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Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials

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Aims Three randomized trials of implantable cardioverter defibrillator (ICD) therapy vs medical treatment for the prevention of death in survivors of ventricular fibrillation or sustained ventricular tachycardia have been reported with what might appear to be different results. The present analysis was performed to obtain the most precise estimate of the efficacy of the ICD, compared to amiodarone, for prolonging survival in patients with malignant ventricular arrhythmia.

Methods and Results Individual patient data from the Antiarrhythmics vs Implantable Defibrillator (AVID) study, the Cardiac Arrest Study Hamburg (CASH) and the Canadian Implantable Defibrillator Study (CIDS) were merged into a master database according to a pre-specified protocol. Proportional hazard modelling of individual patient data was used to estimate hazard ratios and to investigate subgroup interactions. Fixed effect meta-analysis techniques were also used to evaluate treatment effects and to assess heterogeneity across studies. The classic fixed effects meta-analysis showed that the estimates of ICD benefit from the three studies were consistent with each other (P heterogeneity=0·306). It also showed a significant reduction in death from any cause with the ICD; with a summary hazard ratio (ICD:amiodarone) of 0·72 (95% confidence interval 0·60, 0·87; P=0·0006). For the outcome of arrhythmic death, the hazard ratio was 0·50 (95% confidence interval 0·37, 0·67; P<0·0001). Survival was extended by a mean of 4·4 months by the ICD over a follow-up period of 6 years. Patients with left ventricular ejection fraction $\leq$35% derived significantly more benefit from ICD therapy than those with better preserved left ventricular function. Patients treated before the availability of non-thoracotomy ICD implants derived significantly less benefit from ICD therapy than those treated in the non-thoracotomy era.

Conclusion Results from the three trials of the ICD vs amiodarone are consistent with each other. There is a 28% reduction in the relative risk of death with the ICD that is due almost entirely to a 50% reduction in arrhythmic death. **(Eur Heart J 2000; 21, 2071–2078, doi.10.1053/euhj. 2000.2476)**

Key Words: Amiodarone, implantable cardioverter defibrillator, meta-analysis, cardiac arrest, ventricular tachycardia.

Introduction

Patients who survive out-of-hospital cardiac arrest or symptomatic sustained ventricular tachycardia are at considerable risk of recurrence of these arrhythmias and of death[1]. There is wide consensus that these patients require some form of long-term therapeutic intervention, and consequently placebo-controlled trials have not been performed to evaluate therapeutic strategies for prolonging life. A primary question over the past decade has been whether therapy with the implantable cardioverter defibrillator (ICD) is superior to medical therapy. Based on the results of one small trial comparing amiodarone to other drugs[2] and upon modestly positive results from primary prevention trials in patients with recent myocardial infarction or with congestive heart failure[3], amiodarone is the most widely used antiarrhythmic therapy in this patient population.

There are only three randomized controlled trials evaluating the ICD against antiarrhythmic therapy in patients with sustained ventricular arrhythmia that have been performed and published[4]. Although the AVID study was the largest of the three trials, it was stopped early and it had the shortest follow-up. Due to longer follow-up in CIDS and CASH, there were more deaths in these two studies combined than in AVID. Thus combination of the data from the three trials provides the most precise and least biased estimate of ICD benefit

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over prolonged follow-up. None of the three studies was large enough to allow precise estimation of treatment effects in patient subgroups.

A meta-analysis based upon consolidation of individual patient data from the three studies into a single master database was done. The goals were (1) to assess the degree of consistency of the benefit of the ICD vs amiodarone amongst the three study estimates, (2) to provide the most precise estimate of the efficacy of the ICD, and (3) to investigate the extent to which specific patient subgroups benefit differently from ICD therapy.

Methods

Planning process and protocol

Planning for this analysis was started before completion of the three trials when it became apparent that the same patient population and similar interventions were being evaluated by the three studies. A detailed protocol was developed which specified the primary outcomes of interest, the analytic techniques to be used, and the specific patient subgroups to be studied. The protocol was finalized after the initial presentation of the AVID study results but before the unblinding of the CIDS and CASH results.

The goal of this analysis was to compare the ICD and amiodarone, and therefore only data pertaining to the amiodarone and ICD treatment arms of the CASH study are included in this analysis. None of the propafenone or metoprolol patients in CASH were included in this analysis. Thirteen of the 509 patients (2·6%) in the antiarrhythmic drug group of the AVID study received sotalol at hospital discharge. Because to exclude them would disrupt the original randomization procedure of AVID, we decided to include them. All follow-up data available in the three studies were included in the analyses. Because relatively few patients were followed beyond 6 years, figures were curtailed at this time point. The 'epicardial era' for ICD implantation was defined as ending on 1 July 1991. However, a few patients randomized before this date had a non-thoracotomy ICD and vice versa. Some patients received an epicardial device because of patient-specific technical problems. In order to prevent bias, we decided to divide the population based on date of implantation as it provided a relatively unbiased and efficient way to investigate the effect of implant method on ICD efficacy; recognizing there is confounding with whatever other changes in patient management occurred pre- and post-1991.

Data extraction and consolidation

Based upon the agreed protocol, each study extracted individual patient data corresponding to the required set of data fields. These were transferred by electronic means to the AVID study coordinating centre where they were merged into a master database. All three studies classified cause of death using the method of Hinkle and Thaler[7].

Data analysis

Analyses were performed on the pooled database utilizing individual patient data. The effect of treatment on various fatal outcomes was investigated by means of proportional hazards modelling[8] and log rank testing[9]. This method was also used to investigate the influence of various baseline clinical and demographic characteristics on the size of the ICD treatment effect as well as to adjust for any study effect not accounted for by measured baseline covariants. All analyses were by intention-to-treat. While pooled patient data provides the opportunity for optimal investigation, we also performed meta-analysis using fixed effects[10] and random effects methods[11] with very similar results. The fixed effects method results are presented. The prolongation of life attributable to therapy was calculated by computing the difference in the areas under the two survival curves.

Results

Features of the individual studies

Table 1 summarizes key features of the studies. Patient eligibility differed slightly between the studies. CASH only included patients with previously documented ventricular fibrillation, whereas CIDS and the AVID study included patients with either ventricular fibrillation or symptomatic sustained ventricular tachycardia. Additionally, CIDS included patients with unmonitored syncope who were shown to have ventricular tachycardia. The mean follow-up was longest in CASH, with some patients being followed almost ten years. The AVID study had the shortest follow-up (mean 1·51 years), partly due to the fact that it was stopped earlier than expected. The AVID study was the largest, with 1016 patients, while CASH randomized only 191 patients to the ICD/amiodarone comparison. However, because of longer follow-up, the total patient years of follow-up was greatest in CIDS. The mean duration of follow-up from the pooled database was $2{\cdot}33 \pm 1{\cdot}89$ years. Table 1 also shows the event rates for death and arrhythmic death for both treatment groups of the three studies. The event rates were higher for patients in the AVID study than for those in CASH and CIDS. The proportion of deaths (in amiodarone patients) classified as arrhythmic were similar; AVID study (45%), CASH (54%) and CIDS (44%). The higher mortality rate in AVID is not explained by patient eligibility criteria of that study as they were almost the same as those of CIDS.

Table 1 Features of the studies

	AVID	CASH*	CIDS
Dates of study performance	1993–97	1986–97	1990–97
Medical treatment	Amiodarone/sotalol	Amiodarone	Amiodarone
Eligibility	CA, VF, VT	CA, VF	CA, VF, VT, syncope
Mean follow-up (years)	1·51	4·48	2·96
Number of patients			
Amiodarone	509**	92	331
ICD	507	99	328
Total follow-up (patient years)			
Amiodarone	738	373	957
ICD	801	483	995
Deaths (rate)			
Amiodarone	122 (16·5%)	35 (9·4%)	98 (10·2%)
ICD	80 (10·0%)	37 (7·7%)	83 (8·3%)
Arrhythmic deaths (rate)			
Amiodarone	55 (7·4%)	19 (5·1%)	43 (4·5%)
ICD	24 (3·0%)	7 (1·5%)	30 (3·0%)

*Includes only ICD and amiodarone patients from CASH.
**Includes 12 patients discharged from hospital receiving sotalol.
CA=cardiac arrest; ICD=implantable cardioverter defibrillator; VF=ventricular fibrillation; VT=symptomatic sustained ventricular tachycardia.

Table 2 Patient characteristics and treatment received in the three studies

	AVID (n=1016)	CASH (n=191)*	CIDS (n=659)
Age (years)	65 ± 11	58 ± 11	63 ± 10
Male gender	79%	80%	85%
Prior myocardial infarction	67%	51%	77%
Any coronary artery disease	82%	75%	83%
Non-ischaemic cardiomyopathy	15%	11%	10%
No structural heart disease	3%	10%	3%
Left ventricular ejection fraction	32 ± 13	45 ± 18	34 ± 14
CABG at baseline	10%	15%	1%
NYHA class ≥3	9%	19%	11%
Presenting arrhythmia			
VF	45%	100%	48%
VT, with syncope	21%	0%	13%
VT, other	34%	0%	25%
Syncope	0%	0%	14%
ICD arm, number of patients	507	99	328
Thoracotomy	5%	44%	10%
No ICD	3%	0%	6%
Received amiodarone	26%	0%	16%
Discharged on beta-blocker	44%	0%	53%
Amiodarone arm, number of patients	509	92	331
Received amiodarone	97%	98%	100%
Received ICD	12%	5%	16%
Discharged on beta-blocker	20%	0%	23%

CABG=coronary artery bypass graft surgery; CHF=congestive heart failure; ICD=implantable cardioverter defibrillator; NYHA=New York Heart Association; VF=ventricular fibrillation; VT=ventricular tachycardia.

Baseline clinical characteristics

Table 2 summarizes the clinical characteristics of patients in the three studies. In general, the patients enrolled in the AVID study and in CIDS were very similar. Patients enrolled in CASH were younger and had a higher left ventricular ejection fraction than in the other two studies. In CIDS and the AVID study just under half of the patients were enrolled with a presenting diagnosis of ventricular fibrillation; 14% of CIDS patients presented with unmonitored syncope.

Treatment

Table 2 also summarizes therapy actually delivered to the two treatment arms of the three studies. There were

Table 3 Baseline characteristics of patients: pooled database

	ICD n=934	Amiodarone n=932
Age (years)	63 ± 11	64 ± 10
Male gender (%)	81	82
Left ventricular ejection fraction	34 ± 15	33 ± 14
NYHA class (CHF symptoms) ⩾3	9%	12%
Prior myocardial infarction	69%	69%
Non-ischaemic cardiomyopathy	12%	13%
No heart disease	4%	3%
Presenting arrhythmia		
Ventricular fibrillation	51%	52%
Ventricular tachycardia	44%	43%
Syncope	5%	4%
Randomized in the 'epicardial era'*	9%	8%
Discharge beta-blocker	42%	19%
Discharge ACE inhibitor	63%	64%
Discharge ASA	51%	51%

*Randomized before 1 July 1991.
CHF=congestive heart failure; ACE=angiotensin converting enzyme; NYHA=New York Heart Association.

differences in ICD therapy among the three studies largely because CASH was initiated several years before the era when non-thoracotomy ICDs were available. In CASH, 44% of patients had a thoracotomy ICD compared with 10% of CIDS patients and 5% of AVID patients. There was a post-randomization imbalance in beta-blocker use in both AVID and CIDS, with higher rates of use of beta-blockers in the ICD treatment arm. None of the amiodarone or ICD group patients in CASH received a beta-blocker at hospital discharge. Rates of crossover during follow-up of ICD patients to receive amiodarone, and vice versa, were similar in CIDS and the AVID study.

Baseline patient characteristics of the pooled database

Table 3 shows the patient characteristics of the pooled database. There were no significant differences between the two treatment groups, except in the use of beta-blockers at the time of discharge from hospital. The mean left ventricular ejection fraction was just under 35%, the presenting arrhythmia was ventricular fibrillation in half the patients and coronary artery disease was by far the most common underlying condition.

Analysis of the pooled database

There were significant reductions in both all-cause mortality and in arrhythmic death with the ICD. For total mortality, the hazard ratio (ICD:amiodarone) was 0·73 (95% confidence interval 0·60, 0·87, $P<0·001$), and for arrhythmic death the hazard ratio was 0·49 (95% confidence interval 036, 0·67; $P<0·001$). For all non-arrhythmic deaths, the hazard ratio was 0·93 (95% confidence interval 0·73, 1·17; $P=0·517$). Figure 1 shows the cumulative risk of fatal events for the outcomes of all-cause death and of arrhythmic death. For the outcome of death, the two treatment arms separate incrementally for the first 3 to 4 years and then appear to come closer together. For arrhythmic death there appears to be steady incremental separation throughout the 6 years between the two treatment arms. The prolongation of life by the ICD over amiodarone was 2·1 months at 3 years of follow-up and 4·4 months at 6 years.

Subgroup interactions

The effect of clinical and demographic variables was investigated in the analysis of subgroup interactions in the pooled database. The main question being asked in this analysis was: 'Is the benefit of the ICD significantly different in any particular pre-defined subgroups?' Table 4 summarizes the results of this analysis showing, for each subgroup, the number of patients in the group, the hazard ratio for death (ICD:amiodarone) and its 95%

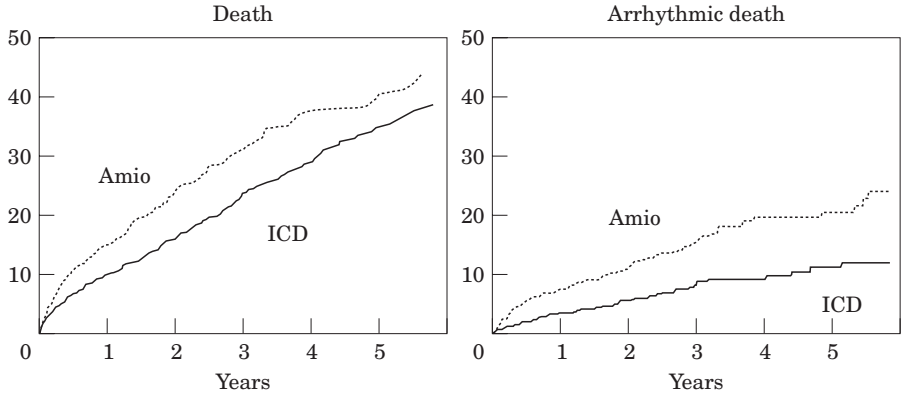

Figure 1 **Cumulative risk of fatal events or the amiodarone (. . . .) and ICD (—) treatment arms.**

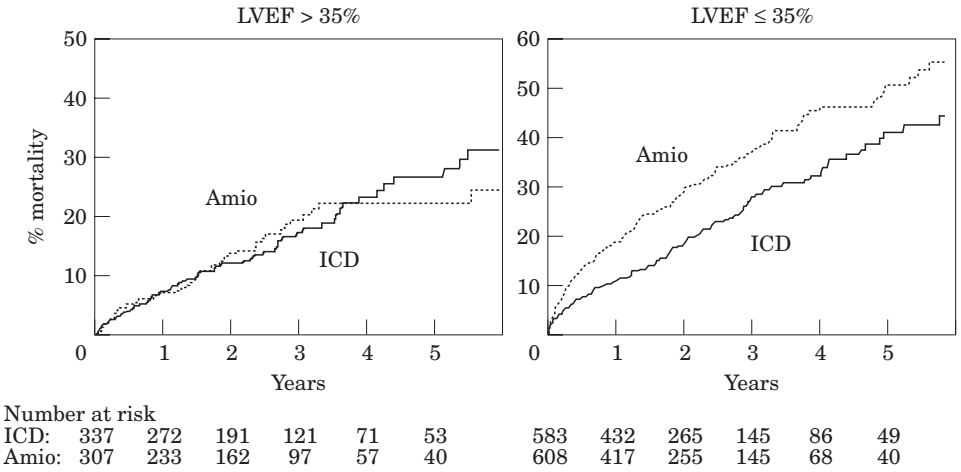

Figure 2 **Cumulative risk of death for patients with left ventricular ejection fraction (LVEF) >35% and ≤35%.**

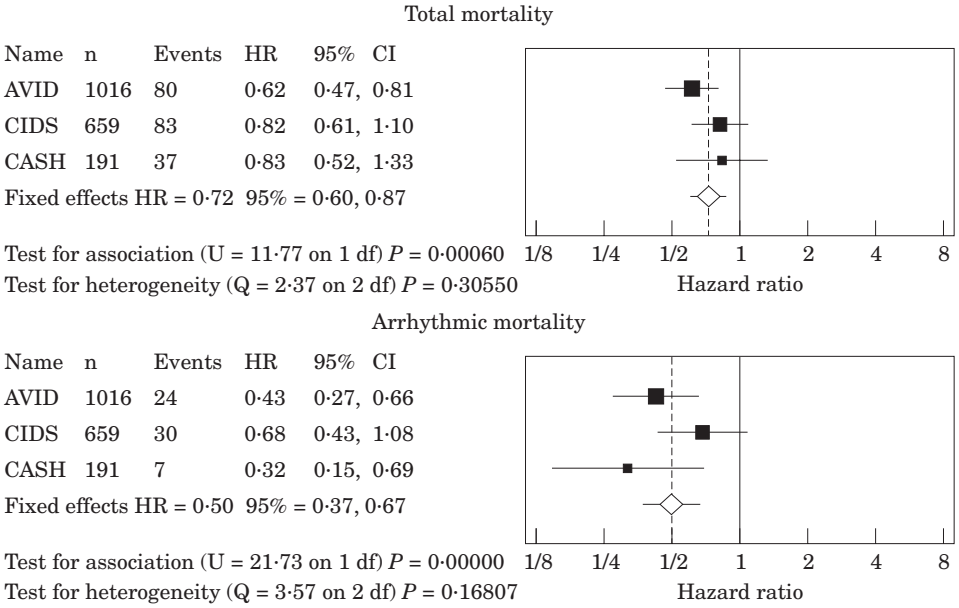

Figure 3 **Results of the fixed effects meta-analysis (see text for explanation).**

confidence interval. The interaction *P* value is the result of testing whether the effectiveness of the ICD over amiodarone is truly different between complementary patient subgroups. This analysis showed that there were two statistically significant subgroup interactions. Patients with left ventricular ejection fraction >35% had significantly less benefit from the ICD than those with ejection fraction of ≤35% ($P=0{\cdot}011$). Patients treated in the 'epicardial era', defined as being randomized before 1 July 1991, had significantly less benefit from the ICD than those randomized after this time. The effect of beta-blocker use at discharge from hospital (a post-randomization factor) was also investigated. There was no significant interaction between beta-blocker use at discharge and ICD benefit ($P=0{\cdot}095$). Figure 2 shows the cumulative risk of death for patients, according to left ventricular ejection fraction, dichotomized at 35%, illustrating the extent to which the efficacy of the ICD over amiodarone appears to be dependent upon the degree of left ventricular dysfunction.

Meta-analysis

Figure 3 shows the results of meta-analysis performed according to the fixed effects method. Total mortality and arrhythmic mortality are shown separately. The

Table 4 Subgroup interactions

Subgroup	n	HR	95% CI	*P* (interaction)
LVEF				
>35%	643	1·2	0·81, 1·76	
≤35%	1189	0·66	0·53, 0·83	0·011
Presenting arrhythmia*				
VT	809	0·73	0·54, 0·99	
VF	934	0·78	0·61, 1·01	0·766
Prior myocardial infarction				
Yes	1268	0·74	0·60, 1·02	
No	564	0·79	0·55, 1·49	0·591
Epicardial era**				
Yes	151	1·52	0·92, 2·50	
No	1081	0·69	0·56, 0·85	0·029
Discharge beta-blocker***				
Yes	566	0·58	0·38, 0·89	
No	1266	0·88	0·71, 1·09	0·095
Non-ischaemic cardiomyopathy				
Yes	225	0·78	0·45, 1·37	
No	1607	0·77	0·63, 0·94	0·885
Coronary artery disease				
Yes	1493	0·78	0·63, 0·95	
No	339	0·80	0·48, 1·33	0·973
NYHA class (CHF symptoms) ≥3	1637	0·74	0·59, 0·91	
<3	195	0·75	0·48, 1·17	0·516
CABG at baseline				
Yes	131	1·40	0·26, 3·17	
No	1701	0·73	0·60, 0·89	0·106

*Excludes syncope, **implant before 1 July 1991.
***Beta-blocker use at discharge from hospital.

LVEF=left ventricular ejection fraction; CHF=congestive heart failure; NYHA=New York Heart Association; VF=ventricular fibrillation; VT=symptomatic sustained ventricular tachycardia; HR=hazard ratio; CI=confidence interval.
Hazard ratios of <1 or >1 indicate a reduction or increase, respectively, in mortality with the ICD compared to amiodarone.

results of each individual study are presented numerically and graphically. The summary hazard ratio, its 95% confidence interval and its *P* value (for association) are shown.

The fixed effects analysis is a classical meta-analysis technique that is perhaps more conservative than analysis of the pooled database. One clear advantage is that it provides a formal statistical assessment (test of heterogeneity) of whether the participating studies are sufficiently similar to be combined in a meta-analysis. In the fixed effects analysis, the *P* value of the test for heterogeneity among the three studies was non-significant, indicating that the trials had similar results in spite of some differences in design, execution and an apparent difference in results. For mortality, only the AVID Study showed a nominally significant benefit from the ICD. The summary hazard ratio from the three studies is 0·72 (95% confidence interval 0·60, 0·87; $P=0·0006$). Both the AVID study and CASH demonstrated a significant reduction in arrhythmic death with the ICD, whereas CIDS showed a trend towards a benefit. The summary hazard ratio for arrhythmic death was 0·50 (95% confidence interval 0·37, 0·67; $P<0·0001$).

Discussion

Main findings

This analysis demonstrates that the results of the three secondary prevention ICD trials are consistent with one another. It initially might have appeared that the studies had different results, as the AVID study reported a statistically significant reduction in mortality with the ICD compared to medical therapy, while the other two studies did not demonstrate a statistically significant difference in risk of death. The lack of any evidence of heterogeneity among the studies in the fixed effects analysis indicates that these differences in treatment benefit are not major and are likely due to play of chance. All three studies observed some reduction in death from the ICD, with the benefit being almost twice as large in the AVID study as it was in the other two studies. The AVID study, however, was stopped early due to observation of a greater than expected benefit of the ICD. Early study termination because of benefit does create a bias in favour of reporting larger treatment

effects; which could partly explain the discrepancy between the results of the AVID and the other two studies. It might appear that the meta-analysis adds little to our knowledge because the AVID study was positive and it was the largest of the three trials. However, the AVID study was relatively short in duration and although it has a large number of patients it contributed only 202 of the 455 deaths that occurred in the three studies. As it is the actual outcome events that directly affect statistical power, only 45% of the power of the pooled analysis comes from AVID study patients. AVID by stopping early due to an observed benefit may have overestimated the effect of the ICD. Combining the results of all three studies gives the most precise and unbiased estimate of the efficacy of the ICD vs amiodarone.

The ICD is expected to exert its benefit on mortality specifically by prevention of deaths due to ventricular arrhythmia. The fact that the ICD had a very large effect on the outcome of arrhythmic death, and almost no effect (compared to amiodarone) on non-arrhythmic deaths, adds biological plausibility to the findings of this overview. Arrhythmic death was rather dramatically reduced, with a relative risk reduction of 50% in favour of ICD compared to amiodarone. The steady divergence of the survival curves depicting arrhythmic death for the ICD and amiodarone treatment arms contrasts with the lack of divergence after 3 years of the curves depicting the effect on death from any cause. This suggests that competing non-arrhythmic causes of death may, over time, reduce the benefit of the ICD.

It has been recently suggested that the lack of statistically significant ICD benefit in CASH and CIDS indicates a lack of certainty that the ICD is superior to amiodarone[12]. This meta-analysis clearly indicates that the three studies are indeed consistent and that the ICD is more effective than amiodarone. This analysis provides the most precise estimate of the benefit of the ICD over amiodarone for prevention of death, which is a relative risk reduction of 27%. The annual death rate was reduced by the ICD from 12·3% per year to 8·8% per year, an absolute reduction of 3·5% per year. Thus an ICD would have to be implanted in 29 patients to save one life per year of follow-up. The effectiveness of the ICD over amiodarone is not large as, over 6 years of follow-up, the prolongation of life is only just over a third of a year. The AVID study has reported that the prolongation of life with the ICD during a 3 year follow-up, is modest. The present analysis now extends that finding to a follow-up period of 6 years.

Patient groups

The analysis of the interactions between specific predefined patient subgroups and ICD treatment effect raises important hypotheses about which patients benefit from ICD therapy. Patients receiving ICDs in the 'epicardial era' required a thoracotomy for implantation of their ICD. They appear to derive no benefit from the ICD, probably because of an increased peri-operative risk of dying. The best estimate of the ICD benefit in the (more modern) non-thoracotomy era is a relative reduction in the risk of death of slightly more than 30%.

There was also an important interaction between left ventricular ejection fraction and ICD benefit. Patients with better preserved left ventricular function appeared to obtain little or no benefit from the ICD, whereas those with moderate to severe left ventricular dysfunction obtained a significant benefit from the ICD. These data show that in the one-third of patients surviving ventricular fibrillation or sustained ventricular tachycardia who have reasonable left ventricular function, survival is similar whether they receive the ICD or amiodarone therapy. Both the AVID[13] and CIDS[14] studies have previously reported that patients with lower left ventricular ejection fraction appear to have a greater benefit from ICD therapy. However, in both of these reports the *P* value associated with this effect (interaction *P* value) did not reach statistical significance. The power of meta-analysis is that by increasing sample size we can better evaluate observations made in individual studies. Even though in the present study the effect of ejection fraction is statistically significant, it should still be interpreted cautiously as it is a subgroup analysis that ought to be confirmed by a prospective study. Nonetheless, considering the high relative cost of ICD therapy, it would appear to be a very important hypothesis to investigate.

The post-randomization imbalance in beta-blocker use observed in the AVID study and in CIDS somewhat reduces the reliability of these studies to measure the specific impact of ICD therapy, as some of the observed benefit of the ICD may have been due to this concomitant therapy. Two factors suggest that beta-blocker imbalance was not a major factor conditioning the study results. The beta-blocker imbalance did not occur in CASH, which observed a benefit from the ICD consistent with that of CIDS and AVID. Secondly, in the subgroup analysis, the effect of the ICD was not significantly influenced by the presence, or absence, of discharge beta-blocker use.

Methodology

Two different analytic methods were used; an analysis of the pooled databases (stratified by study) and a fixed effects meta-analysis. The meta-analytic method makes fewer assumptions about the similarity of the studies in design and execution; whereas the pooled analysis offers more scope for graphic presentation. Both methods yielded very similar results.

Conclusions

In patients surviving sustained ventricular tachycardia or fibrillation the trials of ICD therapy vs amiodarone are consistent with one another and they demonstrate a 28% relative reduction in death with the ICD. The ICD

prolonged life an average of 4 months during 6 years of follow-up. Assessment of left ventricular ejection fraction appears to stratify those who respond best to the ICD. The ICD is therefore the preferred treatment, especially in those with moderate to severe left ventricular dysfunction.

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