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Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients With Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia—AMIOVIRT

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OBJECTIVES The purpose of this multicenter randomized trial was to compare total mortality during therapy with amiodarone or an implantable cardioverter-defibrillator (ICD) in patients with nonischemic dilated cardiomyopathy (NIDCM) and nonsustained ventricular tachycardia (NSVT).

BACKGROUND Whether an ICD reduces mortality more than amiodarone in patients with NIDCM and NSVT is unknown.

METHODS One hundred three patients with NIDCM, left ventricular ejection fraction ≤0.35, and asymptomatic NSVT were randomized to receive either amiodarone or an ICD. The primary end point was total mortality. Secondary end points included arrhythmia-free survival, quality of life, and costs.

RESULTS The study was stopped when the prospective stopping rule for futility was reached. The percent of patients surviving at one year (90% vs. 96%) and three years (88% vs. 87%) in the amiodarone and ICD groups, respectively, were not statistically different ($p = 0.8$). Quality of life was also similar with each therapy (p = NS). There was a trend with amiodarone, as compared to the ICD, towards improved arrhythmia-free survival ($p = 0.1$) and lower costs during the first year of therapy ($8,879 vs. $22,039, $p = 0.1$).

CONCLUSIONS Mortality and quality of life in patients with NIDCM and NSVT treated with amiodarone or an ICD are not statistically different. There is a trend towards a more beneficial cost profile and improved arrhythmia-free survival with amiodarone therapy. (J Am Coll Cardiol 2003; 41:1707–12) © 2003 by the American College of Cardiology Foundation

The optimal therapy for prevention of sudden death in patients with nonischemic dilated cardiomyopathy (NIDCM) and asymptomatic nonsustained ventricular tachycardia (NSVT) has not been determined. The results of Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) and Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT) suggest that amiodarone therapy in patients with a NIDCM may have a beneficial or neutral effect on survival (1,2). An implantable cardioverter-defibrillator (ICD) effectively prevents sudden cardiac death (SCD) and improves total mortality compared to antiarrhythmic drug therapy in some patient groups (3–5). However, whether ICDs also reduce mortality in patients with NIDCM and asymptomatic NSVT is unknown. Therefore, the purpose of this multicenter trial was to compare total mortality in patients with NIDCM and asymptomatic NSVT randomly assigned to therapy with amiodarone or an ICD.

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METHODS

Study design. Ten centers participated in this trial (see Appendix), and the institutional review boards approved the study protocol. Subjects were randomly assigned to receive either amiodarone or an ICD. Randomization was stratified by center. Patients were enrolled between August 1996 and September 2000, and follow-up ended June 30, 2001. Patients who refused study participation were followed in a voluntary registry.

Inclusion criteria for the study included a NIDCM, an ejection fraction ≤0.35, asymptomatic NSVT, New York Heart Association functional class I to III, and age ≥18 years. A NIDCM was defined as left ventricular dysfunction in the absence of coronary artery disease (CAD) or disproportionate to the severity of CAD. Nonsustained VT was defined as at least three consecutive ventricular premature depolarizations with a rate >100 beats/min, lasting <30 s and not associated with symptoms of cerebral hypoperfusion. Optimal medical therapy with angiotensin-converting

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Abbreviations and Acronyms

CAD	= coronary artery disease
ICD	= implantable cardioverter-defibrillator
NIDCM	= nonischemic dilated cardiomyopathy
NSVT	= nonsustained ventricular tachycardia
SCD	= sudden cardiac death
VF	= ventricular fibrillation
VT	= ventricular tachycardia

enzyme inhibitors, beta-blockers, and potassium-sparing diuretics was strongly encouraged and attempted throughout the duration of the study. Exclusion criteria included syncope, pregnancy, a contraindication to amiodarone or defibrillator therapy, or concomitant therapy with a Class I antiarrhythmic drug.

The primary end point of the study was total mortality. Secondary end points consisted of SCD, non-SCD, noncardiac death, syncope, arrhythmia-free survival, quality of life, and costs. Arrhythmia-free survival was defined as freedom from death, syncope, appropriate ICD therapy, and sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). Patients who underwent cardiac transplantation were censored from data analysis beginning on the day of transplantation.

Study design rationale. Electrophysiologic testing has not been found useful for risk stratification in patients with NIDCM and asymptomatic NSVT (6–8). Therefore, amiodarone and the implantable defibrillator were used empirically to determine whether either therapy was more effective than the other.

A control group was not included because this would have substantially increased the required sample size, making the study less feasible. Furthermore, it was felt that the absence of a control group would not invalidate the results of the study. No previous study has demonstrated a negative effect of amiodarone or an ICD on survival (1–5,9–12). Therefore, if a difference in mortality between the amiodarone and ICD groups was observed, it was felt reasonable to assume that the mortality difference was not due to a negative effect of amiodarone or the ICD. On the other hand, if the two therapies were found to be equivalent, it was felt that differentiation between a neutral versus an equally positive effect on survival would be possible based on analysis of the stored electrograms recorded by the implantable defibrillators. If episodes of VT or VF were documented by the stored electrograms, this would imply that the patients treated with amiodarone would have experienced similar arrhythmias in the absence of amiodarone.

Sample size calculation. During the anticipated follow-up duration of two years, the expected total mortality rates were 20% in the patients treated with amiodarone and 10% in the patients treated with an ICD (1–3). An 80% power to identify a reduction in total morality from 20% to 10% was calculated to require 219 patients in each group ($p < 0.05$, two-sided *t* test).

Therapy and follow-up. Amiodarone therapy was initiated at a dose of 800 mg/day. The amiodarone dosage was decreased to 400 mg/day after seven days and to 300 mg/day after one year. Among the patients treated with amiodarone, thyroid function studies, aspartate and alanine transaminase plasma levels, and a chest X-ray were obtained at baseline and every four months during follow-up. Serum concentrations of amiodarone and desethylamiodarone were obtained four months and one year after initiation of amiodarone therapy.

Implantable defibrillators were inserted using conventional non-thoracotomy techniques. A successful implant was achieved in each patient. Defibrillator follow-up was performed every four months. This included evaluation of stored electrograms and sensing and pacing functions. No patient was lost at follow-up.

Outcome classification. An events committee determined the causes of death. Each of the three members of the events committee independently evaluated all information available regarding each death. To assure a blinded review, all references to amiodarone or ICD therapy were removed from the reviewed documents, including the death certificate, other relevant medical records, and interviews with family members. The members of the events committee adjudicated differences in the cause of death and a consensus was reached. The stored electrograms and all available clinical data were used to determine the appropriateness of ICD therapies.

Quality of life. Quality of life was measured using the Quality of Well Being Schedule and the State Trait Anxiety Inventory (13,14). Patients completed both questionnaires at the time of randomization and during follow-up visits.

Cost analysis. Inpatient and outpatient cost data were collected for the 24 patients who received care within the University of Michigan Health System. Data from the University of Michigan Health System cost accounting system were used. Data were gathered for a one-year interval, starting at the time at which the patient entered the trial. There was no attempt to eliminate costs for noncardiac care. Drug costs, based on wholesale costs, were calculated only for the drugs for which dosage information was collected, including amiodarone, beta-blockers, angiotensin converting enzyme inhibitors, digoxin, diuretics, warfarin, and aspirin.

Statistical analysis. All analyses were based on intention-to-treat. Primary and secondary end points were compared between the two groups with a log-rank test, and survival curves were constructed using Kaplan-Meier methods. Continuous variables are expressed as mean ± 1 SD and were compared using Student *t* test, except for comparisons between baseline and one-year quality-of-life scores within the two study groups, which were compared with a paired *t* test. A chi-squared or Fisher's exact test was used to compare nominal variables. A $p < 0.05$ was considered statistically significant.

A data safety monitoring board evaluated the results every

Table 1. Patient Characteristics

	Amiodarone	ICD	p Value
n	52	51	—
Age (yrs)	60 ± 12	58 ± 11	0.5
% Female	26	33	0.3
LVEF	0.23 ± 0.08	0.22 ± 0.10	0.5
Duration of NIDCM (yrs)	3.5 ± 3.9	2.9 ± 4.0	0.6
Diabetes mellitus (%)	36	31	0.6
Hypertension (%)	67	58	0.4
CAD > 70% (%)	3/27 (11.0%)	2/41 (4.9%)	0.3
Heart rate (beats/min)	78 ± 14	80 ± 17	0.7
RBBB (%)	8	16	0.2
LBBB (%)	53	42	0.3
NYHA class (%)			0.9
I	13	18	
II	63	64	
III	24	16	
# NSVT beats	12 ± 21	8 ± 7	0.2
NSVT (beats/min)	151 ± 20	160 ± 27	0.4
NSVT identified (%)			0.7
ECG	8	6	
Event monitor	29	26	
Holter monitor	2	6	
Hospital telemetry	61	62	

CAD >70% = one major epicardial coronary artery with a 70% or greater stenosis; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NIDCM = nonischemic dilated cardiomyopathy; # NSVT = number of beats of nonsustained ventricular tachycardia; NSVT identified = technique used to identify nonsustained ventricular tachycardia; NYHA = New York Heart Association; RBBB = right bundle branch block.

10 deaths. Prospectively determined stopping rules consisted of a mortality difference at a significance level of <0.025, or a significance level of >0.025 (90% power) based on a power calculation conditional on holding outcomes stable and assuming enrollment of 600 patients.

RESULTS

Patient characteristics. The clinical characteristics of the patients at the time of enrollment into the study are shown in Table 1. At the conclusion of the study, the mean amiodarone dosage for patients randomized to amiodarone was 303 ± 93 mg/day. The serum concentrations of amiodarone 4 and 12 months after initiation of amiodarone therapy were 1.65 ± 0.93 and 1.53 ± 0.77 mg/dl, respectively, and 1.25 ± 0.56 and 1.26 ± 0.46 mg/dl, respectively, for desethylamiodarone. Concomitant drug therapy at the last follow-up visit is described in Table 2. The mean duration of follow-up was 2.0 ± 1.3 years (range 0.1 to 4.8 years).

Table 2. Concomitant Drug Therapy at Last Follow-Up

	Amiodarone	ICD	p Value
Beta-blocker (%)	50	53	0.5
ACE inhibitor (%)	81	90	0.4
Digoxin (%)	67	71	0.5
Diuretic (%)	67	71	0.5
Spironolactone (%)	19	20	0.9

ACE = angiotensin-converting enzyme; ICD = implantable cardioverter-defibrillator.

Main findings. At the first interim analysis in September 2000, the study enrollment was discontinued because the prospective stopping rule for the inability to demonstrate statistical significance was reached. The one- and three-year survival rates among the 52 patients treated with amiodarone were 90% and 87%, respectively, compared with 96% and 88%, respectively, among the 51 patients treated with an ICD (Fig. 1; p = 0.8) . The distribution of sudden versus non-SCDs was similar between patients treated with amiodarone or an ICD (p = 0.7; Table 3).

Arrhythmia-free survival rates at one and three years were 82% and 73%, respectively, among the patients treated with amiodarone (Fig. 2). Among the patients treated with an ICD, the arrhythmia-free survival rates at one and three years were 78% and 63%, respectively (p = 0.1). Over the entire duration of the study, 5.8% of the patients treated with amiodarone and 3.9% of the patients treated with an ICD (p = 0.7) had syncope. Ventricular tachycardia or VF was the cause of syncope in each patient with an ICD in whom it occurred. An appropriate ICD therapy was delivered in 16 patients for ventricular arrhythmias that had a mean rate of 218 ± 40 beats/min (range 170 to 284 beats/min).

Quality of life assessment. The average values for the Quality of Well Being Schedule and the State Trait Anxiety Inventory at baseline and at one year were similar among patients treated with amiodarone or an ICD (Table 4). At one year, the Quality of Well Being Schedule and the State Trait Anxiety Inventory scores were not significantly different between patients treated with an ICD who did (67 ± 15 and 73 ± 22, respectively) and did not (68 ± 16 and 82 ± 31, respectively; both >0.05) receive appropriate ICD therapies.

Cost analysis. The total cost of medical care in the first year after entry into the study was $8,879 ± $27,614 in the amiodarone group, compared with $22,079 ± $22,039 in the ICD group (p = 0.1).

Discontinued therapy, crossovers, and complications. Twenty-five patients initially treated with amiodarone had the drug discontinued because of adverse side effects 17.8 ± 13.3 months (range 1.2 to 43.8 months) after initiation of therapy. An ICD was inserted 26.1 ± 16.9 months after entry into the study in eight patients initially treated with amiodarone because of near-syncope with documented VT (n = 2), cardiac arrest (n = 2), or amiodarone intolerance (n = 4). Among the cohort of patients treated with a defibrillator, one subsequently received amiodarone (200 ± 0 mg/day) for frequent appropriate defibrillator therapies, eight received amiodarone (200 ± 0 mg/day) for the treatment of atrial fibrillation, and two received amiodarone (150 ± 71 mg/day) for other reasons. Three patients underwent cardiac transplantation (Table 3).

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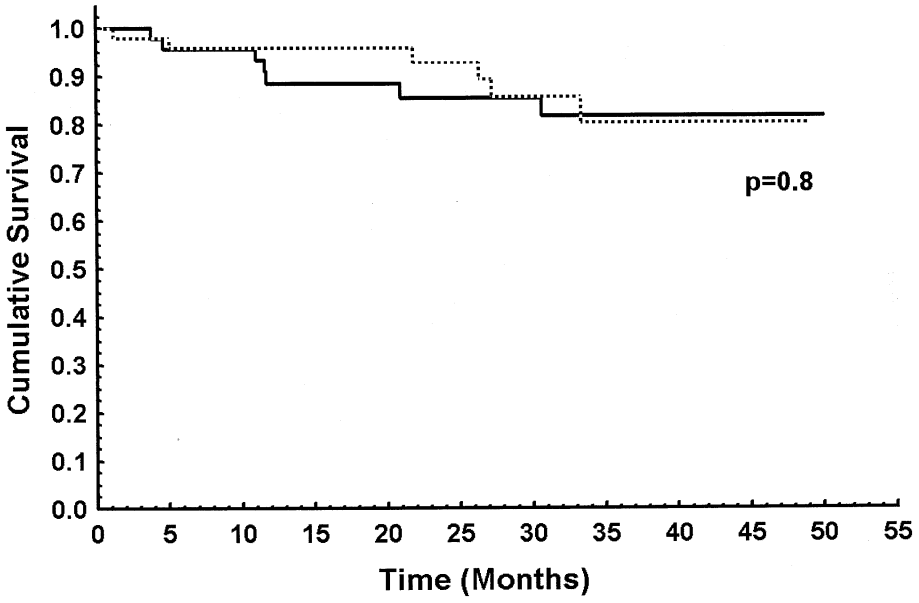

Figure 1. Kaplan-Meier estimates of cumulative survival among patients treated with amiodarone **(solid line)** or an implantable defibrillator **(dotted line)**.

DISCUSSION

Main findings. The three-year survival rate of approximately 89% was not statistically different among patients with NIDCM and NSVT who were treated with amiodarone or an ICD. There was a trend towards improved arrhythmia-free survival with amiodarone therapy. The quality of life with each therapy was not statistically different. A trend towards a 60% cost savings was observed with amiodarone therapy.

Efficacy of amiodarone. In the present study, amiodarone therapy was associated with a trend towards improved arrhythmia-free survival. This difference was primarily due to the frequent occurrence of ventricular arrhythmias with a mean rate >210 beats/min in the ICD group. Syncope among the patients treated with an ICD only occurred in the setting of a treated ventricular arrhythmia. It is likely that, left untreated, at least some of the ventricular arrhythmias treated by the ICDs would have resulted in syncope or cardiac arrest. The relatively rapid rate of the ventricular arrhythmias treated by the ICD, the association of syncope with ventricular arrhythmias, and the arrhythmia-free survival rates provide strong evidence that amiodarone and the ICD had an equally beneficial, as opposed to neutral, effect on survival. However, arrhythmia-free survival is biased against the ICD, because asymptomatic tachycardias were not recognized in the patients treated with amiodarone.

Table 3. Deaths and Transplants

	Amiodarone	ICD	p Value
n	52	51	—
# Deaths (%)	7 (13.5)	6 (11.8)	0.8
# Cardiac deaths (%)	5 (71)	4 (67)	0.9
# SCD (%)	2 (40)	1 (25)	0.7
# Non-SCD (%)	3 (60)	3 (75)	0.7
# Noncardiac (%)	2 (29)	2 (33)	0.9
# Cardiac transplant (%)	2 (4)	1 (2)	0.8
Duration of follow-up (yrs)	1.8 ± 1.4	2.2 ± 1.2	0.4

ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death.

Quality of life. In the present study, neither therapy had a statistically significant effect on quality of life. Therefore, the decision to treat with amiodarone or an ICD should not be influenced by quality-of-life issues in this patient population.

Cost analysis. During the first year of treatment, amiodarone therapy was associated with costs that were approximately 60% less than the costs associated with ICD therapy. This observation trended towards statistical significance. Other studies have also found the total costs associated with amiodarone therapy to be much less than treatment with an ICD (15–17).

Amiodarone, underlying heart disease, and efficacy. In two prior primary prevention trials among patients with CAD, the ICD was associated with improved survival compared to pharmacologic therapy, which was generally amiodarone (3,4). In the present study, the one- and three-year mortality rates in both groups were approximately the same as the mortality rates associated with ICD therapy in MADIT and MUSTT, and substantially better than the mortality rates associated with pharmacologic therapy, essentially amiodarone, in those trials (3,4). This suggests that amiodarone may be more effective in preventing death among patients with NIDCM than among patients with CAD.

Early study termination. Trial designs typically include a prospective stopping rule for futility. The mortality rates in the present study were less than expected in both groups. The lower-than-expected mortality rates may be partially attributable to concomitant medical therapy with angiotensin-

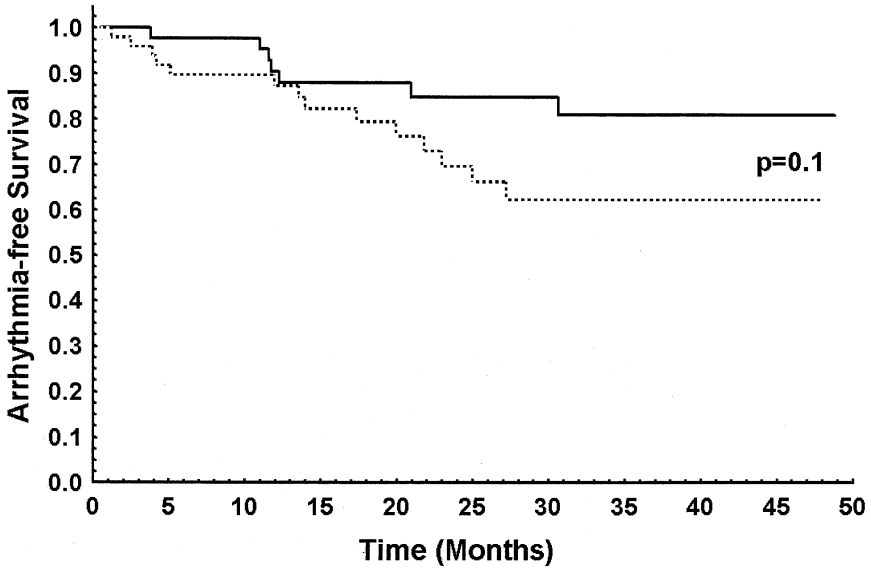

Figure 2. Kaplan-Meier estimates of arrhythmia-free survival among patients treated with amiodarone **(solid line)** or an implantable cardioverter-defibrillator **(dotted line)**.

converting enzyme inhibitors, spironolactone, and beta-blockers (18–25).

Discontinuation of amiodarone and crossovers. Amiodarone was discontinued in approximately a third of patients in the present study. This is a lower rate than was observed in MADIT (3). However, this may be the reality of treating patients with amiodarone. The use of an intention to treat analysis mitigates some of the effects of discontinued or crossover therapy. The clinical implication is that when faced with a patient who has a NIDCM and asymptomatic NSVT, initial therapy with amiodarone is associated with a similar mortality rate as initial therapy with an ICD.

Previous studies. Only one previous published study has addressed the value of an ICD at preventing SCD in patients with a NIDCM (26). In this previous study, 104 patients with new onset NIDCM, without documented ventricular arrhythmias were randomized to standard medical therapy or an ICD. Patients treated with an ICD did not have improved survival compared with patients treated with standard medical therapy. This previous study is different from the present study in at least two important ways. First, only patients with new-onset NIDCM were included. The present study excluded patients with newly diagnosed NIDCM. Patients with new-onset NIDCM may be at lower risk for SCD than patients with an established NIDCM. Second, the previous trial included patients irrespective of ventricular arrhythmias (26). The present study had inclusion criteria that included asymptomatic NSVT.

Limitations. The major limitation of this trial is that there was not a control group of patients treated neither with amiodarone nor an ICD. This raises the possibility that the addition of either amiodarone or an ICD to standard medical therapy may not have incremental value. However, given the improvement in arrhythmia-free survival with amiodarone, this seems unlikely. The second important limitation is sample size. Post hoc power calculations permit detection of the observed mortality differences with a power of 3%. This suggests that important statistical differences between amiodarone and defibrillator therapy may still exist. However, with the observed mortality rates, approximately 12,000 patients would have been required to achieve a power of 80%.

Clinical implications. In all prior primary or secondary prevention trials, the ICD was felt to be more effective than pharmacologic therapy in prolonging survival (3–5,11,12). The results of these studies have fueled the dramatic growth in the use of ICDs in the U.S. over the past few years (27). Although most or all of the subjects in these prior trials had CAD, there has been a strong tendency in clinical practice to apply the results to all patients potentially at risk of sudden death. The present study seems to represent a departure from the usual interpretation of superiority of the ICD over amiodarone demonstrated in previous studies (3–5,11,12). Not only was total mortality found not to be statistically different with amiodarone and ICD in patients with NIDCM and NSVT, but there was also a trend

Table 4. Quality of Life Scores

	Amiodarone	ICD	p Value
Quality of Well-Being Schedule*			
Baseline	70 ± 17	67 ± 15	0.5
1 year	70 ± 22	74 ± 19	0.5
p Value	0.9	0.2	
State Trait Anxiety Inventory†			
Baseline	79 ± 21	75 ± 25	0.5
1 year	67 ± 20	61 ± 17	0.4
p Value	0.1	0.1	

*The score range is 0 to 110. A higher level of general well-being is associated with a greater value. †The score range is 40 to 160. A greater value is associated with a lower level of anxiety.

ICD = implantable cardioverter-defibrillator.

towards amiodarone being more effective than the ICD in preventing symptomatic VT.

The lack of statistically different survival rates and the trend towards a substantial cost savings with amiodarone provide an argument favoring amiodarone as the initial therapy to prevent death among patients with NIDCM and NSVT.

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APPENDIX

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