Randomized Comparison of Antiarrhythmic Drug Therapy With Implantable Defibrillators in Patients Resuscitated From Cardiac Arrest: The Cardiac Arrest Study Hamburg (CASH)

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Randomized Comparison of Antiarrhythmic Drug Therapy With Implantable Defibrillators in Patients Resuscitated From Cardiac Arrest

The Cardiac Arrest Study Hamburg (CASH)

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Background—We conducted a prospective, multicenter, randomized comparison of implantable cardioverter-defibrillator (ICD) versus antiarrhythmic drug therapy in survivors of cardiac arrest secondary to documented ventricular arrhythmias.

Methods and Results—From 1987, eligible patients were randomized to an ICD, amiodarone, propafenone, or metoprolol (ICD versus antiarrhythmic agents randomization ratio 1:3). Assignment to propafenone was discontinued in March 1992, after an interim analysis conducted in 58 patients showed a 61% higher all-cause mortality rate than in 61 ICD patients during a follow-up of 11.3 months. The study continued to recruit 288 patients in the remaining 3 study groups; of these, 99 were assigned to ICDs, 92 to amiodarone, and 97 to metoprolol. The primary end point was all-cause mortality. The study was terminated in March 1998, when all patients had concluded a minimum 2-year follow-up. Over a mean follow-up of 57±34 months, the crude death rates were 36.4% (95% CI 26.9% to 46.6%) in the ICD and 44.4% (95% CI 37.2% to 51.8%) in the amiodarone/metoprolol arm. Overall survival was higher, though not significantly, in patients assigned to ICD than in those assigned to drug therapy (1-sided $P=0.081$, hazard ratio 0.766, [97.5% CI upper bound 1.112]). In ICD patients, the percent reductions in all-cause mortality were 41.9%, 39.3%, 28.4%, 27.7%, 22.8%, 11.4%, 9.1%, 10.6%, and 24.7% at years 1 to 9 of follow-up.

Conclusions—During long-term follow-up of cardiac arrest survivors, therapy with an ICD is associated with a 23% (nonsignificant) reduction of all-cause mortality rates when compared with treatment with amiodarone/metoprolol. The benefit of ICD therapy is more evident during the first 5 years after the index event. **(*Circulation*. 2000;102:748-754.)**

Key Words: heart arrest ■ defibrillation ■ cardioversion ■ antiarrhythmia agents ■ resuscitation

Survivors of cardiac arrest secondary to a sustained ventricular arrhythmia carry a high risk of death after the index event. In ≈75% of cases, death is the result of recurrent cardiac arrest, with a 2-year incidence between 20% and 45%[1–4]; nonarrhythmic deaths account for the remaining fatalities.

Several recent studies have provided evidence that class I antiarrhythmic drugs are less effective than class III drugs in patients with ventricular arrhythmias,[5,6] most likely because of proarrhythmic effects.[7,8] Since their introduction in 1980,[9] numerous reports have shown that implantable cardioverter-defibrillators (ICDs) reduce sudden cardiac death[10–17]; more recently, randomized trials have shown that ICDs reduce all-cause mortality rates compared with amiodarone or no antiarrhythmic drugs in the therapeutic[18] or prophylactic treatment[19] of high-risk patients, respectively.

In 1987, when ICDs were still considered investigational tools by most clinicians and 3 years before other randomized ICD trials began, the Cardiac Arrest Study Hamburg (CASH) was initiated, with the aim of investigating, in patients resuscitated from cardiac arrest, the impact on overall survival of initial therapy with an ICD as compared with that with 3 antiarrhythmic drugs: amiodarone, metoprolol, or propafenone. Assignment to propafenone was discontinued on the request of the Safety Monitoring Board in March 1992, after an interim analysis conducted on 58 patients showed a 61% higher all-cause mortality rate than in 61 ICD patients during a follow-up of 11.3 months.[20] The study continued to enroll and assign patients to amiodarone, metoprolol, and ICD. This article reports the final results of CASH.

Methods

Study Design

CASH is a prospective, multicenter, randomized comparison of 2 treatment strategies (ICD versus antiarrhythmic drugs) for patients resuscitated from cardiac arrest secondary to documented sustained

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ventricular arrhythmias. Patients were excluded from the study if cardiac arrest occurred within 72 hours of an acute myocardial infarction, cardiac surgery, electrolyte abnormalities, or proarrhythmic drug effect.

Eligible patients were randomized to ICD or drug treatment. In the drug arm, 3 antiarrhythmic agents were tested: amiodarone, metoprolol, and propafenone. The ratio of randomization assignment between the ICD and the drug arm was 1:3 (ie, ICD/amiodarone/metoprolol/propafenone=1:1:1:1)

The primary end point was all-cause mortality. Secondary end points were sudden death and recurrence of cardiac arrest at 2-year follow-up. Sudden death was defined as death within 1 hour after the onset of symptoms or an unwitnessed death; cardiac arrest was defined as sudden circulatory collapse requiring resuscitation.

Diagnosis

The patients' history was assessed and a physical examination performed. If all diagnostic tests−including exercise testing, thallium scintigraphy, coronary angiography, ergonovine test, right ventriculography, right ventricular biopsy and MRI−were negative, the diagnosis of no organic heart disease was made. Programmed electrical stimulation (PES) was performed with up to 3 extrastimuli from 2 right ventricular sites during sinus rhythm and basic drive pacing (8 beats) at cycle lengths of 640, 510, and 440 ms.

Therapy

Amiodarone was administered orally at a loading dose of 1000 mg/d for 7 days, followed by a maintenance dose of 200 to 600 mg/d. Metoprolol was initiated at a dose of 12.5 to 25.0 mg/d and increased within 7 to 14 days to a maximum of 200 mg/d, if tolerated. All patients assigned to the antiarrhythmic drug arm underwent repeat predischarge 24-hour Holter monitoring, PES, and exercise testing: Response to serial drug testing did not affect the therapy assignment obtained by randomization.

Cardiac Pacemakers, Inc, devices were used throughout the study (Ventak AID, Ventak AICD, Ventak P, Ventak PRx, Ventak Mini) in patients assigned to ICDs. All patients assigned to ICD therapy were given an epicardial device until June 1991 and an endocardial device from July 1991. In patients requiring surgical revascularization, implantation of epicardial and endocardial devices was performed at the time of or 7 to 15 (mean 10±3) days after coronary artery bypass grafting, respectively. Predischarge defibrillation testing was performed to verify appropriate sensing and defibrillation functions. Rate was the only criterion selected for detection of a sustained ventricular arrhythmia.

Recruitment and Follow-Up

The investigational review board of each institution approved the study. Recruitment of patients began in March 1987. Patients were evaluated at months 2, 4, 6, 12, 18, and 24 and every 12 months thereafter until termination of the study, as well as at time of events. The last patient was enrolled in March 1996. The study was terminated in March 1998, when all patients had concluded a minimum follow-up of 2 years.

Statistical Analysis

We hypothesized that therapy with ICDs would in the worst case be as effective as with antiarrhythmic drugs.[2–4,21–23] Accordingly, the α-level for comparison of survival distributions between the ICD and the antiarrhythmic drug arms was based on a 1-sided test, and the significance test was set at a 0.025 level. Analysis was performed according to the intention-to-treat principle. The design had a power of 80% to detect a difference of 19 percentage points in 2-year mortality rates between the 2 arms (50% expected mortality rate in patients assigned to the drug arm, 31% in the ICD arm). A sample size of 390 patients, with a 1:3 ratio of randomization between ICD and drug arms, was estimated to be sufficient.

At the time of planning of the study, no precautions were stated concerning multiple group comparisons and multiple looks into the data. Because of the unexpectedly long recruitment time and subsequent data in the literature showing life-threatening proarrhythmic effects by class Ic antiarrhythmic agents,[5,7,8] in March 1992 the Safety Monitoring Board required to perform an interim analysis to prevent further patients being assigned to a possibly harmful treatment. Consequently, the overall significance level for comparisons of the ICD group with each of the 3 drug groups (ie, ICD versus propafenone, ICD versus amiodarone, and ICD versus metoprolol) was adjusted according to Bonferroni inequality.[20]

Time to occurrence of clinical events (ie, total mortality, sudden death, and cardiac arrest recurrence) in the 2 arms (ICD versus antiarrhythmic drugs) was analyzed by means of the Kaplan-Meier method.[24] The cumulative survival functions had been compared by means of the log-rank (Mantel-Cox) test.[25] For calculation of hazard ratios, the Cox proportional regression model was used with the patients grouped as randomized (intention-to-treat).[26]

Results

Baseline Characteristics

The index arrhythmia was ventricular fibrillation in 293 (84%) patients and ventricular tachycardia in 56 (16%) patients. After elimination of patients assigned to propafenone, there remained 288 patients who were randomly assigned to an ICD, amiodarone, or metoprolol. The baseline characteristics of these 288 patients (Table 1) were similar in the 2 treatment groups (99 patients assigned to an ICD, 189 patients assigned to amiodarone [92 patients] or metoprolol [97 patients]). The mean age was 58±11 years, 80% of the patients were men, 73% had an underlying coronary artery disease, and 10% had no organic heart disease.

The mean (±1 SD) left ventricular ejection fraction was 0.46±0.19 in the ICD arm and 0.46±0.17 in the drug arm (amiodarone, 0.44±0.17; metoprolol, 0.47±0.17). The majority of patients were in New York Heart Association functional class II: 59% in the ICD arm and 56% in the drug arm (57% in the amiodarone group and 55% in the metoprolol group). During hospitalization after the index event, 19% of patients in the ICD arm and 21% in the drug arm underwent coronary revascularization.

Therapy

All patients randomized to ICD received the assigned therapy. An epicardial system was used in 55 patients and an endocardial system in 44 patients. Two patients assigned to amiodarone refused to start drug therapy. The daily maintenance doses of amiodarone and metoprolol throughout the study were 225±75 mg and 85±73 mg, respectively. Table 2 lists the concurrent therapies at discharge.

Primary Analysis

Over a mean follow-up of 57±34 months, the crude death rates were 36.4% (CI 26.9% to 46.6%) in the ICD and 44.4% (CI 37.2% to 51.8%) in the antiarrhythmic arm. Figure 1 illustrates survival (life-table) distributions in the 2 study arms. Overall survival was higher, though not significantly, in patients assigned to ICD than in those assigned to drug therapy (1-sided P [unadjusted for multiple looks] =0.081, hazard ratio 0.766 [97.5% CI upper bound 1.112]). These survival figures represent a decrease in death rates (Kaplan-Maier estimates) of 41.9%, 39.3%, 28.4%, 27.7%, 22.8%, 11.4%, 9.1%, 10.6%, and 24.7% at years 1 to 9 of follow-up, respectively. Figure 2 illustrates survival (life-table) distribu-

TABLE 1. Baseline Clinical Characteristics of Patients Assigned to Receive ICDs or Antiarrhythmic Drugs

Characteristics	Defibrillator Group (n=99)	Amiodarone Group (n=92)	Metoprolol Group (n=97)
Age, y	58±11	59±10	56±11
Male sex, %	79	82	79
Underlying disease, %			
Coronary artery disease	73	77	70
Dilated cardiomyopathy	12	10	14
Others	6	2	5
No heart disease	9	11	11
Left ventricular ejection fraction	0.46±0.19	0.44±0.17	0.47±0.17
Congestive heart failure at enrollment, %			
NYHA class I	23	25	32
NYHA class II	59	57	55
NYHA class III	18	18	13
Findings on baseline ECG			
Heart rate, bpm	81±17	80±17	76±16
Corrected QT interval, ms	437±42	430±51	430±48
Bundle-branch block, % of patients	17	23	19
Exposure time to primary events, mo	4,767.36	4,169.41	5,078.40

tions in the 2 drug groups. The crude death rates in the amiodarone group were at 43.5% (CI 33.2% to 54.2%), similar to those at 45.4% (CI 35.2% to 55.8%) in the metoprolol group ($P=0.845$).

Secondary Analyses

The crude sudden death rates were 13.0% (CI 7.9% to 19.6%) in the ICD arm and 33.0% (CI 27.2% to 41.8%) in the antiarrhythmic arm. Figure 3 illustrates long-term survival distributions in the 2 study arms. Survival free of sudden death was significantly higher in patients assigned to ICD than in those assigned to drug therapy (1-sided $P=0.005$, hazard ratio 0.423 [97.5% CI upper bound 0.721]). These survival figures represent a decrease in sudden death rates of 81.8%, 86.7%, 76.2%, 78.3%, 80.8%, 73.1%, 64.3%, 56.7%, and 60.6% at years 1 to 9 of follow-up, respectively. Figure 4 illustrates the survival distributions free of sudden death in the 2 drug groups. The crude sudden death rates in the amiodarone group were at 29.5% (CI 19.4% to 40.8%), similar to those at 35.1% (CI 25.2% to 48.8%) in the metoprolol group ($P=0.467$).

TABLE 2. Concurrent Therapies at Discharge in ICD and Antiarrhythmic Drug Arms

Therapy at Discharge	Defibrillator Group (n=99)	Amiodarone Group (n=92)	Metoprolol Group (n=97)
ICD	99	0	0
Amiodarone	0	90	0
Metoprolol	0	0	96
Digitalis	26	23	15
Diuretic agents	33	25	30
Nitrates	29	27	24
Calcium channel blockers	26	15	12
ACE inhibitors	45	40	40
Aspirin	57	41	40
Warfarin	9	6	9

The crude rates of nonfatal cardiac arrest were 11.1% (CI 6.9% to 16.5%) in the ICD and 19.5% (CI 12.2% to 25.6%) in the antiarrhythmic arm. Survival free of cardiac arrest was higher, though not significantly, in patients assigned to ICD than in those assigned to drug therapy (1-sided $P=0.072$, hazard ratio 0.481 [97.5% CI upper bound 1.338]). The decrease in cardiac arrest rates of patients assigned to ICD therapy was 61.8%, 65.5%, 59.2%, 53.8%, 50.4%, 58.6%, 49.2%, 52.8%, and 42.1% at years 1 to 9 of follow-up, respectively.

Among patients with inducible sustained ventricular arrhythmia at baseline PES, death rates were 49.4% (CI 42.9% to 57.2%) in 46 assigned to ICD and 52.6% (CI 47.9% to 59.4%) in 88 assigned to drug treatment ($P=0.290$). Of patients noninducible at baseline PES, death rates were 35.7% (CI 26.4% to 45.7%) in 51 assigned to ICD and 49.3% (CI 42.9% to 56.2%) in 100 assigned to drug treatment ($P=0.170$).

Over a mean follow-up of 37±26 months, a similar outcome was observed in 55 patients receiving an epicardial ICD and in 44 receiving an endocardial ICD ($P=0.189$).

Six (6.1%) patients in the ICD arm and 11 (5.8%) in the drug arm crossed over or added the other therapy by 24 months. Three (3.0%) patients assigned to ICD and none of those assigned to amiodarone received β-blockers during follow-up.

There were no significant differences concerning the hazard ratios for death from any cause in subgroups defined according to left ventricular ejection fraction, NYHA class,

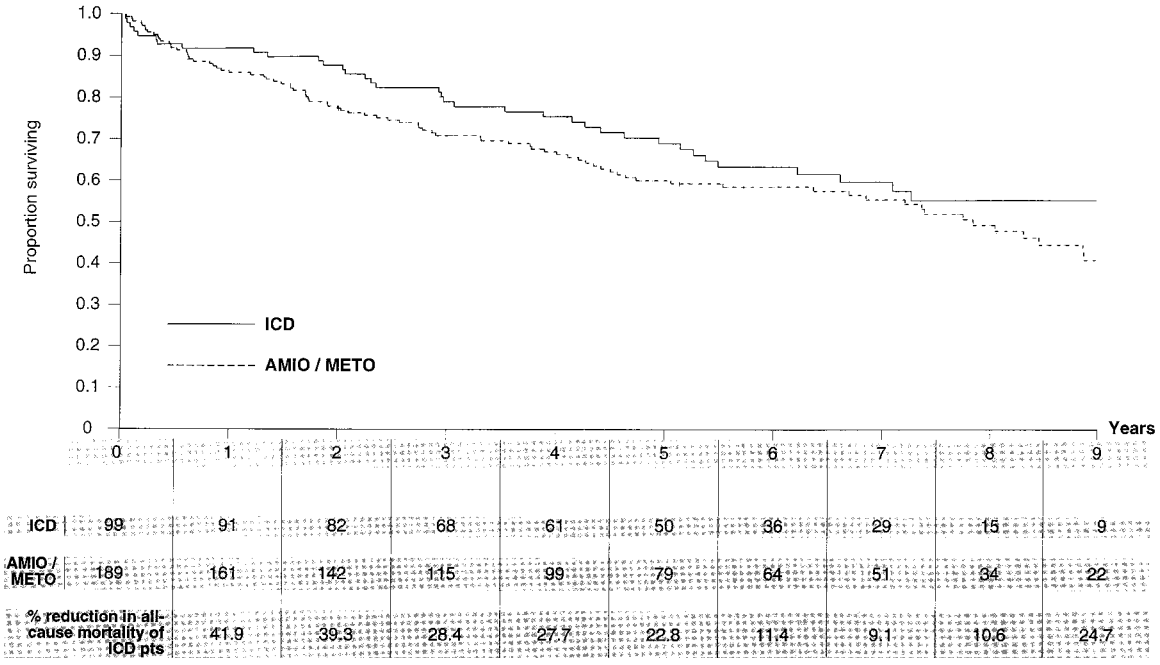

Figure 1. Long-term overall survival in ICD and drug arms. AMIO indicates amiodarone; METO, metoprolol; and pts, patients.

and presence of organic heart disease (Table 3). However, a trend toward a higher benefit from ICD therapy was observed for subgroups with lower ejection fraction and higher NYHA functional class.

Complications of Therapy

Among patients assigned to the amiodarone limb, no evidence of drug-related pulmonary toxicity was found, whereas hyperthyroidism was observed during follow-up in 3 (3.3%) of the patients. Drug discontinuation was required in 9 (9.8%) patients assigned to amiodarone and 10 (10.3%) to metoprolol.

Five (5.1%) patients, of whom 3 (5.4%) having received an epicardial and 2 (4.5%) an endocardial ICD, died perioperatively. Within the same time frame, 2 (1.1%) patients in the antiarrhythmic drug arm (amiodarone, 2 patients; metoprolol, 0 patients) died (*P* versus ICD arm=0.029). Other complications included infection in 3 patients (requiring explantation in 2), hematoma or seroma in 6 patients, pericardial effusion in 1 patient, pleural effusion in 3 patients, and pneumothorax in 1 patient. Dislodgment or migration of system leads occurred in 3 patients and device dysfunction in 5 patients. Overall, the complication rate in this arm during follow-up was 23.0%, including an explantation rate of 2.1%.

Discussion

CASH was the first prospective randomized study evaluating the impact of ICD versus antiarrhythmic drug therapy on

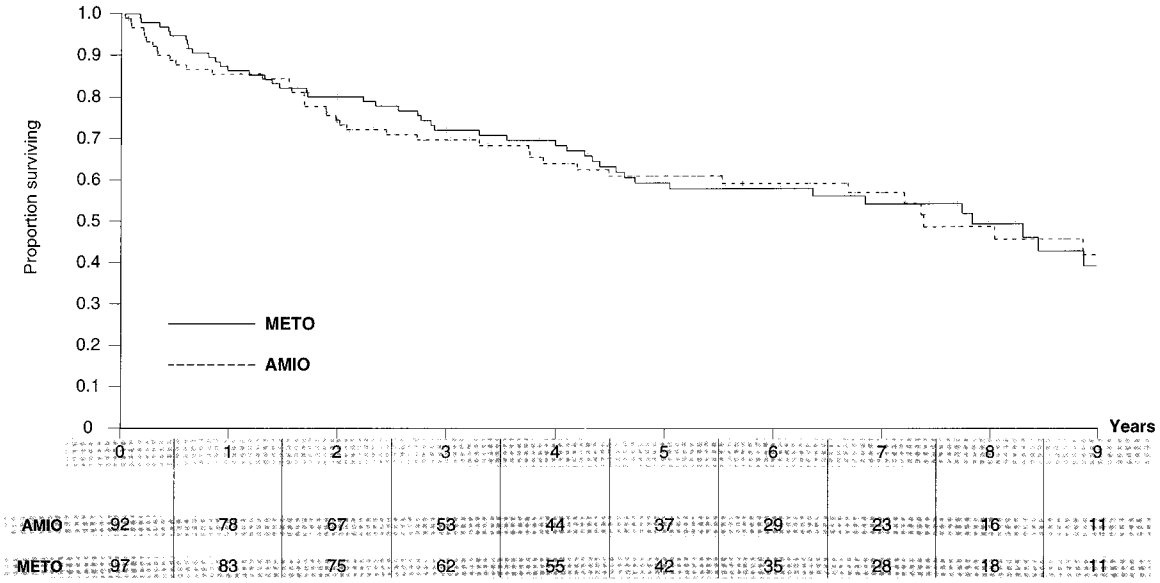

Figure 2. Long-term overall survival in amiodarone (AMIO) and metoprolol (METO) groups.

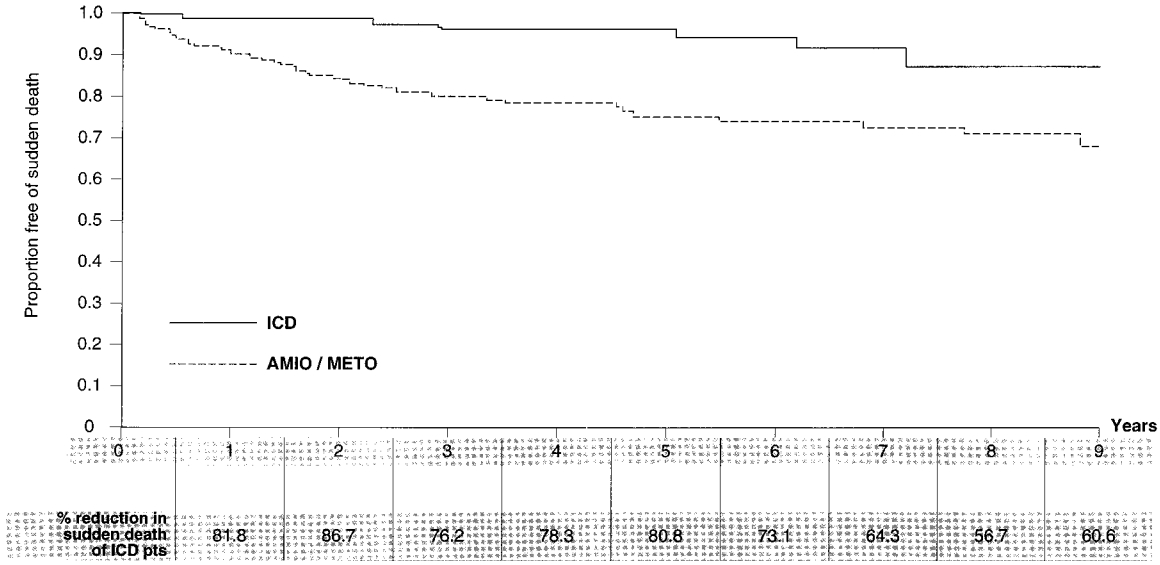

Figure 3. Long-term survival free of sudden death in ICD and drug arms. AMIO indicates amiodarone; METO, metoprolol; and pts, patients.

all-cause mortality in survivors of sustained ventricular arrhythmias. It should be emphasized that although randomized studies testing ICD versus alternative therapies became well accepted in the 1990s, this was not the case when CASH was initiated, because many physicians considered ICD therapy still investigational. A unique feature of this study was also that of patients assigned to drug treatment, 1 group included therapy with a pure β-blocker. The final results of CASH confirm, though not with a statistical level of significance, the beneficial role of ICD therapy in the treatment of cardiac arrest survivors during long-term follow-up.

Although ICDs have undisputedly proven effective to reduce sudden death,[10–17] the debate has continued about whether this effect would translate into a reduction of total mortality rates and if so, to what extent.[27–29] To appropriately address this issue, randomized controlled trials have been demanded that prospectively compare ICD with the best antiarrhythmic drug therapy in categories of patients at risk.[27–31] Recent trials conducted with the use of these methods have produced conflicting results. The benefit of ICD therapy, either used prophylactically or in response to ventricular arrhythmias, could be demonstrated in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)[19] and the Antiarrhythmic Versus Implantable Defibrillators (AVID) trial.[18] In the former study, ICDs were compared with "conventional" therapy (mostly amiodarone) in patients after myocardial infarction with low left ventricular ejection fraction, spontaneous nonsustained ventricular tachycardia, and inducible nonsuppressible sustained ventricular arrhythmias. In AVID, they were compared with empiric amiodarone (97%) or sotalol (3%) in patients with near-fatal ventricular fibrillation (45%) or syncopal or hemodynamically nontolerated ventricular tachycardia (55%). Therapy with an ICD resulted in a 54% 2-year reduction of all-cause mortality in MADIT and 27% 2-year reduction of all-cause mortality in AVID. In another study, the CABG Patch trial,[32] no benefit was shown if prophylactic ICDs were implanted at the time of surgical revascularization in patients with low left ventricular ejection fraction and an abnormal signal-averaged ECG. The different results obtained with these randomized

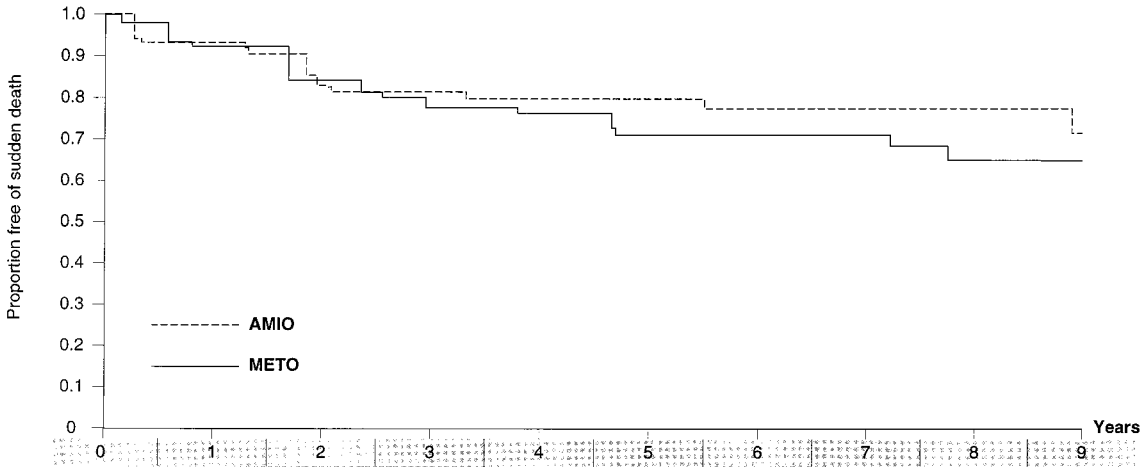

Figure 4. Long-term survival free of sudden death in amiodarone (AMIO) and metoprolol (METO) groups.

TABLE 3. Hazard Ratios and Confidence Intervals Versus Antiarrhythmic Drug Treatment During Follow-Up According to Cutoff Values of Left Ventricular Ejection Fraction and NYHA Class and to Presence or Absence of Organic Heart Disease and Response to Programmed Electrical Stimulation

	Patients, ICD/AA	Heart Rate	95% CI
Left ventricular ejection fraction			
≤35%	36 /74	0.529	0.226 to 1.239
≥35%	63/115	0.685	0.307 to 1.530
NYHA class			
III	25 /40	0.228	0.035 to 1.184
I or II	74/149	0.596	0.264 to 1.354
Organic heart disease			
Yes	90/168	0.638	0.350 to 1.164
No	9 /21	0.230	0.020 to 2.617

AA indicates antiarrhythmic drugs.

controlled trials outline the necessity to identify patient categories at higher risk of sudden death that might most benefit from an ICD.

In CASH, the ICD and drug arms were well balanced with respect to patient baseline clinical characteristics and initial treatment of ischemia. The mean left ventricular ejection fraction did not differ in the 2 arms, nor did the distribution of NYHA functional class, with ≈50% of patients being in class II. Compared with AVID,[18] the higher mean value of ejection fraction observed in this study probably reflects a larger population of patients without organic heart disease in CASH.

In patients assigned to ICDs, the reduction of all-cause mortality was evident throughout the study duration. Reduction of all-cause mortality in ICD patients was related to the large effect of this therapy in the prevention of sudden death. When analyzed during a long-term follow-up, response to baseline PES did not appear to discriminate between patients at higher and patients at lower benefit from ICD.

In CASH, the 4% perioperative mortality rate observed in the first 15 patients receiving an endocardial device does not reflect current trends[33] and might have contributed to an underestimation of ICD benefit in this trial.

Mortality rates in the amiodarone and metoprolol groups contributed in a similar number to the overall mortality in the drug arm. This finding is not completely unexpected. In fact, previous studies in patients after myocardial infarction have shown that among all antiarrhythmic agents (including amiodarone), β-blockers are the most effective treatment to reduce all-cause mortality rates during follow-up and that part of their effectiveness is related to a reduction in sudden cardiac death.[34] Sudden death accounted for a similar proportion of all deaths in both groups. These findings reflect a substantially similar impact of the 2 drugs in the clinical outcome of cardiac arrest survivors.

Rates of crossover in the ICD (6%) and in the drug arm (6%) were low. Most crossovers occurred because of arrhythmia recurrence rather than because of intolerance to the drug or device. In patients assigned to ICD therapy, antiarrhythmic drugs were added to eliminate inappropriate discharges associated with supraventricular arrhythmias triggering defibrillation. The discontinuation rate of randomly assigned treatments during follow-up was low (ICD arm, 2.1%; drug arm, 10.0%).

Limitations of the Study

In CASH, the long recruitment time exposed the study to complexities driven by rapid changes in ICD and conventional therapy and by accumulation of new knowledge. Among responsible causes were the small number of participating centers and their reluctance to enroll patients for potential ICD therapy in the early phase and to deny such therapy in the late phase of the study. Also, the 0.46 mean ejection fraction reported in the whole cohort suggests a disproportional representation of relatively healthy patients in CASH, as compared with AVID.[18] On the basis of these observations, we cannot exclude a selection bias that if present, might have influenced the outcome of CASH and possibly led to underestimation of the benefit of ICD therapy. In fact, although collected in more heterogeneous patient categories over a markedly shorter follow-up than in CASH, data from AVID suggest that patients who appear to most benefit from ICD treatment are those with a low (ie, <35%) rather than those with a relatively well-preserved left ventricular ejection fraction.[18]

The 19.6% 2-year all-cause mortality rate observed in the amiodarone and metoprolol groups was less than half the mortality rate used to calculate the trial sample size, thus rendering CASH underpowered to test the working hypothesis.

Conclusions

In the present study, a 23% (nonsignificant) reduction in all-cause mortality rate was found in patients receiving ICD therapy compared with amiodarone/metoprolol over a long-term follow-up. The reduction was much larger, 61%, for sudden cardiac death. No differences were found in all-cause mortality and sudden death rates between patients assigned to amiodarone and those assigned to metoprolol.

Appendix

The investigators of the Cardiac Arrest Study Hamburg are as follows: Universitäts-Krankenhaus Eppendorf, Hamburg: K.H. Kuck, MD, R. Cappato, MD, J. Siebels, MD, R. Rüppel, MD, M.A.E. Schneider, MD, P. Kalmar, MD, H. Kalkowski, MD, H. Greten, MD, G. Kreymann, MD; as of 1994, T. Meinertz, MD; Allgemeines Krankenhaus Barmbek, Hamburg: P. Spiller, MD, H. Heihn, MD; Marienkrankenhaus, Hamburg: P. Ostendorf, MD, A. Kleinebenne, MD; Allgemeines Krankenhaus Altona, Hamburg: K. von Ohlshausen, MD, H. Breuer, MD; Allgemeines Krankenhaus Wandsbek, Hamburg: V. Sill, MD, G.W. Priester, MD; Allgemeines Krankenhaus Harburg, Hamburg: T. Pop, MD, M. Kleinert, MD; Allgemeines Krankenhaus St Georg, Hamburg: T. Meinertz, MD, J. Johns, MD; as of 1994, K.H. Kuck, MD, R. Cappato, MD, J. Siebels, MD; RWTH Aachen, Aachen: P. Hanrath, MD, C. Stellbrink, MD.

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