Secondary prevention of sudden cardiac death

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Sudden cardiac death is still the largest cause of natural death in western countries, especially in patients with coronary artery disease and in those who have already experienced an episode of resuscitated out-of-hospital cardiac arrest or ventricular tachycardia.

Prevention of arrhythmia recurrences (i.e. secondary prevention) in these patients remains a challenge for the cardiologist. To date no studies have demonstrated that drug therapy can be of some value in preventing arrhythmia recurrences or sudden death in these patients, and only cardioverter-defibrillator (ICD) implantation resulted effective in reducing mortality rate. It remains, however, to be defined which patients who survived an out-of-hospital cardiac arrest or who already experienced a sustained ventricular tachycardia could benefit the most from an ICD, but to date no invasive or non-invasive tests have proven to be effective for this stratification.

Vaughan-Williams class II and III drugs could be of some value in reducing tachycardia cycle length thus increasing antitachycardia pacing efficacy and reducing ICD shocks.

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Introduction

Sudden cardiac death (SCD), defined as unexpected natural death from cardiac causes within a short period of time, remains the single largest cause of natural death in the western world (Fig. 1). In the United States, between 300 000 and 400 000 patients die suddenly each year[1]. Although a fatal arrhythmic event may occur also in healthy subjects, autopsy studies have confirmed that a coronary event is responsible for at least half of the episodes of SCD[2].

Patients who survived an out-of-hospital cardiac arrest or symptomatic sustained ventricular tachycardia (VT) are at considerable risk of recurrence of these events and death, and represent a challenge for electrophysiologists.

Secondary prevention of sudden cardiac death with antiarrhythmic drugs

Pharmacological prevention of fatal arrhythmia recurrences in patients who survived an out-of-hospital cardiac arrest is associated with a high recurrence rate of non-fatal and fatal arrhythmia.

Earlier uncontrolled studies evaluated the effectiveness of amiodarone in preventing arrhythmia recurrences. In the study by Herre et al.[3], for instance, 462 patients with VT/ventricular fibrillation (VF) were treated with amiodarone. Recurrence rates were 19, 33 and 43% at 1, 3 and 5 years respectively, with amiodarone withdrawal in 37% of patients.

In the ESVEM (Electrophysiologic Study Versus Electrocardiographic Monitoring)[4] 486 patients with inducible sustained VT/VF during electrophysiologic study (EPS) and ≥ 10 premature ventricular complexes per hour during 48-hour Holter monitoring, were randomized to determine whether ECG monitoring or EPS drug testing was superior in predicting long-term outcome. In this study amiodarone was not tested and sotalol showed to be superior to the other tested drugs (Fig. 2). Nevertheless, over a 6-year follow-up period, there were 150 recurrences of arrhythmia and 46 deaths among the 269 patients receiving drugs predicted to be effective.

This demonstrates that – whichever the method used to guide ventricular arrhythmia suppression – there is a high recurrence rate.

Similarly, in the CASCADE Trial (Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation)[5], 228 patients who survived a cardiac arrest were randomized to receive empirical amiodarone or conventional class I drug therapy guided by EPS or Holter monitoring. Even if amiodarone demonstrated to be superior to conventional drug therapy in terms of

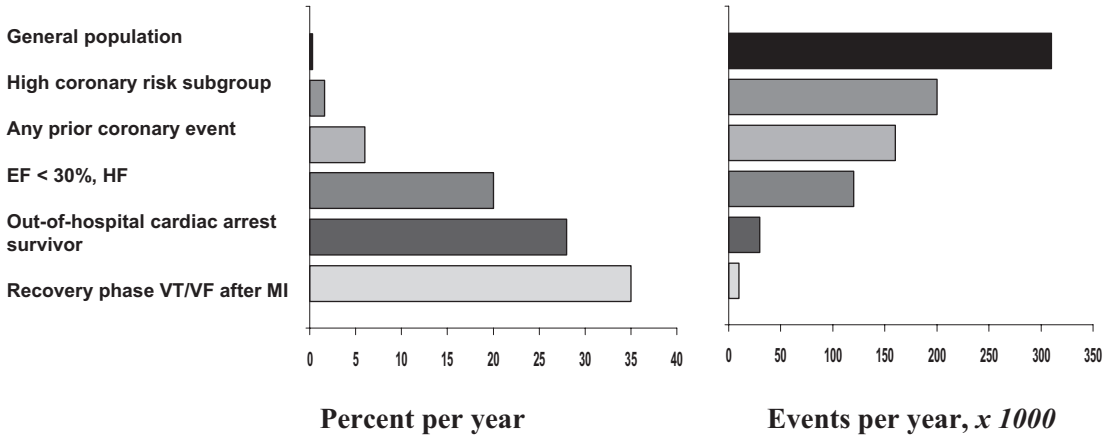

Figure 1. *Relation between the incidence and annual sudden cardiac death in population subgroups. EF = ejection fraction; HF = heart failure; MI = myocardial infarction; VF = ventricular fibrillation; VT = ventricular tachycardia.*

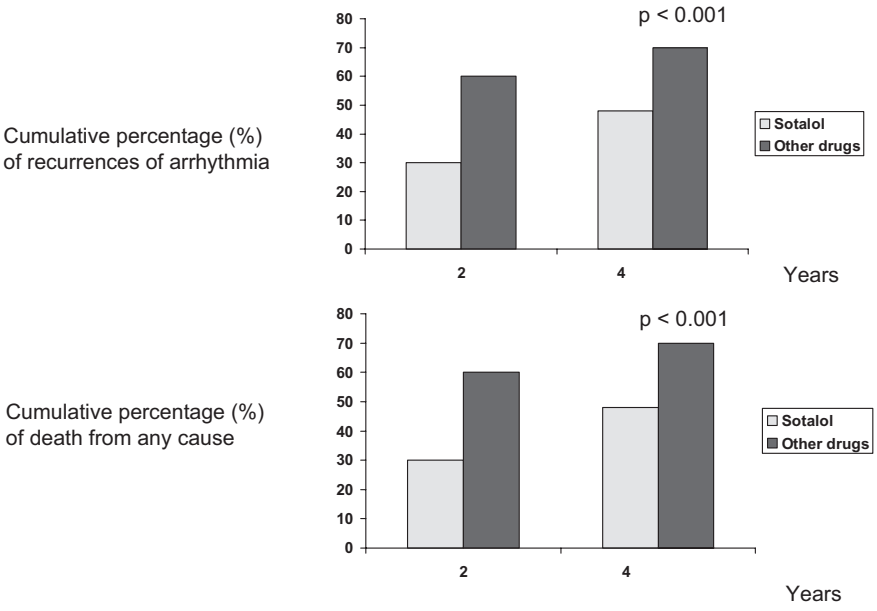

Figure 2. *Results of the ESVEM trial. From Mason[4], modified.*

cardiac death and sustained ventricular arrhythmia recurrences, the survival rate free of this combined endpoint was 30% at a 6-year follow-up.

The CAST study (Cardiac Arrhythmia Suppression Trial)[6] demonstrated that class I antiarrhythmic drugs for VT/VF have an unacceptable high incidence of proarrhythmia. In addition, even if class III drugs have shown to be more effective than class I, their use is still associated with a significant incidence of recurrent arrhythmic events.

Secondary prevention of sudden cardiac death with implantable cardioverter-defibrillators

To date, there are only three randomized controlled studies evaluating the implantable cardioverter-defibrillator (ICD) against antiarrhythmic therapy in patients with sustained ventricular arrhythmia. Although the AVID (Antiarrhythmics Versus Implantable Defibrillators)[7] was the largest of the three trials, it was stopped earlier than expected and therefore it has the shortest follow-up.

The CIDS (Canadian Implantable Defibrillator Study)[8] and CASH (Cardiac Arrest Study Hamburg)[9] have longer follow-ups and have therefore more deaths than AVID. Thus, a meta-analysis[10] of these data provides the most precise and least biased evaluation of ICD benefit over prolonged follow-up.

The mean duration of follow-up of the three trials was 2.33 ± 1.89 years. Even if event rates were higher in AVID, the proportion of deaths classified as arrhythmic (in the amiodarone group) was similar in the three studies: 45% in AVID, 54% in CASH, and 44% in CIDS.

Pooling the data from the three databases, the hazard ratio for total mortality (ICD:amiodarone) was 0.73 (95% confidence interval 0.60-0.87, $p < 0.001$) and for arrhythmic death was even lower (hazard ratio 0.49, 95% confidence interval 0.36-0.67, $p < 0.001$) (Figs. 3 and 4).

The obtained prolongation of life with ICD was 2.1 months at 3 years of follow-up and 4.4 months at 6 years.

The only variable capable of discriminating a greater beneficial effect of ICD was the ejection fraction: in fact, patients with a left ventricular ejection fraction > 35% had a significant less benefit from ICD than those with left ventricular ejection fraction ≤ 35%.

Furthermore, the use of beta-blockers at discharge did not have a significant interaction with ICD benefit.

A particularly interesting aspect of AVID[11] is the analysis of patients with hemodynamically stable sustained VT. These patients (n = 440) were not included in the main study, but they were followed up in the

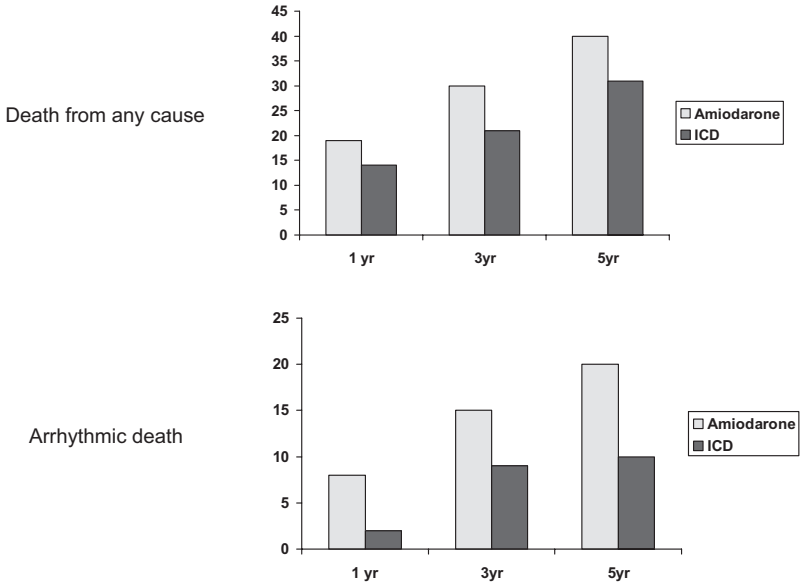

Figure 3. *Results of the AVID, CASH, CIDS meta-analysis. ICD = implantable cardioverter-defibrillator. From Connolly et al.[10], modified.*

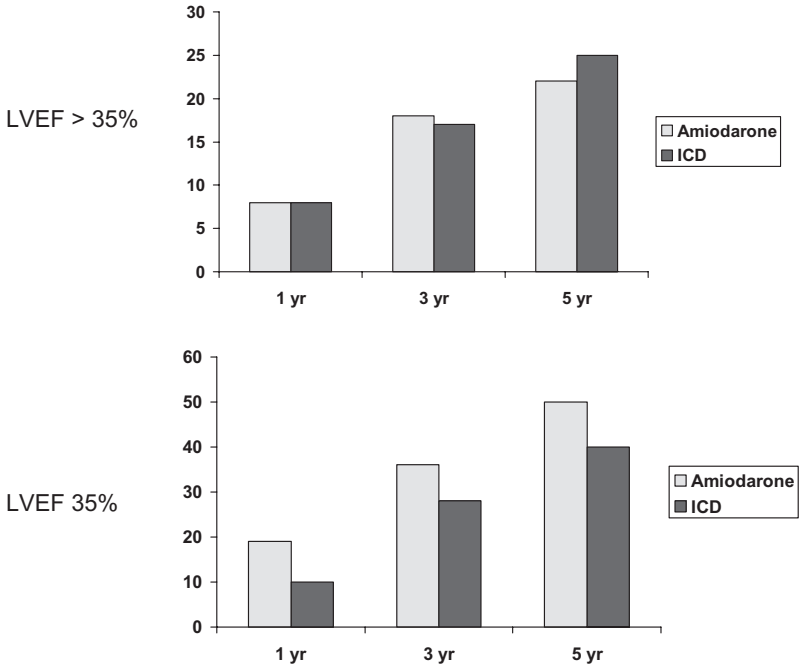

Figure 4. *The AVID, CASH, CIDS meta-analysis: effect of left ventricular ejection (LVEF) on total mortality. ICD = implantable cardioverter-defibrillator. From Connolly et al.[10], modified.*

AVID registry. Patients with stable VT tended to have a higher mortality rate (33.6 vs 27.6%) at 3 years with a relative risk of death of 1.22 (p = 0.07). This trend persisted also after adjustment for the main predictors of mortality (older age, lower ejection fraction, use of antiarrhythmic drugs before the index event, history of congestive heart failure, no beta-blocker therapy at discharge) (Figs. 5 and 6).

The data are comparable with an older study by Olson et al.[12]. In this study the authors analyzed the predictors of sudden death in 122 patients treated with amiodarone for sustained VT and found that – over a median of 19.5 months of follow-up – sudden death mortality was nearly identical in patients with stable (25%) and unstable (24%) VT.

The AVID registry investigators[11] conclude that – due to the fact that antiarrhythmic drug therapy is more common in patients with stable VT – VT stability may only be the result of a slowing down of a VT that otherwise would have been "unstable" in nature.

Conclusions

SCD remains the single largest cause of natural death in the western world. Despite the increased use of ICDs for SCD primary prevention and the slowly growing development of programs of public access defibrillation, solution to this dramatic problem is far from being found.

Neither drug therapy nor an attentive stratification strategy is able to reduce recurrences or identify patients who are at high risk of recurrences.

Invasive (EPS) and non-invasive tests have proven to be of no value at all in this subset of patients and also the stability of index VT cannot be considered as a positive prognostic factor, as demonstrated by the AVID registry[11].

To date, only ICD has proven to be effective in reducing total and arrhythmic mortality in patients who survived a cardiac arrest or who suffered a sustained VT and its implantation is mandatory in these patients.

Effectiveness of ICD is not so consistently proven in patients with left ventricular ejection fraction > 35% or with a correctable cause of VT/VF (ischemia, hypokalemia, etc.) and the indication to ICD implant should be evaluated individually in these patients.

Although drug therapy has no efficacy in reducing total mortality and arrhythmia recurrences, the use of class III drugs could be of same value in reducing VT cycle length, thus reducing ICD shocks and favoring efficacy of antitachycardia pacing during arrhythmia recurrences.

The use of class I drugs should instead be avoided since they have an important proarrhythmic effect in these patients and may increase the mortality rate.

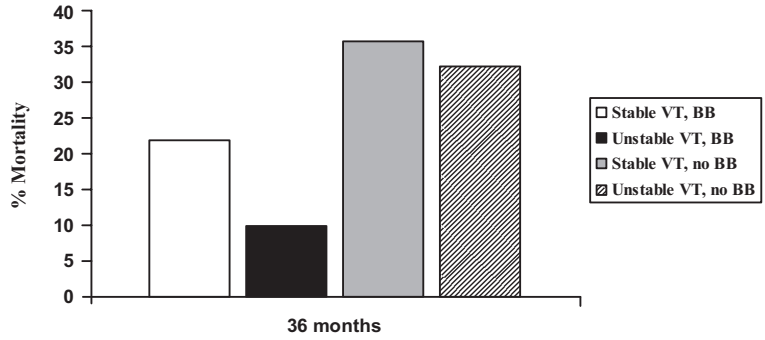

Figure 5. *Mortality for patients with stable or unstable ventricular tachycardia (VT) as a function of whether or not beta-blockers (BB) were prescribed at discharge. From Raitt et al.[11], modified.*

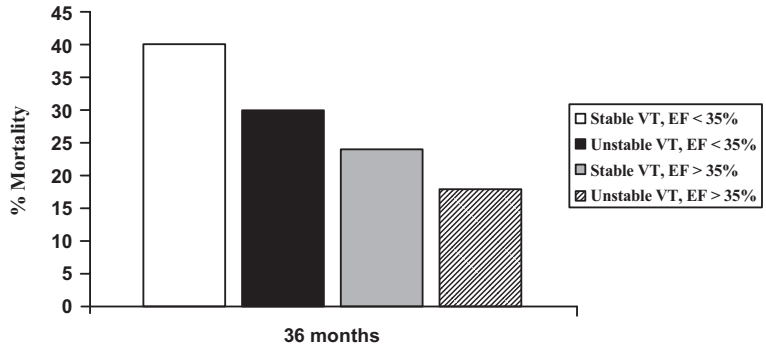

Figure 6. *Mortality of patients with stable or unstable ventricular tachycardia (VT) as a function of left ventricular ejection fraction (EF). From Raitt et al.[11], modified.*

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