Implantable defibrillator therapy

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ABSTRACT

Sudden cardiac death (SCD) is the most important cause of death in the industrialised world. Treatment with antiarrhythmic drugs (AAD), however, proved disappointing in preventing SCD. From drugs with electrophysiological properties, only treatment with β-blockers has been shown to improve clinical outcome. This lack of efficiency of AADs heralded a new era of secondary and primary prevention trials, comparing implantable cardioverter-defibrillator (ICD) with drug therapy. Three large randomised secondary prevention trials were conducted in patients with prior myocardial infarction who were resuscitated from VT or VF. Meta-analysis of these three studies show consistent ICD benefit. This ICD benefit is also observed in three large randomised primary prevention trials in patients with a prior myocardial infarction and left ventricular dysfunction. The beneficial effect of ICD therapy proves to be significantly more pronounced in patients with the lowest left ventricular ejection fraction (26-30%). In patients with nonischaemic dilated cardiomyopathy and low ejection fractions, however, currently the only evidence-based indication for ICD implantation is secondary prevention.

INTRODUCTION

Sudden cardiac death (SCD) is the most important cause of death in the industrialised world. It is defined as ‘... unexpected death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of onset of symptoms...’. As tachyarrhythmias are the recorded rhythm in over 80% of victims presenting with SCD, in the context of this paper arrhythmic death will be considered to be synonymous to SCD. In Western Europe and the USA, the incidence of SCD rate reaches up to 1% of the general population, accounting for about 350,000 SCDs a year in Europe. In the 20 to 75 age group of the general population in the Maastricht area in the Netherlands, an overall incidence of 1:1000 SCD was recorded as well. The incidence of SCD, however, markedly increases in the presence of coronary artery disease, a history of previous coronary events, impaired left ventricular function or the combination of a previous myocardial infarction with low ejection fraction.

From these risk factors, reduced left ventricular ejection fraction appears to be the single most important risk factor for mortality and SCD. In patients with a history of myocardial infarction, low ejection fraction and nonsustained ventricular tachycardias (VTs), the five-year incidence of SCD is even >20%. Despite increasing knowledge on basic life support in the general population, survival to hospital discharge after an out-of-hospital SCD is as low as 9%, emphasising the importance of both primary and secondary prevention strategies. Use of antiarrhythmic drugs (AAD) and implantable cardioverter-defibrillators (ICD) have been considered the mainstay of therapy. However, from the drugs with electrophysiological properties, only treatment with the β-adrenergic receptor antagonists has been shown to improve clinical outcome. Therefore, these β-blockers should be regarded as mandatory in high-risk patients.
Treatment with all other AADs, however, proved to be either harmful or at best have a neutral effect on all-cause mortality (table 1). The lack of efficiency of AADs in preventing SCD heralded a new era of secondary and primary prevention trials, comparing ICD with drug therapy.

Three large randomised secondary prevention trials of ICD versus AADs have been conducted in patients resuscitated from ventricular fibrillation (VF) or VT. The AVID (Antiarrhythmic drug Versus Implantable Defibrillator) trial and the CIDS (Canadian Implantable Defibrillator Study) enrolled patients with previous VF or VT for randomisation of ICD therapy versus mainly amiodarone. In the AVID trial only a minority of patients received sotalol.12-15 The CASH (Cardiac Arrest Survival in Hamburg) trial randomised cardiac arrest survivors to ICD versus amiodarone or metoprolol.16 A meta-analysis of these three studies showed a consistent ICD benefit, with a significant reduction in death from any cause with the ICD (hazard ratio 0.72), which is almost entirely due to a 50% reduction in arrhythmic death.17 This beneficial effect of ICD therapy is significantly more pronounced in patients with a left ventricular ejection fraction <35%.

However, as SCD is often the initial symptom of ischaemic heart disease, primary prevention strategies have been studied extensively as well. MADIT (Multicentre Automatic Defibrillator Implantation Trial) demonstrated a 54% reduction in total mortality within two years with ICD therapy in patients with prior myocardial infarction, reduced left ventricular ejection fraction (<0.35), spontaneous asymptomatic nonsustained VT and inducible, nonsuppressible sustained VT during programmed electrical stimulation.18 MUSTT (Multicentre Unsustained Tachycardia Trial) tested the hypothesis that AAD therapy guided by electrophysiological testing would reduce the risk of sudden death among patients with coronary artery disease, a left ventricular ejection fraction of <40% and asymptomatic, nonsustained VT. Patients were randomised to no therapy or to electrophysologically guided AAD or ICD therapy.19 In MUSTT, antiarrhythmic therapy caused a 28% reduction in cardiac arrest or death from arrhythmia, which was almost entirely due to ICD therapy, and not to AAD therapy. Electrophysiological testing proved of poor prognostic value to identify patients at risk for SCD. Finally, underscoring the lack of efficiency of AADs in preventing SCD, no difference in outcome was seen between patients receiving no therapy or AAD therapy.

Further analyses of the aforementioned ICD prevention trials demonstrate that patients with the lowest left ventricular ejection fractions benefit most from ICD therapy. AVID data showed no ICD survival benefit in patients with a left ventricular ejection fraction >0.35, whereas for patients with a left ventricular ejection fraction of 0.20 to 0.34, there was a significantly improved survival.18 In CIDS, patients with the highest mortality risk, as based on age, left ventricular ejection fraction <0.35 and NYHA class III or IV, demonstrated a 50% relative risk reduction of death in the ICD group, whereas in the three lower risk quartiles, there was no benefit.19 In MADIT, patients were included with an ejection fraction ≥0.35. However, benefit from ICD therapy was concentrated almost exclusively in those patients with a left ventricular ejection fraction <0.26.20

### MADIT II

MADIT II tested the survival benefit of primary prevention with ICD implantation in patients with a prior myocardial infarction and a left ventricular ejection fraction <0.30.21 Ventricular arrhythmias were not required for inclusion. And given its poor prognostic value to determine the risk for SCD in patients with coronary heart disease, no additional invasive electrophysiological testing was performed. Patients were randomly assigned to receive an ICD (742 patients) or conventional medical therapy (490 patients). Mean left ventricular ejection fraction was 0.23 in both treatment groups. Concomitant drug use did not differ between groups: in particular, use of β-blockers and of ACE inhibitors was 70% in both treatment groups. After an average follow-up of 20 months, the trial was stopped when mortality differences between the two groups reached the prespecified efficacy boundary. Mortality rates were 19.8% in the conventional therapy group and 14.2% in the ICD group, a relative risk reduction of 31%.

Given the impact of this landmark trial on medical logistics and expenditure, further risk stratification within the MADIT II population seems warranted. The authors state

### Table 1

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PATIENTS (N)</th>
<th>DESIGN</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAST</td>
<td>1498</td>
<td>Flecainide/encainide versus placebo post-MI and PVC</td>
<td>Excessive death</td>
</tr>
<tr>
<td>SWORD</td>
<td>3121</td>
<td>D-sotalol versus placebo post-MI and EF &lt;0.40</td>
<td>Excessive death</td>
</tr>
<tr>
<td>EMIAT</td>
<td>1486</td>
<td>Amiodarone versus placebo post-MI and EF &lt;0.40</td>
<td>No change</td>
</tr>
<tr>
<td>CAMIAT</td>
<td>1202</td>
<td>Amiodarone versus placebo post-MI and NSVT &gt;10 PVC/h</td>
<td>No change</td>
</tr>
</tbody>
</table>

Primary prevention trials demonstrated neutral (amiodarone) or deleterious (class Ic and class III antiarrhythmic drugs) effects on total mortality. MI = myocardial infarction, PVC = premature ventricular contractions, EF = ejection fraction, NSVT = nonsustained ventricular tachycardia.
that subgroup analyses showed no significant differences in the beneficial effect of ICD therapy on survival in subgroups stratified according to, amongst others, ejection fraction and QRS interval. However, in accordance with observations in previous ICD trials, hazard ratios with 95% confidence intervals do suggest a trend towards increased beneficial effect of ICD therapy in patients with the highest risk for SCD, i.e., patients with QRS intervals >0.15 sec and left ventricular ejection fractions <0.25.

**ICD THERAPY IN NONISCHAEMIC DILATED CARDIOMYOPATHY**

Thus, so far ICD trials have convincingly shown that implantation of an ICD in patients with a prior myocardial infarction and advanced left ventricular dysfunction improves survival. Although over 60% of the populations of ICD trials are in New York Heart Association functional class (NYHA) II-III heart failure, it is uncertain if the data can be extrapolated to patients with nonischaemic dilated cardiomyopathy and low left ventricular ejection fractions. Undoubtedly, these patients do have an increased risk of dying suddenly as well. Depending on the functional class, one-year mortality rates range between 14 to 44% in NYHA III to IV. Up to 50% of these deaths is supposedly due to ventricular tachyarrhythmias. Nevertheless, risk stratification for primary prevention in these patients is difficult. A small primary prevention trial (CAT) with 104 patients with recent onset nonischaemic cardiomyopathy and a left ventricular ejection fraction <0.30 did not provide evidence in favour of prophylactic ICD implantation in these patients, and was stopped prematurely. Another small primary prevention trial (AMIOVERT) compared amiodarone treatment with ICD therapy in 103 patients with nonischaemic dilated cardiomyopathy and an ejection fraction <0.35, and asymptomatic nonsustained VT defined as >3 beats, less than 30 seconds, >100 bpm. The study lasted four years without a demonstrated survival benefit from either treatment. The study, however, may not be conclusive. It combined data from the randomised and registry groups, which seems a methodological flaw. Ongoing trials such as DEFINITE (Defibrillators In Nonischaemic Cardiomyopathy Treatment Evaluation) and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) will have to provide useful data on the role of ICD and amiodarone in patients with nonischaemic cardiomyopathy. DEFINITE is a primary prevention study comparing ICD therapy versus optimal medical therapy, including β-blockers and ACE inhibitors, in nonischaemic cardiomyopathy patients with a left ventricular ejection fraction <0.35 and spontaneous ventricular arrhythmia (nonsustained VT or >10 PVCs/h) on Holter monitoring. After including 458 patients, the enrolment phase was completed in August 2002. Results are to be expected this year. SCD-HeFT is an ongoing prospective, clinical trial enrolling 2500 patients with nonischaemic cardiomyopathy and a left ventricular ejection fraction <0.35. On top of standard medical care, patients will be allocated to placebo, amiodarone or ICD therapy.

**CONCLUSION**

For primary prevention of SCD, ICD implantation seems warranted in patients with ischaemic cardiomyopathy with a low left ventricular ejection fraction. In patients with nonischaemic dilated cardiomyopathy and low left ventricular ejection fractions, however, currently the only evidence-based indication for ICD implantation is secondary prevention.

**REFERENCES**


ABOUT THE COVER

‘Havenloods’

Marjoke Schulten

Marjoke Schulten (1970) attended the Academy of Art in Rotterdam where she graduated in ‘Free Graphics’. At the same time she studied Art and Culture Sciences at the Erasmus University, she completed this study in 2001. Since 1995 she teaches history of art at the Grafisch Lyceum Rotterdam. Besides her studies, Marjoke has always been developing her own professional practice as pictorial artist.

In her recent work she translates her home base Rotterdam to the mythical upper- and underworld. She sees the Rotterdam harbour as a meeting place between water and land; two worlds with each its own dynamic in which you can travel. Returning elements in her etchings are ships, cranes, sailors and fish. In addition to several individual expositions she has exhibited her work at many group expositions in the Netherlands and in France.

An original print of ‘Havenloods’ is available at a price of € 200. You can order the print at Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands or by e-mail: galerie-unita@planet.nl.