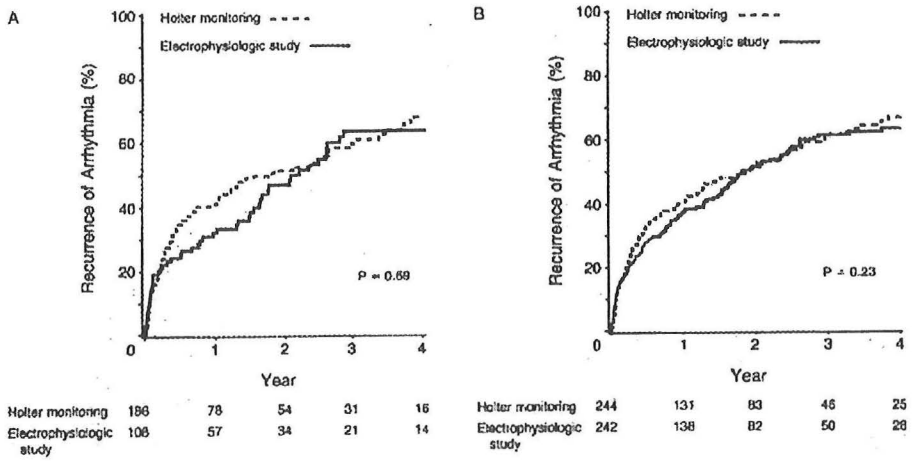

Figure 4. Results of ESVEM.[12] Probability of a recurrence of arrhythmia, according to study group, in the 296 patients receiving a drug predicted to be effective (Panel A) and in all 486 randomized patients (Panel B)

In clinical practice, amiodarone was often the agent of last-resort in patients with history of cardiac arrest who failed EP-guided therapy.[14] Even when it was ineffective at

suppressing inducible VT, patients appeared to benefit from the drug.[15] These findings led some to question the need for EP study or even consideration of other antiarrhythmic agents.[16,17] Beta-blocking agents appeared to convey benefit in survivors of sudden death as well. In a randomized study of patients with symptomatic sustained ventricular arrhythmias, the incidence of symptomatic arrhythmia and sudden death combined was virtually the same in patients who received EP-guided therapy compared with those receiving empiric metoprolol (46 percent vs. 48 percent, respectively).[18]

As the ICD was developed during the 1980s, it became a mainstay of therapy for patients with prior ventricular arrhythmias. The toxicity of amiodarone and the relatively high recurrence on beta-blockers and other antiarrhythmic medications had led to frequent abandonment of EP study and drug therapy in favor of ICD therapy. On the other hand, there were no randomized data to support ICD over alternate approaches and cost issues were raised. This led to the development of the AVID trial, as well as CIDS and CASH.

AVID: The Antiarrhythmics Versus Implantable Defibrillator (AVID) trial attempted to answer the question of whether drug therapy (as guided by EP study, or empirically chosen amiodarone) or ICD would result in improved survival in patients with previous hemodynamically-significant ventricular arrhythmias.[19] Randomized in AVID were patients with primary cardiac arrest due to ventricular fibrillation (VF), documented sustained primary ventricular tachycardia (VT) with syncope, and documented sustained primary VT accompanied by systolic blood pressure <80mmHg or chest pain or near-syncope and left ventricular ejection fraction of $\leq$ 40%. Not enrolled, but included in a registry, were the following 4 other categories: documented sustained primary VT, systolic blood pressure <80 mmHg or chest pain or near-syncope but left ventricular ejection fraction >40%; documented sustained primary VT but hemodynamically stable; out-of-hospital documented sustained VT, or cardiac arrest due to VF associated with transient or correctable cause; and out-of-hospital unexplained syncope with structural heart disease and symptomatic VT/VF induced at invasive electrophysiology study.

The results of AVID were as follows. Of 6035 patients screened, 1016 were entered in the randomized trial and 4621 entered the registry. Of the 509 patients assigned drug therapy, only 13 both received sotalol and were found to have their arrhythmias suppressed with the agent. Thus, this became a trial comparing amiodarone with ICD (which was assigned in 507 patients). AVID was stopped prematurely after mean follow-up of 18 months when the steering committee concluded that a significant benefit was present in the ICD-treated patient group. The 1, 2, and 3-year moralities were reduced by 39%, 27%, and 31%, respectively (p=0.02, Figure 5). Since the trial was terminated prematurely, there was only an average of 2.9 month extension of life, however. The benefit of the ICD was seen primarily in patients with EF < 35%; in fact, amiodarone and ICD were equivalent in patients with EF > 35%.[20] Further information was gleaned from the registry population. Among patients with stable VT, VT/VF with "transient" or "correctable" cause, and unexplained syncope, mortality was similarly high in comparison with patients in the trial. This suggests that these patients would be candidates for ICD therapy (even though they were initially considered to be of lower

risk).[21,22] AVID does not stand alone, as two other similar trials were conducted contemporaneously.

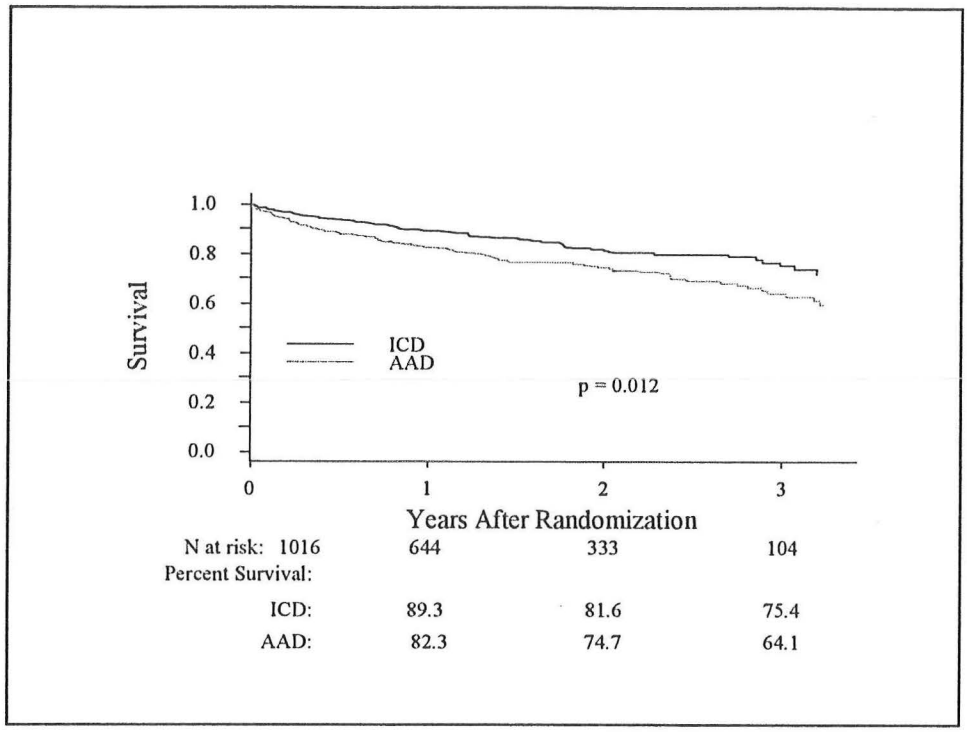

Figure 5. Overall survival of randomized patients in AVID. Survival was better among patients receiving the ICD ($p<0.02$).[19]

CIDS and CASH: Cardiac Arrest Study Hamburg (CASH) was conducted from 1987-1998 to compare empiric drug therapy (metoprolol, propafenone or amiodarone) with ICD in survivors of sudden cardiac death. This was open-label, randomized trial with the primary endpoint of total mortality. An interim analysis showed excessive mortality in the propafenone limb after 287 patients were enrolled,[23] but the study was completed with the remaining limbs, and a total of 349 patients entered. There was a significant reduction in sudden death for patients with the ICD (81.8% reduction after 1 year, for example), but the 23% reduction in total mortality did not meet statistical significance. There was no difference in mortality between amiodarone and metoprolol.[24]

The Canadian Implantable Defibrillator Study (CIDS) is in many ways similar to AVID and CASH, including patients with clinical sustained VT or sudden death; in addition, patients with syncope and inducible VT were enrolled. Among 659 patients enrolled, there was no significant difference between amiodarone and ICD (annual mortality of 10.2% and 8.3%, respectively).[25] However, the authors noted that the findings were not inconsistent with AVID, and this view is supported by a meta-analysis of AVID, CASH, and CIDS,[26] which showed the studies were consistent with each other. It concluded that the ICD results in a 28% reduction in the relative risk of death that is due almost entirely to a 50% reduction in arrhythmic death.

The combined data from AVID, CASH, and CIDS has led to the ICD being first-line therapy for survivors of lethal ventricular arrhythmias, although an argument can be made for amiodarone therapy in patients with preserved left ventricular function.

Primary prevention: Reduction of risk in patients who have not yet experienced a potentially lethal arrhythmia.

As noted above, depressed left ventricular ejection fraction is the most important of the risk factors for sudden death, and in patients with ischemic heart disease, ventricular ectopy plays an additional role. These criteria have played a major role in determining the population for attempts at primary prevention of sudden death.

The identification of nonsustained VT (NSVT) is rarely difficult, although careful analysis of the electrocardiogram may be necessary. It may be observed during Holter or telemetry monitoring, or during exercise testing. The arrhythmia is defined by a ventricular rhythm at 110-120 beats per minute, and may be as short as 3 beats or as long as 30 beats or 30 seconds. Several criteria have been developed for determining whether a wide QRS complex tachycardia is ventricular or supraventricular in origin, [27] but diagnosis of NSVT often is more easily accomplished by simply observing dissociation of the P wave. A run of wide complex tachycardia that begins with a short PR interval is diagnostic of VT (except in the rare circumstance of intermittent preexcitation). An example of NSVT is shown in figure 6.

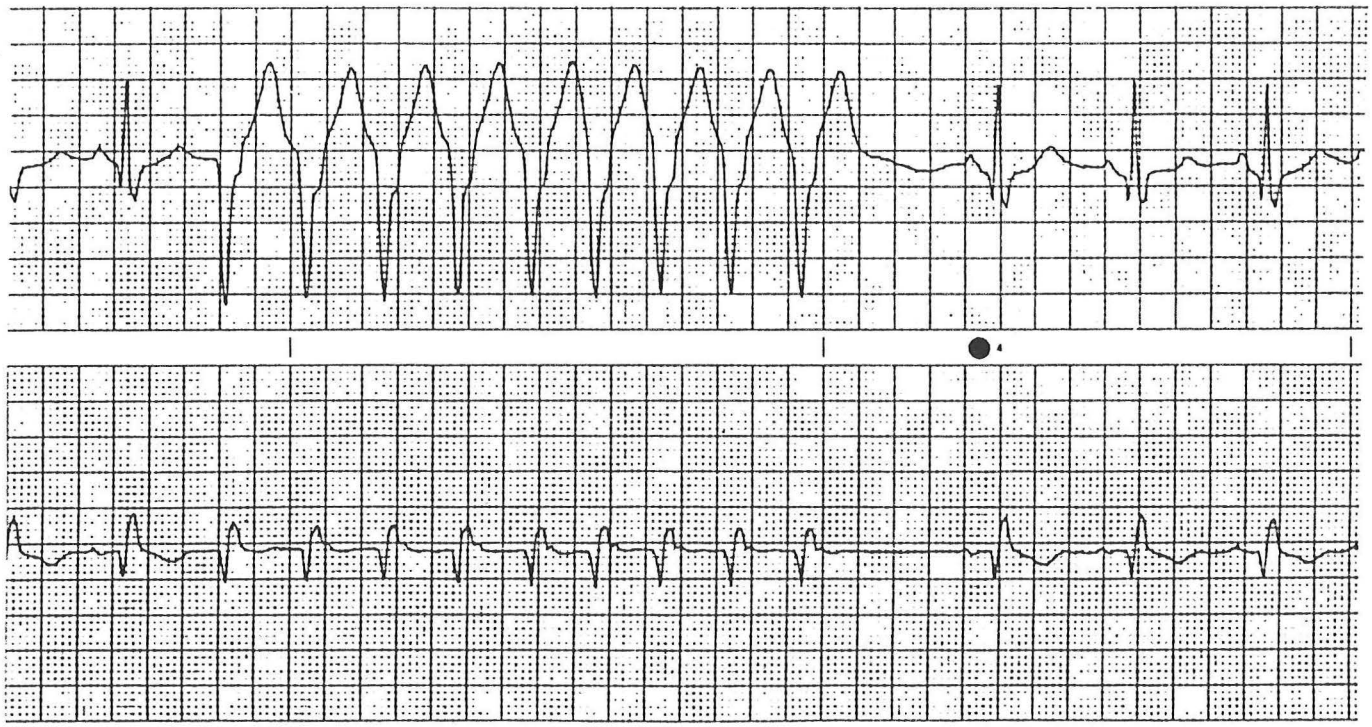

Figure 6. Nonsustained ventricular tachycardia.[28]

CAST: The Cardiac Arrhythmia Suppression Trial was a landmark study in terms of our understanding of risk stratification and pharmacologic prophylaxis from sudden death. Based on the PVC suppression hypothesis, patients with prior myocardial infarction (with EF < 55% for acute MI and <40% if over 90 days post-infarct) and high grade ventricular ectopy (6 or more PVCs/hour) were randomized to one of three drugs (flecainide, encainide or moricizine) or placebo in this double-blind trial.[7] All agents were assessed before randomization to assure that the ectopy was successfully suppressed. The primary end point was a reduction of arrhythmic death in the drug-treated groups (single sided test, due to confidence that the drugs would not do harm). The limbs with flecainide and encainide were terminated in 1989, after an average of 9.7 months, due to excess mortality (total mortality 7.7% for flecainide and encainide, compared with 3.0% in the placebo group). See figure 7. Of note, when patients received beta blocking drugs in addition to the study drug, there was no difference in mortality, suggesting that beta blocking drugs protect against the proarrhythmia of the IC medications. Also of note, the risk from the agents persisted over time, unlike the case with class IA and III agents, where their proarrhythmia (torsades de pointes) tends to be greatest after initiation.

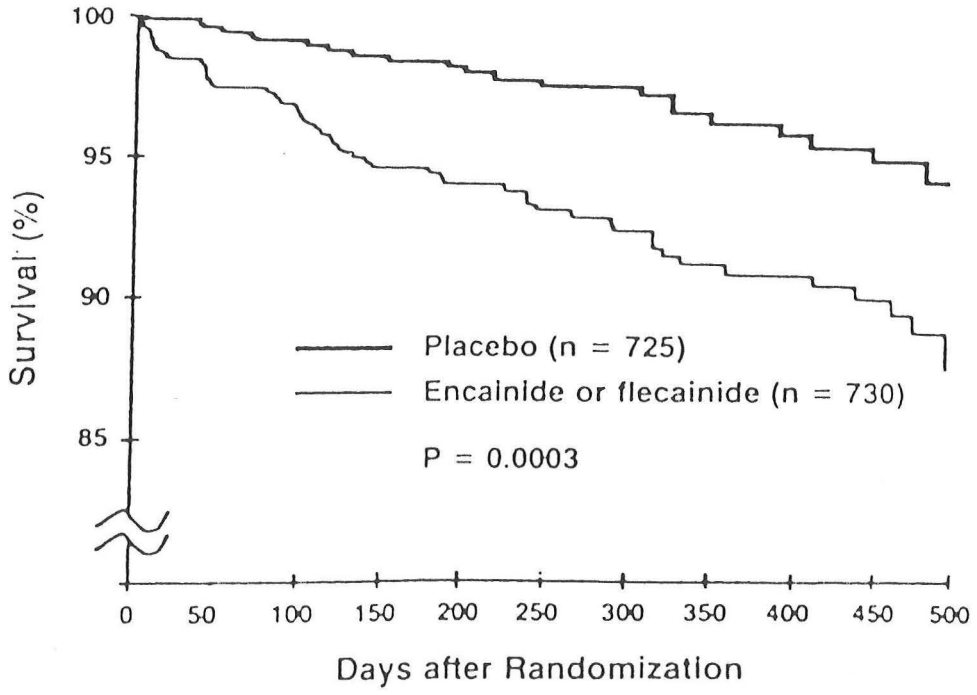

Figure 7. Overall survival in CAST, demonstrating excess mortality with flecainide and encainide.[7]

CAST was continued with CAST II, using moricizine versus placebo, but this trial was stopped due to increased acute mortality in patients during the 2-week dose-ranging stage of the trial, which previously had not been assessed in terms of adverse response. During follow-up on randomized therapy, however, there was no significant harm or benefit of

moricizine (mortality 8.4% with moricizine and 7.3% with placebo).[29] CAST and CAST II demonstrated conclusively that simply reducing ventricular ectopy did not reduce risk, but in fact could cause increased mortality. The findings resulted in "black box" warnings on all class IC agents (including propafenone), and led to encainide's being removed from the market. Of note, the use of flecainide has increased after the initial decline following CAST, but primarily for treatment of atrial fibrillation. It is now approved for supraventricular arrhythmia suppression with a structurally normal heart.

CAST and CAST II had a surprisingly low mortality among the placebo-treated patients, so it would have been unlikely that any intervention would have demonstrated benefit. Nevertheless, the findings are consistent with other trials demonstrating an excess in mortality in patients treated with class I agents.

TRIALS WITH CLASS III AGENTS: Since the PVC-suppression hypothesis proved to be incorrect, and class I agents appear to result in excess mortality, trials have concentrated on empiric therapy with class III agents for reduction in mortality.

Sotalol, which is a racemic mixture of the *d*- and *l*- stereoisomers, showed promise in the ESVEM trial, as discussed above. There is the suggestion that *d,l*-sotalol reduces mortality post-infarction, and at least it does not appear to increase mortality.[30] In contrast, the *d*-stereoisomer (which lacks the beta-blocking characteristics of the *l*-stereoisomer or the racemic mixture) has been shown to increase risk in survivors of myocardial infarction.[31] Dofetilide, a recently release "pure" class III agent, was recently studied in patients with congestive heart failure and in patients with prior myocardial infarction; there was no significant improvement in mortality but likewise there was no added risk associated with the agent.[32] Similar results recently were released on the investigational agent, azimilide, showing no change in mortality post-infarction. These data suggest little utility of these agents for the treatment of ventricular arrhythmias (except perhaps in conjunction with ICD), but they give comfort in prescribing the drugs for patients with structural heart disease and atrial fibrillation (where class I agents may increase mortality).

AMIODARONE SECONDARY PREVENTION TRIALS:

Amiodarone is a complex drug. It is a potassium channel blocker, prolonging refractoriness in all cardiac tissues, so it is considered a class III antiarrhythmic agent. It also slows conduction by blocking sodium channels and has weak calcium channel and beta-adrenergic blocking properties. Thus, amiodarone shares properties with all 4 major antiarrhythmic drug classes. Amiodarone has a large volume of distribution. Because its onset of action with oral administration is prolonged, loading doses must be given. The patient with life-threatening arrhythmias is usually given 1200 to 1600 mg orally per day for 7 to 14 days, after which the dosage is reduced to a daily maintenance dose of 400 mg. Very high-dose loading regimens (up to 2400 mg/day for 7 days) have been described, with generally favorable results. Although loading can be accomplished more rapidly via the intravenous route, adverse effects are more likely to occur. Therapeutic plasma concentrations of amiodarone range from 1.0 to 3.0 mcg/ml. There is a poor

correlation between plasma levels and efficacy but a good correlation between the plasma concentration and side effects, so that adverse effects occur frequently at plasma concentrations above 2.5 mcg/ml. Amiodarone has a very long elimination half-life (30 to 110 days) although cardiac effects can diminish substantially within a week. Its presence in plasma can be measured for as long as 9 months. Amiodarone interacts with warfarin, digoxin, flecainide, quinidine, and procainamide. Its concomitant administration with beta blockers, diltiazem, and verapamil may precipitate profound bradycardia.[33]

Amiodarone has numerous and frequent adverse effects that generally are dose related. The most concerning is lung toxicity.[34] Pulmonary fibrosis is especially likely to occur in patients with preexisting lung disease, elderly patients, and those receiving large doses. It is eventually seen in 5 to 15 percent of those who receive at least 400 mg per day for an extended period, although frequency is less at lower doses. The typical symptoms are dyspnea, cough, weight loss, fever, and pleuritic chest pain. The chest x-ray typically shows pulmonary infiltrates, and pulmonary function tests usually reveal a reduction in diffusion capacity. All patients on amiodarone should be followed closely for symptoms of pulmonary toxicity, and they should regularly have a chest x-ray. Pulmonary function testing at baseline is necessary, and is repeated either on a regular basis (where it is likely that the DLCO will indeed fall) or in response to pulmonary findings. In addition to lung toxicity, eye complications are frequent. Most of these are mild, with asymptomatic or minimally symptomatic corneal deposits. Rarely, blindness due to optic neuritis has been reported. Thyroid function disturbance is common, occurring in up to 15%, usually with hypothyroidism but occasionally with hyperthyroidism. Gastrointestinal side effects include constipation and abdominal pain. Neurologic side effects include tremor, ataxia, sleep disturbance, headache, and a peripheral neuropathy. Patients on chronic amiodarone often develop a mild elevation of hepatic enzymes, but hepatitis is rare. Although these hepatic effects are almost always reversible, fatal cirrhosis has been reported. Fortunately, proarrhythmia with amiodarone occurs rarely. Amiodarone will occasionally exacerbate conduction disturbances, so caution should be exercised with use in patients with bundle branch block. Its weak negative inotropic effect may exacerbate congestive heart failure, although most patients with left ventricular systolic dysfunction tolerate chronic oral therapy without difficulty. In fact, in randomized, placebo-controlled studies in patients with congestive heart failure, amiodarone caused an improvement in the left ventricular ejection fraction. Finally, amiodarone therapy, especially at doses of 400 mg/d, results in photosensitivity and a blue/gray discoloration of sun-exposed areas of the skin.[32]

A further concern is the potential for amiodarone to increase the defibrillation threshold (energy required for defibrillation).[35] Although many trials compare drugs and defibrillators, in clinical practice, about 50% of ICD patients require an antiarrhythmic agent also to treat atrial fibrillation or to suppress ventricular arrhythmias. An understanding of the interaction with the function of the ICD is critical in this situation.[36]

PRIMARY PREVENTION TRIALS USING AMIODARONE:

GESICA: The Grupo de Estudio de la Sobrevida en la Insurficiencia Cardiaca en Argentina (GESICA) study was a landmark in comparing amiodarone vs placebo in a diverse population with congestive heart failure (class II to IV, with mean EF 20%) from a single South American country.[37] Of note, only 39% had a history of myocardial infarction, so the majority had nonischemic cardiomyopathy (with 9% Chagas disease). PVCs (>10/h) were present in 71% and nonsustained VT was present in 33%. The amiodarone was dosed at 600 mg daily for 14 days, followed by 300 mg/d for 2 years. Side effects were reported in just 6.1%, usually for sinus bradycardia. Among 516 patients, amiodarone significantly reduced overall mortality by 28% (from 41.4% to 33.5%; see figure 8). In addition, the functional capacity increased with amiodarone, with higher proportion who had improved by at least one functional class ($p<0.03$).

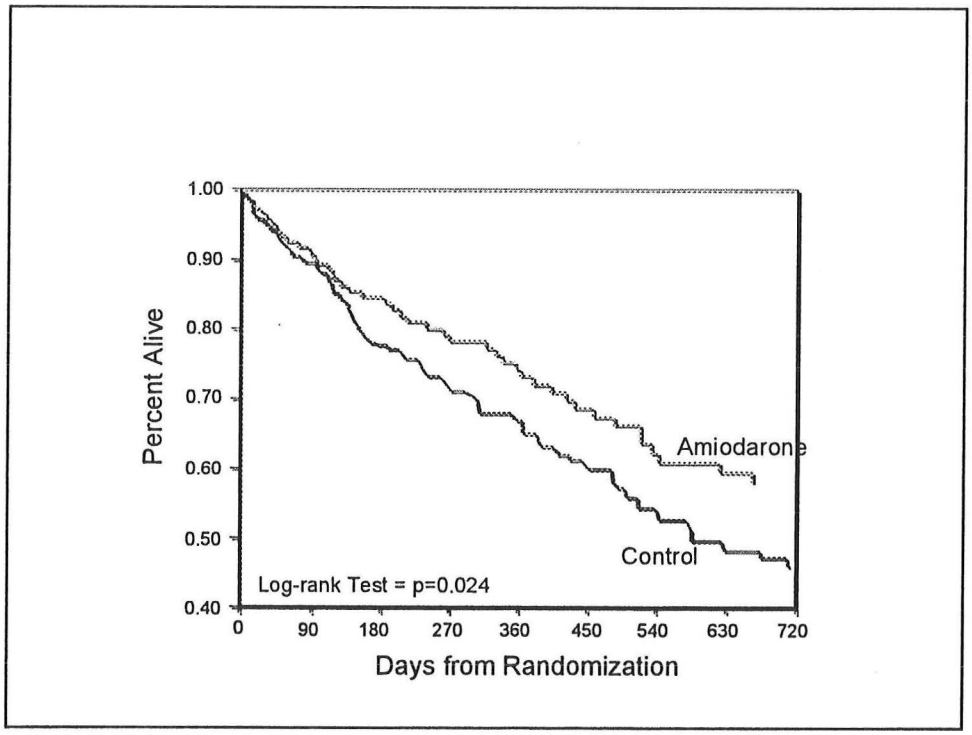

Figure 8. Total mortality in GESICA, showing benefit of amiodarone over control (p=0.024).[37]

CHF-STAT: The results of GESICA conflicted with those of CHF-STAT (Congestive Heart Failure-Survival Trial of Antiarrhythmic Therapy), which was published about the same time.[38] This study enrolled patients with high grade ventricular ectopy (10 or more PVCs/hr) and ejection fraction of 40% or less, to be randomized in a double-blind placebo-controlled comparison of amiodarone vs placebo. The amiodarone was dosed at 800 mg/d for 14 days, followed by 400 mg/day for 50 weeks, and then 300 mg/d. Among the 674 patients enrolled, amiodarone did not reduce mortality (2-year survival of 69.4% for amiodarone and 70.8% for placebo), nor was sudden death altered. There was no difference in survival between the patients where an 80% reduction of ventricular ectopy

was achieved, versus the patients where such a reduction in PVCs was not accomplished. A trend toward reduction in mortality (p=0.07) was seen among the 29% with nonischemic cardiomyopathy, however. The results in the different patient groups are shown in figure 9.

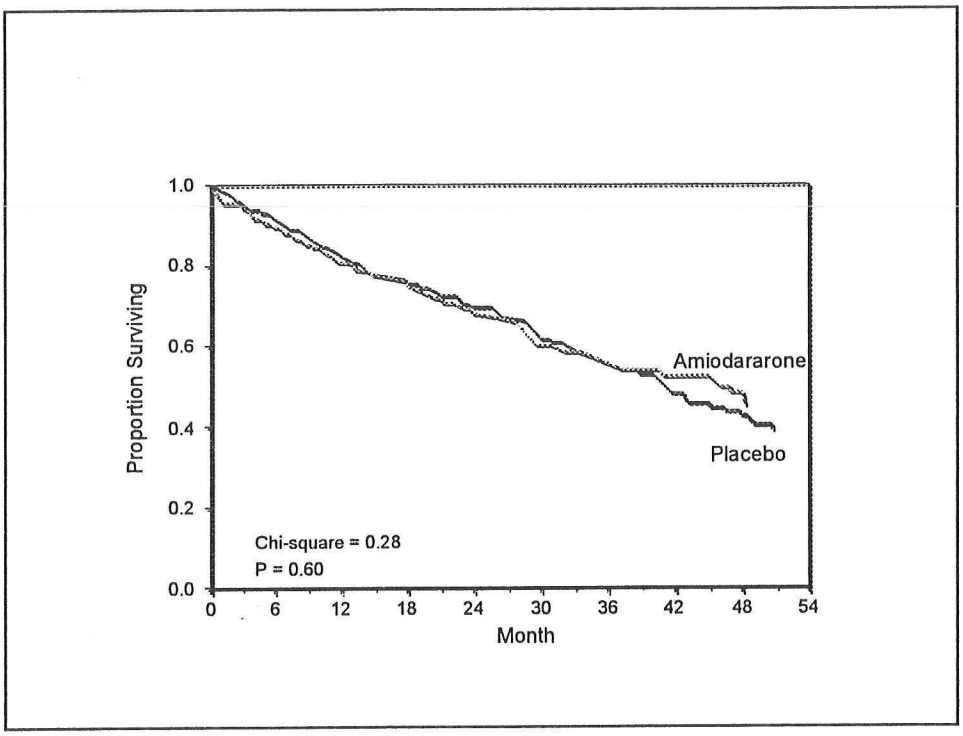

Figure 9. Overall mortality in CHF-STAT.[38] In contrast to GESICA, there was no significant treatment effect of amiodarone (p=0.28).

The findings of GESICA and CHF-STAT may disagree on the basis of the types of patients enrolled. GESICA enrolled a greater proportion of patients with primary nonischemic cardiomyopathy, including Chagas disease. CHF-STAT, on the other hand, enrolled a population typical of the VA system: men with ischemic heart disease. The frequency of withdrawal may have affected CHF-STAT, since there was a 41% treatment withdrawal rate (vs just 3% in GESICA). The results of these two trials suggested to some that amiodarone might be of benefit in the patient with nonischemic, but not ischemic, cardiomyopathy. However, further data soon became available (and indeed are still being collected).

CAMIAT and EMIAT: The European Myocardial Infarct Amiodarone Trial (EMIAT) and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) were published back-to-back in 1997, and provided further information on primary prevention in patients post-MI.

CAMIAT was designed to assess the effect of amiodarone on the risk of resuscitated ventricular fibrillation or arrhythmic death among patients post-MI with 10 or more PVCs/hour or at least 1 run of nonsustained VT.[39] Amiodarone was administered at 10 mg/kg for 2 weeks, followed by 300-400 mg/d for 3.5 months, then 200-300 mg/d for 4 months, followed by 200 mg/d (5-7 d/wk) up to 16 months. A total of 1202 patients were enrolled in this double-blind trial. Resuscitated ventricular fibrillation or arrhythmic death among those receiving study drug (the primary end point) was reduced in the amiodarone group compared with placebo (3.3% vs 6.0%; p=0.016); see figure 9. All-cause mortality was not changed, however. Of note, early discontinuation of the study agent was seen in 36% receiving amiodarone and 26% of those receiving placebo.

EMIAT, in contrast, enrolled only patients having ejection fraction of <40%, independent of the presence of PVCs.[40] Amiodarone was dosed at 800 mg/d for 14 days, 400 mg/d for 14 weeks, and then 200 mg/d thereafter. As with CAMIAT, all cause mortality was not altered by amiodarone, but the drug did result in a 35% risk reduction in arrhythmic death. In contrast, however, all cause mortality was the primary endpoint in this trial. Amiodarone was discontinued in 38% vs discontinuation in 21% taking placebo, again potentially reducing the likelihood of demonstrating any benefit.

Meta-analysis of trials with amiodarone in patients with prior MI or congestive heart failure has been undertaken.[41] In studies with a total of 6553 patients, total mortality was reduced 13%. Pulmonary toxicity was estimated to be 1% per year. Thus, the data for amiodarone as primary prevention of sudden death are somewhat conflicting. At least there is no harm, and the agent may be of some benefit in patients with nonischemic cardiomyopathy. In addition, it clearly reduces ventricular ectopic complexes. Finally, the agent is considered to be first-line for the treatment of patients with congestive heart due to its efficacy in this arrhythmia and neutral effect on mortality.[42]

DRUGS vs ICD FOR PRIMARY PREVENTION:

During the 1980s, support for EP-guided antiarrhythmic drug therapy was based on non-randomized data. Consistent findings were that a positive electrophysiology (EP) study in patients post-MI predicted a poor prognosis, but survival was better among patients in whom inducible VT/VF was suppressed by antiarrhythmic drug therapy. However, these studies were small and nonrandomized, so the stage was set to prospectively assess the utility of EP study and EP-guided therapy for primary prevention.

MADIT: The Multicenter Automatic Defibrillator Implantation Trial (MADIT), an industry-sponsored study, was initiated in 1990. The trial was designed to test whether the ICD improves all-cause mortality in high-risk patients post myocardial infarction.[43] Patients with prior MI (over 3 weeks previous) left ventricular ejection fraction of 35% or less, and nonsustained VT (3-30 beats at 120 bpm) all underwent EP study. If the EP study was positive, it was repeated after acute procainamide infusion. Only those patients who remained inducible ("non-suppressible") were enrolled (total of 198 patients) to receive either an ICD or "conventional" medical therapy as chosen by the physician. This medical therapy consisted of amiodarone (74%), class I antiarrhythmic

agents (10%), sotalol (7%), and beta-blocker alone (8%). Of note, 15% received beta-blocker overall (including sotalol), compared with 26% of the ICD group having beta-blocker alone. The trial was stopped prematurely after mean 27 months when the safety committee found that the difference between groups was substantial (p=0.009). [44] After 1 year the freedom from mortality from any cause was 97% for the ICD group, compared with 77% in the drug-treated group, and at 2 years the survival was 87% vs 68% (see figure 10). The result of this trial led to FDA re-labeling the ICD to be indicated for primary prevention in the MADIT-like population.

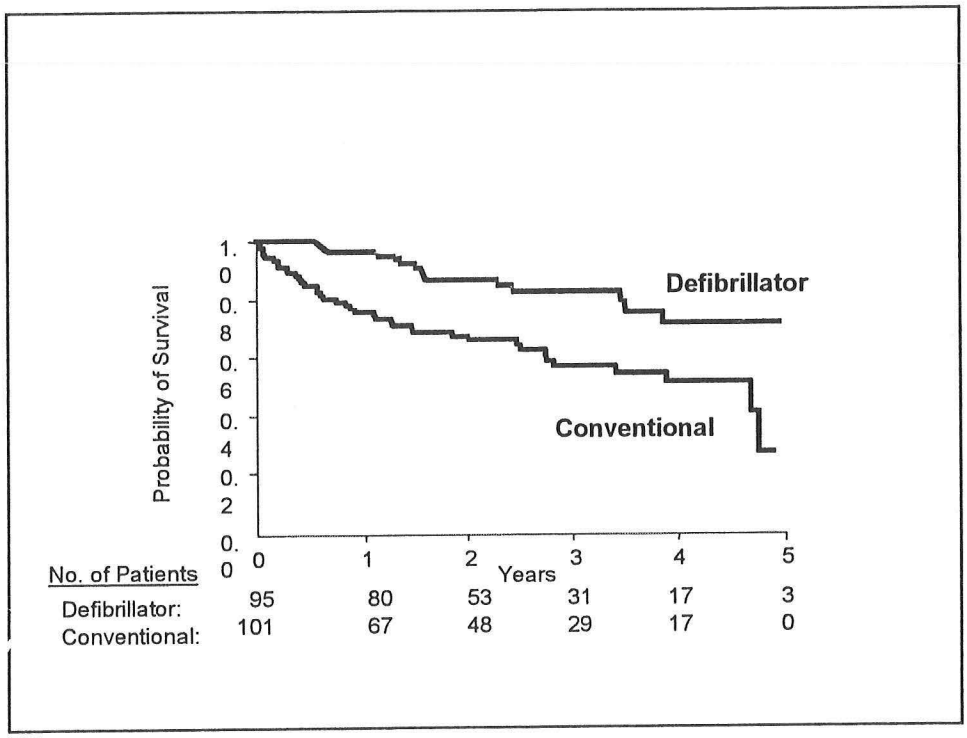

Figure 10. Survival in MADIT, demonstrating survival benefit of ICD over "conventional therapy".[44].

MADIT has limitations. Unavailable was the number of patients studied to identify the 196 patients enrolled. No registry was maintained, nor do is there information on the patients who were induced but had their arrhythmia suppressed by procainamide. Furthermore, the active control may have increased mortality in the non-ICD group, especially since we now recognize the class I agents increase mortality in survivors of myocardial infarction.

MUSTT: The Multicenter UnSustained Tachycardia Trial (MUSTT) was designed in the 1980s and started in 1989 to test the hypothesis that antiarrhythmic therapy guided by EP testing could reduce the risks of sudden death and cardiac arrest among patients with coronary artery disease, left ventricular dysfunction (left ventricular ejection fraction 40% or less), and spontaneous nonsustained VT.[45] It was sponsored by the NIH, but had further sponsorship from drug and device manufacturers. Patients underwent

programmed electrical stimulation, with positive study defined by sustained VT induced by up to 3 extrastimuli or VF induced with up to 2 extrastimuli. Patients with positive EP study were randomized to antiarrhythmic treatment or no antiarrhythmic treatment. Patients with negative study were followed and not treated with antiarrhythmic therapy. A total of 2202 patients were enrolled, and 704 had positive EP study and were randomized. Patients were followed for a median of 39 months. Among the 351 patients with positive EP study, 45% were discharged on antiarrhythmic therapy and 46% received an ICD because drug therapy was ineffective. The rate of cardiac arrest or death from arrhythmia was significantly less in the patients receiving therapy, in comparison to the untreated patients (18% vs 12% at 2 years, p=0.04); this was the primary end point for the trial.

The most important finding in MUSTT was the difference between those treated with the ICD and those treated with antiarrhythmic medication. The relative risk of all cause mortality for ICD patients was 0.24 compared with EP-guided drug therapy and 0.27 compared with no antiarrhythmic therapy. Thus, all benefit from EP-guided therapy was due to the ICD. In fact, further analysis has shown that although there was some risk-stratification with EP testing (identifying a higher risk group with a positive study), the patients with ICDs fared better even than those patients with negative EP study.[46] In a Kaplan-Meier analysis, two-year and five-year rates of cardiac arrest or death due to arrhythmia were 12 and 24 percent, respectively, among the patients in the registry, as compared with 18 and 32 percent among the patients with inducible tachyarrhythmias who were assigned to no antiarrhythmic therapy (adjusted P<0.001). The survival curves are shown in figure 11.

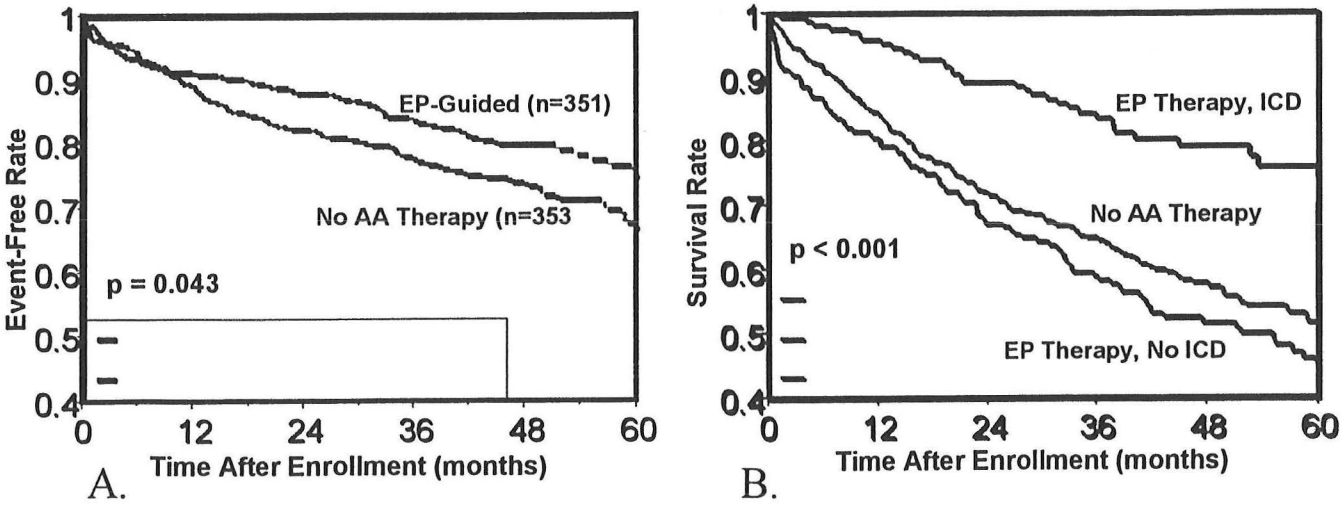

Figure 11. Results of MUSTT.[45] Panel A: EP guided therapy was associated with improvement in survival from cardiac arrest or death (primary end point). The benefit was due to the ICD alone, as shown in the panel B, where total survival for the three groups is illustrated..

The result of MADIT and MUSTT are consistent in demonstrating a benefit of the ICD in post-infarct patients with nonsustained VT and positive EP study. What remained to be determined in the post-infarct population was the true significance of nonsustained VT and whether the EP study was necessary.

MADIT II attempted to answer the questions posed above.[48] Unlike, MADIT, it enrolled post-infarct patients without regard to ventricular tachycardia or EP study. The cut-off for the ejection fraction in this population was 30%. Because of MADIT's result, each patient underwent EP study, and if positive, they received an ICD. The patients with negative studies were then randomized to ICD or not, with both groups receiving beta-blockers and ACE inhibitors. A total of 1200 patients were enrolled in 71 US and 5 European centers. On November 21, 2001, the trial was stopped prematurely due to a 30% reduction in mortality from sudden death. The New England Journal of Medicine will publish the results in March 2002. If the FDA labels the ICD for patients fitting MADIT II criteria, it is estimated that the population eligible for ICD will double.

An additional primary prevention study that has received less attention is the CABG-Patch trial. This trial randomized patients who were undergoing CABG and were considered to be at high risk for sudden death (left ventricular ejection fraction of 35% or less and positive signal averaged ECG) to receive epicardial ICD or not at the time of surgery.[49] The result was neutral, with no benefit from the prophylactic ICD. The results of the trial provided 2 important messages. First, the risk of sudden death in patients with ischemic burden may be reduced by revascularization (as has been suggested elsewhere).[50,51] And second, the signal averaged ECG may not be useful for risk stratification in this population.

Where are we still lacking data?

The trials in patients post-MI still leave a large population at risk for sudden death for whom as yet the proper treatment is not established. Patients with nonischemic cardiomyopathy remain at high risk, and although they may benefit from ICD,[52,53] at present implantation cannot be justified. Even with clinical syncope, in the absence of spontaneous or inducible VT, placement of an ICD is considered category 3 (not recommended) by American College of Cardiology practice guidelines; the exception being the pre-transplant patient, where ICD is considered to be justified.

The Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT) was designed to address the question of optimal management of patients with congestive heart failure, independent of presence of coronary artery disease, ventricular ectopy or EP study.[48] Sponsored by the NIH, in collaboration with industry, the trial completed enrollment of 2521 patients by July, 2001. Eligible patients had left ventricular ejection fraction of 35% or less and class II or III heart failure, with no history of symptomatic or sustained VT. In an equal distribution, patients were randomized to single-chamber ICD, amiodarone or placebo (with the two drug arms being double-blind). The end point is all cause mortality, after

mean follow up of 2.5 years. The study is ongoing, with results expected in 2003. In addition to mortality, the trial will examine cost-effectiveness and health-related quality of life.

Conclusions:

Clinical cardiac electrophysiology, once considered "voodoo" or a passing phase (compared, for example to ballistocardiography), is now performed according to data emanating from well-conducted randomized trials. Although some important questions remain to be answered, more and more we are practicing evidence-based medicine.

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