The Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) Trial: clinical rationale, study design, and implementation

Christian Jons¹, Peter Steen Hansen², Arne Johannessen¹, Gerhard Hindricks³, Pekka Raatikainen⁴, Ole Kongstad⁵, Håkan Walfridsson⁶, Steen Pehrson⁷, Henrik Almroth⁸, Juha Hartikainen⁹, Anders Kirstein Petersen², Leif Spange Mortensen¹⁰, and Jens Cosedis Nielsen²* on behalf of the MANTRA-PAF Investigators

¹Gentofte University Hospital, Copenhagen, Denmark; ²Skejby University Hospital, Aarhus, Denmark; ³Leipzig University Hospital, Leipzig, Germany; ⁴Oulu University Hospital, Finland; ⁵Lund University Hospital, Sverige, Sweden; ⁶Department of Cardiology, Heartcenter, University Hospital Linköping, Linköping, Sweden; ⁷Rigshospitalet, Copenhagen, Denmark; ⁸University Hospital, Örebro, Sweden; ⁹Kuopio University Hospital, Kuopio, Finland; and ¹⁰Uni-C, Aarhus, Denmark

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Aims
No large randomized multicentre trial has evaluated the efficacy of radiofrequency ablation (RFA) vs. anti-arrhythmic drug (AAD) therapy as a first-line treatment of paroxysmal atrial fibrillation (AF).

Methods and results
The Medical ANtiarrhythmic Treatment or Radiofrequency Ablation (MANTRA-PAF) trial is a randomized, controlled, parallel group, multicentre study designed to test whether catheter-based RFA is superior to optimized AAD therapy in suppressing relapse within 24 months of symptomatic and/or asymptomatic AF in patients with paroxysmal AF without prior AAD therapy. The primary endpoint is cumulative AF burden on repeated 7 days Holter monitoring. Secondary endpoints are: thromboembolic events, hospitalization due to arrhythmia, pro-arrhythmic events, procedure/treatment-related side effects, health economics, quality of life, and change in left ventricular function. Ten centres in Scandinavia and Germany are participating in the study. Enrolment was started in 2005 and as of November 2008, 260 patients have been enrolled into the study. It is expected that enrolment will end by March 2009, when 300 patients have been included.

Conclusion
The MANTRA-PAF trial will determine whether catheter-based RFA is superior to optimized AAD therapy as a first-line treatment in suppressing long-term relapse of symptomatic and/or asymptomatic AF.

Keywords
Atrial fibrillation • Radiofrequency ablation • Anti-arrhythmic drugs • Randomized trial

Introduction
Radiofrequency ablation (RFA) therapy has revolutionized treatment of atrial fibrillation (AF), and is recommended as a second-line therapy in the current guidelines.¹ Several studies have proved the superiority of ablative therapy over medical therapy in treating paroxysmal, persistent, and chronic AF in patients who have already been treated with at least one anti-arrhythmic drug (AAD).²–⁴ Only one small study has compared ablation therapy as a first-line therapy,⁵ also in favour of ablative therapy, but with limited impact due to a small study size, few participating centres, and a short follow-up duration of the study subjects.
Ablative therapy has been shown to be safe\textsuperscript{6} and cost-effective,\textsuperscript{7,8} and a recent meta-analysis\textsuperscript{9} stated the need for a large-scale randomized multicentre trial designed to compare optimal medical treatment vs. RFA as a first-line therapy for AF.

The Medical ANtiarrhythmic Treatment or Radiofrequency Ablation (MANTRA-PAF) trial was designed to test whether catheter-based RFA is superior to optimized AAD therapy in suppressing long-term relapse of symptomatic and/or asymptomatic AF in patients with paroxysmal AF without prior AAD therapy.

**Study design**

**General**

The MANTRA-PAF trial is a randomized, controlled, parallel, multicentre study. Patients with paroxysmal AF are randomly assigned to medical anti-arrhythmic treatment or RFA with 50\% of the patients assigned to each treatment arm. The first patient was randomized in June 2005. A total of 300 patients will be included and followed for a period of 24 months after inclusion. As of November 2008, 260 patients have been enrolled, and enrolment is expected to be completed by March 2009.

**Population**

Study subjects are recruited in 10 centres in Scandinavia and Germany. Inclusion and exclusion criteria are presented in Table 1. Patients who meet the eligibility criteria and none of the exclusion criteria will be recruited by the responsible electrophysiologist at each enrolling centre. Reasons for exclusion are recorded for eligible patients not enrolled. The enrolment cascade and follow-up procedure are presented in Figure 1.

**Informed consent and ethical considerations**

The study is conducted in accordance with the Helsinki declaration, and accepts from the Ethics Committee of Aarhus County and the local ethical committee, whenever necessary, were obtained before study initiation. Patients only participate after informed written and verbal consent. Well in advance of the oral information taking place, the patient receives written information about the study to allow for careful reading. Oral information includes information about the research project, risks, and possible side effects.

**Baseline evaluation**

Before randomization, a full baseline evaluation is performed, including medical history, physical examination, 12-lead ECG, 7-day Holter, SF-36, blood samples, and an echocardiogram. The echocardiogram is performed to ensure a left ventricular ejection fraction (LVEF) of \( \geq 40\% \), no severe mitral valve insufficiency, and no gross enlargement of the left atrium (\( \geq 50 \) mm).

**Randomization**

Block randomization is used with stratification for centre, sex, and hypertension. Patients are computer randomized utilizing a 24 h automatic telephone randomization/voice-response system, the PARAVOX system, with logging of all calls and call attempts. Each randomized subject will remain member of the treatment group to which he or she was originally assigned (intention-to-treat), regardless of subsequent protocol adherence. The date of randomization will be used as time zero for analysis.

**Table 1** Inclusion and exclusion criteria for the MANTRA-PAF study

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Patients ( \leq 70 ) years of age with paroxysmal atrial fibrillation, who are considered as candidates for anti-arrhythmic drug therapy initiation</td>
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<tr>
<td>At least two episodes of symptomatic paroxysmal atrial fibrillation within the preceding 6 months</td>
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<tr>
<td>If persistent, i.e. in need of DC or medical cardioversion, the atrial fibrillation episodes must have lasted (&lt; 7 ) days</td>
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<tr>
<td>Previous or ongoing chronic treatment with class IC or class III anti-arrhythmic drugs</td>
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<tr>
<td>Contraindication to both class IC and class III anti-arrhythmic drugs (i.e. contraindication to only one of the two groups is not an exclusion criterion)</td>
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<tr>
<td>Previous atrial fibrillation ablation</td>
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<tr>
<td>Severely enlarged left atria (( \geq 50 ) mm)</td>
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<tr>
<td>Left ventricular ejection fraction (&lt; 0.40 ) (during sinus rhythm or atrial fibrillation with RR intervals ( \geq 600 ) ms) or ‘eye-balled’ reduction of systolic function to less than ‘moderately decreased’</td>
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<tr>
<td>Contraindication to anticoagulation treatment with vitamin K antagonists</td>
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<tr>
<td>Expected surgery for structural heart disease during the follow-up period</td>
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<tr>
<td>Moderate or severe mitral valve disease</td>
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<tr>
<td>NYHA III–IV</td>
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<tr>
<td>Planned pregnancy during the follow-up period</td>
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<tr>
<td>Secondary atrial fibrillation (e.g. post-surgery, infection, and hyperthyroidism)</td>
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<tr>
<td>Patient does not want to participate</td>
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</table>

NYHA, New York Heart Association functional classification.
\section*{Intervention}

\subsection*{Pulmonary vein ablation}

The invasive procedure was standardized to optimize the comparability of results obtained from different centres. The study ablation procedure is outlined and described in Figure 2. The endpoint of the ablation procedure was pulmonary vein ablation indicated by the absence of high-frequency electrical activity ($>0.2$ mV) inside the encircled areas around the pulmonary veins. Only RFA was utilized. Stable INR above or equal to 2.0 for at least 3 weeks before the procedure must be documented. All patients undergo transoesophageal echocardiography (TEE) within 24 h before the procedure to exclude thrombi in the left atrial appendage (LAA). The presence of an LAA thrombus does not exclude the patient from catheter treatment, but postpones this until a new TEE has documented resolution of the thrombus.

\subsection*{Post-ablation procedure drug and ablation treatment}

If clinically indicated, amiodarone may be given for 3 months after the procedure. If contraindication for amiodarone is present or serious side effects appear, class IC AAD may be prescribed. If the patient is without symptomatic relapse after 3 months of follow-up, AAD treatment is stopped. If symptomatic relapse(s)
are documented more than 3 months after the initial RFA procedure, the patient is offered re-ablation. Supplementary antiarrhythmic medication can be prescribed at the discretion of the responsible electrophysiologist if clinically indicated. In this case, the Holter monitorings will be done as scheduled, despite this drug treatment and the estimated benefit from catheter ablation will be assessed with AA drugs. Additional AF ablation procedures may be performed throughout the study period at the discretion of the treating centre. If atrial flutter (atypical or typical) is documented during the study period, the patient is offered a new ablation procedure. Effort will be made to document any relapse of symptomatic arrhythmia by either 12-lead ECG or Holter monitoring.

**Anti-arrhythmic drug treatment**

Class IC AAD treatment (flecainide or propafenone) is a first-line therapy for patients without contraindications (structural heart disease, reduced left ventricular function, or ischaemic heart disease). Otherwise, amiodarone is the drug of choice, and also sotalol may be prescribed at the discretion of the responsible electrophysiologist/cardiologist. Shift from one AAD to another can be done during the study course. If necessary, AADs can be supplemented by AV conduction blocking agents (digoxin, calcium antagonists, and beta-blockers). If the patient is treated with class IC AADs, a combination with AV conduction blocking agents is recommended. Combination of several AADs is not allowed. Recommended drugs and initial maintenance doses are shown in Table 2. Initiation and control of AAD treatment is according to institutional standards at the involved centres. An aggressive rhythm control strategy, including multiple DC conversions and subsequent trials of AAD therapy when needed, is encouraged. The use of AAD treatment is monitored closely throughout the study period in both treatment arms.

**Anticoagulation**

Patients randomized to RFA are anticoagulated to obtain a stable INR of 2.0–3.0 at least 3 weeks before the operation. Anticoagulation treatment is continued for a minimum of 3 months after the procedure. If the CHADS2 score is lower than 2, anticoagulation therapy may be stopped 3 months after the RFA procedure, aspirin (75–150 mg/day) may be started at the discretion of the responsible electrophysiologist. In patients (ablated or medically treated) with a CHADS2 score ≥2, anticoagulation therapy is continued throughout the study period. Patients randomized to AAD treatment who have a CHADS2 score lower than 2 may be treated with anticoagulation INR (2.0–3.0), aspirin (75–150 mg/d), or left without anticoagulation therapy at the discretion of the responsible electrophysiologist.

**Crossover**

All participating centres are encouraged to refrain from doing RFA (pulmonary vein isolation) in patients randomized to AAD to reduce crossover in the study period. Before allowing crossover to ablation in the AAD arm, each patient must have tried

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**Table 2** Recommended anti-arrhythmic drugs and corresponding initial doses used in the study

<table>
<thead>
<tr>
<th>1st choice</th>
<th>2nd choice</th>
<th>3rd choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>Propafenone</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Dose</td>
<td>100 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td></td>
<td>twice a day</td>
<td>twice a day</td>
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</tbody>
</table>

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**Figure 2** Study ablation procedure. Mandatory ablation lines are shown in blue and optional lines in orange. Transseptal access to the left atrium is done by standard technique and the patient is anticoagulated according to standard institutional criteria. Percutaneous transvenous radiofrequency catheter ablation is done under the guidance of the computer-based mapping system CARTOTM. Ablation around both left- and right-sided pulmonary veins (1) is mandatory, and is done using an irrigated catheter (Navistar Cool Flow®) or an 8 mm non-irrigated catheter (Navistar D5®) with a maximum energy settings at 40 W/55°C/17 mL saline/min, alternatively 80 W/55°C (8-mm tip). Care is taken to avoid excessive heating of the posterior wall of the left atrium—maximum energy 30 W/55°C/17 mL saline/min alternatively 50 W/55°C (8 mm tip). A ‘roof line’ between the two ablated areas (2) is obligatory, whereas an ablation line from left inferior pulmonary vein to mitral annulus is optional (3). Right atrial cavo-tricuspid isthmus block is performed only if common-type flutter has previously been documented. If previous cavo-tricuspid isthmus block has been performed, the lesion is tested for completeness and supplementary radiofrequency ablation is performed if necessary. The radiofrequency ablation procedural endpoint is elimination of high-frequency electric activity (>0.2 mV) inside the encircled areas, either documented by CARTO-mapping or by the use of Lasso catheter(s). Heparin may or may not be neutralized at the end of the procedure. Coumarin treatment may be paused or continued until the procedure according to institutional standards.
treatment with appropriate doses of all possible agents that are judged to be clinically relevant for this particular patient. Amiodarone is not considered clinically relevant for younger patients without comorbidity, class IC AADs are not considered relevant for patients with concomitant structural heart disease, and sotalol is not used in all centres. Only after trials of every AAD not contraindicated in the patient have revealed insufficient antiarrhythmic effect or unacceptable side effects, RFA is allowed. Similarly, AAD treatment is allowed in the RFA group, if deemed necessary. Despite any crossover in treatment, all patients will be regarded as belonging to the group they were randomized to.

Patient follow-up

Patients are seen in the institutional outpatient clinic after 3, 6, 12, 18, and 24 months. The follow-up procedure is outlined in Figure 1. The following information is collected:

- A quality of life (QoL) assessment using the SF-36 forms at 12 and 24 months.
- Seven days Holter monitoring at 3, 6, 12, 18, and 24 months.
- Individual patient log-books are filled in with the following data: (i) time of start and end of symptomatic arrhythmia, (ii) date of start and end of sick-leave periods, (iii) date and cause of contact with general physicians, (iv) date and cause of hospitalization, (v) date and cause of outpatient clinic contact, and (vi) date and cause of contact with privately practicing cardiologist.
- Transthoracic echocardiography at 12 and 24 months with measurement of LVEF, left atrial longitudinal and transversal diameters, and atrial contribution to transmitral flow judged by Doppler measurement [if sinus rhythm (SR) is present].

A register of all patients who are screened and fulfills inclusion criteria, but for one or more reasons are not included in the trial, has been established.

Endpoints

Primary endpoint

The primary endpoint is cumulative AF burden (symptomatic or asymptomatic) during 7-day Holter recordings after 3, 6, 12, 18, and 24 months of follow-up, i.e. the percentage of time in AF/AT periods ≥1 min of total time (nominal 35 days). Apart from the AF/AT measure for the cumulated 35 days, the percentage will be reported for every follow-up.

Secondary endpoints

The MANTRA-PAF trial is not powered for all secondary objectives, but the following data will be compared by treatment arm:

- Complications (including thromboembolic events, major bleeding episodes, pro-arrhythmic events, and treatment-related side effects).
- Quality of life assessed by SF-36 Health Survey Questionnaire.
- Health economics (including number of DC cardioversions, cardiovascular hospitalizations, and costs of AADs).
- Time to first AF recurrence (after 3 months blanking period).
- Freedom from AF/AT periods ≥1 min during 7-day Holter recording after 2 years of follow-up.
- Burden of symptomatic AF/AT during 7-day Holter recordings after 3, 6, 12, 18, and 24 months of follow-up: duration and percentage of time in AF/AT periods ≥1 min with symptoms of total time (35 days).
Freedom from symptomatic AF/AT periods ≥1 min during 7-day Holter recording after 2 years of follow-up.

Chronic AF (continuous AF during 7-day Holter monitoring after 24 months follow-up, together with AF during the immediately foregoing 8 weeks).

Left ventricular systolic function by 2D transthoracic echocardiography.

In cases where a Holter is missing from one or more follow-ups, the algorithm shown in Figure 3 will be used. The analysis of freedom from AT/AF at 2 years of follow-up is based solely on Holter performed at 2-year follow-up, and will be done for all patients included in the trial using the algorithm in Figure 3.

Ascertainment of secondary endpoints, such as adverse events, will be carried out by each local centre and reported to the coordinating centre. Adverse events will be documented and classified using the definitions and classifications presented below. To determine the cause of death, every effort will be made to obtain an autopsy on patients who die from any cause, and if possible, a pathological analysis of the heart is performed.

### Table 3 Adverse events: classification and definitions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Serious</td>
<td>Any clinical event resulting in death. Life-threatening complication, persistent or significant disability/incapacity requiring inpatient hospitalization. Prolonged hospitalization. Intervention to prevent a permanent impairment of a body function or damage to a body structure.</td>
</tr>
<tr>
<td>Not serious</td>
<td>All AEs not meeting the definition of serious AE, including events resulting in a transient impairment of a body function that resolves spontaneously or with minimal intervention. This includes minor bleeding, oozing, or ecchymosis from intravenous puncture sites.</td>
</tr>
<tr>
<td>Unanticipated</td>
<td>An event not previously identified in nature, severity, or degree of incidence in this protocol. Any other serious problem associated with the treatment that relates to the rights, safety, or welfare of subjects.</td>
</tr>
</tbody>
</table>

Every AE will be classified as serious or not serious and known or unanticipated according to this table. The outcome of each AE will be assessed according to the following classifications: Resolved: patient fully recovered with no observable residual effects; Improved: patient’s condition improved, but residual effects remain; Unchanged: AE is ongoing; Worsened: patient’s overall condition worsened; Hospitalization: AE required or prolonged hospitalization; Permanent disability: AE resulted in a permanent impairment of a body function or damage to a body structure. Causality of every AE will be assessed according to the following classification: Procedure-related: The event is directly related, by timing and/or pathophysiology, with therapeutic procedures described in this protocol; Possibly procedure-related: the AE may be associated with therapeutic procedures described in this protocol by timing and/or pathophysiology; Not related: the AE is not associated with therapeutic procedures described in this protocol.
**Adverse events**

An important part of the study is to estimate the safety and the occurrence and severity of adverse events in the two treatment arms. For this study, an adverse event is defined as any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring in a subject during the course of the study, whether or not it is related to treatment. Physical findings (including vital signs) observed at follow-up, or pre-existing physical findings that have worsened compared with baseline, are adverse events if the investigator determines these as clinically significant.

All serious and/or unanticipated adverse events and patient deaths, whether or not related to the treatment given, must be reported to the coordinating investigator within 24 h of receipt of information by the investigational site. Documentation includes a description of the event, date of onset, severity, relationship to treatment, required intervention, duration, and outcome. All adverse events will be monitored until they are adequately resolved or explained. To ensure standardized safety evaluation across investigational sites, assessment of seriousness, intensity, outcome, and causality of an adverse event will be made by the investigator in the local centre according to definitions and classifications presented in Table 3 and the accompanying text.

For every adverse event, any subsequent medical treatment of the adverse event will be documented and reported to the coordinating investigator as appropriate. Patient monitoring will continue until the event has subsided, resolved, or in the case of permanent impairment, until the event has stabilized, and the overall clinical outcome may be determined. An ongoing adverse event will be handled as a single event.

**Sample size and statistical considerations**

The distribution and range of AF burden was difficult or impossible to estimate from the literature at the time of trial initiation, and thus power calculations were based on assumptions regarding the presence of stable SR at the end of the primary study period. It was assumed that 60% of AAD-treated patients and 75% of RFA patients would be in stable SR after 2 years. By including 150 patients in each treatment arm, the difference between the two groups can be detected with a power of 80% using a two-sided test and a significance level of 5%. All analyses will be carried out according to the intention-to-treat-principle.

**Conflict of interest:** none declared.

**Funding**

The total budget for the study is ~750,000 Euro. Study expenses will be covered on a fifty-fifty basis with commercial sponsoring ( Biosense Webster, Johnson & Johnson) and non-commercial funding (e.g. Danish Heart Association). Study participants will have their transport expenses for follow-up visits covered, but do not receive further economical compensation for their participation in the study.

**References**