
Review Article

Evaluation of antiarrhythmic drug efficacy in patients with an ICD

Unlimited potential or replete with complexity and problems?

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A report from a Study group, proposed by A. J. Camm, London, of the Working Groups on Arrhythmias and Cardiac Pacing of the European Society of Cardiology; co-sponsored by the North American Society of Pacing and Electrophysiology. The Study Group was convened on 29 August 1997 at Saltsjöbaden, near Stockholm. The meeting was chaired by A. J. Camm, London, and C. M. Pratt, Houston. Based on the presentation and discussions, a first draft of the documents was prepared by C. Pratt and J. Camm which was then circulated to all members three times for their review. All members of the Study Group approved the final manuscript. This report represents the opinion of the members of this Study Group and does not necessarily reflect the official position of either society.

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Introduction

Data from clinical trials support the premise that, in specified populations, the implantable cardioverter-defibrillator is an effective form of therapy for the prevention of arrhythmic death due to ventricular tachyarrhythmias^[1–3]. The studies in which clinical benefit from the implantable cardioverter-defibrillator has been demonstrated are those that enrolled patients in

whom a life-threatening ventricular tachycardia or cardiac arrest had occurred. Selected subsets of asymptomatic patients at high risk for a ventricular tachycardia event may also benefit from prophylactic implantable cardioverter-defibrillator implantation^[4].

A natural extension for the use of implantable cardioverter-defibrillators is in the testing of antiarrhythmic drugs in patient populations at high risk for arrhythmic death with an implantable cardioverter-defibrillator already implanted. Background implantable cardioverter-defibrillator therapy allows the investigation of antiarrhythmic drugs using a randomized, placebo-controlled design which would otherwise be considered neither feasible nor, in some instances, ethical. In many such trials that are already underway the primary end-point includes the reduction of 'appropriate implantable cardioverter-defibrillator shocks'. Conceptually, this seems to be straightforward, and might be considered a reasonable 'surrogate' to establish the efficacy of an antiarrhythmic agent in patients in whom

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■ This paper is dedicated to the memory of Ronald W. F. Campbell (Ronnie) whose enthusiasm for and insight into clinical cardiology research is truly missed.

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placebo-controlled data are otherwise impossible to obtain.

This conference explored a variety of issues relevant to the use of implantable cardioverter-defibrillator end-points in clinical trials of antiarrhythmic drugs. Because of advances in implantable cardioverter-defibrillator technology, the storage, retrieval and accurate interpretation of implantable cardioverter-defibrillator electrograms also offers the potential to define precisely the clinical events that appear arrhythmic in nature. The benefits and limitations of this potential role are also explored. The degree to which an implantable cardioverter-defibrillator provides the necessary safety net to test new drugs is discussed in the context of the life-threatening proarrhythmic potential associated with antiarrhythmic drug therapy. Drug-associated torsades de pointes ventricular tachycardia or incessant ventricular tachycardia^[5,6] are potentially lethal consequences of antiarrhythmic therapy. A complicating factor is that antiarrhythmic drugs can also interfere with device therapy by increasing the ventricular defibrillation threshold^[7,8] reducing tachycardia cycle lengths, reducing the efficacy of antitachycardia pacing, etc., thus reducing the effectiveness of the implantable cardioverter-defibrillator to serve as a 'safety net'. A particularly difficult issue is the degree to which the results of data on antiarrhythmic drug efficacy and safety acquired in an implantable cardioverter-defibrillator end-point trial can be extrapolated to patient populations in which the device is not used. Our conference discussed these and other challenging issues with the goal of enhancing the design and interpretation of clinical trials featuring implantable cardioverter-defibrillator end-points.

Background: antiarrhythmic drug survival trials

Experience from antiarrhythmic drug trials points to a major influence of patient selection on trial outcome. Unintentionally, low risk groups were identified in the Cardiac Arrhythmia Suppression Trial (CAST)^[9,10] and Survival With ORal D-sotalol (SWORD) trial^[11,12]. Based on these trials, patients remote from infarction and those with a relatively preserved left ventricular ejection fraction have a low risk of arrhythmic death. Such subgroups, with very low placebo arrhythmic death rates, are not appropriate in primary prevention trials using an implantable cardioverter-defibrillator. A prospectively planned analysis of the European Myocardial Infarct Amiodarone Trial (EMIAT)^[13,14] trial revealed that measuring heart rate variability at baseline identifies an asymptomatic high-risk group for arrhythmic death in whom amiodarone may significantly reduce arrhythmic death. The Danish Investigation of Arrhythmia and Mortality ON Dofetilide (DIAMOND) trials^[15,16] selected patients with left ventricular ejection fraction $\leq 35\%$; and evaluated both an acute heart

failure and an early post-myocardial infarction population. In these trials, dofetilide, an I_k blocker, as is d-sotalol, was safe and was associated with a reduction in atrial fibrillation and hospitalization for heart failure despite having no effect on total mortality. The wide discrepancy in the outcome of clinical trials of similar antiarrhythmic drugs, such as SWORD (Survival With Oral d-sotalol) and DIAMOND, suggest that the details of study design, including patient selection, are critical to the chances of establishing benefit.

Representative ongoing implantable cardioverter-defibrillator clinical trials

A list of completed and ongoing trials with primary clinical end-points is contained in Table 1; these serve as a background for our discussion of trials with an 'implantable cardioverter-defibrillator shock' end-point. In the majority of the clinical trials listed in Table 1, the primary end-point is all-cause mortality. Many of these implantable cardioverter-defibrillator trials are just underway and/or in the planning phase; some are completed. In the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, patients who had already suffered a life-threatening arrhythmic event had improved survival with implantable cardioverter-defibrillator therapy compared to antiarrhythmic drug therapy (primarily amiodarone). The AVID trial is pivotal because it is the first large, randomized trial in secondary prevention demonstrating a mortality reduction with implantable cardioverter-defibrillator therapy. The preliminary results of two additional 'secondary prevention' trials, the Cardiac Arrest Study of Hamburg (CASH) and the Canadian Implantable Defibrillator Study (CIDS)^[17], are consistent with the results of AVID. All three 'secondary prevention' trials have in common the inclusion of patients with clinical documentation of previous cardiac arrest or haemodynamically significant sustained ventricular tachycardia. For the near future, the results of the AVID trial will represent the 'gold standard' of implantable cardioverter-defibrillator results, and will impact the future development of antiarrhythmic drugs. It will not be ethical to consider an implantable cardioverter-defibrillator vs antiarrhythmic drug mortality trial until substantial evidence supports the possibility that the new drug is at least as good as an implantable cardioverter-defibrillator in preventing death. A fundamental step in this process will be a drug vs placebo or drug vs active comparator study in patients with life-threatening ventricular arrhythmias 'protected' by an implantable cardioverter-defibrillator.

Several implantable cardioverter-defibrillator trials focus on primary prevention, that is in patients who are likely to suffer, but have not yet suffered, a life-threatening ventricular tachycardia event. These trials (completed, planned or underway) are powered to assess all-cause mortality (Table 1). The Multicenter

Table 1 Representative implantable cardioverter-defibrillator trials with clinical end-points

Trial	Type of prevention	Aetiologic heart disease	Number of patients	LVEF	Arrhythmia marker	Alternate therapy	Primary end-point
AVID	Secondary	Multiple	1016	Any	VT _s /VF	AA drug	Total mortality
BEST-ICD	Primary	CHD	1200	≤35	None	AA drug	Total mortality
CASH	Secondary	Multiple	390	Any	VT _s /VF	Conventional AA drugs	Total mortality
CIDS	Secondary	Multiple	650	Any	VT _s /VF syncope and VT ₁	Conventional AA drug	Total mortality
CABG-Patch	Primary	CHD	900	≤0.35	SAECG	None	Total mortality
Dutch CES	Secondary	Multiple	60	Any	VT ₂ /VF	Conventional AA drug	Cost effectiveness
DINAMIT	Primary	CHD	525	≤35	Low HRV	Conventional AA drugs	Total mortality
MADIT	Primary	CHD	196	≤0.36	VT _{ns} /VT ₁	AA drug	Total mortality
MADIT II	Primary	Multiple	1200*	≤0.30	VPC ≥ 10/HR, pairs	Conventional	Total mortality
MUSTT	Primary	CHD	704	≤0.40	VT _{ns} /VT ₁	None	SCD/CA
SCD HeFT	Primary	Multiple	2500	≤0.35	None	None/AA drug	Total mortality

*Sequential design. CA=cardiac arrest; CHD=coronary heart disease; SCD=sudden cardiac death; AA=antiarrhythmic drug; VF=ventricular fibrillation; VT₁=ventricular tachycardia inducible by programmed ventricular stimulation; VT_s=spontaneous sustained ventricular tachycardia; VT_{ns}=spontaneous non-sustained ventricular tachycardia; SAECG=signal averaged electrocardiogram; HRV=heart rate variability; VPC=ventricular premature complexes; HR=hour.

AVID^[3]=Antiarrhythmics Versus Implantable Defibrillators; BEST-ICD^[62]=The Beta-Blocker Strategy Plus ICD Trial; CASH^[1]=Cardiac Arrest Study Hamburg; CIDS^[17]=Canadian Implantable Defibrillator Study; CABG-Patch^[18]=Coronary Artery Bypass Graft-Patch Trial; Dutch CES^[63]=Dutch Cost-Effectiveness trial; DINAMIT^[22]=Defibrillation IN Acute Myocardial Infarction Trial; MADIT^[4]=Multicenter Automatic Defibrillator Implantation Trial; MADIT II^[21]=Multicenter Automatic Defibrillator Implantation Trial II; MUSTT^[19]=Multicenter Unsustained Tachycardia Trial; SCD HeFT^[20]=Sudden Cardiac Death HEart Failure Trial.

Automatic Defibrillator Implantation Trial (MADIT) is the first successful trial of implantable cardioverter-defibrillator therapy used for 'primary prevention'^[4]. Patients without previous symptomatic ventricular tachycardia events were enrolled using a combination of criteria: non-sustained ventricular tachycardia, previous Q wave myocardial infarction, left ventricular ejection fraction ≤35%, and inducible sustained ventricular tachycardia or ventricular fibrillation not suppressible by procainamide or an equivalent drug. The outcome in this trial was in favour of the implantable cardioverter-defibrillator-treated group vs the conventional therapy group which was not pre-specified (primarily amiodarone). There are issues involving imbalances in background therapy (e.g. beta-blockers) that confound the interpretation of the MADIT trial. The beneficial effect of implantable cardioverter-defibrillator therapy in MADIT has not been consistently seen in other primary prevention trials. A highly selected patient population in the MADIT trial appear to benefit from implantable cardioverter-defibrillator therapy, but a 'high-risk group for arrhythmic death' in the CABG Patch Trial failed to benefit from implantable cardioverter-defibrillator therapy^[18]. Such mixed results might imply that the indications for implantable cardioverter-defibrillator therapy may ultimately be a sequence of 'therapeutic niches' based on the populations studied in ongoing and future clinical trials (Table 1). Another possibility is that the populations selected, as well as other details of study design, may be as important in determining implantable cardioverter-defibrillator vs drug outcome as the respective therapies themselves.

In both MADIT and MUSTT (Multicenter Unsustained Tachycardia Trial)^[19], patients were required to have spontaneous non-sustained ventricular tachy-

cardia and inducible sustained ventricular tachycardia. The CABG-Patch used a different arrhythmic risk marker, the signal-averaged electrocardiogram. The Sudden Cardiac Death Heart Failure Trial (SCD HeFT)^[20] requires a left ventricular ejection fraction ≤35% and symptomatic heart failure, and the MADIT II^[21] trial focuses on low left ventricular ejection fraction (≤30%). The Defibrillator IN Acute Myocardial Infarction Trial (DINAMIT)^[22] utilizes depressed heart rate variability and low ejection fraction (Table 1).

The primary end-points chosen in these trials also vary, though most specify all-cause mortality. The CASH trial is unusual in that the primary end-point in the implantable cardioverter-defibrillator group is all-cause mortality, but the three-drug comparison groups specify death from any cause *plus* non-fatal cardiac arrest as the primary end-point. In CIDS the originally selected primary endpoint of arrhythmic death by the Hinkle-Thaler definition^[23] was changed to all-cause mortality. The primary end-point in MUSTT is sudden cardiac death plus non-fatal cardiac arrest, similar to the CAST approach. Similar study design issues and patient selection may likewise powerfully influence the results of trials focusing on implantable cardioverter-defibrillator shock end-points. These issues comprise the remainder of these conference proceedings.

Study designs utilizing 'implantable cardioverter-defibrillator shock' as the surrogate end-point

An important new area of investigation is the testing of antiarrhythmic drugs in patients with life threatening

Table 2 Alternative study designs in implantable cardioverter-defibrillator trials

	Design no. 1	Design no. 2	Design no. 3A	Design no. 3B
Group studied or proposed population	Asymptomatic — high risk for arrhythmic death (primary prevention) or previous arrhythmic event (secondary prevention)	Asymptomatic — high risk for arrhythmic death	Previous event (VT/VF or CA) or asymptomatic — high risk for arrhythmic death	Previous event (VT/VF or CA) or asymptomatic — high risk for arrhythmic death
Implantable cardioverter-defibrillator at baseline	No	No	Yes	Yes
Design				
Alternative primary end-points	1. All-cause mortality	1. All-cause mortality 2. All-cause mortality + appropriate ICD shocks	1. Appropriate ICD shocks 2. All-cause mortality 3. Both 1 & 2	1. Appropriate ICD shocks 2. All-cause mortality 3. Both 1 & 2

ICD=implantable cardioverter defibrillator; ®=randomization; VT=sustained ventricular tachycardia requiring intervention; VF=ventricular fibrillation; CA=cardiac arrest. See text for discussion.

ventricular arrhythmia who have an implantable cardioverter-defibrillator. In general, these trials are designed for one of two purposes: (1) to explore the potential clinical benefit of reducing the frequency of spontaneous arrhythmias and reduce the need for device intervention, particularly to reduce shock therapy and; (2) to determine if antiarrhythmic drug administration reduces the requirement for appropriate device intervention to such an extent that the drug might be used as primary therapy. In the latter context, implantable cardioverter-defibrillator discharge serves as a 'surrogate' for mortality. This 'surrogate' concept is replete with design and interpretative challenges which must be addressed before extrapolation of data to patients without an implantable cardioverter-defibrillator is valid^[24].

Arrhythmia trials focusing on implantable cardioverter-defibrillator end-points might assume a variety of design forms. Four alternative implantable cardioverter-defibrillator trial designs are presented in Table 2. The first design format compares implantable cardioverter-defibrillator to antiarrhythmic drug therapy in a randomized fashion for either primary or a secondary prevention. This simulates the AVID or MADIT study designs. In such a trial, the primary end-point would focus on mortality, not 'appropriate implantable cardioverter-defibrillator shocks'. The second design form (Table 2) without background implantable cardioverter-defibrillator is a randomization of high-risk patients to two pharmacological treatment groups. Patients would subsequently have implantable cardioverter-defibrillator implantation when clinically

justified, on an individual patient basis. In the past, trials of antiarrhythmic drug therapy have been subject to this problem^[25–27] and in the future, trials of severe heart failure evaluating ACE inhibitors or A-2 receptor blockers may include a large number of patients with implantable cardioverter-defibrillators as a 'bridge-to-transplant'. The implantation of such implantable cardioverter-defibrillator devices on an 'as needed' basis has the potential to create bias and cause problems with interpretation, which may confound the primary end-point (mortality) by imbalances in 'successful implantable cardioverter-defibrillator shocks'. If only small numbers of patients are fitted with an implantable cardioverter-defibrillator they might be censored from the trial or the fitting of the device might be considered an end-point in itself. If large numbers of patients receive an implantable cardioverter-defibrillator an end-point, such as 'appropriate implantable cardioverter-defibrillator shock', may need to be considered. Prospective statistical approaches to incorporate the evaluation of implantable cardioverter-defibrillator discharges as a primary or secondary end-point will be required for appropriate interpretation.

In Table 2, the third design includes patients who already have an implantable cardioverter-defibrillator for a previously documented arrhythmic event, who are randomized to an antiarrhythmic drug vs placebo (Design 3A) or an active control drug (Design 3B). The primary end-point might be 'appropriate implantable cardioverter-defibrillator discharge' and/or all-cause mortality. The comparison of one drug limb vs placebo is much easier to interpret than the use of two active

treatment strategies. The assumption inherent in such a design is that the implantable cardioverter-defibrillator will effectively treat both the spontaneous arrhythmia not prevented by the antiarrhythmic drug as well as drug-induced proarrhythmia. This theoretical design has many potential variations, four actual samples are detailed below.

Current trial designs with a primary end-point of 'implantable cardioverter-defibrillator shock'

The details of four actual implantable cardioverter-defibrillator protocols are presented in Table 3. All four trials have recruited patients and have a primary end-point including 'appropriate implantable cardioverter-defibrillator shock'. They are identified as Protocols A–D; the identification of the sponsor and the antiarrhythmic drug have been removed as they are not relevant to the discussion. The substantial differences in these four protocol designs suggest that the results of antiarrhythmic drug efficacy and safety may be influenced as much by important design issues as by the intrinsic antiarrhythmic properties of the drugs tested. For instance, in the four protocols listed in Table 3, enrolment of patients with new implantations vs remote implantable cardioverter-defibrillator implantation vary. In general, the protocols recruiting patients with remote implantable cardioverter-defibrillator implants require a recent 'appropriate implantable cardioverter-defibrillator discharge', although the interval between implantation and recruitment varies between protocols. All protocols specify that the implantable cardioverter-defibrillator have interrogation capacity and arrhythmia printout capability, none of the four protocols pre-specify the exact technical capabilities of the implantable cardioverter-defibrillator devices that can be included in the trial, which could create disparity in the quality of information provided by implantable cardioverter-defibrillator devices. The implantable cardioverter-defibrillators could have a wide variety of arrhythmia documentation capacity. Of some interest is the fact that none of the four protocols mandate a standardized approach (algorithm) for programming of arrhythmia detection or therapy.

The four protocols in Table 3 contain other important variations in study design features and assumption. All protocols selected a 12-month follow-up, yet the estimated sample sizes reflect a significant discrepancy in expected implantable cardioverter-defibrillator discharge rates. Although all trials are placebo-controlled, only one tests a dose-range of the antiarrhythmic drug (protocol C). Since this protocol also plans the smallest sample size, it has projected a very high implantable cardioverter-defibrillator shock rate. Baseline non-invasive electrophysiological study is required prior to hospital discharge in all protocols, but, the simulation protocol algorithm is not standardized in any of the

protocols. During follow-up, there is no systematic plan to repeat electrophysiological study testing of the implantable cardioverter-defibrillator or to systematically analyse, reprogramming after implantable cardioverter-defibrillator shocks.

A key issue is the definition of the primary end-point and its consequences. As seen in Table 3, the definition of the primary implantable cardioverter-defibrillator end-point varies. In two studies, the primary end-point is 'appropriate implantable cardioverter-defibrillator shocks' plus total mortality (protocols A, C); the remaining two protocols (B, D) designate the primary end-point as 'appropriate implantable cardioverter-defibrillator shock' alone. Of these, one selects mean time to first 'appropriate implantable cardioverter-defibrillator shock' (Protocol D) while a second (Protocol B) specifies the percent of patients who are 'appropriate implantable cardioverter-defibrillator shock-free' at one year. We will explore the consequences of choosing a specific primary end-point.

Another important area in which the protocols vary is the definition of the time from which the 'appropriate implantable cardioverter-defibrillator shocks' are initially counted. Rather than counting shocks from the time of randomization, two of these four protocols pre-specify a delay after randomization before counting implantable cardioverter-defibrillator events, to 'attain steady state plasma concentration of the study drug'. Neither early nor implantable cardioverter-defibrillator implantation-related events will be captured by such an approach, a bias that represents a deviation from the intention-to-treat principle^[28]. However, in-hospital early implantable cardioverter-defibrillator discharges during antiarrhythmic drug initiation might be considered less prognostically relevant than implantable cardioverter-defibrillator shocks months later as an outpatient so that an analysis of implantable cardioverter-defibrillator shock temporal distribution might be important.

The four protocols vary substantially in the projected one-year placebo implantable cardioverter-defibrillator discharge event rate (a range of 35–75%). Clearly, they cannot all be correct! Only protocol D pre-specifies an interim analysis to adjust the sample size relative to the actual event rate observed (protocol D) rather than relying solely on a wide spectrum of observed historical control estimates. A representative sample of the wide spectrum of published implantable cardioverter-defibrillator discharge rates are listed in Table 4. This variation in published event rates explains the variation in estimating expected implantable cardioverter-defibrillator shock rates in the protocols listed in Table 3.

In general, the protocols in Table 3 excluded patients with unstable angina. None excluded patients with measurable ischaemia nor mandated testing for or quantifying ischaemia. Depending upon the drug(s) tested, the proarrhythmic potential of antiarrhythmic therapy may be related to the extent of ischaemia; as identified in the CAST^[29]. Likewise, while decompensated (NYHA

Table 3 Comparative features of implantable cardioverter-defibrillator protocols

Patient population	1. Sample size 2. Placebo 3. Duration	ICD testing (inducible/terminated)	Primary end-point	Secondary end-point	Statistical analysis	Additional comments
Protocol A • New ICD (w/in 3 mo) • Old ICD generator replaced (≥ 1 shock w/in 6 mo)	1. n = 350 2. yes vs 1 dose 3. 12 mo	• pre-discharge • 3 mo • adequate safety (<10 J below maximum energy of ICD to terminate)	• time to first appropriate ICD shock or death	• mean time to shock for successive shocks • total # of ICD shocks per group	• estimated event rate: placebo = 35% drug X = 20% • 80% power to detect difference; $\alpha = 0.05$	• analysis begins with 1st dose • prospective subset analysis: LVEF $\leq 30\%$ vs >30% • amio d/c for 3 mo
Protocol B • Pre-ICD trans thoracic 72 h transvenous 48 h • Post ICD ≥ 1 ICD d/c, ≤ 6 mo	1. n = 360 2. yes, vs 1 dose 3. 12 mo	• testing after 3–5 days of blinded drug assignment (in-pt only)	• % patients in each group free of appropriate ICD shock	• time to 1st ICD shock • total # ICD shocks • time to arrhythmic death	• estimated placebo event rate = 50% • 80% power ($\alpha = .05$) to detect 33% reduction	• ICD shock ≤ 48 hr not counted • amio d/c 1 mo
Protocol C • New ICD (≤ 30 d) implant • Old ICD (>30 d), must have ≥ 1 ICD d/c w/in 1 yr • Inducible+ICD terminated	1. n = 160 2. placebo and 3 doses of drug 3. 12 mo	• pre-discharge non-invasive EPS • 3 mo noninvasive EPS • *must have DFT ≥ 10 J below maximum ICD energy	• time to 1st ICD shock & death	• time to all ICD shocks and death • total # ICD shocks • time to all appro. ATP events	• estimated placebo event rate = 75% • new = 60% • 30 = 93% • mortality = 5%	• pre-specified analysis: LVEF $\leq 35\%$ LVEF >35% • explore 3 doses over 4-fold dose range • amio d/c ≥ 2 mo
Protocol D • New: in-hospital • Old: requires washout non-invasive EPS but 'ICD event' not required	1. n = 150 2. placebo and 1 dose of drug with down titration 3. 12 mo	• noninvasive PES day #3 of study drug • repeat noninvasive EPS @ 1 mo & 12 mo	• time to 1st ICD shock (only)	• total # patients free of ICD shocks • total # ATP Rx • time to, frequency of symptomatic arrhythmia w/o ICD or ATP	• $\alpha = 0.05$ • 80% power to detect 30% difference adjusted for placebo rate in first 30 pts	• efficacy evaluation begins post-hosp d/c • stratified randomization • interim analysis to plan other studies w/o adjustment or p-value

amio = amiodarone; ATP = tiered pacing termination of VT; d = day; d/e = discharge; DFT = defibrillation threshold; EPS = electrophysiologic study; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; mo = month; pt = patient; w/o = without; yr = year; % = percent.

Table 4 The reported incidence of implantable cardioverter-defibrillator shocks in various trials

Study	Number of patients	Mean follow-up (months)	Percent patients with ICD shock
Böcker ^[37]	107	12	48%
Böcker ^[38]	603	26	49%
Myerburg ^[64]	60	16	63%
Huang ^[65]	53	18	32%†; 29%‡
Grimm ^[66]	241	36	42%
Kelly ^[67]	90	17	51%
Hook ^[31]	48	15	60%
Saksena ^[68]	200	12	33%
Echt ^[69]	68	9	54%*

*Includes all shocks (no interrogation); †on amiodarone; ‡control, not on amiodarone.

IIIb and IV) heart failure was excluded, none of the protocols defined a standard strategy to manage heart failure. The relationship between antiarrhythmic efficacy and the severity of left ventricular dysfunction and heart failure is a clinically important interaction. Finally, no attempt is made in any of these protocols to encourage the use of beta-blockers despite the consistent demonstration of improved outcome in patients on antiarrhythmic therapy taking beta-blockers.

In summary, the four trials in Table 3 have a wide variation in protocol assumptions, with many potential impediments to meaningful comparison as well as risk-benefit interpretation. Given the problems in study design, how will we interpret a finding of no difference?

Complexities in interpreting 'appropriate implantable cardioverter-defibrillator shock' as the primary end-point

A major challenge is to define 'appropriate implantable cardioverter-defibrillator shock'* in such a way as to be the most relevant surrogate to represent an improved clinical outcome. It is obvious that all 'appropriate' implantable cardioverter-defibrillator shocks are not of equal clinical relevance. While device data logs allow the distinction of 'appropriate implantable cardioverter-defibrillator shocks' (for ventricular tachycardia/ventricular fibrillation) from inappropriate shocks, it may also be desirable to distinguish appropriate

*The term 'appropriate implantable cardioverter-defibrillator shock' will eventually become unnecessary when implantable cardioverter-defibrillator diagnostics become more accurate. Already, innovations such as ventricular electrocardiogram width, and atrial and ventricular sensing, coupled with supporting algorithms, have refined the diagnosis of ventricular tachyarrhythmias by implantable devices. For the time being we have chosen to retain the term 'appropriate implantable cardioverter-defibrillator shock' because the diagnostic accuracy of the majority of implantable devices is not adequate for our purposes, and because stored electrogram data cannot always be interrogated and analysed.

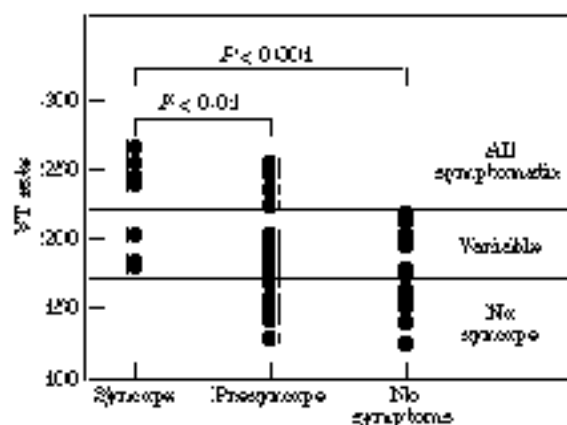


Figure 1 The relationship of the rate of sustained VT to the likelihood of symptoms.

implantable cardioverter-defibrillator shocks with minimal or no symptoms from documented ventricular tachyarrhythmic events associated with syncope or presyncope^[30,31].

Severe symptoms (including syncope) are usually, but not invariably associated with ventricular tachycardia cycle lengths of <250 ms (Fig. 1). Important clinical modifiers of the threshold ventricular tachycardia rate that will result in severe symptoms include the extent of left ventricular dysfunction and heart failure status^[32,33]. With tiered therapy implantable cardioverter-defibrillator devices, ventricular pacing termination of certain ventricular tachycardia events is feasible^[34]. These ventricular tachycardia events, although at a slower rate than required to trigger an implantable cardioverter-defibrillator shock, are still clinically relevant. Presumably, a full description of the various tiered therapy arrhythmic events will best characterize differences between placebo and antiarrhythmic drugs, but will introduce a potentially complicated problem of weighted end-points. Full disclosure must include the realization that antitachycardia pacing (ATP)-related therapy of a slow ventricular tachycardia may either induce^[35] or prevent^[36] a faster unstable ventricular tachycardia or ventricular fibrillation; i.e. an ATP proarrhythmic or antiarrhythmic effect.

Defining 'appropriate implantable cardioverter-defibrillator shocks'

Documented arrhythmic events that are represented as 'appropriate implantable cardioverter-defibrillator shocks' serve as a surrogate for sudden death^[37]. Documentation of the 'appropriateness' of implantable cardioverter-defibrillator shocks requires careful analysis of stored electrograms in the implantable cardioverter-defibrillator as well as any ECG evidence that is available. The accuracy of this assessment is dependent upon the electrogram storage capabilities of the implantable cardioverter-defibrillator. Device

reprogramming is often performed based upon the analysis of the stored electrograms. Device reprogramming can dramatically reduce the incidence of 'inappropriate implantable cardioverter-defibrillator shocks' (for non-sustained ventricular tachycardia, or atrial arrhythmias). The protocol can greatly improve the assessment of arrhythmic end-points by specifying that implantable cardioverter-defibrillator devices be limited to those with sophisticated electrogram storage, interrogation and analysis. A procedure for evaluating the stored electrograms by an expert committee blinded to study drug assignment assures the most objective analysis.

Ventricular tachycardia rate-based definition

For implantable cardioverter-defibrillator discharge to be a meaningful surrogate for cardiac arrest, a rate cut-off definition is essential. A conservative cut-off-rate of >240 beats \cdot min has been suggested as a surrogate for sudden death^[38]. Most ventricular tachyarrhythmias at a rate >240 beats \cdot min⁻¹ are either ventricular flutter or ventricular fibrillation, are rarely self-terminating and are usually symptomatic (Fig. 1). This does not necessarily indicate that such a rapid ventricular tachycardia is always symptomatic before termination by an appropriate implantable cardioverter-defibrillator discharge. In fact, patients with electrocardiographically documented ventricular fibrillation preceding a spontaneous implantable cardioverter-defibrillator shock, may have no ventricular tachycardia preceding ventricular fibrillation and only mild or no prodromal symptoms prior to the shock.

In general, both deaths and appropriate device interventions should be included in the primary end-point. Obviously, deaths must be considered trial end-points, but device interventions need not lead to the patient being censored from the trial. The time to first device intervention, restricted or not to the treatment of fast or very fast ventricular tachyarrhythmias, is only one of many potential outcome parameters. It is important that patients with device intervention events remain in the trial and on trial medication in order to gather as much outcome parameter data as is possible. To censor patients at the time of the first device intervention depletes the trial population such that other significant end-points and outcome events, including death, would not be assessed in a sufficiently large population. In other words, it is not enough to measure 'shock-free survival' as a primary end-point if most events are shocks and the population surviving shock-free is a small proportion of the original sample.

An implantable cardioverter-defibrillator is not merely a passive monitor in a trial of antiarrhythmic therapy for patients fitted with an implantable cardioverter-defibrillator. The implantable cardioverter-defibrillator will also offer, in response to programmed parameters, interventions that will disturb the signal, for example arrhythmic death, which is intended to be quantified in order to measure the antiarrhythmic

efficacy of a particular therapy. More than this, the implantable cardioverter-defibrillator intervention may be proarrhythmic in that intervention mistakenly or inappropriately applied to non-fatal rhythms may induce fatal or near fatal events. For example, an implantable cardioverter-defibrillator may deliver anti-tachycardia pacing in response to sinus tachycardia, supraventricular tachycardia, atrial fibrillation, non-sustained ventricular tachycardia or slow ventricular tachycardia, which stimulates fast ventricular tachycardia or ventricular fibrillation. The resulting arrhythmia may be an actual or near death event and will be included as such within the trial outcome measurements. The bradycardia prevention pacing offered by an implantable cardioverter-defibrillator may also be antiarrhythmic (for example, ventricular rate smoothing which will minimize the likelihood of torsades de pointes) or proarrhythmic (for example, asynchronous pacing including a ventricular or supraventricular tachyarrhythmia). Thus, an implantable cardioverter-defibrillator may, materially but unpredictably adjust the likelihood of events that may trigger device interventions.

Extrapolation to non-implantable cardioverter-defibrillator populations

The protocols in Table 3 all involve background implantable cardioverter-defibrillator therapy. There is no consensus regarding the degree to which (if any) the observation of drug efficacy in preventing implantable cardioverter-defibrillator shocks can be extrapolated to similar patients without an implantable cardioverter-defibrillator. Even if the non-implantable cardioverter-defibrillator population closely resembles the implantable cardioverter-defibrillator patients demographically, the assumption of comparable efficacy may not be justified, since the efficacy of drug therapy in addition to an implantable cardioverter-defibrillator may be very different from the efficacy of drug alone. For example, antiarrhythmic drug therapy alone may reduce symptomatic non-fatal arrhythmic events but increase fatal events, whilst when drug and device are used in combination, both non-fatal and fatal events might be reduced. On the other hand, drug therapy may convert sustained ventricular tachycardia to non-sustained arrhythmias. However, due to the rapid intervention of implantable cardioverter-defibrillator therapy, 'mortality' benefit of drug therapy may be underestimated by implantable cardioverter-defibrillator interventions. There are no actual examples of such data extrapolation, and there is no regulatory precedent to suggest such implantable cardioverter-defibrillator-shock results could lead to drug approval for a non-implantable cardioverter-defibrillator based population. In general, in the U.S., the labelled indication of a new drug applies specifically and only to types of patients studied.

Table 5 Theoretical true event rates of a 1-year implantable cardioverter-defibrillator end-point trial

	Placebo	Drug A	Drug B	Drug C
ICD shock end-points alone				
% pts with ≥ 1 appropriate ICD shock at 12 mo [primary end-point]	48	60	32	31
% pts with ICD shock (CL ≤ 240 ms)	12	23	19	7
% pts with symptomatic shock	18	29	26	12
ICD end-points and death				
% death	8	10	12	8
% death plus % pts with ≥ 1 ICD shock	50	65	40	35
% death plus & ICD shock (CL ≤ 240 ms)	20	31	28	14
% death plus % symptomatic ICD shock	24	37	34	18

n=number of patients; ICD=implantable cardioverter defibrillator; pts=patients; mo=months; CL=cycle length; %=percent.
See text for discussion of the results.

Impact of antiarrhythmic drug selected for study

Antiarrhythmic therapy can reduce the frequency of appropriate implantable cardioverter-defibrillator shocks, but some antiarrhythmic drugs can increase rather than decrease defibrillation threshold; causing arrhythmic events more resistant to successful implantable cardioverter-defibrillator shock therapy; a unique implantable cardioverter-defibrillator 'proarrhythmia'. Increased defibrillation thresholds have been reported in individual patients with many Vaughn Williams class I drugs^[39-41]. In contrast, certain class III drugs (dofetilide, D,l sotalolol, d-sotalol) have been reported to lower defibrillation energy requirements^[42-44]. Amiodarone, which has a complex electrophysiological profile, produces increased defibrillation energy requirement in some patients which could lead to defibrillation failure^[45]. Traditional proarrhythmic effects can also occur with antiarrhythmic therapy in patients with an implantable cardioverter-defibrillator, for instance, torsades de pointes ventricular tachycardia. Class I antiarrhythmics can produce sustained (incessant) ventricular tachycardia, especially with class IC use^[6].

Implantable cardioverter-defibrillator therapy has not been shown to be effective for antiarrhythmic drug-associated ventricular tachycardia such as torsades de pointes or incessant ventricular tachycardia. Multiple recurrences of drug-induced ventricular tachycardia could defeat implantable cardioverter-defibrillator therapy, and culminate in death. Thus, antiarrhythmic therapy could decrease 'appropriate implantable cardioverter-defibrillator shocks; (positive primary end-point), but cause lethal proarrhythmic effects in a subset. A theoretical dichotomy between the primary efficacy end-point (in terms of reducing 'appropriate implantable cardioverter-defibrillator shocks') while increasing mortality, points to the complexity of interpreting a combined end-point of implantable cardioverter-defibrillator discharge and death.

The proarrhythmic potential of inappropriate implantable cardioverter-defibrillator therapy must also be considered. For example, both monomorphic sustained ventricular tachycardia and polymorphic varieties of sustained and non-sustained ventricular tachycardia may be provoked by overdrive pacing or inappropriate implantable cardioverter-defibrillator discharge. Should such arrhythmias prove fatal their contribution to the mortality end-point (and usually the primary end-point) would confuse the result with respect to extrapolation to non-implantable cardioverter-defibrillator populations. Conversely, antiarrhythmic drugs that prolong repolarization (I_{Kr} blocker) might decrease implantable cardioverter-defibrillator discharges for monomorphic ventricular tachycardia (antiarrhythmic effect) while increasing implantable cardioverter-defibrillator shocks required for pause-dependent polymorphic ventricular tachycardia (proarrhythmic effect).

Theoretical results of an implantable cardioverter-defibrillator end-point trial

The theoretical results of a parallel, 1-year trial comparing implantable cardioverter-defibrillator patients assigned to either placebo or to one of three antiarrhythmic drugs (or doses), utilizing implantable cardioverter-defibrillator end-points, are represented in Table 5. Even assuming that 'appropriate' implantable cardioverter-defibrillator shocks have been precisely defined and documented, a new set of obstacles in interpretation exist in assessing clinical benefit. The primary end-point in this theoretical trial is the 'percent of patients with ≥ 1 appropriate implantable cardioverter-defibrillator shock' (Table 5). The results reveal a placebo implantable cardioverter-defibrillator shock event rate of 48%; drugs B and C significantly reduce implantable cardioverter-defibrillator shocks compared to placebo (the primary end-point). However, there are other important differences between drugs B and C. Drug B appears to suppress slower ventricular tachycardia, but

is associated with an increased number of serious ventricular tachycardia/ventricular fibrillation events (cycle length <240 ms) and increases symptomatic events. In contrast, drug C is consistent in reducing both slower and more serious arrhythmic events. Analysing the combined implantable cardioverter-defibrillator shocks plus death suggests drug C will be useful, whereas drug B is better than placebo as regards the primary implantable cardioverter-defibrillator end-point, but should be considered unsuitable for use with an implantable cardioverter-defibrillator. Drug A has a consistently proarrhythmic profile. Since slower ventricular tachycardia may lead to serious symptoms in patients with a low left ventricular ejection fraction, symptomatic implantable cardioverter-defibrillator shocks may also be an important marker for clinical benefit.

Evaluation of the time-course of implantable cardioverter-defibrillator shocks (Kaplan–Meier analysis) may also reveal a component of potential proarrhythmia. For instance, observed increase in early implantable cardioverter-defibrillator shocks using an I_{Kr} blocker (presumed torsades) may be masked by a later suppression of implantable cardioverter-defibrillator shocks for monomorphic sustained ventricular tachycardia (an antiarrhythmic effect). This would be evident on evaluation of the time-course display of the Kaplan–Meier curve.

A complete profile of all the implantable cardioverter-defibrillator end-points, including deaths, best characterize the differences between drugs and placebo. As the results from drugs B and C demonstrate, limiting consideration to the single primary implantable cardioverter-defibrillator end-point (percent of patients with ≥ 1 implantable cardioverter-defibrillator shock), fails to differentiate a potentially adverse drug (drug B) from a potentially beneficial therapy (drug C). Pacing termination of slower ventricular tachycardia (ATP) may also occur frequently and is an additional factor that should not be ignored in assessing implantable cardioverter-defibrillator shock frequency as an efficacy end-point (not included in the example in Table 5). All implantable cardioverter-defibrillator and ATP end-points must be interpreted in the context of the more definitive (albeit less frequent) end-point of total mortality.

The major implication from these theoretical data presented in Table 5 is that a predefined primary implantable cardioverter-defibrillator end-point should be regarded as an arbitrary efficacy signal to be interpreted in the context of other outcome data. Considered in isolation, 'reduction of implantable cardioverter-defibrillator shocks' is only a potential surrogate that may or may not reflect patient benefit. While the focus of this discussion has been on an implantable cardioverter-defibrillator efficacy end-point, antiarrhythmic therapy resulting in a neutral outcome for mortality (drug=placebo) with no signals of proarrhythmia could provide compelling evidence of drug safety in a high-risk ventricular tachycardia/ventricular fibrillation population.

These four implantable cardioverter-defibrillator protocols (A–D) focus upon the 'time to first appropriate implantable cardioverter-defibrillator shock'. Partly, this is preferred because it is an easily definable end-point, but also because similar types of end-points (e.g. time to first symptomatic attack of atrial fibrillation) have been successfully used in supraventricular arrhythmia trials. However, alternative evaluations of implantable cardioverter-defibrillator shock results may be more relevant to estimating potential patient benefit. In implantable cardioverter-defibrillator-based trials, some patients will be expected to have no implantable cardioverter-defibrillator shocks for the duration of the trial, while others will experience repetitive implantable cardioverter-defibrillator shocks, sometimes clustered in a short interval.

In order to present a comprehensive picture of the beneficial effect of an antiarrhythmic drug on appropriate implantable cardioverter-defibrillator shocks, a group of secondary analyses are required, for example: (1) total number of shocks in each treatment group; (2) number of patients in each group that are implantable cardioverter-defibrillator event free; (3) number of patients in each group with two or more implantable cardioverter-defibrillator shocks; (4) the total and average number of days that the patients in each treatment group are 'implantable cardioverter-defibrillator shock-free'; (5) the rate of implantable cardioverter-defibrillator shocks per year of patient exposure by treatment group; (6) the number of implantable cardioverter-defibrillator shocks associated with severe symptoms; (7) number of appropriate implantable cardioverter-defibrillator shocks for cycle length (CL) <240 ms; (8) for antiarrhythmic drugs that prolong repolarization (e.g. I_{Kr} blocker) a breakdown of implantable cardioverter-defibrillator shocks for monomorphic ventricular tachycardia and pause-dependent polymorphic ventricular tachycardia should be included.

Such a comprehensive analysis can best define potential patient benefit while also allowing the detection of even subtle proarrhythmia. Clearly, the best outcome for an antiarrhythmic drug would be a significant reduction, compared to placebo, in time to first implantable cardioverter-defibrillator shock, as well as a reduction in each secondary implantable cardioverter-defibrillator shock end-point.

Can implantable cardioverter-defibrillator interrogation clarify the cause of death?

Early models of the implantable cardioverter-defibrillator provided limited information in the form of data logs of average or individual RR intervals. Current third and fourth generation implantable cardioverter-defibrillator devices also assess and report information regarding suddenness of arrhythmia onset, rate stability and morphology. The available information is

dependent upon the specific lead system. If a dedicated bipolar system is used for recording, only localized signals are obtained. On the other hand, if an integrated bipolar system, or one which records from shocking electrodes, is used, atrial activity and the ventricular electrogram morphology can be analysed in greater detail. Because in general it reflects a change in the direction of ventricular activation, a change in electrogram morphology is thought to be diagnostic of a ventricular arrhythmia. Notably, however, bundle branch block also alters electrocardiogram morphology. Conversely, some ventricular arrhythmias produce electrogram morphologies virtually identical to those resulting from arrhythmias of supraventricular origins, rendering morphology criteria for arrhythmia classification neither completely sensitive nor specific^[46–48]. Nevertheless, stored data from implantable cardioverter-defibrillators is generally desirable for assignment of clinical trial end-points because: (1) when arrhythmic causes of death or morbidity are considered, the history is notoriously inaccurate and imprecise for classification; (2) the quantitative and objective nature of stored information can potentially improve the sensitivity and specificity of end-point assignment by avoiding subjective and qualitative interpretation; and (3) arrhythmia information can be incorporated into the temporal sequence of clinical events antecedent to death.

Although the use of objective, qualitative data is desirable for implantable cardioverter-defibrillator end-point assignment, its accuracy will only be as good as the precision of the data generated and its analysis. Unfortunately, this may be highly variable in multicenter trials that use a multiplicity of devices. In addition, ventricular tachycardia detection algorithms are far from perfect. First, for an event to be stored, an abnormality must be detected. Furthermore, electrogram amplitude can deteriorate to a point that ventricular fibrillation remains undetected and a terminal rhythm is called bradycardic rather than tachycardic^[49,50]. The evaluation of electrograms is subjective; it is possible to do only limited qualitative analysis of the tracing to assign similarity or difference from baseline recordings. Finally, there are few published data on intra- and inter-observer variation in the assignment of specific arrhythmic events detected by the implantable cardioverter-defibrillator.

Technology is being developed to improve the diagnostic accuracy and quality of stored information from implantable cardioverter-defibrillators. Detection algorithms are constantly being improved, and new techniques are being developed to diagnose more precisely the arrhythmia and its mechanism^[51]. These techniques include analysis of the atrioventricular relationship, multi-point endocardial-sensing, phase analysis, fast Fourier transform analysis and the incorporation of physiological parameters such as intracardiac pressures, dP/dt, systolic time intervals, mixed venous oxygen, impedance and indices of ischemia^[52–56]. An exciting new technology, implantable event recorders, has been developed in order to record, analyse and store information about the cardiac rhythm and possibly,

in the future, to monitor other physiologic data^[57]. Devices incorporating these technologies should provide more accurate monitoring for the assessment of antiarrhythmic drugs but would not provide any safety-net therapy for drug-related or drug-resistant arrhythmia.

A major limitation of implantable cardioverter-defibrillator device interrogation involves the availability of ECG information at the time of death. It is more likely than not that the implantable cardioverter-defibrillator will be buried with the patient. Frequently, even if retrieved, there are technical difficulties with device interrogation, or the implantable cardioverter-defibrillator may have been programmed off prior to death. In a previous implantable cardioverter-defibrillator trial, despite extraordinary efforts to recover and use implantable cardioverter-defibrillator electrograms to assist assessment of the cause of death, it was only possible to retrieve meaningful implantable cardioverter-defibrillator interrogation information in less than one-third of the death^[58]. In the AVID trial implantable cardioverter-defibrillator interrogation information and stored electrograms were available for analysis in less than 102 deaths.

Even when implantable cardioverter-defibrillator information is available from the hours preceding death, sustained ventricular tachycardia events with appropriate implantable cardioverter-defibrillator shocks may not accurately classify a death as arrhythmic. The clinical situation may overwhelm the importance of frequent sustained ventricular tachycardia in the final hours of a patient's life; for instance, when observed in a patient hospitalized with progressive end-stage heart failure^[56,58].

In summary, stored electrogram data from current implantable cardioverter-defibrillators provide useful information for classifying arrhythmic events in living patients. Unfortunately, stored electrograms are less useful in the classification of deaths because the data are often unavailable and terminal arrhythmias may be irrelevant to the true cause of death. However, the consistent use of sophisticated data storage and telemetry could significantly improve the classification of arrhythmic events and, when available, death classification. As a result of implantable cardioverter-defibrillator analysis of electrograms at the time of death, arrhythmic death might be further categorized as: (1) fatal ventricular tachycardia/ventricular fibrillation despite appropriate device function; (2) fatal ventricular tachycardia/ventricular fibrillation with device malfunction; (3) fatal asystole with device malfunction; (4) fatal asystole despite appropriate device function. Such an 'electrical' classification should be interpreted in the context of the entire clinical situation.

Statistical perspective

As noted in Table 3, some of the implantable cardioverter-defibrillator trials propose a primary

combined end-point of 'appropriate implantable cardioverter-defibrillator discharges' plus death. There are many statistical challenges associated with handling multiple outcome measures (end-points) which impinge on the design, analysis, and reporting in such a clinical trial^[59]. Problems are enhanced by the limited size of trials, such as those that we are considering. Often there is an exaggerated desire to categorize trials as either 'positive' or 'negative', obsessions with $P < 0.05$ and manipulative instincts tend to emphasize the more positive results obtained post-hoc by data dredging, and distorted reporting often occurs. A partial solution to this problem is a careful definition of a pre-defined primary end-point. However, this is not a panacea and can over-simplify the genuinely more complex reality of a multi-outcome process such as the situation considered here; combining 'appropriate implantable cardioverter-defibrillator shocks' with clinical end-points such as cardiac arrest and death.

One approach is to correct for multiple significance testing across several outcome measures by demanding more extreme P -values (e.g. by Bonferroni correction)^[60], but this does not take account of reasonable clinical priorities. Also, the inter-relationships between outcomes make such correction procedures over-conservative and then over-emphasize significance testing. There are global test statistical techniques which take into account multiple outcome measures and their inter-correlation^[61], but they are quite complex and over-emphasize testing results to the detriment of estimation of the magnitude of meaningful clinical treatment differences.

In the case of the implantable cardioverter-defibrillator end-point trial theoretical results presented in Table 5, death is relatively uncommon as compared to 'appropriate implantable cardioverter-defibrillator shocks'. Thus, if the primary end-point is time to first implantable cardioverter-defibrillator shock or death, it is a useful efficacy summary, provided each constituent outcome is also analysed separately in a secondary analysis. However, such a composite can be hard to interpret, and fails to take into account the different clinical importance and different frequencies of these two vastly discrepant constituent outcomes. It often gives too much weight to the most common of the contributory outcomes (in this case, 'appropriate implantable cardioverter-defibrillator shock') which is often the least severe and clinically relevant event. This will be particularly misleading if the relatively rare outcome (death) is adversely affected by the antiarrhythmic drug, while the common component of the primary end-point (implantable cardioverter-defibrillator shock) shows a beneficial effect. Such an interpretative problems inherent with implantable cardioverter-defibrillator trials in which 'implantable cardioverter-defibrillator shock events' are likely to exceed the number of deaths by 5–10-fold. A detailed understanding of the interrelationships and time sequences of multiple outcome measures is useful in determining how best to use all available outcome data. Meticulous clinical trial design with pre-

specified end-point definitions, objective classification and pre-specified analysis priorities assist in the most objective and clinically relevant interpretation.

Overall, a statistical strategy for handling multiple outcomes is best agreed upon at the design stage of a clinical trial; that is, it should be pre-specified. Attention to pre-defined statistical rigour should not override the benefits of flexibility based on the results of clinical experience, as exemplified by the scenarios depicted in Table 5. Statistical formality without over-complexity, avoidance of data dredging, clinical understanding and common sense all play a role in formulating a sensible and appropriate strategy for the analysis which will result in an appropriate, objective clinical interpretation.

Recommendations for implantable cardioverter-defibrillator end-point trials

Patient selection

- Special consideration should be given to patient selection. Patients with a new or recent implantable cardioverter-defibrillator implant appear to have a higher incidence of implantable cardioverter-defibrillator shocks than patients with an old implantable cardioverter-defibrillator implant. Limiting enrolment to patients with an antecedent ventricular tachycardia/ventricular fibrillation event receiving a new or recent implant, will increase the statistical power of the 'implantable cardioverter-defibrillator shock end-point'.
- If patients with either old and new implantable cardioverter-defibrillator implants are to be enrolled, a stratified randomization to ensure balance of implantable cardioverter-defibrillator shock event rates should be considered. A pre-specified minimum percent of new implantable cardioverter-defibrillator implant patients (e.g. $\geq 50\%$ of enrolment), should be considered.
- Patients with new or relatively unstable angina and/or decompensated clinical heart failure are not appropriate candidates for an implantable cardioverter-defibrillator end-point trial. Enrolment should include only patients on standardized medical regimens for heart failure and ischemia. Every effort should be made to maximize the use of beta-blockers and ACE inhibitors. If revascularization is required, randomization should be considered after a recovery period.

Design issues

- An implantable cardioverter-defibrillator end-point trial is a reasonable context in which to explore a dose-range of an antiarrhythmic drug, both with respect to minimally effective and maximally tolerated doses.

- The protocol should specify minimally acceptable implantable cardioverter-defibrillator technical standards. At a minimum, in addition to tiered therapy, an implantable cardioverter-defibrillator device should have excellent ECG storage and morphology recognition capabilities. Ideally, a study would be limited to a third or fourth generation implantable cardioverter-defibrillators made by one manufacturer, although this is probably impractical, and might limit recruitment.
- The protocol should contain a pre-specified methodology to define 'appropriate implantable cardioverter-defibrillator shocks'. The assessment of 'appropriate implantable cardioverter-defibrillator shocks' should include all shocks for ventricular tachycardia/ventricular fibrillation, defined as: (1) implantable cardioverter-defibrillator shocks for ventricular tachycardia with a *cycle length* <250 ms; and/or (2) implantable cardioverter-defibrillator shocks which are associated with syncope/pre-syncope.
- The outcome parameter of 'free of device intervention' is critically dependent on the precise programming of the implantable cardioverter-defibrillator. Thus if this outcome is to have any meaning, an attempt must be made to standardize device programming, or to document and preferably ensure a similar distribution of intervention criteria in both treatment limbs. The frequency of ATP pacing must also be collected.
- The timing of in-hospital and outpatient testing for defibrillation threshold and ventricular tachycardia rate should be pre-specified and protocol mandated. Maximal acceptable increases in defibrillation threshold and ventricular tachycardia rate during initial in-patient testing on study medication should be defined in the protocol. Strong consideration should be given to standardize (and mandate) a minimal frequency of periodic outpatient testing at specified interval(s), if the test drug alters defibrillation energy requirements or ventricular tachycardia rates.
- The classification of implantable cardioverter-defibrillator electrograms should be performed by a committee with expertise in implantable cardioverter-defibrillator electrogram interpretation. This committee should adhere to a pre-specified protocol for implantable cardioverter-defibrillator electrogram interpretation, and be blinded to treatment assignment. There should be an effort to define intra- and inter-observer reproducibility of arrhythmia classification assignment.
- For implantable cardioverter-defibrillator end-point trials, the most clinically interpretable primary end-point is probably time to first *appropriate implantable cardioverter-defibrillator shock or death*. However, other potentially clinically relevant outcome events should also be considered as secondary end-points, including the frequency of ATP pacing.
- Even if a patient has an appropriate device intervention (implantable cardioverter-defibrillator shock), the patient should not be censored; rather followed for the duration of the trial, to include subsequent events including death.

Statistical analysis

- A pre-specified methodology regarding the statistical methodology to analyse the combined primary end-point should be stated. A prospective statistical approach to also consider other secondary implantable cardioverter-defibrillator end-points of interest (e.g. paced termination of ventricular tachycardia, implantable cardioverter-defibrillator shocks for symptomatic ventricular tachycardia) should be defined. The inherent problem of the proposed combined implantable cardioverter-defibrillator primary end-point is that the less severe events (implantable cardioverter-defibrillator shock events) are common and will receive too much weight relative to the less common constituent of the primary end-point (death).
- Consideration should be given to include a protocol-directed interim analysis to confirm the estimated 'implantable cardioverter-defibrillator event rate'. Adjustment of sample size should be included in the protocol as an option, depending on the magnitude of differences between the expected and the observed implantable cardioverter-defibrillator event rate.

Regulatory issues

- The validity of extrapolating the positive results of antiarrhythmic efficacy in an implantable cardioverter-defibrillator trial to other populations at risk for arrhythmic death without an implantable cardioverter-defibrillator is not established, has no precedent and may not be appropriate. Adverse antiarrhythmic drug results in an implantable cardioverter-defibrillator trial would, in similar fashion, require care when extrapolating to a non-implantable cardioverter-defibrillator population.
- At the time of this review, one antiarrhythmic drug has demonstrated a significant reduction in implantable cardioverter-defibrillator shock rates. However, ATP pacing episodes were not reported^[70]. Two trials have been completed or stopped, but neither is yet published. At present, there has been no regulatory example of an application for approval of an antiarrhythmic drug to reduce implantable cardioverter-defibrillator shocks and/or decrease implantable cardioverter-defibrillation threshold.
- Presumably, even a neutral result with antiarrhythmic drug, with no evidence of proarrhythmia, could be used as supporting evidence for safety in a high risk ventricular tachycardia/ventricular fibrillation population.

References

- [1] Siebels J, Cappato R, Ruppel R *et al.*, for the CASH Investigators. Preliminary results of the Cardiac Arrest Study Hamburg (CASH). *Am J Cardiol* 1993; 72: 109F-113F.

- [2] Siebels J, Kuck KH. Implantable cardioverter defibrillator compared with antiarrhythmic drug treatment in cardiac arrest survivors (the Cardiac Arrest Study Hamburg). *Am Heart J* 1994; 127: 1139–44.
- [3] The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near fatal ventricular arrhythmias. *N Engl J Med* 1997; 337: 1576–83.
- [4] Moss AJ, Hall J, Cannom DS *et al.*, for the Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmias. *N Engl J Med* 1996; 335: 1933–40.
- [5] Hohnloser SH, Singh BN. Proarrhythmia with Class III antiarrhythmic drugs: definition, electrophysiologic mechanisms, incidence, predisposing factors, and clinical implications. *J Cardiovasc Electrophysiol* 1995; 6: 920–36.
- [6] Sagie A, Strasberg B, Kusnec J *et al.* Rapid suppression of flecainide induced incessant ventricular tachycardia with high dose intravenous amiodarone. *Chest* 1988; 93: 879–80.
- [7] Gottlieb CD, Horowitz LN. Potential interactions between antiarrhythmic medication and the automatic implantable cardioverter defibrillator. *PACE* 1991; 14: 898–904.
- [8] Echt DS, Gremillion ST, Lee JT *et al.* Effects of procainamide and lidocaine on defibrillation energy requirements in patients receiving implantable cardioverter defibrillator devices. *J Cardiovasc Electrophysiol* 1994; 5: 752–60.
- [9] The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989; 321: 406–12.
- [10] The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; 327: 227–33.
- [11] Waldo AL, Camm AJ, de Ruyter H *et al.*, for the SWORD Investigators. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after myocardial infarction. *Lancet* 1996; 348: 7–12.
- [12] Pratt CM, Camm AJ, Cooper W *et al.*, for the SWORD Investigators. Mortality in the survival with oral d-sotalol (SWORD) trial. Why did patients die? *Am J Cardiol* 1998; 81: 869–76.
- [13] Julian DG, Camm AJ, Frangin G *et al.*, for the European Myocardial Infarct Amiodarone Trial Investigators. Randomised trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: EMIAT. *Lancet* 1997; 349: 667–74.
- [14] Janse MJ, Malik M, Camm AJ *et al.* Identification of post acute myocardial infarction patients with potential benefit from prophylactic treatment with amiodarone. A substudy of EMIAT (the European Myocardial Infarct Amiodarone Trial). *Eur Heart J* 1998; 19: 85–95.
- [15] DIAMOND Study Group. Dofetilide in patients with left ventricular dysfunction and either heart failure or acute myocardial infarction: rationale, design and patient characteristics of the DIAMOND studies. *Clin Cardiol* 1997; 20: 704–10.
- [15] The DIAMOND Study Group. Dofetilide a new class III antiarrhythmic drug prevents atrial fibrillation in patients with congestive heart failure in normal sinus rhythm. Results of the DIAMOND-CHF study (Abstr). *J Am Coll Cardiol* 1999; 33: 132A.
- [17] Connolly SJ, Gent M, Roberts RS *et al.* Canadian Implantable Defibrillator Study (CIDS): study design and organization. *Am J Cardiol* 1993; 72: 103F–8F.
- [18] Bigger JT Jr. Prophylactic use of implantable cardioverter defibrillators in patients at risk of ventricular arrhythmias after coronary artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) patch trial investigators. *N Engl J Med* 1997; 337: 1569–75.
- [19] Buxton AE, Lee KL, DeCarlo L *et al.* Nonsustained ventricular tachycardia in coronary artery disease: relation to inducible sustained ventricular tachycardia. MUSTT Investigators. *Ann Intern Med* 1996; 125: 35–9.
- [20] Bardy GH, Lee KL, Mark DB, and the SCD-HeFT Pilot Investigators. The Sudden Cardiac Death in Heart Failure Trial: pilot study (Abstr). *PACE* 1997; 20: 1148.
- [21] Moss AJ, Connom DS, Dubert JP *et al.*, for the MADIT II Investigators. Multicenter Automatic Defibrillator Implantation Trial II (MADIT II): design and clinical protocol. *Ann Noninvasiv Electrocardiol* 1999; 4: 83–91.
- [22] Nisam S, Mower M. ICD trials: an extraordinary means of determining patient risk? *PACE* 1998; 21: 1341–6.
- [23] Hinkle LE, Thaler HT. Clinical classification of cardiac deaths. *Circulation* 1982; 65: 457–64.
- [24] Kim SG, Fogoros RN, Furman S *et al.* Standardized reporting of ICD patient outcome: the report of a North American Society of Pacing & Electrophysiology Policy Conference, February 9–10, 1993. *Pacing Clin Electrophysiol* 1993; 16: 1358–62.
- [25] Greene HL. The CASCADE Study: randomized antiarrhythmic drug therapy in survivors of cardiac arrest in Seattle. CASCADE Investigators. *Am J Cardiol* 1993; 72: 70F–74F.
- [26] Dolack GL. Clinical predictors of implantable cardioverter-defibrillator shocks (results of the CASCADE trial). Cardiac Arrest in Seattle, Conventional versus Amiodarone Drug Evaluation. *Am J Cardiol* 1994; 73: 237–41.
- [27] The CASCADE Investigators. Randomized antiarrhythmic drug therapy in survivors of cardiac arrest (the CASCADE study). *Am J Cardiol* 1993; 72: 280–7.
- [28] Böcker D, Block M, Isbruch F *et al.* Comparison of frequency of aggravation of ventricular tachyarrhythmias after implantation of automatic defibrillators using epicardial versus non-thoractomy lead systems. *Am J Cardiol* 1993; 71: 1064–8.
- [29] Echt DS, Leibson PR, Mitchell B *et al.*, and the CAST Investigators. Mortality and morbidity in patients receiving encainide, flecainide or placebo. *N Engl J Med* 1991; 324: 781–8.
- [30] Grimm W, Flores BF, Marchilinski FE. Symptoms and electrocardiographically documented rhythm preceding spontaneous shocks in patients with implantable cardioverter defibrillator. *Am J Cardiol* 1993; 71: 1415–18.
- [31] Hook BG, Callans DJ, Kleiman RB *et al.* Implantable cardioverter defibrillator therapy in the absence of significant symptoms: Rhythm diagnosis and management aided by stored electrogram analysis. *Circulation* 1993; 87: 1897–1906.
- [32] Kou WH, Calkins H, Lewis RR *et al.* Incidence of loss of consciousness during automatic implantable cardioverter-defibrillator shocks. *Ann Intern Med* 1991; 115: 942–5.
- [33] Bansch D, Brunn J, Castrucci M *et al.* Syncope in patients with an implantable cardioverter defibrillator incidence, prediction and implications for driving restrictions. *J Am Coll Cardiol* 1998; 31: 608–15.
- [34] Wietholt D, Block M, Isbruch F *et al.* Clinical experience with antitachycardia pacing and improved detection algorithms in a new implantable cardioverter defibrillator. *J Am Coll Cardiol* 1993; 21: 885–94.
- [35] Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989; 117: 151–9.
- [36] Exner DV, Gillis AM, Sheldon RS *et al.* Telemetry documented, pace terminable ventricular tachycardia in patients with ventricular fibrillation. *Am J Cardiol* 1998; 81: 235–8.
- [37] Böcker D, Block M, Isbruch F *et al.* Do patients with an implantable defibrillator live longer? *J Am Coll Cardiol* 1993; 21: 1638–44.
- [38] Böcker D, Bansch D, Henecke A *et al.* Potential benefit from implantable cardioverter defibrillator therapy in patients with and without heart failure. *Circulation* 1998; 98: 1636–43.
- [39] Stevens SK, Haffajee CI, Naccarelli GV *et al.* Effects of oral propafenone on defibrillation and pacing thresholds in patients receiving implantable cardioverter defibrillators. *J Am Coll Cardiol* 1996; 28: 418–22.

- [40] Jung W, Manz M, Pizzulli L *et al.* Effects of chronic amiodarone therapy on defibrillation threshold. *Am J Cardiol* 1992; 70: 1023–7.
- [41] Movsowitz C, Marchlinski FE. Interactions between implantable cardioverter-defibrillators and class III agents. *Am J Cardiol* 1998; 82: 411–81.
- [42] Tacker WA, Niebauer MJ, Babbs CF *et al.* The effect of newer antiarrhythmic drugs on defibrillation threshold. *Crit Care Med* 1980; 8: 177–80.
- [43] Wang M, Dorian P. dL and d-sotalol decrease defibrillation energy requirements. *PACE* 1989; 12: 1522–9.
- [44] Dorian P, Newman D. Effect of sotalol on ventricular fibrillation and defibrillation in humans. *Am J Cardiol* 1993; 72: 72A–9A.
- [45] Jung W, Manz M, Pizzulli L *et al.* Effects of chronic amiodarone therapy on defibrillation threshold. *Am J Cardiol* 1992; 70: 1023–7.
- [46] Gilberg JM, Olson WH, Bardy GH *et al.* Electrogram width algorithm for discrimination of supraventricular rhythm from ventricular tachycardia (Abstr). *PACE* 1994; 17: 866.
- [47] Ruetz LL, Bardy GH, Mitchell LB *et al.* Clinical evaluation of electrogram width measurements for automatic ventricular tachycardia (Abstr). *PACE* 1996; 19: 582.
- [48] Osswald S, Cron TA, Sterns L *et al.* New ICD technologies: first clinical experience with dual chamber sensing for differentiation of supraventricular arrhythmias. *PACE* 1998; 21: 292–5.
- [49] Bardy GH, Olson W, Barnes J *et al.* Ventricular fibrillation cycle length spectrum: measured values in comparison to sensed values as a function of ICD sensitivity setting (Abstr). *PACE* 1993; 16: 585.
- [50] Bardy GH, Ivey T, Stewart R *et al.* Failure of the automatic implantable cardioverter defibrillator to detect ventricular fibrillation. *Am J Cardiol* 1986; 58: 1107–8.
- [51] Cohen TJ, Liem LB. Biosensor applications to antitachycardia devices. *PACE* 1991; 14: 322–8.
- [52] Prevot E, Vesin JM, Schmidiager H *et al.*, on behalf of the HRVF study investigators. Analysis of heart rate variability at the onset of spontaneous ventricular tachyarrhythmias as retrieved from a defibrillator. *Eur Heart J* 1977; 18: 592.
- [53] Vetter R, Celka P, Vesin JM *et al.* Subband modeling of the human cardiovascular system: new insights into cardiovascular regulation. *Ann Biomed Eng* 1998; 26: 293–307.
- [54] Cohen TJ, Liem LB. A hemodynamically responsive antitachycardia system. Development and basis for design in humans. *Circulation* 1990; 82: 394–406.
- [55] Kaye GC, Astridge P, Perrins J. Tachycardia recognition and diagnosis from changes in right atrial pressure waveform — a feasibility study. *PACE* 1991; 14: 1384–92.
- [56] Wood MA, Ellenbogen KA, Kapadia K *et al.* Comparison of right ventricular emepdance, pulse pressure and maximal dP/dt for determination of hemodynamic stability of ventricular arrhythmias associated with coronary artery disease. *Am J Cardiol* 1990; 66: 575–82.
- [57] Krahn AD, Klein GJ, Norris C *et al.* The etiology of syncope in patients with negative tilt table and electrophysiological testing. *Circulation* 1995; 92: 1819–24.
- [58] Pratt CM, Greenway PS, Schoenfeld MH *et al.* An exploration of th precision of classifying sudden cardiac death: Implications for the interpretation of clinical trials. *Circulation* 1996; 93: 519–24.
- [59] Pocock SJ. Clinical trials with multiple outcomes: a statistical perspective. *Con Clin Trials* 1997; 18: 530–45.
- [60] Pocock SJ, Geller NL, Tsiatis AA. The analysis of multiple endpoints in clinical trials. *Biometrics* 1987; 43: 487–98.
- [61] O'Brien PC. Procedures for comparing samples with multiple endpoints. *Biometrics* 1984; 40: 1079–87.
- [62] Raviele A, Bongiorni MG, Brignole M *et al.* Which strategy is 'best' after myocardial infarction? The Beta-blocker Strategy Plus Implantable Cardioverter Defibrillator Trial: rationale and study design. *Am J Cardiol* 1999; 83: 104D–11D.
- [63] Wever EFD, Hauer RNW, van Capelle FJI *et al.* Randomized study of implantable defibrillator as first-choice therapy versus conventional strategy in post-infarct study death survivors. *Circulation* 1995; 91: 2195–2203.
- [64] Myerburg RJ, Luceri RM, Thurer R *et al.* Time to first shock and clinical outcome in patients receiving an implantable cardioverter-defibrillator. *J Am Coll Cardiol* 1989; 4: 508–14.
- [65] Huang SKS, Tan de Guzman WLT, Chenarides JG *et al.* Effects of long-term amiodarone therapy on the defibrillation threshold and the rate of shocks of the implantable cardioverter-defibrillator. *Am Heart J* 1991; 122: 720–7.
- [66] Grimm W, Flores BT, Marchlinski FE. Shock occurrence and survival in 241 patients with implantable cardioverter-defibrillator therapy. *Circulation* 1993; 7: 1880–8.
- [67] Kelly PA, Cannom DS, Garan H *et al.* The automatic implantable cardioverter defibrillator: efficacy, complications and survival in patients with malignant ventricular arrhythmias. *J Am Coll Cardiol* 1998; 11: 1278–86.
- [68] Saksena S, Poczobutt-Johanos M, Castle LW *et al.* Long-term multicenter experience with a second-generation implantable pacemaker-defibrillator in patients with malignant ventricular tachyarrhythmias. The Guardian Multicenter Investigators Group. *J Am Coll Cardiol* 1992; 19: 490–9.
- [69] Echt DS, Armstrong K, Schmidt P *et al.* Clinical experience, complications, and survival in 70 patients with the automatic implantable cardioverter-defibrillator. *Circulation* 1985; 71: 289–96.
- [70] Pacifico A, Hohnloser SH, Williams JH *et al.* for the d,l-Sotalol Implantable Cardioverter-Defibrillator Study Group. Prevention of implantable-defibrillator shocks by treatment with sotalol. *N Eng J Med* 1999; 340: 1855–62.