Long-Term Comparison of the Implantable Cardioverter Defibrillator Versus Amiodarone

Eleven-Year Follow-Up of a Subset of Patients in the Canadian Implantable Defibrillator Study (CIDS)

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Background—The implantable cardioverter defibrillator (ICD) is superior to amiodarone for secondary prophylaxis of sudden cardiac death. However, the magnitude of this benefit over long-term follow-up is not known. Thus, our objective was to evaluate the long-term consequences of using amiodarone versus an ICD as first-line monotherapy in patients with a prior history of sustained ventricular tachycardia/ventricular fibrillation or cardiac arrest.

Methods and Results—A total of 120 patients were enrolled at St Michael’s Hospital in the Canadian Implantable Defibrillator Study (CIDS) and were randomly assigned to receive either amiodarone (n=60) or an ICD (n=60). The treatment strategy was not altered after the end of CIDS unless the initial assigned therapy was not effective or was associated with serious side effects. After a mean follow-up of 5.6±2.6 years, there were 28 deaths (47%) in the amiodarone group, compared with 16 deaths (27%) in the ICD group (P=0.0213). Total mortality was 5.5% per year in the amiodarone group versus 2.8% per year in the ICD group (hazard ratio of amiodarone: ICD, 2.011; 95% confidence interval, 1.087 to 3.721; P=0.0261). In the amiodarone group, 49 patients (82% of all patients) had side effects related to amiodarone, of which 30 patients (50% of all patients) required discontinuation or dose reduction; 19 patients crossed over to ICD because of amiodarone failure (n=7) or side effects (n=12).

Conclusions—In a subset of CIDS, the benefit of the ICD over amiodarone increases with time; most amiodarone-treated patients eventually develop side effects, have arrhythmia recurrences, or die. (Circulation. 2004;110:112-116.)

Key Words: arrhythmia ■ antiarrhythmia agents ■ defibrillator, implantable

Three large randomized controlled trials (Canadian Implantable Defibrillator Study [CIDS], Antiarrhythmics Versus Implantable Defibrillators Trial [AVID], and Cardiac Arrest Study Hamburg [CASH]) demonstrated a risk reduction in overall mortality after implantable cardioverter defibrillator therapy compared with antiarrhythmic therapy (primarily amiodarone) in survivors of ventricular tachycardia/ventricular fibrillation (VT/VF), although this benefit did not reach statistical significance in the CIDS study. A meta-analysis of these 3 trials showed a significant reduction in death from any cause with the ICD, with a summary hazard ratio (ICD:amiodarone) of 0.72 (95% CI, 0.60 to 0.87; P=0.0006). After the publication of the trials and their meta-analysis, the standard of care changed to ICD implantation as the preferred treatment for VT/VF survivors. However, the individual trials followed patients for a relatively short period of time; neither the CIDS nor CASH studies demonstrated a significant benefit of the ICD over amiodarone, and it is not known if the benefits of the ICD over amiodarone diminish, remain constant, or increase beyond the average 2- to 5-year time frame evaluated in the published trials (ie, if the respective mortality curves converge, remain parallel, or diverge). In addition, some subgroups of patients may receive less benefit than others. For example, patients with an ejection fraction >35% in subgroup analysis appear to derive little or no benefit from the ICD over amiodarone in these trials. In CIDS, younger patients with better NYHA functional class also appear to derive less benefit (over the time frame studied) from the ICD. At the conclusion of CIDS, the steering committee made no formal recommendations regarding ongoing management of the patients assigned to amiodarone.

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A decision was made at our institution, at termination of CIDS, to recommend to those patients randomized to amiodarone that they remain on assigned therapy unless they had arrhythmia recurrence or significant side effects. Prior reports have shown a marked variation in the efficacy and tolerability of amiodarone for prevention of
sudden cardiac death, and only few data over a long time frame are available. The long-term efficacy, toxicity, and tolerability of amiodarone and the long-term benefit of the ICD versus amiodarone in VT/VF survivors randomly assigned to therapy have not been reported previously. We followed all patients originally randomized in CIDS at St Michael’s Hospital and report our experience with up to 11 years of follow-up.

Methods
Inclusion Criteria and Randomization
The details of the CIDS study have been published elsewhere. CIDS was a secondary prevention randomized trial that enrolled 659 patients with a history of resuscitated VT/VF or unmonitored syncope with inducible VT and left ventricular ejection fraction (LVEF) <35%. A total of 328 and 331 patients were randomized to receive either ICD or amiodarone, respectively. Randomization was stratified by clinical center and by LVEF (≥35% and <35%). The study was approved by the St Michael’s Hospital Research Ethics Board, and each patient provided written informed consent.

Amiodarone
Amiodarone was initiated and maintained according to the CIDS protocol. Patients randomized to amiodarone received ≤1200 mg/d for ≥1 week in the hospital and ≤400 mg/d for ≥10 weeks. After the loading dose, patients received a maintenance dose of 200 to 400 mg daily.

Study Design
At St Michael’s Hospital, a total of 120 patients were enrolled and followed in CIDS between October 1990 and March 31, 1998. All patients were informed of the CIDS results at the conclusion of the study and advised to remain on assigned therapy unless adverse events occurred. All agreed and were followed in the Arrhythmia Clinic. All patients who had been enrolled in CIDS were thus maintained on their assigned therapy (ICD or amiodarone) after the formal termination of CIDS and only received the alternative therapy in case of therapy failure (defined for amiodarone as sustained VT, unmonitored syncope, or cardiac arrest) or adverse effects requiring permanent therapy discontinuation. During follow-up, all patients were reviewed every 6 months with a clinical examination and laboratory investigations, including liver enzymes, thyroid function tests, and an ECG.

Outcome Events
The primary end point was all-cause mortality. Secondary end points were cause-specific mortality, amiodarone-related side effects, amiodarone discontinuation, ventricular arrhythmia recurrence, as well as the composite end point of total mortality or ventricular arrhythmia recurrence or discontinuation of amiodarone attributable to severe side effects. Side effects were recorded by the investigators whether or not they required dose reduction or discontinuation of amiodarone. Amiodarone side effects were considered significant if dose reduction or discontinuation of amiodarone was required and included thyroid disorders, hepatitis, dermatological side effects, pulmonary, cardiac, gastrointestinal, and ophthalmic side effects, and neurotoxicity.9–12

In patients with an ICD, each detected stored arrhythmia episode was reviewed and classified as appropriate (treatment for ventricular arrhythmia) or inappropriate (treatment for other reasons). Cause-specific mortality was adjudicated by an external validation committee during the main study or by the investigators according to CIDS criteria after the end of CIDS. A modified Hinkle-Thaler system was used to classify deaths; presumed arrhythmic death was defined as instantaneous or un witnessed death or death after a few hours after the onset of symptoms in a previously stable patient based on a narrative description of events by patient’s relatives and hospital records.

Cointervention
Cardiac medications were allowed in treatment groups at the discretion of the treating physicians.

Statistical Analysis
Data are expressed as mean±SD. Survival curves and the cumulative event rates were calculated by Kaplan-Meier method and compared by the log-rank test. The 2 treatment groups were compared according to an intention-to-treat principle. We calculated the hazard ratios and the 95% confidence interval values using a Cox proportional-hazards model to investigate the influence of various baseline characteristics on the size of the treatment benefit.

Results
Follow-Up
Patients participating in CIDS at our institution were randomly assigned to receive either amiodarone (n=60 patients) or an ICD (n=60 patients) and were followed until April 2002 for a mean of 5.6±2.6 years, median of 5.92 years (range, 0.08 to 11.08). Follow-up was complete in the ICD group, but 3 patients were lost to follow-up in the amiodarone group after 9, 23, and 35 months. For the mortality analysis, their data were censored at the time of last follow-up.

Patient Characteristics
There were no significant differences between the 2 groups in baseline characteristics with respect to mean age, gender, LVEF, NYHA functional class, β-blocker use, underlying coronary artery disease, history of myocardial infarction, rate of percutaneous coronary intervention or coronary artery bypass grafting, and history of diabetes mellitus or hypertension (Table 1). The index arrhythmia is also summarized in Table 1.

| TABLE 1. Baseline Characteristics of all CIDS Patients at St Michael’s Hospital |
|-----------------------------|-----------------------------|
| Amiodarone (n=60) | ICD (n=60) |
| Age, mean±SD | 64±8.7 | 64±9.2 |
| Male, % | 50 (83) | 50 (83) |
| EF, mean±SD | 32.1±11.1 | 33.9±12.5 |
| NYHA class, % |
| 1–2 | 57 (95) | 57 (95) |
| 3–4 | 3 (5) | 3 (5) |
| CAD, % | 48 (80) | 48 (80) |
| History of MI, % | 31 (52) | 36 (60) |
| Percutaneous coronary intervention, % | 2 (3) | 4 (7) |
| β-Blocker, % | 21 (35) | 23 (38) |
| Diabetes mellitus, % | 11 (18) | 7 (12) |
| Hypertension, % | 14 (23) | 13 (22) |
| Index arrhythmia |
| VF | 27 | 18 |
| VT | 23* | 35 |
| Syncope/inducible VT | 10 | 7 |

*P=0.044; all other P values were not significant.
Concomitant Medications
The rate of use of other nonantiarrhythmic cardiac medications was similar in the 2 groups during follow-up. However, at baseline and at last follow-up, more patients in the ICD group received sotalol compared with the amiodarone group (38 versus 7 patients and 14 versus 7 patients, respectively). At last follow-up, 2 additional patients received ß-blockers (n=23) and 2 patients discontinued ß-blockers (n=21) in the amiodarone and ICD groups, respectively. At baseline, 15 versus 19 patients received lipid-lowering therapy and 35 versus 29 patients received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in the amiodarone and ICD groups, respectively.

Amiodarone Doses
The average total daily amiodarone doses were 398±39 mg at 2 months and 306±89 mg at last follow-up. The average total daily amiodarone doses at last follow-up were 311±88 mg in patients who died, 300±86 mg in patients who discontinued amiodarone, and 342±67 mg in patients with documented or presumed arrhythmia recurrence. There were no significant differences in amiodarone doses between the groups at last follow-up.

Fatal Outcomes
During follow-up, there were 28 deaths (47%) in the amiodarone group compared with 16 deaths (27%) in the ICD group (P=0.0213, Figure 1), with 43% lower risk of all-cause mortality in the ICD group compared with amiodarone. The ICD reduced total mortality significantly from 5.5% per year in the amiodarone group to 2.8% per year in the ICD group (hazard ratio of amiodarone: ICD, 2.011; 95% CI, 1.087 to 3.721; P=0.0261). There were fewer presumed arrhythmic deaths in the ICD group (n=2) compared with the amiodarone group (n=12), P=0.049. Cause-specific mortality for both ICD and amiodarone groups is listed in Table 2.

Amiodarone Efficacy and Tolerability
By the end of follow-up, 40 patients assigned to amiodarone either symptomatic nonfatal arrhythmia recurrence (n=12) or had died (n=28). The incidence rate of nonfatal ventricular arrhythmia recurrence was highest in the early follow-up period and gradually decreased with long-term follow-up. Among the 12 patients with nonfatal arrhythmia recurrences, 5 patients had VT, 5 patients had VT with syncope requiring cardioversion, 1 patient had VF, and 3 patients had unexplained syncope. Twenty-five of the 28 deaths were not preceded by a nonfatal symptomatic arrhythmia recurrence. Figure 2 shows the Kaplan-Meier estimates of overall survival, freedom from death or arrhythmia recurrence, and amiodarone discontinuation for side effects.

Adverse Effects
In the amiodarone group, 49 patients (82% of all patients) had side effects related to amiodarone; 30 patients (50% of all patients) had either symptomatic nonfatal arrhythmia recurrence (n=12) or had died (n=28). The incidence rate of nonfatal ventricular arrhythmia recurrence was highest in the early follow-up period and gradually decreased with long-term follow-up. Among the 12 patients with nonfatal arrhythmia recurrences, 5 patients had VT, 5 patients had VT with syncope requiring cardioversion, 1 patient had VF, and 3 patients had unexplained syncope. Twenty-five of the 28 deaths were not preceded by a nonfatal symptomatic arrhythmia recurrence. Figure 2 shows the Kaplan-Meier estimates of overall survival, freedom from death or arrhythmia recurrence, and amiodarone discontinuation for side effects.

Amiodarone and ICD Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>(95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt;75 vs &lt;75 y)</td>
<td>1.469</td>
<td>(0.620, 3.476)</td>
<td>0.382</td>
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<td>Sex (M vs F)</td>
<td>1.526</td>
<td>(0.754, 3.089)</td>
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<td>EF (≤35% vs &gt;35%)</td>
<td>1.904</td>
<td>(0.915, 3.962)</td>
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<tr>
<td>Arrhythmia (VF vs VT)</td>
<td>1.058</td>
<td>(0.663, 1.690)</td>
<td>0.8121</td>
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<tr>
<td>NYHA (class 3, 4 vs 1, 2)</td>
<td>1.324</td>
<td>(0.320, 5.478)</td>
<td>0.6983</td>
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<tr>
<td>Coronary artery disease (yes vs no)</td>
<td>2.473 (1.306, 4.684)</td>
<td>0.0054</td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass grafting (yes vs no)</td>
<td>1.401 (0.733, 2.679)</td>
<td>0.3081</td>
<td></td>
</tr>
<tr>
<td>ß-Blocker (yes vs no)</td>
<td>1.220</td>
<td>(0.646, 2.302)</td>
<td>0.5395</td>
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<tr>
<td>Sotalol (yes vs no)</td>
<td>1.516</td>
<td>(0.641, 3.589)</td>
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<tr>
<td>Amiodarone vs ICD</td>
<td>1.943</td>
<td>(1.050, 3.596)</td>
<td>0.0344</td>
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Significant multivariate predictors, by Cox proportional hazards analysis

<table>
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<tr>
<th>Variable</th>
<th>OR</th>
<th>(95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Amiodarone vs ICD</td>
<td>1.956</td>
<td>(1.056, 3.622)</td>
<td>0.033</td>
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<tr>
<td>Coronary artery disease (yes vs no)</td>
<td>2.491 (1.314, 4.721)</td>
<td>0.005</td>
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</table>

Table 2. Classification of all Fatal Outcomes in the Amiodarone and ICD Groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amiodarone (n=60)</th>
<th>ICD (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presumed arrhythmic death</td>
<td>12*</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Vascular death</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Noncardiac death</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

*P=0.049
patients) had side effects requiring dose reduction or discontinuation, and 13 of these patients had serious adverse effects that required discontinuation of amiodarone. Reported side effects are summarized in Table 2.

All patients tolerated the ICD well, and none had severe side effects requiring permanent removal of the ICD and crossover to amiodarone therapy. During follow-up of the ICD group, 68 procedures were performed in addition to the initial implants; 50 defibrillators were replaced because of battery end of life (n = 41), pocket infections (n = 3), or other reasons (n = 6); 18 leads were replaced because of lead fracture (n = 16) or lead failure/dislodgment (n = 2); 41 patients underwent 2 or more procedures to replace the device or to change a lead (23 patients underwent 2 procedures, 15 patients had 3 procedures, 1 patient had 5 procedures, 1 patient had 6 procedures, and 1 patient had 7 procedures). No patient died perioperatively; 1 patient had pneumothorax, 1 patient had deep vein thrombosis, and 1 patient had pocket hematoma postoperatively. ICD therapy was turned off in 2 patients on the patient’s request because of terminal cancer.

Crossover

In the amiodarone group, 19 patients crossed over to ICD therapy because of adverse effects (n = 12) or arrhythmia recurrence (n = 7). Five other patients assigned to amiodarone therapy had recurrent syncpe/VT but did not crossover to the ICD. One of these patients refused the ICD; in the others, the amiodarone dose was increased, and with subsequent follow-up, 2 of these 5 patients died. By the end of follow-up, 26 patients in the ICD group were receiving or had received amiodarone.

Frequency of ICD Discharges

During follow-up, 70% of the ICD therapy group had appropriate therapy (appropriate shock or appropriate anti-tachycardia pacing [ATP]); 30 patients (50%) received any inappropriate therapy, including ATP only (n = 9 patients), 1 shock only with or without ATP (n = 14 patients), or 2 or more inappropriate shocks with or without ATP (n = 7 patients).

Discussion

Our data suggest that the strategy of using amiodarone as first-line monotherapy for secondary prevention of sudden cardiac death results in a substantial risk of sudden death, a high incidence of adverse effects, and arrhythmia recurrences with long-term follow-up. This subset of CIDS demonstrates a significant benefit of ICD therapy over amiodarone in reducing total mortality; this benefit extends to at least 11 years of follow-up.

Several randomized clinical trials1–4 provided evidence of increased survival in patients with resuscitated VT/VF who received an ICD compared with those who were treated with amiodarone. However, only the AVID study demonstrated a statistically significant mortality benefit of the ICD over amiodarone. The relatively short time frame of these studies left uncertainties regarding the duration of potential benefit of the ICD and made an assessment of the cost efficacy of the ICD over a clinically relevant time frame (eg, 10 years) difficult. We have demonstrated for the first time that the superiority of ICD over amiodarone in reducing overall mortality increases over this time frame, as shown by the continued divergence of the 2 survival curves after the initial 5 years. All survival curves eventually reach zero, but whether survival curves for ICD- and amiodarone-treated patients converge, remain parallel, or diverge after 5 years is not clear from previous randomized studies owing to limited follow-up duration. In the CASH study, there was a 57 ± 34-month follow-up, but only 29 patients were followed 5 or more years, and there was no explicit comparison of patients treated with the ICD to those treated with amiodarone (approximately half of the non-ICD patients were randomized to metoprolol). Our study is in contrast to nonrandomized data reported by Newman et al,13 which suggested that the ICD versus medical treatment survival curves converge beyond 4 years of follow-up.

The combined end points of death, arrhythmia recurrence, and serious side effects in patients treated with amiodarone in this subset of CIDS represent the most unbiased estimate (because patients received amiodarone by random assignment) of the long-term efficacy of amiodarone for the secondary prevention of sudden death reported thus far. This combined end point is comparable to the drug failure rate (defined as the occurrence of either sudden death or sustained ventricular arrhythmia or the need to discontinue the drug due to side effects) of 50% by year 5 reported by Weinberg et al.14 Weinberg et al14 also reported a 32% probability of remaining alive and receiving amiodarone at 5 years. These rates are also comparable to the arrhythmia recurrence rate (defined as recurrence of VT/VF or sudden cardiac death) of 43% per year at 5 years reported by Herre et al.18 In the meta-analysis of the CIDS, AVID, and CASH trials, the mortality in the amiodarone arm at 5 years was approximately 40%.4 At 3 years, the rate of concomitant use of amiodarone in ICD patients was 33.7% in AVID2 and 21.7% in CIDS,1 and the use of ICD in amiodarone patients was 24.3% in AVID and 18.6% in CIDS. In CASH,3 drug discontinuation was required in 9.8% of patients assigned to amiodarone, and the crossover
in the amiodarone group was 6%, mostly because of arrhythmia recurrences.

The incidence of side effects was similar to that reported in previous studies.7–12,14–20 The amiodarone doses in the current study were similar to the mean daily dose of 308 mg in the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT).10 The mean doses in patients with adverse effects or drug failure were representative of commonly used doses and, thus, excessively high or low doses, respectively, are unlikely to account for the rates of drug discontinuation or arrhythmia recurrence.

It may be perceived that patients should have been offered an ICD at the time of formal CIDS study termination. However, the data that now allow us to make that clinical recommendation with confidence were not present in the year 2000. At that time, there were no long-term data available on the ultimate outcome of patients receiving amiodarone for the secondary prophylaxis of sudden death who had been stable for more than 3.6 years. Furthermore, the CIDS study itself did not show prolonged survival in the ICD group compared with the amiodarone group. The originally assigned amiodarone therapy was continued for clinical reasons.

The present study has insufficient patients to definitively address the question of long-term efficacy of the ICD over amiodarone in subgroups with well-preserved LV function. In CIDS, reduced LV function, advanced age, and poor NYHA class identified high-risk groups who will benefit from ICD therapy.6 In AVID, depressed LV function but not advanced age nor functional class predicted ICD efficacy.21

There are limitations to this analysis. The secondary end points were not blinded after the end of CIDS and were defined only by the investigators. This was a subset of the entire CIDS study, and the results may not be representative of the entire CIDS population. However, patients were randomly assigned to treatment and stratified by center; the comparisons made in this study are only possible if all patients continue randomly assigned therapy after the initial study. As a result, such a study is unlikely to be duplicated. Our study is consistent with previous trials, which showed that ICD therapy led to a significant reduction in all-cause mortality compared with amiodarone. Clinicians should continue to be encouraged to consider ICD implantation as first-line therapy for secondary prevention of sudden cardiac death with the expectation of long-term benefit.

Acknowledgments

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References

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