Electrophysiologically Guided Amiodarone Therapy Versus the Implantable Cardioverter-Defibrillator for Sustained Ventricular Tachyarrhythmias After Myocardial Infarction
Results of Long-Term Follow-Up
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OBJECTIVES
We sought to compare the long-term survival rates of patients with sustained ventricular tachyarrhythmia after myocardial infarction (MI) who were treated according to the results of electrophysiological (EP) study either with amiodarone or an implantable cardioverter-defibrillator (ICD).

BACKGROUND
Patients with sustained ventricular tachyarrhythmias after MI are at high risk of sudden cardiac death (SCD). However, data comparing the long-term survival rates of patients treated with amiodarone or ICD, according to the results of EP testing, are lacking.

METHODS
Patients underwent a first EP study at baseline and a second one after a loading dose of amiodarone of 14 ± 2.9 g. According to the results of the second EP study, patients were classified either as responders or non-responders to amiodarone; non-responders were eventually treated with an ICD.

RESULTS
Eighty-four consecutive patients with MI (78 men; 21–77 years old; mean left ventricular (LV) ejection fraction 36 ± 11%) were consecutively included. Forty-three patients (51%) were responders, and 41 patients (49%) were non-responders to amiodarone therapy. During a mean follow-up period of 63 ± 30 months, SCD and total mortality rates were significantly higher in the amiodarone-treated patients (p = 0.03 and 0.02, respectively).

CONCLUSIONS
The long-term survival of patients with sustained ventricular tachyarrhythmias after MI, with depressed LV function, is significantly better with an ICD than with amiodarone therapy, even when stratified according to the results of the EP study. These patients should benefit from early ICD placement, and any previous amiodarone treatment seems to have no additional value. (J Am Coll Cardiol 2002;39:1813–9) © 2002 by the American College of Cardiology Foundation

Until recently, electrophysiologically (EP) guided antiarrhythmic drug therapy was considered as the best conservative approach for the management ventricular tachycardia (VT) in patients at high risk of sudden cardiac death (SCD) (1,2). After the results of the Cardiac Arrhythmia Suppression Trial (CAST), class III drugs, particularly amiodarone, have been advocated as the best anti-arrhythmic drugs available to treat these patients (3–6). However, amiodarone is usually prescribed empirically because the usefulness of EP testing in predicting its efficacy remains controversial (2,7–13).

Very recently, several trials have demonstrated that the implantable cardioverter-defibrillator (ICD) is superior to anti-arrhythmic drug treatment for the secondary prevention of SCD (14–17); however, these trials suffer from an imbalance in the use of beta-blockers, which could have favored the beneficial effect of ICD (16,18). Furthermore, in some of them, the cost per life-years saved was very high; thus, careful patient selection before ICD implantation is justified (18). Interestingly, the Canadian Implantable Defibrillator Study (CIDS) investigators have shown, in a subgroup analysis, that patients at the highest risk of death, identified on the basis of age, poor ventricular function and poor functional status, benefited the most from ICD therapy, whereas the lower-risk patients had little, if any, benefit (19,20).

We are unaware of a study that compared EP-guided amiodarone therapy with ICD therapy in terms of survival in patients with sustained ventricular tachyarrhythmias. The present study was thus performed prospectively to evaluate the long-term outcomes in patients with sustained ventricular tachyarrhythmia after myocardial infarction (MI) treated with either amiodarone or ICD therapy, according to the results of the EP study.

METHODS
Patients and treatment. Patients were recruited at our institution between January 1987 and December 1995. Patients between 20 and 80 years old who had an MI and a first episode of documented, sustained VT or ventricular fibrillation (VF) and inducible, sustained ventricular tachyarrhythmia during ventricular stimulation were consecutively enrolled in the study. The study protocol was in
agreement with the guidelines of the Ethics Committee of our institution and was explained to all patients; oral consent was obtained from each patient.

The study group consisted of 84 consecutive patients (78 men [93%] and 6 women [7%]; mean age 60 ± 10 years). All patients had a previous MI, and eight of them had their arrhythmic event within two to four weeks after the MI. The clinical presentation was syncope in 24 patients (29%), palpitations in 23 patients (27%), dizziness in 17 patients (20%), angina pectoris in nine patients (11%), aborted SCD in nine patients (11%) and dyspnea in two patients (2%). The mean left ventricular ejection fraction (LVEF) was 36 ± 11%. The clinical documented arrhythmia was VT in 73 patients and VF in 11 patients.

All patients underwent programmed ventricular stimulation while not receiving anti-arrhythmic drugs. A total of 81 patients had a baseline EP study: three patients (4%) could not be studied in the basal state, as anti-arrhythmic drug withdrawal was considered unsuitable because of spontaneous VT recurrence. In these three patients, the cycle length of the documented clinical VT was used as the index arrhythmia, to be compared with the cycle length of induced VT treated with amiodarone.

After a mean loading dose of amiodarone of 1.2 g/day during 8 to 15 days, all 84 patients underwent a second EP study. According to the result of this second programmed ventricular stimulation, patients were classified as "responders" or "non-responders" to amiodarone therapy.

The ventricular pacing protocol that we applied is described elsewhere (21). Briefly, three pacing cycle lengths with up to three extrastimuli at two stimulation sites at twice the diastolic threshold in the right ventricle were used. The end points of the pacing protocol were sustained, monomorphic VT, VF or completion of the protocol.

**Definitions.** Patients were considered as "amiodarone predicted responders" (group 1) after the second EP study if, compared with baseline, VT was: 1) non-inducible; 2) slowed to a mean cycle length ≥400 ms and was hemodynamically well tolerated; or 3) slowed by >15 beats/min and was hemodynamically well tolerated. "Amiodarone predicted non-responders" (group 2) were inducible patients with: 1) VF; 2) a VT cycle length <400 ms; 3) VT slowed by <15 beats/min; or 4) any hemodynamically non-tolerated VT. The induced ventricular arrhythmia was considered as tolerated if it did not cause cardiovascular collapse, angina, near syncope, dizziness or confusion or systolic pressure <90 mm Hg after 5 min in the supine position.

According to the results of the second EP study, responders continued their amiodarone therapy at doses of 400 mg/day for three months and 200 mg/day thereafter. Non-responders stopped amiodarone and underwent ICD placement. The best concomitant non-anti-arrhythmic drug treatment was prescribed to the patients according to their underlying cardiac disease.

Patients’ follow-up data were obtained by consulting the flow chart completed during their regular follow-up visit or by telephone contact with their physician.

"Sudden cardiac death" was defined as death of cardiac origin occurring unexpectedly within 1 h of the onset of new symptoms or death that was unwitnessed and unexpected, unless a specific non-cardiac cause of death was confirmed (22). In all cases of out-of-hospital death, contact with the physician and patient’s family was used to classify the patient’s death.

**Statistical analysis.** The baseline characteristics of the patients are expressed as the mean value ± SD or proportion (%). The two groups were compared using parametric or non-parametric tests (Student t, Wilcoxon, Mann-Whitney U or chi-square test). Survival curves for both groups were determined according to the Kaplan-Meier method and were compared using the log-rank test. The Cox proportional hazards model was used to adjust for imbalances in baseline prognostic factors and to investigate potential subgroup effects. For all analyses, p < 0.05 was considered statistically significant. Data were analyzed according to the on-treatment principle. Statistical analyses were performed using S-Plus, version 4.0 (MathSoft International, Bagshot, U.K.)

**RESULTS**

The clinical characteristics of the study group are presented in Table 1. Both groups are comparable in terms of gender distribution, LVEF, localization of MI, multiple MIs, multivessel coronary artery disease, previous coronary artery bypass graft surgery, New York Heart Association (NYHA) functional class and concomitant beta-blocker therapy. However, group 1 patients (amiodarone predicted responders) were significantly older than group 2 patients (62 ± 9 vs. 57 ± 10 years, p = 0.007), and fewer responders to amiodarone were treated with angiotensin-converting enzyme (ACE) inhibitors (63% vs. 88%; p = 0.02).

During the first EP study, monomorphic sustained VT was induced in 79 patients, and VF was induced in 2. The mean cycle length of induced monomorphic VT was 306 ± 63 ms. According to the results of the second EP study, while on amiodarone (mean dose 14 ± 2.9 g orally during a loading period of 8 to 15 days), 43 patients (51%) were
classified as “amiodarone predicted responders” (group 1), and 41 (49%) as “amiodarone predicted non-responders” (group 2). The mean cycle length of the sustained ventricular arrhythmia induced during the first EP study was not significantly different between groups 1 and 2 (304 ± 55 vs. 307 ± 72 ms), nor was the loading dose of amiodarone (14.2 ± 3.1 vs. 13.8 ± 3 g).

In group 1, during the second EP study with amiodarone therapy, sustained VT was induced in 30 patients (70%); its cycle length was significantly prolonged from 304 ± 55 to 426 ± 47 ms (p < 0.0001). The remaining 13 patients had no sustained ventricular arrhythmia induced. In group 2, sustained VT was induced in 39 patients, with no significant change in the basic cycle length (307 ± 72 vs. 316 ± 63 ms), and in two patients, only VF was inducible. The ventricular effective refractory period (VERP) at baseline was similar in both groups and significantly prolonged after amiodarone loading; there was a non-significant trend toward a greater prolongation of the VERP in group 1 compared with group 2 (p = 0.06).

The clinical presentation of the index arrhythmia differed between the groups: non-tolerated VT (expressed as syncope or SCD) was significantly more frequent in group 2 patients (p = 0.02), but palpitations were significantly more frequent in group 1 patients (p < 0.001).

According to the results of the second EP study, amiodarone therapy was continued in responders, and all non-responders received an ICD (6 epicardial systems and 35 non-thoracotomy lead systems). There were no complications related to the ICD, and all patients were discharged alive.

Seventeen patients (39%) in group 1 had side effects during amiodarone therapy, requiring withdrawal of the drug in six patients: two patients had subsequent ICD placement, and four were switched to d,l-sotalol therapy. Four more patients from group 1 underwent subsequent ICD placement because of the recurrence of VT. One patient in group 1 and three patients in group 2 underwent heart transplantation; furthermore, in six group 2 patients (15%), amiodarone was added again to their drug regimen to lower the incidence of device therapies.

Mortality. During a mean follow-up period of 63 ± 30 months (range 2 to 123 months) (group 1: 56 ± 30; group 2: 70 ± 28; p = NS), 24 patients died (29%) (Table 2). Death occurred in 18 patients in group 1 (42%) and in six patients in group 2 (15%). Ten patients (12%) suffered an SCD: nine patients in group 1 (21%) and one patient in group 2 (2%). Seven patients (8%) suffered a non-SCD: five patients in group 1 and two in group 2. Seven patients (8%) had a non-cardiac death: four in group 1 and three in group 2.

The actuarial total mortality rate was significantly lower in group 2 compared with group 1: 0%, 0% and 9% in groups 1 and 2 versus 12%, 21% and 42% in group 1 at one, three and six years, respectively (p = 0.02) (Fig. 1). Placement of an ICD
was associated with a 78% reduction in total mortality, compared with amiodarone therapy at six-year follow-up.

The actuarial SCD rate was significantly lower in group 2 compared with group 1: 0%, 0% and 3% in group 2 versus 2%, 8% and 29% in group 1 at one, three and six years, respectively (p < 0.03) (Fig 2).

The only predictive variable for both total mortality and SCD mortality was a “favorable” response to amiodarone therapy; syncope or aborted SCD, as the clinical presentation of the index arrhythmia, was predictive of SCD (p = 0.04). No other tested variable (Table 1) in the Cox proportional hazards model was predictive of either global mortality or SCD mortality.

No clinical or EP variable could differentiate inducible from non-inducible patients in group 1. Three (23%) of 13 non-inducible patients died, all suddenly; there was no statistically significant difference in the global and SCD rates (p = 0.3 and 0.8, respectively) between patients with or those without inducible, sustained VT after amiodarone loading dose in group 1.

Finally, there was a non-significant trend toward a higher non-SCD rate in group 1 (5 deaths) compared with group 2 (2 deaths) (p = 0.07).

**DISCUSSION**

This study compares the long-term survival rates in patients who had an MI and a first episode of sustained ventricular tachyarrhythmia, treated with either amiodarone or an ICD, according to the results of programmed ventricular stimulation. Our study was not randomized, but reflects the commonly used clinical practice of placing an ICD when anti-arrhythmic drugs fail. The present study demonstrates that total mortality and SCD are significantly higher in patients treated with amiodarone, even when there is a favorable response to the drug. These results are in agreement with other published studies comparing anti-arrhythmic drug treatment and ICD therapy in patients with sustained ventricular tachyarrhythmias (14,16,17); however, in these studies, amiodarone was given empirically, and the effect of amiodarone on VT was not tested in an EP study (7,23,24).

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**Table 2. Causes of Death**

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 84)</th>
<th>Group 1 (n = 43)</th>
<th>Group 2 (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (months)</td>
<td>63 ± 30</td>
<td>56 ± 30</td>
<td>70 ± 28</td>
</tr>
<tr>
<td>Total deaths</td>
<td>24 (29%)</td>
<td>18 (42%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>SCD</td>
<td>10 (12%)</td>
<td>9 (21%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>NSCD</td>
<td>7 (8%)</td>
<td>5 (12%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Noncardiac deaths</td>
<td>7 (8%)</td>
<td>4 (9%)</td>
<td>3 (7%)</td>
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</table>

Data are presented as the mean value ± SD or number (%) of patients.

NSCD = nonsudden cardiac death; SCD = sudden cardiac death.

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**Figure 1.** Global survival was significantly better among patients treated with the implantable cardioverter-defibrillator (ICD), compared with amiodarone.
Clinical characteristics. Aborted SCD was rare in our study group: the majority of our patients had sustained VT but not VF. The clinical presentation of the index arrhythmia was aborted SCD or syncope in 39% of our patients, which is significantly lower than the rates in other published studies (14,16,17). Only 23% of our patients were in NYHA functional class III or IV, and 55% of the patients had an LVEF $\geq$35%. Thus, part of our study group can be considered as being at low risk, compared with other study groups, in which there was a higher proportion of patients with non-tolerated VT as the index arrhythmia (14,16,17,25,26); this probably explains the lower total mortality rate in our study group compared with other study groups.

Group 1 patients had significantly more palpitations and less syncope than group 2 patients, as the clinical expression of their index arrhythmia. Hemodynamic tolerance has been considered as a favorable end point during EP drug testing and, by definition, characterized our group 1 patients (7,10,27). These two elements could suggest that group 1 patients had a lower risk of dying suddenly, compared with group 2 patients. This was not confirmed in our study: patients treated with amiodarone still have considerably high sudden and total mortality rates and do less well than patients treated with an ICD. Electrophysiologic data during amiodarone therapy (VT cycle length and VERP) were not predictive of the outcome, indicating that EP study has no additional value in the management of these patients. The significant increase in inducible VT cycle length to hemodynamically tolerated levels in group 1 was associated with a modest increase (14%) in VERP, compared with previous studies (VERP prolongation of 19% to 23%), in which slowing of the VT cycle length prevented SCD (8,28–32). Thus, it is possible that the limited effect of amiodarone on VERP in our patients could not prevent faster VT, leading subsequently to SCD, but not inducible during EP study. Furthermore, in group 1, the outcome of patients with or without inducible sustained VT after a loading dose of amiodarone did not differ significantly.

Comparison with other studies. The results of our study are in agreement with recently published data from the Anti-arrhythmics Vs. Implantable Defibrillator (AVID) registry (33,34): patients with seemingly low-risk VT have a mortality similar to that of the higher risk, AVID-eligible patients with VT. Therefore, patients with post-MI VT clearly benefit from ICD therapy, compared with amiodarone, even if the drug response appears favorable during the EP study. This strongly suggests that this approach should be abandoned because of the inability to predict amiodarone inefficacy using an invasive study. Consequently, according to a recent subgroup analysis of CIDS data, and on health and economic grounds, it would be better if amiodarone
were prescribed using simple clinical predictors such as age, functional status and LVEF that help target patients who might not have an additional benefit from expensive ICD therapy (19).

The better outcome in terms of global mortality in our ICD-treated patients, compared with group 1 patients, is essentially related to a far lower SCD rate, as expected with ICD therapy (35,36). There was also a trend toward a lower non-SCD rate in our ICD group, suggesting that several selection biases might have been introduced; however, other published studies have shown an unexpected significant reduction in the non-SCD rate in patients treated with an ICD when compared with amiodarone therapy (16,30,37). Both of our groups had a rate of SCD similar to that in earlier studies, but they differ in a lower overall death rate, owing to a lower non-SCD rate (4,36,37). This could be due to several biases (36,37) and might be explained by a different observed study group, owing to the inclusion of lower-risk patients, use of specific inclusion criteria, introduction of new drug treatments (e.g., beta-blockers, ACE inhibitors) or the fact that our study was observational in design and did not follow randomized patients.

Although responders and non-responders to amiodarone were similar in terms of multiple clinical variables (Table 1), group 1 patients were significantly older than group 2 patients. This unexpected finding was not reported in other studies testing amiodarone efficacy and is probably related to our specific inclusion criteria used for the definition of group 1 patients. Younger age could have resulted in the better outcome in ICD patients (group 2). However, the significant difference in terms of both total mortality and SCD still persists after adjustment for age in the multivariate analysis. Finally, an imbalance in ACE-inhibitor therapy could have favored the outcome in ICD-treated patients (38).

**Study limitations.** Our study is a single-center, prospective, observational study that included a limited number of patients during a nine-year follow-up period. This could have introduced several biases because there was a significant evolution during the recruitment period in the global management of patients with ischemic heart disease (30,31). However, long recruitment periods were also observed in the Cardiac Arrest Study Hamburg (CASH) and AVID trials (7,10). Our study group is quite homogeneous, representing 91% of post-MI patients with sustained VT referred for EP evaluation, and our group 2 patients represent 94% of all patients implanted with an ICD for sustained VT after an MI; thus, only a few patients escape our protocol during this long inclusion period. As stated earlier, an important limitation of our non-randomized study is the significant imbalance in ACE-inhibitor therapy, as well as the trend toward an imbalance in beta-blocker use in the amiodarone group, which might explain a higher mortality rate.

The role of programmed ventricular stimulation in assessing the protective effect of amiodarone is still controversial. The criteria we used to evaluate amiodarone efficacy during the second EP study were non-inducibility and good hemodynamic tolerance of induced VT; both end points have been considered as good prognostic indexes by several authors (12,39), but they turned out to have no prognostic value in our study. Furthermore, VERP was also not predictive of the outcome in either group. Therefore, the data suggest that these end points must be abandoned or that EP testing is not valid during amiodarone therapy. The loading dose of amiodarone was prescribed during a period varying between 8 and 15 days, which could induce a bias in the study, and amiodarone plasma levels were not measured. However, the loading dose of amiodarone in our study is in accordance with the dose used in other studies (17,24,39,40).

**Conclusions.** Our study demonstrates that patients with depressed LV function, having suffered sustained VT after MI, have a better long-term outcome when treated with an ICD, compared with amiodarone therapy, even if stratified according to the results of the EP study. These patients should benefit from early ICD placement; any previous amiodarone treatment seems to have no additional value.

**References**


