

The MINERVA study design and rationale: A controlled randomized trial to assess the clinical benefit of minimizing ventricular pacing in pacemaker patients with atrial tachyarrhythmias

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Background Dual-chamber (DDD) pacing has generally been regarded as “physiologic pacing” and therefore expected to be superior to ventricular pacing. Major randomized trials have so far failed to demonstrate significant reductions in the incidences of mortality, stroke, and heart failure. It has been shown that unnecessary ventricular pacing in patients with sinus node dysfunction or only intermittent atrioventricular block is associated with ventricular desynchronization and increased risk of atrial tachyarrhythmias (ATA).

Methods The MINImizE Right Ventricular pacing to prevent Atrial fibrillation and heart failure (MINERVA) study is a prospective, multi-center, randomized, international, single-blind, controlled trial designed to determine whether physiologic pacing through the managed ventricular pacing (MVP) algorithm combined with preventive atrial pacing (PAP) and atrial antitachycardia pacing (ATP) is superior to standard DDD pacing in terms of 2-year reduction in death, permanent ATA, and cardiovascular hospitalizations. Patients with standard class I or II indications for permanent DDD pacing and history of ATA will receive a Medtronic EnRhythm implantable pacemaker (Medtronic, Minneapolis, MN). After a 1-month run-in period, patients will be randomized in a 1:1:1 manner to the DDD (control group, all OFF), the DDDRP (MVP + PAP + ATP ON), and the MVP group (only MVP ON). Up to 1,300 patients will be included in approximately 70 centers in Europe, the Middle East, and Asia.

Conclusions The MINERVA study will make an important contribution to the management of patients with paroxysmal ATA and accepted indications for dual-chamber pacemaker implantation by determining whether physiologic pacing combined with PAP and ATP is superior to standard DDD pacing in terms of reduction of mortality, incidence of permanent ATA, and cardiovascular hospitalizations. (Am Heart J 2008;156:445-51.)

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Background

Atrial tachyarrhythmia (ATA) and heart failure are growing challenges in modern health care systems.¹⁻³ Enormous efforts are being made to prevent these disorders and/or to treat patients who have them. However, detailed retrospective analyses of major randomized cardiac pacing trials^{4,6} have shown that not only ventricular (VVI/R) but also dual-chamber (DDD) pacing, the latter until now being regarded as physiologic pacing, may induce ATA, heart failure (HF), and even increase mortality,⁷ not only in patients with sinus node dysfunction (SND). Morbidity and mortality appear to be clearly linked to the amount of ventricular pacing delivered by patients' implantable pulse generators (IPGs).⁵ Furthermore, atrial-based pacing has been shown to be largely free from these side-effects of pacing.⁸⁻¹⁰ However, as the possibility of developing atrioventricular (AV) block can

Table I. Inclusion and exclusion criteria

Inclusion criteria

- Class I or class II indications for dual-chamber pacing.
- Previous implantation of an EnRhythm dual-chamber IPG within the last 2 wk.
- History of ATAs (1 episode of atrial fibrillation, flutter or tachycardia in the last 12 m documented by ECG or holter ECG).

Exclusion criteria

- Less than 18 years of age.
- Pregnancy.
- Unwillingness or inability to give informed consent or to commit to follow-up schedule.
- Medical conditions that preclude protocol-required testing or limit study participation.
- Enrolment or intention to participate in another clinical trial during the course of this study.
- Life expectancy of <2 y.
- Candidacy for ICD or cardiac resynchronization therapy device implantation.
- Anticipated major cardiac surgery within the course of this study.
- Permanent third-degree AV block or history of AV node ablation.
- History of permanent AF.
- Atrial fibrillation ablation (left pulmonary veins) or other cardiac surgery <3 m.
- Uncontrolled hyperthyroidism.

never be precluded, only a minority (11%) of patients with SND receive atrial pacing (AAI/R) pacemakers.¹¹

To combine the advantages of AAI/R pacing and DDD/R pacing (safety of ventricular backup pacing), a new pacing mode, managed ventricular pacing (MVP), has recently been developed. This provides true AAI/R pacing, monitors AV conduction, and switches to DDD/R pacing if intrinsic AV conduction fails.

Newer-generation pacemakers (EnRhythm, Medtronic, Minneapolis, MN) feature preventive atrial pacing (PAP) and atrial antitachycardia pacing (ATP) algorithms¹²⁻¹⁴ in combination with MVP to treat ATA in patients with SND and/or AV block. Accordingly, the MINimize Right Ventricular pacing to prevent Atrial fibrillation and heart failure (MINERVA) study was designed to investigate whether the time to a primary end point composed of death from any cause or permanent ATA or cardiovascular hospitalization is longer under full IPG therapy (MVP + PAP + ATP = DDDRP group) than under standard DDD pacing (DDD group). For explanatory reasons, and to analyze secondary end points, the study will include a third group, in which only the MVP algorithm will be activated (MVP group) while PAP and ATP remain inactivated.

Study

MINERVA is a prospective, randomized, single-blind, controlled trial enrolling up to 1,300 patients in approximately 70 centers in Italy, Germany, Spain, Portugal, Greece, The Netherlands, Austria, Slovakia, Switzerland, Kuwait, Hong Kong, Israel, Taiwan, and France. The first implantation took place in February

2006 and the study (including patient enrollment, follow-up, and data analysis) is expected to last 4 years. To date (April 2008), 550 patients have been enrolled. Patients with standard class I or II indications for permanent DDD¹⁵ pacing who meet the inclusion criteria (Table I) are eligible for the study. After approval of the study protocol by the respective review board institutions, the participating centers may start to enroll patients who have given their written informed consent.

A web site (<https://medtronic.clinsource.com/isapi/edc.dll>) has been specifically designed for the MINERVA study by Clinsource, Brussels, Belgium. Through this site the randomization and data entered in electronic case report forms are completed and sent to a central database.

MINERVA Study is registered on the <http://www.clinicaltrials.gov> website (ID number: NCT00262119).

Primary study objective

The main objective is to compare the impact of full therapy (MVP pacing mode, atrial preventive, and antitachycardia pacing therapies) with that of standard DDD pacing on the 2-year incidence of a composite clinical end point composed of death from any cause, permanent ATA, and cardiovascular hospitalizations.

Atrial tachyarrhythmia is considered permanent if the investigator decides not to cardiovert the patient and if ATA is present at 2 consecutive follow-up visits and is documented on 10-second device rhythm strips printed during IPG interrogation at the time of the visits.

Hospitalization is defined as an unplanned admission to a hospital involving an overnight stay or resulting in death. Daycare admissions are not included in the primary end point. Cardiovascular hospitalization includes unplanned hospitalization for heart failure, arrhythmia, angina, myocardial infarction, stroke, transitory ischemic attacks (TIA), syncope, acute coronary syndrome, pulmonary embolism, renal dysfunction, or other cardiovascular events. The cardiovascular nature of the events recorded is adjudicated by an independent event adjudication committee (see Appendix A). Hospitalizations during the run-in period before randomization and those due to device reinterventions which are not related to MVP or atrial therapies will be recorded but will not be considered primary end points.

Primary end-point comparison will be made between DDDRP and DDD group.

Secondary study objectives

Secondary objectives are:

1. Incidence of persistent ATA in the 3 arms (at least 7 consecutive days with 22 hours of ATA per day, as recorded by the IPG, or at least 1 day with an episode of ATA lasting at least 22 hours, as recorded by the IPG, interrupted by electrical or chemical cardioversion). The use of "7 consecutive days with

22 hours of ATA per day, as recorded by the IPG” as a device measurement of persistent ATA, is deemed to parallel the clinical definition in the ACC/ESC guidelines;

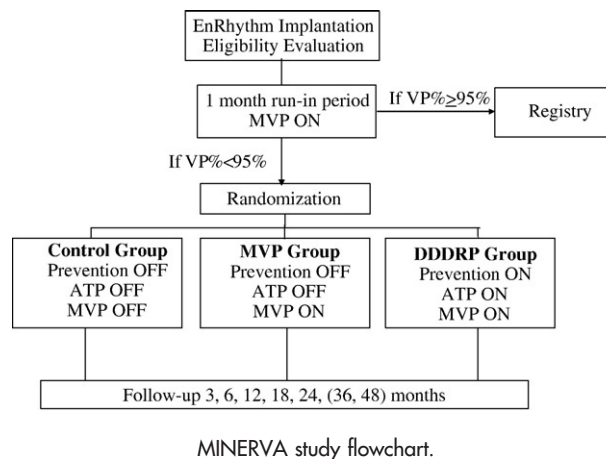
2. Burden of the clinical composite end-point events in the 3 arms;
3. Subjects' symptoms at each follow-up visit in the 3 arms;
4. Heart failure medications in the 3 arms;
5. Cumulative amount of ventricular pacing (%VP) at each follow-up visit in the 3 arms;
6. Incidence of cardiovascular death in the 3 arms;
7. Incidence of any hospitalization in the 3 arms;
8. ATA burden in the 3 arms;
9. Adverse events over time in the 3 arms;
10. Development of AV block and pacemaker dependency in the 3 arms;
11. Identification of predictors of stroke, TIA, and arterial embolism (in particular to evaluate whether ATA duration >5 minutes, >6 hours, >1 day, >2 days, or >7days predicts stroke, TIA, and arterial embolism) in the 3 arms;
12. Echocardiographic analysis of left ventricular fractional shortening and ejection fraction and dilatation of the left atrium in the 3 arms;
13. Clinical outcomes in all patients with MVP ON and comparison of outcomes in patients with and without optimized AV delay;
14. Time to development of the composite end point among all randomized subjects in predefined subgroups of patients;
15. Frequency, type, and associated cost of health care use and utility among patients in the 3 arms.

Subject selection and device characteristics

Investigators will screen their consecutive patients for inclusion/exclusion on the basis of age, pacemaker indication,¹⁵ conduction history, and cardiovascular medical history. Patients with a class I or II indication for dual-chamber pacing with at least 1 episode of ATA within the last 12 months which has been documented by electrocardiogram (ECG) and who have given their written informed consent will be invited to participate in the study.

Enrolled patients will undergo implantation of a commercially available Medtronic EnRhythm IPG with 2 commercially available bipolar leads. Device implantation will be followed by a 4-week run-in period. The EnRhythm IPG is a modern dual-chamber pacemaker with a new pacing algorithm, MVP, designed to ensure intrinsic AV conduction and to reduce unnecessary ventricular pacing. During intact AV conduction, the device provides true atrial pacing (AAI/R) with immediate ventricular backup pacing if AV conduction fails. If loss of AV conduction is detected for at least 2 of 4 atrial depolarizations, the device switches to the DDD/R mode.

Figure 1



On the basis of periodic AV conduction checks, the device switches back to AAI/R when intrinsic AV conduction has been restored. The device provides information on the amount of pacing in both chambers and on the burden of ATA over time. Furthermore, it features special PAP algorithms to prevent ATA and special therapeutic ATP algorithms which enable organized ATA to be overpaced.

Study design

During the 1-month run-in period after device implantation, all IPGs will be programmed to MVP ON, PAP OFF, and ATP OFF. In patients with an episode of persistent ongoing ATA during the run-in period, cardioversion is favored, so that as many patients as possible are in sinus rhythm at the 1-month follow-up visit. During this visit, the pacemaker systems will be checked for system integrity, threshold values, and the %VP that has been delivered since implantation. Patients with %VP $\geq 95\%$ or patients who refuse to be randomized will be followed up in a study registry. Randomization will be balanced with respect to presence/absence of AV block and LVEF ($< 40\%$ or $\geq 40\%$), and patients will be assigned in a 1:1:1 manner to (a) standard DDD pacing (DDD group), (b) pacing with MVP + PAP + ATP (DDDRP group), and (c) MVP without PAP or ATP (MVP group). In this parallel-group design, patients will be followed up in their respective therapy groups 3 and 6 months after implantation and thereafter every 6 months until 48 months after implantation. The study design is depicted in Figure 1.

No medications or treatments, apart from the pacemaker programming requirements, are required or prohibited in this trial, unless they are investigational or conflict with the inclusion/exclusion criteria. Initiations of drug therapy and changes in doses of ongoing

medication are permitted. Any current medication will be documented during the study visits.

Device programming

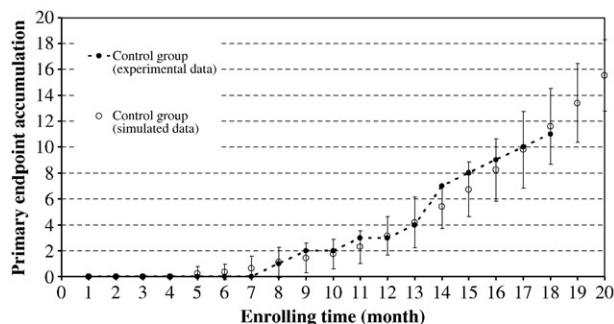
There is no mandatory PAP and ATP programming in the study. It was recommended to follow the ATP programming derived from the results of previous studies.^{16,17} Antitachycardia pacing is advised to be programmed to start after a 1-minute delay from the onset of ATA if atrial cycle length is ≥ 200 milliseconds. During ATP, 10 ramp stimulations (13 initial pulses, A-S1 interval = 91% of AA cycle), 10 burst + stimulations (11 initial pulses, A-S1 interval = 84% of AA cycle, S1S2 interval = 81% of AA cycle, S2S3 interval = 20 milliseconds, interval decrement = 10 milliseconds), and 10 different ramp stimulations (13 initial pulses, A-S1 interval = 81% of AA cycle) are advised to be programmed. For PAP programming, it was recommended to maintain the nominal device values.

In all patients during the run-in period, and in the control group patients after the first month follow-up visit, programming of the AV interval after spontaneous atrial depolarization (sensed AV delay) and after atrial stimulation (paced AV delay) is to be left entirely to the discretion of the physician, to respect current clinical practice. This will not be changed after randomization unless the center/patient participates in the AV-delay optimization substudy, in which a simple ECG method will be used to optimize AV synchrony. Patients who have been paced at $\geq 40\%$ of the time during the run-in period since device implantation despite the MVP algorithm having been activated and patients in the study registry are candidates for this substudy. It is the aim of this substudy to determine whether AV-delay optimization improves the study results in patients with $\%VP \geq 40\%$ despite MVP being activated.

Statistical considerations

Sample-size calculation is based on the results of several major pacemaker and implantable cardioverter defibrillator studies. The 2-year incidence of the composite end point “cardiovascular death + stroke” was found to be 11% in the CTOPP trial¹⁸; the incidence of “all-cause death + stroke” was 14% in the MOST trial⁴ and 11% in the ICARUS study.¹⁹ The composite end point “all-cause death + stroke + heart failure hospitalizations” was 19% in the MOST trial⁴ and 16% in the ICARUS study.¹⁹ Furthermore, in the ICARUS study¹⁹ the 2-year incidence of the end point “all-cause death + stroke + heart failure hospitalizations + permanent ATA” was 21%, and that of the end point “all-cause death + stroke + heart failure hospitalizations + permanent ATA + ATA hospitalizations” was 37%. The 2-year incidence of permanent ATA was 5.4% in the ICARUS study¹⁹ and 5.6% in the CTOPP trial.¹⁸ For the control group (DDD group) in the MINERVA

Figure 2



Comparison of real and simulated accumulation of primary end point in the control group of the MINERVA trial.

study, the 2-year incidence of the primary end point “all-cause death + permanent ATA + cardiovascular hospitalization” was therefore estimated as 37%. As the aim is to show a 30% risk reduction for this composite end point in the DDDRP group (26%)—with a power of 80%, a CI of 95%, and an assumed rate of 10% loss to follow-up—the sample size was estimated to approximate $n = 310$ patients per study group. Assuming that $<5\%$ of the patients enrolled will be followed up in the registry, around 1,000 patients will be enrolled in the study. An interim analysis will be performed when 300 patients have been enrolled in the control (DDD) group; if the real incidence of the composite end point turns out to be $<37\%$, the sample size could be increased to 1,300 patients. As the third study arm (MVP group) is only needed for secondary end-point analysis, it does not influence sample size calculations.

The time to an event will be calculated in each subject who has an event; in those without an event, a censored time-to-event will be adopted. Primary analyses will be performed by means of a Cox proportional hazard regression model on an as-randomized basis.

Sample size control system

Estimation of the statistical power and sample size of randomized clinical trials is based on several hypotheses and data, such as, for example, the incidence of the primary end point in the study population of patients treated with a conventional therapy. In some cases, this incidence is not precisely known, owing to a lack of published data, which makes it difficult to estimate sample sizes reliably. To compare the theoretical and experimental incidence of the end point in the control group of the MINERVA trial, a Monte Carlo simulation program able to estimate the theoretical accumulation of the primary end point in a randomized parallel study has been developed by the study management team. Comparison with the experimental accumulation rate is then

performed to confirm sample size hypotheses. At the end of each month, the actual enrollment rate for the 3 randomized arms of the trial is entered into the program and the Monte Carlo program applies a probability of end point occurrence to each enrolled patient (excluding those who had an end point in previous months). This probability is associated with the study hypotheses of a 2-year end-point incidence of 37%, 26%, and 18% (according to the assumed 30% risk reduction) in the DDD, MVP, and DDDRP groups, respectively. Real data on the occurrence of the primary end point are continuously monitored via standard case-report forms for the control group in the study. Figure 2 shows the comparison between real and simulated data. The preliminary observation of a good agreement between experimental and theoretical data so far suggests that the estimations of end-point incidence used to evaluate the study sample size are appropriate, thus confirming that the MINERVA trial is appropriately powered to test the experimental therapies used.

Study organization

The MINERVA trial was designed by an independent steering committee composed by the authors of the present paper. The study is supported by Medtronic. An independent biostatistician (Prof Erik Cobo, Technical University of Catalonia, Barcelona, Spain) is responsible for the data analysis plan.

Discussion

So far, major randomized trials^{4,18,20} have failed to demonstrate the superiority of physiologic pacing over ventricular pacing in patients with SND. In most of the cohorts investigated, dual-chamber pacing, regarded as physiologic, has been compared with VVI/R pacing. No reductions in mortality, incidence of stroke, or heart failure have been seen.^{4,21} The results of smaller studies that have compared AAI/R with VVI/R pacing suggest that not only atrial fibrillation^{8,10} but also thromboembolic events, the severity of heart failure, and even all-cause mortality⁸ are reduced with pure atrial pacing. These and other study results support the hypothesis that atrial pacing might be more physiologic than dual-chamber pacing. It appears that ventricular pacing, more pronounced in the form of VVI/R pacing than if performed in a dual-chamber pacing mode, has negative effects on the heart. Abnormal ventricular activation induced by right ventricular (RV) pacing causes mechanical dyssynchrony, thereby impairing left ventricular function.²²⁻²⁴ These detrimental effects of RV pacing can be demonstrated not only on a mechanistic level; they also translate into deterioration of important clinical end points, such as hospitalization due to heart failure^{4,5} and mortality.⁷ Despite the adverse effects of RV pacing and the advantages of AAI/R pacemakers, only about 11% of the pacemakers implanted in patients with SND are AAI/R

pacemakers.¹¹ This is due to the risk of developing AV block, with a 1.1% to 1.7% per year probability that these patients will require implantation of a ventricular lead.²⁵

The adverse effects of RV pacing are not only confined to the ventricles. Progressive atrial dilatation and increased risk of atrial fibrillation^{22,26} are typically observed in chronic RV pacing. This may in part explain the heterogeneity of the results of studies performed to investigate the effects of atrial pacing on the prevention of ATA.²⁷ In such studies, the beneficial electrophysiologic effects of PAP^{12,14,28,29} and ATP^{13,30} algorithms might, at least in part, have been hidden by the detrimental effects of RV pacing. Summaries of most of the above-cited studies are given in the works of Savelieva et al³¹ and Ricci et al.³²

Very recently, the SAVE PACE trial³³ showed a 40% reduction in the relative risk of developing persistent ATA in patients with sinus-node disease managed with dual-chamber minimal ventricular pacing. Sweeney et al³³ also showed that persistent ATA occurrence is significantly associated with a more frequent indication for AV node ablation and pulmonary vein ablation. Their study, however, was not large enough to show a difference in mortality and/or cardiovascular hospitalizations. The SAVE PACE results strongly support the MINERVA trial rationale, although the 2 studies answer complementary questions and the 2 study populations are different: only 38% of the patients in SAVE PACE had a history of previous ATA versus 100% in the MINERVA study.

To combine the advantages of atrial and dual-chamber pacing, a new algorithm, MVP, has recently been developed. This has been demonstrated to significantly reduce the amount of unnecessary ventricular pacing³⁴ even in comparison with the Medtronic Search AV algorithm,³⁵ which was used in the majority of patients in the SAVE PACE trial.

Conclusions

The MINERVA study will yield important information for the management of patients with paroxysmal ATA and accepted indications for dual-chamber pacemaker implantation, by determining whether physiologic pacing combined with PAP and ATP is superior to standard DDD pacing in terms of reduction of mortality, permanent ATA incidence, and cardiovascular hospitalizations. This will be the first study to answer the question of whether real dual-chamber physiologic pacing reduces the incidence of important clinical end points in a population of patients with sinus-node disease with a history of previous ATA.

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Appendix A. Adverse event adjudication committee members

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