Catheter Ablation versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) - Study Design

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Background: Electrical isolation of the pulmonary veins by catheter ablation is an emerging treatment modality for the treatment of atrial fibrillation (AF) and is increasingly used in patients with heart failure.

Methods: The catheter ablation versus standard conventional treatment in patients with left ventricular dysfunction and atrial fibrillation trial (CASTLE-AF) is a randomized evaluation of ablative treatment of atrial fibrillation in patients with left ventricular dysfunction. The primary endpoint is the composite of all-cause mortality or worsening of heart failure requiring unplanned hospitalization using a time to first event analysis. Secondary endpoints are all-cause mortality, cardiovascular mortality, cerebrovascular accidents, worsening of heart failure requiring unplanned hospitalization, unplanned hospitalization due to cardiovascular reason, all-cause hospitalization, quality of life, number of therapies (shock and antitachycardia pacing) delivered by the implantable cardioverter-defibrillator (ICD), time to first ICD therapy, number of device-detected ventricular tachycardia and ventricular fibrillation episodes, AF burden, AF free interval, left ventricular function, exercise tolerance, and percentage of right ventricular pacing. CASTLE-AF will randomize 420 patients for a minimum of 3 years at 48 sites in the United States, Europe, Australia, and South America. (PACE 2009; 32:987–994)

atrial fibrillation, catheter, ablation, ventricular dysfunction

Introduction

It is estimated that atrial fibrillation (AF) affects around 2.3 million people in North America and 4.5 million people in the European Union. AF is a major cause of stroke; it adversely affects quality of life (QoL) and is associated with increased mortality. Despite advances in antiarrhythmic drug (AAD) therapy, AF continues to be associated with significant morbidity. Although AAD therapy is currently considered a first-line option, recent data indicate that more than 35% of subjects will have recurrence of AF despite best AAD therapy, and more than 30% of subjects will discontinue the drugs because of adverse reactions. Furthermore, although recent trials have indicated equivalence of rhythm and rate control strategies in some patient populations, 25–35% of subjects with AF who are rate controlled will continue to have activity-limiting symptoms. Newer measures to prevent, treat, and potentially cure AF did recently emerge.

With the introduction of AF ablation targeting the pulmonary vein (PV) foci Haissaguerre and colleagues introduced a new treatment modality targeting the cure of this arrhythmia. Since then, multiple efforts have been introduced to refine the AF ablation procedure. A few major approaches of ablating AF have evolved and are listed as follows: PV isolation targets the isolation of only those PVs that manifest arrhythmogenic foci, PV encircling targets all of the PVs without regard to the initiation of ectopic beats, and last but not least the PV antrum isolation targets the areas in front of the PV. All these approaches have been shown to be associated with a high level of safety and efficacy in suppressing AF.

Heart failure (HF) affects close to 5 million patients in the United States and causes substantial morbidity and mortality. It is often a chronic and lethal condition, contributing to 2 million hospitalizations annually and resulting in mortality rates after the initial diagnosis that approach or exceed those of many malignancies. Furthermore, HF, as well as AF, has important economic consequences on the health-care system.

As indicated in several major heart failure trials, e.g. Studies of Left Ventricular Dysfunction (SOLVD), or Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT), the prevalence of AF rises with the degree of HF, from 5% of AF prevalence in New York Heart Association (NYHA) functional class I patients up to 50% in NYHA class IV patients.
HF remains a powerful predictor of the development of AF. Indeed, from 38-year follow-up (FU) of the Framingham study, HF was associated with approximately a five-fold increase in the risk of developing AF.\textsuperscript{13}

In the DIAMOND study, patients suffering from congestive HF (CHF) and randomized to the treatment arm showed a significantly reduced risk of hospitalization for worsening of CHF as compared to patients randomized to placebo. It has been suggested that the beneficial effects of the study therapy on conversion of AF to sinus rhythm may have played a role.\textsuperscript{14}

AF is a marker of increased mortality in patients with underlying cardiac disease. Most evidence suggests that patients with HF and AF have a worse prognosis than patients with HF but no AF.\textsuperscript{13} The 2-year mortality in patients with left ventricular (LV) dysfunction and AF reported by Zareba and colleagues was 39%.\textsuperscript{15}

In the CHF-STAT study, patients suffering from CHF and AF, and converted from AF to sinus rhythm, tended to have a significantly better prognosis; the Kaplan-Meier survival analysis indicated that those converted patients had a significantly better survival compared with patients who did not convert (approximately 60% vs 30% at 4 years, P = 0.04).\textsuperscript{16}

There is, therefore, good reason to pursue a method to interrupt the deleterious ring: HF, which facilitates AF, and AF, which deteriorates HF.\textsuperscript{17}

Presumably, permanent conversion from AF to sinus rhythm could help to improve cardiac output, exercise tolerance, and QoL.

Chen et al. demonstrated that PV isolation can be safely and effectively performed in patients with AF and impaired LV systolic function, and could be considered a feasible therapeutic option.\textsuperscript{18} Haissaguerre et al. reported that restoration and maintenance of sinus rhythm by catheter ablation without the use of drugs in patients with CHF and AF significantly improve cardiac function, symptoms, exercise capacity, and QoL.\textsuperscript{19} Tondo and colleagues reported that catheter ablation in patients with LV dysfunction is feasible, not associated with higher procedural complications, and provides a significant improvement in LV performance, symptoms, and QoL.\textsuperscript{20} The PV Antrum Isolation vs AV Node Ablation With Biventricular Pacing for Treatment of AF in Patients With CHF (PABA-CHF) study has shown that patients suffering from HF and AF treated with PV isolation improve in ejection fraction, 6-minute walking distance, and QoL when compared to patients treated with AV node ablation and biventricular pacing.\textsuperscript{21} The purpose of catheter ablation versus standard conventional treatment in patients with LV dysfunction and AF (CASTLE-AF) is to test the hypothesis that ablation of AF by achieving PV isolation will improve mortality and morbidity in patients suffering from impaired LV function and AF when compared to conventional treatment.

**Study Aim**

**Objective**

The primary objective of the CASTLE-AF study is to evaluate the effectiveness of catheter-based radiofrequency ablation of AF, compared to conventional treatment, on the composite endpoint of “all-cause mortality or worsening of HF requiring unplanned hospitalization.”

**Primary Endpoint**

The primary study endpoint is the composite of all-cause mortality or worsening of HF requiring unplanned hospitalization using a time to first event analysis.

**Secondary Endpoints**

The secondary study endpoints are all-cause mortality, cardiovascular mortality, cerebrovascular accidents, worsening of HF requiring unplanned hospitalization, unplanned hospitalization due to cardiovascular reasons, all-cause hospitalization, QoL, number of delivered implantable cardioverter-defibrillator (ICD) therapies (shock and ATP), time to first ICD therapy, number of device-detected ventricular tachycardia/ventricular fibrillation episodes, AF burden, AF-free interval, LV function, exercise tolerance, and percentage of right ventricular pacing.

**Methods**

This is a prospective, randomized, controlled, international multicenter clinical trial, sponsored partially by Biotronik GmbH, Berlin, Germany. The study will be conducted open-label. Data management will be carried out by a Contract Research Organization (Center for Clinical Research Cologne). The echocardiographic core laboratory will be at Klinikum Coburg, Germany. All serious adverse events will be reported to an independent Data and Safety Monitoring Board and classified by a blinded Endpoint and Adverse Event Committee.

**Screening and Enrollment**

All patients implanted with a dual-chamber ICD with Home Monitoring\textsuperscript{®} capabilities and history of paroxysmal or persistent AF will be screened for the study (Table I).

For the purpose of this study, the following definitions will be used: “Paroxysmal AF is defined as recurrent AF (≥2 episodes) that terminates spontaneously within seven days. Persistent
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Table I.

Patient Selection

Inclusion Criteria:

1) Symptomatic paroxysmal or persistent AF (paroxysmal: $\geq 2$ symptomatic or one documented AF episode lasting 30 seconds or more in the last 3 months; persistent: $\geq 1$ documented episode in the last 3 months).
2) Failure or intolerance of Amiodarone or unwillingness to take Amiodarone. According to the American College of Cardiology/American Heart Association/European Society of Cardiology 2006 Guidelines for the Management of Patients with Atrial Fibrillation, it is recommended to discontinue Amiodarone at enrollment.
3) LV dysfunction with left ventricular ejection fraction $\leq 35\%$ (measured in the last 6 weeks prior to enrollment).
4) NYHA class $\geq II$.
5) Indication for ICD therapy due to primary prevention.
6) Dual chamber ICD with Home Monitoring capabilities (Lumax DR-T or equivalent successor) already implanted.
7) The patient is willing and able to comply with the protocol and has provided written informed consent.
8) Sufficient GPRS-network coverage in the patient's area.
9) Age $\geq 18$ years.

Exclusion criteria:

1) Documented left atrial diameter $> 6$ cm (parasternal long-axis view).
2) Contraindication for chronic anticoagulation therapy or heparin.
3) Previous left heart ablation procedure for atrial fibrillation.
4) Acute coronary syndrome, cardiac surgery, angioplasty, or cerebrovascular accident within 2 months prior to enrollment.
5) Untreated hypothyroidism or hyperthyroidism.
6) Enrollment in another investigational drug or device study.
7) Indication for cardiac resynchronization therapy.
8) Woman currently pregnant, breastfeeding, or not using reliable contraceptive measures during fertility age.
9) Mental or physical inability to participate in the study.
10) Listed for heart transplant.
11) Cardiac assist device implanted.
12) Planned cardiovascular intervention.
13) Life expectancy $\leq 12$ month.
14) Uncontrolled hypertension.
15) Requirement for dialysis due to terminal renal failure.
16) Participation in another telemonitoring concept.

AF is defined as AF which is sustained beyond seven days, or lasting less than seven days but necessitating pharmacologic or electrical cardioversion. Included within the category of persistent AF is 'longstanding persistent AF' which is defined as continuous AF of greater than 1-year duration. Documentation of AF can be obtained by electrocardiogram, Holter, Loop Recorder, ICD memory, or any other suitable device.

Study Conduct

Following verification of the inclusion and exclusion criteria and documentation of the demographic data and medical history, ICD programming and Home Monitoring parameters are adapted to facilitate the continuous monitoring of AF episodes.

The investigational site will plan the date for baseline testing, which will be performed 5 weeks later. In case of randomization to the ablation arm, the investigational site will also plan the date of the ablation procedure, which will be performed as soon as possible after baseline evaluation. Figure 1 illustrates study flow chart.

Run-In Period

After enrollment, a run-in period of 5 weeks will follow, during which an optimization of HF medication, comprising diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and $\beta$-blockers as per the American College of Cardiology/American Heart Association (ACC/AHA) 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult, will be performed. In particular, $\beta$-blockers and ACE inhibitors/ARBs should be adjusted to the maximum tolerated doses, and Aldosterone Antagonists should be considered whenever indicated as per the Guideline. In this period, the performance of
the Internet-based telemonitoring system, Home Monitoring, will also be assessed in terms of successful daily transmissions; improvements will be obtained by patient’s education in order to avoid inadequate use of the system. Changes of cardiovascular medications will be documented.

Baseline Testing

At the end of the run-in period, the optimization of the medical therapy for heart failure will be verified and the following exclusion criteria will be re-evaluated: (1) acute coronary syndrome, cardiac surgery, angioplasty, or cerebrovascular accident since enrollment; (2) listed for heart transplant; and (3) requirement for renal dialysis due to terminal renal failure. If all the re-evaluated exclusion criteria are not applicable, then a baseline evaluation will be performed; otherwise, the patient will be dropped out. Echocardiographic measurements will be performed in agreement with the standard operating procedures of the appointed core laboratory; the following parameters will be assessed: left atrial diameter, LV fractional shortening, LV ejection fraction, LV end-systolic diameter, LV end-diastolic diameter and volumes. Each patient will perform a 6-minute-walk test.

Ablation Procedure

Subjects assigned to the catheter AF ablation strategy will undergo ablation as soon as possible after baseline evaluation. Before ablation, a transesophageal echocardiography has to be performed in order to rule out presence of atrial thrombi. It is strongly recommended to perform the echocardiography within 24 hours prior to ablation. In case of presence of thrombi, the procedure will be postponed until thrombi will be dissolved, but not longer than 4 weeks. If, after that period, thrombi are still present, the ablation will not be performed anymore.

The aim of the procedure is to achieve isolation of all four PVs and to restore sinus rhythm. The anticoagulation regimen will be prescribed as follows: half-dose low molecular weight Heparin...
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for 3 days postablation; Coumadin should be initiated, or continued, for 6 months postablation and then possibly stopped at the discretion of the investigator. The international normalized ratio (INR) will be maintained between 2 and 3. A total of 6 months after successful ablation, and in the absence of any recurrence of AF, antiarrhythmic drugs should be discontinued. Rare short-lasting episodes (less than 30 seconds) recorded in the early postblanking period will be considered as insignificant. If routinely performed, a spiral computer tomography (CT) scan will identify presence of stenosis of any PV and will serve as basis in case of suspected stenosis during FU.

The ablation system selection is left to the discretion of the investigator, but the investigator must have performed at least 50 AF ablation procedures, comprising pulmonary vein isolation, with the same approach. The ablation will be classified as acutely successful if: (1) all four PVs are isolated and (2) sinus rhythm is restored (if not already present). Isolation of the PVs will be proven by identifying the presence or absence of local vein potentials in the vein during sinus rhythm or pacing, typically from the distal coronary sinus, at a slow rate (vein entry). Isolations will be documented by short strips of PV intracardiac electrograms. Sinus rhythm can be restored also by means of electrical cardioversion. If required, any additional lesion in the left as well as in the right atrium, including coronary sinus, superior vena cava, and inferior vena cava, is permitted.

In case of unsuccessful ablation, a second attempt will be made within 4 weeks. If after the second attempt the outcome is also failure, the patient will be associated to the intention-to-treat population; no additional ablations will be performed. Any time during the course of the study, additional ablations may be done if the subject has recurrence(s) of AF except during the 12 weeks of blanking period following either the initial ablation or a chronic redo.

Conventional Treatment

Subjects assigned to the conventional measures strategy will be treated according to the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult and the ACC/AHA/European Society of Cardiology 2006 Guidelines for Management of Patients with Atrial Fibrillation.1,23 Efforts to maintain sinus rhythm in this study arm are recommended. In case of rate control strategy, although no standard method for assessment of heart rate control has been established, criteria for rate control vary with patient age but usually involve achieving ventricular rates between 60 and 80 beats per minute at rest, and between 90 and 115 beats per minute during moderate exercise. Anticoagulation will be initiated, if not already started, and maintained throughout the study. The INR will be maintained between 2 and 3.

Follow-Up

All patients will have Home Monitoring activated, and those randomized to the ablation arm will be continuously monitored on a daily basis. The investigator will be promptly informed in case of recurrence of AF. In case of recurrences outside the postablation blanking period, it is recommended to perform additional ablation(s), unless clinically contraindicated.

At 3, 6, 12, 24, and 36 months after baseline, all patients will undergo a regular FU visit. Patients completing the multiples of 12 months while the study is still ongoing will have additional FU visits, which will be equal to all the other planned visits. FU windows will be ±14 days for the 3-month and 6-month visits, and ±30 days for the remaining others. Echocardiographic measurements will be performed as described previously.

After the end of the study, the patients may be contacted by phone to assess their vital status.

QoL Questionnaires

Prior to the FU examinations, each patient will be asked to complete two QoL questionnaires, at baseline and at all planned FU visits. The Minnesota Living with Heart Failure and the EuroQoL EQ-5D questionnaires will be used in all study centers. The Minnesota Living with Heart Failure questionnaire is a well-validated but highly disease-specific tool whereas the EuroQoL is designed to assess both general and disease-specific QoL in patients with heart failure.

Management of Home Monitoring

After activation of the Home Monitoring function in the ICD, the device will send a regular, daily message, and in addition, an event-triggered message after occurrence of specified events in particular with respect to AF episodes and missing event messages.

Symptoms Diary

A symptom diary will be used to assess the relationship between recurrences of AF and symptoms. At enrollment, every patient receives a diary to record typical heart failure and AF symptoms, such as chest pain, dizziness, breathlessness, swollen feet or ankles, fatigue or weakness, nausea, palpitations, sleep disorders, and racing heart.

In addition, visits to a general practitioner (GP) and to a hospital will also be recorded.
On the day of the symptomatic episode, the patient is asked to document the type and severity of symptom(s) and to state if there was contact to the GP and/or a hospital visit. The patient is asked to bring the diary at every planned FU visits, which will be examined by the investigator to detect any unreported AEs and/or hospitalizations.

### Statistical Methodology

#### Primary Hypothesis

The null hypothesis $H_0$ is that the two survival curves are identical, and the one-sided alternative hypothesis $H_1$ is that the survival curve of the ablated patients’ treatment group is superior to the other one. Specifically, let $\pi_1$ and $\pi_2$ denote the event rates in the ablated patients’ treatment group and the conventional treatment group, respectively. The hypothesis to be tested is $H_0: \pi_1 = \pi_2$.

Where $\omega = \ln(1 - \pi_2)/\ln(1 - \pi_1)$ denotes the hazard ratio, which is assumed to be constant over time (proportional hazards assumption). $H_0$ is tested against the one-sided alternative hypothesis $H_1: \pi_1 < \pi_2$, that is, the risk for an event is assumed to be higher in the conventional treatment group.

#### Analysis

The study is designed as a three-stage adaptive group sequential test procedure with survival endpoint, where the inverse normal method is used to combine the separate stage information. The decision regions result from monotonically decreasing critical values according to O’Brien and Fleming. For a one-sided test with $\alpha = 0.025$, they are given by $3.471$, $2.454$, and $2.004$ with corresponding significance levels $0.0003$, $0.0071$, and $0.0225$, respectively. The primary endpoint is tested by a one-sided Mantel-Haenszel log-rank test stratified by type of AF (paroxysmal, persistent, or longstanding persistent). From the sequence of log-rank statistics, the (under $H_0$) stochastically independent increments are calculated: The inverse normal combination test is used to combine the independent increment to a global test statistic. After the first interim analysis, the study can be stopped with the rejection of the null hypothesis if the one-sided log-rank test yields a $P$-value lower than $0.0003$. Otherwise, based on a new sample size calculation in the interim analysis, the necessary number of events required for yielding a statistically significant result in the final analysis will be calculated. In the final analysis, the null hypothesis can be rejected if the test statistic that is based on the inverse normal method exceeds the critical value $2.004$. This procedure preserves the overall Type I error rate of $\alpha = 0.025$.

#### Sample Size Calculation

A hazard ratio of $\omega = 1.25$ is considered clinically relevant and worth detecting. It is expected, however, that the hazard of an event is, in the relative sense, 50% higher in the conventional treatment group as compared to the ablated patients’ treatment group. It is further assumed that within one FU period (36 months), the event rate in the conventional treatment group is 50%. A hazard ratio of $\omega = 1.5$ corresponds to a risk reduction to 37%. The power is 80% if log rank tests are performed after 65, 130, and 195 events. Assuming an accrual time of 24 and an FU time of 36 months, a total of 367 patients is expected to yield the necessary number of events if the accrual rate is constant. Under these assumptions, the interim analyses should take place after about 25 and 40 months, respectively. The final analysis is conducted after 60 months. Hence, it is assumed that 367/24 $\approx 15.3$ patients will be recruited per month. Including 10–15% dropouts, a total sample size of $N = 420$ patients is needed. Thus, it is expected that the planned number of patients is achieved when performing the first interim analysis. These estimates will be validated and, if necessary, modified. If the assumptions are correct, no reduction in patient number is expected. However, under $H_1$, the expected duration is reduced from 60 to 50.5 months with corresponding expected 163.4 events.

#### Recurrence of AF in Ablation Arm

### Definition and Detection of Recurrence of AF

For the purposes of this study, any sustained episode of AF lasting 30 seconds or more is classified as recurrence. Atrial flutter with a rate faster than the programmed detection level will also be detected as recurrence. The investigator, or a nominated person at the site, will get all the details of the episode, including the duration, via Home Monitoring, either by an event-triggered message or a regular basis with a daily trend message. For patients belonging to the ablation arm, episodes lasting 30 seconds or more occurring outside the...
blinking period of 12 weeks will be reported to the investigator, who will decide whether to plan a re-do or not. Recurrences within the blinking period will be named “early recurrences”; they will be collected but will not trigger any action.

**Definition and Detection of Burden of AF**

Multiple episodes of AF, all lasting less than 30 seconds, will not be classified as a recurrence. However, such episodes may have a clinical significant impact requiring medical intervention. The sum of the durations of all such episodes (eventually also comprising episodes which could have been longer than 30 seconds) within the day, expressed as a percentage with respect to 24 hours, is defined as AF burden.

**Summary**

The CASTLE-AF trial is a randomized controlled trial to evaluate the effectiveness of catheter-based radiofrequency ablation in patients with AF and heart failure compared to conventional treatment, with the composite endpoint of all-cause mortality or worsening of HF requiring unplanned hospitalization. Patient enrollment has been started in January 2008 and expected to end in December 2010. The outcome of the trial should define the value of AF ablation in patients suffering from AF and left ventricular dysfunction.

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