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STUDY DESIGN

A clinical and health-economic evaluation of pulmonary vein encircling ablation compared with antiarrhythmic drug treatment in patients with persistent atrial fibrillation (Catheter Ablation for the Cure of Atrial Fibrillation-2 study)

Emanuele Bertaglia[1]*, Giuseppe Stabile[2], Gaetano Senatore[3], Andrea Colella[4], Maurizio Del Greco[5], Heinz Goessinger[6], Filippo Lamberti[7], Martin Lowe[8], Roberto Mantovan[9], Nicholas Peters[10], Claudio Pratola[11], Pekka Raatikainen[12], Pietro Turco[13], and Roberto Verlato[14]

[1] *Ospedale Civile, Mirano, Italy;* [2] *Casa di Cura San Michele, Maddaloni, Italy;* [3] *Ospedale Civile, Ciriè, Italy;* [4] *Ospedale Careggi, Florence, Italy;* [5] *Ospedale Santa Chiara, Trento, Italy;* [6] *AKH, Vienna, Austria;* [7] *Ospedale San Giovanni, Roma, Italy;* [8] *Heart Hospital, London, UK;* [9] *Ospedale Ca'Foncello, Treviso, Italy;* [10] *St Mary's Hospital, London, UK;* [11] *Ospedale Sant'Anna, Ferrara, Italy;* [12] *University of Oulu, Oulu, Finland;* [13] *Casa di Cura Villa Maria, Cotignola, Italy; and* [14] *Ospedale Civile Cosma, Camposampiero, Italy*

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KEYWORDS
Atrial fibrillation;
Catheter ablation

Aims Catheter Ablation for the Cure of Atrial Fibrillation 2 study is a prospective, randomized trial aimed to demonstrate the efficacy of catheter ablation with combined lesions in the right and left atria, in preventing atrial fibrillation (AF) recurrences among patients with recurrent persistent AF refractory to one antiarrhythmic drug, in comparison with the best pharmacological therapy.
Methods and results Enrolment is limited to patients aged between 18 and 70 years who have experienced at least one documented relapse of persistent AF during antiarrhythmic drug therapy. One hundred and twenty-six patients will be randomized to ablation or antiarrhythmic drug therapy in a 2:1 manner. In the ablation group, the patients will undergo right and left atrial linear ablation. Control group patients will be treated with the best antiarrhythmic drug. After an initial blanking period of 2 months patients will be followed for 24 months. Primary endpoint of the study is the absence of documented persistent atrial tachyarrhythmias relapse during the first 24 months after the blanking period. Enrolment is scheduled in 14 centres in Italy, UK, Austria, and Finland. Seventy-two patients have currently been enrolled.
Conclusion This study will provide important data about the efficacy of catheter ablation in comparison with antiarrhythmic drugs for the treatment of persistent AF.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia. It is present in 0.4% of the overall population and affects 4% of patients >60 years and up to 15% of patients >70 years.[1,2] Atrial fibrillation is associated with a two-fold risk of cardiac and overall mortality.[2] Despite its clinical importance, medical control of AF is difficult.[3] Recently, the conventional strategy of repeated electrical cardioversions in patients using antiarrhythmic drugs was demonstrated to be unsuccessful in preventing AF relapse.[4–7] Antiarrhythmic drugs were also associated with a considerable number of side effects, which mitigate the beneficial effects of normal sinus rhythm.[8]

Therefore, several non-pharmacological strategies to manage AF are being investigated.[9–18] Among these strategies, percutaneous catheter ablation seems to be one of the more promising approaches to cure AF. The first attempts at this strategy tried to reproduce the Maze operation.[11–15] However, the discovery of the pulmonary veins' (PVs) pivotal role in the initiation and perpetuation of AF soon directed attention to the focal ablation of AF,[16,17] or

* Corresponding author. Tel: +39 0415794258; fax: +39 0415794309.
E-mail address: bertagliaferro@alice.it

circumferential radiofrequency ablation around the PVs ostia.[18,19]

In a non-randomized study, circumferential catheter ablation was superior to antiarrhythmic drugs in reducing mortality and improving quality of life.[19] More recently, the results of two prospective, randomized studies demonstrated the efficacy of catheter ablation combined or not with pharmacological therapy to cure AF in comparison with pharmacological therapy alone in patients refractory to antiarrhythmic drugs.[20,21]

Catheter Ablation for the Cure of AF (CACAF-2 Study) is a prospective, randomized trial aimed to demonstrate the efficacy of percutaneous radiofrequency ablation with combined lesions in the right and left atria, in preventing AF recurrences among young to middle-aged patients with recurrent persistent AF refractory to one antiarrhythmic drug, in comparison with the best pharmacological therapy.[22]

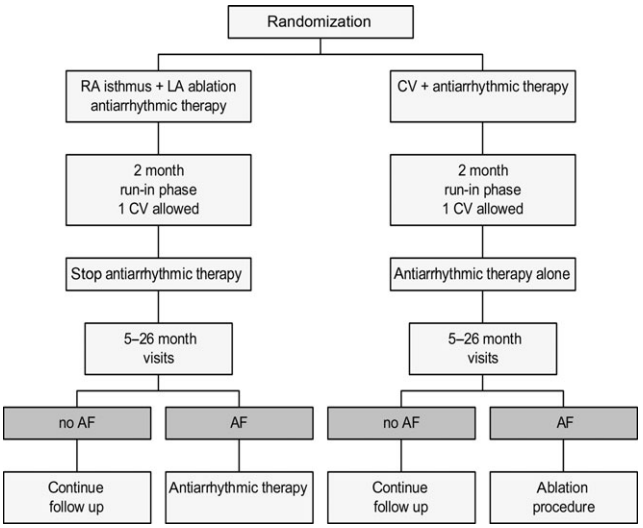

Figure 1 Flow-chart of CACAF 2 Study. Run-in phase, blanking-period.

Methods

Patients

Enrolment into the trial is limited to patients aged between 18 and 70 years who have experienced at least one documented relapse of persistent AF during antiarrhythmic drug therapy, and, upon cardioversion, sinus rhythm was maintained for 60 min or more.

Exclusion criteria are: (i) prior use of more than one antiarrhythmic drug (Class I or Class III); (ii) permanent AF, i.e., AF as the sole rhythm for >6 months before the enrolment; (iii) paroxysmal AF, i.e., self terminating AF episodes lasting <7 days; (iv) presence of an implanted device (pacemaker or cardioverter-defibrillator); (v) a left atrial diameter (antero-posterior) >50 mm; (vi) previous ablation for AF; (vii) congestive heart failure New York Heart Association (NYHA) Class II-III-IV; (viii) left ventricular ejection fraction $<40\%$; (ix) unstable angina or acute myocardial infarction within 3 months; (x) need for cardiac revascularization or other cardiac surgery within 6 months; (xi) presence of a separate requirement for antiarrhythmic drug treatment, which will require an antiarrhythmic drug not previously tried for AF suppression; (xii) prior atrial surgery; (xiii) contraindication to treatment with warfarin or other bleeding diathesis; (xiv) severe chronic renal or hepatic impairment.

The study is performed in accordance with the European Standard for Clinical Investigation of medical devices for human subjects (EN ISO 14155: 2003) and in accordance with the Declaration of Helsinki.

Randomization and patient treatment

After informed consent is obtained, randomization takes place via closed envelopes. The randomization scheme is done per centre and is set-up in order to achieve a balanced distribution of treatments per centre.

Each patient is randomized to ablation (Ablation group) or antiarrhythmic drug therapy alone (Control group) in a 2:1 manner (*Figure 1*).

Ablation group

Ablation group patients will undergo right and left atrial linear ablation. Left atrium and PVs are explored using a transseptal approach. Real-time three-dimensional left atrial maps are reconstructed using a non-fluoroscopic navigation system (CARTO™, Biosense Webster Inc., Diamond Bar, CA, USA). Maps are acquired during AF or pacing from the coronary sinus. Radiofrequency pulses are delivered using a 3.5-mm NAVISTAR® THERMOCOOL® catheter (Biosense Webster Inc.) with temperature limitation of 43°C and radiofrequency energy up to 42 W. Radiofrequency energy is delivered up to 120 s until local electrogram amplitude is reduced $\geq 80\%$. To reduce the risk of the catheter tip overheating, a fine back-and-forth movement of the catheter is recommended during radiofrequency delivery at the ablation site. The ablation lines consist of contiguous focal lesions deployed at a distance ≥ 5 mm from the ostia of the PVs, creating a circumferential line around each PV. In addition, the left inferior PV is connected to the mitral annulus (mitral isthmus), and a left atrial roof line connecting the superior encirculations of the PV ostia will be created.

A remap process is performed after spontaneous restoration of normal sinus rhythm or electrical cardioversion during coronary sinus pacing, using the preablation anatomic map for acquisition of new points. Each PV ostium is considered completely isolated when: (i) at least three points acquired inside the encircling have an electrogram potential lower than 0.1 mV, or 80% lower than the electrogram potential recorded before the ablation at the same site; and (ii) pacing from at least three points inside the encircling with a stimulus of amplitude two-fold greater than the threshold and 2 ms duration allows local capture without left atrial capture (exit block). Use of circular decapolar mapping catheter (LASSO®, Biosense Webster Inc.) to confirm PV isolation is suggested but not mandatory.

Electrophysiological demonstration of conduction block of the mitral isthmus and of the left atrial roof is not mandatory.[23] The block along the line connecting the mitral valve to the lower lateral PV is evaluated by pacing from the distal electrodes of the coronary sinus catheter; the endpoint is the recording on the distal electrodes of the ablation catheter, positioned on that line, of a double potential with an isoelectric line of at least 150 ms.

Patients with conduction along cavo-tricuspid isthmus undergo inferior vena cava–tricuspid annulus isthmus ablation after completion of the left atrial ablation, in a single session.

The antiarrhythmic drug regimen is discontinued after the blanking period. Patients have to be on oral anticoagulant therapy for at least 1 month before, and 3 months after the ablation. Decisions concerning the need for anticoagulation after this period will be at the discretion of the referring physician.

Control group

Control group patients will be treated with the best antiarrhythmic drug (by preference amiodarone) and eventually undergo a transthoracic electrical cardioversion. Patients have to be on oral anticoagulant therapy for at least 1 month before, and 3 months after the electrical cardioversion.

Follow-up

A blanking period of 2 months is scheduled in order to allow the consolidation of radiofrequency lesions in Ablation group patients, and the antiarrhythmic drug to become efficacious in the Control group patients. At the end of the blanking period, one electrical cardioversion is allowed to restore sinus rhythm in the event of persistent AF recurrence. In the event of another persistent AF recurrence, Ablation group patients will be allowed to restart the antiarrhythmic drug regimen, and Control group patients will be allowed to undergo radiofrequency ablation (*Figure 1*).

After the 2-month blanking period, patients will be followed-up for 24 months. Outpatient visits and ECG recordings will be scheduled at 2, 5, 8, 11, 14, 17, 20, 23, and 26 months. In order to exclude asymptomatic AF recurrences, 24-h Holter monitoring will be scheduled at 2, 5, 8, 14, 20, and 26 months; moreover, each patient will be provided with a personal device that has the capability of recording a single-lead ECG during an event and also transmitting the recording to a monitoring centre. The monitoring period will start immediately after the blanking period and continue for 24 months. The patients will be asked to record 30 s of ECG once a week, and 30 s of ECG in the event of palpitations. Patients will be also pro-actively followed by the monitoring centre.

Transthoracic echocardiograms will be performed on the first day post-procedure and at 5, 14, and 26 months to collect information regarding pericardial effusion, volume parameters, and valve abnormalities.

All patients in the Ablation group will undergo transoesophageal echocardiography at 5 months to exclude pulmonary vein stenosis.

Primary endpoint

Primary endpoint of the study is the absence of documented persistent atrial tachyarrhythmia relapse (presence of atrial tachyarrhythmias on a minimum of 2 consecutive transtelephonic recordings performed 1 week apart) during the first 24 months after the 2-month blanking period.

Secondary endpoints

Secondary endpoints include:

(1) Total absence of any documented atrial tachyarrhythmias lasting >30 s during the first 24 months after the 2-month blanking period.
(2) Procedural success, defined as creation of continuous ablation lines, assessed at the end of the ablation procedure, in the absence of complications.
(3) Time to first recurrence of any atrial tachyarrhythmias lasting >30 s after the 2-month blanking period.
(4) Clinical success in association with antiarrhythmic drugs, defined as absence of documented persistent atrial tachyarrhythmia relapse combining ablation procedure and antiarrhythmic drugs in patients who have failed the primary endpoint.
(5) Quality of life, assessed by measuring the change in health status using the General Health Survey (SF-36) at the end of the screening period, and at 14 and 26 months follow-up.
(6) Health-economic cost-parameters such as days of hospitalization, resources, and drugs used during hospitalizations will be collected. During the follow-up, prescribed drugs and all hospital and doctor visits that will occur for events related to AF will be captured on the case report forms, and should include a precise assessment of the duration, materials used, laboratory costs, and number of staff involved. Patients will be interviewed during their scheduled outpatient visits regarding such visits to other physicians and/or institutions.

At the end of follow-up, absolute costs per patient will be calculated for each group according to an intention-to-treat analysis. A comparison of costs corrected for the number of patients in sinus rhythm at the end of the study will also be performed.

Statistical analysis

The sample size computation is based on the assumption that the true rate of freedom from atrial tachyarrhythmia recurrence at 26 months for the Ablation group is 70% and that for the Control group is 40%. In order to obtain 90% power to show statistical significance between the Ablation group and the Control group, using a 2:1 randomization for the Ablation group and the Control group, we require 39 subjects in the Control group and 77 subjects in the Ablation group. This sample size is based on the exact binomial distribution using nQuery Advisor. We foresee a 7% rate of patient dropout during the follow-up period. Thus, 84 patients in Ablation group and 42 patients in Control group will need to be enrolled. Therefore, the total number of study patients will be 126.

Continuous variables will be presented as mean (SD). Categorical variables will be presented as percentages (%).

Comparisons between the 2 groups will be made by Fisher's exact test for categorical variables and unpaired *t* test for continuous variables. A P value <0.05 will be considered statistically significant.

Among enrolled patients the actuarial probability of freedom from atrial tachyarrhythmias will be calculated by the method of Kaplan–Meier. Differences between the curves of the 2 groups will be tested for significance by log-rank statistics.

Results

Enrolment is scheduled in 14 centres in Italy, UK, Austria, and Finland. At this time, the study protocol has been approved by 13 centres, 10 centres have begun to enrol, and 72 patients have been enrolled: 48 have been randomized to the Ablation group, and 24 to the Control group. Final results are expected in July 2010.

Discussion

Catheter Ablation for the Cure of Atrial Fibrillation 2 Study is a randomized controlled study of catheter ablation treatment in patients with persistent AF. Right and left atria ablation has recently been introduced as a therapeutic option, in patients who have already failed standard therapy, with promising results.[16–19] Despite the increasing use of catheter ablation for the treatment of AF,[24] only 2 randomized, controlled studies in patients refractory to antiarrhythmic drugs have been published.[20,21] These 2 studies have left several unresolved questions: enrolment was reserved to a selected number of centres; follow-up was limited to the first 12 months after ablation; the success rate of RF ablation in patients with a recent history of AF is unknown; and the role of antiarrhythmic drugs combined with RF ablation is not clear. Moreover, we have no consistent data on the efficacy of catheter ablation in maintaining sinus rhythm in comparison with antiarrhythmic drugs in patients with persistent AF. Indeed, persistent AF represents 22% of all AF, and is an important burden for the Health System because it requires electrical cardioversion and hospitalization to be terminated.[25]

Catheter Ablation for the cure of Atrial Fibrillation 2 Study will provide important information about the efficacy and safety of catheter ablation for the treatment of persistent AF. Although the study is not fully powered to detect a statistically significant effect of catheter ablation on survival, CACAF-2 will be the first randomized trial to compare the cost of catheter ablation with the cost of antiarrhythmic drug therapy for the management of persistent AF.

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Appendix

Chairman: Emanuele Bertaglia, MD. Steering Committee: Emanuele Bertaglia, MD (Chairman); Gaetano Senatore, MD; Giuseppe Stabile, MD. Study Coordinator: Jan Clou. Safety Monitoring Committee: Hein Heidbüchel, MD; Stephan Willems, MD; Harry Crijns, MD. Participating centres (listed in alphabetical order): Camposampiero—Italy (R. Verlato, P. Baccillieri, P. Turrini); Ciriè—Italy (G. Senatore, G. Donnici, M. Fazzari); Cotignola—Italy (P. Turco, B. El Jamal); Ferrara—Italy (C. Pratola, E. Baldo, R. Ferrari, P. Notarstefano); Florence—Italy (A. Colella, L. Padeletti); London Heart Hospital—UK (M. Lowe); London St Mary's Hospital—UK (N. Peters, W. Davies, P. Kanagaratnam); Maddaloni—Italy (G. Stabile, A. De Simone); Mirano—Italy (E. Bertaglia, P. Pascotto, F. Zerbo, F. Zoppo); University of Oulu—Finland (P. Raatikainen); Rome—Italy (F. Lamberti, R. Nardo); Trento—Italy (M. Del Greco, M.Disertori); Treviso—Italy (R. Mantovan, V. Calzolari, P. Stritoni); Vienna—Austria (H. Goessinger, M. Gwechenberger, P. Ritter).

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