Clinical Investigation

Brief Rapid Communication

Long-term Benefit of 1-Year Amiodarone Treatment for Persistent Complex Ventricular Arrhythmias After Myocardial Infarction

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Background. In the Basel Antiarrhythmic Study of Infarct Survival trial, low-dose amiodarone improved 1-year survival in patients with asymptomatic complex ventricular arrhythmias persisting 2 weeks after myocardial infarction. To assess whether this beneficial effect persisted despite discontinuation of amiodarone after 1 year, the long-term outcomes of all patients of the amiodarone-treated group (initially n=98) and those of the control group (n=114) were assessed.

Methods and Results. After a mean follow-up of 72 (55–125) months, information on 96% of patients (203 of 212) was obtained regarding survival or cause of death. The probability of death after 84 months according to actuarial life-table analysis (Kaplan-Meier) was 30% for the amiodarone-treated patients and 45% for control patients. For the total follow-up, mortality remained significantly lower in the amiodarone group versus the control group regarding all deaths (p=0.03) as well as cardiac death (p=0.047). This mortality reduction was entirely due to the first-year amiodarone effect, since there was no significant mortality difference between groups when considering survival after discontinuation of amiodarone only.

Conclusions. These data suggest that the beneficial effect of amiodarone on survival in this high-risk group of patients persists for several years. In addition, the results stress the importance of early treatment after myocardial infarction, whereas the rate of sudden death and all cardiac death is low (1.6% and 4.1% per year, respectively) during late follow-up and therefore may not warrant further therapy.

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KEY WORDS • prognosis • antiarrhythmic therapy • amiodarone • myocardial infarction

Mortality after myocardial infarction is highest in the first 6–12 months after the acute event; thereafter, it becomes as low as in chronic stable coronary artery disease.1,2 Thus, measures of infarct size and ventricular arrhythmias are strong and independent predictors of death during the first year after myocardial infarction,2,3 whereas their predictive power diminishes afterward, and progression of disease increases in importance. Medical therapy to prevent death after myocardial infarction, therefore, might be particularly important during the high-event, first year after infarction, whereas there is considerable uncertainty as to how long secondary preventive therapy should be continued. For β-blocker therapy, there is some evidence for a prolonged effect based on the Norwegian multicenter study on timolol,4 but one can only speculate about the outcome if the treatment had been stopped in all patients at the end of the double-blind period. Accordingly, these authors encouraged similar follow-up analyses to better evaluate new therapies. With respect to the effects of antiarrhythmic therapy after myocardial infarction, the Basel Antiarrhythmic Study of Infarct Survival (BASIS)5 showed that among patients with asymptomatic persistent complex ventricular arrhythmias after myocardial infarction, low-dose amiodarone improved survival during the first year after the index infarction. Since amiodarone was discontinued at the end of the trial in all patients, the long-term follow-up of the BASIS study population provided the opportunity to assess whether the observed beneficial effect persisted despite discontinuation of amiodarone therapy or whether and when mortality curves of the amiodarone and control groups would start to converge. Because of the potentially important clinical implications of these long-term observations, the present follow-up study was undertaken.

Methods

The methods used in the BASIS study have been described in detail previously.5,6 In short, survivors of myocardial infarction with asymptomatic complex ventricular arrhythmias persisting at hospital discharge
(Lown grade III–IVb arrhythmias in at least 2 of 24 hours of Holter ECG recording) were randomized into three treatment groups: group A, individualized antiarhythmic therapy starting with class I antiarrhythmic drugs; group B, low-dose amiodarone (200 mg/day after an initial loading dose of 1,000 mg for 5 days); and group C, a control group without antiarrhythmic therapy. Because of this special design, the study could not be performed in a double-blind fashion.5,6 For the present analysis, only patients of groups B and C were considered. Amiodarone therapy was discontinued in all group B patients after their 1-year follow-up visit and a 24-hour Holter ECG recording performed after 8 weeks without amiodarone therapy. Sev-erity of arrhythmias was assessed by number of ventricular premature beats per hour and by occurrence of repetitive ventricular ectopic activity as percentage of hours with arrhythmias according to Lown class III or IV. Further antiarhythmic treatment was left to the discretion of each patient’s private physician; at the last follow-up, only six and seven patients, respectively, were still on antiarhythmic therapy (two and four taking amiodarone). A final follow-up was obtained in January 1992 to assess long-term survival of group B and C patients. Based on telephone calls to private physicians and patients as well as on review of hospital records and death certificates, patients were categorized as alive or dead. Causes of death were defined as sudden, nonsudden cardiac, noncardiac, and unknown, using the same definitions as previously described.5 Analyses were performed according to an actuarial life-table analysis (Kaplan-Meier) with and without taking into account first-year events. Proportions of patients were compared using the \( \chi^2 \) test and Student’s \( t \) test where appropriate (SYSTAT program). A two-tailed value of \( p<0.05 \) was considered indicative of a significant difference. Values \( \pm 1 \) SD are given.

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Results

Arrhythmia Recurrence After Discontinuation of Amiodarone Therapy

Discontinuation of amiodarone resulted in a nonsignificant increase in number of ventricular premature beats per hour (from 14±46 to 25±57) and a significant increase in the prevalence of Lown class III ventricular ectopic activity (present in 15.2±25.9% versus 33.3±35.2% of recorded hours) and Lown class IV (present in 1.2±3.0% versus 4.0±9.8% of recorded hours; both \( p<0.05 \)) from the last Holter ECG recording on amiodarone and that 2 months after drug withdrawal.

Mortality

After a mean follow-up of 72 (55–125) months, data regarding survival or cause of death were available in 203 of 212 patients (96%). In five control patients and four patients of the amiodarone group, no complete follow-up was possible, leaving 109 control patients and 94 amiodarone-treated patients available for the present analysis. In four of these nine patients lost to follow-up (three control patients, one amiodarone patient), the last information obtained was 1 year after the index infarction (all alive), whereas in the others, indirect evidence of survival could be traced for another 2–4 years only. The probability of death after 84 months according to actuarial life-table analysis was 30% for amiodarone-treated patients and 45% for control patients. As shown in Figure 1, total mortality remained significantly lower throughout the entire follow-up in the amiodarone group compared with the control group regarding all deaths \( (p=0.03) \). A similar reduction was observed with respect to cardiac death \( (p=0.047) \). This was entirely due to the first-year effect, since there was no significant mortality difference between groups when late follow-up was considered only (Figure 2). The survival curve of the control group was virtually linear after the first 12 months; that of the amiodarone-treated patients was linear after about 18 months.

Altogether, 53 of 109 control patients (49%) and 31 of 94 (33%) patients of the amiodarone group died after the index infarction. The causes of death during late follow-up (12–125 months) did not differ significantly with respect to sudden (six versus 14), nonsudden cardiac (eight versus nine), noncardiac (five versus nine), and unknown (seven versus six) cause of death in formerly amiodarone-treated patients and control patients, respectively. Thus, total cardiac mortality rate in the control group was 11.4% in the first year after

FIGURE 1. Graph: Probability of survival from the index infarction (month 0) to the last follow-up in patients treated with low-dose amiodarone for 1 year (Basel Antiarrhythmic Study of Infarct Survival [BASIS]-amiodarone group) and in control patients. There was significantly better survival in amiodarone-treated patients during the first year (BASIS) that persisted up to 84 months.

FIGURE 2. Graph: Probability of survival during the extended follow-up (12–84 months) for patients treated for 1 year with low-dose amiodarone (Basel Antiarrhythmic Study of Infarct Survival [BASIS]-amiodarone group) and control patients. Note that curves remain parallel after some initial divergence without crossing during the entire follow-up.
myocardial infarction versus only 4.1% per year during the following 6 years. The corresponding sudden death rates were 8.8% for the first year and 1.6% per year thereafter (p<0.01). For comparison, total mortality in the amiodarone group was 5.1% and 2.6% per year in the following 6 years, and corresponding sudden cardiac death rates were 4.1% and 1.1% per year, respectively.

During late follow-up, total mortality was 58% in 90 patients with a baseline left ventricular ejection fraction of ≤0.40 and only 28% in 113 patients with ejection fraction >0.40 (p<0.01); there were no significant differences during that time period between groups initially treated with amiodarone and no antiarrhythmic therapy if groups were subdivided according to baseline left ventricular function. The failure to detect differences attributable to amiodarone could be because no such differences exist or because of weaknesses in this small post hoc analysis.

Discussion

The results of the present study suggest that the beneficial effect of low-dose amiodarone treatment for the first year after myocardial infarction in patients with asymptomatic complex ventricular arrhythmias lasts for several years. The consistent separation of the two survival curves over a period of 84 months indicates a distinct delaying of death in the group initially treated with amiodarone. This was true despite evidence of recurrence of ventricular arrhythmias after discontinuation of amiodarone therapy, suggesting that suppression of ventricular premature beats may not be the most important effect of amiodarone in improving survival of these patients. In addition, these results stress the importance of early treatment of ventricular arrhythmias after myocardial infarction, since the rate of sudden death and all cardiac death is low after the first year after myocardial infarction and does not seem to warrant further therapy.

Similar observations have been reported for β-blocking therapy after myocardial infarction, and it is of interest that the survival curves in the present analysis are remarkably similar to those found during an extended follow-up of the Norwegian Multicenter Study on Timolol After Acute Myocardial Infarction.4 In both studies, the curves diverged during the first 12–18 months and stayed parallel thereafter, indicating a distinct delaying of death in the treated groups. Although it was speculated that this might have been due to continuation of open-label timolol in the majority of patients in the β-blocker trial, the same observation was made despite discontinuation of amiodarone in the present study. There are many postinfarction β-blocker trials; unfortunately, no follow-up data are available after discontinuation of therapy. On the other hand, the present study cannot answer the question of whether the treated patients would have fared even better during long-term follow-up if amiodarone treatment had been continued.

The importance of early treatment of ventricular arrhythmias to define a most effective antiarrhythmic treatment has led the Cardiac Arrhythmia Suppression Trial (CAST) investigators to restrict patient enrollment in CAST II to the first 90 days after acute myocardial infarction (versus 2 years in CAST I).6 Similarly, the Canadian7 and European8 studies of amiodarone after myocardial infarction enroll patients only early after the acute event, which seems to be crucial, according to the present findings.

Our observations would imply that it may be important to identify high-risk patients for sudden cardiac death based on persistent ventricular arrhythmias early after myocardial infarction and to treat them effectively for 1 year. Since the rate of sudden death and all cardiac death is relatively low after the first year after myocardial infarction, antiarrhythmic drug treatment with amiodarone may be discontinued after this initial high-event period. Further prospective studies will be necessary to decide whether no additional antiarrhythmic therapy is needed—as suggested by the present analysis—or whether a new risk evaluation might be appropriate at this point in time.

References

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