TREATMENT OF SUDDEN CARDIAC DEATH SURVIVORS: DRUGS VERSUS DEVICE

Patients who survive an episode of sustained ventricular trachycardia (VT) or out-of-hospital ventricular fibrillation (VF) are known to have a high recurrence rate of 10% to 20% at 2 years. Until the early 1990s, the preferred therapy for this high-risk population remained unclear. A variety of therapies have been proposed, including serial drug testing guided by Holter monitor or electrophysiologic study, empiric amiodarone, direct surgical ablation, electrophysiology-guided amiodarone therapy, and implantable cardioverter defibrillator (ICD). Despite its proven efficacy in preventing recurrent sudden cardiac death (SCD), the ICD was not subjected to a prospective randomized trial against other effective therapies until recently. Many electrophysiologists thought that such a trial would be unethical because it would withhold obviously effective therapy from high-risk patients. But the continued miniaturization and case of implantation of the ICD, coupled with its high price and the widening influence of managed care which resisted this costly therapy, made such trials inevitable. It became clear in the early 1990s that detailed definition of the efficacy and relative cost of the ICD was necessary to justify both its expanding implantation and its cost. Very recently, a few important clinical trials have provided information about the management of patients who survived an episodes of SCD.

The debate as to whether anti-arrhythmic therapy was best guided by Holter monitoring or invasive electrophysiologic study (EPS) led to the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial. In this trial, 486 patients who had been resuscitated from sudden cardiac death or electrocardiographically documented VT or unmonitored syncope, were randomized Holter-versus EPS-guided treatment, with imipramin, mexiletine, procainamide, quinidine, sotalol, pirmenol or propafenone. In the Holter limb, drug efficacy was defined as 100% suppression of VT runs> IS beats, 80% suppression of pairs, and 70% suppression of PVCs. Electrophysiologic study efficacy was defined as suppression of the VT inducibility (no VT induced > IS beats in duration). The primary endpoint was recurrence of arrhythmia in a patient receiving a drug predicted to be effective by serial testing. Secondary endpoints included death from any cause, death from cardiac cause, and death from arrhythmia. Of 242 electrophysiologic study limb patients, 108 (45%) achieved efficacy, whereas 187 (77%) of 244 Holter monitoring patients achieved efficacy. There was no statistical difference (P = 0.69) between the two techniques in predicting arrhythmia recurrence (58% recurrence rate at 2 years). Compared with other drugs tested, sotalol had a statistically lower recurrence rate of arrhythmia (P < 0.001), death from any cause (P < 0.004), death from cardiac cause (P < 0.02), and death from arrhythmia (P = 0.04).

The main finding of ESVEM was that Holter monitoring was equally predictive of arrhythmia recurrence, when compared with serial electrophysiologic testing. In the author's perspective, the high 2-year arrhythmia recurrence rates utilizing both techniques, suggest that serial testing, using either method has limited value in this patient population. The higher efficacy of sotalol may be secondary to a combination of its beta-blocker and Class III antiarrhythmic effects. Recent data from ESVEM demonstrated that arrhythmia recurrence of Class I patients plus a beta-blocker was similar to sotalol, and both were better that Class I agents without a beta-blocker. Although sotalol appeared more effective than the other drugs in this study, the lack of a placebo group limits this interpretation. The results of ESVEM are limited by the fact that patients were required to have both frequent PVCs and inducible VT. Previous studies have shown that these findings are relevant to < 35% of the sustained VTNF population.
The Cardiac Arrest Study in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE)13 evaluated antiarrhythmia drug treatment of 228 survivors of out-of-hospital VF not associated with a Q wave MI. Patients qualified if they had ≥ 10 PVCs/h on Holter, and had inducible sustained VT or VF. Patients were randomized to empiric treatment with amiodarone (n = 113) or electrophysiologic study-guided treatment (n = 115), using conventional antiarrhythmic therapy (Class I antiarrhythmics). The primary endpoint was cardiac survival. The mean EF of randomized patients was 35%;: 10%. Of note, 46% of patients received ICDs. Patients treated with amiodarone had better "cardiac survival" (defined as cardiac mortality, syncope/ICS shock, resuscitated cardiac arrest) than the conventional treated group (P = 0.007). In addition, the amiodarone patients had greater survival free of sustained arrhythmias (P = 0.00). There were no significant differences in outcomes between conventionally treated patients whose inducible arrhythmias were or were not suppressed. Amiodarone was associated with a \% 0% 3-year pulmonary toxicity rate. Although amiodarone appeared superior to guided therapy with conventional agents, only 4% of the amiodarone groups had no cardiac death or sustained arrhythmia by 6-year followup. Therefore, ICD therapy may be a better alternative to either of the pharmacologic approaches. Given the high recurrence rate in the empiric amiodarone group, serial guided therapy, using amiodarone may provide a more predictive approach when drugs are used without ICDs.

To compare the efficacy of antiarrhythmia therapy against an ICD in survivors of sudden cardiac death unrelated to MI, the Cardiac Arrest Study, Hamburg (CASH) trial4 was initiated. Total mortality was the primary endpoint, with secondary endpoints of hemodynamically unstable VT and incidence of drug withdrawal. Patients were randomized to empiric amiodarone, metoprolol, propafenone, or an ICD within 3 months of their cardiac arrest. Published data from the first 287 patients have shown that the total mortality, although lowest in the ICD section, was similar (about 14%) in the ICD, amiodarone, and metoprolol sections of the study. When compared with the ICD, the propafenone section was associated with significantly higher incidence of total mortality and cardiac arrest recurrence. For that reason the safety monitoring board recommended the deletion of the propafenone treatment limb, and this study is now being continued with amiodarone, metoprolol, and ICD limbs. Enrollment in this trial has recently been completed (n = 349), and findings suggest that the final results are consistent with the interim analyses, except that total mortality was statistically lower (P = 0.047) in the ICD group, compared with the combined metoprolol plus amiodarone-treated groups. The results of CASH suggest that Class I therapy is not as effective as ICD therapy in survivors of cardiac arrest. ICD therapy appears to have a better sudden death and overall survival compared with the antiarrhythmic drug-treated limbs of the study. The potential benefit of a beta-blocker in this study is consistent with beneficial effects noted in other retrospective studies15,16.

The primary objective of the Antiarrhythmics versus Implantable Defibrillator (AVID) Trial17,18 was to determine whether "best" antiarrhythmic therapy (empiric amiodarone or guided sotalol) or ICD therapy is superior in reducing total mortality in patients with a history of sustained VT/VF. Secondary objectives included quality-of-life assessment and costeffectiveness of the two study sections. Of the 1,016 patients (22.2% of the registered group) who were randomized (50% to CD and 50% to antiarrhythmic therapy). Enrollment was stopped prematurely (April 7, 1977) because of a significant survival advantage in the ICD group. In the ICD group, 89.3%, 81.6%, and 75.4% survived 1, 2, and 3 years, respectively, compared with 82.3%, 74.7%, and 64.1% in the drug group (P < 0.02). Thus, 1-, 2-, and 3-year mortality was reduced by 39%, 27%, and 3%, respectively, with the majority of ICD benefits occurring in the first 9 months. The ICD only extended survival by 2.8 months, although the premature termination of this trial may cause some underestimation of the ICD benefit, and have detrimental effects in any cost-benefit analysis. ICD benefit was most prominent in patients with EF < 35%, with no statistical benefit of the ICD noted in patients with EF > 35%. Patient characteristics were similar in the two treatment groups, except that the ICD group had a lower incidence of prior atrial fibrillation/flutter and Class III CHF patients, and a higher number of patients discharged on a beta-blocker. However, multivariate analysis showed that the beneficial effects of ICD therapy persisted after adjustment of other factors19,20.

The Canadian Implantable Defibrillator Study (CIDS)21 was randomized, multicenter trial comparing the efficacy of ICD therapy (n = 328) to amiodarone.
The Cardiac Arrest Study in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE) evaluated antiarrhythmia drug treatment of 228 survivors of out-of-hospital VF not associated with a Q wave MI. Patients qualified if they had >10 PVCs/h on Holter, and had inducible sustained VT or VE. Patients were randomized to empiric treatment with amiodarone (n = 113) or electrophysiologic study-guided treatment (n = 115), using conventional antiarrhythmic therapy (Class I antiarrhythmics). The primary endpoint was cardiac survival. The mean EF of randomized patients was 35%;: 1: 10%. Of note, 46% of patients received ICDs. Patients treated with amiodarone had better "cardiac survival" (defined as cardiac mortality, syncope/ICS shock, resuscitated cardiac arrest) than the conventional treated group (P = 0.007). In addition, the amiodarone patients had greater survival tree of sustained arrhythmias (P = 0.001). There were no significant differences in outcomes between conventionally treated patients whose inducible arrhythmias were or were not suppressed. Amiodarone was associated with a 10% 3-year pulmonary toxicity rate. Although amiodarone appeared superior to guided therapy with conventional agents, only 41% of the amiodarone groups had no cardiac death or sustained arrhythmia by 6-year followup. Therefore, ICD therapy may be a better alternative to either of the pharmacologic approaches. Given the high recurrence rate in the empiric amiodarone group, serial guided therapy, using amiodarone may provide a more predictive approach when drugs are used without ICDs.

To compare the efficacy of antiarrhythmia therapy against an ICD in survivors of sudden cardiac death unrelated to MI, the Cardiac Arrest Study, Hamburg (CASH) trial was initiated. Total mortality was the primary endpoint, with secondary endpoints of hemodynamically unstable VT and incidence of drug withdrawal. Patients were randomized to empiric amiodarone, metoprolol, propafenone, or an ICD within 3 months of their cardiac arrest. Published data from the first 287 patients have shown that the total mortality, although lowest in the ICD section, was similar (about 14%) in the ICD, amiodarone, and metoprolol sections of the study. When compared with the ICD, the propafenone section was associated with significantly higher incidence of total mortality and cardiac arrest recurrence. For that reason the safety monitoring board recommended the deletion of the propafenone treatment limb, and this study is now being continued with amiodarone, metoprolol, and ICD limbs. Enrollment in this trial has recently been completed (n = 349), and findings suggest that the final results are consistent with the interim analyses, except that total mortality was statistically lower (P = 0.047) in the ICD group, compared with the combined metoprolol plus amiodarone-treated groups. The results of CASH suggest that Class I therapy is not as effective as ICD therapy in survivors of cardiac arrest. ICD therapy appears to have a better sudden death and overall survival compared with the antiarrhythmic drug-treated limbs of the study. The potential benefit of a beta-blocker in this study is consistent with beneficial effects noted in other retrospective studies.5,6

The primary objective of the Antiarrhythmics versus Implantable Defibrillator (AVID) trial was to determine whether "best" antiarrhythmic therapy (empiric amiodarone or guided sotalol) or ICD therapy is superior in reducing total mortality in patients with a history of sustained VT/VF. Secondary objectives included quality-of-life assessment and cost-effectiveness of the two study sections. Of the 1,016 patients (22.2% of the registered group) who were randomized (50% to CD and 50% to antiarrhythmic section), only 2.8% of the drug section was discharged on sotalol; the remaining were treated with amiodarone. Enrollment was stopped prematurely (April 7, 1977) because of a significant survival advantage in the ICD group. In the ICD group, 89.3%, 81.6%, and 75.4% survived 1, 2, and 3 years, respectively, compared with 82.3%, 74.7%, and 64.1% in the drug group (P < 0.02). Thus, 1-, 2-, and 3-year mortality was reduced by 39%, 27%, and 31%, respectively, with the majority of ICD benefits occurring in the first 9 months. The ICD only extended survival by 2.8 months, although the premature termination of this trial may cause some underestimation of the ICD benefit, and have detrimental effects in any cost-benefit analysis. ICD benefit was most prominent in patients with EF < 35%, with no statistical benefit of the ICD noted in patients with EF > 35%. Patient characteristics were similar in the two treatment groups, except that the ICD group had a lower incidence of prior atrial fibrillation/flutter and Class III CHF patients, and a higher number of patients discharged on a beta-blocker. However, multivariate analysis showed that the beneficial effects of ICD therapy persisted after adjustment of other factors.9,20

The Canadian Implantable Defibrillator Study (CIDS) was randomized, multicenter trial comparing the efficacy of ICD therapy (n = 328) to amiodarone.
(n = 331) in 659 patients with prior cardiac arrest or hemodynamically unstable VT. The enrollment criteria included documented VF, out-of-hospital cardiac arrest requiring defibrillation, documented sustained VT ~ 150 beats/min causing presyncope or angina in a patient with an EF::;= 35%, or syncope with documented spontaneous VT ~ 10 seconds or induced sustained VT. The primary endpoint was to compare these two therapies in reducing arrhythmic death. Secondary endpoints included quality-of-life assessment and cost efficacy analyses, all-cause mortality, nonfatal recurrence of VF, sustained VT causing syncope, or cardiac arrest requiring external cardioversion or defibrillation. Preliminary results suggest that the ICD trended toward overall improvement in survival (P = 0.07), producing a 20% reduction in mortality compared with amiodarone. Many of the ICD patients took beta-blockers, sotalol, and had amiodarone added.

The results of CASH, AVID and CIDS support using the ICD as first-line therapy to prolong total survival or sudden death survival in patients at high-risk for sudden death. Future cost efficacy and quality-of-life analysis will help clinicians in prescribing the most effective therapy. The results from these studies have helped clarify the ICD versus antiarrhythmic drug controversy. Whether amiodarone would have compared better with the ICD if serial electrophysiologic testing and other predictors of outcome had been used, is not known at this time.

Mohammed A. Habbab, FACP, FACC
Division of Electrophysiology and Pacing
Department of Adult Cardiology
Prince Sultan Cardiac Center
P.O. Box 7897 (ISO)
Riyadh 11159, Saudi Arabia

References


