



The midlands trial of empirical amiodarone versus electrophysiology-guided interventions and implantable cardioverter-defibrillators (MAVERIC): a multi-centre prospective randomised clinical trial on the secondary prevention of sudden cardiac death

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KEYWORDS

ICD;
electrophysiology;
amiodarone;
sudden cardiac death

Abstract **Aims** MAVERIC was a randomised clinical trial designed to test the possibility of prospectively identifying patients who would benefit most from the implantable cardioverter-defibrillator (ICD) by electrophysiology (EP) study in the context of secondary prevention of sudden cardiac death (SCD) through comparing EP-guided interventions (anti-arrhythmic drugs, coronary revascularization, and ICD) against empirical amiodarone therapy.

Methods Two hundred and fourteen survivors of sustained ventricular tachycardia (VT), ventricular fibrillation (VF) or SCD were randomized to either treatment strategy, pre-stratified for haemodynamic status at index event, and followed up for a median of 5 years.

Results Of the 106 amiodarone arm patients, 89 (84%) received the drug and 5 (5%) received an ICD after crossing over. Of the 108 EP arm patients, 31 (29%) received an ICD, 46 (43%) received anti-arrhythmic drugs only (mainly amiodarone or sotalolol) and 18 (17%) received coronary revascularization but no ICD. No significant differences in survival or arrhythmia recurrence existed between the two treatment arms after

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6 years. However, ICD recipients had a lower mortality than non-ICD recipients, regardless of allocated treatment (hazard ratio = 0.54, $p=0.0391$).

Conclusions Prospective selection of patients to receive the ICD by EP study did not improve survival compared with empirical amiodarone therapy among survivors of VT, VF or SCD, whereas ICD implantation improved survival regardless of allocated treatment. On this basis, routine EP study has no role in the management of such patients, who should be offered empirical ICD therapy according to the results of other secondary prevention ICD trials.

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Introduction

In the treatment of patients who are presented with life-threatening ventricular arrhythmias, AVID showed that empirical implantable cardioverter-defibrillator (ICD) therapy was significantly better in preventing death than anti-arrhythmic drugs, principally empirical amiodarone [1]. These results were supported by CIDS and CASH [2,3]. In these secondary prevention trials, the benefit has not been large, with an overall relative risk reduction of 28% for death [4]. Using retrospective multivariate analysis, the CIDS investigators identified a subgroup in whom all the survival benefit from ICD therapy is concentrated: the quartile with the highest baseline risk as determined by advanced age, reduced left ventricular ejection fraction (LVEF) and poor NYHA functional status [5]. This opens up the possibility of more refined targeting of ICD therapy, which will not only result in major cost savings, but also minimize the negative impact on the patient's lifestyle, such as from inappropriate shocks and restrictions on driving.

The MAVERIC trial, initiated before the other major trials (AVID, CASH and CIDS) were completed, sought prospectively to identify patients who would benefit most from ICD therapy by electrophysiology (EP) testing and deliver a mortality benefit over empirical amiodarone therapy comparable to that achieved by empirical ICD implantation. The alternative, to compare EP-guided ICD implantation with empirical ICD implantation, would have been scientifically more appealing but not economically feasible in the United Kingdom. Moreover, it generally takes a larger sample size to prove equivalence than a statistically significant difference between two treatments.

In MAVERIC, the decision to implant an ICD depended on the patient's estimated risk for future life-threatening ventricular arrhythmias, as determined by the presenting arrhythmia, LVEF, scope for coronary revascularization, and baseline EP or Holter abnormalities. Despite the inherent shortcomings of these criteria, they were and probably

still are the best methods available for the purpose of risk stratification [6,7]. In MAVERIC, the high but not the low risk patients received the ICD.

Methods

Study conduction

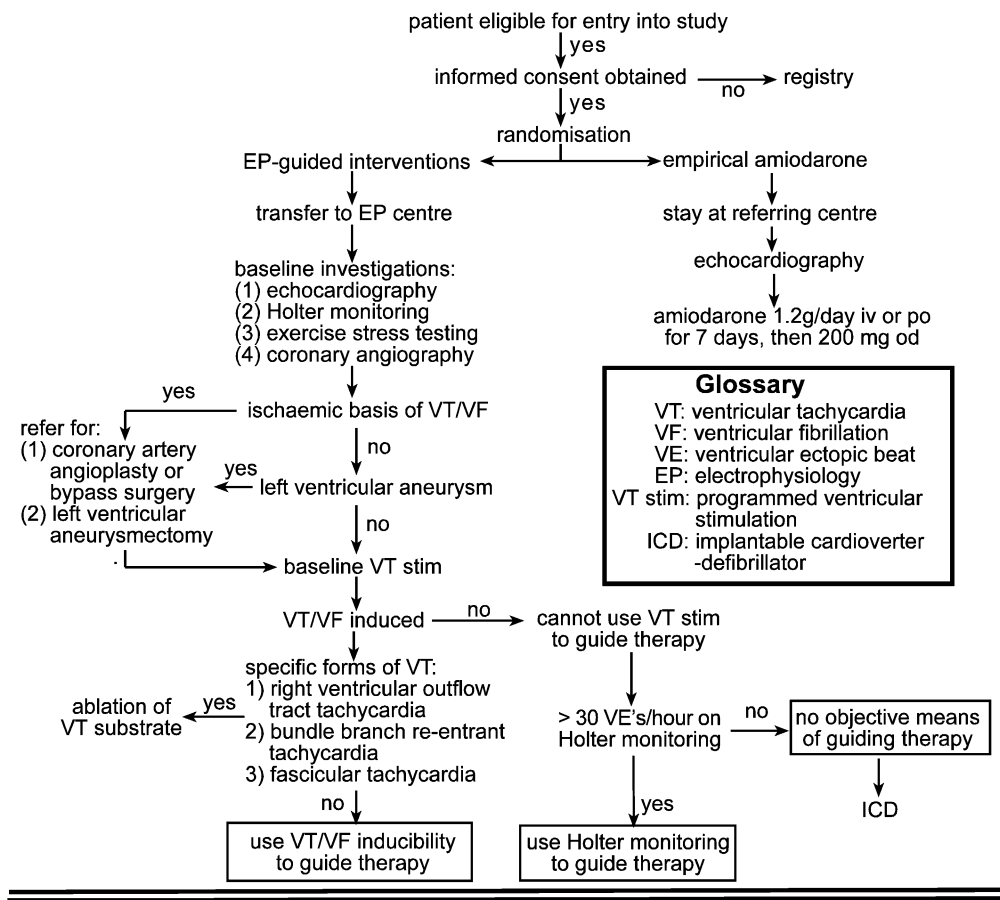
MAVERIC was conducted in the Midlands region (population 9.1 million) of the UK and involved all the local hospitals with the approval of their local research ethics committees. All survivors of sustained ventricular tachycardia (VT) (i.e. > 30 s), ventricular fibrillation (VF) or sudden cardiac death (SCD) in the absence of an acute myocardial infarction in the last 48 h were eligible for inclusion, provided they did not have a likely life expectancy of < 6 months from a non-arrhythmic cause or were of child-bearing age. Eligible patients who gave informed consent to join the trial were randomized by sealed envelopes to either empirical amiodarone therapy or EP-guided interventions with pre-stratification for haemodynamic status at index event; otherwise they entered the study's registry (Fig. 1). A clinical event was considered haemodynamically unstable if the patient required resuscitation, was syncopal or had a systolic blood pressure of < 80 mmHg. Baseline characteristics including demographics, past medical history and family history were recorded at initial presentation. A baseline estimation of LVEF by either echocardiography or left ventriculography was also obtained.

Trial recruitment ran from February 1997 to January 1999. Data were frozen for analysis in January 2003, when the median follow-up was 60 months.

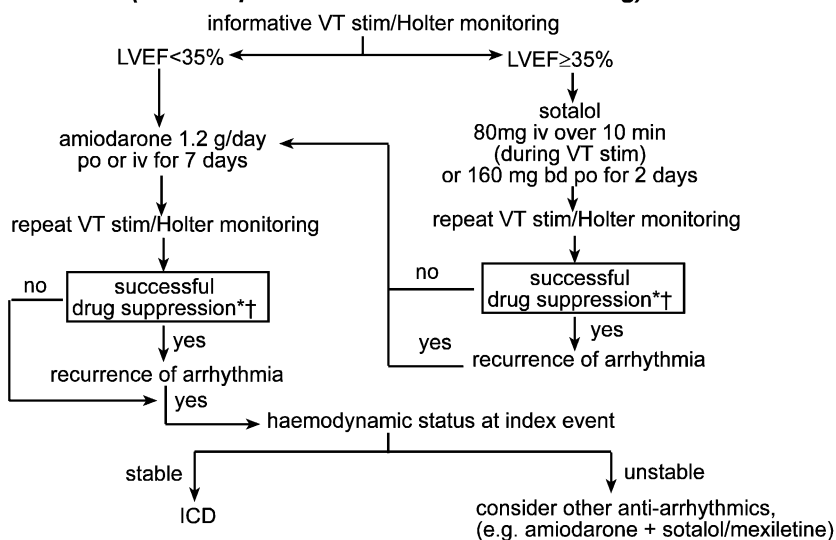
Study protocol

The MAVERIC protocol was as shown in Fig. 1. Investigation for possible myocardial ischaemia with exercise stress testing and coronary angiography was

MAVERIC PROTOCOL



Using VT stim/Holter monitoring to guide therapy (VT stim preferred over Holter monitoring)



VT stim used to guide therapy
 *successful suppression of haemodynamically unstable VT/VF if:
 1) VT rendered haemodynamically stable
 2) VT/VF becomes non-inducible
 *successful suppression of haemodynamically stable VT if
 1) VT cycle length increases by > 100 msec
 2) VT becomes harder to induce by ≥ 1 stage of stimulation protocol

Holter monitoring used to guide therapy
 †successful suppression if:
 1) >75% reduction of single VE's
 2) >90% reduction of couplets
 3) >90% reduction of non-sustained VT

Figure 1 Protocol for the MAVERIC trial. od = once daily, bd = twice daily.

mandatory for patients in the EP arm but discretionary for patients in the amiodarone arm. Coronary revascularization by either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting surgery (CABG) was administered according to current guidelines [8]. Left ventricular aneurysmectomy was performed if indicated. After any appropriate coronary revascularization had been completed, patients in the EP arm underwent serial programmed ventricular stimulation by a protocol modified from Wellens et al. [9]. The protocol comprised six stages, with drive cycles of 600 ms and 400 ms and up to three extra-stimuli from either the right ventricular apex or outflow tract. Positive end-points were defined as the induction of either a sustained monomorphic VT of >30 s duration or VF. When VT/VF was non-inducible, Holter monitoring could be used as an alternative means of assessing arrhythmia suppression if the patient had >30 ventricular ectopic beats per hour on average [10]. If neither programmed ventricular stimulation nor Holter monitoring could be used for assessing arrhythmia suppression, an ICD was implanted. The definitions of successful arrhythmia suppression were as stated in Fig. 1, and the sequence of anti-arrhythmic drugs tried was determined by the patient's LVEF. If arrhythmia suppression with either sotalol or amiodarone was unsuccessful, further treatment depended on haemodynamic status of the index event: if haemodynamically unstable, the patient received an ICD; otherwise, various combinations of anti-arrhythmic drugs (such as the combined use of sotalol or mexiletine with amiodarone) were tried.

In the EP arm, when specific forms of VT particularly amenable to ablation (Fig. 1) or misdiagnosis of supraventricular tachycardia with aberrant conduction as VT was suspected, a full EP study was performed, with radiofrequency ablation if appropriate.

End-points

The trial's primary end-point was death; the secondary end-points were VT/VF/SCD recurrence and cross-over in treatment. Follow-up for death was through the Office of National Statistics of the United Kingdom, and for hospitalization and arrhythmia recurrence through scrutiny of study patients' case notes every 3 months. The cause and mode of death were decided by two adjudicators independent of all other aspects of study conduction through scrutiny of the deceased's case notes. Deaths which were sudden (i.e. within 1 h of onset of symptom) but without any documentary

evidence of arrhythmia were classified as sudden cardiac rather than arrhythmic deaths.

Statistical analyses and power calculation

Baseline characteristics were compared with the unpaired *t*-test or contingency table. Survival and recurrence-free survival were depicted as Kaplan–Meier curves and compared with the log-rank statistic by the intention-to-treat principle. A *p*-value of <0.05 was regarded as significant. Multivariate analysis on factors that might affect survival was conducted with logistic regression. A sample size of 200 was estimated to have a 90% power to detect a 50% relative risk reduction in mortality.

Results

Out of 689 patients meeting the inclusion criteria, 214 joined the trial. Of the 122 trial patients haemodynamically stable at index event, 60 were in the EP arm and 62 in the amiodarone arm. Of the 92 trial patients haemodynamically unstable at index event, 48 were in the EP arm and 44 in the amiodarone arm.

Baseline characteristics

The two arms were comparable for all characteristics examined except for age, which was lower for the EP arm than for the amiodarone arm (65.9 ± 10.3 years versus 68.5 ± 9.4 years, $p = 0.051$) (Table 1). By virtue of pre-stratified randomization, the two arms were also comparable in the proportion of patients haemodynamically stable at index event.

Treatments received

Of the 62 patients haemodynamically stable at index event in the amiodarone arm, 54 (87%) were maintained on amiodarone only. Six patients (10%) crossed over to the EP arm: 4 received an ICD; 1 received radiofrequency ablation of VT substrate and 1 received combined mexiletine and amiodarone therapy. Two patients (3%) died of cardiogenic shock shortly after randomization before completion of amiodarone loading.

Of the 60 patients haemodynamically stable at index event in the EP arm, 33 (55%) were maintained on anti-arrhythmic drugs only (20 on amiodarone alone; 9 on sotalol alone; 1 on amiodarone and mexiletine; 1 on sotalol and mexiletine; 2 on

Table 1 Comparisons of baseline characteristics between the two treatment arms in the MAVERIC trial

Characteristics	Electrophysiology-guided interventions	Empirical amiodarone therapy	<i>p</i>
Male gender	82.5%	77.4%	0.357
Age	65.9 ± 10.3	68.5 ± 9.4	0.051
Left ventricular ejection fraction < 35%	37.7%	34.7%	0.545
Haemodynamically stable at index event	55.6%	58.5%	0.681
Hypertension	34.3%	29.3%	0.431
Diabetes	15.8%	17.0%	0.806
Congestive cardiac failure	27.8%	22.7%	0.387
Previous myocardial infarction	61.2%	60.4%	0.912
Valve disease	7.5%	3.8%	0.248
Family history of sudden death	6.5%	4.8%	0.575

mexiletine alone). Seven patients (12%) received coronary revascularization but no ICD (4 had CABG only; 1 had CABG and left ventricular aneurysmectomy; 1 was maintained on amiodarone after CABG; 1 was maintained on amiodarone after PTCA). Fourteen patients (23%) received an ICD (4 received an ICD only; 6 were maintained on amiodarone after receiving an ICD; 2 were maintained on sotalol after receiving an ICD; 1 was maintained on mexiletine after receiving an ICD; 1 received an ICD after PTCA). Three patients (5%) were successfully treated with radiofrequency ablation (1 for VT substrate; 2 for supraventricular tachycardia substrate). Three patients (5%) died shortly after randomization before receiving full EP-guided interventions.

Of the 44 patients haemodynamically unstable at index event in the amiodarone arm, 35 (80%) were maintained on amiodarone only. Six patients (14%) were intolerant of amiodarone: 2 were switched over to sotalol but 4 were not maintained on any other anti-arrhythmic therapy. Three patients (7%) had recurrences while on amiodarone and crossed over to the EP arm (1 received CABG and remained on amiodarone; 1 received an ICD, and 1 received a permanent pacemaker as the syncopal episode was deemed to be due to heart block induced/aggravated by amiodarone).

Of the 48 patients haemodynamically unstable at index event in the EP arm, 13 (27%) were maintained on anti-arrhythmic drugs only (10 on amiodarone alone; 2 on sotalol alone and 1 on sotalol and mexiletine). Eleven patients (23%) received coronary revascularization but no ICD (9 received CABG alone; 1 was maintained on amiodarone after CABG; 1 was maintained on amiodarone and sotalol after PTCA). Seventeen patients (35%) received an ICD (8 received an ICD only; 4 received an ICD after

CABG; 5 were maintained on amiodarone after receiving an ICD). One patient (2%) had sotalol-induced long QT syndrome precipitating polymorphic VT and was managed simply by withdrawal of sotalol. Two patients (4%) had co-existent uncontrolled atrial fibrillation and were treated with atrioventricular nodal ablation and permanent pacemaker implantation. Two patients (4%) died shortly after randomization before receiving full EP-guided interventions. Two patients (4%) withdrew from the study shortly after randomization.

Overall, of the 106 amiodarone arm patients, 89 (84%) received the drug and 5 (5%) received an ICD after crossing over. Of the 108 EP arm patients, 31 (29%) received an ICD, 46 (43%) received anti-arrhythmic drugs only (mainly amiodarone or sotalol) and 18 (17%) received coronary revascularization but no ICD.

Death

After a maximum of 6 years follow-up (median 5 years), there was no significant difference in survival between the two treatment arms, with or without pre-stratification for haemodynamic stability at index event (Fig. 2). However, there was a statistically non-significant trend for patients randomized to EP-guided interventions to have an initially worse but subsequently better survival experience than patients randomised to empirical amiodarone therapy, especially when the index event was associated with haemodynamic compromise.

Event-free survival

For the composite end-point of death and recurrence of arrhythmia, the amiodarone arm had

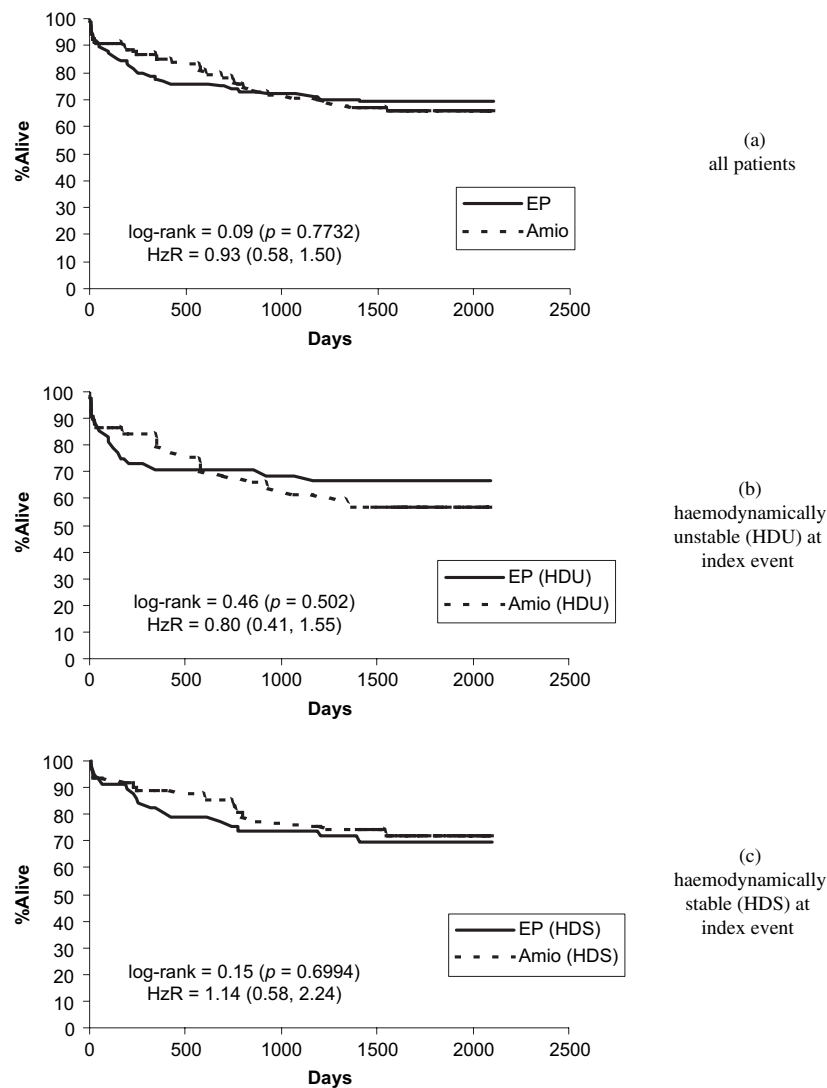


Figure 2 Survival curves of electrophysiology-guided interventions (EP) and empirical amiodarone (Amio) therapy in the MAVERIC trial.

a slightly better experience than the EP arm throughout follow-up, but the difference did not reach statistical significance (log-rank = 1.42, $p = 0.2335$).

Effects of ICD implantation on survival

When the survival experiences of all trial patients were compared according to whether they received an ICD or not rather than their allocated treatments, ICD recipients consistently did better than non-ICD recipients, and the difference reached statistical significance (Fig. 3(a)). However, the survival benefit of ICD implantation was more marked for patients haemodynamically

unstable at index event than those haemodynamically stable at index event (Fig. 3(b) and (c)).

In terms of baseline characteristics (Table 2), ICD recipients were significantly younger and also less likely to have diabetes than non-ICD recipients, but the two groups were otherwise comparable in other respects.

Multivariate analysis on factors affecting survival

Age, LVEF < 35%, diabetes and congestive cardiac failure were independently associated with an increased risk for death (Table 3). ICD implantation was associated with a reduced risk for death but

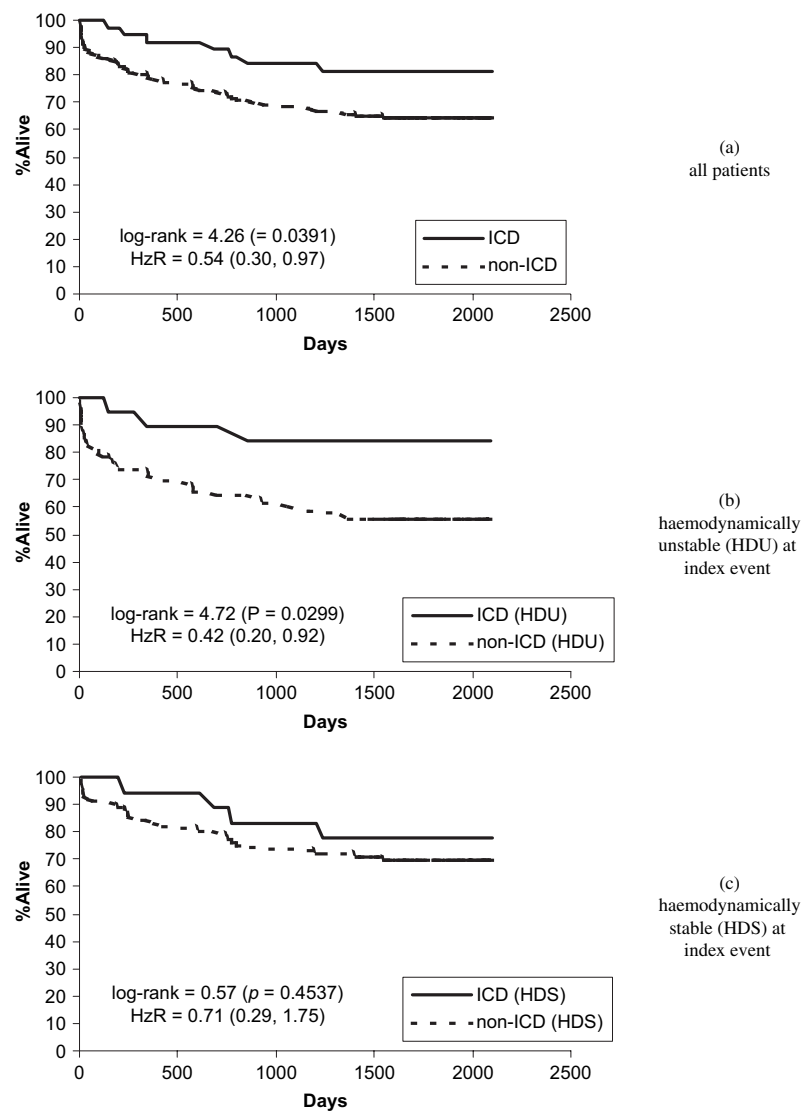


Figure 3 Survival curves of recipients and non-recipients of the implantable cardioverter-defibrillator in the MAVERIC trial.

the association did not reach statistical significance ($p = 0.080$).

Discussion

The overall neutral results of MAVERIC imply that empirical amiodarone therapy is just as effective as EP-guided interventions in the secondary prevention of SCD. The sample size in this trial was relatively small but comparable to those in CASH [3] and MADIT-I [11].

MAVERIC was different from other secondary prevention trials such as AVID, CIDS and CASH in two crucial respects. First, patients haemodynamically stable at index event were included in

MAVERIC (>50% of the study population) but excluded from the other studies. Second, MAVERIC compared empirical amiodarone therapy against EP-guided interventions rather than against empirical ICD therapy. In MAVERIC, ICD therapy was guided by programmed ventricular stimulation rather than routinely indicated in the EP arm, which accounted for its relatively low utilization rate (29%). These two factors may explain why EP-guided ICD implantation did not achieve the same survival benefit over empirical amiodarone therapy in MAVERIC as empirical ICD therapy in other secondary prevention trials [1–4].

In MAVERIC, ICDs were implanted only in patients considered at high risk either by their presentation or risk stratification by EP study. Yet, ICD implantation was associated with a greatly

Table 2 Comparisons of baseline characteristics between the ICD and non-ICD recipients

Characteristics	ICD recipients	Non-ICD recipients	<i>p</i>
Male gender	84.3%	79.0%	0.465
Age	62.7 ± 9.0 years	68.1 ± 9.8 years	0.002
Left ventricular ejection fraction < 35%	47.4%	38.1%	0.288
Haemodynamically stable at index event	50.0%	58.2%	0.336
Hypertension	34.3%	31.3%	0.722
Diabetes	5.3%	18.8%	0.042
Congestive cardiac failure	26.4%	24.5%	0.807
Previous myocardial infarction	71.1%	58.6%	0.151
Valve disease	2.7%	6.3%	0.379
Family history of sudden death	7.9%	5.2%	0.499

ICD: implantable cardioverter-defibrillator.

improved survival in the trial. This suggests that the prognosis of even the “high-risk” patients was so much improved by ICD therapy that it actually became better than that of the “low-risk” patients. This benefit just became non-significant with multivariate analysis, but this is likely to be due to the sample size involved. However, even though the majority of ICD recipients were in the EP arm, the survival benefit conferred by ICD implantation did not translate into an overall survival advantage for the whole treatment arm. This most probably reflects a dilution effect on the survival benefit by the poor prognosis of other “low-risk” patients who did not receive ICDs.

MAVERIC did not directly compare EP-guided against empirical ICD implantation, and it may be argued that such a direct head-to-head comparison would have been better. However, such a comparison will have to be an equivalence trial, which will require a large sample size. If MAVERIC had

demonstrated survival benefit from EP-guided ICD implantation over empirical amiodarone therapy comparable to that observed for empirical ICD implantation over empirical amiodarone therapy in other secondary prevention trials, then such a direct head-to-head comparison would have been indicated. The neutral results of MAVERIC obviate the need for such a comparison. However, this does not mean that more precise targeting of ICD therapy is unnecessary or impossible. There is emerging evidence that empirical ICD therapy is better than anti-arrhythmic (amiodarone) therapy in only certain subgroups of survivors of VT, VF or SCD [5, 12–14].

MAVERIC shows that EP study has a minimal impact on the diagnosis of patients presented with VT, VF or SCD. The substrate of nearly all broad complex tachycardias can be identified from the surface ECG. In MAVERIC, only 2 of 108 patients in the EP arm were found to have a supraventricular cause for their broad complex tachycardias.

Table 3 Multivariate analysis on factors which might affect survival

Factors	Odds ratio for death	<i>p</i>
Male gender	0.96 (0.44–2.11)	0.920
Age	1.06 (1.03–1.10)/year	0.001
Left ventricular ejection fraction < 35%	2.56 (1.33–5.00)	0.005
Haemodynamically stable at index event	0.75 (0.397–1.449)	0.393
Hypertension	0.67 (0.34–1.33)	0.254
Diabetes	2.63 (1.15–6.03)	0.022
Congestive cardiac failure	2.25 (1.08–4.70)	0.030
Previous myocardial infarction	1.29 (0.67–2.51)	0.448
Valve disease	0.69 (0.15–3.09)	0.630
ICD implantation	0.43 (0.17–1.11)	0.080

ICD: implantable cardioverter-defibrillator.

However, for both these patients, a supraventricular cause for their tachycardias was strongly suspected from the presentation ECGs. Thus if the diagnosis of VT is clear from the surface ECG, diagnostic EP study is unnecessary. As this trial does not support a role for EP testing in risk stratification either, EP study should be reserved for patients with an uncertain diagnosis.

In MAVERIC, coronary revascularization was not part of the randomized treatments. In the amiodarone arm, it was left to the discretion of the attending physician. In the EP arm, an aggressive revascularization policy was pursued, with coronary angiograms performed in all patients and coronary revascularization attempted as far as it was technically feasible. Thus MAVERIC could not address the role of coronary revascularization in the management of survivors of VT, VF or SCD. The CABG Patch trial showed that prophylactic ICD implantation in patients with coronary artery disease, a depressed LVEF and an abnormal signal-averaged ECG at the time of elective CABG did not confer any survival benefit [15], but that was in the context of primary prevention of SCD. In contrast, the AVID registry showed that coronary revascularization produced a survival benefit of its own and did not diminish that of ICD therapy in the secondary prevention of SCD [16]. Consequently, coronary revascularization should be recommended to survivors of VT, VF or SCD according to current guidelines [8].

In conclusion, MAVERIC shows that prospective selection of patients to receive in ICD by EP study combined with aggressive coronary revascularization did not improve survival compared with empirical amiodarone therapy among survivors of VT, VF or SCD. On the other hand, ICD recipients had a significantly better survival experience than non-ICD recipients, even though this observation was based on non-randomized data. The overall results of MAVERIC suggest that the methods used to select patients for ICD implantation in this trial were not sensitive enough to identify all high-risk patients who would benefit from the therapy, and routine EP testing and aggressive coronary revascularization do not add value in the management of such patients. On this basis, patients presented with VT, VF or SCD should be offered empirical ICD therapy according to the results of other secondary prevention ICD trials [1–4].

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