Current Perspectives

Interpretation of Outcomes of Antiarrhythmic Clinical Trials
Design Features and Population Impact

Robert J. Myerburg, MD; Raul Mitrani, MD; Alberto Interian, Jr, MD; Agustin Castellanos, MD

The results of the Cardiac Arrhythmia Suppression Trials (CAST and CAST II) were a watershed in attitudes about management of cardiac arrhythmias. On the basis of the then-prevailing assumption that premature ventricular contractions (PVCs) in the presence of recent myocardial infarction identified a risk for life-threatening arrhythmias and that they also served as the trigger for fatal arrhythmias, it was logical to determine whether suppression of ambient arrhythmias would protect against fatal events. Despite the outcomes of these trials, ambient arrhythmias are still viewed as a marker of risk (perhaps somewhat lower than previously thought) and as pathophysiological triggers under proper conditions. However, the concept that suppression of asymptomatic PVCs is an appropriate preventive strategy has fallen under the weight of evidence from those studies. In addition, new concepts of proarrhythmia emerged from CAST and other sources of information. After CAST, a variety of trials testing therapy with other drugs and with implantable devices were implemented, some of which are now completed. The various trials differ in regard to therapeutic strategies, designs, and patient populations. With the flow of new information that has been forthcoming and is anticipated to continue during the next few years, it is important to keep the strengths and limitations of clinical trial designs in perspective and to consider the extent to which the results of any one trial or group of trials can be generalized.

This review is intended to analyze general features of trial design that influence their interpretation, application, and clinical impact. It is not intended as a critique of individual trials. The factors discussed include (1) specific outcomes measures; (2) the type of controls used; (3) intention-to-treat versus on-therapy analysis; (4) comparison of therapeutic efficacy, efficiency, and equilibrium; (5) significant negative outcomes; and (6) population impact of trial outcomes. The importance and limitations of these various elements of trial strategy are analyzed, and issues regarding integration of new data into the practice of cardiology are highlighted. To achieve this goal, discussions about both antiarrhythmia trials and studies of other therapies in cardiovascular medicine are included.

Outcomes Measures

Clinical trials of antiarrhythmic therapy may be designed to measure effects on three general categories of outcomes: mortality, morbidity, and quality of life (Fig 1). For clinical impact, no outcome is more definitive than an effect on mortality, and the majority of therapeutic trials in cardiovascular medicine test for the possibility of a mortality benefit as either a primary or secondary end point. Despite the prime importance of mortality end points, the other categories of therapeutic response—effects on morbidity and quality of life—also provide clinically useful information and may be used as primary end points for appropriately directed trials.

There have been disputes about the need to adhere to all-cause mortality measures when death is used as a primary end point. The recent trend, however, has been to use this end point as opposed to total cardiovascular fatalities or death caused by more specific mechanisms, such as arrhythmias, myocardial infarction, or heart failure. Among the limitations of using arrhythmic death as a primary end point is the often discussed issue, still unresolved, regarding accurate classification of such deaths. In addition, the phenomenon of competing risks, in which risks of multiple mechanisms of death may coexist and “compete” for causation of the terminal event (Fig 1), favors the use of total deaths as the preferred measure of mortality outcome. Replacing one mechanism of death by another in a short time period neutralizes the direct benefit of an intervention, in whole or in part, and may yield no net improvement in outcome.

Mortality benefit can be expressed as a relative or absolute reduction in fatal event rate within a defined period of time or at a normalized time of follow-up. It can also be expressed as a measure of duration of extension of life or interval benefit. For patients or groups with primary electrical disorders of the heart, without significant competing risks, the former is an adequate and appropriate measure of benefit. Effective therapy can be expected to save lives in an absolute sense over an extended period of time. However, the majority of patients for whom antiarrhythmic therapies are used for life-threatening arrhythmias have chronic and progressive diseases, and fatal arrhythmias are just one part of the pathophysiological spectrum. The ultimate outcome relates to the underlying disease state as much as to any one manifestation. In these groups, it is appropriate to add extension of life to the expression of mortality benefit. Such measures can be applied to the data from appropriately designed trials and are com-
Clinical trials in many areas of cardiovascular medicine have commonly been designed to evaluate complex primary end points. We use this term to describe a primary end point that incorporates two or more different categories of outcome, which may include both fatal and nonfatal events. This strategy is usually used to increase the power of small studies or those anticipated to have low event rates. It has a potential conceptual flaw, however, because fatal and nonfatal cardiovascular events may have different pathophysiological mechanisms that may respond divergently to an intervention. In addition, the extent to which one category of outcome dominates the terminating events can influence the interpretation of clinical impact. The implied benefit to the underrepresented end point may create a perception that extends beyond the true benefit. For example, many of the lipid-lowering drug trials report on primary end points that combine coronary heart disease deaths and nonfatal myocardial infarctions. However, because event rates were not balanced, benefits predominantly reflect nonfatal event rates. In the Lipid Research Clinics cholestyramine study, only 20% of the total cardiovascular events in the placebo group were fatal cardiac events, and therefore the combined end point was dominated largely by a reduction in nonfatal events. In the Helsinki Heart Study, because 85% of the confirmed events were nonfatal myocardial infarctions, the identification of a primary end point that includes a mortality benefit is potentially misleading. In fact, cardiovascular mortality differences between the gemfibrozil-treated and placebo groups were not statistically significant. Balance was somewhat better in the CARE trial, which tested the effects of pravastatin in patients with prior myocardial infarction and the carvedilol trial in patients with mild heart failure symptoms. Both used complex primary end points, but about one third of the risk reduction in CARE and 30% in the carvedilol study were attributable to effects on fatal events. When event rates are anticipated to be too low to adequately power a trial for identification of a mortality difference, it is more appropriate to design trials with larger numbers and to use secondary end points. Merging underpowered categories of outcome events into a complex primary end point to increase total event numbers may create an unwarranted illusion of benefit in one or more of the categories of outcome.

Efficacy measures in antiarrhythmic therapy trials, in addition to mortality, may include impact on morbidity and outcomes related to symptoms and quality-of-life improvement (Fig 1). For non–life-threatening arrhythmias, morbidity and quality of life are primary issues, but for most ventricular arrhythmia trials, mortality outcomes have been the focus of trial design. Nonetheless, a therapy that fails to achieve a mortality benefit can provide a clinically important antiarrhythmic benefit for morbidity or quality-of-life outcomes, as long as there is no adverse mortality effect. This point is highlighted by the data and analyses from two recently reported trials of amiodarone in post–myocardial infarction patients, EMIAT and CAMIAT. The fact that the European Myocardial Infarction Amiodarone Trial (EMIAT) used total mortality as its primary end point, whereas CAMIAT (the Canadian Myocardial Infarction Amiodarone Trial) used resuscitated ventricular fibrillation or arrhythmic death as its primary end point, has been the source of some discussion. Most clinical trialists would favor the EMIAT design, using total mortality as the primary end point. Nonetheless, despite the previously stated concern about arrhythmic death classification, the data from the two trials complement each other nicely. Both suggested that use of amiodarone in the patient populations studied had little if any total mortality benefit, but they also suggested a significant antiarrhythmic benefit. Either as a primary endpoint or as a secondary endpoint, survival from arrhythmic death or resuscitated ventricular fibrillation was significantly improved by the drug. In contrast, total mortality was not benefited as a primary end point and was insignificantly benefited as a secondary end point. These observations support a conclusion that amiodarone may have clinical value in such patients as an antiarrhythmic agent for morbidity and quality-of-life uses, without evident adverse effect on mortality. Thus, although we agree with the use of total mortality as the primary end point in trials seeking to identify a mortality effect, we also believe that this does not negate the value of companion trials using different end points. As an example, the data from EMIAT and CAMIAT can be appropriately merged to demonstrate different measures of clinical impact.

EMIAT and CAMIAT evaluated amiodarone in high-risk post–myocardial infarction patients, whereas other trials have studied its use in different population subgroups. In the analysis of outcome, it is important to recognize population differences in attempts to apply the observations to a general population. An example is the two amiodarone trials in patients with heart failure, CHF-STAT and GESICA. CHF-STAT was a Veterans Administration–sponsored placebo-controlled trial of amiodarone in patients with heart failure.
and ambient ventricular arrhythmias. GESICA compared standard therapy plus empirical amiodarone and standard therapy without amiodarone in patients with heart failure. There was no specific requirement for ventricular arrhythmias, although most of the patients in the study did have ambient arrhythmias. In CHF-STAT, amiodarone demonstrated no mortality benefit for the total population, but a subgroup analysis identified a trend suggesting that the nonischemic cardiomyopathy group might benefit from amiodarone therapy. The coronary artery disease subgroup (70% of the enrollees) showed no benefit. In contrast, the GESICA investigators reported a mortality benefit of amiodarone in their study population, which was dominated by patients with nonischemic cardiomyopathy (60% of the patients). Thus, the subgroup of ischemic cardiomyopathy demonstrated neutral mortality outcomes, similar to EMIAT and CAMIAT, whereas nonischemic cardiomyopathy patients (not included in EMIAT or CAMIAT by design) may have differed. Neither CHF-STAT nor GESICA allows a definitive conclusion that amiodarone has a mortality benefit for nonischemic cardiomyopathy, according to considerations of population size and study design, but they do raise the question for future studies. These results highlight the importance of etiologic uniformity for proper interpretation of clinical trials.

**Placebo-Control Versus Positive-Control Studies**

Alternative therapy comparisons, or positive controls, have been used in all of the major trials of secondary prevention after survival from life-threatening arrhythmias or of prevention of sudden cardiac death among extremely high-risk patients. The reason is based on the ethical consideration that, for known high-risk patients, therapy that might be effective should not be withheld. Although the ethical considerations are properly the controlling influence in study designs for these populations, they do create problems for interpretation of data. In a placebo-controlled trial without significant imbalances after randomization, the so-called “natural history” of the randomized study population can be determined. In orthodox terms, true natural history refers to the outcome of an untreated population. In practical usage, it refers to outcomes in the presence of “standard therapy” among a population to be randomized to one or more “test therapies.” Unfortunately, the various standard therapies in the two or more arms of a trial may become unbalanced by the actions of study physicians or the physicians treating patients. Imbalance is difficult to control and becomes the subject of post hoc debates about interpretation of outcomes.

In the absence of serious imbalances, orthodox or practical measures of natural history determined in a placebo group make it possible to estimate absolute mortality benefit from the outcome data. In contrast, in a positive-controlled trial using a comparison therapy, absolute benefit cannot be determined. In CASCADE, for example, a comparison of amiodarone to “conventional therapy” (class I antiarrhythmic drugs), the outcome with amiodarone was superior to that of the “control subjects.” However, it is impossible to determine whether amiodarone improved on the natural history outcome, conventional therapy worsened the natural history outcome, or some other permutation of the two outcomes occurred. Consider this point in the context of interpretation of the data from CAST and CAST II. In a placebo-controlled trial, this arm represents natural history of population, assuming adequate balance of population characteristics between placebo and treated arms. Without a placebo arm, it is not possible to determine extent to which difference between T1 and T2 represents benefit, adverse outcome, or a combination.

**Figure 2. Interpretation of trials using positive controls.** A, Curve illustrates hypothetical natural history of population among which two therapies (T1 and T2) are to be compared. In a placebo-controlled trial, this arm represents natural history of population, assuming adequate balance of population characteristics between placebo and treated arms. B, C, and D illustrate constant difference between T1 and T2, but position of two curves varies in relation to natural history curve. Natural history curve (dashed line) is same in all four panels. B, T2 has no significant adverse effect or benefit, and it approaches natural history. Difference between T1 and T2 is accounted for by benefit of T1. C, Condition in which T1 has no significant benefit and difference between two curves is magnitude of an adverse effect of T2. D suggests relationship in which natural history is between T1 and T2, suggesting that part of difference is due to benefit of T1 and part due to adverse effect of T2. Without placebo arm, it is not possible to determine extent to which difference between T1 and T2 represents benefit, adverse outcome, or a combination.
superior to therapy 2. In Fig 2B, 2C, and 2D, the two outcome
curves demonstrate the same relative magnitude of advantage
of therapy 1 compared with therapy 2. However, because the
position of the natural history curve (dashed line) is unknown
in the absence of a placebo-controlled arm, the interpretation
of the relative difference, in relation to natural history, is
speculative. Three possible explanations for the difference are
illustrated. Fig 2B suggests that therapy 2 has limited or no
mortality benefit, and its outcome is close to natural history.
This suggests that all of the difference is attributable to
benefit of therapy 1. The outcome in Fig 2C attributes most of
the difference to adverse effects of therapy 2, similar to the
outcome of CAST in the presence of placebo. Therapy 1
therefore provides no benefit to the patients, although its
apparent outcome is better than that of therapy 2, creating a
risk of misinterpretation. The true impact is that the apparent
benefit is spurious; neither therapy should be used, because
one has no effect and the other does harm. In Fig 2D, a natural
history curve floats somewhere between the two observed
outcome curves, with a greater or lesser absolute benefit of
therapy 1 over therapy 2. However, it is impossible to know
exactly how much of the apparent benefit is true benefit,
because the position of the natural history curve is unknown.
Without knowing the magnitude of the absolute benefit of
therapy 1, impact analysis of the data is subject to error.

For the specific case of antiarrhythmic drug therapy, in
contrast to other forms of cardiovascular therapy, the problem
is further confounded by a phenomenon referred to as
proarrhythmic/antiarrhythmic equilibrium. This concept
derives from the fact that for antiarrhythmic drugs, the most
serious adverse effect is fatal proarrhythmia. It is difficult,
clinically, to distinguish antiarrhythmic benefits from com-
peting proarrhythmic effects or between failure to prevent
clinical arrhythmias caused by underlying disease and gener-
ically similar fatal proarrhythmic events. Therefore, the
dissection of gross mortality rates into true benefit, adverse
effects, and outcomes due to either neutralized benefit or to
failure of therapy is problematic (Fig 1). Consequently,
arrhythmic death outcomes, as a component of total mortal-
ity, may be contained by the interaction of multiple generi-
cally similar outcomes. Clinical trials of antiarrhythmic drug
therapy have this special limitation in regard to risk/benefit
considerations, whether placebo-controlled or positive-com-
parison in design. It is much easier to distinguish fatal
cerebral hemorrhage from fatal cardiac events with the use of
thrombolytic therapy in acute myocardial infarction.

The dilemmas presented in this analysis must be confronted
each time a positive-control (comparison therapy) trial outcome
is analyzed. Valid outcome statements are limited to relative
risk, and absolute benefit cannot be determined with certainty.
Probability can be used in an attempt to gain insight. For
instance, it is generally accepted that amiodarone has limited
proarrhythmic effects, and a number of placebo-controlled trials
have demonstrated the absence of adverse outcomes. However,
these trials were carried out in specific populations, and
their applicability to other groups is uncertain. Nothing replaces
the accuracy of a concurrent placebo-controlled arm to measure
absolute outcome in a specific study population. Thus, as
positive-control trial outcomes are integrated into practice strut-
gegies, we should recognize that a CAST-like awakening may be
lurking in some of these databases.

### Intention-to-Treat Versus On-Therapy

**Analysis of Outcomes**

Intention-to-treat analysis is the most commonly used method
for analyzing outcomes data. The rationale is the fact that
drug tolerance and compliance are important elements of
drug efficacy, and compliance failures and crossovers are
important components of the total efficacy evaluation. For
placebo-controlled trials and perhaps some medical/surgical
comparison trials, it is hard to argue with that logic. However,
in complex, multiarm trials, especially those without a pla-
cebo control, intention to treat can cause serious problems in
interpretation. When trials are designed to compare multiple
antiarrhythmic strategies for patients at risk for life-threatening
arrhythmias, crossover from one positive therapy to
another positive therapy may be required and can be con-
founding. An example emerges from the partial data reported
from the Cardiac Arrest Study of Hamburg (CASH), in which
the propafenone arm was stopped early because of adverse
outcome. The data were analyzed on the basis of intention to
treat. However, a number of the deaths attributed to
propafenone occurred after nonfatal breakthrough arrhyth-
mias or drug intolerance forced their crossover into the other
active therapy categories (metoprolol, amiodarone, and im-
plantable defibrillators). Analysis of the propafenone mortal-
ity events demonstrates that a significant number of the
propafenone-attributed deaths occurred among patients who
were not receiving the drug at the time of death. The
significance of the difference between propafenone and other
therapies may disappear in an on-therapy analysis. Thus,
although the data do suggest adverse morbidity and quality-
of-life issues related to propafenone, a true adverse mortality
effect should not be considered proven on the basis of the
intention-to-treat analysis. Consider further (in the absence
of CAST) a hypothetical trial comparing amiodarone with
flecainide in a population of patients with ischemic heart
disease at high risk for life-threatening ventricular arrhyth-
mas. If the study design allowed crossover and 26% of the
patients on amiodarone had to have amiodarone therapy
stopped, as was observed in CAMIAT, an intention-to-treat
analysis might have implied that amiodarone did harm
compared with flecainide. Both the EMIAT and CAMIAT
investigators presented their data by both intention-to-treat
and on-treatment analyses. The on-treatment analyses in both
studies reinforced and strengthened the concept that amiod-
arone is an effective antiarrhythmic agent, without modifying
the total mortality end point. Although on-treatment analyses
may, in some circumstances, bias outcome data, it was a
helpful way to manage the data because it provides the reader
of those reports the opportunity to interpret the impact of
antiarrhythmic effect. In addition, if it was of value in these
relatively straightforward drug-versus-placebo trials, the dual
analysis becomes even more valuable in a multiple-interven-
tion trial without a placebo arm, such as CASH.
Efficacy Versus Efficiency of Therapeutic Interventions

Most trial outcomes focus on therapeutic efficacy, based on the fractional or relative reduction of end-point events in a treatment group compared with a placebo or an alternative treatment group. However, if event rates in a study population are low, relative outcome improvements may have only limited impact on the total treated population, even if very large fractional reductions of outcome events are demonstrated. We have used the term therapeutic efficiency in referring to the relationship between relative risk and absolute event rates. Efficiency considerations are an integral part of economic impact analyses of clinical trials but have attracted less attention as a method for defining clinical impact. Fig 3, based on the recently reported AVID trial data,19 illustrates some economic impact analyses of clinical trials but have attracted less attention as a method for defining clinical impact. Fig 3, based on the recently reported AVID trial data,19 illustrates this point. AVID (Antiarrhythmics Versus Implantable Defibrillators) was a study of implantable cardioverter-defibrillator (ICD) therapy versus amiodarone or sotolol in survivors of cardiac arrest or hemodynamically or clinically significant ventricular tachycardia (VT). The trial was stopped early because of a large relative benefit of ICD therapy. At 2 years of follow-up, the data demonstrated that the drug-treated comparison group (the majority of whom received amiodarone had a 25% total mortality rate. Assuming that this represents the natural history (ie, amiodarone and sotolol have neither benefit or adverse effect), an assumption that is subject to error, the outcome attributable to ICD therapy represents an impressive 27% reduction in relative risk, based on the observed 18% mortality rate in the ICD group at 2 years. Although the conclusion is precisely correct from a statistical viewpoint, the efficacy statement does not address the issue of efficiency among the target population. Specifically, because of the inability to prospectively identify the patients from among the total population at risk who are going to have events during follow-up, many more patients will have to receive the defibrillators than will benefit from them in order to protect the universe of patients identified by the AVID criteria (Fig 3). If amiodarone and sotolol provide no benefit and do no harm, the ICD benefit for the total treated population is extrapolated to total treated population, reduction of fatal events among total population is 27%.

Efficiency is a measure of therapeutic benefit in relation to economic costs. When relative reduction is extrapolated to total treated population, reduction of fatal events among total population is 7%.

**Figure 3. Efficacy and efficiency in AVID.** A, Implantable cardioverter-defibrillator (ICD)-treated subgroup had an 18% mortality rate at 2 years, vs 25% in drug-treated group, a 27% reduction among population having events. B, When relative reduction is extrapolated to total treated population, reduction of fatal events among total population is 7%.

Efficacy and efficiency are the two important consideration of clinical trials. Efficacy is the measure of how well a treatment works compared to a control group. Efficiency, on the other hand, is the measure of how much benefit the treatment provides for the cost. In the context of cardiovascular trials, AVID (Antiarrhythmics Versus Implantable Defibrillators) trial demonstrated a 54% relative reduction in all-cause mortality in Comparison group (the majority of whom received amiodarone vs drug therapy (ICD)). This reduction is significant and demonstrates the benefit of ICD therapy. However, the absolute benefit of ICD therapy is lower than the relative benefit. In a similar analysis of MADIT (Multicenter Antiarrhythmic Defibrillator Intervention Trial), a 54% relative reduction in all-cause mortality represents a 17% absolute reduction. If the antiarrhythmic drugs in the control group provide a beneficial effect, the ICD benefit is completely neutralized by a beneficial effect of these drugs, the true magnitude of ICD-attributable benefit may be lower.

Despite the apparently low efficiency rates, the absolute reductions of risk for all-cause mortality in AVID and MADIT are among the better outcomes in cardiovascular trials. Absolute risk reductions comparable to these trials were demonstrated in the carvedilol–heart failure databases, which demonstrated absolute rates of 4.6% and 10.9%. However, similar analyses for several of the lipid-lowering trials demonstrated much lower efficiencies (Fig 5). For example, in the Helsinki heart study, the 34% reduction of cardiovascular events in the gemfibrozil-treated group ac-
TRIAL | EFFICACY (Relative R.R.) | RISK (Placebo) | EFFICIENCY (Absolute R.R.)
--- | --- | --- | ---
LRC - Cholestyramine [19*] (CV Mortality) | -24% | 2.0% | -0.4% |
HELSINKI - Gemfibrozil [19*] (Faul & Non-fatal CV Events) | -34% | 4.1% | -1.4% |
HMG-CoA Reductase [18*, 20*] (CV Mortality) [16 males] | -28% | 3.7% | -1.7% |
CARE - Pravastatin [22] (FATAL Coronary Events & Non-fatal MI) | -24% | 9.4% | -3.0% |
GISSI - Streptokinase | -15% | 13.0% | -2.3% |
U.S. Carvedilol Study Group | -65% | 7.8% | -4.6% |
MOCHA - Carvedilol | -73% | 15.4% | -10.9% |

**Figure 5.** Efficacy and efficiency among various cardiovascular trials. Patterns of efficacy and efficiency are illustrated from data contained in seven reports cited in text (References 8, 9, 10, 21, 22, 23, 24). Lipid-lowering studies demonstrated excellent efficacy for both primary and secondary prevention. However, efficacy was low, with more general primary prevention trials being lowest. Only carvedilol trials in heart failure demonstrated efficiencies on the order of magnitude of those observed in MADIT and AVID (see Fig 4). RR indicates risk reduction; LRC, Lipid Research Clinics; CV, cardiovascular; [19*], primary prevention trial; [20*] secondary prevention trial; and MI, myocardial infarction.

Table 2: High-risk groups among patients in the highest-risk subgroups because they yield event rates high enough to design trials with relatively small numbers of patients (Fig 4). In exchange, they provide data applicable to only small numbers of the total sudden death risk population.5,25 MADIT was a study of very-high-risk post–myocardial infarction patients with low ejection fractions, ambient nonsustained VT, inducible sustained VT, and failure of antiarrhythmic therapy to suppress inducible arrhythmias.26 In contrast, AVID studied out-of-hospital cardiac arrest survivors with similar ejection fractions but no other arrhythmia requirements.19 Each of these two trials demonstrated a major benefit in favor of the defibrillator (see Fig 4), but each represents only a small proportion of the total sudden death risk population (Fig 6). It is important to appreciate, nonetheless, that because they represent two different populations, the impact of the AVID and MADIT data are additive.

In contrast to MADIT and AVID, CABG-Patch was a study that enrolled patients undergoing bypass surgery for conventional ischemic indications, without requirements for qualifying arrhythmias but with ejection fractions in a range similar to those in MADIT and AVID. It showed no benefit of defibrillators compared with negative controls in its primary outcome measure, total mortality.26 The interpretation of this difference may be as simple as the fact that reversal of an ischemic marker of risk reduces the probability of an arrhythmic mortality event, even though the total mortality figures available from CABG-Patch suggest that it was a high-risk group for total mortality (Fig 4). Another interpretation might be based on the fact that MADIT and AVID both had active arrhythmia markers (nonsustained VT and inducibility in MADIT and cardiac arrest or sustained VT population pools, such as those with coronary risk factors who have not yet had events and the unselected general population. Most of the recently reported major trials enrolled patients in the highest-risk subgroups because they yield event rates high enough to design trials with relatively small numbers of patients (Fig 4). In exchange, they provide data applicable to only small numbers of the total sudden death risk population.5,25 MADIT was a study of very-high-risk post–myocardial infarction patients with low ejection fractions, ambient nonsustained VT, inducible sustained VT, and failure of antiarrhythmic therapy to suppress inducible arrhythmias.26 In contrast, AVID studied out-of-hospital cardiac arrest survivors with similar ejection fractions but no other arrhythmia requirements.19 Each of these two trials demonstrated a major benefit in favor of the defibrillator (see Fig 4), but each represents only a small proportion of the total sudden death risk population (Fig 6). It is important to appreciate, nonetheless, that because they represent two different populations, the impact of the AVID and MADIT data are additive.

**Figure 6.** Population impact of emerging implantable defibrillator trials. Estimates of incidences and absolute numbers of sudden cardiac deaths among six defined populations are shown. Arrows indicate that trials such as MADIT, AVID, and CASH have impact on a small fraction of total number of sudden cardiac deaths. It is likely that SCD-HeFT represents a larger fraction of population at risk. Even though each of these categories is additive because they represent different subgroups, they do not approach a cumulative majority of patients at risk for sudden death. EF indicates ejection fraction; VF/VT, ventricular fibrillation/tachycardia; and MI, myocardial infarction.

**Population Impact of Outcomes of the Emerging Trials**

Analyses of risk for sudden cardiac death have highlighted the fact that the highest-risk subgroups, on which much attention is focused because of the magnitude of risk of sudden cardiac death, identify only a small proportion of the total of 300,000 sudden cardiac deaths that occur in the United States annually.25 Although concentration of risk may be achieved by considering time-dependent influences,5 the majority of the potential victims are hidden within larger population pools, such as those with coronary risk factors who have not yet had events and the unselected general population. Most of the recently reported major trials enrolled patients in the highest-risk subgroups because they yield event rates high enough to design trials with relatively small numbers of patients (Fig 4). In exchange, they provide data applicable to only small numbers of the total sudden death risk population.5,25 MADIT was a study of very-high-risk post–myocardial infarction patients with low ejection fractions, ambient nonsustained VT, inducible sustained VT, and failure of antiarrhythmic therapy to suppress inducible arrhythmias.26 In contrast, AVID studied out-of-hospital cardiac arrest survivors with similar ejection fractions but no other arrhythmia requirements.19 Each of these two trials demonstrated a major benefit in favor of the defibrillator (see Fig 4), but each represents only a small proportion of the total sudden death risk population (Fig 6). It is important to appreciate, nonetheless, that because they represent two different populations, the impact of the AVID and MADIT data are additive.

In contrast to MADIT and AVID, CABG-Patch was a study that enrolled patients undergoing bypass surgery for conventional ischemic indications, without requirements for qualifying arrhythmias but with ejection fractions in a range similar to those in MADIT and AVID. It showed no benefit of defibrillators compared with negative controls in its primary outcome measure, total mortality.26 The interpretation of this difference may be as simple as the fact that reversal of an ischemic marker of risk reduces the probability of an arrhythmic mortality event, even though the total mortality figures available from CABG-Patch suggest that it was a high-risk group for total mortality (Fig 4). Another interpretation might be based on the fact that MADIT and AVID both had active arrhythmia markers (nonsustained VT and inducibility in MADIT and cardiac arrest or sustained VT
in AVID, which serve as specific identifiers of benefit for implantable defibrillator therapy. The encouraging aspect of the latter interpretation is the possibility that active arrhythmia markers provide information specific for ICD benefit, which can serve to improve efficiency of ICD usage. Fig 6 demonstrates the position of the study populations in each of these trials in relation to the general analysis of risk of sudden cardiac death.

Another study, SCD-HeFT (Sudden Cardiac Death–Heart Failure Trial), promises to add even more insight into the emerging concepts of therapy. SCD-HeFT is a recently begun placebo-controlled trial of implantable defibrillator versus antiarrhythmic therapy with amiodarone in patients who have ejection fractions ≥35% and NYHA functional class II or III heart failure. There are no arrhythmia requirements. It is, in effect, a heart failure counterpart to the CABG-Patch trial, because this new trial requires conventional therapy for heart failure in all limbs and compares the two active therapies with placebo. The patients do not have an arrhythmic indication dictated by manifest arrhythmias, clinically or by electrophysiological testing. Similarly, a follow-up study to MADIT has begun. MADIT II will enroll patients who have prior myocardial infarction, ejection fractions ≤30%, and PVCs (≥10 per hour or couplets). Patients will be randomized to receive or not to receive ICDs. An attempt will be made to minimize use of antiarrhythmic drugs and maximize ACE inhibitor and β-adrenergic blocker use in both groups. These new trials will study other population segments presumed to be at risk for sudden death and should provide additional information about the role of various therapies. They also may be applicable to larger subgroups than either MADIT or AVID. If no differences are observed between ICD, amiodarone, and placebo in SCD-HeFT, this will further support the notion from CABG-Patch, MADIT, and AVID that an active clinical arrhythmia marker provides resolution power for ICD benefit.

The reported outcomes of trials such as MADIT,23 AVID,24 and CABG-Patch25 address segments of the population that are highly specific and represent relatively small numbers. They do not have major impact on the general public health problem of sudden death. Epidemiological interventions for primary disease prevention and reduction of secondary event rates have been applied with some success to more general populations (see Fig 5), but they have limited efficiency. To achieve greater efficiencies, much more focused identification of subgroups, within the general population, at risk for sudden death is required. This may ultimately emerge from genetic or clinical markers identifying individuals at specific risk for life-threatening arrhythmia.2 In the meantime, the piece-meal approach mandated by ethical consideration is gradually providing new insights into the problem of sudden death prevention. Cumulatively, our understanding is beginning to increase.

Conclusions

Interpretation of outcomes of clinical trials of antiarrhythmic therapies and their application to the practice of medicine are exercises in circumspection. Distinctions between statistical validity and clinical or population impact may be difficult. Most large clinical trials are, in fact, designed with proper data management strategies. However, as outcomes are translated and applied to practical clinical use, questions about impact and the extent to which observations can be generalized must be faced continuously. To achieve this, both relative and absolute analyses of data should be strongly emphasized in all clinical trial reports.

Despite limitations and difficulties in interpretation, clinical trials provide the best methods for evaluating the effectiveness and safety of new therapies. Attention to the concerns listed in this commentary will help to minimize their limitations and keep their outcomes in proper perspective.

Acknowledgment

Dr Myerburg is funded in part by the American Heart Association Chair in Cardiovascular Research at the University of Miami, and by grant HL21735 from the NIH, NHLBI.

References


KEY WORDS: antiarrhythmia agents □ defibrillation □ arrhythmia □ trials □ death, sudden □ population
Interpretation of Outcomes of Antiarrhythmic Clinical Trials: Design Features and Population Impact

Robert J. Myerburg, Raul Mitrani, Alberto Interian, Jr and Agustin Castellanos

Circulation. 1998;97:1514-1521
doi: 10.1161/01.CIR.97.15.1514

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/97/15/1514

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/