The DATAS rationale and design: a controlled, randomized trial to assess the clinical benefit of dual chamber (DDED) defibrillator

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Abstract

Single chamber (SC) implantable cardioverter defibrillators (ICDs) have several limitations that might be relevant during follow-up, like atrial pacing requirements, inadequate therapies, sustained atrial tachyarrhythmias and difficulties to achieve an accurate diagnosis of the arrhythmia. Dual chamber (DC) ICDs offer an attractive and rational solution, although controversy remains if the costs and complexity of these devices offer a real clinical advantage. The Dual Chamber & Atrial Tachyarrhythmias Adverse Events Study (DATAS) was designed to analyze the ability of DC ICD, DDED, to reduce clinically significant adverse events compared with SC ICD in a non-selected population with conventional indications for ICD implantation. This is a prospective, multicentre, randomized, open labelled study, with three arms: two of them (simulated SC ICD and true DC ICD) cross-over, and the third (true SC ICD) parallels the other two. The composite primary end point comprises four Clinically Significant Adverse Events (CSAE): (1) all-cause mortality, (2) invasive intervention, hospitalization or prolongation of hospitalization due to cardiovascular cause, (3) inappropriate shocks, and (4) sustained symptomatic atrial tachyarrhythmias that (a) require urgent termination or (b) last more than 48 h leading to therapeutic intervention. Secondary end points constitute each of the

KEYWORDS

implantable cardioverter defibrillators; atrial fibrillation; ventricular tachyarrhythmias; clinical trial

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individual components of CSAE, cardiovascular status, quality of life and a detailed analysis of atrial and ventricular arrhythmias. To date (June 2003) there have been 343 patients enrolled from 947 screened patients. The projected enrolment includes 360 patients and the conclusion of the study is expected at the beginning of 2005. © 2003 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

Controlled clinical studies have demonstrated that the implantable cardioverter defibrillator (ICD) is more effective than antiarrhythmic drugs in reducing death (AVID, MADIT, MUSTT) [1-4], leading to widespread use of these devices. Nevertheless, presently available single chamber (SC) ICDs have at least four main limitations that might be relevant during follow-up: (1) loss of AV synchrony in patients requiring pacing [5, 6]; (2) inappropriate therapies [7, 8] despite the activation of so-called "additional criteria" [9]; (3) sustained atrial tachyarrhythmias for which no therapy is provided [10, 11]; (4) difficulties to achieve an accurate diagnosis of the arrhythmia from the stored electrograms [12, 13].

These problems might be circumvented by using standard antiarrhythmic therapies (drugs, electrical cardioversion, ablation) [14-16] and/or dual chamber ICDs [17, 18]. Dual chamber (DC) ICDs offer an attractive solution, although there are some concerns about atrial lead related complications, value of atrial therapies and AV discrimination algorithm performance [19, 20]. Recent data from two controlled studies have questioned long-term safety and efficacy of these devices [21, 22]. In fact, to date there is only a consensus on implantation of DC ICD in patients with marked sinus dysfunction or 2nd-3rd degree AV [17, 23], and controversy remains if the costs and complexity of the implants offer a real clinical advantage.

The Dual Chamber & Atrial Tachyarrhythmias Adverse Events Study (DATAS) was designed to analyze the ability of DC ICD, DDED [24], to reduce clinically significant adverse events compared with SC ICD in a non-selected population with conventional indications for ICD implantation.

Justification of the study

Four main situations in which DC ICD is potentially beneficial in comparison with SC ICD can be anticipated to be:

1. Loss of normal atrial rate and atrioventricular synchrony. Over 15% of ICD patients may need atrial pacing-sensing, half of them undetectable at the time of ICD pre-implant evaluation [25-29]. Drugs commonly used to treat heart failure or arrhythmias, betablockers, sotalol and amiodarone [30, 31], frequently cause bradycardia at optimal doses for which VVI pacing may offer a suboptimal backup [32, 33].

2. Inappropriate discrimination of supraventricular and ventricular events. Inappropriate therapies and shocks may hamper quality of life [34], cause proarrhythmia, hospitalization and even death [35, 36]. The percentage of patients with inadequate shocks in single chamber devices may reach 40% [7, 10], the most frequent causes being a fast ventricular rhythm caused by atrial fibrillation (AF) or sinus tachycardia. Nevertheless, although enhanced criteria (i.e. sudden onset, stability and width) can improve the specificity of the diagnostics to more than 90%, the sensitivity can be reduced to 80% or less [37-39].

3. Accuracy in the diagnosis of arrhythmias by stored electrograms. Analysis of morphology of stored ventricular electrograms can provide some clues as to the site of origin of arrhythmias [13, 40], however, the ability for such differential diagnosis is limited. Direct recording of atrial rhythm by a dedicated atrial lead should allow more accurate discrimination [41]. Recognition of more than one tachycardia (a condition not rare in ICD recipients) is not possible without atrial electrograms [42].

4. Prevention and/or therapy of significantly prevalent atrial tachyarrhythmias. In the AVID population one fourth of the patients had AF [1], and the same high prevalence has been found in other series of patients after ICD implantation [7, 8]. Data from SOLVD studies suggest that atrial fibrillation is associated with increasing mortality by impairing left ventricular systolic function [43]. Therefore, prevention and management of AF may improve outcome. Atrial therapies, have demonstrated a high success rate in suppressing atrial arrhythmias [44-48]. Efficacy of atrial antitachycardia
pacing ranges from 55% to 66% and the adjusted success rate of atrial shock for atrial fibrillation is more than 60% [46]. Adequate timing of therapies for AF can avoid the dangerous consequences of conversion to sinus rhythm in patients without anticoagulation [49].

Reasons commonly used not to implant DC ICDs include [20,50,51]: (1) higher cost of DC devices, (2) higher complication rate, related to the insertion of an atrial lead, (3) prolongation of operation and hospitalization time, (4) higher complexity of follow-up procedures, (5) low compliance of patients with the atrial shocks, and (6) uncertainties about a clinically significant reduction in adverse events during follow-up.

The main issue to be clarified is whether tolerability and reduction of significant clinical problems of DC ICD are offset by the potential benefits in the majority of ICD patients. It should be emphasized that the investigators feel strongly that it is this clinical benefit that needs to be measured as opposed to “pure electrical phenomena” with uncertain clinical implications.

Study objectives

This clinical study is designed to assess the ability of DDED DC ICD to reduce clinically significant adverse events in patients with class I indication for VVE-VVI conventional ICD therapy. The primary end point is a composite comprising four so-denominated “Clinically Significant Adverse Events” (CSAE): (1) all-cause mortality, (2) invasive intervention, hospitalization (> 24 h) or prolongation of hospitalization due to cardiovascular cause, (3) inappropriate shocks (two or more episodes with inappropriate shocks), and (4) sustained symptomatic atrial tachyarrhythmias that (a) require urgent termination or (b) last more than 48 h leading to therapeutic intervention. CSAE will not include cardiac catheterization with/without revascularization scheduled routinely during follow-up. The primary objective of this trial is to determine whether use of DDED ICD results in a significant decrease in the number of primary end points.

Secondary end points constitute each of the individual components of CSAE, cardiovascular status (functional and echo parameters), quality of life and a detailed analysis of atrial arrhythmias (types, burden, time course, consequences, etc). Secondary objectives are:

1. Number of each of the components of the CSAE.
2. Arrhythmia related: atrial tachyarrhythmia, frequency and burden, ventricular tachyarrhythmia frequency and burden number of appropriate shocks, number of inappropriate shocks, need for reprogramming, need for medication/RFA for arrhythmia control, pacemaker syndrome and development of dual chamber pacing indication.
3. Cardiovascular related: NYHA functional class, exercise capacity, left ventricular ejection fraction (LVEF), reduction of medication (diuretics...).
4. Quality of life: evaluated by the SF-36, Minnesota living test, with heart failure and Symptom Checklist instruments.

Study design, randomization and data collection

The DATAS is a, prospective, multicentre, randomized, open labelled study, with three arms (two of them cross-over and the third parallels the other two) (Fig. 1). About 36 centres in Spain, Germany, Italy, United Kingdom, Portugal and Israel will participate. The projected enrolment includes 360 patients. The first implant took place in November 2000 and the duration of the study (including patient enrolment, follow-up, data analysis, and regulatory approval) was expected to be 48 months. To date (June 2003) there are 343 patients enrolled from 947 screened patients. Documented approval of the investigational plan by the Institutional Review Board (IRB) or Ethics Committee (EC) affiliated with the study centre is required for starting the study. Patient written informed consent is also required before enrolment.

A web site (http://www.rdes.com/datas) has been specifically designed for this study by an independent company (Remote Data Entry System S.L., Barcelona, Spain). Through this site the randomization and data entry with electronic case report forms are completed and sent to a central database, where the Data Revision Committee can review them.

The study design is depicted in Fig. 1. Patients will be randomized to one of three arms: SC ICD (“SC true arm”), DC ICD initially programmed as SC (SC simulated) ICD (“SC sim arm”) and DC ICD initially programmed as a DDED (“DC true arm”).

No waiting period after implant has been allowed in order to evaluate the lead fixation issues, and the possible beneficial mechanisms for atrial prevention pacing algorithms. On the other hand a 1-month wash out period after the cross-over is
included to avoid influence of the remodeling associated with pacing mode.

The randomization procedure will be centralized through the web site, balancing the sample size of all three arms over the different centres. At the beginning of the study there will be at least six consecutive patients to be enrolled by a participating centre. A log of all excluded patients is kept in each centre to avoid any possible selection bias. Later enrolment must also include at least three consecutive patients.

Patients will be followed-up at 1, 4, 8, 9, 13 and 17 months. At enrolment, 8 and 17 months, the quality of life questionnaires, 6 min walk test and echo parameters will be recorded, as well as reevaluation of the cardiovascular history.

An Adverse Events Advisory Committee has been created to analyze blindly: (1) the classification of adverse events and validation of primary end points; (2) the classification and validation of device episodes related to adverse events.

**Patient eligibility criteria**

All patients’ candidates for ICD will be initially screened in each centre (Fig. 1). The study population will include those patients who are appropriate candidates for standard Class I criteria for a single chamber implantable cardioverter defibrillator (ICD).

Exclusion criteria will be the accepted indications (symptomatic sinus node disease, all 2nd AV block, except asymptomatic Mobitz I, and all 3rd degree AV block) and contraindications (permanent atrial tachyarrhythmias) for dual chamber pacing. Patients without structural heart disease, an
indication for biventricular pacing or with a previous system implanted (ICD or pacemaker) will also be excluded.

ICD devices and programming

DDD devices are to be used for this investigation, which must have automatic atrial tiered antitachycardia therapies and may be programmed in monitor mode to store data from atrial arrhythmic events without delivering atrial therapy. Devices used in the trial included Jewel AF (model 7250) and GEM III AT (model 7276; Medtronic Inc., Minneapolis, MN, USA) as dual chamber devices and GEM family (Medtronic Inc, Minneapolis, MN, USA) as single chamber devices. The dual chamber algorithm (PR Logic) discriminates between supraventricular and ventricular tachycardias, and detects AT/AF accurately and continuously [45,52].

The atrial lead could be any commercially available bipolar atrial pace/sense lead with tip-ring spacing $\leq 10$ mm, and the ventricular lead could be any commercially available ventricular pace/sense leads with two defibrillation coils.

Intraoperative implantation procedures will be performed according to the standards of each centre. Programming the ICD should also meet clinical standards in every centre, but some general rules were strongly recommended:

- Supraventricular arrhythmia discrimination in SC by using stability criteria
- A VT zone with ATP therapies
- Low pacing rates (50 bpm or less) in SC and, in DC, 70 bpm was encouraged to prevent atrial tachyarrhythmias, but with prolonged AV intervals (recommended values: paced AV 230 ms and sensed AV 200 ms) in an attempt to reduce right ventricle pacing.
- Therapies for atrial arrhythmias were programmed as follows: nominal pacing therapies with no delay after detection; for atrial arrhythmias as soon as detected, first high energy shock automatically delivered in less than 24 h after episode onset, and programming for subsequent episodes at the investigator’s discretion and according to patient tolerance.

Statistical analysis

The main objective is reduction of the number of CSAE. The primary response variable is the sum of the four CSAEs. The main comparison is SC ICD (SC true) versus DDD ICD (DC true). It should be noted that: (a) the DC true group will double the number of patients since it will pool together patients from the two cross-over arms (DC true SC sim and SC sim-DC true) and (b) the SC true group will be followed for a longer period of time (17 months). In order to get a single response measure, the addition of the number of any of these four CSAE was defined as the primary end point. This variable will be sensitive both to reductions in the number of patients with CSAE as well as in the number of CSAEs per patient. SC simulated will be used for a precise evaluation of the impact of dual chamber therapy on atrial tachyarrhythmia burden and SVT/VT discrimination.

The main statistical analysis (p-values and confidence intervals) will be based on the ordinal Mann—Whitney—Wilcoxon statistical method [53]. To take into account the different follow-up for the two groups (twice 8 months versus 17 months), the ranks will be calculated for the rate of CSAE instead of the proportion of CSAE.

Sample size and power for the main analysis

The assumed effect of the DC treatment is a reduction of 15% both in the proportion ($P \%$) of patients with tendency to develop a CSAE (from 30% to 15%), as well as in the mean ($M$) of CSAE over all patients (from 6 to 5.1). The estimated sample size was 200 (DC true) versus 100 (SC true) patients followed for 8 months, with a two sided $\alpha = 0.05$, and a power of 88.8%. The power of the study has been explored through simulation of 10,000 samples with the SAS system. The number of replications allows for a confidence interval ($1 - \alpha = 0.95$) in the estimation of the power with an amplitude equal to $\pm 1\%$. To protect against dropouts, observational compliance, losses to follow-up, or protocol deviations the sample size was fixed at 360 patients (120 patients per arm).

Other considerations

If the treating physician decides that a patient could benefit from programming to the opposite treatment arm, the premature cross-over should be authorized by the adverse event committee. The intention to treat principle will be assured by counting CSAE in the original arm as it represents a normal medical situation of success and failure of delivering the planned therapy. The main analysis will be fully specified in a blind statistical
analysis plan approved by the steering committee before the end of the trial.

Discussion

Key issues in the study design

Since the primary objective is to compare DDED ICD (DC true) to VVEV ICD (SC true) in terms of reducing CSAE, at first glance, a simple two-arm comparison might suffice. However, some of the questions related to atrial arrhythmias and VT/SVT discrimination could only be answered with direct information about atrial activity, i.e., through direct recordings of atrial electrograms. In addition, a cross-over design provides intraindividual comparisons. These considerations would argue in favour of a study design in which all patients get a DC device but half of them are initially programmed as an SC device (as far as therapy is concerned but providing full information about events), crossing over later to DC therapy. Nevertheless, this study design would penalize the “SC programmed” population with all the risks associated with DC devices, mainly a more complex implantation procedure and a potential for a higher surgical and electrode-related complication rate. In addition, it is conceivable that the atrial electrode could transiently “irritate” the atrial chambers.

Therefore a three-arm design was chosen, having a true SC arm and two DC arms. One DC arm will be programmed as an “SC only therapy” (or “simulated SC arm”) and the other as a DC therapy (“true DC arm”). These two DC arms will undergo a cross-over programming after half of the projected follow-up period (8 months). With this design all three groups of therapy may be compared in similar conditions for number and length of follow-up, and the very important aspects included in the secondary objectives will be appropriately analyzed.

Other studies and DATAS

Two somewhat similar studies have recently been published. The DAVID trial [22] assessed the hypothesis that dual chamber pacing was superior to backup ventricular pacing in patients with standard indications for ICD implantation and LVEF of 40% or less without indications for anti-bradycardia pacing. The study was prematurely stopped because the conditional power for the original alternative (DDDR-70 being better than VVI-40) was less than 10%. In fact, “…a trend (p<0.03) towards a worse outcome with DDDR-70 pacing was established…” . It was also found that “Patients who survived to the 3-month follow-up have worse 12-month event-free rates when the percentage of right ventricular pacing by ICD interrogation was 41–100% (75.9%) than when less than 40% (86.9%) (p = 0.09)” . The authors feel that their own along with recently published data [54] suggest that right ventricular stimulation is inappropriate and causes increased heart failure by the mechanism of ventricular desynchronization. The specific programming choices (AV interval was not controlled) could have affected their results, since nearly 60% of all ventricular beats were paced in the DDDR-70 group.

In the study of Deisenhofer et al. [21], 92 patients were randomly assigned to a VVI-ICD or a DDD ICD during a mean follow-up of 7.5 months. Although DDD ICDs allowed a better rhythm classification, the applied detection algorithms offer no advantages in avoiding inappropriate therapies during SVTs. It should be emphasized that in these series, 75% of inappropriate therapies in the DDD ICD group were due to atrial sensing problems, either oversensing or undersensing. This seems to be an unexpectedly high rate. In the DATAS trial we will enrol patients implanted in 36 European centres and we will be able to assess the actual rate of atrial lead related complications in a large number of expert centres.

In contrast, in DATAS: (a) the recommended programming includes an AV interval of 200 ms (instead of 180 ms) or whatever was needed to avoid ventricular pacing; (b) the devices can treat atrial tachyarrhythmias electrically; (c) no cut-off value of LVEF was required; (d) resynchronization indication was an exclusion criterion; and (e) each arm will have a 17 month follow-up.

Final considerations

When the DAVID was published, the Steering Committee of DATAS felt that the potentially deleterious effect of ventricular pacing should be checked. The mean percentage of ventricular paced beats in the 62 patients assigned to the DDD arm, who completed the first 8-month follow-up period, was 36%, far below the 60% found in DAVID, and below the 40% security limit described in MOST and DAVID. Since safety is not of concern in DATAS, and in view of some design differences (i.e., a true VVI arm) there is no reason to stop the study.

The DATAS design (with a VVI true arm and longer follow-up) will provide important information
about the effects of AV discrimination algorithms, atrial antibradycardia and antitachycardia therapies (with long AV delays to prevent unnecessary ventricular stimulation) and will help to define the actual indications for dual chamber defibrillators.

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Appendix

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References

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