

Rationale and design of the FreezeAF trial: A randomized controlled noninferiority trial comparing isolation of the pulmonary veins with the cryoballoon catheter versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation

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Background Atrial fibrillation is the most commonly encountered clinical arrhythmia, and there are an increasing number of patients with paroxysmal atrial fibrillation treated by catheter ablation. The criterion standard is the isolation of the pulmonary veins (PVs) using radiofrequency (RF) energy in combination with an open irrigated tip catheter. The procedure remains technically challenging with a significant number of complications. So far, no randomized comparisons between the outcome of cryoballoon versus RF ablation are available.

Study Design The object of this randomized clinical trial is to compare the efficacy of isolating the PVs with either the cryoballoon or the open irrigated tip RF catheter. Two hundred forty-four patients with paroxysmal atrial fibrillation will be randomized for either RF or cryoballoon. With both techniques, PV isolation will be performed. Primary end point of the study is freedom from atrial fibrillation without antiarrhythmic drugs and without persistent complications at 6 and 12 months. Clinical success will be evaluated using Holter electrocardiogram and event recordings for at least 7 days. Within 6 months, no redo procedure is performed; and a redo after 6 months is performed with the previously used energy source. Secondary end points include the mid- and long-term clinical success, procedural data, and cost-effectiveness.

Conclusion The FreezeAF trial will examine for the first time in a randomized trial whether PV isolation with the cryoballoon is not relevantly inferior to open irrigated RF ablation in patients with paroxysmal atrial fibrillation during follow-up. It will additionally directly compare acute procedural success and safety of the procedures. (Am Heart J 2010;159:555-560.e1.)

Atrial fibrillation (AF) is a common and disabling cardiac arrhythmia, affecting 600,000 to 700,000 persons in Germany. In addition to hemodynamic compromise and higher mortality rates, AF causes an increased risk of systemic emboli arising from the left atrium (LA). The risk of stroke in patients with nonvalvular AF is 5 to 7 times greater than that in comparable patients without AF;

overall, 20% to 25% of ischemic strokes are due to cardiac emboli, of which half arise in patients with nonvalvular AF.^{1,2} In addition to such proven mortality and morbidity risks, AF is associated with a substantial burden of symptoms, stemming from the arrhythmia itself, exacerbation of comorbid conditions such as congestive heart failure, and associated anxiety over possible sequelae as well as the substantial burden of adverse effects from antiarrhythmic drugs (AADs).³ Currently available treatments are unsatisfactory for many reasons. Antiarrhythmic drug treatment has a relatively low efficacy even in patients with paroxysmal atrial fibrillation (PAF), with frequent recurrences and a high incidence of intolerable drug adverse effects.³ Isolation of pulmonary veins (PVs) using radiofrequency (RF) energy has shown considerable clinical success in the treatment of PAF. Success rates vary from 60% to 86%.⁴⁻⁹ However, RF ablation has also been associated with serious complications, including PV

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stenosis, thromboembolic complications, cardiac perforation with pericardial tamponade, and rarely phrenic nerve palsies or esophageal fistulae.^{5,10,11} Furthermore, RF can be painful, whereas freezing with cryotherapy may be pain free.

CryoCath Technologies (Montreal, Quebec, Canada) has developed the Arctic Front Cardiac CryoAblation Catheter System (with the FlexCath Steerable Sheath) to allow the rapid formation of continuous cryoablation lesions at the PV ostia. Preclinical data have demonstrated long-term effectiveness of balloon cryoablation for permanent electrical isolation of the PVs. Results from these preclinical studies suggest that no pulmonary venous stenosis and no thromboembolic incidents have occurred.^{12,13} The most frequent complications were right-sided phrenic nerve palsies.^{12,14,15} Current experience with the cryoenergy in humans is based on a feasibility study¹⁴ and a nonrandomized clinical study.¹⁶ In this nonrandomized clinical study, 346 consecutive patients have undergone a successful cryoablation therapy. Pulmonary vein isolation was achieved in 97%, whereas freedom from documented PAF was achieved in 74% after a median follow-up of 12 months. No death and no PV narrowing occurred. In 26 patients (7.5%), a phrenic nerve palsy could be observed. The majority of the patients recovered within 6 months; all patients recovered within 12 months.¹⁶

Based on these encouraging results, this randomized clinical study has been designed to provide valid scientific evidence of the safety and effectiveness of the Arctic Front Cardiac CryoAblation Catheter System (with a FlexCath Steerable Sheath) to electrically isolate PVs in patients with AF by comparing it with RF energy, which represents the most widely accepted and used energy form in AF ablation procedures.

Methods

Study design

This study is designed as a randomized, controlled, prospective, noninferiority clinical trial, where the efficacy and safety of the cryoballoon ablation system (CE certificated) will be compared with the standard ablation technique with RF energy (PV isolation using an irrigated tip RF catheter). The primary study aim is to investigate whether the new cryoballoon ablation system (Arctic Front Cardiac CryoAblation Catheter System and FlexCath Steerable Sheath, CryoCath Technologies Inc) is at least as effective as RF open irrigated tip ablation in electrically disconnecting the PVs for the treatment of PAF with respect to the absence of atrial arrhythmias and without persistent complications after 6 and 12 months. Furthermore, the differences in terms of procedural complications such as PV stenosis, phrenic nerve injuries, cerebrovascular accidents (CVA), pericardial tamponade, pain score, and levels of cardiac inflammatory markers are compared between the treatment groups. The mid- and long-term clinical success as well as the cost-effectiveness of both systems will be evaluated.

Table I. Inclusion criteria

Inclusion criteria

1. Documented PAF: 2 episodes of PAF within the last 3 m; at least 1 episode of PAF must be documented
2. Age 18-75 y
3. Documented inefficacy of at least 1 AAD including β -blockers

Table II. Exclusion criteria

Exclusion criteria

1. LA size >55 mm
2. LA thrombus
3. Previous LA ablation/surgery
4. Unstable angina
5. Myocardial infarction within 3 m
6. Cardiac surgery or PTCA within 3 m
7. Mitral prosthesis
8. EF <40%
9. Heart failure NYHA III-IV
10. Hypertrophic cardiomyopathy
11. Thrombocytosis, thrombocytopenia
12. Any condition contraindicating chronic anticoagulation
13. Stroke or TIA within 6 m
14. Uncontrolled hyperthyroidism
15. Pregnancy
16. Life expectancy <1 y

PTCA, Percutaneous transluminal coronary angioplasty; EF, ejection fraction; NYHA, New York Heart Association.

This study is designed according to the consensus statement of the recently published recommendations by Calkins et al.¹⁷

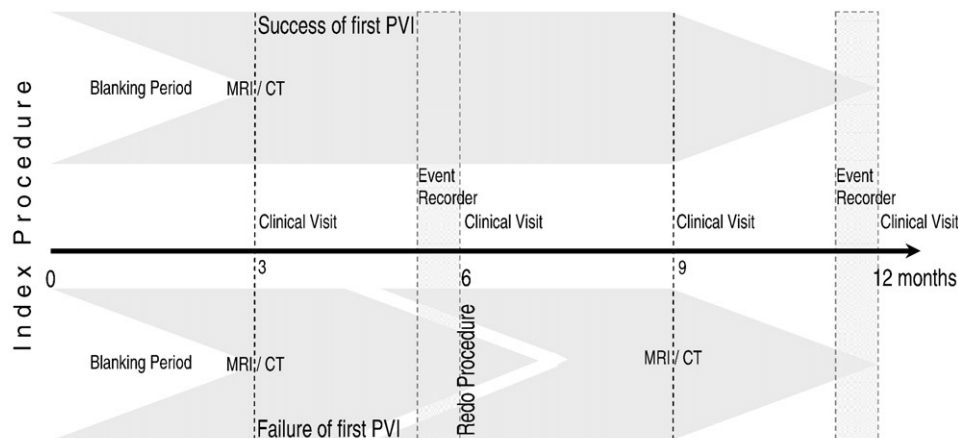
Founding was granted in equal parts by St Jude Medical and Medtronic to optimize the monitoring device capacity (event recorders and Holter electrocardiograms [ECGs]). None of the companies were involved in the study design, analysis, and interpretation. The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting and editing of the paper, and its final contents.

Eligibility criteria

Patients with PAF between 18 and 75 years can be enrolled in the study. Eligible patients must have had at least 2 episodes of AF within the last 3 months. At least 1 episode must be documented by ECG recording. At least 1 AAD therapy (including β -blocker) must be proven to be ineffective in the patients' medical history.

Patients with a previous LA ablation or surgery are excluded as well as patients with an LA diameter >55mm or a persistent LA thrombus. The ejection fraction of the left ventricle must be at least 40%; those who have heart failure New York Heart Association III to IV are excluded. Patients with a previous myocardial infarction, heart surgery, transient ischemic attack (TIA), or stroke can be enrolled until 3 or 6 months have passed from the acute event, respectively. Furthermore, all patients who are receiving an AAD medication other than β -blockers after the index procedure will be classified as nonresponders.

Figure 1



Follow-up of the FreezeAF trial. Blanking period: 3 months. Clinical visits include an interview, ECG, and Holter ECG. Earliest date for redo procedure: 6 months after index procedure. MRI (magnetic resonance imaging)/CT scans: 3 months after last ablation procedure. Seven-day Holter ECG: 6 and 12 months after index procedure.

The complete inclusion and exclusion criteria are outlined in Tables I and II.

On admission, a transesophageal echocardiography to exclude LA thrombus is performed. In addition, it is recommended to perform a computed tomography (CT) or magnetic resonance imaging scan of the LA to evaluate anatomical abnormalities of the LA and the PVs.

Once a patient has provided informed, written consent and meets inclusion and no exclusion criteria, he is randomly assigned to 1 of the 2 strategies.

Randomization

The randomization numbers will be allocated to the 2 groups in balanced permuted blocks using the random number generator of the validated software SAS (Cary, NC). To avoid any potential of predicting the group allocation of future patients, the block length is fixed in a separate document that is withheld from the study site. Sealed envelopes are produced labeled with the randomization number. Inside the sealed envelope, a data sheet defines the group allocation of the patient with the respective randomization number. On enrollment in the study, each patient receives the randomization envelope in consecutive order of inclusion in the study. Basic characteristics of the patient and day of randomization are documented on the data sheet to allow a check of whether the randomization scheme was observed strictly.

Ablation procedure

After venous and arterial access, a single or double transseptal puncture is performed. In both groups, a PV angiography must be performed before and after PV isolation for all of the PVs. Pulmonary vein potentials must be recorded before and after PV isolation with a circular mapping catheter. In group 1, the RF ablation procedure is performed using an open 4-mm irrigated tip catheter in combination with a 3-dimensional (3D) navigation system. It is recommended that the 3D navigation system should

be able to display all mapping and ablation catheters. An antral PV isolation will be performed. In group 2, a cryoablation of the PV ostia using either the 28-mm or the 23-mm cryoballoon will be attempted. At least 2 cryoenergy applications of 300 to 360 seconds must be performed in each PV. Additional cryoenergy applications can be delivered if necessary to achieve complete isolation. The 28-mm cryoballoon should be used preferentially for all veins. If a complete isolation could not be achieved with the 28-mm cryoballoon ablation, a switch over to the 23-mm balloon is possible; otherwise, touch-ups with a conventional cryocatheter (Freezor Max, CryoCath) will be performed.

In both groups, the aim is to completely isolate the PVs. The upper limit of RF or cryoenergy applications is dependent on the procedure duration and the clinical condition at the time of the procedure and is left to the physician's decision. After the ablation, all the PVs should be assessed with angiography to detect an ablation-mediated PV stenosis.

Anticoagulation. All patients should be anticoagulated 4 weeks before and at least 6 months after the index procedure. During the procedure, the activated clotting time must be kept between 250 and 350 seconds by intravenous heparin administration.

Antiarrhythmic drugs. All AADs should be discontinued 4 to 5 half-life periods before the procedure. No AAD will be prescribed (except β -blocker) after the procedure.

Follow-up

All patients will be monitored during the hospital stay after the procedure (the first 24-48 hours). Additional clinical visits will be performed at 3, 6, 9, and 12 months after the last procedure. Another magnetic resonance imaging or CT scan should be performed at the third month to reevaluate the PVs, and at least one 24-hour Holter ECG recording to screen for symptomatic or asymptomatic atrial arrhythmias (AF, atrial tachycardia) has to be done. An event recorder or Holter ECG to reveal the long-term recurrences will be given at the 6- and 12-month follow-up

Table III. Primary end point**Primary end point**

Combined end point defined as absence of atrial arrhythmias and absence of persistent complications during the 6 and 12 m after the isolation procedure*

*A blanking period of 3 m will be maintained after the index procedure.

Table IV. Secondary end points**Secondary end points**

1. Long-term clinical success
2. Total radiation exposure
3. Total procedure duration
4. Pain sensation during the procedure
5. Quality of life
6. Changes in cardiac markers
7. Bleedings
8. Costs

(for minimum of 7 days, preferably 14 days).¹⁸ In case of a recurrence, a second procedure can be performed 6 months after the index procedure. The procedure of choice for the recurrences will be the same modality to which the patient originally had been randomized (Figure 1).

Primary and secondary end points

The primary end point is a combined end point defined as absence of atrial arrhythmias and absence of persistent complications. This end point will be evaluated 6 and 12 months after the index procedure. With this setting, the 6-month follow-up will evaluate the clinical outcome of only 1 ablation procedure, whereas the 12-month follow-up will include redo procedures. As the assessment after 12 months is clinically more relevant, the end points are ordered by importance; and a related multiple test procedure is applied in the analysis (see below).

The secondary end points include procedural data, quality of life, and cost-effectiveness and are outlined in Tables III and IV.

Statistical considerations

Test problem and analysis of primary end point. The primary objective of this trial is to demonstrate noninferiority of isolating PVs procedure with the cryoballoon catheter (CC) as compared with RF isolation with respect to the primary end points “absence of atrial arrhythmias and absence of persistent complications 6 and 12 months after the procedure,” respectively. For this purpose, the following test problems will be assessed: null hypothesis $H_0: p_{CC} - p_{RF}$ (rate of absence of atrial arrhythmias and absence of persistent complications 12 months after the procedure with CC) $- p_{RF}$ (rate of absence of atrial arrhythmias and absence of persistent complications 12 months after the procedure with RF) $\leq -\delta$ versus alternative hypothesis $H_1: p_{CC} - p_{RF} > -\delta$, where $\delta = 0.15$ defines the noninferiority margin that is deemed to be acceptable in view of the advantages of CC with respect to aspects other than the primary

Table V. Definitions**Definitions**

Acute procedural success	Successful isolation of all PVs
Clinical success	Absence of any atrial arrhythmia sustaining >30 s evaluated either by telemetric monitoring, 24-h Holter ECG recordings, or event recorder Midterm clinical success: up to 6 m after the procedure Long-term clinical success: up to 12 m after the procedure
Procedure-related complications	Any new PV stenosis, phrenic nerve palsy, CVA, bleedings, or vascular complications that occur during and/or within 48 h after the procedure
Persistent complications	Any procedure-related complication lasting >6 m after the procedure and either classified as major complication or still symptomatic
PV stenosis	Angiographic late lumen loss of any PV in comparison to the preprocedural data Minor: asymptomatic or stenosis <50%; Major: symptomatic or stenosis >50%. Three months after the procedure, a CT, a magnetic resonance tomography, or an echocardiography will be performed to reevaluate the severity grade of the stenosis. If a stenosis is detected, a repeated diagnosis will be performed at 3 to 6 m.
Phrenic nerve palsy	Radiological restricted movement of the diaphragm Minor: asymptomatic or <50% restriction Major: symptomatic or >50% restriction In cases of persistent symptoms due to phrenic nerve palsy, at least 1 fluoroscopy will be performed up to the 3 to 6 m of follow-up to verify the restriction of the diaphragm.
Bleedings and vascular complications	Minor: any bleeding or vascular complication (hematoma, pseudoaneurysm, atriovenous fistula) requiring prolonged hospitalization but could be managed conservatively Major: any bleeding or vascular complication requiring additional therapy (ie, surgery, transfusion therapy)
CVA	Every new TIA or stroke after the index procedure.
Quality of life	Before and at every clinical visit, patients will be asked to complete a standardized questionnaire to evaluate the symptomatic and life restrictiveness originating from the arrhythmia. Our modified Short Form-12 questionnaire refers in 14 questions to the physical, physiologic, emotional, and social consequences of illness, as well as symptom burden, general well-being, and current medication. ²²
Pain	After venous and arterial puncture and after the complete procedure, the patients will be asked to grade their sensation of pain (range 1-10).
Costs	Standard prices for consumable material such as catheters, electrodes, and refrigerant per EP study will be evaluated. Purchase or leasing prices, that is, for a mapping system or the cryo console, will not be considered.

end point. The analogous test problem is formulated for the end point after 6-month follow-up. These test problems will be analyzed applying the noninferiority test for rates according to

Farrington and Manning¹⁹ at a 1-sided significance level of $\alpha = 2.5\%$. The following multiple test procedure for hierarchically ordered hypotheses is applied to account for the multiplicity in primary end points: The null hypothesis formulated for the 6-month outcome is only tested if the null hypothesis for the 12-month outcome can be rejected; otherwise, both null hypotheses are accepted. If both null hypotheses can be rejected, the null hypotheses of $H_0\gamma$ are tested at 1-sided level of $\alpha = 2.5\%$ for margins $\gamma < \delta$ as long as $H_0\gamma$ has to be accepted for a value γ_{STOP} . Then, noninferiority of CC as compared with RF has been shown for all noninferiority margins $\gamma < \gamma_{STOP}$. This multiple test procedure controls the overall type I error rate α .^{20,21}

Confirmatory analysis will be primarily based on the full analysis set that is consistent with the intention-to-treat (ITT) principle by including all patients who were randomized to the 2 groups. This approach reflects the idea that the study should match as close as possible the conditions in clinical practice. However, the per protocol (PP) analysis plays an important role particularly in noninferiority studies; and therefore, the results of the PP analysis set are to be interpreted and discussed with special attention in parallel to the ITT analysis (also see the online Appendix).

Determination of the sample size

Sample size calculation is based on the following considerations. In view of the advantages of CC as compared with RF in dimensions other than the primary end points, an inferiority by a difference in rates of 0.15 for CC as compared with RF with respect to the 2 primary outcomes is deemed to be acceptable. Therefore, the noninferiority range was set equal to $\delta = 0.15$. On the basis of previous studies and experiences with the procedures,¹⁶ equal rates of $p_{CC} = p_{RF} = 0.78$ are assumed for sample size calculation. Under these assumptions, the sample size required to achieve a power of $1 - \beta = 80\%$ for the 1-sided Farrington-Manning¹⁹ test at level $\alpha = 2.5\%$ amounts to $2 \times 122 = 244$ patients. To cope with the uncertainty about the assumed overall rate of 0.78, a sample size review is performed after 150 patients are randomized or the outcome of the primary variable is available for 100 patients, respectively, depending on which of the events occurs first. No significance test is performed then; and hence, there is no option for early stopping with rejection of the null hypothesis. Instead, the overall rate for the primary variable is estimated based on the available data; and the sample size is recalculated using the obtained value in the sample size formula (ie, $p_{CC} = p_{RF} =$ estimated overall rate) and leaving the values for α , $1 - \beta$, and δ as above. It was shown that this procedure does not affect the type I error rate of the analysis (Table V).²³

Discussion

Catheter ablation of AF becomes more important in clinical routine. New technologies are developed to simplify and shorten the therapy. So far, the criterion standard of this therapy to isolate the PVs is RF energy with an open irrigated tip catheter. New technologies must be as safe and effective as the RF energy. To answer this question, randomized studies with a defined patient cohort and no crossover rates are needed.

The FreezeAF trial will examine for the first time in a randomized trial whether PV isolation with the cryoballoon is not relevantly inferior to RF ablation in terms of AF during follow-up, and will additionally directly compare acute procedural success and safety of the procedures. Using cryoenergy, it seems that the major complication is phrenic nerve palsy. The risk of this can be reduced by continuously monitoring the phrenic nerve during ablation of the right upper PV either by fluoroscopy or by pacing maneuvers. So far, all phrenic nerve palsies that occurred recovered spontaneously.¹⁶ Other severe complications such as PV stenosis or esophagoatrial fistula are not yet reported. The procedure can be performed without additional 3D navigation system. New developments like modifications of the balloon anatomy or over-the-wire techniques to enable circular PV potential recordings during cryoablation will contribute to a further simplification of the ablation procedure. Altogether, these developments can make the procedure safer and may enable even less-experienced centers to perform PV isolation.

Conclusion

The FreezeAF trial will examine for the first time in a randomized trial whether PV isolation with the cryoballoon is not relevantly inferior to RF ablation in terms of AF during follow-up and will additionally directly compare acute procedural success and safety of the procedures.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med* 1987;147:1561-4.
2. Wang TJ, Larson MG, Levy D, et al. Temporal relation of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;107:2920-5.
3. Lafuente-Lafuente C, Mouly S, Longas-Tejeiro MA, et al. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation. A systematic review of randomized controlled trials. *Arch Intern Med* 2006;166:719-28.
4. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1999;339:659-66.
5. Cappato R, Calkins H, Chen SA, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circulation* 2005;111:1100-5.
6. Haissaguerre M, Shah DC, Jais P, et al. Electrophysiological breakthroughs from the left atrium to the pulmonary veins. *Circulation* 2000;102:2463-5.
7. Karch MR, Zrenner B, Deisenhofer I, et al. Freedom from atrial tachyarrhythmias after catheter ablation of atrial fibrillation: a randomized comparison between 2 current ablation strategies. *Circulation* 2005;111:2866-8.
8. Oral H, Knight BP, Tada H, et al. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation* 2002;105:1077-81.

9. Ouyang F, Bänsch D, Ernst S, et al. Complete isolation of left atrium surrounding the pulmonary veins: new insights from the double-Lasso technique in paroxysmal atrial fibrillation. *Circulation* 2004;112:2090-6.
10. Cappato R, Calkins H, Chen SA, et al. Prevalence and causes of fatal outcome in catheter ablation of atrial fibrillation. *J Am Coll Cardiol* 2009;53:1798-803.
11. Sacher F, Monahan KH, Thomas SP, et al. Phrenic nerve injury after atrial fibrillation catheter ablation: characterization and outcome in a multicenter study. *J Am Coll Cardiol* 2006;47:2498-503.
12. Sarabanda AV, Bunch J, Johnson SB, et al. Efficacy and safety of circumferential pulmonary vein isolation using a novel cryothermal balloon ablation system. *J Am Coll Cardiol* 2005;49:1902-12.
13. Garan A, Al-Ahmad A, Mihalik T, et al. Cryoablation of the pulmonary veins using a novel balloon catheter. *J Interv Card Electrophysiol* 2006;15:79-81.
14. Van Belle Y, Janse P, Rivero-Ayerza MJ, et al. Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications, and short-term outcome. *Eur Heart J* 2007;28:2231-7.
15. Tse HF, Reek S, Timmermans C, et al. Pulmonary vein isolation using transvenous catheter cryoablation for treatment of atrial fibrillation without risk of pulmonary vein stenosis. *J Am Coll Cardiol* 2003;42:752-8.
16. Neumann T, Vogt J, Schumacher B, et al. Circumferential pulmonary vein isolation with the cryoballoon technique: results from a prospective 3-center study. *J Am Coll Cardiol* 2008;52:273-8.
17. Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. *Europace* 2007;9:335-79.
18. Hindricks G, Piorkowski C, Tanner H, et al. Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. *Circulation* 2005;112:307-13.
19. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Stat Med* 1990;9:1447-54.
20. Bauer P, Kieser M. A unifying approach for confidence intervals and testing of equivalence and difference. *Biometrika* 1996;83:934-7.
21. Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. *Clinical Trials* 2008;5:225-39.
22. Ware JE, Kosinski M, Keller SDA. 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220-33.
23. Friede T, Mitchell C, Müller-Velten G. Blinded sample size re-estimation in non-inferiority trials with binary endpoints. *Biomed J* 2007;49:903-16.

Appendix A. Details of statistical analysis

Test problem and analysis of primary end point—continued

Each patient's allocation to the different analysis populations (full analysis set according to the ITT principle, PP analysis set, safety analysis set) will be defined before the analysis. The allocation will be documented in the statistical analysis plan.

During the data review before the start of any analysis, deviations from the protocol will be assessed as “minor” or “major.” Major deviations from the protocol will lead to the exclusion of a patient from the PP analysis set. If a patient discontinues from the study prematurely, missing data with respect to the primary outcome variable will be replaced by ICA-r method (ICA, input case analysis).²¹

Analysis of secondary end points

The secondary variables will be analyzed descriptively by tabulation of the measures of the empirical distributions. According to the scale level of the variables, means, SDs, median, first and third quartiles, as well as minimum and maximum or absolute and relative frequencies, respectively, will be reported. Logistic regression models will be applied to assess the effects of

potential risk factors on primary and secondary efficacy variables. In addition, for variables with longitudinal measurements, the time courses of individual patients and summarized by treatment groups will be compared. Descriptive *P* values of the corresponding statistical tests comparing the treatment groups and associated 95% CIs will be given.

The safety analysis will be based on the set of all patients for which one of the procedures was applied. Adverse and serious adverse events as well as complications will be tabulated; absolute and relative frequencies, the severity, and the relationship to the procedure will be given and compared between the groups. Cardiac markers will be described and interpreted with respect to the reference values, and the measures describing the empirical distributions of the changes will be calculated. In addition, for each cardiac marker, shift tables presenting changes between the categories “normal” and “abnormal” will be given per treatment group.

Appendix B. Notes

This protocol is part of the doctoral thesis of Danielle Hoeren.