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Review

Amiodarone: What Have We Learned from Clinical Trials?

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Summary: Amiodarone is an antiarrhythmic agent commonly used in the treatment of supraventricular and ventricular tachyarrhythmias. This paper reviews clinical trials in which amiodarone was used in one of the treatment arms. Key postmyocardial infarction trials include EMIAT and CAMIAT, both of which demonstrated that amiodarone reduced arrhythmic but not overall mortality. In patients with congestive heart failure (CHF), amiodarone was associated with a neutral survival in CHF/STAT and improvement in survival in GESICA. In patients with nonsustained ventricular tachycardia, the MADIT trial demonstrated that therapy with an implantable cardioverter-defibrillator (ICD) improved survival compared with the antiarrhythmic drug arm in such patients, most of whom were taking amiodarone. In sustained VT/VF patients, the CASCADE trial demonstrated that empiric amiodarone lowered arrhythmic recurrence rates compared with other drugs guided by serial Holter or electrophysiologic studies. Several trials including AVID, CIDS, and CASH have demonstrated the superiority of ICD therapy compared with empiric amiodarone in improving overall survival. Clinical implications of these trials are discussed.

Key words: amiodarone, clinical trials, ventricular tachycardia

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Introduction

Over the last decade, innovative advances in antiarrhythmic drug and nonpharmacologic therapies, such as the implantable cardioverter-defibrillators (ICD) and catheter ablation, have significantly altered physicians' practice patterns in the treatment of arrhythmias. Amiodarone is an antiarrhythmic agent that is effective in treating patients with ventricular and supraventricular tachyarrhythmias. Although its pharmacokinetics are complex and its long half-life delays the onset of its protective effect, its once a day dosing ensures patient compliance. Amiodarone's hemodynamic profile makes it useful in patients with left ventricular dysfunction. In addition, end-organ toxicity can be minimized by using low chronic maintenance doses.

This paper reviews key aspects of the major arrhythmia trials in which amiodarone was one of the primary treatment arms. To consolidate available data, this paper will review these trials based on the following clinical scenarios: (1) Postmyocardial infarction (MI) trials, (2) primary prevention trials in high-risk patients, and (3) secondary prevention trials in patients with previous sustained ventricular tachycardia (VT) or ventricular fibrillation (VF).

Postmyocardial Infarction Trials

After a patient survives an MI, their risk of death from nonarrhythmic and arrhythmic cardiac causes remains high. The highest risk is in the patients with the largest infarction (lowest ejection fractions) and is increased further in patients with frequent and complex ventricular arrhythmias. Other noninvasive risk stratifiers include latent ischemia, an abnormal signal-averaged electrocardiogram (SAECG), and decreased heart rate variability.[1] The risk of sudden death in this patient population and the dismal 20% survival rates of out-of-hospital cardiac arrest victims[1] have spurred interest in prophylactic therapies as a primary preventative strategy in patients post MI.

Beta blockers, angiotensin-converting enzyme (ACE) inhibitors, 3-hydroxy-3-methylglutaryl (HMG) Conzyme A re-

ductase inhibitors and aspirin have all been demonstrated to improve survival post MI.[2–7] Despite a marked suppression of ventricular ectopic activity, the Class IC antiarrhythmics, flecainide and encainide, increased total and arrhythmic mortality rate in the placebo-controlled Cardiac Arrhythmia Suppression Trial (CAST).[8] Other Class I and III agents have had disappointing results [d-sotalol in the Survival with Oral d-Sotalol (SWORD) trial[9] and mexiletine in the International Mexiletine and Placebo Antiarrhythmic Coronary Trial (IMPACT)[10]]. Short-term proarrhythmic responses followed by long-term neutral effects were noted with d,l-sotalol in the Julian trial and moricizine in CAST II.[7, 11, 12] Other class I antiarrhythmic agents including quinidine, procainamide, disopyramide, and propafenone, have been poorly studied in the post-MI setting.

Amiodarone is a unique antiarrhythmic with Class I, II, III, and IV effects. It is an effective anti-ischemia agent, has a good hemodynamic profile, and has a low incidence of ventricular proarrhythmia. Given these characteristics, amiodarone may be useful in reducing mortality in patients post MI. Several trials have studied the usefulness of amiodarone in the post-MI setting.

BASEL Antiarrhythmic Study of Infarct Survival (BASIS)

The BASIS trial[13] prospectively investigated the effects of antiarrhythmic therapy on arrhythmic events and mortality in patients with persisting, asymptomatic, complex ventricular arrhythmias after acute MI. The study consisted of 312 patients, not taking antiarrhythmic drugs, who had Lown III–IVb ventricular arrhythmias on a predischarge Holter after an MI. Patients were randomized to amiodarone (200 mg/day after loading), individualized antiarrhythmic therapy (predominantly quinidine or mexiletine), or no antiarrhythmic therapy. Beta blockers were concomitantly used in 21% of the patients receiving amiodarone and 28% of the other patients. Persisting complex ventricular arrhythmia in the control group was associated with a 13.2% 1-year mortality. Amiodarone therapy was associated with a reduced total mortality ($p = 0.048$) and arrhythmic mortality ($p = 0.024$). A follow-up study[14] showed that the beneficial effects of amiodarone on survival persisted for several years despite the discontinuation of amiodarone therapy after 1 year.

The POLISH Amiodarone Trial

The POLISH trial[15] was designed to study the effect of empiric amiodarone therapy on mortality after an MI in patients who were not candidates to receive beta-blocking agents. Primary endpoints included cardiac and all-cause mortality. A secondary endpoint was to assess the effect of amiodarone on reducing Lown IV arrhythmias. The trial was a multicenter, parallel, double-blind, placebo-controlled study randomizing 613 patients.

Amiodarone statistically reduced cardiac death from 10.7 to 6.2% ($p = 0.048$). Total survival, the primary endpoint of the study, was reduced from 10.7 to 6.9% ($p = NS$). The incidence of Lown IV arrhythmias was significantly ($p < 0.001$) reduced in the amiodarone group (7.5%) compared with the placebo group (19.5%). Further analysis of this study demonstrated that the majority of benefit was in patients with well-preserved left ventricular function. No beneficial effect was noted from amiodarone use in patients with ejection fractions of ≤40%.

Spanish Study on Sudden Death

In the Spanish Study on Sudden Death,[16] 368 patients post MI were randomized to treatment with amiodarone (200 mg/day), metoprolol (100–200 mg/day), or no antiarrhythmic agent. Patients were followed for a mean of 2.8 years. Although amiodarone improved survival by 15.4% compared with the metoprolol group ($p = 0.006$), there was no significant difference in survival between the amiodarone and control groups ($p = 0.19$). Holter studies demonstrated that both beta blockers and amiodarone reduced heart rate, but only amiodarone statistically ($p < 0.001$) reduced ventricular ectopic activity.

European Myocardial Infarct Amiodarone Trial (EMIAT)

EMIAT[17] was performed to assess the efficacy of amiodarone in reducing mortality in patients with depressed left ventricular function following an MI. This multicenter, randomized placebo-controlled study enrolled 1,486 patients within 5–21 days of an MI who had an ejection fraction of ≤ 40% (Table I). Patients were stratified into groups of patients with ejection fractions < 30% and 30–40%. The primary endpoint was all-cause mortality, and secondary endpoints included cardiac mortality, arrhythmic death, and combination of arrhythmic death and resuscitated cardiac arrest. Follow-up ranged from 1 to 2 years (median 21 months).

Amiodarone reduced arrhythmic death by 35% ($p = 0.05$) and the combined endpoint of arrhythmic death and resuscitated cardiac death by 32% ($p = 0.05$). However, amiodarone had no beneficial or detrimental effect on cardiac mortality or all-cause mortality (102 deaths in the placebo group; 103 deaths in the amiodarone group). In the group receiving amiodarone and a beta blocker (44.5%), mortality was lower ($p = 0.06$) than in those not receiving beta blockers. No added benefit was noted in patients treated with ACE inhibitors.

Canadian Amiodarone Myocardial Infarction Trial (CAMIAT)

CAMIAT[18] tested the hypothesis that amiodarone could reduce arrhythmic death among survivors of recent MI (6–45 days post MI) who had frequent [≥ 10 premature ventricular contractions (PVC)/h] or any run of VT on a baseline Holter recording (Table I). This multicenter randomized, double-blind, placebo-controlled trial studied 1,202 patients (606 amiodarone; 596 placebo). Patients were loaded with 10 mg/kg for 2 weeks, then maintained on 400 mg amiodarone a day. Amiodarone was reduced to 200 mg a day by 8 months if ventricular ectopy suppression was noted on Holter. Of random-

TABLE I Selected features of EMIAT and CAMIAT

	EMIAT	CAMIAT
Entry criteria		
days post-MI	5–21	6–45
LVEF	<40%	No requirement
Ectopy	Not required	≥ 10 PVCS/h or ≥ 1 run
No. of patients	1486	1202
Double-blind Rx	Amiodarone-placebo	Amiodarone-placebo
Primary endpoint:	Total mortality	AD/resuscitated VF
Secondary endpoint:	CD, AD, AD+ resuscitated CA	AD, CD, TM
Placebo event rate	7.8%	4.2%
Amiodarone dosing after loading	200 mg/day	1 g/week - 300 mg/day
Follow-up	≥ 1 year	2 years
Patients on beta-blocker	44% (amiodarone) 45% (placebo)	60% (amiodarone, placebo)
Principal finding	Amiodarone reduced (p = 0.05) AD by 35%; no effect on total mortality	Amiodarone reduced AD/resuscitated VF (p = 0.029); no effect on total mortality

Abbreviations: LVEF = left ventricular ejection fraction, MI = myocardial infarction, AD = arrhythmic death, CD = cardiac death, TM = total mortality.

ized patients, 82.4% were treated with aspirin, 61.1% with beta blockers, and 31.5% with ACE inhibitors.

Patients were followed for a minimum of 1 year and a maximum of 2 years (mean 1.79 years). The primary endpoint was to assess the effects of amiodarone on a composite of arrhythmic death and resuscitated VF. Secondary endpoints included arrhythmic death, cardiac death, and all-cause mortality. Intention-to-treat analysis demonstrated that amiodarone significantly (p = 0.029) reduced the relative risk of arrhythmic death or resuscitated VF by 38.2%, from 6.9% in the placebo group to 4.5% in the amiodarone group. Amiodarone use reduced all cause mortality by 18% although this was not statistically significant (p = 0.29). The amiodarone group, who took concomitant beta blockers, had a more favorable prognosis (p = 0.006). Amiodarone suppressed PVCs in 84% of patients compared with only 35% in the placebo group. There were insufficient outcome data to assess whether suppression of PVCs by amiodarone predicted a group less likely to have a lethal arrhythmic event.

Clinical Perspective on Amiodarone Post-Myocardial Infarction Trials

The above trials demonstrated consistent safety in the use of amiodarone in patients post MI. In EMIAT and CAMIAT, high-risk patients demonstrated a reduction in arrhythmic death but not in total mortality. CAMIAT was not powered to predict overall survival benefit. The POLISH trial suggests that amiodarone is beneficial in reducing cardiac mortality in patients who have contraindications to beta blockers. In both EMIAT and CAMIAT, addition of beta blockers to amiodarone appeared to improve prognosis compared with those patients treated with amiodarone alone. Sim *et al.*,[19] in a meta-analysis of eight amiodarone post-MI trials (n = 4,125) including EMIAT and CAMIAT, noted a 21% reduction in overall mortality in the patients treated with amiodarone when compared with those given placebo. Another meta-analysis, the Amiodarone Trials Meta-Analysis (ATMA), of 6,500 patients after an acute MI or with CHF[20] reported that amiodarone reduced arrhythmic death and total mortality when a meta-analysis of all of the above trials plus amiodarone heart failure trials was performed (Fig. 1). Thus, in high-risk patients post MI who require antiarrhythmic therapy, amiodarone appears to be a safe alternative. Although the effect of amiodarone on overall mortality remains controversial, amiodarone treatment of

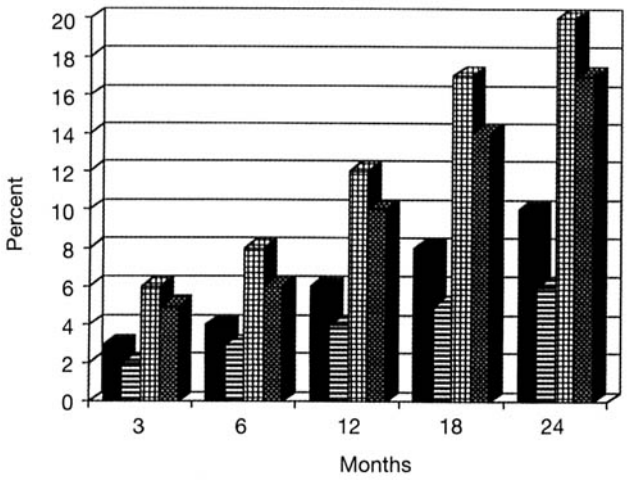

FIG. 1 Arrhythmic death (AD), sudden death (SD), and total mortality (TM) rates over 24 months of follow-up in the 6,500 patient ATMA meta-analysis study of the use of prophylactic amiodarone (amio) on mortality in eight postmyocardial infarction and nine congestive heart failure trials.[20] ■ = Control (AD/SD), ▤ = amio (AD/SD), ▦ = control (TM), ■ = amio (TM).

high-risk patients post MI seems reasonable since it appears to reduce death from arrhythmic causes.

Amiodarone: Primary Prevention Trials in Congestive Heart Failure

Patients with congestive heart failure (CHF) represent the largest group of patients who can be targeted for primary sudden death prevention. Five-year survival rates average about 25% in men and 38% in women, with 50% dying from progressive pump dysfunction and 50% dying suddenly.[21] Over 60% of patients with CHF will have ≥ 30 PVC/h and 50% will have concomitant nonsustained VT.[21] The presence of nonsustained VT is associated with an even higher mortality rate. Therapies that have been demonstrated to prolong survival in patients with CHF include ACE inhibitors, carvedilol, bisoprolol, losartan, and nitrates in combination with hydralazine. The majority of data suggests prolongation of survival mainly by nonarrhythmic mechanisms.[7]

Use of Antiarrhythmic Agents in Congestive Heart Failure

Class I agents appear to have a detrimental effect on post-MI survival even in patients with frequent ventricular ectopic activity. In patients with left ventricular dysfunction, Class I agents are associated with lower efficacy and higher proarrhythmic rates. There are no data to suggest that Class I antiarrhythmics improve survival in patients with CHF. In the Stroke Prevention Atrial Fibrillation Study (SPAF I), patients in heart failure receiving antiarrhythmic drugs such as quinidine and procainamide had a 5.8 times increased risk of cardiac death.[22] In patients with preserved left ventricular function, no statistical worsening in survival was noted. Patients with CHF with atrial fibrillation treated with class I antiarrhythmics were reported to have a lower 2-year overall and sudden death survival than a group treated with amiodarone and ACE inhibitors.[23] Amiodarone has a favorable hemodynamic and low proarrhythmic profile in patients with a depressed ejection fraction. This has led to further studies assessing the role of amiodarone in improving survival in patients with left ventricular dysfunction.

Cleland *et al.*[24] studied 22 patients with CHF in a double-blind crossover design comparing amiodarone with placebo. Amiodarone significantly reduced complex arrhythmias at rest and with exercise. In a nonrandomized trial,[25] Cleland *et al.* noted that survival was significantly better (p = 0.01) in the amiodarone group. Nicklas *et al.*[26] studied 101 patients with severe CHF and asymptomatic ventricular ectopy. Although amiodarone did not reduce overall mortality or sudden death, ventricular ectopy was reduced and the drug was well tolerated. Estudio Piloto Argentino de Muerte Subita y Amiodarone (EPAMSA)[27] was a pilot study of 127 patients with an ejection fraction of < 35% and asymptomatic Lown II, IV ventricular arrhythmia. Amiodarone reduced total 1-year mortality by 71%, from 28.6 to 10.5% (p = 0.02), and sudden cardiac death from 20.4 to 7.0% (p = 0.04). These and other pilot studies[28] led to several larger scale prospective trials.

Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiac en Argentina (GESICA)

The objective of the GESICA[28] trial was to study the effect of low-dose amiodarone in patients with severe CHF who had no symptomatic ventricular arrhythmias. The study was a multicenter, prospective, parallel study of 516 patients randomized to optimal standard treatment with and without amiodarone (300 mg/day). Of these patients, 39% had a prior history of MI; the remaining 61% of patients had nonischemic dilated cardiomyopathy or Chagas disease (Table II). Patients were stratified according to the presence of nonsustained VT.

By intention-to-treat analysis, amiodarone statistically reduced total mortality by 28%, from 41.4% in the control group to 33.5% in the amiodarone group (p = 0.024), which was the primary endpoint of the study. This beneficial difference appeared after 90–120 days of therapy and persisted to the end of the study. In addition, amiodarone trended to decrease the incidence of death from progressive heart failure (risk reduction 23%, p = 0.16) and sudden death (risk reduction 27%, p = 0.16). Patients without nonsustained VT had a 24.5% risk reduction (p = 0.16) and those with nonsustained VT had a 34% risk reduction (p = 0.054) in overall mortality.

Substudy analysis[29] noted 2-year death and sudden death rates of 50.3% in patients with nonsustained VT versus 30.9% in those without VT (p < 0.0002). Two-year sudden death rates increased from 8.7% in patients without nonsustained VT compared with 23.7% in patients with nonsustained VT (p < 0.001). Thus, in patients with CHF, the presence of nonsustained VT was an independent risk marker for increased mortality and sudden death. A further substudy[30] reported

TABLE II Selected features of GESICA and CHF-STAT

	GESICA	CHF-STAT
No. of patients	516	674
LVEF (%)	<35	≤40
Ischemic cardiomyopathy (%)	39	70
NYHA III/IV (%)	79	43
Mean heart rate (beats/min)	90	80
Atrial fibrillation (%)	29	15
> 10PVCs/h (%)	71	100
Nonsustained VT (%)	33	77
Primary endpoint (%)	TM	TM
Placebo event rate (%)	21.0	9.4
Follow-up (median)	13 months	45 months
Treatment withdrawal (%)	3	41
Principal finding	Amiodarone reduced TM (p = 0.024)	TM (p = NS) TM in non-ischemic patients trended (p = 0.07) favorably

Abbreviations: LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, PVC = preventricular contraction, VT = ventricular tachycardia, TM = total mortality, NS = not significant.

that amiodarone improved survival in patients with a resting heart rate of ≥ 90 beats/min but did not alter survival in patients with resting heart rates < 90 beats/min.

Amiodarone in Patients with Congestive Heart Failure and Asymptomatic Ventricular Arrhythmia (CHF-STAT)

CHF-STAT[31] was performed to determine whether amiodarone (400 mg/day for 50 weeks, then 300 mg/day after loading) could reduce overall mortality in 674 patients with CHF (ejection fraction ≤ 40%) and asymptomatic ventricular arrhythmias (≥ 10 PVCs/h). The study was multicenter, double blind, and placebo controlled. Of these patients, 71% had ischemic cardiomyopathy and two-thirds of the patients had ejection fractions of < 30% (Table II).

Although there were 274 deaths during follow-up (median of 45 months), there was no difference between the amiodarone and placebo groups in total mortality ($p = 0.60$) and sudden death ($p = 0.43$). Two-year survival rates were 69.4% in the amiodarone versus 70.8% in the placebo group. Amiodarone had no significant effect in overall mortality in patients with ischemic heart disease ($p = 0.61$); however, amiodarone tended to improve survival in the nonischemic heart disease group ($p = 0.07$). Amiodarone significantly reduced heart rate and PVCs/h. After 6 months of therapy, the amiodarone group had an 8.8% increase in left ventricular ejection fraction (LVEF) compared with 3.3% for patients receiving placebo.

Although 80% of patients in CHF-STAT had nonsustained VT, those without nonsustained VT had a lower use of beta blockers ($p < 0.002$) and a higher ejection fraction ($p < 0.001$). After adjusting for differences in variables, the presence of nonsustained VT tended ($p = 0.07$) to be an independent predictor for all-cause mortality but not for sudden death.[32] Only ejection fraction was an independent predictor of sudden death.

Recent data[33] from the CHF-STAT data base demonstrated that amiodarone has a significant ($p = 0.002$) potential to convert patients with atrial fibrillation to sinus rhythm and control the ventricular response (20% reduction, $p = 0.001$ at 2 weeks) when compared with the control group. A lower mortality rate ($p = 0.04$) was noted in patients receiving amiodarone who converted to sinus rhythm than in amiodarone-treated patients who remained in atrial fibrillation.

Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)

Up to 50% of patients with CHF die suddenly.[1, 21] Although ACE inhibitors improve pump survival, their effect on sudden death is minimal.[7, 34] SCD-HeFT[35] has been initiated to test the hypothesis that amiodarone or an ICD will improve survival in patients with New York Heart Association (NYHA) II–III CHF and ejection fractions ≤ 35% without a previous history of a sustained ventricular tachyarrhythmia. This three-armed study (conventional therapy versus amiodarone plus conventional therapy versus an active-can nonthoracotomy ICD plus conventional therapy) will study all-cause mortality in 2,500 patients. The projected mortality with conventional therapy is about 25%. Secondary endpoints of SCD-HeFT include comparing cardiac and arrhythmic mortality, morbidity, health-related quality of life, and cost of care. As of December 1998, 578 patients have been randomized into this study.

Clinical Perspective of Congestive Heart Failure Trials

Amiodarone appears to have a neutral effect on survival of patients with CHF. Amiodarone statistically suppresses ventricular arrhythmias and appears to have a low incidence of ventricular proarrhythmia. Therefore, it should be considered a safe agent in patients with CHF who require antiarrhythmic therapy for symptomatic ventricular and supraventricular arrhythmias. Both GESICA and CHF-STAT suggest a beneficial effect on patients with nonischemic cardiomyopathy and a neutral effect with ischemic cardiomyopathy. Subgroups of patients with concomitant nonsustained ventricular tachycardia or resting heart rates > 90 beats/min may have increased benefit with amiodarone treatment. The results of SCD-HeFT may ultimately determine whether prophylactic use of amiodarone or an ICD will be useful in the improvement of survival in high-risk patients with CHF. Meta-analysis studies[19, 20] have reported that amiodarone statistically reduced mortality in this patient population when compared with controls. In the meantime, other treatments such as beta blockers and ACE inhibitors that prolong survival should be used concomitantly.

Nonsustained Ventricular Tachycardia in Patients with Left Ventricular Dysfunction

The association of nonsustained VT in patients with a previous MI and left ventricular dysfunction is associated with a 2-year mortality rate of about 30%.[36] Wilber *et al.*[37] have demonstrated that the induction of sustained ventricular tachycardia by programmed electrical stimulation is a significant ($p < 0.001$) independent predictor of sudden death or recurrent sustained arrhythmias with a 50% 2-year mortality.

Multicenter Automatic Defibrillator Implantation Trial (MADIT)

The primary objective of MADIT[38] was to determine whether an ICD implanted in high-risk patients [nonsustained VT; prior Q wave-MI; ejection fraction ≤ 35%; inducible sustained VT not suppressed by an antiarrhythmic drug (predominantly intravenous procainamide) at electrophysiologic study] would result in a significant reduction in death when compared with conventional treatment. There were 101 patients randomized to drug therapy (80 on amiodarone) and 95 randomized to ICD therapy. The study was terminated in March 1996 after a statistically lower mortality was demonstrated in the ICD group. There were 39 (39%) deaths in the antiarrhythmic group compared with 15 (12%) in the ICD group ($p = 0.009$). Death from cardiac causes was reduced by 59% in the ICD group. Of note is that 60% of patients who received ICDs had a shock discharge within 2 years of enrollment. Subanalyses from the MADIT database have reported a 2-year mortality of 8% in MADIT noninducible patients,

20% in MADIT inducible but suppressible patients, and 25% in inducible but nonsuppressible patients who refused randomization into the study.

Clinical Perspective

This is the first randomized trial to demonstrate that an ICD could improve survival in a high-risk population. The use of a specially designed statistical approach limited the number of patients required to obtain these results. Of concern is that a large number of conventionally treated patients (23%) were not taking antiarrhythmic drugs at the time of death compared with a large number of ICD patients taking concomitant antiarrhythmics (44%). In addition, more patients in the ICD group (27%) than in the antiarrhythmic drug group (8%) were taking beta blockers. This disproportionate use of beta blockers may have had an added protective effect in the ICD group. Despite these concerns, the FDA approved the indication for routine implantation of an ICD in such patients. Whether these results will be supported by the Multicenter Unsustained Tachycardia Trial (MUSTT)[39] and whether a lower-risk group of patients can receive benefit from an ICD (1,200 patients post MI with an ejection fraction of ≤ 30%, ≥ 10 PVCs/h without the use of programmed stimulation) will be determined in MADIT II.[35] Cost-effective analysis of the MADIT population demonstrated that ICD therapy would cost $27,000 per life year saved.[40] Based on findings of this study, we recommend ICD implantation in patients with ischemic cardiomyopathy with nonsustained VT who have inducible sustained VT that persists after intravenous procainamide.

Multicenter Unsustained Tachycardia Trial (MUSTT)

The MUSTT[39] trial has recently completed enrollment and patient follow-up. Final results are not available at the time of this writing. MUSTT tested the hypothesis that electrophysiologically (EP)-guided antiarrhythmic drugs, including amiodarone, and/or ICD therapy will reduce the risk of arrhythmic death or cardiac arrest in patients with unsustained VT and left ventricular dysfunction. A secondary objective was to determine whether antiarrhythmic therapy guided by programmed electrical stimulation will reduce the incidence of sudden death. The predictive value of SAECG recordings is also being analyzed as a substudy.

Criteria for qualifying include > 1 week post-MI, LVEF < 40%, and nonsustained VT. MUSTT enrollment is currently complete. There were 704 patients with inducible sustained VT, randomized to serial-guided electrophysiologic testing using multiple different antiarrhythmic agents or an ICD in patients who had persistent inducible sustained VT. Two control groups treated with beta blockers and ACE inhibitors are being followed: one group randomized from the patients with inducible sustained VT, the remaining arm from noninducible patients. Implantable cardioverter-defibrillators were implanted in over 50% of patients randomized to serial therapy. In a preliminary analysis, the ability to induce sustained VT (30% of the first 1,480 enrolled patients) was no different in patients with shorter than with longer runs of nonsustained VT.[41] Follow-up is complete and preliminary results were reported at the 1999 American College of Cardiology meetings. The reported data demonstrated a statistical improvement in decreasing arrhythmic death or cardiac arrest in the serial electrophysiologically guided group compared with the inducible group treated conservatively. This benefit was mainly secondary to ICD use in this group. The follow-up of the noninducible patients has not yet been reported.

Amiodarone Trials in Patients with Sustained Ventricular Tachycardia/Ventricular Fibrillation

Amiodarone has been reported to be efficacious in over 60% of patients with sustained VT/VF,[1] and data exist to suggest that amiodarone is more effective than other antiarrhythmic drugs.[42] Since amiodarone and ICDs have often been used after other antiarrhythmic therapies have failed, few prospective controlled data with these therapies have existed in the past. In patients with previous sustained VT/VF and/or in those who survived a cardiac arrest, data from several studies to determine the best therapy (amiodarone vs. other drugs vs. ICD) to prolong survival[43–45] are now available (Table III).

TABLE III Amiodarone/ICD trials in sustained ventricular tachycardia/ventricular fibrillation

	AVID	CIDS	CASH
No. of patients	1,016	659	349
Therapy	ICD vs. empiric amiodarone or guided sotalol	ICD vs. empiric amiodarone	ICD vs. empiric amiodarone, metoprolol, or propafenone
Primary endpoint	TM	TM	TM
Drug event rate (%)	17.7	8.3	9.8
Principal finding	ICD group decreased TM by 39% ($p < 0.02$) compared with amiodarone or sotalol group	ICD group decreased TM by 19.6% ($p = 0.072$) compared with amiodarone group	ICD group decreased TM by 30%($p = 0.0047$) compared with metoprolol or amiodarone group

Abbreviations: ICD = implantable cardioverter-defibrillator, TM = total mortality.

Cardiac Arrest Study in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE) Study

The CASCADE[42] study evaluated antiarrhythmic drug treatment of 228 survivors of out-of-hospital ventricular fibrillation not associated with a Q-wave MI. Patients qualified if they had ≥ 10 PVCs/h in Holter and had inducible sustained VT or VF. Patients were randomized to empiric treatment with amiodarone (n = 113) or EP study-guided treatment (n = 115) using conventional antiarrhythmic therapy (Class I antiarrhythmics). The primary endpoint was cardiac survival (cardiac mortality, resuscitated cardiac arrest, syncope with an ICD shock). The mean age of the study group was 62 years and 82% of the patients had coronary artery disease. The mean ejection fraction of randomized patients was 35 ± 10% and 45% of the patients had a history of CHF. Of note, 46% of patients received concomitant ICDs.

Patients treated with amiodarone had better "cardiac survival" (defined as cardiac mortality, syncope/ICD shock, resuscitated cardiac arrest) than the conventionally treated group ($p = 0.007$). In addition, the patients treated with amiodarone had greater survival free of sustained arrhythmias ($p = 0.001$). There were no significant differences in outcomes between conventionally treated patients whose inducible arrhythmias were or were not suppressed. The amiodarone-treated group had a higher incidence of serious side effects, including a 10% incidence of pulmonary toxicity, over a 3-year period.

CASCADE: Clinical Perspective

Although amiodarone appeared superior to guided therapy with conventional agents, only 41% of the amiodarone group had no cardiac death or sustained arrhythmia by 6 years follow-up. Therefore, ICD therapy may be a better alternative to either of the above pharmacologic approaches. The conclusions of this study are limited by the fact that the control group was an active treatment group. Some of the differences between the groups may have been secondary to worsening from conventional therapy and not from amiodarone improving outcome measures. Given the high recurrence rate of VT/VF in the empiric amiodarone group, serial-guided therapy using amiodarone may provide a more predictive approach when drugs are used without ICDs.

Cardiac Arrest Study Hamburg (CASH)

The CASH trial[43] was initiated to compare the efficacy of empiric antiarrhythmic therapy against an ICD in survivors of sudden cardiac death unrelated to MI (Table III). The primary endpoint was to assess the effects of therapy on total mortality, with secondary endpoints assessing the recurrence of hemodynamically unstable VT and the incidence of drug withdrawal. In patients with ICDs, ICD discharges occurring during syncope were counted as VF recurrences; those occurring during presyncope and/or documented VT were also counted as VT recurrences. Baseline studies and pre- and post-therapy programmed electrical stimulation were performed. Patients were randomized to empiric amiodarone, metoprolol, propafenone, or an ICD within 3 months of their cardiac arrest.

An interim report of findings from the first 287 patients has been published.[42] Although sudden cardiac death was lowest in the ICD arm, total mortality was similar in the ICD, amiodarone, and metoprolol arms of the study. Since a significantly higher incidence of total mortality and cardiac arrest recurrence was found in the propafenone arm compared with the ICD arm, the safety monitoring board recommended deletion of the propafenone treatment limb. The study was continued with amiodarone, metoprolol, and the ICD treatment arms. Preliminary results reported at national meetings demonstrated that the ICD arm decreased total mortality and sudden death by 30% compared with the combined metoprolol and amiodarone treatment arms of the study ($p = 0.047$).

Antiarrhythmics versus Implantable Defibrillators (AVID) Study

The AVID trial[44] studied whether "best" antiarrhythmic therapy (empiric amiodarone or guided sotalol) or ICD therapy is superior in reducing total mortality in patients with a history of sustained VT/VF. Secondary objectives include quality of life assessment and cost effectiveness of the two study arms.

After 1,016 patients were randomized, enrollment was stopped prematurely (April 7, 1997) because of a significant survival advantage in the ICD group.[43] In the ICD group, 89.3, 81.6, and 75.4% survived 1, 2, and 3 years, respectively, compared with 82.3, 74.7, and 64.1% in the drug-treated group ($p < 0.02$). Thus, annual mortality was reduced by 39, 27, and 31% over a 3-year period by the ICD. The majority of the ICD benefit occurred in the first 9 months and only extended survival by 2.8 months because of the premature termination of the study. The benefit of ICDs was most prominent in patients with an ejection fraction of < 35%. Patient characteristics were similar in the two treatment groups, except that the ICD group had a lower incidence of prior atrial fibrillation/flutter, a lower incidence of class III patients with CHF, and a higher use of concomitant beta blockers. In addition, the ICD group had a higher number of patients discharged on a beta blocker. The average hospital charges for the ICD group was $66,600 versus $34,000 for the drug-treated group. The registry group of patients was clinically similar to the patients randomized into the trial.[45,46] Recent data[47] from the AVID registry population demonstrated similar high mortality rates in all of the entry subgroups suggesting that ICD therapy is appropriate for cardiac arrest survivors of ventricular fibrillation, syncopal ventricular tachycardia, symptomatic ventricular tachycardia, stable ventricular tachycardia, ventricular tachycardia/fibrillation with transient/correctable cause, and unexplained syncope.

Canadian Implantable Defibrillator Study (CIDS)

The CIDS trial (Table III)[48] was a randomized, multicenter trial comparing the efficacy of ICD therapy (n = 328) with amiodarone (n = 331) in 659 patients with prior cardiac arrest

or hemodynamically unstable VT. Enrollment criteria included documented ventricular fibrillation, out-of-hospital cardiac arrest requiring defibrillation, documented sustained VT ≥ 150 beats/min causing presyncope or angina in a patient with an ejection fraction of ≤ 35%, or syncope with documented spontaneous VT ≥ 10 s or induced sustained VT. The primary endpoint compared the above two therapies in reducing arrhythmic death. Secondary endpoints include quality of life assessment and cost efficacy analyses, all-cause mortality, nonfatal recurrence of VF, sustained VT causing syncope, or cardiac arrest requiring external cardioversion or defibrillation. Patients were followed for 3 to 5 years.

Preliminary results were presented by Dr. Connolly at the 1998 NASPE sessions. He reported that all-cause mortality was 25% in the ICD versus 30% in the amiodarone group. Thus, the ICD group trended ($p = 0.072$) toward overall improvement in survival by 19.6% compared with amiodarone after 3 years of follow-up. The results are confounded by the fact that many of the patients with ICDs took concomitant beta blockers (four times greater than the amiodarone group), sotalol, and amiodarone (30%). In addition, 22% of the amiodarone treatment group later had an ICD inserted.

Clinical Perspective (CASH, AVID, CIDS)

The results of the AVID, CIDS, and CASH trials consistently support ICD therapy as front-line therapy to prolong total and/or sudden death survival in patients at high risk for sudden death. These results are consistent with multiple previous retrospective studies[1] and small prospective trials such as the Dutch Cost-Effectiveness Study.[49] The annual mortality rate was twice as high in the AVID drug-treated group than in the CIDS or CASH groups (Table III). The results of all of these studies are confounded by the fact that many of the ICD patients took concomitant beta blockers, sotalol, and amiodarone. Future cost efficacy and quality of life analysis will help clinicians in prescribing the most effective therapy. Whether amiodarone would compare better with ICD if serial electrophysiologic testing and other predictors of outcome[50] had been used is not known at this time.

Conclusion

Many variables confound the interpretation of clinical trials as reviewed in this article. These variables include the timing of the intervention, drug dose or preparation, concomitant treatment, inclusion and exclusion criteria, comorbid variables, population size, the types of control group, intention-to-treat versus on therapy analysis, length of follow-up, outcome measures, and the power of the study to predict such endpoints.[7,51] Although the results of the above trials have altered prescribing habits for the last decade, therapy for a given patient needs to be individualized. Given the fact that about 80% of patients who have an out-of-hospital cardiac arrest do not survive, primary prevention will have the largest potential impact in the fight against sudden death. Myerburg *et al.*[51] have explained the importance of choosing the highest risk yield patient groups for studies and therapies. Although many therapies may be statistically effective, these same therapies may be inefficient and cost ineffective. Thus, in AVID,[44,51] although ICD therapy reduced mortality by 27% (25% in the drug arm vs. 18% in the ICD arm), the efficiency of the treatment was only 7%. Preliminary results of cost-effective analyses suggest that even in this high-risk population, an ICD may be five times less cost effective than an ICD in the MADIT population who had no history of a prior sustained ventricular tachyarrhythmia.

Many high-risk patients require therapy for atrial fibrillation and symptomatic arrhythmias. In general, Class I agents are associated with a lower efficacy and higher incidence of proarrhythmia in these patients. Amiodarone has been demonstrated to be a safe alternative in this group of patients.

As demonstrated in MADIT I, high-risk patients can be identified for aggressive therapy in a cost-effective manner.[38] However, the CABG-Patch study[52] demonstrated that patients with a depressed ejection fraction undergoing coronary bypass surgery did not have survival benefit from the implantation of an ICD. Thus, all high-risk groups may not benefit by aggressive prophylactic therapy. Trials such as SCD/HeFT may alter our prophylactic use of amiodarone and/or the ICDs in the future.

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