

Articles

Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT

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Summary

Background Ventricular arrhythmias are a major cause of death after myocardial infarction, especially in patients with poor left-ventricular function. Previous attempts to identify and suppress arrhythmias with various antiarrhythmic drugs failed to reduce or actually increase mortality. Amiodarone is a powerful antiarrhythmic drug with several potentially beneficial actions, and has shown benefit in several small-scale studies. We postulated that this drug might reduce mortality in patients at high risk of death after myocardial infarction because of impaired ventricular function, irrespective of whether they had ventricular arrhythmias.

Methods The European Myocardial Infarct Amiodarone Trial (EMIAT) was a randomised double-blind placebo-controlled trial to assess whether amiodarone reduced all-cause mortality (primary endpoint) and cardiac mortality and arrhythmic death (secondary endpoints) in survivors of myocardial infarction with a left-ventricular ejection fraction (LVEF) of 40% or less. Intention-to-treat and on-treatment analyses were done.

Findings EMIAT enrolled 1486 patients (743 in the amiodarone group, 743 in the placebo group). Median follow-up was 21 months. All-cause mortality (103 deaths in the amiodarone group, 102 in the placebo group) and cardiac mortality did not differ between the two groups. However, in the amiodarone group, there was a 35% risk reduction (95% CI 0–58, $p=0.05$) in arrhythmic deaths.

Interpretation Our findings do not support the systematic prophylactic use of amiodarone in all patients with depressed left-ventricular function after myocardial infarction. However, the lack of proarrhythmia and the reduction in arrhythmic death support the use of amiodarone in patients for whom antiarrhythmic therapy is indicated.

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Introduction

Ventricular arrhythmias are one of the main causes of death in survivors of acute myocardial infarction. The European Myocardial Infarct Amiodarone Trial (EMIAT) was conceived at the end of 1988, after many studies of antiarrhythmic drugs that block the sodium-channel (class I) showed no efficacy in the suppression of arrhythmias and prevention of death in survivors of myocardial infarction.^{1–3} Later, the Cardiac Arrhythmia Suppression Trials proved that in survivors of myocardial infarction at low risk of death, the suppression of ventricular extrasystoles with the sodium-channel-blocking drugs flecainide and encainide, and possibly moricizine, was associated with excess mortality.^{4,5} Apart from β -adrenergic blocking agents, the only antiarrhythmic drug that showed any promise in the late 1980s was amiodarone, although the number of patients studied was too small to allow definite conclusions about the drug's effect on all-cause mortality.^{6–8} We, therefore, decided to conduct a large trial of amiodarone in survivors of myocardial infarction at increased risk of death.^{9,10}

Although the presence of frequent or complex ventricular arrhythmias is an independent risk factor for mortality after myocardial infarction,^{11–13} and most trials of antiarrhythmic drugs have used such ventricular arrhythmias as an entry criterion, there is no evidence that suppression of ventricular arrhythmias leads to a reduction in overall mortality. Moreover, the single most powerful independent predictor of mortality, including sudden death, is left-ventricular dysfunction.^{13,14} Thus, we decided to adopt a different approach from the other trials by taking no account of the presence of symptomless arrhythmias and by choosing depressed left-ventricular ejection fraction (LVEF) as the main entry criterion. We expected that most patients with left-ventricular dysfunction would subsequently suffer from lethal arrhythmias, even if ventricular arrhythmias were not initially present. In addition to its antiarrhythmic properties, amiodarone has anti-ischaemic actions and does not aggravate heart failure, properties that may have an additional beneficial effect on survivors of myocardial infarction.

The aim of this randomised placebo-controlled double-blind trial was to assess the effect of amiodarone on all-cause mortality, cardiac mortality, and arrhythmic death in survivors of myocardial infarction with depressed left-ventricular function.

EMIAT was a joint venture between the Working Group on Arrhythmias of the European Society of Cardiology and Sanofi Recherche.

Methods

We recruited patients for this randomised double-blind placebo-controlled trial from the coronary-care units of participating European hospitals between Nov 30, 1990, and Oct 30, 1995. A log-book was kept of all patients with documented myocardial infarction surviving 5 days. Eligible patients were those aged 18–75 years who had a LVEF on multiple-gated nuclear angiography (MUGA) of 40% or less. MUGA was done 5–21 days after admission to the coronary-care unit.

We excluded women of childbearing age who were not using reliable contraception and individuals who had: treatment with amiodarone in the previous 6 months; documented bradycardia (under 50 beats per min); second-degree or third-degree atrioventricular block; sinus pauses of more than 2.5 s unless controlled by a pacemaker; clinically significant hepatic disease; a history of documented thyroid dysfunction, long QT syndrome, severe angina or congestive heart failure refractory to conventional therapy; a need for antiarrhythmic therapy other than β -blockers or digoxin; a likelihood of imminent cardiac surgery; and other contraindications for amiodarone.

Computer-generated randomisation was done in balanced blocks of four patients, and lists were prepared and kept at the Independent Statistical Centre (Clinical Pharmacology Unit, Claude Bernard University, Lyon). This centre was also responsible for conducting the interim analyses of efficacy and safety, and for packaging the study treatments. Stratification was based on clinical centre and ejection fraction. Treatment allocation was assigned under masked conditions by the EMIAT Coordinating Centre (Sanofi, Montpellier), and sent by fax to the investigators. The Coordinating Centre had no access to the treatment code.

Before randomisation, patients from each centre were stratified according to their ejection fraction—31–40% and 30% or less. The accuracy of the MUGA equipment in each centre was validated by the Ejection Fraction Committee. The normal range for ejection fraction was determined individually for each

centre. The lower limit of the normal range was 40% or more for all centres.

Patients were then randomly assigned amiodarone or placebo. The daily regimen was 800 mg for 14 days, 400 mg for 14 weeks, and then 200 mg until the end of the study follow-up. The maximum follow-up was 2 years and the minimum follow-up 1 year, according to the time of enrolment.

Patients were assessed at baseline, 2 weeks, 2 months, and then every 4 months up to 2 years. 24 h ambulatory electrocardiographic (Holter) monitoring was done at baseline, 2 weeks, and 4 months. Chest radiography was done at baseline, 2 months, and annually. Laboratory data, including measurement of serum concentrations of potassium creatine kinase, aspartate aminotransferase, alanine aminotransferase, and thyrotropin, were collected at baseline, 2 weeks, and at months 2, 4, 8, 16, and 24.

The investigators notified the Coordinating Centre about any deaths and major adverse side-effects by fax within 24 h of the event. The Coordinating Centre forwarded these data to the Independent Statistical Centre.

The Validation Committee reviewed deaths under masked conditions. We used the following criteria to classify the cause of death.

Cardiac deaths were grouped into three categories: "sudden", "non-sudden", or "unwitnessed" presumed cardiac. Sudden cardiac deaths occurred within 1 h of new symptoms, or in a patient with no symptoms or stable symptoms, and with no left-ventricular failure. Non-sudden cardiac deaths occurred more than 1 h after the onset of symptoms. Unwitnessed, presumed cardiac deaths were unexpected and not witnessed, within 24 h of the patient's being known to be well and with no symptoms or stable cardiovascular symptoms.

Sudden and non-sudden cardiac deaths were grouped into documented, non-documented arrhythmic deaths, or non-arrhythmic deaths, such as rupture and electromechanical dissociation. Unwitnessed deaths were presumed to be cardiac if there was no alternative diagnosis. We defined sudden death from myocardial infarction as a cardiac death, but not as an arrhythmic death endpoint.

The Validation Committee also reviewed, under masked conditions, all arrhythmic events, suspected cases of pulmonary toxicity, biochemical alterations of thyroid hormones and liver enzymes, as well as evidence of clinical dysthyroidism and hepatic disorders.

The ambulatory electrocardiographic records were analysed centrally at the Holter Reading Centre.

The study protocol was approved by an ethics committee in each country or centre, and all patients had to give informed consent to take part in the trial.

Study medication was stopped in patients with sustained ventricular tachycardia (≥ 30 s), symptomatic unsustained ventricular tachycardia, pulmonary infiltrate with no specific clinical cause, or intolerable side-effects. However, all patients were followed up and included in the intention-to-treat analysis. Compliance was assessed by follow-up visits and tablet counts. Data on mortality was sought for all patients at the end of the planned follow-up.

The sample size calculations were based on a 15% 2-year mortality rate in the placebo group and a 35% reduction of risk in the amiodarone group, with type I and type II error rates of 0.05 and 0.20, respectively. These calculations indicated that 1500 patients should be enrolled.

The primary analyses were by intention to treat, but we also did an on-treatment (efficacy) analysis of outcome events in eligible patients while on study medication or within 3 months of early permanent discontinuation. The primary endpoint was all-cause mortality and the secondary endpoints were cardiac mortality, arrhythmic death, and arrhythmic death plus resuscitated cardiac arrest.

At baseline (day of enrolment) continuous and categorical variables were compared by the *t* test and χ^2 test, respectively. Survival curves of the proportion of patients who remained event-free, according to treatment group and ejection-fraction

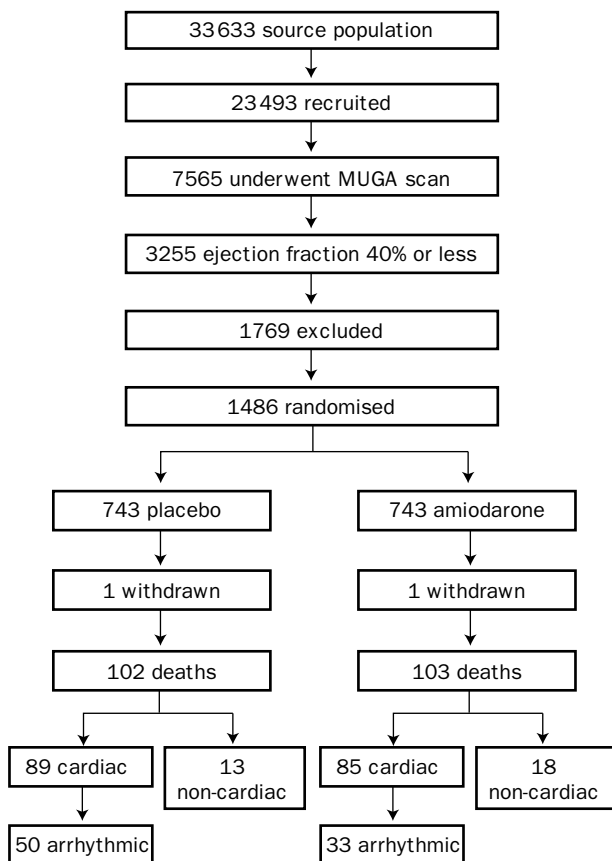


Figure 1: Trial profile

	Placebo (n=743)	Amiodarone (n=743)
Mean (SD) age in years	60.2 (9.2)	59.6 (9.7)
M/F	631/112	623/120
Medical history		
Myocardial infarction	191 (26%)	233 (32%)
Angina pectoris	245 (33%)	267 (36%)
Diabetes	122 (17%)	123 (17%)
New York Heart Association class		
I	366 (50%)	335 (45%)
II/III	372 (50%)	407 (55%)
Anterior infarction	546 (74%)	523 (70%)
Left-ventricular ejection fraction		
31–40%	55%	52%
≤30%	45%	48%
Mean (SD)	30.2 (7.6)	30.2 (7.0)
VPB ≥10 per h, or 3 VPBs on Holter	279 (41%)	269 (39%)
Mean (SD) creatine kinase activity (IU/L)	2471 (2016)	2340 (2192)
Mean (SD) heart rate (bpm)	74.6 (14.3)	74.1 (14.2)
Mean (SD) systolic blood pressure (mm Hg)	118 (17.2)	119 (16.7)
Concomitant medication		
Thrombolytics	239 (59%)	215 (56%)
β-blockers	333 (45%)	325 (44%)
Digoxin/digitoxin glycosides	88 (11%)	101 (13%)
ACE inhibitors	428 (58%)	438 (59%)
Calcium antagonists	98 (13%)	109 (15%)
Diuretics	273 (37%)	279 (38%)

VPB=ventricular premature beats. ACE=angiotensin-converting enzyme.

Table 1: **Baseline characteristics of patients**

stratum, were calculated by the Kaplan-Meier method¹⁵ and compared by the log-rank test stratified by ejection fraction. We calculated the risk ratio and 95% CI values by Cox's proportional hazards model,¹⁶ stratified by ejection fraction. Cox's proportional hazards model was also used to adjust for baseline imbalances in prognostic variables between groups.

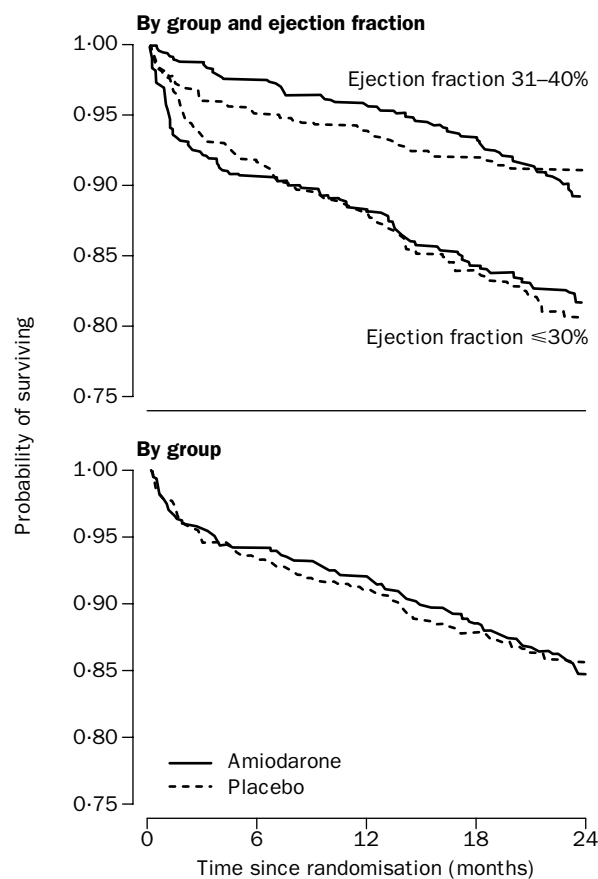
Rules for censoring of data were defined before the randomisation code was broken. For the intention-to-treat analysis, the follow-up was censored on the date of the last planned visit for complete follow-up, the end of the trial, or the date of death. For the on-treatment analysis, data were censored at 3 months after permanent discontinuation of study medication, or at the end of the follow-up as defined above.

Formal interim analyses were planned by the Safety Committee and done after the occurrence of every 60 deaths, with total mortality as the endpoint. The stopping guidelines for mortality were based on asymmetrical boundaries for benefit and harm.¹⁷ We followed the Peto¹⁸ approach with statistical guidelines for efficacy fixed at $p < 0.001$. For safety monitoring, a report was produced every 4 months, and a fixed type-I error rate of 0.01 (one sided) was chosen as a statistical guideline. The committee also reviewed other adverse side-effects.

The Safety Committee did three interim analyses and recommended continuation of the study on each occasion. However, one analysis showed higher mortality among patients in the amiodarone group who were receiving digoxin or digitoxin than among those who were not; this difference in mortality was not significant. The Steering Committee was informed and advised investigators to adhere more strictly to the protocol, which stated that the dosage of digoxin or digitoxin should be halved on enrolment. This adverse trend did not continue.

Results

We recruited 26 493 patients from 75 centres in 15 European countries. 7565 of the patients underwent a MUGA scan, and in 3255 (43%) the LVEF was 40% or less. We excluded 1769 patients with ejection fractions in the acceptable range because of lack of consent (409), imminent cardiac surgery (286), other serious illness (205), congestive cardiac failure (179), amiodarone



Patients at risk	Placebo	Amiodarone
743	693	658
743	743	743
547	547	547
469	469	469
743	743	743

Figure 2: **Kaplan-Meier estimates of all-cause mortality by group and ejection fraction**

treatment within the previous 6 months (142), essential antiarrhythmic treatment (142), and other contra-indications (406). Thus, 1486 patients were considered eligible, gave informed consent to participate, and were

	Placebo	Amiodarone	Risk ratio (95% CI)	p
Intention-to-treat analysis by EFS				
Number in analysis	743	743		
All-cause mortality	102	103	0.99 (0.76–1.31)	0.96
Total cardiac mortality	89	85	0.94 (0.70–1.26)	0.67
Arrhythmic death	50	33	0.65 (0.42–1.00)	0.05
Arrhythmic death and resuscitated cardiac arrest	61	42	0.68 (0.46–1.00)	0.05
Non-cardiac mortality	13	18	1.37 (0.67–2.79)	
Non-arrhythmic cardiac mortality	39	52	1.31 (0.86–1.98)	
Intention-to-treat analysis by EFS and history of MI				
Number in analysis	736	734		
All-cause mortality	101	101	0.94 (0.71–1.24)	0.64
Total cardiac mortality	88	83	0.88 (0.65–1.19)	0.40
Arrhythmic death	50	33	0.63 (0.41–0.98)	0.04
Arrhythmic death and resuscitated cardiac arrest	61	42	0.65 (0.44–0.96)	0.03
On-treatment analysis*				
Number in analysis	732	735		
All-cause mortality	90	84	1.01 (0.75–1.36)	0.95
Total cardiac mortality	80	70	0.94 (0.68–1.30)	0.71
Arrhythmic death	45	23	0.55 (0.33–0.91)	0.02
Arrhythmic death and resuscitated cardiac arrest	59	30	0.55 (0.35–0.85)	0.006

EFS=ejection-fraction stratum; MI=myocardial infarction.

*Total patient-year exposure: placebo=1206; amiodarone=1065.

Table 2: **Endpoints by groups**

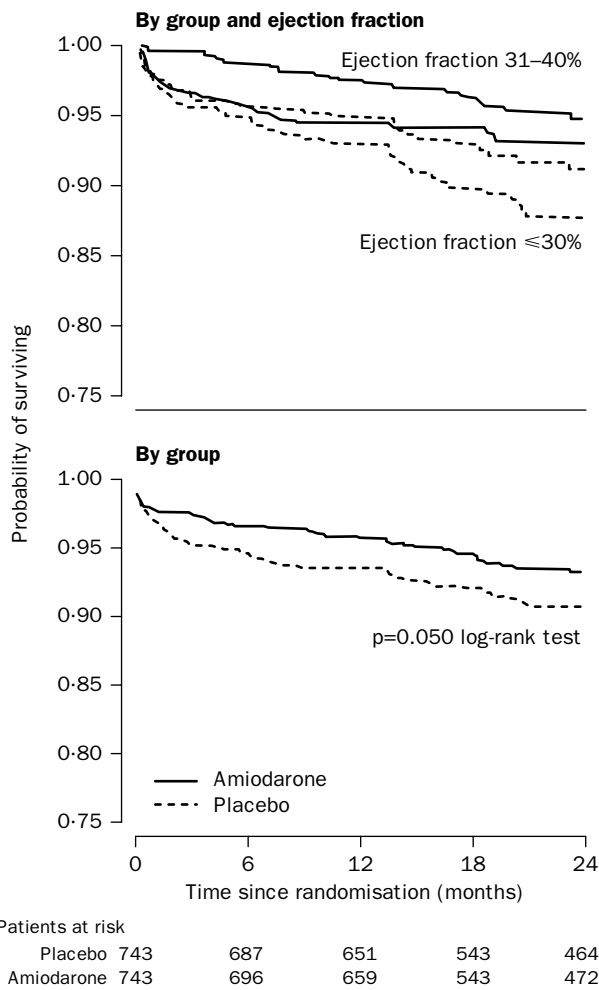


Figure 3: Kaplan-Meier estimates of arrhythmic deaths and resuscitated cardiac arrest by group and ejection fraction

enrolled in the trial, with a mean time of 15 days (± 3.9) after the index myocardial infarction. There were 743 patients in the placebo group and 743 patients in the amiodarone group. Subsequently, we found that four patients (two in the amiodarone group, two in the placebo group) did not fulfil all the eligibility criteria, but they were retained in the trial. The trial profile shows overall patient numbers during the study (figure 1).

The baseline characteristics of patients in the two groups were broadly similar, but there were some between-group differences that may have affected outcome—eg, ejection fraction, New York Heart Association functional class, peak concentrations of creatine kinase, and a history of myocardial infarction (table 1). Of especial interest was the difference in previous myocardial infarction: 191 (26%) placebo-group patients versus 233 (32%) amiodarone-treated patients.

Two patients were lost to follow-up and 1484 patients were followed up to the end of the trial. 205 patients died. The Validation Committee classified 31 of these deaths as non-cardiac and 174 as cardiac. Of the 174 cardiac deaths, 83 (48%) were arrhythmic (figure 1). In addition, there were 20 survivors of resuscitated cardiac arrest.

All-cause mortality did not differ between the treatment groups (risk ratio 0.99, $p=0.96$), even after patients were grouped by ejection fraction (figure 2). Similarly, there was no difference in total cardiac mortality (risk ratio 0.94,

	Placebo (n=102)	Amiodarone (n=103)
Non-arrhythmic cardiac death		
Reinfarction	3 (2.9%)	10 (9.7%)
LVF/CS/EMD	29 (28.4%)	30 (29.1%)
Surgery	3 (2.9%)	3 (2.9%)
Other or unknown	4 (3.9%)	9 (8.7%)
Total	39 (38.2%)	52 (50.5%)
Non-cardiac death		
Cerebrovascular	4 (3.9%)	4 (3.9%)
Cancer	4 (3.9%)	6 (5.8%)
Respiratory	1 (1.0%)	4 (3.9%)
Septic	3 (2.9%)	4 (3.9%)
Uraemia	1 (1.0%)	0 (0.0%)
Total	13 (12.7%)	18 (17.5%)

LVF=left-ventricular failure; CS=cardiogenic shock; EMD=electromechanical dissociation.

Table 3: Non-arrhythmic cardiac deaths and non-cardiac deaths

$p=0.67$). By contrast, there was a 35% risk reduction (95% CI 0–58, $p=0.05$) in arrhythmic deaths among amiodarone-treated patients. A similar risk reduction was observed after the addition of resuscitated cardiac arrest (table 2, figure 3). There were more deaths from non-arrhythmic cardiac and non-cardiac causes in amiodarone-group patients than in placebo-group patients (table 3).

A history of myocardial infarction significantly increased the risk of death (24% vs 10%, $p<0.0001$). We, therefore, did a further analysis to adjust for this variable and the baseline imbalances in prognostic variables. The adjusted differences in all-cause and cardiac mortality between the treatment groups were not significant (table 2).

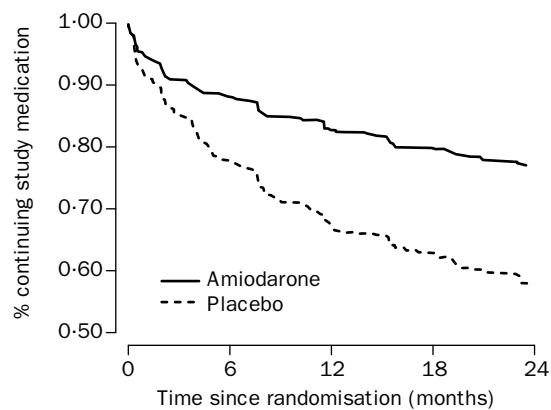
Baseline ambulatory electrocardiograms were evaluable in 1367 patients, of whom 191 died. The mortality rate was higher in those with frequent or complex arrhythmias than in those without arrhythmias (112/548 [20%] vs 79/819 [10%]). However, the group without arrhythmias was larger and comprised 60% of the trial population. Of the 191 deaths, 79 (41%) occurred in the group without baseline arrhythmias, and among these deaths 36 (45%) were classified as arrhythmic. In intention-to-treat analysis of the subgroup of 548 patients with arrhythmias at baseline (40% of the trial population), the difference between the amiodarone and placebo groups in arrhythmic deaths did not achieve significance, but there was a significant reduction in the combined endpoint of arrhythmic deaths and resuscitated cardiac deaths ($p=0.048$) in amiodarone-treated patients compared with patients in the placebo group.

During the trial, 284 (38.5%) amiodarone-group patients discontinued their study medication compared with 158 (21.4%) placebo-group patients (figure 4). The main causes of discontinuation of study medication are shown in table 5. There was no significant difference in

Reason for discontinuation	Placebo (n=743)	Amiodarone (n=743)
Endocrine disorders	12 (1.6%)	44 (5.9%)
Nervous-system disorders*	1 (0.1%)	4 (0.5%)
Gastrointestinal disorders	3 (0.4%)	10 (1.3%)
Hepatic disorders	2 (0.3%)	6 (0.8%)
Pulmonary disorders	3 (0.4%)	6 (0.8%)
Skin rash/sensitivity	1 (0.1%)	9 (1.2%)
Vision disorders	1 (0.1%)	4 (0.4%)
Myocardial and valve disorders	13 (1.7%)	4 (0.5%)
Heart rate and rhythm disorders	21 (2.8%)	24 (3.2%)
Miscellaneous	8 (1.1%)	10 (1.3%)
Poor compliance	58 (7.8%)	70 (9.4%)
Other	32 (4.3%)	88 (11.8%)

*Central and peripheral.

Table 4: Causes of early discontinuation of study medication



Patients on treatment	0	6	12	18	24
Placebo	743	612	549	441	355
Amiodarone	743	544	447	343	281

Figure 4: Percentage of patients continuing study medication

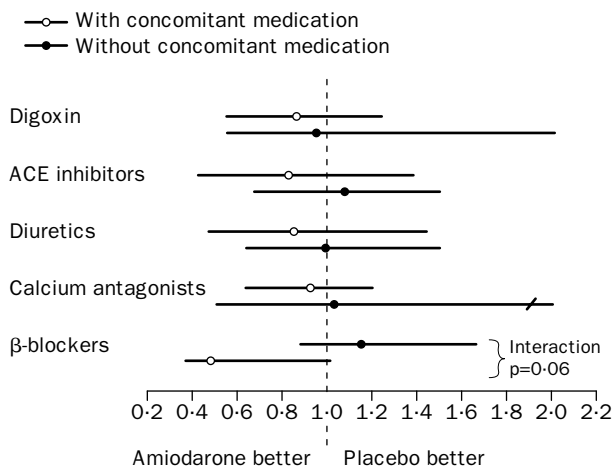


Figure 5: Intention-to-treat analysis of 2-year total cardiac mortality by concomitant medication at baseline

the major risk factors for mortality and arrhythmic events between those patients who continued amiodarone treatment and those who did not.

The on-treatment analysis showed a more striking risk reduction than was shown in the intention-to-treat analysis in arrhythmic deaths among the patients taking amiodarone compared with those taking placebo (table 2).

Adverse side-effects are shown in table 7. There were three deaths in the amiodarone group from pulmonary fibrosis, which was confirmed on necropsy; however, two of these patients had pre-existing pulmonary disease and should not have been included in the trial. Biochemical

Adverse effects	Placebo (n=743)	Amiodarone (n=743)
Clinical hypothyroidism*	0 (0.0%)	11 (1.5%)
Clinical hyperthyroidism*	4 (0.5%)	12 (1.6%)
Gastrointestinal disorders	15 (2.0%)	22 (3.0%)
Nervous-system disorders*	8 (1.1%)	10 (1.3%)
Pulmonary disorders	30 (4.0%)	39 (5.2%)
Vision disorders	5 (0.7%)	5 (0.7%)
Skin disorders	0 (0.0%)	8 (1.1%)
Arrhythmia, except bradycardia	41 (5.5%)	23 (3.1%)
Bradycardia	1 (0.1%)	10 (1.4%)
Liver disorders	6 (0.8%)	15 (2.0%)

*Cases assessed by Validation Committee. †Central and peripheral.

Table 5: Severe adverse effects

thyroid disorders were common, but in the amiodarone group, clinical hypothyroidism and hyperthyroidism were observed in only 11 (1.5%) and 12 (1.6%) patients, respectively. No torsade de pointes was documented in EMIAT.

As expected in survivors of myocardial infarction, several other drugs were used concomitantly throughout the trial (table 1). After the reports of the benefits of inhibitors of angiotensin-converting enzyme (ACE) were published, in 1992, the proportion of patients receiving these agents increased. Concomitant treatment with ACE inhibitors, diuretics, calcium antagonists, digoxin, or digitoxin had no effect on differential treatment group mortalities. However, we found a strong tendency towards favourable interaction between use of β -blockers and cardiac mortality (figure 5), independently of left-ventricular function.

Discussion

EMIAT showed that amiodarone was associated with a significant reduction in arrhythmic deaths and resuscitated cardiac arrests among patients discharged from hospital with depressed left-ventricular function after recent myocardial infarction. However, neither a significant nor corresponding reduction in all-cause or total cardiac mortality was seen because of increased non-cardiac, or cardiac but not arrhythmic, mortality. Thus, EMIAT does not support the systemic prophylactic use of this regimen of amiodarone in survivors of myocardial infarction. Nevertheless, amiodarone therapy does lead to a reduction in arrhythmic death with no proarrhythmic effect, only a few minor side-effects, and a neutral effect on total mortality.

Our findings warrant a discussion of the rationale and background of this trial, the factors that might explain its outcome, and our interpretation of the findings.

Patients recovering from myocardial infarction are at substantial risk of sudden arrhythmic death and symptomatic arrhythmic events.^{1,2} There is a sound rationale for the use of antiarrhythmic drugs in such patients. However, the results of trials of antiarrhythmic drugs have mostly been adverse:^{4,5,19,20} antiarrhythmic drug therapy was associated with increased deaths, in most cases sudden and presumably arrhythmic, that were attributed to a proarrhythmic effect. Yusuf and colleagues' meta-analysis²¹ of trials of antiarrhythmic drugs after myocardial infarction showed that sodium-channel blockers were harmful and that calcium-channel antagonists had no beneficial effects; by contrast, a favourable effect was observed with the use of amiodarone in a small population. Similarly, Teo and colleagues' meta-analysis²² of placebo-controlled trials of amiodarone after myocardial infarction or in patients with heart failure suggested that survival substantially improved with the use of amiodarone. The lack of efficacy of sodium-channel blockers has been variously ascribed to proarrhythmic and negative inotropic effects.²³ An interaction with ischaemia has also been proposed.²⁴ On the other hand, although amiodarone is predominantly thought of as an antiarrhythmic drug, it is also an anti-ischaemic agent.^{25,26} Importantly, amiodarone seems to have little or no proarrhythmic potential. Thus, we decided that it was appropriate to design and conduct a mortality trial with amiodarone among survivors of myocardial infarction at high risk of cardiac death.

Unlike the antiarrhythmic drugs used in previous trials,

mainly sodium-channel and potassium-channel blockers, amiodarone has several actions.²⁷ Amiodarone has a blocking effect on sodium, calcium, and potassium channels, and also has antiadrenergic and anti-ischaemic effects. Lethal arrhythmias in postinfarction patients are likely to be the result of re-entry.²⁸ In our study, the prolongation of the ventricular refractory period combined with adrenergic blockade might have contributed to the reduction in arrhythmic deaths in the amiodarone-treated group.

EMIAT showed that amiodarone therapy had no effect on the primary endpoint of 2-year all-cause mortality, irrespective of the stratum of left-ventricular function. However, amiodarone was associated with a reduction in arrhythmic deaths among high-risk patients after myocardial infarction. Our finding of a significant reduction in arrhythmic deaths and resuscitated cardiac arrests in the amiodarone group suggests that any possible proarrhythmic effects of amiodarone do not outweigh its antiarrhythmic benefit. But this reduction in arrhythmic deaths was balanced by an excess of five non-cardiac deaths and 13 cardiac but non-arrhythmic deaths. This excess may have resulted from chance or from the imbalance in significant prognostic factors between the groups, but may also have been partly attributable to the adverse side-effects of amiodarone, such as, the three deaths caused by pulmonary fibrosis.²⁹ In our study, fatal reinfarction contributed to the non-arrhythmic mortality associated with amiodarone treatment. This finding is, at first, difficult to explain because amiodarone is an antianginal drug.³⁰ However, most of the lethal reinfarctions (11 of 13) occurred in patients who had a history of myocardial infarction before the index infarction, a group that was over-represented in the amiodarone group. Another explanation for the failure of amiodarone to reduce non-arrhythmic death is that, by preventing arrhythmic death, amiodarone treatment did not preclude death from other non-arrhythmic mechanisms. The results of EMIAT underline the importance of using all-cause mortality, rather than an antiarrhythmic effect, as the primary endpoint in a survival study of an antiarrhythmic drug.

After adjustment for the imbalance in covariates between the groups, there was some evidence of a reduction in all-cause and total cardiac mortalities. Is this reduction real and would it have been statistically significant if the trial had been larger? The original power calculations were based on the pilot study of the Canadian Arrhythmia Myocardial Infarction Amiodarone Trial,⁸ the Basel Antiarrhythmia Study of Infarct Survival,⁶ and the partially completed Polish Amiodarone Trial⁷ which showed that an all-cause mortality reduction of 35–50% might be achieved with amiodarone. We also knew, at the time when EMIAT was planned, that poor ventricular function was a more powerful predictor of mortality than was the frequency of ventricular ectopic activity. Two studies showed that patients with an LVEF below 40% would have a 2-year mortality of 15%, of which the arrhythmic component would be about half.^{13,14} However, there were only limited and inconsistent data on the effect of amiodarone on the mortality of patients with poor left-ventricular function. We, therefore, elected to recruit patients on the basis of poor ventricular function alone and, assuming a 2-year mortality of 15% in the placebo group, designed the study to detect a 35% reduction in all-cause mortality in the amiodarone group. For the

endpoint analyses, a conventional two-sided test of significance was judged to be essential, since previous studies of antiarrhythmic drugs had clearly shown the possibility of an adverse outcome associated with the active agent. Thus, we calculated that 1500 patients were needed. In fact, we recruited 1486 patients, and our a-priori assumptions proved to be correct: mortality in the placebo group was 14% (102 of 743), and the arrhythmic deaths constituted half (49%) of the placebo-group mortality (50 of 102). Thus, EMIAT had sufficient power to detect a 35% reduction in mortality in the amiodarone group. However, a much larger trial would have been necessary to detect the small apparent reduction in all-cause mortality suggested by EMIAT.

We assessed left-ventricular function accurately by MUGA scanning, which was well validated and approved centrally. Unlike some previous studies of antiarrhythmic drugs such as the Cardiac Arrhythmias Suppression Trial,⁴ in which mortality among placebo-group patients was lower than expected, the selection process in EMIAT resulted in the anticipated number of trial endpoints. EMIAT showed that many arrhythmic deaths occurred in patients who did not have frequent or complex ventricular ectopic activity at baseline. Thus, if we had used such ectopic activity as the only entry criterion, the power of the trial would have been reduced. Other stratification criteria, such as heart rate variability^{31,32} or baroreceptor sensitivity,³³ which are more likely to predict the occurrence of arrhythmic events could have been used but were not fully appreciated when EMIAT was planned. But since there was a significant reduction in arrhythmic events with amiodarone, it seems unnecessary to speculate whether better selection for arrhythmic risk would have changed the results of the trial. Nonetheless, it might have been appropriate to exclude patients at risk of early death because of pump failure (very low ejection fraction) or reinfarction (adverse coronary anatomy). Such exclusion criteria may have reduced the cardiac but non-arrhythmic mortality associated with amiodarone therapy.

In some previous trials of postinfarction antiarrhythmic drugs, patients were recruited up to 1 year after the index infarction. However, most patients die within the first few months after infarction. Thus, in EMIAT patients were enrolled and randomly allocated treatment before discharge from hospital. Furthermore, the loading dose of study medication was administered quickly to ensure drug activity before discharge. Early recruitment plus high dosing may have accounted for the increased early mortality in patients with very poor ventricular function (figure 2), which contrasted with the antiarrhythmic advantages associated with amiodarone.

Many of the adverse side-effects associated with amiodarone are sufficiently troublesome to force discontinuation of the drug.³⁴ In our study clinically relevant pulmonary,²⁹ hepatic,³⁵ and thyroid disorders^{36,37} occurred in a small proportion of amiodarone-treated patients, and were much as we had anticipated, for example, there was no torsade de pointes.³⁸ However, many biochemical abnormalities and minor side-effects occurred, which accounted for the high rate of discontinuation of study medication.

This high rate of discontinuation suggests that although the primary analysis should be by intention to treat, a second on-treatment (efficacy) analysis should also be done. The effect of amiodarone continues after discontinuation of the drug. We, therefore, decided to

conduct the on-treatment analysis by censoring patients from further analysis for 3 months after permanent early discontinuation of study medication. But these analyses may be of limited value because such a large proportion of patients (amiodarone 38.5%, placebo 21.4%) discontinued study medication. In any event, both analyses gave similar results.

Analyses of the interaction between use of concomitant medications at baseline and the mortality endpoints suggested that there was an important interaction with β -blockers. There were fewer cardiac deaths among amiodarone-treated patients who were receiving concomitant β -blockers than among those who were not, probably because β -blockers were not prescribed to patients at high risk of cardiac death. However, of those patients who receive β -blockers, there was a substantial reduction in cardiac and arrhythmic mortality among those who were also given amiodarone. This finding indicates that β -blockers confer additional benefit to the efficacy of amiodarone, a finding also reported for the treatment of sustained ventricular tachyarrhythmias.³⁹ We did not anticipate this interaction before the start of the trial, and its implications must be interpreted with caution.

Our findings do not support the systematic prophylactic use of amiodarone in patients with poor left-ventricular function after myocardial infarction, irrespective of the presence of symptomless ventricular ectopic activity. However, the 35% risk reduction of fatal and resuscitated arrhythmic events associated with amiodarone shows that this drug affords protection from arrhythmic death in this high-risk population. In addition, no proarrhythmia was associated with amiodarone treatment. Thus, it may be possible to identify groups of patients at high risk of arrhythmia for whom amiodarone will offer a substantial survival benefit. Since we found such a substantial antiarrhythmic effect, balanced by non-arrhythmic mortality, it may also be possible to achieve a significant reduction in all-cause mortality among infarct survivors at high risk of sudden arrhythmic death with a different drug regimen, such as a lower loading dose, and a shorter duration of treatment.

Our findings contrast with the disappointing results of most previous trials of antiarrhythmic drugs after myocardial infarction. Thus, the clinician may be encouraged to consider amiodarone for patients with symptomatic or sustained and potentially dangerous arrhythmias, even after myocardial infarction,

Although subgroup analysis suggests that amiodarone may be useful in some patients, definitive indications will require further clinical trials. Our results must be interpreted together with those of other placebo-controlled amiodarone survival studies. Review of the pooled data may suggest new or prophylactic indications for the use of amiodarone, but such conclusions must await formal meta-analysis or further clinical trials.

European Myocardial Infarct Amiodarone Trial Study Participants—Austria: Innsbruck (F Dienstl, A Dienstl), Wien (K Steinbach, M Nürnberg, H Weber, T Binder); *Belgium:* Antwerpen (R Ranquin, C Convens), Bruges (Y Vandekerckhove, E Van der Stichele), Bruxelles (I Blankoff, S Carlier, A Depaepe, C Gassavolis), Gent (L Jordaens, R Tavernier), Liège (J Boland, J L Waucquez); *Finland:* Espoo (U Idänpää-Heikkilä, R Sipilä); *France:* Bayonne (J Kayanakis), Clamart (G Motte, C Sebagn), Lille (J Lefieffre, L Guedon), Lyon (P Touboul, B de Breyne, M Gallet, M Lopez), Montpellier (R Grolleau-Raoux, F Leclercq), Nancy (E Aliot, N Sadoul), Nantes (H Le Marec, J C Chevallier), Rennes (J C Daubert, J M Baisset), Schiltigheim

(B Brechenmacher, J B Caillard), Tours (B Charbonnier, G Pacouret), Vandoeuvre (B Brembilla Perrot, N Danchin); *Germany:* Berlin (D Andresen), Cottbus (U Kreutzer, J Kolditz), Düren (H Simon, B Zentgraf), Hamburg (T Meinertz, M Volkmer, K Kuck, M Antz), Hannover (H Klein, G Claus), Heidelberg (J Brachmann, K Freigang), Lübeck (J Potratz, G Taubert), Magdeburg (H Klein, S Grund), Mainz (N Treese, A Liebrich), München (L Goedel-Meinen, M Hofmann, F G Nowak, K Coppenrath), Münster (M Borggrefe, J Brunn); *Greece:* Athens (S Mouloupoulos, A Antoniou), Pireus (D V Cikkinos, G Athanassopoulos); *Italy:* Bari (P Rizzon, M Di Biase), Bologna (D Bracchetti, F Naccarella, B Magnani, A Capucci), Mestre (E Piccolo, A Raviele), Milano (A Lotto, A Finzi), Varese (G Binaghi, A M Giorgio); *Netherlands:* Amsterdam (A Vermeulen), Capelle Aan Den Yssel (W M Muijs van der Moer, S L Nio), Deventer (D J A Lok, M J C Osinga-Meek), Dordrecht (J B L ten Kate), Dordrecht (P Breuls), Heerlen (J A Kragten, J H M de Warrimont-Henquet), Rotterdam (D C A Von Hoogenhuyze), Tilburg (N J Holwerda); *Norway:* Bergen (O Johm, K Breivik); *Poland:* Warsaw (L Ceremuzinski, T Chamiec); *Portugal:* Coimbra (L Providência, G Alves), Lisboa (C Ribeiro, A Bordalo); *Spain:* Barcelona (J Cinca, A Moya, A Bayes de Luna, X Viñolas), Madrid (C Moro Serrano, A Hernandez-Madrid), Valencia (J Cosin, M J Sancho-Tello, A Salvador, M Amela); *Sweden:* Lund (B Olsson, E Pantev); *Switzerland:* Basel (F Burkart, M Pfisterer), Bern (M Gertsch, T Chatterjee); *Geneva* (W Rütishauser, M Zimmermann), Lausanne (L Kappenberger, M Framer), Sion (P Vogt, D Fellay), Zurich (F W Amann, E Schuiki); *UK:* Derby (M W Millar-Craig, A V Joy), Glasgow (R J Northcote), Gwent (J Davies, W Covell), Kent (B Gould, A Brian), Isleworth (T W Greenwood, E Ramhamadany), Leicester (J Skehan, Y Haider), London (A J Camm, H A Staunton, J Cleland, F Habib).

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