STUDY DESIGN

Design and rationale of a randomized study to compare amiodarone and Class IC anti-arrhythmic drugs in terms of atrial fibrillation treatment efficacy in patients paced for sinus node disease: the PITAGORA trial

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Aims Many sinus node disease (SND) patients suffer from atrial fibrillation (AF). Anti-arrhythmic drugs (AADs) are the therapeutic mainstay for AF prophylaxis. The PITAGORA trial has a multicentre, prospective, randomized, single blind design to compare amiodarone with Class IC AADs in patients who have an AF history and are paced for SND.

Methods and results Starting from January 2001, 176 patients received a Medtronic AT500 pacemaker. AADs were randomly assigned with a 3:2 ratio between Class III and Class IC. Randomization was stratified in order to assign two patients to amiodarone and one patient to sotalol every three Class III AAD patients. After a 5-month observational period, Ramp or Burst+ ATP therapies were enabled in a randomized way, maintained for 4 months, and then crossed over. Total follow-up period is 21 months. The primary long-term objective is to show the non-inferiority of IC AADs compared with amiodarone in terms of time to first occurrence of a composite endpoint (death, atrial cardioversion, hospitalizations due to AF or heart failure, or change of AADs). Data will be analysed on an intention-to-treat basis. The primary short-term objective is to compare Ramp vs. Burst+ efficacy in terminating atrial tachyarrhythmias treated by the device. Secondary endpoints are major clinical events, medication toxicity, symptoms, AF burden, and quality-of-life.

Conclusion Given the high morbidity and healthcare costs associated with AF, new therapeutic strategies are needed. The results of the PITAGORA trial may help in guiding AADs therapy and ATP programming in SND patients suffering from AF.

AF is not a benign condition.3 For many clinicians, maintenance of sinus rhythm remains the main therapeutic goal. In patients with AF, prophylactic anti-arrhythmic drugs (AAD) are used to maintain sinus rhythm.4-21 Amiodarone has been shown to be the most effective AAD in several randomized trials, with evidence suggesting superiority of amiodarone over quinidine,5 disopyramide,7 sotalol,19 and either sotalol or propafenone.20,21 In contrast, a high proportion of patients discontinue amiodarone because of adverse events.10,11,20

KEYWORDS
Anti-arrhythmic drug therapy; Anti-tachycardia pacing; Sinus node disease; Atrial fibrillation

Introduction

Patients with sinus node disease (SND) receiving an implanted cardiac pacemaker exhibit a high prevalence of atrial fibrillation (AF).1,2

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As AAD therapy has poor long-term efficacy when used alone, with 50–70% of patients eventually progressing to chronic AF, interest in the role of combinations of therapies (hybrid therapy) has recently increased. The rationale underlying hybrid therapy is that a combination of modalities of intervention in AF might have a synergistic effect, with the efficacy of each intervention building upon the others. At present this concept is particularly in the prevention of AF recurrence, but hybrid therapy has also been used both in facilitating restoration to sinus rhythm and in the control of heart rate. Many authors have shown that anti-tachycardia pacing (ATP) therapies are safe and effective in terminating supraventricular atrial arrhythmias.

The impact of ATP therapies is still debated: the ATTEST study showed that combined atrial prevention and termination therapies did not reduce AF burden or frequency in patients with pacing indication and AF history, while Gillis et al. have recently shown a significant correlation between high ATP termination efficacy and AF burden reduction in patients paced for bradycardia and frequent symptomatic AF. Boriani et al. have shown that flecainide in SND patients is associated with higher ATP therapy efficacy, compared with amiodarone, sotalol, and beta-blockers, leading to the rationale that flecainide used in combination with pacemakers able to deliver ATP therapies may show enhanced capabilities in AF treatment.

The aim of the PITAGORA trial is to compare amiodarone and Class IC anti-arrhythmic efficacy in terms of the incidence of a composite endpoint, which is defined as the time to the first occurrence of one of the following adverse events: death, hospitalization for AF or heart failure, atrial cardioversion, or AAD change owing to failure of AF prophylaxis or adverse events.

Methods

Multicentre trial

One hundred seventy six patients were enrolled in 27 Italian cardiology centres (see appendix).

Enrolment period

The enrolment period was between January 2001 and December 2003.

Study design

The PITAGORA trial is a prospective, randomized, single blind study. AADs were randomly assigned between Class III and Class IC with a 3:2 ratio. Randomization was stratified in order to assign two patients to amiodarone and one patient to sotalol every three Class III AAD patients. After a 5-month observational period, with the pacemaker programmed in DDD(R) mode, Ramp or Burst+ ATP therapies were enabled in a randomized way, maintained for 4 months, and then crossed over or adverse events.

Study objectives

The primary long-term objective is to show the non-inferiority of Class IC AAD compared with amiodarone in terms of the incidence of the primary endpoint, which is defined as the time to the first occurrence of one of the following adverse events: death, hospitalization for AF or heart failure, atrial cardioversion or AAD change owing to failure of AF prophylaxis or adverse events.

The primary short-term objective is to compare Ramp vs. Burst+ efficacy in terminating device-treated atrial tachyarrhythmias.

Secondary endpoints are major clinical events, medication toxicity, AF burden, AF frequency, AF symptoms, atrial arrhythmia cycle length, number of patients in sinus rhythm, number of patients crossing over between therapy arms, cost benefit by comparing hospitalization costs of each approach, and quality-of-life measured by self-administered questionnaires in amiodarone vs. Class IC AAD at the end of the study. Comparison of AF burden or other clinical outcomes between the first 5-month observation period, with the pacemaker programmed in DDD(R) mode, and following periods, with ATP therapies enabled, is expected to allow evaluation of the synergistic effect of AAD and ATP in the treatment of AF.

Patient selection

Patients eligible for study participation suffered from SND and had indications for pacemaker implantation, having one of the following conditions: symptomatic SND with a documented sinus pause > 3s or an asymptomatic sinus pause > 5s; chronic sinus bradycardia with rates < 50 bpm, an inability to increase rate > 10 bpm with exercise, and symptoms of fatigue and dyspnoea on exertion referable to chronotropic incompetence; sinus bradycardia, rate < 50 bpm, which restricts the use of long-term medical therapy for angina, hypertension, or supraventricular tachyarrhythmias. Other inclusion criteria required age greater than 18 years, at least three episodes of symptomatic (paroxysmal or persistent) atrial tachyarrhythmia in the 12 months before enrolment, at least one episode in the last 3 months, at least one atrial tachyarrhythmia episode documented by ECG or Holter recording, but sinus rhythm at the implantation. Other eligibility conditions were that it must have been possible to implant both atrial and ventricular bipolar leads, and that patients were expected to remain on a stable regimen of drugs with a primary anti-arrhythmic effect throughout the follow-up duration. Exclusion criteria were as follows: patients with permanent AF, patients with left ventricular dysfunction (LVEF < 40%), intolerance to amiodarone or Class IC AAD, patients with AF because of a reversible cause, patients already implanted with a pacemaker, candidates for an implantable cardioverter defibrillator (ICD), patients having had cardiac surgery within the last month before implant, patients with a life expectancy of less than 2 years, patients with a mechanical right heart valve, patients unable to interrupt anticoagulation therapy, pregnant patients, patients suffering from thyroid disease, patients unable to attend follow-up.

Device characteristics

The pacemakers (AT500, Medtronic Inc, Minneapolis, USA) have been described previously. This device offers treatment of each atrial tachyarrhythmia episode by a programmable set of automatic atrial ATP therapies. It is possible to programme three different therapies selecting between ‘Burst+-’ (constant drive coupled with up to two extrastimuli) and ‘Ramp’ (decremental drive). Each therapy may be delivered up to 10 times if the episode is not terminated. The device software includes three pacing algorithms dedicated to prevent AF occurrence. These consist of an atrial overdrive algorithm for maintenance of a pacing rate just above the intrinsic rate [atrial pacing preference (APP)], an atrial overdrive mode designed to avoid short-long intervals [atrial rate stabilization (ARS)] following a premature atrial contraction (PAC), and an algorithm designed to inhibit early recurrence of AF following a mode switching episode [post-mode switching overdrive pacing (PMOP)].

AAD therapy

AAD therapy was chosen randomly for each patient with a 3:2 ratio between Class III and Class IC AAD. In particular randomization was
stratified in each centre in order to have two patients assigned to amiodarone and one patient assigned to sotalol every three patients assigned to Class III AAD. In this way the number of patients assigned to amiodarone was balanced with the number of patients assigned to Class IC. If a patient was randomized to a Class IC AAD, the investigator was free to choose flecainide or propafenone. Recommended AAD doses were the following: amiodarone, 200 mg per day; sotalol, 160–240 mg per day; propafenone, 450–750 mg per day; flecainide, 200 mg per day. Amiodarone was given at a dose of 600 mg per day for 10 days, followed by 400 mg per day for 10 days, after which a daily maintenance dose of 200 mg per day was administered. In patients who developed intolerable side effects, investigators were allowed to change AAD agent. AAD treatment was required to remain stable after implantation; any change of drug or dosage was considered a study outcome.

Data collection before pacemaker implantation

Baseline clinical data were collected at study enrolment. These data included a complete clinical history designed to assess cardiopulmonary symptoms and past events, the occurrence and characteristics of AF before randomization, determination of functional class at baseline with the New York Heart Association (NYHA) Classification, a baseline economic questionnaire.

Implantation and pacemaker programming

Only patients in sinus rhythm were enrolled in the study. When both atrial and ventricular bipolar leads were positioned, adequate capture thresholds, sensing and impedance measurements were required.

The pacemaker was then programmed to DDD(R) mode. The required lower and upper pacing rates were 60 and 120 bpm, respectively. An AV delay long enough to permit supraventricular conduction to take place, but still within the physiologic range, was recommended but not required.

Follow-up

Follow-up visits were scheduled at 5th, 9th, 13th, 17th, and 21st months, and included an interim clinical history designed to assess cardiopulmonary symptoms, functional class, and interim events, including hospitalizations, tests, and physician visits, a general physical examination, analysis of the cardiac rhythm with a 12-lead ECG and 30-s rhythm strip, analysis of the pacing system, including atrial capture threshold, sensing and impedance measurements (paying particular attention to any effects of AADs on these parameters), and assessment of AF frequency and burden via pacemaker diagnostics. Specific adverse event forms and endpoint forms were used to document clinical events.

Electrical cardioversion, AAD change, and AF/HF-related hospitalizations, that represent study endpoints, were left to physician’s discretion.

Outcome events and outcome committee

The primary long-term endpoint is the first occurrence of death, atrial cardioversion, hospitalization for AF/HF, or AAD change owing to AF prophylaxis failure or adverse events. These are some of the major adverse events that may occur in paced patients with SND. The rationale for choosing this composite endpoint was based on the expected event rate that should yield adequate statistical power described in the sample size paragraph. The criteria for heart failure hospitalization were need for supplemental oxygen therapy, need for repeated doses of intravenous diuretics, need for intravenous pressors or inotropes, poor response to more conservative outpatient therapy.

Data on major clinical events were obtained at follow-up visits and, when necessary, by telephone. An outcome committee of two physicians, not involved as study investigators and blinded to treatment assignment, monitored case report forms data and classified deaths, primary endpoints, and other clinical events. In particular, deaths were classified according to a variation of the Hinkle-Thaler clinical classification system.

Data analysis

The incidence of the primary endpoint will be calculated for all patients, irrespective of whether they actually received the assigned treatment; therefore, the intention-to-treat approach will be the primary method of analysis.

The upper limit of the one-sided 95% confidence interval will be calculated for the difference between the incidence of the primary endpoint in the two study groups.

The survival curves for the two main arms will be compared using the log-rank test.

Sample size

Sample size was evaluated for the long-term primary objective to test the non-inferiority of Class IC AAD compared with amiodarone in terms of the incidence of the primary endpoint.

In non-inferiority trials, the objective is to demonstrate with reassuringly high confidence, i.e. one-sided confidence interval equal to 95% or higher, that the new treatment is no worse than the established treatment within an acceptable margin of difference. The size of the acceptable margin mainly depends on the smallest clinically significant difference. Efficacy comparable with the standard strategy may be sufficient to justify the alternative when an advantage in safety, cost, long-term therapy applicability or patients’ quality-of-life is demonstrated. In the PITAGORA trial, non-inferiority will be considered to be established if the upper boundary of the confidence interval did not exceed 10%, which was considered the smallest clinically significant difference.

A sample size of 176 patients was calculated based on the hypothesis of 38% incidence of the primary endpoint in the amiodarone group and 27% in the Class IC group, with a significance level of 5% (one-sided) and a power of 80% and considering 10% patients lost to follow-up.

Discussion

Randomized controlled trials have become the standard method used to evaluate different therapeutic modalities and strategies.

Roy et al. showed that amiodarone is more effective than sotalol or propafenone in the maintenance of sinus rhythm in patients with AF. The observed difference in efficacy was striking, with amiodarone about twice as effective; therefore, investigators concluded that amiodarone warrants consideration as first- or second-line therapy in patients in whom maintenance of sinus rhythm is desired. Amiodarone is particularly selected in patients with recurrent AF, with structural heart disease, and with LV dysfunction. In contrast, other studies have shown that a high proportion of patients discontinue amiodarone because of adverse events.

Boriani et al. have recently shown that Class IC AADs are associated with higher ATP therapy efficacy when compared with Class III AAD. Therefore, the rationale exists to consider a complementary role between Class IC AAD and ATP therapies delivered by new generation pacemakers implanted in SND patients with indications for permanent pacing.

The PITAGORA trial has the objective to demonstrate that Class IC AAD therapy is no worse than amiodarone in terms of the incidence of the primary endpoint, which is defined as...
the time to the first occurrence of one of the following adverse events: death, hospitalization for AF or heart failure, atrial cardioversion, or AAD change owing to failure in AF prophylaxis. Non-inferiority is considered to be established if the upper boundary of the confidence interval does not exceed 10%, the smallest clinically significant difference.

Given the high morbidity associated with AF and the enormous costs to our healthcare system caused by this very common problem, new strategies are needed. The results of the current study may also contribute to defining the role, if any, of ATP therapies used in combination with AADs in SND patients suffering from AF.

Appendix


References

16. Van Gelder IC, Crijns HJGM, Van Gilst WH et al. Efficacy and safety of flecainide in the current study may also contribute to defining the role, if any, of ATP therapies used in combination with AADs in SND patients suffering from AF.

Appendix


References