Treatment and Prevention of Sudden Cardiac Death

Effect of Recent Clinical Trials

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Tremendous strides have been made in recent years in the treatment and prevention of sudden cardiac death. Large scale trials have now established several interventions that may improve survival in patients susceptible to sudden cardiac death. In patients who have had a sustained ventricular tachyarrhythmia, the current therapy of choice is an implantable cardioverter defibrillator. For prophylaxis of sudden cardiac death in patients without a previous event, several approaches should be considered. β-Adrenergic blocking agents are an effective pharmacologic therapy in patients following myocardial infarction, and their efficacy has also most recently been demonstrated in patients with congestive heart failure. There is no Vaughan Williams class I or III antiarrhythmic drug that has demonstrated efficacy as a prophylactic agent to reduce mortality in these populations, with the possible exception of amiodarone. The best therapeutic approach for prophylactic therapy to prevent sudden cardiac death appears to be the implantable cardioverter defibrillator; however, its use can be justified only in patients at high risk for developing sudden cardiac death. Further work is needed to identify the high risk populations in which this therapy is warranted.

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The problem of sudden cardiac death has commanded the attention of the medical community. In its classic depiction, a patient who has been clinically stable dies unexpectedly either during sleep or within a short time after the onset of terminal symptoms. Frequently, the cause of such an event is an arrhythmia; timely treatment may prevent death. Because adequate treatment is rarely readily available, the survival rate from a sudden cardiac death episode is dismal. Thus, tremendous efforts have been expended along 2 fronts. First, effective treatment strategies need to be identified that prevent episodes in patients who are known to be at high risk for sudden cardiac death (such as those with previously documented episodes). Second, it would be ideal to identify the high-risk populations who should be treated before an episode of sudden cardiac death occurs.

Although many early therapeutic studies have been disappointing, recent clinical studies have charted a favorable course in this field. This review will summarize the advances made in the therapeutic approach to these patients and the identification of appropriate patients in whom to consider these approaches.

Whereas many of the recent large-scale studies have been criticized for various pitfalls, when viewed as pieces of a larger puzzle, they provide a perceptibly clearer image of how to deal with the problem than has been available in the past. This review will present a coherent summary of the lessons learned from these trials. Because most of the patients at risk have coronary artery disease, most studies have focused on this subgroup. Thus, the best information available is on the treatment and prevention of sudden cardiac death in patients with coronary artery disease.

BACKGROUND

About 400,000 episodes of sudden cardiac death occur per year in the United States. Less than 20% of these are due to acute transmural myocardial infarc-
Cobb et al reported on the survival of sudden cardiac death. Although myocardial ischemia may be an important precipitant for sudden cardiac death, a substantial fraction of cases likely result from reversible arrhythmia. Several studies have addressed the precision of the diagnosis of sudden cardiac death. Despite expert classification, the mechanism of sudden cardiac death is not always arrhythmia. Pratt et al evaluated autopsy findings and the results of interrogating implantable defibrillators in 17 patients classified clinically as having had sudden cardiac death. Seven patients had autopsyped nonarrhythmic causes of sudden cardiac death, and only 7 had any evidence of a defibrillator discharge (indicating a detected tachycardia) near the time of death. Thus, the classification “sudden cardiac death” encompasses diverse causes, including arrhythmias. For this reason, recent studies have focused on the end point of total mortality. Where possible, I will also highlight total mortality.

Because no placebo-controlled trials have been done of the treatment of patients with a history of sudden cardiac death, the literature has to be examined carefully to identify appropriate benchmarks against which to measure the success of interventions designed to prevent recurrent sudden cardiac death. Cobb et al reported on the survival of patients who were successfully resuscitated from out-of-hospital ventricular fibrillation. These patients received either no therapy or empiric medical therapy. The authors noted a 1-year mortality of 32% and a 2-year mortality of 47% in patients who had no evidence of myocardial necrosis associated with their episode of ventricular fibrillation; presumably in these patients, the out-of-hospital ventricular fibrillation was primarily arrhythmic. The mortality in this subgroup of patients was similar to that noted in the larger group of patients who did not have an acute transmural MI on electrocardiography. Of note, at least 60% of these patients had been prescribed an antiarrhythmic medication. This study was done when clinical practice differed from current standards; differences in the use of cardiac medications, such as β-adrenergic blocking agents, may affect survival. In a smaller, more recent study, 54 patients with clinical sustained ventricular tachyarrhythmias and inducible ventricular tachycardia during electrophysiologic studies were treated with only β-adrenergic blocking agents. The rate of either recurrence or sudden death was approximately 42% at 1 year and 46% at 2 years. It is, therefore, reasonable to estimate the 1-year mortality as 30% and to use this as a benchmark by which strategies to prevent recurrent sudden cardiac death can be measured.

TREATMENT OF LIFE-THREATENING VENTRICULAR ARRHYTHMIAS

Given the high recurrence rate following an episode of sudden cardiac death, treatment has been considered mandatory. One approach that has been considered in patients with severe coronary artery disease who have had an episode of ventricular fibrillation is revascularization. Myocardial ischemia may serve as the main precipitant of ventricular fibrillation or may be a contributing factor. Because most patients who have had an episode of sudden cardiac death have substantial coronary artery disease, it is critically important to evaluate the clinical scenario to determine whether the primary cause of sudden cardiac death was myocardial ischemia. In a retrospective study that described the outcomes of 300 patients with coronary artery disease who had presented with ventricular fibrillation and were treated with an implantable cardioverter defibrillator (ICD), the incidence of appropriate ICD shocks was the same in the group who had undergone concomitant coronary artery bypass grafting as in the group who had not. This suggests that in many patients with ventricular fibrillation, a distinct arrhythmogenic substrate exists, independent of myocardial ischemia, that needs to be addressed therapeutically. The main treatment options for ventricular arrhythmias include empiric medical therapy, Holter-guided medical therapy, electrophysiologic testing–guided medical therapy, ICD, or catheter ablation. Despite its usefulness in many patients, including some with ventricular tachycardia, catheter ablation has not been assessed as a therapeutic strategy to prevent recurrent sudden cardiac death due to lethal ventricular arrhythmias.

Because of the high recurrence rate, empiric medical therapy has, in general, been abandoned as an approach to patients with aborted sudden cardiac death. The one agent that has been considered to have some promise as empiric therapy is amiodarone (Table). Herre et al evaluated 427 patients treated with amiodarone for either sustained ventricular tachycardia or an episode of resuscitated sudden cardiac death not associated with acute MI. They noted a 1-year mortality of about 20% and a 2-year mortality of about 35%. Although this may represent a substantial improvement over historic control groups, the high recurrence rate of arrhythmia—19% at 1 year and 26% at 2 years—suggests that there may be an opportunity for other therapeutic approaches to enhance survival. This concept is supported by the Antiarrhythmics Versus Implantable Defibrillators trial in which 1016 patients with hemodynamically significant ventricular tachycardia or ventricular fibrillation were randomly assigned to receive either an ICD or antiarrhythmic drug therapy. Most of the group treated with antiarrhythmic drugs received empiric amiodarone therapy. The 1- and 2-year mortality rates in this group were 17.7% and 25.3%, respectively. The ICD-treated group had a significantly better survival rate. Thus, therapeutic approaches are available, in addition to empiric amiodarone therapy, that can be implemented to improve survival.

Regarding the use of other antiarrhythmic drugs for the treatment of ventricular tachyarrhythmias, there are 2 major issues. First, the strategic choice of guiding antiarrhythmic drug therapy by either noninvasive monitoring or invasive electrophysiologic testing has been the subject of considerable debate. The noninvasive monitoring approach includes documentation that the use of an antiarrhythmic...
drug suppresses a substantial portion of the patient's ventricular ectopy. This has sometimes been supplemented by the documentation of efficacy with the results of a stress test. The invasive approach includes documentation that treatment with an antiarrhythmic drug suppresses the inducibility of sustained ventricular tachycardia with programmed ventricular stimulation. The other important issue affecting the use of antiarrhythmic drugs is the end point considered to identify a drug that would be considered effective.

The largest study to directly compare the invasive and noninvasive approaches was the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM). In this study, 486 patients were randomly assigned to receive therapy based on one of the approaches, although each patient was eligible for treatment guided by either approach. In the invasive approach, only 13% of all drug trials resulted in an efficacy rating, and in the noninvasive approach, only 38% of all drug trials resulted in an efficacy rating, suggesting that it is difficult to find an “efficacious” antiarrhythmic drug by either approach. The study revealed similar outcomes in the 2 groups. Further evaluation of the actual outcomes in each of the groups indicates that, using the ESVEM method, neither approach is acceptable; 1-year recurrence rates were 32% to 41% in the 2 groups. Even the use of sotalol hydrochloride, which was identified as the most efficacious of the drugs tested, was associated with a 1-year recurrence rate of 20%. As the shortcomings of the ESVEM have been hotly debated, the investigators reanalyzed their data to adjust for some of these critiques, with no significant change in the findings. Given the high recurrence rate using both strategies, it is questionable whether either strategy provides adequate control of life-threatening ventricular arrhythmias. The only other randomized study to compare these 2 approaches was a small study that demonstrated that electrophysiologic testing–guided therapy is superior to the noninvasive strategy.

Although neither Holter-guided nor electrophysiologic testing–guided antiarrhythmic drug therapy may yield optimal results, data suggest that the latter may result in better outcomes under certain conditions (Table). Specifically, focusing on the results of using an antiarrhythmic drug that has been shown by serial electrophysiologic testing to be effective shows that mortality seems to be significantly reduced. This may be even more pronounced with the use of sotalol. The recurrence rate remains significant, however (Table). In addition, another notable drawback to this approach is that a drug that prevents the inducibility of ventricular tachycardia during electrophysiologic testing can be identified in only a fraction of eligible patients.

An approach not tested in the ESVEM study is amiodarone therapy guided by electrophysiologic testing. In a study of 100 patients, Horowitz et al found no recurrences in 20 patients in whom the inducibility of ventricular tachycardia was suppressed; however, sudden death has been reported in patients who have had no inducible ventricular tachycardia while taking amiodarone. Despite promising results with the use of amiodarone, the value of this strategy is likely to be limited because ventricular tachycardia is rendered noninducible with amiodarone in only 10% to 20% of patients, and large-scale studies have demonstrated a rate of withdrawal from active treatment of 30% to 40% within 5 years.

Thus, the overall clinical experience with antiarrhythmic drug therapy for life-threatening ventricular arrhythmias has been disappointing for several possible reasons. First, patients taking these medications are plagued by proarrhythmia—the development of new, potentially life-threatening arrhythmias or aggravation of the underlying arrhythmia. Whereas this occurs in few pa-
patients treated with these medications, the patients at highest risk for proarrhythmia are precisely those who are most likely to need treatment of life-threatening ventricular arrhythmias. Another major drawback of medications is that they represent a fixed therapy that must be effective under a wide variety of conditions, such as changes in the underlying substrate, in the autonomic tone, and in coronary perfusion or ischemia. The techniques available to evaluate the efficacy of medications cannot assess all of the effects of these conditions. Finally, the medications may intrinsically have low efficacy for the treatment of life-threatening ventricular rhythms. These problems may be difficult to overcome.

The ICD has emerged as a promising alternative to antiarrhythmic drug therapy. Although it is not designed to prevent recurrences, it has been highly effective at terminating ventricular tachycardia or fibrillation. Observational studies have demonstrated excellent survival in patients with previous sudden cardiac death or ventricular tachycardia treated with an ICD; the 1-year mortality for 1478 patients treated with an epicardial ICD system was 12.2%, and for 1356 patients treated with the less-invasive endocardial system (current preferred approach), the 1-year mortality was 6.9%. Becker et al used a case-control study design to compare the outcomes of patients with coronary artery disease and sustained ventricular tachycardia or fibrillation treated with either an ICD (n = 50) or sotalol (n = 50). All patients treated with sotalol had inducible sustained ventricular tachyarrhythmias at baseline electrophysiologic testing, but these were not inducible during treatment. Survival in the ICD group was significantly better (Table). Wever et al randomly assigned 60 survivors of cardiac arrest to either early ICD implantation or electrophysiologic testing–guided antiarrhythmic drug therapy. Because of the inefficacy of antiarrhythmic drug therapy, only a few patients were treated with this approach, and those who were had a substantial mortality or recurrence rate of 67%. More than half the patients assigned to the antiarrhythmic drug therapy group were ultimately treated with an ICD. In addition to the better outcomes in the ICD group, this group underwent fewer invasive procedures, fewer therapy changes, and had fewer days in a hospital. Thus, the use of ICD was recommended as first-choice therapy for survivors of sudden cardiac death.

The lack of large-scale randomized clinical trials comparing the efficacy of ICD therapy with antiarrhythmic drug therapy prompted the Antiarrhythmics Versus Implantable Defibrillators study. In this study, patients with hemodynamically significant ventricular tachycardia or ventricular fibrillation were randomly assigned to either the use of ICD or antiarrhythmic drug therapy. The 2 drugs studied were amiodarone and sotalol. In the antiarrhythmic drug therapy group, however, 356 of 509 patients were considered to have a contraindication to the use of sotalol and were therefore treated empirically with amiodarone. Of the remaining 153 patients, 137 received empiric amiodarone, and only 13 received either Holter- or electrophysiologic testing–guided sotalol therapy. Thus, 97% of the antiarrhythmic drug therapy group was treated with amiodarone. This trial can, therefore, be considered a trial of empiric amiodarone therapy vs ICD therapy. The study demonstrated a 38% reduction in total mortality at 1 year and 25% reductions in years 2 and 3 in the ICD group. The 1- and 2-year mortality rates in the ICD group were 10.7% and 18.4%, respectively. Preliminary results of the Cardiac Arrest Study Hamburg and the Canadian Implantable Defibrillator Study were recently presented. Both studies found significantly improved survival in the ICD group. Thus, these trials have established the ICD as the premier therapy for patients with life-threatening ventricular arrhythmias. Furthermore, ICD therapy should now be the benchmark by which to measure any other therapeutic strategy.

As the Antiarrhythmics Versus Implantable Defibrillators study compared ICD therapy with that of empiric amiodarone, it is not possible to conclude that ICD therapy is better than amiodarone therapy when efficacy is established by electrophysiologic testing. However, the low rate of efficacy, the need for prolonged hospitalization for drug loading, and the high rate of discontinuation remain significant problems that will limit the widespread applicability of amiodarone in these patients.

S U D D E N C A R D I A C D E A T H P R O P H Y L A X I S

Having established the therapeutic options in the group at highest risk for sudden cardiac death, it is now reasonable to consider whether there are viable strategies to prevent sudden cardiac death in other patient groups. Given the poor survival of patients with out-of-hospital sudden cardiac death, it is critically important to identify strategies that can be implemented to prevent the initial episode of sudden death. The groups that have been most extensively studied are patients who have had MIs and those with congestive heart failure. Myriad studies have established that various clinical factors can identify subgroups in these populations who are at particularly high risk for sudden cardiac death. Two of these factors have been left ventricular dysfunction and frequent ventricular ectopic activity. Despite the identification of these factors, therapeutic trials have, in general, been disappointing. Interventions designed to have salutary effects may, in fact, result in excess mortality. The possible therapeutic options are similar to those discussed previously and include empiric medical therapy, Holter-guided medical therapy, electrophysiologic testing–guided medical therapy, and the ICD.

When considering medical therapy for the prevention of sudden cardiac death, the initial agent of choice should be a β-adrenergic blocking agent. In a meta-analysis including more than 53,000 patients, these agents were shown to be associated with a significant improvement in survival in patients following an MI (relative risk reduction, 19%; 95% confidence interval [CI], 13%-25%). β-Adrenergic
blocking agents are also emerging as important agents in patients with congestive heart failure; in this group, carvedilol—a new nonselective β-adrenergic blocking agent and α1-receptor blocker, has been shown to reduce mortality. Given the demonstrated efficacy of β-adrenergic blocking agents, it is important to consider whether treatment with β-adrenergic blocking agents is enough for the prophylaxis of sudden cardiac death. No data are available to answer this question adequately, but some data are available on the efficacy of β-adrenergic blocking agents in patients with ventricular tachycardia. Steinbeck et al randomly assigned 115 patients with ventricular tachycardia to receive β-adrenergic blocking agent therapy or electrophysiologic testing–guided therapy. Although the overall results for the 2 groups were similar, the 1-year recurrence or sudden death rate in the group that received β-adrenergic blocking agents exceeded 40%. Furthermore, this was significantly greater than the recurrence or sudden death rate (10% at 1 year) noted in patients treated with an arrhythmic drug proved to be efficacious by electrophysiologic testing. This suggests that there is considerable room for improvement in the treatment of serious ventricular arrhythmias beyond what can be achieved with β-adrenergic blocking agents. In addition, in both the European Myocardial Infarct Amiodarone Trial and Canadian Amiodarone Myocardial Infarction Arrhythmic Trial, there appeared to be an interaction between the use of β-adrenergic blocking agents and amiodarone; amiodarone therapy appeared to have a greater effect on reducing mortality in those patients taking β-adrenergic blocking agents. This, again, supports the concept that therapeutic options can be added to β-adrenergic blocking agents to reduce mortality due to tachyarrhythmias. Given the important role of β-adrenergic blocking agents in reducing mortality, it is important to consider how the choice of additional therapies affects the use of β-adrenergic blocking agents. For example, in the Antiarrhythmics Versus Implantable Defibrillators trial, more patients in the ICD group than in the antiarrhythmic drug therapy group were taking β-adrenergic blocking agents.

Because of the strong evidence that frequent ventricular ectopy is associated with an increased risk of sudden cardiac death, the use of antiarrhythmic drug therapy to suppress ventricular ectopy in patients with a history of MI was widespread. The Cardiac Arrhythmia Suppression Trial definitively demonstrated that not only is this strategy ineffective it is also dangerous. Patients treated with antiarrhythmic drugs that were effective in suppressing their ventricular ectopy had an increased mortality compared with patients given placebo (relative risk, 2.5). Combined results of multiple studies of Vaughan Williams class I antiarrhythmic agents used following MI have confirmed this. The Survival With Oral D-Sotalol trial evaluating the class III antiarrhythmic drug, sotalol, had similar findings. The only agent that has demonstrated some promise as a prophylactic agent following MI is amiodarone. In a compilation of several studies, there was a survival benefit, albeit with wide confidence intervals (relative risk reduction, 29%; 95% CI, 3%-49%). The recent European Myocardial Infarct Amiodarone Trial and Canadian Amiodarone Myocardial Infarction Arrhythmic Trial have shed further light on this question. Both studies evaluated the prophylactic use of amiodarone following an MI, the former using an ejection fraction criterion for entry and the latter using a ventricular ectopy criterion for entry. In both trials, despite a reduction in the combined end points of resuscitated cardiac arrest and arrhythmia mortality, no differences in total mortality were noted between the group receiving placebo and the one receiving amiodarone.

A meta-analysis of all trials of amiodarone therapy was recently performed that included 5101 patients who had had an MI and 1452 patients with congestive heart failure. With one type of analytic approach, there was a 13% reduction in the relative risk for total mortality (95% CI, 1%-22%) in favor of amiodarone therapy. This was due to a 29% reduction in the relative risk for arrhythmic or sudden death (95% CI, 15%-41%) in favor of amiodarone. Using a more conservative analytic approach, however, only a trend remained for a reduction in total mortality (15% reduction; P = .08). Furthermore, when the patients who had had an MI and those who had congestive heart failure were evaluated in subgroup analyses, no significant reduction in total mortality was noted in the subgroup who had had an MI. In this subgroup, there was a 35% reduction in the relative risk for arrhythmic or sudden death (95% CI, 16%-50% in favor of amiodarone). In the subgroup with congestive heart failure, there was a 17% reduction in total mortality (95% CI, 1%-30%). Thus, amiodarone use may be associated with a mild protective effect, but the magnitude of its effect is unclear. Clearly, however, its use does not increase mortality—an important consideration in the use of antiarrhythmic drugs in these patients.

A large-scale trial of antiarrhythmic drug therapy guided by electrophysiologic test results in patients who have not previously had ventricular tachycardia or fibrillation has not yet been completed. Early studies have suggested that the inducibility of ventricular tachycardia in patients without previous sustained ventricular tachycardia or syncope identifies a high-risk population for the development of ventricular tachycardia or sudden cardiac death. Furthermore, antiarrhythmic therapy guided by the results of electrophysiologic testing has been suggested to be beneficial. Data to support this therapeutic approach are insufficient, however.

Several factors have propelled the ICD to the forefront of prophylactic therapy to prevent sudden cardiac death. These include the technological achievements allowing the ICD to be implanted transvenously in the pectoral area and the clinical success of the device in the higher risk patients with a previous episode of a life-threatening ventricular arrhythmia. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) was the first large-scale randomized trial to evaluate the...
Bypass Graft Patch study in which measured. Another recently com-
mark by which other options may be established the ICD as a bench-
mately 96% vs 76%). Although there may be mul-
tiered ICD therapy may reduce the incidence of ischemia, which may be an important trigger for ventricular tachyarrhythmias in these patients; thus, the benefit of ICD therapy may be delayed until ischemia resur-
facing. Although there may be multiple explanations for the divergent findings of these 2 studies, the most appropriate conclusion is that the Coronary Artery Bypass Graft Patch trial did not select a population at high enough risk to demonstrate a benefit of intervention with an ICD. Several other large-scale ICD trials are in progress that should shed further light on which populations may benefit from this therapy.

The MADIT investigators recently reported the cost-effective-
ness of the ICD in that trial. The cost of the defibrillator was about $20,000, with a total cost for the initial hos-
pital stay in the ICD group of about $45,000. This compared with a total cost of about $19,000 in the conven-
tional therapy group. The incremental cost-effectiveness ratio for the ICD group was $27,000 per life-year saved, which is similar to the cost-
effectiveness of ICD therapy reported in other studies.

The Figure demonstrates the current role of the ICD. There is clearly a continuum of patients in whom the probability of sudden cardiac death steadily increases. When this probability crosses a certain threshold, the risk-benefit ratio and cost-effectiveness of ICD implantation become favorable. The goal for the next few years is to better define the appropriate level of risk within the shaded area that justifies implanting an ICD. This will be determined by the relative risks, benefits, and costs of implanting this device.

CONCLUSIONS

For many years, there has been much frustration among physi-
cians and investigators involved in the treatment and prevention of sud-
ner cardiac death. Tremendous strides have been made in the past several years in this area. Large-
scale trials have now established several interventions that may im-
prove survival in patients susceptible to sudden cardiac death. In pa-
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gestive heart failure and that, when possible, they should be used. No class I or III antiarrhythmic drug has demonstrated efficacy as a prophy-
lactic agent to reduce mortality in these populations, with the pos-
sible exception of amiodarone. The best therapeutic approach for pro-
phylactic therapy against sudden cardiac death appears to be the ICD; how-
ever, its use can be justified only in patients at high risk for this event. New strategies and approaches may be developed to target drug therapy in specific populations using either a current or newly developed antiarrhythmic drug. Given the effi-
cacy of the ICD and the low mor-
bidity and mortality rate from implantation, any new approach to treat high-risk populations should be compared with the ICD. Finally, fur-
ther work is needed to identify the high-risk patients in whom therapy is warranted.
REFERENCES


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