SPECIAL REPORT

Clinical Investigation of Antiarrhythmic Devices

A Statement for Healthcare Professionals From a Joint Task Force of the North American Society of Pacing and Electrophysiology, the American College of Cardiology, the American Heart Association, and the Working Groups on Arrhythmias and Cardiac Pacing of the European Society of Cardiology

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SANJEEV SAKSENA, MD, FACC, Chairman; ANDREW E. EPSTEIN, MD, FACC,
RALPH LAZZARA, MD, FACC, JAMES D. MALONEY, MD, FACC,
DOUGLAS P. ZIPES, MD, FACC, Co-Chairmen; DAVID G. BENDITT, MD, FACC,
A. JOHN CAMM, MD, FACC, MICHAEL J. DOMANSKI, MD, FACC, JOHN D. FISHER, MD, FACC,
BERNARD J. GERSH, MB, FACC, GERVASIO A. LAMAS, MD, FACC,
MICHAEL H. LEHMANN, MD, FACC, DANIEL E. NICKELSON, MA,
ERIC N. PRYSTOWSKY, MD, FACC, D. GEORGE WYSE, MD, FACC, PhD, Members

Cardiac pacemakers, implantable cardioverter-defibrillators, and electrode catheter systems are essential for the treatment of patients with cardiac arrhythmias. The widespread and rapidly expanding use of these antiarrhythmic devices has focused attention on the need for thorough, efficient, and practical assessment of their safety, efficacy, and clinical usefulness. In general, the effectiveness of these devices is well documented. Their capabilities may be enhanced through incorporation of existing technology and future innovations, and it is anticipated that the range of clinical indications requiring intervention and the demand for use of antiarrhythmic devices will continue to grow.

A multidisciplinary policy conference was held November 15 and 16, 1993, in Washington, DC, to facilitate formal communication among interested parties involved in the development and use of antiarrhythmic devices. Participants included representatives of divisions of the Food and Drug Administration (FDA) responsible for overseeing the premarket release evaluation and post-market release surveillance of antiarrhythmic devices and the Health Industry Manufacturers Association, representing the device manufacturing industry.

This statement focuses on the types of clinical evaluation necessary for commercial release and subsequent assessment of antiarrhythmic devices. Generally, the term *clinical investigation* describes the broad area of scientific studies pertaining to human pathophysiology and therapeutics. In this report, the term *clinical evaluation* refers to a specific class of clinical investigations performed as part of a government-mandated biomedical regulatory mission (Fig 1).

This statement is based on a consensus of a joint task force comprising physicians and other healthcare professionals representing the North American Society of Pacing and Electrophysiology, the American College of Cardiology, the American Heart Association, and the Working Groups on Arrhythmias and Pacing of the European Society of Cardiology. The FDA and the Health Industry Manufacturers Association provided the task force with information and recommendations. This report also describes the essential elements of clinical evaluations to assess the safety, efficacy, and clinical performance of antiarrhythmic devices as proposed by the task force.

Diagnostic and therapeutic advances in the performance of antiarrhythmic devices are often incremental and based on a well-developed foundation of knowledge. There is a large body of technical and clinical experience regarding implantable antibradycardia pacing systems. Most recent developments represent incremental improvements in sophistication and
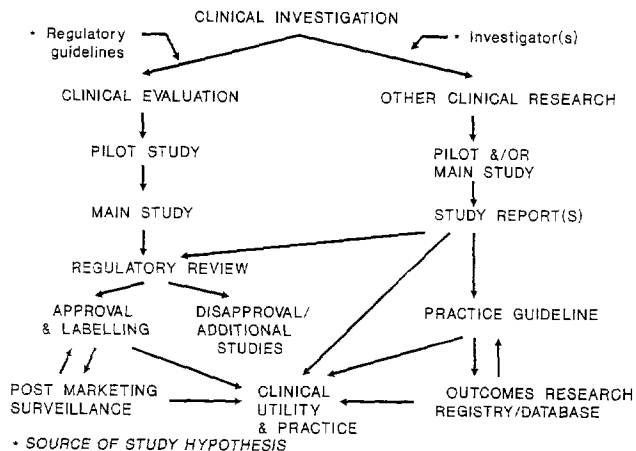
Figure 1. Schematic diagram showing the relation between different types of clinical investigation undertaken in development of an antiarrhythmic device, its clinical application, and its commercial release. The phases of clinical evaluation and subsequent process are detailed at left. Other clinical investigations performed for scientific inquiry are delineated at right. Interrelations between the two processes and their relations to practice guidelines, outcomes research, clinical usefulness, and post-marketing studies are broadly presented.

physiological operation. The circumscribed nature of such improvements should be considered when device performance is evaluated. When a major therapeutic innovation or clinical application of emerging technology is proposed, the clinical evaluation may be broader and the investigative requirements more rigorous.

Significant differences exist between the investigation of antiarrhythmic drugs and the investigation of antiarrhythmic devices: there can be no blinding in a study of devices; it is usually far more difficult to withdraw a device than a drug; a surgical procedure that incurs some degree of morbidity and mortality is often required for implantation of a device; devices may be more expensive initially than drugs; and some current devices may not prevent cardiac arrhythmias but only treat recurrences. Because of these concerns, considerable medical and technical expertise is required to design the appropriate clinical evaluation. A clear understanding of the clinical implications associated with proposed changes in a device or new concepts is crucial to optimize assessment and foster innovation, thus ultimately bringing technological advances to the patient in a timely, cost-effective manner.

The task force recognizes that clinical investigation of antiarrhythmic devices encompasses two distinct processes: (1) clinical evaluation (regulatory process) to ascertain the safety and efficacy of a proposed device or change in a device for a given use and (2) clinical research initiated by the medical community and aimed at establishing the nature and extent of medical benefit associated with the development of a device (Fig 1). The latter process may be initiated before, during, or after the regulatory process. Often, however, medically directed trials continue throughout the useful life of a device and at any point may affect the regulatory issue of device "labeling," a process based on the presentation of sound medical

evidence in which national or international regulatory bodies determine a formal indication (or modify an existing indication) for specific clinical application of a device.

A major goal of the task force is to define the device evaluation process in the context of optimal care of the patient with arrhythmia. Crucial to achieving this goal are promotion of trust among physicians, regulators, and manufacturers and recognition that realistic solutions to complex problems require flexibility based on reasonable medical and scientific judgment. To this end, physicians should clearly define the critical medical issues associated with investigation of a particular device. Furthermore, the task force recommends consideration of appropriately collected and validated information regarding the device and its uses. Physicians and manufacturers recognize that regulatory agencies have an obligation to assess the safety and efficacy of a device. Physicians seek unbiased, well-founded recommendations regarding the important medical/scientific issues that need to be addressed during clinical evaluation of an antiarrhythmic device. Manufacturers need efficient, medically realistic, and predictable guidelines for clinical evaluation, with feasible study end points. All are concerned with the ethics of biomedical investigation, as well as innovative, cost-effective health care and increased research opportunities. This statement presents a general framework for facilitating efficient, scientific assessment of current and evolving antiarrhythmic devices, specifically, cardiac pacemakers, implantable cardioverter-defibrillators, and electrode catheter systems.

Phases of Clinical Investigation

The goal of all clinical investigative studies of antiarrhythmic devices is to characterize their proper clinical application. The design of these studies reflects many factors related to the device, the patient, the medical team, therapeutic alternatives, and the risk-benefit ratio. Clinical investigation includes research to test specific hypotheses and clinical evaluation of device performance for regulatory approval (Fig 1). Clinical evaluation studies are as scientifically rigorous as other clinical research but are directed at fulfilling the regulatory mission. Evaluation studies are designed to ensure reasonable safety and efficacy and are supplemented with regulatory post-market release surveillance studies. The proposed phases of clinical evaluation studies are outlined in Fig. 1. Completion of these phases is followed by regulatory review and recommendations related to commercial release.

Technological development is an evolutionary process and has a natural history. Depending on the nature of the device and the results of early studies, the evolution of new technology may take different courses. The time periods when different types of investigations are undertaken in the life cycle of a device also vary. Clinical evaluation studies of devices fall into three broad categories: the pilot study, the main study determining commercial release, and postmarketing safety surveillance. The rationale for these categories is that the goals of each type of study can differ markedly.

In general, after conception and early development of a new technology, preclinical testing takes place, followed by a limited-scale clinical feasibility or pilot study conducted at a small number of sites. The overall goal of pilot studies is to demonstrate the clinical feasibility of a new device and protocol, as well as provide an estimate of its short-term safety and efficacy. A relatively small number of patients from a few centers are enrolled in these studies, which may or may not be randomized. Pilot studies are needed to identify major toxicity and potentially serious problems at an early stage and to determine whether there is sufficient efficacy to justify proceeding with the main study. Pilot studies also provide an invaluable opportunity for refining the device and protocol. This phase is particularly important for investigators to acquire new skills needed in application of the procedure and to identify unforeseen problems, for example, in study design. Duration of a pilot study is governed by the time needed to resolve unanticipated complications, inefficacy, or issues of safety. The pilot phase may be brief (eg, no technical skills must be learned) or protracted (eg, unanticipated problems occur or technical skills needed to use the device are difficult to learn). Embarking on a large-scale clinical evaluation prematurely can yield misleading data on the true usefulness and efficacy of a device. Technical difficulties should be corrected before concluding that the device or procedure is seriously flawed.

The main study for clinical evaluation of a device should be comprehensive and designed to provide more extensive long-term evidence of safety and efficacy. The type of study undertaken depends on the research question under investigation. Clinical evaluation studies may seek to demonstrate either superiority or equivalence of a particular technology with respect to existing options. Other types of clinical investigations (shown as other clinical research in Fig 1) may test other specific hypotheses. A study should have one major hypothesis, but a number of secondary hypotheses may also be tested within one clinical investigation.

After commercial release, surveillance studies are needed to determine if adverse effects that may be attributable to the device exist that were not recognized in preapproval studies. During this phase, other clinical questions can also be addressed, including quality of life and cost. These issues may sometimes be the primary or secondary end points of preapproval studies. Clinical outcomes research is best performed after market release of a device to establish guidelines for its use in medical practice. Innovations in use of a device, combining approved components from different manufacturers or systems to form a hybrid system, may benefit individual patients. Alternatively, there may be "orphan" indications for a device. In these instances, follow-up data collection and scientific examination are still required. Clinical utility of an antiarrhythmic device is determined by the therapeutic significance of clinical research results, based on data generated from clinical evaluation studies, other clinical research, post-market release surveillance data, outcomes research, and registry/database analyses.

Figure 2. Relation between technology evolution and clinical indications with respect to types of clinical evaluation appropriate for antiarrhythmic device studies. Study design relative to specific categories shown in this figure is discussed in the text. Both evolving technology and indications are classified as novel or an incremental evolution with respect to existing status.

Principles of Clinical Evaluation of Antiarrhythmic Devices

The regulatory approval process must ensure that devices for which marketing approval is sought are safe and effective for their intended use. Clinical evaluation studies designed to establish safety and efficacy must demonstrate that the device is at least as effective and safe as the existing standard treatment or that it provides a benefit, compared with the natural history of the disease. As a result, in clinical evaluation studies offered for regulatory approval, a device is generally compared with either the current standard or no treatment. A variety of study designs can be considered when selecting the appropriate evaluation process. In any study conducted for such a purpose, informed patient consent is essential. The patient-consent form should include all elements for well-informed patient participation.

Selection of Study Design

A study design matrix suggesting the clinical evaluation necessary to assess the function and therapeutic implications of specific device innovations is presented in Fig. 2. Device innovations for which only limited clinical evaluation may be necessary for regulatory purposes include those that do not alter efficacy and probably do not alter safety. Such innovations may be assessed in part by "bench" testing. Device innovations that are evolutionary in ease of use but unaltered in basic function (category A in Fig 2) generally should not require a randomized clinical trial. Innovative devices that expand indications for use or are technologically distinct imply greater benefits, greater risks, and greater uncertainty; they may be used for existing or new indications (categories B and D respectively in Fig 2). Comprehensive clinical evaluation is necessary to establish efficacy, safety, and appropriate labeling. Comprehensive trials are also needed for approval of applications of existing or evolutionary technology for a new indication (category C); either randomized or observational study designs may be used.

In a randomized clinical trial patients are assigned to treatment or comparison groups by chance. Randomization

reduces the potential for bias, resulting in study groups that are more likely to be comparable. Importantly, randomization also ensures that it is mathematically appropriate to use statistical analysis. The randomized clinical trial is the most scientifically rigorous approach to comparing treatments. It is also usually the most resource- and time-intensive approach. The standard used for comparison may be current treatment of the disease or its natural history if there is no effective treatment. In any clinical trial, it is ethical to randomly assign patients to different study groups if two or more treatments are available but it is not known which of the treatments is more effective. An observational study of treatment effect is reasonable only when the natural history of the disease is well characterized, (for instance, cardiac arrest unresponsive to advanced cardiac life support). For historical controls to be useful, there should have been no significant change in the natural history of the disease or the effectiveness of therapies other than those under evaluation. A randomized clinical trial is not needed when the treatment effect is large or the natural history of the disease is well characterized, as in the cardiac arrest example. It is also not needed when the difference between the device for which approval is sought and the existing device is only an engineering modification that does not fundamentally change the interaction of the device with a biological system, for example, the addition of improved telemetry capability to an implantable defibrillator.

In clinical evaluations a randomized clinical trial is most appropriate for investigating novel technology or new indications for previously approved devices (categories B, C, and D in Fig 2). Randomized clinical trials are usually needed to show superiority of novel technology. Small, nonrandomized trials are unlikely to detect a clinical difference when there are minor changes in previously approved technology (category A in Fig 2). In this latter situation, clinical evaluation may be designed to establish equivalence of therapies. An equivalency study has a hypothesis that is compatible with a one-sided statistical test such as the t test, ie, "device A is no worse than device B, for the end point of X." For purposes of equivalence, there also must be a priori agreement concerning the magnitude of an "important" difference in study end points, referred to as "tolerance." The study population and its expected event rate must be well characterized. These factors will have a major impact on sample size. Under some circumstances, a comparative trial may not be needed.

It is proposed that a randomized clinical trial is needed for clinical evaluation studies when

- The device delivers energy to the patient in a fashion different from a device approved for the same or a similar indication, for example, a new mechanism of myocardial stimulation by an implantable pacemaker.
- The device is used in an anatomical location that significantly alters its functional outcome from its current use, for example, use of a defibrillator for atrial rather than ventricular arrhythmia management.
- A new indication is sought for a device; for example, validating the use of diagnostic information yielded by

the device for making a treatment decision, such as use of an ultrasound array on a catheter to guide ablation before understanding the usefulness of such images.

In studies designed for regulatory approval, the sponsor must demonstrate that intervention with the device either favorably alters the natural history of the disease (if there is no current treatment), improves quality of life without an adverse effect on survival, or produces an effect at least as beneficial as the current standard of therapy. If the treatment is demonstrably better than the current standard, approval is highly probable. If there is a difference, then its magnitude must be examined to determine if it is clinically relevant, ie, what tolerance is acceptable. This question defines study design in terms of sample size and cost and time needed to implement the study and requires a clinical judgment. These concerns about sample size apply equally to randomized clinical trials and studies in which a comparison is made to a known standard. It should be emphasized that a randomized clinical trial is not necessarily a larger trial. Instead, the size of the trial determines the minimum tolerance that can be resolved by the study. These guidelines provide a reasonable framework for deciding what type of study is appropriate for a given device and/or indication but do not eliminate the need for medical judgment.

Clinical Evaluation Studies: Structure and Analysis

These studies should be expeditious and conducted with both scientific rigor and realism. They should be designed by a planning committee whose members possess the appropriate expertise, including the regulatory agency staff, its medical experts, and outside consultants. A data and safety monitoring board and an end point (events) committee should also be involved in the studies. Interim analyses using appropriate statistical monitoring techniques are recommended to elicit efficacious outcomes. With careful planning and coordination, appropriately documented positive results from such studies should lead to rapid and expeditious commercial release of the device. During the time between completion and analysis of the main study and commercial release, the new device should be available for use under the provisions of the investigative device exemption and approved protocol at existing study sites.

Selection of an appropriate control or comparison group for the main study is critical. An important function of the planning committee should be to define the comparison group (eg, historical, concurrent, or randomized) on an individual basis. The characteristics of the two groups being compared should be similar. While randomization is the best way to achieve comparability, it may not always be feasible or necessary, and appropriate statistical adjustments may be needed to ensure comparability.

The planning committee should categorize the device as either novel (ie, innovative) or evolutionary (ie, marginally changed) as shown in Fig. 2. Novel technology should be compared with the current standard, and randomization may be feasible; evolutionary technology may not require compar-

ison with the standard, and randomization to a standard or new device may not be feasible or necessary. When the novel feature can be programmed "on" or "off," consideration should be given to a randomized crossover design within the same patient group.

Easily evaluated end points such as total mortality are generally the most suitable for objective analysis. In other instances, this end point may not be appropriate, for example, if the primary purpose of a device is other than to prolong life. Approval of devices that are intended to improve quality of life or prevent morbidity requires alternative measurements. Inclusion of quality-of-life measures is an important milestone in the evolution of device research. Measurement of end points in this domain should reflect baseline measures to control for existing psychosocial and functional status that may confound subsequently obtained quality-of-life measures. This approach is recommended to decrease the problem of falsely attributing causation to device technology. In each phase of the clinical investigation, it is essential to obtain patients' perceptions of the device and recovery from implantation. The selection of end points for clinical evaluation of a device should follow the same principles as those for any clinical investigation.

When the usefulness of a device involves very few patients, the term *orphan technology* may be applied. Because commercial impact may be relatively small, the cost of bringing such devices through the regulatory process may be prohibitive. The task force believes these concerns could be addressed in the regulatory process by two different approaches. Tolerance, as defined above, could be sufficiently acceptable to justify a modest-sized study. Alternatively, governmental support of the clinical evaluation process would be needed.

It is recommended that the study sponsor and representatives of the regulatory agency discuss the prospective clinical evaluation of a device. Such a discussion can define the appropriate study design for a given application and reasonable tolerance level(s) given the likely event rate(s). In making these decisions it is necessary to provide reasonable assurance of safety and efficacy without inhibiting innovation critical to improvements in patient care.

Clinical Evaluation of Cardiac Pacing Systems

Review of Past Guidelines

Since 1976 there have been several types of FDA submissions by device manufacturers, including pre-market release notification, investigational device exemption, pre-market approval, pre-market release approval supplement, and post-market release surveillance reports. Guidelines for clinical evaluation of pacemakers were initially proposed in 1983. In the intervening 12 years, clinical studies have been conducted and pre-market release approval has been granted for the addition of dual-chamber (atrial and ventricular) sequential pacing capability, single- and dual-chamber rate response, and physiological sensors. The North American Society of Pacing

and Electrophysiology (NASPE) guidelines suggested that 30 devices be implanted for 90 days and an additional 70 devices be implanted for 30 days. In some cases (eg, for the addition of physiological sensors), the sample sizes were slightly increased to accommodate physiological testing, but the initial 100 devices were adequate to provide clinical and statistical evidence of the functional effectiveness and safety of the device.

Although the 1983 NASPE guidelines proved valuable, it is now apparent that clinical evaluation study requirements may need to be more rigorous in some circumstances. Ultimately, the clinical evaluation study must be capable of demonstrating relative safety and effectiveness (equivalent or superior) of the bradycardia pacing device in terms of the patient population for which its use is intended. The extent of the clinical study necessary depends on the balance between the degree of technical and clinical innovation, potential for risk to the patient, and potential for benefit to the patient. When analyzing patient risk, an essential component is any change that may be imposed on the most important functions of a pacemaker, ie, bradycardia support and sensing of spontaneous cardiac activity. These primary functions should be differentiated from diagnostic features such as event counters and other passive device characteristics.

Recommended Clinical Evaluation Studies for Cardiac Pacemakers

Minimal or no clinical evaluation is necessary for pacemakers and pacing systems derived from previously approved and thoroughly tested pacing systems that have undergone defeaturing. (Defeaturing refers to software-based "lockout" of an existing nonessential function.) Bench tests should confirm that the device functions within specifications.

Limited clinical evaluation of a new feature is required (without reevaluation of the older, previously approved device hardware or software) for devices with passive diagnostic features, temporary therapeutic features, or permanent nonessential features with minor therapeutic implications. However, the devices are essentially identical to the parent device in basic pacing and sensing functions. Rigorous bench testing of temporary functions, diagnostic features, and permanent nonessential features is performed before the device is introduced clinically. Thus, evaluation should consist of limited clinical observation of the specific feature in action. Acceptable studies in addition to bench testing include (1) acute testing in limited numbers of patients, (2) testing the accuracy of diagnostic features against a standard, and (3) observation of the feature in action. Examples of such device modifications include activation of new diagnostic or temporary therapeutic features in an existing unit without a software or hardware change, and addition of rate-adaptive atrioventricular delay or rate-adaptive post-ventricular/atrial refractory period.

An extensive clinical evaluation is needed when a change in a previously approved device may affect its essential functions. Such a change is defined as a substantial or novel change. Examples of such devices include first-time design of a brady-

cardia pacemaker by a manufacturer using newly developed technology and a new single sensor for rate-adaptive pacing.

In studies to evaluate such devices, a control group or a crossover design with the novel feature activated or deactivated may be used, with the study group as its own control. Alternatively, observational studies with well-characterized historical controls may be used. Because the safety and efficacy of many standard cardiac pacemakers is well known, historical controls are acceptable in some instances, eg, a first-time design of a new bradycardia pacemaker. The goals of these studies are based on the expected or desired claims made for the product. However, unless a manufacturer claims superiority for a specific device, the goal of these studies should be to show equivalence with standard therapy.

A randomized clinical trial generally should be performed for previously approved or novel types of devices being evaluated for a new clinical indication for purposes of device labeling (categories C and D in Fig 2). These clinical studies may occur at any time after the initial commercial release of a specific pacemaker. Specific examples where these guidelines may apply include DDD-pacing in idiopathic hypertrophic/dilated cardiomyopathy or DDD/AAI pacing to prevent atrial fibrillation. Patients receiving a standard therapy should serve as the control. Crossover or parallel designs may also be used in such studies. Historical controls may be appropriate when the natural history of a particular disease is well known.

Investigators must recognize that when two different pacing modes or options are tested in parallel study, research subjects who have received implants of the older device (the control group) cannot easily change to the improved device at the end of the study. This is in marked contrast with most pharmaceutical studies where, at the end of the study, the control group is easily switched to the most beneficial therapy. Thus, to protect subjects in the experimental group, the ability to activate or deactivate the test feature on either a short- or long-term basis should be incorporated into the study design whenever possible.

Primary and secondary end points must be clinically relevant and prospectively selected. Mortality should always be reported but may not be the primary end point for all clinical studies. Other appropriate clinical end points to define new indications for cardiac pacemakers may include nonfatal arrhythmias, such as atrial fibrillation; quality of life, using standard, validated instruments; or relevant physiological parameters.

Long-term Surveillance

After approval of any pacemaker or pacing system, post-market release surveillance studies are indicated to determine whether any adverse effects develop that were not apparent during the preapproval phase. Long-term surveillance has previously been based on manufacturers' registries of returned equipment or voluntary participation by multiple clinical centers. Recent action by regulatory authorities has increased manufacturers' responsibilities in monitoring the safety and

efficacy of their systems or devices. However, the task force favors the maintenance of a multicenter registry with reporting mechanisms separate from those maintained by manufacturers.

Clinical Evaluation of Implantable Cardioverter-Defibrillators

Evolution of Implantable Cardioverter-Defibrillator Therapy

Implantable cardioverter-defibrillators have gone through a striking technological evolution, with widespread therapeutic application within a decade of their clinical introduction. The growing maturity of the field is reflected in the recent adoption of a generic function code (NASPE/British Pacing and Electrophysiology Group defibrillator code) comparable to that used for pacemakers. Third-generation (or "tiered therapy") devices capable of providing energy-efficient shocks (biphasic waveforms), antitachycardia pacing, and backup VVI pacing have already been released commercially. The advent of transvenous electrode systems has reduced surgical mortality. In addition, the recommendations of the American College of Cardiology and NASPE address clinical indications in malignant ventricular arrhythmias. Comparative trials with pharmacotherapy are in progress. Studies are also under way to evaluate potential expanded indications as well as the role of implantable cardioverter-defibrillators in the management of atrial and nonsustained ventricular tachyarrhythmias.

Clinical Evaluation of Implantable Cardioverter-Defibrillator Devices

Clinical evaluation of new implantable cardioverter-defibrillators currently requires equivalency testing. These devices are effective in preventing sudden cardiac death. A new device or modification of an existing device should be at least as effective and safe as devices that are currently available. Other goals can be envisioned, however, and it is important that a hypothesis be carefully developed for each planned clinical evaluation.

Pre-market release evaluation of implantable cardioverter-defibrillators entails pilot study and main study components as described above. Previous NASPE recommendations (1987 and 1991) concerning minimum number of devices, number of centers, and duration of follow-up should be reviewed by the planning committee based on study design considerations and the hypothesis to be tested.

Study Design for Clinical Evaluation

Randomized or observational study designs can be appropriate. In randomized clinical trials patients are randomly assigned to one or two treatment limbs, representing either two different implantable cardioverter-defibrillator devices or implantable cardioverter-defibrillator therapy versus an alternative therapy. While often desirable, such trials may not always be feasible outside of a unique window of time follow-

ing introduction of a particular device. For example, randomized clinical trials of transvenous versus epicardial lead systems might have been feasible when transvenous leads were first introduced. However, it would now be difficult to obtain medical or ethical support for such a randomized trial, given the known lower mortality accompanying implantation of transvenous leads. In contrast, an automatic atrial defibrillator system or a totally new source-output waveform still falls within the window of opportunity for a randomized clinical trial.

The primary purpose of a limited observational evaluation of an implantable cardioverter-defibrillator is to demonstrate safety, with the assumption that strong experimental and possibly other clinical data exist to support efficacy or that efficacy of the new device can be shown to be equivalent to that of a market-released device. Such a study involves a single limb, namely, device treatment, and is observational, usually relying on clinically comparable historical rather than concurrent controls. Adjustments for known predictors of outcome may be appropriate to minimize selection or temporal biases.

The planning committee may recommend that no premarket release study is necessary if it is deemed that a device innovation, although clinically advantageous, has minimal potential adverse effects on safety. An example is altered spatial configuration of generator components to reduce device volume.

Post-Market Release Surveillance

Long-term monitoring of the safety of a device after its commercial release requires post-market release surveillance studies. This type of study is best done with a registry or database. The major purpose of such a study is to locate and follow up device implantees and monitor them for premature component failure or other unexpected problems. The number of patients and duration for this type of surveillance is determined by a calculation that allows detection of an event rate with a 95% confidence interval. A broad-based committee may be helpful for setting requirements for each individual study. Extended surveillance of patients enrolled in the study would allow for a long-term follow-up. If the study involves a wide spectrum of sites (high- and low-volume centers, academic and private practice settings), these patients would be a representative cross section of device implantees.

Study End Points

End points should be selected on the basis of the primary hypothesis and secondary objectives of each study. Precise definition of end points related to morbidity and mortality in implantable cardioverter-defibrillator studies have been delineated in a 1993 NASPE policy statement. Total mortality need not be the primary end point in all implantable cardioverter-defibrillator studies, although it should always be reported. Total mortality should be a required primary end point when a device is considered novel or modification of an existing device

can have an important impact on mortality. It is suggested that the impact of the innovation equal or exceed a minimum level for a clinically important change in annual mortality in the study population. The planning committee should make an informed judgment as to whether this value might be exceeded in a given investigation. The task force recognizes that patient selection will determine the total mortality rate observed in the study.

In accord with a recent policy statement from NASPE, the primary mortality end point for implantable cardioverter-defibrillator investigations is total mortality. Although subclasses of mortality may be tabulated, study design should be based on estimates of total mortality. This is preferred because of the difficulty inherent in classifying mortality. The minimum duration of patient follow-up should be at least 1 year. Actuarial presentation of the results should be encouraged. All reported proportions should be presented with 95% confidence intervals. Sample sizes and other adjustments should be made by the data and safety monitoring board as the study unfolds.

Efficacy of implantable cardioverter-defibrillators in terminating nonfatal arrhythmia events is expected to become increasingly important and should always be reported. Specific nonfatal event end points will be chosen largely based on the primary objective or hypothesis of the study and/or device modification. As with mortality, actuarial reporting should be encouraged, 95% confidence intervals should be reported for proportions, and careful consideration should be given to whether *events, patients,* or *both* should be used to calculate proportions.

Complications and safety data related to the device or the device implant should always be recorded. These may be categorized by type and may include surgical complications, appropriate/inappropriate therapies, programmer failures/difficulties, and premature component failure. Actuarial analysis of these data should be encouraged. Evaluation of quality of life (perceived symptoms, return to work, functional and psychological status) following application of a device is deemed important. Long-term evaluation of the end points should encompass the patient's baseline status. Patient recovery problems and perceptions of the impact of the implantable cardioverter-defibrillator are recommended.

Patient Selection

Safety and efficacy of a new implantable cardioverter-defibrillator (or antiarrhythmic drug) are influenced by the patient population receiving such therapy. For example, survival is likely to be better in patients with a left ventricular ejection fraction greater than 30% than in those with poorer left ventricular function. Various other clinical factors may have an impact on efficacy and complication rates during implantable cardioverter-defibrillator evaluation, including type of underlying heart disease, psychosocial class, and New York Heart Association functional class. Differences in event rates, which indirectly affect assessment of efficacy, must also

be considered. Given the multiple factors involved, it is critical that comparison groups be as clinically similar as possible to the implantable cardioverter-defibrillator treatment group and that adjustment for relevant covariates be considered. Moreover, inclusion criteria may need to be broadened or new studies with different inclusion criteria may need to be designed to justify application of the safety and efficacy results observed in one particular patient population to a broader group of potential implantees.

Innovation in Implantable Cardioverter-Defibrillators

Physician-led innovation with commercially released devices or system components has traditionally complemented development of devices by broadening therapeutic applications for patient benefit. Clinical innovation is widespread in cardiovascular medicine and may result from ongoing scientific investigations or physician and patient requests for access to restricted technology. Such access is deemed necessary for patient benefit.

In implantable cardioverter-defibrillator therapy, clinical improvisations have involved various innovations in surgical implant technique and a "mix and match" approach to assembling approved components into new hardware configurations. Examples of the latter type of improvisation are the use of Y connectors to yoke together three or more epicardial patch electrodes in patients with high defibrillation thresholds, creation of a nonthoracotomy implantable cardioverter-defibrillator lead system in which an epicardial patch electrode is placed subcutaneously on the chest wall and coupled with a transvenous spring electrode, and other hybrid transvenous implantable cardioverter-defibrillator systems formed by combining approved components from different manufacturers.

Freedom for physicians to improvise with approved device components and surgical techniques for patient benefit must be maintained. Investigators involved in such activities, however, are responsible for informing patients as well as carefully studying such combinations and reporting their independent or cooperative experience with improvised therapy. Moreover, recent guidelines require that, in the context of public forums, any "out of labeling" use of a commercially released device (or component) be clearly indicated as such, with concomitant delineation of alternative, approved therapies. Formal mechanisms must be developed for tracking long-term efficacy and possible complications of improvised medical devices. Finally, although not addressed here, future efforts are needed to deal with liability issues related to improvised therapy.

Clinical Evaluation of Ablation Devices

Evolution of Catheter Ablation

Following the introduction of therapeutic catheter ablation with high energy shocks in 1981, its use became widespread, but at a measured pace because of both the perceived and demonstrated hazards of high energy shocks. Since the intro-

duction of radiofrequency current as ablative energy to produce relatively small circumscribed zones of necrosis, there has been a proliferation of radiofrequency catheter ablation procedures and their applications. Growing use of this therapy in the past 5 years can be attributed primarily to two factors. First, it has been verified that application of radiofrequency current to the endocardium is safer than shocks. Experiments with animals established that small circumscribed lesions produced in mature myocardium were not accompanied by adverse consequences over short and intermediate periods of follow-up. Shock-related complications of myocardial depression and postprocedural sudden death were not observed. Intracardiac application of radiofrequency current is less likely to cause rupture and tamponade, as evidenced by the safe delivery of radiofrequency current into the coronary sinus, unlike delivery of shock. Cumulative experience with thousands of patients with supraventricular arrhythmias has established that the risk of serious complications with radiofrequency catheter ablation is less than 3%, and mortality for the procedure is well below 0.5%. Exact assessment of these low morbidity and mortality rates will require more experience with many thousands of patients. Nonetheless, experience has verified that the acute risks are far less than those attendant on cardiac surgical procedures.

Secondly, radiofrequency catheter ablation has exploited existing technology. Instruments for generating radiofrequency current are widely available and have been used in surgery for many years. Initially the current was delivered through standard electrode catheters, which were later modified to increase the surface area of the electrode tip to produce slightly larger lesions. Subsequently radiofrequency generators have been adapted for use in radiofrequency catheter ablation, including the capacity for temperature monitoring. Catheters have also been designed to facilitate the location of the diverse targets for ablation. The novel aspects of radiofrequency catheter ablation have been in the realm of clinical procedural skills and data analysis rather than the technology used in such procedures.

Study Designs for Catheter Ablation

The types of trials appropriate for catheter ablation must be considered in light of the advanced stage of progress in this therapy. There is agreement in the cardiology community that randomized trials for comparisons of most applications of radiofrequency catheter ablation with cardiac surgery are not necessary, ethical, or feasible. Comparisons with pharmacotherapy by randomized trials to establish a preference for initial therapy have not yet been performed and should be considered.

It is important to stress that the goals of radiofrequency catheter ablation and pharmacotherapy are different and their durations of application are widely disparate. Radiofrequency catheter ablation is effective in the intermediate term with a brief period of application. The goal of radiofrequency catheter ablation is the elimination of arrhythmogenic myocardium;

electrophysiological evidence of elimination or modification of the arrhythmogenic substrate is the criterion for efficacy. Pharmacotherapy is continuous and lifelong. Quality of life is a major end point in most applications of radiofrequency catheter ablation. The psychological impact of individual therapies is a paramount consideration. Radiofrequency catheter ablation produces relief of symptoms and improved quality of life in the intermediate time range. It can be expected to have a higher short-term morbidity and mortality in most types of arrhythmias except when drugs with significant ventricular proarrhythmic or other frequent adverse effects are used. The question to be addressed is whether the outcome is worth the risk of the procedure when the disease is not fatal but impairs quality of life. Well-informed patients can and should answer this question for themselves. Accurate information about ablation procedure-related risk and benefit as well as long-term data on morbidity and mortality with suppressive pharmacotherapy are needed. Patients can then make enlightened personal decisions. Continued careful observation of a growing patient population is sufficient to establish the appropriate role of catheter ablation in most forms of arrhythmias.

Recommendations for Clinical Evaluation of Radiofrequency Catheter Ablation Devices

New devices that do not involve radical departures in technology could be evaluated by testing ex vivo to assure compliance with prescribed standards and by limited observational trials in vivo. In such limited trials, controlled comparisons within the same population of severity, frequency, and drug therapy of the arrhythmia before and after radiofrequency catheter ablation should be used. Electrophysiological evidence of elimination of arrhythmogenic tissue by the ablative procedure should be required. Randomized clinical trials should be considered for novel and radical departures in catheter ablation devices. Such trials should be developed in accord with previously stated guidelines, ie, the pilot studies do not indicate a large treatment effect of the new technology and the natural history of the disorder is not fully characterized. If available, other standard catheter ablation methods should be used in controlled comparisons. Hybrid ablation systems require clinical evaluation under these guidelines. Use of ablation systems with approved components should be permitted. However, investigators are responsible for carefully studying these combinations and reporting their findings. Such data may be used to develop databases or registries for clinical surveillance.

Rapid expansion of the field has yielded a substantial base of empirical information regarding efficacy and safety. The lack of randomized clinical trials reduces the accuracy of comparisons with other forms of therapy. Both safety and efficacy are likely to improve at major centers. Long-term efficacy and safety can be accurately assessed only by mechanisms for long-term surveillance such as registries and databases. Such concerns as late effects of radiation exposure and late appearance of arrhythmias related to scars created by radiofrequency current can be addressed by systematic acquisition of data.

Patient Selection

The therapeutic role of radiofrequency catheter ablation in various arrhythmias has been previously addressed by the North American Society of Pacing and Electrophysiology and the American College of Cardiology (1992 and 1994). There is a consensus among cardiologists that radiofrequency catheter ablation is a preferable or acceptable alternative for initial therapy in symptomatic patients with bundle branch reentrant ventricular tachycardia, atrioventricular reentrant tachycardia, and atrioventricular junctional reentrant tachycardia. It is an acceptable alternative for a wide variety of arrhythmias that are resistant to pharmacotherapy, including atrial tachycardia, atrial flutter, atrial fibrillation (atrioventricular junctional ablation), and idiopathic ventricular tachycardia originating in the right ventricular outflow tract or left ventricle (left septal or verapamil-sensitive ventricular tachycardia). Right ventricular outflow tract and left septal ventricular tachycardias are promising candidates for radiofrequency catheter ablation as initial therapy, but more experience is required to make that recommendation. Radiofrequency catheter ablation in ventricular tachycardia associated with structural heart disease, in which it has been notably less efficacious (except for bundle branch reentrant tachycardia), is acceptable for drug refractory ventricular tachycardia or when implantable cardioverter-defibrillator or surgical ablation therapy is inappropriate or not feasible.

Summary

The goal of radiofrequency catheter ablation and the criterion for efficacy is the elimination of arrhythmogenic myocardium. The application of radiofrequency current in the heart clearly results in lower morbidity and mortality rates than thoracic and cardiac surgical procedures in general, and comparisons of therapy with radiofrequency catheter ablation and therapy with thoracic and cardiac surgical procedures in randomized clinical trials is unwarranted. Trials of radiofrequency catheter ablation versus medical or implantable cardioverter-defibrillator therapy may be indicated in certain conditions, such as ventricular tachycardia associated with coronary artery disease. Randomized trials are recommended for new and radical departures in technology that aim to accomplish the same goals as radiofrequency catheter ablation. Surveillance using registries and/or databases is necessary in the assessment of long-term safety and efficacy.

Recommendations

The task force, on behalf of the sponsoring organizations, recommends that clear goals for various types of antiarrhythmic device investigations be developed and that current methods of clinical evaluation of devices be modified. Issues sur-

rounding clinical investigations—the intensity and method of study, the framing of the study question(s), duration, and role of the government, manufacturers, and clinical investigators— and their relation to timely and appropriate patient care are of critical importance. It is recommended that this report initiate a long-term process to develop an improved understanding of regulatory requirements and how they can best be met by all participants. There is general agreement that flexibility in clinical evaluation studies and their management is desirable to avoid delays and rejections when results are presented to regulatory bodies. There is a need to streamline the process for introducing new technology and developing an accelerated mechanism(s) for significant advances. The evaluation process should be reevaluated from the standpoint of pediatric patients, who are infrequently included in clinical evaluation studies. Finally, there is legitimate concern that often too little is known about the efficacy of devices once they are approved and in general use. The policy conference on which this statement is based also considered issues related to the cost of clinical trials and reimbursement issues concerning devices and services involved in the performance of device trials. Although not discussed here, interim recommendations were made, and it was strongly suggested that these issues be resolved at a later stage. Clinical evaluations, because of their limited scope, are unlikely to identify all the possible adverse effects of antiarrhythmic devices.

1. Develop a better understanding of the scientific requirements for the conduct of valid clinical investigations whether performed for regulatory or clinical research purposes. As a minimum every investigation should have

- A clearly defined hypothesis
- A detailed, explicit methodology for the conduct of the investigation, including patient selection criteria, data elements, an independent safety monitoring group, and specified end points for pilot and main studies
- A randomized clinical trial when novel technology and/or indications are being evaluated. Randomized clinical trials are not needed when the treatment effect is large in pilot studies or the natural history of the disease is well characterized.

2. Communication is needed among all parties before formal proposal and/or initiation of a clinical evaluation based on regulatory requirements. To facilitate such communication, it is recommended that the regulatory agency create a formal advisory committee and that this committee be charged with making recommendations concerning both the priority of the matter proposed for evaluation and study design. Timely and prospective review of clinical evaluation protocols for devices by regulatory bodies is necessary to assess adequacy of study design for meeting stated objectives. External peer review and input from independent clinical scientists is strongly recommended during this process. Independent panels or working groups formed with professional organizations with interests in this area are appropriate and will be beneficial to investigators, sponsors, regulatory agencies, and, ultimately, patients involved in clinical studies.

3. Consistent with patient safety and scientific rigor, the proposed clinical evaluation process for regulatory purposes should be as expeditious as possible. The clinical evaluation should be designed to facilitate and simplify the existing approaches. A pilot study and a larger main study with interim study evaluation could achieve this goal. An accelerated evaluation should be considered for technology offering significant new clinical benefits.

4. Continued surveillance of antiarrhythmic device performance after approval is mandatory, and a more formal, structured process of long-term data collection and analysis should be developed. This objective can be partially achieved by selected post-market release surveillance studies. Registries and databases can provide significant additional information relative to device and system performance, patient safety, and a wide spectrum of clinical experience. A national effort should be made to foster such endeavors as independent entities. The task force recommends registration of devices in a national database, eg, the European Registry of the Implantable Defibrillator. This type of system facilitates long-term follow-up of clinical performance and provides important patient safety and efficacy information.

5. Innovation by physicians with approved devices, components, and surgical techniques for patient benefit is highly desirable. Investigators involved in such activities are responsible for evaluating hybrid systems and reporting their experience in a systematic manner.

6. Estimated costs of a clinical investigation must be considered as part of the overall investigation. These costs have been evaluated for pharmaceutical agents and should be assessed for antiarrhythmic devices. Particular attention should be given to the economic implications of high-cost design for small manufacturers.

7. Support for research on antiarrhythmic devices used in clinical evaluations is inconsistent and often difficult to obtain. A general policy should be established for public and private payers concerning appropriate support for research services provided during an approved clinical evaluation. This support is in the interest of patient care and social responsibility for the goal of public health. The task force recognizes that clinically beneficial device applications may become standard clinical practice based on investigator-initiated clinical research alone. Reimbursement decisions should be determined by scientific review of existing clinical data with respect to clinical efficacy and patient safety.

8. Continued interaction among the interested organizations is highly desirable. Periodic review and discussions using mechanisms such as the task force will identify issues for further action and resolution.

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