Articles

Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials

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Summary

Background There have been 13 randomised controlled trials of prophylactic amiodarone in patients with recent myocardial infarction (MI) or congestive heart failure (CHF). None of these was powered to detect a mortality reduction of about 20%. We undertook a meta-analysis, based on data from individual patients, to provide a more sensitive and accurate assessment of the benefits and risks of prophylactic amiodarone.

Methods Individual data from the studies were abstracted according to a predefined protocol. The summary odds ratios were calculated according to standard methods.

Findings There were eight post-MI and five CHF trials; nine trials were double-blind and placebo-controlled, and four compared amiodarone with usual care. 6553 patients were randomly assigned treatment, of which 78% were in post-MI trials and 22% in CHF trials. 89% had had previous MI. The mean left-ventricular ejection fraction was 31%, and median frequency of ventricular premature depolarisation 18 per h. Total mortality was reduced by 13% (odds ratio 0·87 [95% CI 0·78–0·99], p=0·030) based on classic fixed-effects meta-analysis and by 15% (0·85 [0·71–1·02], p=0·081) with the more conservative random-effects approach. Arrhythmic/sudden death was reduced by 29% (0·71 [0·59–0·85], p=0·0003). There was no effect on non-arrhythmic deaths (1·02 [0·87–1·19], p=0·84). There was no difference in treatment effect between post-MI and CHF studies. The risk of arrhythmic/sudden death in control-group patients was higher in CHF than in post-MI studies (10·7 *vs* 4·1%), and the best single predictor of risk of arrhythmic/sudden death among all patients was symptomatic CHF. The excess (amiodarone minus control) risk of pulmonary toxicity was 1% per year.

Interpretation Prophylactic amiodarone reduces the rate of arrhythmic/sudden death in high-risk patients with recent MI or CHF and this effect results in an overall reduction of 13% in total mortality.

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Introduction

Significant progress has been made during the past decade in reducing the mortality of patients with acute myocardial infarction (MI) by means of thrombolysis and antiplatelet agents. Nonetheless, 1-year mortality in survivors of MI remains unacceptably high, with population-based studies continuing to report rates of more than 10%.[1] A substantial proportion of deaths after hospital discharge are sudden and caused by ventricular fibrillation. Patients with congestive heart failure (CHF) also have a substantial risk of death from arrhythmia.

During the past decade randomised clinical trials have investigated the ability of several antiarrhythmic drugs to reduce premature death in patients at high risk of arrhythmia.[2–5] Apart from β-blockers, no other agent has been conclusively shown to reduce mortality. Indeed, there have been clear increases in mortality with some class 1 and class 3 agents. Amiodarone, however, has several antiarrhythmic actions and unusual pharmacokinetics.[6] The role of prophylactic amiodarone in patients at risk of death from cardiac arrhythmia has been addressed by 13 randomised controlled clinical trials.[7–19] These trials have investigated amiodarone in two overlapping high-risk populations—survivors of MI and patients with CHF. These populations overlap because many patients with previous MI develop left-ventricular dysfunction. Conversely, the most common cause of heart failure is ischaemic heart disease and MI. Only three of the randomised trials of amiodarone[12,16,17] showed a significant reduction in all-cause mortality. However, only three of the studies had a sample size of more than 1000 patients. None was sufficiently large to detect reliably a moderate reduction in mortality of 10–20%. The possibility remains, therefore, that amiodarone does reduce total mortality but that this effect was not detected because of insufficient statistical power.

The two largest amiodarone trials have raised much controversy.[20] The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT)[7] and the European Myocardial Infarction Amiodarone Trial (EMIAT)[8] both reported substantial and statistically significant reduction in the risk of arrhythmic death or resuscitated ventricular fibrillation. Neither trial showed a significant reduction in overall mortality. CAMIAT, with 1202 participants, was designed primarily to detect a 50% reduction in the combined outcome of arrhythmic death or resuscitated ventricular fibrillation; total mortality was a secondary outcome. EMIAT, with 1486 participants, was designed to detect a reduction in total mortality of 33%. Because neither trial had sufficient

Study	Loading dose	Maintenance dose	Additional selection criteria	Planned treatment	Control treatment
After MI					
8	800 mg/day×14 days, 400 mg/day×4 months	200 mg/day	LVEF≤40%	2 years*	Placebo double-blind
7	10 mg/kg/daily×14 days	400 mg/day to 1000 mg/wk	≥10 VPD/h or VT <10 beats	2 years*	Placebo double-blind
9	Intravenous and oral 2700 mg/48 h, 1200 mg/day×4 days, 400 mg/day×3 months	200 mg/day	None	6 months	Placebo double-blind
10	800 mg/day×1 week	400 mg/day 6 of 7 days	Contraindication to β-blocker	1 year	Placebo double-blind
11	600 mg/day×1 week, 400 mg/day×1 week	200 mg/day	LVEF 20–45% and (≥3 VPD/h or VT ≤15 beats)	3 years	No antiarrhythmic
12	1000 mg/day×5 days	200 mg/day	Lown class 3 or 4 B Holter	1 year	No antiarrhythmic
13	600 mg/day×1 month	200 mg/day	Any of VF, VT, previous MI, CHF, new BBB	Not specified	Placebo double-blind
14	10 mg/kg daily×14 days	400 mg/day to 1000 mg/wk	≥10 VPD/h or VT<10 beats	2 years	Placebo double-blind
CHF					
15	800 mg/day×14 days, 400 mg/day×50 weeks	200 mg/day	LVEF ≤40% and ≥10 VPD/h and LVED ≥55 mm or CTR >0·55	1·0–4·5 years; common termination	Placebo double-blind
16	600 mg/day×14 days	300 mg/day	Any two of CTR >0·55, LVEF ≤35%, echo LVED >3·2 cm/m^2	2 years	No antiarrhythmic
17	800 mg/day×2 weeks	400 mg/day	LVEF ≤35% and Lown class 2–5	1 year	No antiarrhythmic
18	400 mg/day×4 weeks	200 mg/day	LVEF ≤30% and Lown class 2–5	1 year	Placebo double-blind
19	600 mg/day×14 days	200 mg/day	None	Not specified	Placebo double-blind

LVEF=left-ventricular ejection fraction; VPD=ventricular premature depolarisation; VT=ventricular tachycardia; VF=ventricular fibrillation, BBB=bundle-branch block; CTR=cardiothoracic ratio; LVED=left-ventricular end-diastolic dimension. *1–2 years for patients enrolled in final year.

Table 1: **Randomised trials of amiodarone after MI and in CHF**

power to detect modest but important reductions in total mortality, it remains unclear whether the beneficial effect of amiodarone on arrhythmic death and resuscitated ventricular fibrillation (observed in both trials) translates into a beneficial effect on total mortality or whether detrimental effects on non-arrhythmic death offset the reductions in arrhythmic death.

One practical way to address this issue is to carry out a systematic meta-analysis of all the relevant randomised trials to obtain a more precise estimate of the effect of amiodarone on arrhythmic/sudden death, total mortality, and non-arrhythmic death. All current trials of amiodarone in survivors of MI or in CHF patients have been completed, and no major amiodarone trials are known to be in progress. An overview of all available trials would also provide the most accurate assessment of the beneficial effect of amiodarone in subgroups of patients, as well as its side-effects, some of which occur infrequently. With these aims, the principal investigators of the amiodarone randomised trials have collaborated to carry out such a meta-analysis. To improve the precision of the primary analysis and to allow issues of the relation between baseline characteristics and the effect of amiodarone to be addressed, data from individual patients in the studies were merged into a master database upon which subsequent analyses were based.

Methods

The criteria for studies to be included were that treatment allocation was randomised and that amiodarone was compared with placebo or with usual care. Potentially eligible studies were identified by literature review, computerised literature search, and discussion with colleagues. The principal investigators of eligible studies were invited to an organisational meeting. A protocol specifying the baseline, follow-up, and outcome data to be collected, and the methods of analysis, was developed and given written approval by all study groups by August, 1995. Each study group then extracted the relevant data for each patient from their study database, following the agreed format. The data were then consolidated by a coordinating centre. There was some variability among studies in their choice and definition of fatal outcomes. The protocol defined two main outcomes for analysis: death from any cause and arrhythmic/sudden death. Most studies recorded the non-fatal event of resuscitated ventricular fibrillation but continued to treat and follow up patients until death or the end of the trial. Although resuscitated ventricular fibrillation was included in the primary analyses of many studies, we decided to concentrate the meta-analysis on actual death. All studies had working definitions for arrhythmic/sudden death that were reasonably similar, but the studies had varying specificity in attributing death to other causes. Rather than attempting to reclassify cause of death, we adopted broad classification as arrhythmic/sudden death, other cardiac or cardiovascular death, and other deaths. Some studies included a small number of deaths of unknown cause and these were classed as other cardiac or cardiovascular for the purposes of this analysis. Data from individual patients were not available from two of the smaller trials,[13,18] and summary data from the original reports were used.

Statistical analysis

The statistical methods used to combine treatment effects over studies followed the approach described by Whitehead and Whitehead[21] for survival data. Each study's data form a series of two-by-two tables, one at each distinct death point. Each table depicts the numbers of patients in the active and control groups who die at that time point and the numbers who survive. The expected number of deaths in the active treatment group, and its variance, are computed under the null hypothesis of no treatment effect based on the hypergeometric distribution. The observed (O) number of deaths, expected (E) number of deaths, and variance (V) are then summed over all death points for the study giving the quantities O_i, E_i, and V_i for the ith study. For studies without individual data, equivalent values can be calculated from the single two-by-two table classifying patients by treatment and death status at the end of the study.

Various treatment effect estimates have been described, and we opted for a method previously used by Peto and colleagues.[22] Although sometimes referred to as a hazard ratio, the quantity $\exp([O_i-E_i]/V_i)$ is an estimate of the odds ratio for the ith study. The corresponding 95% CI is given by $\exp([O_i-E_i]/\sqrt{V_i} \pm 1{\cdot}96/V_i)$.The overall odds ratio and CI can be calculated in a similar way but based on the totals of O_i, E_i, and V_i summed over studies. The Mantel-Haenszel[23] log-rank test yields a p value for the null hypothesis of no overall treatment effect (ie, overall odds ratio=1). A closely related test of heterogeneity allows assessment of whether there is more variability among studies in individual odds ratio than would be expected by chance alone. Supplemental analyses based on the random-effects model[24] were included when there was evidence of heterogeneity.

We investigated the influence of various baseline clinical and demographic characteristics on the size of the amiodarone treatment effect (odds ratio) by similar techniques. For example,

Study	n	Mean follow-up (years)	Mean (SD) age in years	% male	% with history of:			Median VPB/h	Mean (SD) LVEF (%)	% with heart rate >70/min	% with VT	% with early discontinuation of amiodarone
					MI	NIC	Diabetes					
After MI												
8	1486	1·69	60·4 (9·5)	84·4	100	0·1	16·5	2	30·2 (7·3)	56·3	26·9	38·5
7	1202	1·79	63·5 (10·9)	82·3	100	NA	16·6	23	NA	43·5	38·4	37·3
9	1073	0·40	60·4 (12·0)	78·1	100	NA	16·2	NA	NA	NA	NA	15·5
10	613	0·94	59·5 (9·2)	69·2	100	NA	18·9	NA	45·1 (11·1)	83·1	NA	33·8
11	238	2·53	58·8 (10·9)	88·2	100	8·6	16·8	10	34·9 (6·9)	NA	63·4	16·5
12	212	0·94	61·3 (6·8)	83·7	100	NA	19·1	9	43·1 (16·2)	44·9	NA	22·4
13	200	NA	NA	97·0	100	NA	NA	<1	NA	NA	NA	NA
14	77	1·62	64·6 (9·9)	75·3	100	NA	14·3	31	NA	45·2	27·3	54·2
All MI trials	5101	1·34	61·1 (10·5)	81·2	100	1·3	16·8	12·	34·7 (11·1)	55·7	34·9	31·2
CHF												
15	674	2·15	65·0 (8·3)	99·0	62·8	28·6	32·3	118	25·3 (8·3)	73·0	78·7	40·2
16	516	1·10	59·2 (12·6)	80·8	37·2	61·2	14·0	40	19·0 (7·4)	90·9	23·6	4·6
17	127	0·81	61·3 (9·1)	76·4	36·2	63·0	11·0	NA	27·4 (7·1)	NA	NA	6·1
18	101	NA	57·2 (10·3)	85·1	52·5	50·0	NA	57	20·0 (6·3)	NA	62·0	NA
19	34	1·63	68·3 (7·2)	88·2	66·7	30·3	20·6	57	19·0 (5·2)	82·4	63·0	36·8
All CHF trials	1452	1·61	62·2 (10·7)	89·3	50·6	44·8	23·0	84·5	23·6 (8·3)	80·8	56·8	23·2
All studies	6553	1·40	61·3 (10·5)	83·0	89·1	21·2	18·2	18	31·0 (11·5)	62·1	41·7	29·4

NIC=non-ischaemic cardiomyopathy; VPB=ventricular premature beats; LVEF=left-ventricular ejection fraction; VT=ventricular tachycardia; NA=not available.

Table 2: **Characteristics of patients**

to investigate the effect of sex, the individual study data sets were first separated into male and female subgroups. A summary odds ratio was then calculated over studies (as described above) separately for men and women. A heterogeneity test with a single degree of freedom was then used to compare the size of the two odds ratios.

For studies that included placebo controls, the data sets included information on various adverse experiences previously associated with the use of amiodarone sufficiently troublesome to cause early permanent discontinuation of study drug. These data were analysed as non-time-dependent binary events and formally pooled by the Mantel-Haenszel[23] technique, in which each study contributes a two-by-two table (treatment × presence/absence of toxic effect). All analyses were by intention to treat unless otherwise specified.

Results

Study characteristics

Eight of the 13 trials (table 1) had studied patients who had recently had MI (5101 participants, 78%) and five had studied patients with CHF (1452 participants, 22%). Of the post-MI trials, six required patients to be enrolled within 30 days of MI, and the other two specified periods of 45 days or less and less than 60 days. Two studies had no selection criteria for high-risk patients among the total MI population, three used an abnormal Holter electrocardiogram, two abnormal left-ventricular ejection fraction, one a combination of abnormal Holter and abnormal left-ventricular ejection fraction, and one contraindication to β-blocker therapy. The CHF studies selected among the population of patients with symptomatic compensated CHF. To select high-risk patients, four studies used left-ventricular ejection fraction criteria and two used both left-ventricular ejection fraction and Holter criteria. All the trials were randomised; four compared amiodarone with usual care in an unblinded design and the other nine were double-blind and placebo-controlled. Two trials[11,12] also compared amiodarone with another active treatment; however, patients on the other active treatment are not included in this meta-analysis.

Dosing

All 13 trials used a loading dose of amiodarone, between 400 mg/day for 28 days and 800 mg/day for 14 days. One study[9] initiated study medication in the immediate acute phase of MI and used a combined oral and intravenous loading dose of 2700 mg given over 48 h. This dose was lowered midway through the study. The amiodarone maintenance dose was gradually reduced in some studies but in most there was a final maintenance dose that was achieved at between 2 and 6 months (table 1). In CAMIAT and CAMIAT-pilot the dose was variable between 400 mg/day and 1000 mg/week depending on age, weight, and the results of follow-up Holter monitoring. Most studies had a fixed period of follow-up of 1 year (four studies) or 2 years (four studies). The follow-up in the other studies varied between 6 months[9] and up to 4·5 years.[15]

Baseline characteristics

The mean age of patients varied little among studies, and the patients were predominantly male (table 2). 89·1% of patients overall had a history of MI. A history of MI was common in the CHF trials, but in the South American studies,[16,17] most patients had non-ischaemic cardiomyopathy. A history of diabetes mellitus was consistently present in about 18% of patients. Eight trials measured the frequency of ventricular premature depolarisation at baseline; the median frequency varied between 2 and 23 per h in post-MI patients and between 40 and 118 per h in CHF patients. Non-sustained ventricular tachycardia was also common (41·7% of patients). Nine trials measured left-ventricular ejection fraction at baseline (mean 31%); the mean was much lower in trials of CHF patients than in those of post-MI patients. Mean follow-up varied from 0·4 to 2·5 years. The rate of early permanent discontinuation of amiodarone varied from 4·6% to 54·2% of patients, with much lower rates in the non-placebo-controlled trials.

Mortality

Table 3 and figure 1 summarise the separate analyses of total mortality and arrhythmic/sudden death. The individual study results are summarised in table 3 as annual event rates (ie, hazard rates) in amiodarone and control groups. The treatment effect is given as an odds ratio, which can be interpreted approximately as a relative risk or hazard ratio.

The results of the 13 trials combined show a statistically significant odds ratio for total mortality in

	Total mortality					Arrhythmic/sudden death				
	Amiodarone		Control		OR (95% CI)	Amiodarone		Control		OR (95% CI)
	Events/years	Rate/ year (%)	Events/years	Rate/ year (%)		Events/years	Rate/ year (%)	Events/years	Rate/ year (%)	
Study reference										
8	103/1260·4	8·2	102/1252·8	8·1	1·01 (0·76–1·32)	33/1260·4	2·6	50/1252·8	4·0	0·66 (0·43–1·02)
7	57/1090·0	5·2	68/1061·3	6·4	0·82 (0·58–1·16)	24/1090·0	2·2	33/1061·3	3·1	0·71 (0·42–1·19)
9	62/210·7	12·7*	52/212·6	10·7*	1·19 (0·82–1·71)	12/210·7	2·6*	15/212·6	3·2*	0·80 (0·37–1·69)
10	21/290·2	7·2	33/284·0	11·6	0·63 (0·37–1·08)	10/290·2	3·5	20/284·0	7·0	0·51 (0·25–1·04)
11	4/299·3	1·3	9/303·7	3·0	0·48 (0·16–1·43)	3/299·3	1·0	5/303·7	1·6	0·63 (0·16–2·51)
12	5/94·1	5·3	15/105·0	14·3	0·41 (0·17–0·99)	4/94·1	4·2	9/105·0	8·6	0·52 (0·18–1·55)
13	16/156†	10·3	11/188†	5·9	1·94 (0·85–4·41)	4/156†	2·6	3/188†	1·6	1·64 (0·36–7·45)
14	5/81·1	6·2	6/43·7	13·7	0·45 (0·13–1·54)	1/81·1	1·2	4/43·7	9·1	0·14 (0·02–0·86)
15	122/716·3	17·0	132/731·1	18.1	0·94 (0·74–1·21)	50/716·3	7·0	61/731·1	8·4	0·84 (0·58–1·21)
16	87/307·0	28·3	106/262·7	40·4	0·72 (0·54–0·95)	32/307·0	10·4	39/262·7	14·8	0·72 (0·45–1·14)
17	6/57·0	10·5	14/46·3	30·2	0·39 (0·15–0·98)	4/57·0	7·0	10/46·3	21·6	0·39 (0·12–1·22)
18	12/47·9†	25·1	9/50·8†	17·7	1·54 (0·59–4·01)	10/47·9†	20·9	6/50·8†	11·8	1·93 (0·67–5·60)
19	7/32·8	21·4	6/22·8	26·4	0·75 (0·24–2·28)	0/32·8	0	4/22·8	17·6	0·09 (0·01–0·64)
All studies	507/4642·7	10·9	563/4564·8	12·3	0·87 (0·78–0·99)	187/4642·7	4·0	259/4564·8	5·7	0·71 (0·59–0·85)

OR=odds ratio. *Event rate at 6 months. †Estimated from publications.

Table 3: **Mortality summary**

favour of amiodarone (0·87 [95% CI 0·78–0·99], p=0·03) indicating a 13% relative reduction in risk. The odds ratios for individual studies show some variation, and the formal test of heterogeneity was of borderline statistical significance (p=0·058). If the negative trends in two small studies[13,18] are discounted, most of the influence on the test of heterogeneity came from the GEMICA study,[9] the only one that used high-dose intravenous amiodarone in the immediate acute MI period. Without the GEMICA results, the heterogeneity p value is 0·093.

The finding of some evidence of heterogeneity in this analysis implies that there may be more variation in treatment effect among the studies than would be expected from natural sampling variation. Some analysts would argue, therefore, that the test of the summary treatment effect (and thus the width of the associated 95% CI) should incorporate the influence of this heterogeneity by using the random-effects approach of DerSimonian and Laird.[24] With this approach for the total mortality data, the summary odds ratio was 0·85 (95% CI 0·71–1·02; p=0·081). As might be expected, allowance for this additional between-study source of variation slightly widens the 95% CI and increases the p value; however, most analysts would still regard the result as showing a strong trend.

The analysis of cause-specific mortality showed a strong treatment effect for arrhythmic/sudden death (overall odds ratio 0·71 [0·59–0·85], p=0·0003). With the exception of the two smaller studies, the individual odds ratios for this outcome show reasonable consistency (test of heterogeneity, p=0·235). With the random-effects model for the outcome of arrhythmic/sudden death the summary odds ratio was similar, but the 95% CI was slightly wider (0·69 [0·55–0·87], p=0·0016).

Since several trials have found no effect of amiodarone on total mortality despite a reduction in the risk of arrhythmic death, there is much interest in whether amiodarone increases the risk of non-arrhythmic/non-sudden death. Conversely, since amiodarone has been reported to improve left-ventricular ejection fraction, there is also potential for a benefit in the cause group "other cardiac/cardiovascular death", which represented about 43% of all deaths. For that outcome there were 228 events/4564·8 patient years (5·0% per year) in the control groups and 232 events/4642·7 patient years (5·0% per year) in the amiodarone groups (odds ratio 0·98 [95% CI 0·81–1·18], p=0·821). For the outcome of "other death", there were 76 events/4564·8 patient years (1·7% per year) in the control groups and 88 events/4642·7 patient years (1·9% per year) in the

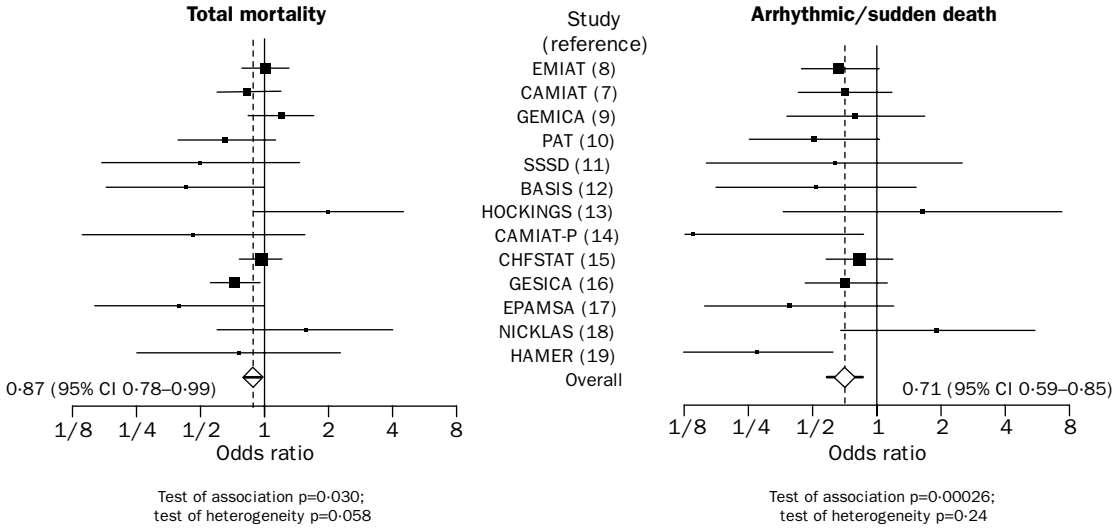

Figure 1: **Overview of results of 13 trials**
Area of square is proportional to amount of information; lines represent 95% CI.

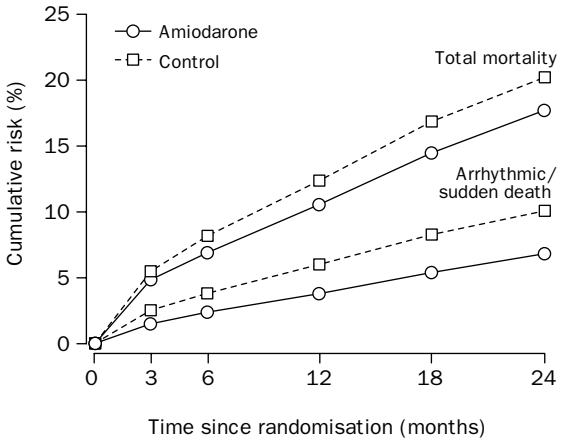

Figure 2: **Cumulative risk of death**

amiodarone groups (odds ratio 1·14 [0·84–1·55], p=0·398). For the outcome of all non-arrhythmic/non-sudden deaths there were 293 events/4564·8 patient years (6·7% per year) in the control groups and 320 events/4692·7 patient years (6·9% per year) in the amiodarone groups (odds ratio 1·02 [0·87–1·19], p=0·84).

In summary, amiodarone reduced the risk of arrhythmic/sudden death by 29% and had virtually no effect on the remaining causes of death, which accounted for 57% of the mortality. When these two effects are combined in the outcome of total mortality, the beneficial effect on arrhythmic/sudden death is diluted but still detectable as a significant 13% reduction. Figure 2 shows the effect of amiodarone treatment over time. The curves for the control group reflect the cumulative risk computed from the pooled control patients as a whole. The time-specific treatment effects were applied to the underlying risk to produce the corresponding experience for amiodarone-treated patients. These estimates are fairly crude but do indicate the kind of absolute risk reduction that might be anticipated for a typical patient in these studies. These plots show that amiodarone continues to exert a beneficial effect over time, even though the degree of benefit becomes attenuated.

Subgroup	Amiodarone		Control		OR (95% CI)	p for difference between subgroups
	Events/years	Rate/year (%)	Events/years	Rate/year (%)		
Type of patients						
After MI	257/3325·8	7·7	285/3263·2	8·7	0·92 (0·78–1·08)	0·43
CHF	222/1113·0	19·9	258/1062·8	24·3	0·83 (0·70–0·99)	
Control						
Placebo	377/3681·4	10·2	399/3608·4	11·1	0·96 (0·84–1·10)	0·006
Other	102/757·4	13·5	144/717·7	20·1	0·64 (0·50–0·82)	
LVEF						
⩾35%	50/1014·8	4·9	72/1059·6	6·8	0·79 (0·55–1·13)	0·58
<35%	258/1807·7	14·3	278/1746·3	15·9	0·88 (0·75–1·04)	
NYHA class						
1 and 2	234/2407·3	9·7	253/2465·8	10·3	0·95 (0·79–1·13)	0·43
3 and 4	177/686·0	25·8	191/613·9	31·1	0·85 (0·70–1·04)	
VPD						
<10/h	69/1278·4	5·4	82/1223·9	6·7	0·78 (0·56–1·08)	0·45
⩾10/h	276/2276·6	12·1	306/2267·9	13·5	0·89 (0·76–1·05)	
Age (years)						
<65	211/2556·7	8·3	242/2420·9	10·0	0·79 (0·66–0·95)	0·22
⩾65	268/1878·1	14·3	299/1899·9	15·7	0·92 (0·78–1·09)	
Sex						
Female	70/672·9	10·4	93/623·8	14·9	0·72 (0·53–0·98)	0·25
Male	409/3764·9	10·9	450/3699·2	12·2	0·88 (0·77–1·01)	
VT						
Absent	163/2033·8	8·0	183/1935·1	9·5	0·83 (0·68–1·03)	0·55
Present	201/1512·7	13·3	221/1534·5	14·4	0·91 (0·75–1·10)	

OR=odds ratio; LVEF=left-venticular ejection fraction; NYHA=New York Heart Assocation; VPD=ventricular premature depolarisations; VT=ventricular tachycardia.

Table 4: **Subgroup analyses for total mortality**

Subgroup	Amiodarone		Control		OR (95% CI)	p for difference between subgroups
	Events/years	Rate/year (%)	Events/years	Rate/year (%)		
Type of patients						
After MI	87/3325·8	2·6	136/3263·2	4·2	0·65 (0·50–0·84)	0·38
CHF	86/1113·0	7·7	114/1062·8	10·7	0·77 (0·59–1·01)	
Control						
Placebo	130/3681·4	3·5	187/3608·4	5·2	0·73 (0·59–0·90)	0·54
Other	43/757·4	5·7	63/717·7	8·8	0·64 (0·43–0·94)	
LVEF						
⩾35%	17/1014·8	1·7	36/1059·6	3·4	0·52 (0·30–0·89)	0·26
<35%	100/1807·7	5·5	139/1746·3	8·0	0·73 (0·57–0·93)	
NYHA class						
1 and 2	87/2407·3	3·6	123/2465·8	5·0	0·73 (0·56–0·96)	0·86
3 and 4	57/686·0	8·3	75/613·9	12·2	0·76 (0·55–1·05)	
VPD						
<10/h	24/1278·4	1·9	39/1223·9	3·2	0·59 (0·36–0·98)	0·38
⩾10/h	110/2276·6	4·8	144/2267·9	6·4	0·76 (0·60–0·98)	
Age (years)						
<65	84/2556·7	3·3	115/2420·9	4·8	0·68 (0·51–0·90)	0·98
⩾65	89/1878·1	4·7	134/1899·9	7·1	0·68 (0·53–0·89)	
Sex						
Female	20/672·9	3·0	43/623·8	6·9	0·46 (0·28–0·76)	0·11
Male	153/3764·9	4·1	207/3699·2	5·6	0·72 (0·59–0·89)	
VT						
Absent	54/2033·8	2·7	76/1935·1	3·9	0·68 (0·48–0·95)	0·56
Present	81/1512·7	5·4	106/1534·5	6·9	0·77 (0·58–1·03)	

OR=odds ratio; LVEF=left-venticular ejection fraction; NYHA=New York Heart Assocation; VPD=ventricular premature depolarisations; VT=ventricular tachycardia.

Table 5: **Subgroup analyses for arrhythmic/sudden death**

Subgroup analyses

Subgroup analyses (tables 4 and 5) examined the effects of study design and baseline characteristics of patients on the amiodarone treatment effect. The outcome of total mortality is of paramount importance clinically; however, it includes a large proportion of deaths that are not responsive to amiodarone and which dilute the amiodarone treatment effect, so detection of subgroup effects is difficult. The outcome of arrhythmic/sudden death was also examined because amiodarone exerted its most pronounced effect on this outcome. It should provide the greatest power to detect subgroup differences. There was no difference in the effectiveness of amiodarone between studies designed to enrol post-MI patients and those enrolling CHF patients. There was no difference between placebo-controlled trials and those that compared amiodarone with usual care in the outcome of arrhythmic/sudden death, but the two types of trials differed significantly in the outcome of total mortality. The effectiveness of amiodarone was not influenced by left-ventricular ejection fraction, New York Heart Association class, or presence or absence of asymptomatic ventricular arrhythmias on Holter electrocardiogram.

Risk predictors for arrhythmic/sudden death

Patients in the CHF studies had a much higher risk of arrhythmic/sudden death and total death than post-MI patients (tables 4 and 5). Patients with advanced left-ventricular dysfunction had substantially higher risks than those without. Higher rates of asymptomatic ventricular

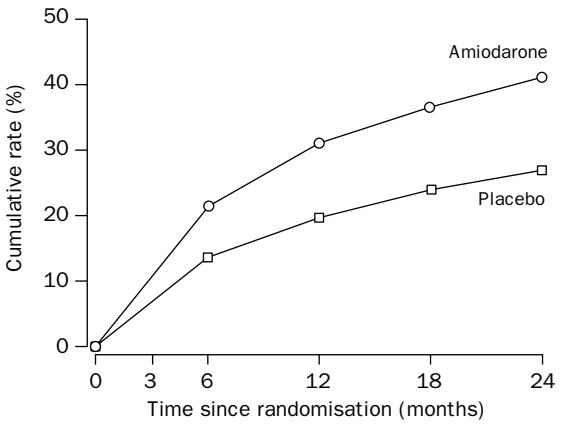

Figure 3: **Cumulative rate of early discontinuation of study medication in placebo-controlled trials**

arrhythmia predicted a higher risk of arrhythmic/sudden death. The most potent single predictor of arrhythmic/sudden death was the presence of symptomatic CHF (New York Heart Association class 3 or 4), which carried a 12·2% annual risk of arrhythmic/sudden death compared with 5·0% for those without these symptoms.

Discontinuation of study medications

In the double-blind placebo-controlled trials, by the end of 2 years, 41% of amiodarone-assigned patients and 27% of control patients had permanently discontinued study medication (figure 3). The 14% difference in rate of discontinuation is primarily related to adverse experiences associated with amiodarone.

On-treatment analysis

To assess the effectiveness of amiodarone in patients who actually received treatment, we did an on-treatment analysis with the conservative approach of including in the analysis all events occurring up to 3 months after early permanent study-drug discontinuation. In this analysis, there was an 18% mortality reduction (odds ratio 0·82 [95%CI 0·72–0·94], p=0·0003) and a 35% reduction in arrhythmic/sudden death (0·65 [0·53–0·80], p=0·0006). The tests of heterogeneity for both analyses were non-significant.

Adverse experiences

In developing the protocol for the meta-analysis, we decided not to include open-label studies without placebo control groups in the assessment of amiodarone toxicity. Table 6 summarises from the double-blind placebo-controlled trials the major adverse experiences associated with early permanent discontinuation of study medication (mean follow-up 1·1 years). Detailed data on side-effects were not available from three of the smaller double-blind studies. Hypothyroidism was the most common serious adverse experience and was more common in amiodarone than placebo groups (net absolute difference 5·9%; p for odds ratio 0·00005; p for heterogeneity=0·40). Hyperthyroidism was much less common, but the difference between the groups was significant (net absolute difference 0·9%; p for odds ratio 0·0043; p for heterogeneity=0·087). Hyperthyroidism was more common in the two European studies. Peripheral neuropathy, lung infiltrates, bradycardia, and liver dysfunction were all more common in amiodarone than in placebo groups (p for odds ratio 0·071, 0·0003, 0·0003, and 0·0072, respectively).

Discussion

This analysis shows that amiodarone reduces the likelihood of the outcome of arrhythmic/sudden death in high-risk patients with recent MI or CHF. On the other hand, amiodarone has little or no effect on the combined outcome of all non-arrhythmic/non-sudden deaths. These two effects combine in the outcome of total mortality to yield a relative risk reduction of 13%, which is conventionally statistically significant (p=0·030) with classic fixed-effects meta-analysis, and of borderline significance (p=0·081) with the more conservative random-effects approach. Since fewer than half of all deaths were arrhythmic/sudden, the effect on total mortality of an agent that reduces the risk of arrhythmic death only is likely to be small. Two trials of amiodarone in survivors of MI,[7,8] which reported significant reductions in arrhythmic/sudden death without a significant reduction in total mortality, have been criticised.[20] One criticism is that these trials do not provide convincing evidence of a benefit from amiodarone because they did not show a reduction in total mortality. The importance of our meta-analysis is that it shows a small but significant reduction in total mortality, which is explained by a substantial reduction in arrhythmic/sudden death. Since this mortality reduction has been identified through meta-analysis and because the statistical significance is marginal (p=0·030), confirmation of the result in a single, very large trial would be desirable.

Lively debate continues about both the role of meta-analysis[25] and the statistical techniques that should be used.[26,27] The methodological debate centres on the issue of heterogeneity. Peto argues strongly for the fixed-effects model, in that heterogeneity reflects inherent differences in study design and cannot be considered random perturbation. The random-effects approach has the theoretical basis that the studies available are a random sample from all those that might have been done. Although this is never the case in reality, proponents of

Study reference	Hypothyroidism*			Hyperthyroidism			Peripheral neuropathy			Lung infiltrates			Bradycardia			Liver function		
	A (%)	P (%)	OR	A (%)	P (%)	OR	A (%)	P (%)	OR	A (%)	P (%)	OR	A (%)	P (%)	OR	A (%)	P (%)	OR
8	7·1	1·3	5·6	2·3	1·1	2·2	0·1	0	· ·	0·3	0·3	1·0	1·5	0	· ·	0·8	0·3	3·0
7	15·7	1·7	10·9	0·7	0·7	1·0	1·0	0·2	6·0	3·1	1·1	2·7	1·3	0·8	1·6	1·0	0·3	3·0
9	0·1	0	· ·	0	0	· ·	0	0	· ·	0·2	0	· ·	3·5	2·3	1·6	0	0·2	· ·
15	9·5	2·1	5·0	0·1	0	· ·	1·5	0·9	1·7	4·8	0·9	5·6	0·9	0	· ·	2·4	0·3	8·2
10	0	0	· ·	3·6	0·3	11·5	0	0	· ·	0·3	0	· ·	7·2	0·3	23·9	0·7	0·6	1·0
14	0	0	· ·	0	0	· ·	0	0	· ·	6·3	0	· ·	0	3·4	· ·	8·3	3·4	2·5
All studies†	7·0	1·1	7·3	1·4	0·5	2·5	0·5	0·2	2·8	1·6	0·5	3·1	2·4	0·8	2·6	1·0	0·4	2·7
(Total events)	(181)	(27)	· ·	(37)	(13)	· ·	(12)	(4)	· ·	(42)	(12)	· ·	(44)	(19)	· ·	(26)	(9)	· ·

A=amiodarone; p=placebo; OR=odds ratio. *Early discontinuation or thyroid replacement therapy. †Total patient-years: A=2580, P=2545.

Table 6: **Major adverse experiences associated with early permanent drug discontinuation in placebo-controlled trials**

this more conservative approach argue heuristically that the presence of heterogeneity must affect the perceived precision of the pooled estimate of efficacy and that the random-effects model is a reasonable way of incorporating this extra source of imprecision. Our group of collaborating amiodarone investigators prespecified in our protocol that the fixed-effects model would be used. However, in response to the review process and the continuing debate, we have included additional random-effects estimates for our key results. For the analyses of both total mortality and arrhythmic death the random-effects model slightly improved the odds ratio in favour of amiodarone, with a slight increase in the width of the associated CI. The use of arrhythmic/sudden death as a cause-specific mortality outcome in these studies is justified on the basis of our understanding of the biological mechanism of amiodarone. However, in practice the classification of cause of death can be somewhat subjective and thus distrusted by some trialists. All but one of the trials in this analysis used a definition of sudden death that depended on onset of symptoms within the hour before death. CAMIAT[7] used a definition of arrhythmic death that focused on the type of symptoms occurring at the moment of collapse, rather than their timing. Thus the definitions used were fairly consistent. However, a greater degree of diversity among definitions of arrhythmic/sudden death would decrease the likelihood that a consistent and marked treatment effect would be found. The fact that a clear and homogeneous reduction of arrhythmic/sudden death was found shows that these ways of classifying death actually do segregate those deaths that can be prevented by an effective antiarrhythmic agent, and that amiodarone is effective against such deaths.

Strong evidence that amiodarone reduces the risk of arrhythmic death does not necessarily imply that it will affect overall mortality. There is a potential for the drug to increase the risk of death from other causes. Even if the risk of non-arrhythmic death is not actually increased by amiodarone, reduction of the arrhythmic component may have little effect on life expectancy because of other major competing risks in this elderly group with established heart disease. For these reasons, demonstration of a direct effect on total mortality is clinically and scientifically important. Only three of the individual studies[12,16,17] reported a significant reduction in total mortality, apparently because none of the studies was designed to detect reduction in mortality of less than 33%. The advantage of meta-analysis is that it increases the power of the statistical analysis by increasing the number of events, which in turn facilitates accurate detection of modest but clinically important treatment effects.

There was a trend towards heterogeneity of treatment benefit for the outcome of total mortality, but not for arrhythmic/sudden death. This finding is due partly to the GEMICA trial,[9] in which there was a non-significant 13% increase in total mortality despite a reduction in arrhythmic/sudden death. GEMICA was the only trial that used high-dose intravenous amiodarone, given acutely during the first day after MI. A dose reduction was required midway through the trial because of excessive mortality on amiodarone. The analysis of the effect of differences in trial design provides some insight into the observed heterogeneity. Although the mortality rate was three times higher in patients in the CHF trials than in post-MI patients, the effect of amiodarone was essentially the same in both groups. Thus, the combination of data from CHF and post-MI patients did not produce heterogeneity. The trials that did not have placebo controls found a significantly greater effect of amiodarone on total mortality than those with such designs. The unblinded follow-up in non-placebo-controlled trials may have led to an imbalance in concomitant therapy in these studies. Amiodarone-group patients might have received more intensive medical follow-up. Another possible explanation for heterogeneity between blinded and unblinded trials is the lower rate of premature permanent discontinuation of amiodarone in the unblinded trials (table 2). This difference may have arisen because patients in open trials would be less likely to discontinue study medication if they knew it to be active. The higher rate of compliance could enhance the effectiveness of amiodarone and partly explain the observed heterogeneity.

Except for β-blockers,[12] all antiarrhythmic drugs, when carefully studied in large randomised trials of high-risk patients, have actually increased mortality.[3,4] Meta-analysis of all post-MI trials of class 1 antiarrhythmic drugs[2] indicated a statistically significant increase in mortality with this whole class of drugs. The Survival With Oral *d*-Sotalol (SWORD) trial[5] found a clear increase in mortality with the pure class 3 drug, *d*-sotalol. Other class 3 drugs, such as dofetilide and azimilide may still prove beneficial, but at present amiodarone occupies a unique position. β-blocker drugs have been shown to reduce mortality in survivors of MI by 20%.[2] A substantial component of the benefit of β-blockers is probably due to an antiarrhythmic effect, because reduction in sudden death is a major mechanism by which these drugs reduce the risk of death. The known actions of amiodarone include a non-competitive adrenergic blockade,[6] which may account for some of its protective effect.

The subgroup analyses suggest that the effect of amiodarone on arrhythmic/sudden death is generally uniform among different types of patients. Contrary to what might be expected, the presence of higher frequencies of symptomless ventricular arrhythmia did not predict a greater effectiveness of amiodarone against arrhythmic/sudden death. The drug had the same relative risk reduction in patients with and without severe left-ventricular dysfunction, which suggests that it is likely to be effective across a broad range of high-risk patients. Patients with more severe left-ventricular dysfunction or with symptomless arrhythmia have higher baseline risks of arrhythmic/sudden death and therefore derive a greater absolute benefit from amiodarone.

The rates of adverse experiences attributable to amiodarone that resulted in early permanent discontinuation of study medication were low. The side-effect that has received the greatest previous attention has been pulmonary toxicity, which can be fatal.[6] The absolute difference in the rates of this side-effect for amiodarone and control patients was 1·1% during an average treatment duration of 1·1 years. Thyroid dysfunction occurred more commonly on amiodarone, but in most cases this disorder can be managed with thyroid hormone replacement or thyroid gland suppression. There is undoubtedly a real adverse effect of amiodarone on liver function, but this effect rarely required discontinuation of study medication, even though most trials had precise and

conservative criteria for this action in the event of liver-enzyme abnormality.

There was a high rate (41%) of early permanent discontinuation of amiodarone. The difference in the rates for amiodarone and placebo was 14%, indicating that only about a third of amiodarone discontinuation was for adverse experiences. This calculation suggests that a lower rate of amiodarone discontinuation should be possible in clinical practice than occurred in these studies. The on-treatment analysis showed a more substantial reduction in the risk of death with amiodarone than did the intention-to-treat analysis (18 *vs* 13%).

This meta-analysis provides strong evidence in support of an important antiarrhythmic action of amiodarone and, unlike some of the individual studies, it suggests that this action results in a small reduction in total mortality. Should amiodarone be used prophylactically in post-MI or CHF patients? Since the relative-risk reduction of amiodarone is similar among different types of patients, the greatest absolute benefit will occur among those whose risk of arrhythmic death is highest. Patients with CHF or severe left-ventricular dysfunction had the highest risk of arrhythmic/sudden death. For example, patients with heart failure symptoms of New York Heart Association class 3 or 4 had a 12·2% annual risk of arrhythmic/death. A 29% reduction in this risk would prevent 3·5 deaths per 100 patient-years of treatment. Thus, prophylactic amiodarone would be a reasonable treatment in patients at particularly high risk.

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