Latest data from Secondary Prevention Implantable Cardioverter-Defibrillator Trials

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**Summary**

The Antiarrhythmics Versus Implantable Cardioverter-Defibrillator (AVID), Cardiac Arrest Study Hamburg (CASH) and the Canadian Implantable Defibrillator Study (CIDS) trials demonstrated that the implantable cardioverter-defibrillator (ICD) was superior to best drug therapy for prolonging survival inpatients with sustained ventricular tachycardia/fibrillation (VT/VF).

Substudies of AVID demonstrated that ICD benefit was highest in patients with ejection fractions < 35%, concomitant beta-blocker therapy and concomitant beta-blocker therapy did not explain the differences in ICD versus amiodarone benefit. The AVID registry substudies demonstrated high mortality rates in all subgroups including VT/VF from transient/correctable causes. ICD therapy reduced mortality in patients with unexplained syncope and inducible VT. Adjusted mortality rates were lower in patients presenting with an out-of-hospital versus in-hospital arrest. Three-year survival rates trended lower in patients with stable versus unstable VT. A CASH substudy demonstrated that VT inducibility predicted a group of patients with lower survival rates than noninducible patients. CIDS substudied demonstrated that patients most likely to benefit from an ICD were ≥ 70 years old, had ejection fractions ≤ 35% and NYHA class III/IV functional class.

**Introduction**

Sudden cardiac death accounts for 350,000-400,000 deaths annually in the United States. However, less than 20% of patients will survive a cardiac arrest and be discharged alive from a hospital [1]. Prior to the implantable cardioverter defibrillator (ICD) era, 50% of sudden cardiac arrest survivors died within 3 years of their event [1]. Since survivors of a cardiac arrest are at high risk for a recurrent arrhythmic event, aggressive management of this group of patients is mandatory. In patients with previous sustained VT/VF, data from several prospective, randomized, controlled studies to determine the best therapy (antiarrhythmic drugs versus ICD) to prolong survival [2-4] have been published. This paper will review initial and substudy data from these trials.

**Antiarrhythmics Versus Implantable Defibrillators (AVID) Study**

The AVID trial [2] studied whether “best” class III antiarrhythmic therapy (empiric amiodarone or guided sotalol) or ICD therapy was superior in reducing intention-to-treat all cause mortality in patients with a history of sustained VT/VF. Secondary objectives included quality of life assessment and cost-effectiveness of the two study arms. Inclusion criteria included the following arrhythmia patients: survivors of a VF arrest: sustained VT/syncope; sustained VT/ejection fraction <40%; and, sustained VT/near syncope. 1016 patients were randomized (509 antiarrhythmic drug; 507 ICD). Only 2.6% of patients received sotalol long-term and 93% of the ICD group had a nonthoracotomy system implanted. The ICD group had a lower incidence of prior atrial fibrillation/flutter and class III CHF patients, a higher use of concomitant beta-blockers (42%) versus only 17% in the drug treated group. Enrollment was discontinued prematurely because of a significant survival advantage in the ICD group. During an 18.2 + 12.2 month follow-up period, death rates were 22.0% + 3.7% in the antiarrhythmic drug versus 15.8 + 3.2% in the ICD group. One, two and three year survival was 89.3%, 81.6% and 75.4% in the ICD group compared to 82.3%, 74.7% and 64.1% in the drug-treated group (P<0.02), resulting in mortality relative risk reductions of 39%, 27% and 31% in ICD patients. ICD benefit appeared to be in reducing arrhythmic death since there was no difference between the two treatments in non-arrhythmic deaths. The majority of the ICD benefit occurred in the first 9 months. Due to the premature termination of the study, survival in the ICD patients was only extended by 2.7 months. In AVID, there were 157 cardiac and 79 arrhythmic deaths. ICD therapy prevented arrhythmic death (p<. 001) but nonarrhythmic death was the same in the two groups [5]. Noncardiac death secondary to pulmonary and renal causes was slightly higher (p=0.053) in the antiarrhythmic drug group [5].

**AVID Substudies**

ICD benefit is highest in patients with an ejection fraction of < 35% and not more effective than amiodarone in
prolonging survival in patients with ejection fractions \( \geq 35\% \) \( \text{pNS} \) \[6,7\]. In the 20-34\% ejection fraction group, ICD therapy was statistically better than antiarrhythmic drug therapy in prolonging survival \( \text{p<. 05} \). In the group with ejection fractions <20\%, ICD benefit trended better than antiarrhythmic drugs but the numbers were too small to meet statistical significance.

In an analysis of the AVID study and registry patients, beta-blocker use was independently associated with improved survival in patients with VF or symptomatic VT who were not treated with specific antiarrhythmic therapies \[8\]. However, beta-blockers did not have a protective effect in patients already receiving amiodarone or an ICD \[8\].

Substudies from the AVID registry have given us useful clinical information. The registry group of patients was similar to the patients randomized into the trial \[9,10\]. Data from the AVID registry population demonstrated similar high mortality rates in all of the entry subgroups including: cardiac arrest survivors of ventricular fibrillation \( (17\%) \), syncopal ventricular tachycardia \( (21.2\%) \), symptomatic ventricular tachycardia \( (19.7\%) \), stable ventricular tachycardia \( (19.7\%) \), ventricular tachycardia/fibrillation with transient/correctable cause \( (17.8\%) \) and unexplained syncope \( (12.3\%) \) \[11\]. The high mortality rate in the "treatable/correctable" groups suggests that their initial event was not secondary to a reversible cause \[12\]. In a substudy of 80 registry patients with unexplained syncope and inducible ventricular tachyarrhythmias, mortality was reduced by treatment with an ICD \( \text{p=. 006} \) \[13\]. Mortality events in this subgroup were not predicted by the induction of ventricular tachycardia induced by programmed stimulation although a low ejection fraction had some trend in predicting mortality \( \text{p=0.06} \).

Epstein et al \[14\] noted that adjusted mortality rates were lower \( \text{p<. 001} \) in patients identified with out of hospital versus in-hospital presentations. Raif et al \[15\] noted that 3-year survival in registry patients trended lower \( \text{p<. 007} \) in patients with stable versus unstable ventricular tachycardia. In the AVID registry, 24.4\% of patients had concomitant atrial fibrillation. After adjustment for differences, a history of atrial fibrillation or flutter remained a significant independent predictor of mortality \( \text{relative risk} =1.20; \text{CI} \ 1.03-1.40, \text{p=0.20} \) \[16\]. Multivariate predictors of worse survival included: older age, severe left ventricular dysfunction, lower systolic blood pressure and a history of congestive heart failure, diabetes, smoking, atrial fibrillation or a preexisting pacemaker \[17\]. Further subanalysis data from AVID suggests that rehospitalization for congestive heart failure is a significant risk factor for subsequent death and may be used as a potential surrogate endpoint for death in the setting of antiarrhythmic interventions \[18\].

**Cardiac Arrest Study Hamburg (CASH)**

The CASH trial \[3\] was initiated to compare the efficacy of empiric antiarrhythmic versus an ICD therapy in survivors of sudden cardiac death unrelated to a myocardial infarction (table I). CASH was a prospective, randomized, multicenter open-label trial. The primary endpoint was to assess the effects of therapy on total mortality with secondary endpoints assessing the recurrence of hemodynamically unstable VT, sudden death and the incidence of drug withdrawal. In ICD patients, ICD discharges occurring during syncope were counted as VF recurrences; those occurring during presyncope and/or documented VT were counted as VT recurrences. Baseline studies and pre- and post-therapy programmed electrical stimulation were performed although these studies were not used as part of the clinical decision making process. Patients were randomized to empiric amiodarone, metoprolol, propafenone or an ICD within 3 months of their cardiac arrest.

In 1992, an interim report of findings from the first 287 patients was published \[19\] after the Data and Safety Monitoring Board recommended premature termination of enrollment in the propafenone limb of the study due to a significantly higher mortality \( (29.5\%) \) and cardiac arrest/sudden death recurrence \( (23\%) \) occurring in this group compared to a 11.5\% total mortality and 0% sudden death rate in patients treated with an ICD. At the time of this analysis, sudden cardiac death was lowest in the ICD arm and total mortality was similar in the ICD, amiodarone and metoprolol arms of the study.

The study was continued with enrollment to the amiodarone \( \text{n=92} \), metoprolol \( \text{n=97} \) and the ICD \( \text{n=99} \) treatment limbs. The mean age was 58 years with a mean ejection fraction of 44-47\%. Over 70\% of the patients had coronary artery disease. The ICD arm decreased total mortality and sudden death by 30\% when compared to the combined metoprolol and amiodarone treatment arms of the study \( \text{p=0.047} \). There was no statistical difference in study endpoints between the amiodarone and metoprolol treatment arms.

**Cash Substudy Results**

A substudy of CASH demonstrated that inducibility by programmed electrical stimulation predicted a group of patients with lower 2-year survival rates compared to noninducible patients \( \text{p<. 001} \) \[20\].

**Canadian Implantable Defibrillator Study (CIDS)**

The CIDS trial \[4,21,22\] was a randomized, multicenter trial comparing the efficacy of ICD therapy \( \text{n=328} \) to
amiodarone (n=331) in 659 patients with prior cardiac arrest or hemodynamically unstable VT. Enrollment criteria included: documented ventricular fibrillation; out-of-hospital cardiac arrest requiring defibrillation; documented sustained VT ≥150 bpm causing presyncope or angina in a patient with an ejection fraction of ≤35% or syncope with documented spontaneous VT ≥10 seconds or induced sustained VT. The primary endpoint compared the above two therapies in reducing arrhythmic death. Secondary endpoints include quality of life assessment and cost efficacy analyses, all caused mortality, nonfatal recurrence of VF, sustained VT causing syncope or cardiac arrest requiring external cardioversion or defibrillation. Patients were followed for three to five years.

In CIDS, all cause mortality was 25% in the ICD versus 30% in the amiodarone group [4]. Thus, the ICD group trended (p=0.072) towards overall improvement in survival by 19.6% compared to amiodarone after three years of follow-up. The results are confounded by the high-crossover rate of this population since many of the ICD patients took concomitant beta-blockers (four times greater than the amiodarone group), sotalol and amiodarone (30%). In addition, 22% of the amiodarone treatment group later had an ICD inserted.

Thus, survival in the amiodarone arm may have been overestimated.

Cids Substudy Results
Sheldon et al [21] reported that having two or more of the following factors identified patients most likely to benefit from an ICD instead of amiodarone: age ≥ 70 years, ejection fraction ≤ 35% and NYHA class III/IV.

A CIDS substudy demonstrated that sotalol decreased mortality in the overall patient population when added to either an ICD or amiodarone [22]. The same substudy reported a statistically higher mortality rate when class I antiarrhythmic agents were added to either amiodarone or an ICD.

Clinical Perspective
The results of the AVID trial support the use of ICD therapy as a front-line therapy to prolong survival in patients at high risk for sudden death. Since overall survival was improved, the ICD may prolong life further through some undefined nonarrhythmic mechanism. Despite their smaller size and other problems in interpreting these trials, the results of CASH and CIDS support the findings of AVID. The results of all three trials, demonstrating ICD superiority in improving survival, are consistent with previous retrospective studies and small prospective trials such as the Dutch Cost-Effectiveness Study [23]. Both CIDS and AVID suggest that patients with sustained VT/VF and depressed ejection fractions less than 35% benefit the most from ICD therapy.

Although the results of these trials are concordant, some differences in the trials exist. AVID and CIDS were powered to determine the overall survival benefit and CASH was not. CIDS had a high treatment crossover rate limiting interpretation of the results of this trial. The annual mortality rate was twice as high in the AVID drug treated group versus CIDS or CASH. Also, it is surprising that in primary prevention trials such as MADIT-I, MUSTT and MADIT-II that an ICD improves survival more than 20% better than in this high risk group of patients who already had a spontaneous sustained ventricular tachyarrhythmias event [24]. In addition, primary prevention trials appear to be more cost-effective than secondary prevention trials when an ICD's benefit is assessed [24,25].

Although amiodarone, sotalol and beta-blockers appear to have a beneficial effect on survival in the above patient population, the lack of placebo controlled studies raise the question of whether these drugs have a beneficial, neutral or adverse effects on survival. If these drugs had an adverse effect on survival, some of the ICD benefit could be from the lack of any proarrhythmic effect. Based on these three trials, estimated 2-year mortality rates of survivors of sustained VT/VF episodes are 40-45% with class I agents, 20-25% with amiodarone or metoprolol and 12-20% in ICD patients. Amiodarone discontinuation rates were only about 4% per year minimizing recurrences secondary to high antiarrhythmic drug withdrawal rates. The results of all of these studies are confounded by the fact that many of the ICD patients took concomitant beta-blockers, sotalol and amiodarone.

Myerburg et al [26] examined the importance of choosing the highest risk yield patient groups for studies and therapies. Although many therapies may be statistically effective, these same therapies may be inefficient and cost ineffective. In AVID, although ICD therapy reduced mortality by 27% (25% in the drug arm versus 18% in the ICD arm), the efficiency of the treatment was only 7%. The absolute reduction in mortality by an ICD in CIDS was only 4.3% and at three years was 11.3% in AVID.

Cost effective analyses suggest that even in the high risk AVID population, an ICD may be five times less cost effective than an ICD in the MADIT population [24,25]. Some of this apparent lack of cost effectiveness is
secondary to the premature termination of the AVID study. The upfront cost of the ICD was included but not amortized over the length of the ICD generator battery life, thus underestimating the cost-benefit of the ICD arm of the study. Obviously, longer ICD generator battery lives and cheaper ICDs will have a positive impact on any ICD cost analysis study.

Based on the above studies, the ACC/AHA recently recommended that ICDs should be prescribed with a class I indication as front-line therapy in patients with hemodynamically destabilizing VT/VF [27]. The above data suggests that ICD therapy is front-line therapy for sustained VT/VF in patients with ejection fractions less than 35% and is a reasonable alternative to sotalol and amiodarone in patients with sustained VT and more preserved ejection fractions. “Reversible causes” of a cardiac arrest remains a class III indication for an ICD based on the premise that AVID registry “treatable/correctable” groups were not truly correctable.

In AVID, patients having ≥ 1 shock in the initial year of follow-up had significant reductions in self-perceived physical functioning and mental well-being [24]. The reduction in quality of life associated with ICD shocks was similar in magnitude to the adverse effects associated with amiodarone. Thus even though an ICD is superior to antiarrhythmic drugs in this setting, 40-70% of ICD patients need the use of a concomitant antiarrhythmic [28], antiarrhythmic drugs such as beta-blockers, sotalol and amiodarone. Pacifico et al [29] demonstrated that sotalol decreased the frequency of ICD shocks/sudden death endpoint (p<.05) when concomitantly used with an ICD and data from the CASCADE trial [5] suggested similar benefit when amiodarone was used in ICD patients, since amiodarone therapy statistically (p=0.32) reduced syncopal ICD shocks when compared to the use of class I agents.

Although ICDs have proven to prolong survival in these secondary prevention trials, studies in the USA have demonstrated that only 34% of patients meeting AVID-like indications receive an ICD [30]. Underprescription of ICD therapy in similar populations is even lower in other countries that have ICD prescribing rates of 20-50% that of the USA.

References


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