Designing comparative effectiveness trials of surgical ablation for atrial fibrillation: Experience of the Cardiothoracic Surgical Trials Network

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Objective: Since the introduction of the cut-and-sew Cox maze procedure for atrial fibrillation, there has been substantial innovation in techniques for ablation. Use of alternative energy sources for ablation simplified the procedure and has resulted in dramatic increase in the number of patients with atrial fibrillation treated by surgical ablation. Despite its increasingly widespread adoption, there is lack of rigorous clinical evidence to establish this procedure as an effective clinical therapy.

Methods: This article describes a comparative effectiveness randomized trial, supported by the Cardiothoracic Surgical Clinical Trials Network, of surgical ablation with left atrial appendage closure versus left atrial appendage closure alone in patients with persistent and long-standing persistent atrial fibrillation undergoing mitral valve surgery. Nested within this trial is a further randomized comparison of 2 different lesions sets: pulmonary vein isolation and the full maze lesion set.

Results: This article addresses trial design challenges, including how best to characterize the target population, operationalize freedom from atrial fibrillation as a primary end point, account for the impact of antiarrhythmic drugs, and measure and analyze secondary end points, such as postoperative atrial fibrillation load.

Conclusions: This article concludes by discussing how insights that emerge from this trial may affect surgical practice and guide future research in this area. (J Thorac Cardiovasc Surg 2011;142:257-64)

⌒⊚ Supplemental material is available online.

Atrial fibrillation (AF) coexists in 50% of patients presenting for mitral valve surgery (MVS), and in at least half of these patients this dysrhythmia has been long-standing

and refractory to medical treatment (persistent or long-standing persistent, in current consensus terminology).[1] The rhythm is presumed to relate to left atrial enlargement from the valvular heart disease. Preoperative AF is associated with reduced postoperative survival and increased risk of stroke. The cut-and-sew Cox maze procedure—introduced in the late 1980s—provided surgeons with a therapeutic approach to help restore sinus rhythm and avert the mortality and morbidity associated with this disease.[2,3] Despite the reported success of this procedure, its complexity initially prevented widespread adoption. The more recent development of tissue ablation technologies and alternative energy sources, however, has simplified the technique and significantly reduced operative time. These improvements have led to substantial growth in the number of procedures performed.

Despite this increased adoption, there is lack of rigorous clinical evidence to establish surgical ablation as an effective clinical therapy. Most available studies have been retrospective, conducted in single centers, and not rigorously controlled. Although 9 randomized trials[4-12] have compared the benefits of added ablation surgery with those of MVS alone, most of these had sample sizes insufficient to draw definitive conclusions, and none enrolled more than 100 patients. Moreover, both randomized and nonrandomized studies have been characterized by significant variations in

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Abbreviations and Acronyms
AF   = atrial fibrillation
CTSN = Cardiothoracic Surgical Clinical Trials
             Network
FDA   = Food and Drug Administration
LAA   = left atrial appendage
MVS   = mitral valve surgery
PVI   = pulmonary vein isolation

the ablation procedure, heterogeneous patient populations, and variations in definition and measurement of the primary end point. Furthermore, few studies included the full gamut of relevant clinical end points. A recent meta-analysis of 5 trials that used freedom from AF within 12 months as a primary end point in patients with nonparoxysmal AF found that surgical ablation greatly increased the odds of being free from AF at 12 months, but the odds ratios had wide confidence intervals and were derived from trials that had considerable heterogeneity in their designs.[13] As such, large-scale trials are needed to provide better evidence for guiding physician and patient decision making.

The need for such evidence is highlighted by 2 recent developments. First, the Comparison of Rate Control and Rhythm Control in Patients With Recurrent Persistent Atrial Fibrillation (RACE) trial found that treatment with antiarrhythmic drugs with the intent to restore normal sinus rhythm did not improve survival or reduce stroke risk relative to the simpler strategy of pharmacologic rate control in patients with persistent AF, thus casting doubts on the benefits of restoring sinus rhythm.[14] Second, the Percutaneous Left Atrial Appendage Closure versus Warfarin for Stroke Prevention in Atrial Fibrillation Patients (PROTECT AF) trial, which evaluated percutaneous closure of the left atrial appendage (LAA) in patients with nonvalvular AF at elevated risk of stroke, found that the efficacy of LAA closure was not inferior to standard therapy with warfarin sodium.[15] These trials raise the question of whether LAA closure with rate control alone would be sufficient in a population with AF and mitral valve disease. Only 1 of the randomized trials on ablation therapy in patients undergoing MVS used LAA closure in both treatment arms. An important outstanding question is whether MVS with LAA closure alone is a viable treatment option relative to surgical ablation.

This article describes a comparative effectiveness randomized trial of surgical ablation with LAA closure versus LAA closure alone in patients with persistent and long-standing persistent AF undergoing MVS. This trial has been designed and is conducted within the Cardiothoracic Surgical Clinical Trials Network (CTSN), which is supported by the National Heart, Lung and Blood Institute, the National Institute of Neurological Disorders and Stroke, and the Canadian Institutes for Health Research (Appendix 1). Nested within this trial is a further randomized comparison of 2 different lesions sets. This article addresses trial design challenges, including how best to characterize the target population, operationalize freedom from AF as a primary end point, account for the effects of antiarrhythmic drugs, and measure and analyze secondary end points, such as postoperative AF load. This article concludes by discussing how insights that emerge from this trial may affect surgical practice and guide future research in this area.

CHARACTERIZATION OF TARGET POPULATION

Surgical ablation does not yet have a clear-cut role as a stand-alone procedure, and the obvious population for evaluating this procedure is patients undergoing concomitant cardiac surgery. This CTSN trial, therefore, focuses on adult patients undergoing MVS for several reasons. It is the most common indication among concomitant procedures; around 50% of patients undergoing MVS with AF also undergo an ablation procedure.[1] Patients who remain in AF after MVS have lower survival than do those in sinus rhythm. Moreover, because the left atrium is routinely opened for MVS, ablation adds little time or risk to the surgical procedure; the surgeon is "already there" for the mitral valve procedure. The protocol targets adult patients with a clinical indication for surgery for the following: organic mitral valve disease, functional nonischemic mitral regurgitation, or ischemic mitral regurgitation with evidence of concomitant structural mitral valve disease. The rationale for defining the target population in this manner is to avoid competition for patients who would qualify for 2 other CTSN trials that enroll patients with severe and moderate ischemic mitral regurgitation (both the latter protocols exclude patients with structural valvular disease).

DEFINING AF

Interpretation of the current literature on surgical ablation is challenging, in part because of varying and inconsistent terminology used to describe the pattern and chronicity of AF. Traditionally, studies used *continuous* and *intermittent* labels, proposed by Cox,[2] where *continuous AF* is defined as AF that does not self-terminate and *intermittent AF* as any AF that self-terminates but may be recurrent. To facilitate comparison of outcomes across trials, we adopted the classification from the 2001 Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation.[16] *Persistent AF* is defined as AF that is not self-terminating and lasts longer than 7 days, or that lasts less than 7 days with the necessity for pharmacologic or electrical cardioversion. *Long-standing persistent AF* is defined as continuous AF longer than 1 year in duration. This definition applies only to AF episodes that are at least 30 seconds in duration and do not have a reversible cause, such as acute pulmonary
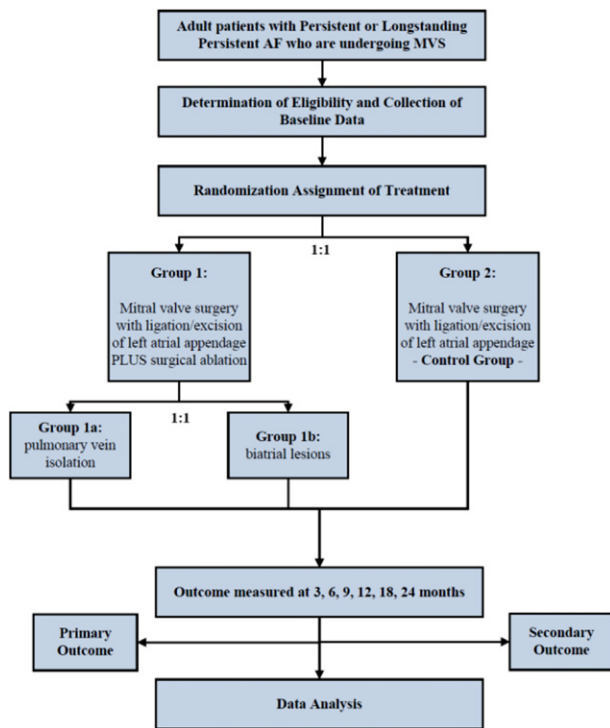
FIGURE 1. Atrial fibrillation *(AF)* trial design. *MVS,* Mitral valve surgery.

FIGURE 2. Pulmonary vein isolation lesion set with bipolar device.

disease or hyperthyroidism. When AF is present for less than 3 months and is paroxysmal, MVS results in conversion to sinus rhythm approximately 80% of the time. By choosing patients with persistent or long-standing persistent AF, we have excluded those patients who move between AF and sinus rhythm sporadically and without intervention, enabling us to attribute elimination of AF to the assigned treatment.

Another critical consideration in trial design is ensuring that the eligibility criteria do not unnecessarily restrict recruitment of patients. To assess the available patient population and highlight those eligibility criteria that may have a major impact on enrollment, CTSN investigators used detailed prospective screening logs. On the basis of these data, eligibility criteria were streamlined, and the protocol no longer excludes patients needing concomitant surgical management of functional tricuspid regurgitation, patent foramen ovale, coronary artery bypass grafting, and aortic arch or aortic valve procedures (Appendix 2).

TREATMENT ARMS

At the induction of anesthesia, patients are randomly allocated in a 1:1 fashion to surgical ablation with LAA closure or to LAA closure alone. Nested within this trial is a further randomized comparison within the ablation arm of 2 different lesions sets: pulmonary vein isolation (PVI) versus a biatrial lesion set patterned after the Cox maze III procedure (Figure 1). Random allocation of lesion set
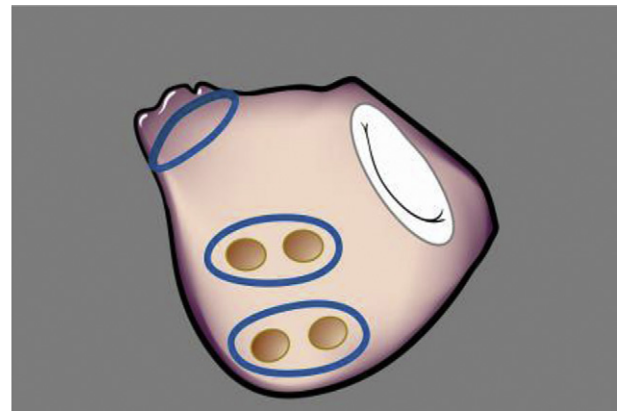
is performed intraoperatively after verification of the absence of left atrial thrombus by transesophageal echocardiography.

An important issue in trial design, especially with complex surgical procedures, is standardization of treatment interventions. Such standardization removes a potentially large source of random variation and thereby improves the efficiency of design and precision of trial results. The CTSN investigators developed treatment guidelines (Appendix E1), which include a pacing protocol (before and after PVI) to confirm acute conduction block at the pulmonary vein level. To date, none of the studies in the literature has assessed acute procedural success (conduction block). Bipolar energy sources are preferred for PVI alone and for the PVI component of the biatrial maze lesion set. For PVI, 2 separate encircling lesions are made around left and right pulmonary veins (Figure 2). For PVI with unipolar energy sources, a box lesion are made, consisting of a continuous ablation line around all 4 pulmonary veins. After PVI, the heart is arrested, and the LAA is excised or excluded. The remainder of the procedure for patients randomly allocated to the biatrial maze lesion set is performed at a point in the operation dictated by the surgeon's standard practice.

In recent years, several energy sources for ablation have been introduced into clinical practice. There do not appear to be significant differences in efficacy or safety of different energy sources. Radiofrequency is the oldest energy source with the largest clinical experience; thus results from any trial that does not incorporate radiofrequency ablation may lack generalizability to the broader surgical community. In this trial, we limited the devices to those based on a radiofrequency energy source. In addition to the linear lesions created by unipolar or bipolar radiofrequency, additional spot lesions will be created at the mitral annulus and isthmus with either unipolar radiofrequency or cryotherapy.

Closure (amputation) of the LAA may be achieved by cut-and-sew technique or by application of a surgical

stapler. Unless contraindicated, all patients will receive class I or III antiarrhythmic drugs beginning within 24 hours of surgery, with drug therapy to be terminated at 3 months. Warfarin sodium is prescribed for patients in both arms throughout the follow-up period.

DEFINING SUCCESS IN ABLATION TRIALS: ESTABLISHING A PRIMARY END POINT

The primary efficacy end point is freedom from AF assessed by 3-day continuous Holter monitoring at 6 and 12 months after ablation. Freedom from postoperative AF is defined as absence of any episode of AF lasting longer than 30 seconds at both 6- and 12-month monitoring time points. The null hypothesis is that there is no difference in the proportion of patients meeting the primary outcome between patients randomly allocated to surgical ablation plus LAA closure or to LAA closure alone. The primary null hypothesis is tested in an intent-to-treat analysis with a .05 level Mantel-Haenszel χ^2 test with stratification by clinical center, the factor on which randomization is stratified. For simplicity, the benefit of ablation between treatment arms is quantified as a simple difference in the proportion of patients free of AF in the 2 groups (expressed as a relative risk with associated 95% confidence intervals).

Patients who die before the 12-month assessment or who are determined by an independent adjudicator to be too ill to undergo AF assessment are considered to have treatment failure. In the primary analysis, patients in both treatment arms who undergo ablation therapy for AF (including surgical ablation or percutaneous catheter ablation) after the index procedure are considered to have treatment failure. The trial incorporates a 3-month blanking period from the time of randomization, which allows time for recovery from the inflammatory effects of the ablation. Events that occur during this period are not taken into account in the primary efficacy analysis. In the primary analysis, the use of antiarrhythmic drugs after the first 3 months is not considered a treatment failure, because the trial is not able to standardize the use of antiarrhythmic drugs by referring cardiologists during the follow-up period.

SAMPLE SIZE ESTIMATION

Sample size estimates must be based on data from the clinical literature and the ability to detect, with high probability, a clinically meaningful presumed benefit of treatment. The reported absence of AF 1 year after MVS among control patients in previously executed randomized clinical trials ranges from approximately 15% to 35%. These trials all reported a relatively large but imprecise benefit of ablation. For example, Doukas and colleagues[10] found an absolute benefit of 35% for ablation in the proportion of patients free of AF at 1 year (95% confidence interval 17%–53%), corresponding to a slightly more than 3-fold increase in the proportion of patients free of AF at 1 year.

For a primary end point assessing freedom from AF at both 6 months and 1 year, we assume that 25% of patients treated with MVS and LAA closure will be free of AF. A total of 260 patients (130 in each group) provides 90% power to detect an absolute increase of 20% (25% vs 45%) in the proportion of patients free of AF according to a 2-tailed .05 level continuity-corrected χ^2 test. The sample size takes into account a single interim analysis in addition to the final analysis. The interim analysis will take place when 50% of patients have been followed up for 1 year and will be conducted at the .003 significance level. The results will be reported only to an independent data and safety monitoring board, which will assess whether the trial should stop early if the results favor either treatment. The final analysis will be conducted at the .049 significance level. The data and safety monitoring board will also monitor for futility; that is, they will recommend stopping the trial if the probability of detecting an absolute 20% benefit for those randomly allocated to MVS plus ablation is less than 20%. Thus, it is possible to carry out a well-designed, prospective clinical trial with a relatively small sample size given the anticipated difference in freedom from AF between the 2 study arms.

AF SECONDARY END POINTS

Designing end points to capture response to treatment in this trial requires an understanding of the episodic nature of AF and the need for rigorous evaluation of postoperative rhythm status. In addition to Holter monitoring at 6 and 12 months, this trial uses transtelephonic monitoring technology to obtain electrocardiographic data from weekly rhythm strips (90 seconds) to assess rhythm activity better during the interval periods. The downside to weekly transtelephonic monitoring is that it (1) requires a higher level of compliance from patients, (2) requires patient education on the use of such devices, and (3) requires consistency in timing of patient transmission to avoid bias from circadian rhythm. As such, this modality of rhythm assessment is probably not reliable enough for use as the primary end point. After the design of the current trial, the Food and Drug Administration (FDA) approved an implantable continuous rhythm monitoring device, which the CTSN is now considering for use in a substudy.

AF Burden

One end point that arises from the use of more frequent rhythm monitoring is *AF load,* which is defined as the proportion of recordings documenting AF in a given patient during spot recordings. Here patients are required to submit rhythm strips on a regular basis from 3 months after surgery until the time of the primary end point assessment. Although this method places greater burden on patients and can result in noncompliance, this form of analysis prevents any single arrhythmia from significantly affecting

the end point, because the overall proportion of arrhythmias encountered is examined at the conclusion of the study.

Freedom From Any Electrocardiographically Documented Atrial Tachyarrhythmia Recurrences

In addition to AF load, another secondary end point of interest is freedom from any electrocardiographically documented atrial tachyarrhythmia recurrences. Although the primary interest is the success of AF ablation, there exists the possibility for induction of other arrhythmias during the process. Freedom from AF, atrial flutter, or atrial tachycardia will be defined by absence of any of these electrocardiographically documented events lasting longer than 30 seconds.

ADDITIONAL CLINICAL SECONDARY END POINTS

Whereas the impact on the occurrence of AF episodes is important to patients, mortality, important adverse events such as stroke, and quality of life are critical for defining the value of a therapy. Although these events themselves have profound effects on patients and their families, their frequencies are low, and evaluating the effect of therapy on survival or stroke as a primary end point with precision would require extremely large sample sizes.

We therefore have included a composite primary safety end point, which is defined as a composite of death, stroke, serious cardiac adverse events, cardiac rehospitalizations, transient ischemic attack, pulmonary embolism, peripheral embolism, excessive bleeding, deep sternal wound infection or mediastinitis, damage to specialized conduction system requiring permanent pacemaker, and damage to peripheral structures, such as the esophagus, within 30 days after the procedure or hospital discharge (whichever is later). In addition, secondary end points include assessing major adverse cardiac and cerebrovascular events, which is relevant to cardiac procedures in general, defined as a non-weighted composite score of death, stroke, worsening heart failure (+1 New York Heart Association functional class); hospitalization for congestive heart failure; and mitral valve reintervention within 12 months of randomization. Survival and differences in the incidence of serious adverse events within 12 months of randomization are also compared between groups with Poisson regression (with exact 95% confidence intervals).

In addition to looking at events that are life threatening or life altering, we measure overall impact on quality of life and hospitalization burden. The long-term impact on quality of life is assessed at 12 months and includes a general health status measure (Short Form-12) and a disease-specific measure (the Atrial Fibrillation Severity Scale). All hospitalization readmissions and total hospital days are measured throughout the duration of follow-up, which is 2 years to assess long-term clinical end points.

DISCUSSION

The prevalence of AF among patients with mitral valve disease presenting for surgery and the development of new ablation techniques that have simplified the cut-and-sew maze technique have led to renewed interest in surgical ablation. Subsequently, questions have emerged as to whether the results from the PROTECT AF trial, which showed equivalence of LAA closure to warfarin sodium in patients with nonvalvular AF, would be applicable to patients with (long-standing) persistent AF undergoing MVS. What then would be the value of surgical ablation and LAA closure relative to excision of the LAA alone in this patient group?

The current literature provides insufficient evidence to address this important clinical issue. Among the numerous device technologies to enter the clinical arena for treatment of AF, only devices using cryoablation have been specifically approved by the FDA for the treatment of AF. The remaining energy sources (radiofrequency, laser, microwave, and ultrasound) have been approved for the ablation of cardiac tissue but not specifically for AF therapy. Clinical trials evaluating the efficacy of these devices for this indication are now under way, but none of these trials provide a randomized comparison to MVS with LAA closure alone. Clearly, surgical ablation procedures have been extensively used in practice and have been the subject of evaluative research. The literature evaluating the effectiveness of surgical ablation as a therapeutic approach is difficult to interpret, however, because of the paucity of rigorously controlled studies and the lack of standardization in procedures, AF classification schemes, and primary end points. The paucity of rigorous clinical evidence regarding the effectiveness of surgical ablation, the fact that nearly half of the patients undergoing MVS do not undergo a concomitant surgical ablation procedure, and recent evidence that LAA closure is not inferior to anticoagulation in a nonvalvular patient group support the argument that there is equipoise to design a trial in patients with (long-standing) persistent AF that compares ablation and LAA closure with LAA closure alone.

The CTSN has designed and is conducting such a comparative effectiveness trial, which requires different manufacturers to support an FDA investigational device exemption application. This trial design, however, is geared toward evaluation of ablation as a therapeutic approach (not a specific device) and will not support FDA approval for any individual device.

The results from this trial will provide several important insights. First, it will offer evidence regarding the comparative benefits of surgical ablation. An open question remains how best to assess benefit in ablation trials, given the episodic nature of this disease. There is currently no accepted standard for defining a successful surgical ablation procedure, and the variations in primary end points have led to difficulty in interpreting the current literature. Some

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studies have used time to first recurrence of AF as a primary end point, with standard Kaplan-Meier methods for analysis, which may be more appropriate for sustained clinical events such as stroke or death.[17] Rhythm status and freedom from AF represent clinical states with intermittent occurrences, thereby rendering the first occurrence less relevant. When AF is detected on an electrocardiogram, the time of detection does not necessarily represent the time that the arrhythmia began, and time-to-event methods are thus less appropriate. Freedom from AF during the first year has become increasingly used as a primary end point. In some trials, success is defined only as freedom from AF at a single postoperative time point (eg, 3 months), whereas in others, a successful outcome requires documentation of normal rhythm that is sustained for a specific period, or success is defined more stringently as absence of AF after discontinuation of all antiarrhythmic drugs. In this trial, AF is measured by 3-day continuous monitoring at 6 and 12 months after ablation, and freedom from AF is defined by absence of AF (lasting >30 seconds) at both time points. This trial will also provide important information on survival, safety, quality of life, functional status, and hospitalization time to help guide treatment decisions.

In addition to providing evidence for making treatment decisions, this trial will generate insights to help shape future clinical research. For example, if ablation is found to offer better AF control than LAA closure alone, the nested subcomparison of different lesion sets will provide preliminary data to inform the design of subsequent trials comparing specific lesion sets and ablation devices. Moreover, the trial compares 2 techniques for postablation heart rhythm monitoring (long-term Holter monitoring vs weekly rhythm strips), which should provide the evidence needed to determine optimal methods for evaluating postoperative rhythm control in the context of a clinical trial. Because more frequent rhythm assessment may reveal otherwise unappreciated episodes of AF, this comparison may also redefine the general definition of freedom from AF, thereby affecting clinical decision-making algorithms (such as those used for anticoagulation). The CTSN investigators are also designing a substudy that includes an implantable monitoring device. Finally, current methods to analyze longitudinal data for complex temporal patterns seen in AF are limited, and so, as mentioned, they are the subject of methodologic exploration by the investigators. A rigorous evidence basis for surgical ablation therapies for persistent or long-standing persistent AF ablation is much needed. This comparative effectiveness trial should provide an important first step in achieving that goal.

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APPENDIX 1. CARDIOTHORACIC SURGICAL TRIALS NETWORK (CTSN)
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APPENDIX 2. INCLUSION AND EXCLUSION CRITERIA
Selected Inclusion Criteria

1. Clinical indications for MVS for the following:

   - Organic mitral valve disease, *or*
   - Functional non-ischemic mitral regurgitation, *or*
   - Ischemic mitral regurgitation with evidence of concomitant structural mitral valve disease

2a. Persistent AF within 6 months before randomization, defined as AF that is not self-terminating and lasting longer than 7 days, or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion.

   - Duration of AF documented by medical history *and*
   - Presence of AF documented by a direct electrocardiographic assessment within 6 months before randomization

2b. Long-standing persistent AF is defined as continuous AF greater than 1 year in duration.

   - Duration of AF documented by medical history *and*
   - Presence of AF documented by direct electrocardiographic assessment on arrival in the operating room

Exclusion Criteria

1. AF without indication for MVS
2. Paroxysmal AF
3. Evidence of left atrial thrombus on intraoperative transesophageal echocardiography
4. Evidence of active infection
5. Mental impairment or other conditions that may not allow subject to understand the nature, significance, and scope of study
6. Surgical management of hypertrophic obstructive cardiomyopathy
7. Previous catheter ablation for AF
8. Life expectancy of less than 1 year
9. Absolute contraindications for anticoagulation therapy
10. Enrollment in concomitant drug or device trials
11. Uncontrolled hypothyroidism or hyperthyroidism
12. Forced expiratory volume in 1 second less than 30% of predicted value or need for home oxygen therapy

APPENDIX E1. TREATMENT GUIDELINES
Surgical Ablation and Pacing Procedures
PVI pacing protocol. None of the studies in the literature assess acute procedural success (conduction block). In the CTSN trial, a pacing protocol (before and after PVI) confirms acute conduction block at the pulmonary vein level. If the patient presents to the operating room in AF, then after institution of cardiopulmonary bypass but before cardioplegic arrest the surgeon will attempt synchronized cardioversion. If the patient does not present to the operating room in AF or if cardioversion is successful, pacing threshold for right and left pulmonary veins will be established and recorded. If the patient presents to the operating room in AF and cardioversion is unsuccessful, the pacing protocol will not be attempted, and the surgeon will conduct ablation according to the lesion set specified. In such instances, we recommend that bipolar ablation devices be applied 3 times and unipolar devices be applied 1 time in performing PVI. This pacing protocol will be followed for all patients after completion of the ablation procedure.

Pulmonary vein isolation. Bipolar energy sources are preferred for PVI alone and for the PVI component of the biatrial maze lesion set. For PVI, 2 separate encircling lesions will be made around left and right pulmonary veins (Figure 2). The right pulmonary veins will be isolated first. Isolation will be confirmed by pacing the pulmonary veins at the previously identified threshold for capture. If no atrial capture is noted, it will be inferred that the right pulmonary veins have been isolated. If atrial capture is observed, additional ablations on the atrial cuff will be performed until isolation is confirmed. This protocol will be repeated for left PVI. For PVI with unipolar energy sources, a box lesion will be made, consisting of a continuous ablation line around all 4 pulmonary veins.

Biatrial maze lesion set. After PVI, the heart will be arrested and the LAA excised or excluded. The remainder of the procedure for patients randomly allocated to the biatrial maze lesion set will be performed at a point in the operation dictated by the surgeon's standard practice. Components will include the following:

- *Left atriotomy:* The left atrium will be opened adjacent to the interatrial groove, anterior to the right pulmonary veins.
- *Connecting lesions from right to left pulmonary veins:* A bipolar device will be used to create separate lesions between superior pulmonary veins and between inferior pulmonary veins, or a unipolar device will be used to encircle all 4 veins (box lesion).
- *Connecting lesion to mitral annulus:* A cryosurgical device or unipolar heat-based device will be used to create a connection from the box lesion to the mitral annulus. This lesion will be directed toward the P3 segment of the mitral valve.
- *Connecting lesion to left atrial appendage:* After excision or exclusion of the LAA (see following text),

a unipolar or bipolar energy source will be used to create a connecting lesion from its orifice to the box lesion.
- *Right atrial lesions:* A vertical right atriotomy will be made beginning from the atrioventricular groove and extending toward the fossa ovalis. A unipolar energy source will be used to connect this lesion to the tricuspid annulus at the 2 o'clock position as viewed by the surgeon (*A* in Figure E1). A unipolar or bipolar energy source will be used to connect the posterior aspect of this atriotomy to the superior and inferior venae cavae (*B* in Figure E1). An incision will be made in the body of the right atrial appendage, and a unipolar energy source will be used to connect the incision to the tricuspid annulus at the 10 o'clock position as viewed by the surgeon (*C* in Figure E1). At the discretion of the surgeon, patients with a history of atrial flutter are candidates for the right atrial isthmus lesion.

Energy Sources
In recent years, several energy sources for ablation have been introduced into clinical practice. There do not appear to be significant differences in efficacy or safety of different energy sources. Radiofrequency ablation is the oldest and most extensively studied mode of ablation in the literature at this time. Given the fact that radiofrequency is the energy source with the largest clinical experience, results from a trial that does not incorporate radiofrequency ablation may lack generalizability to the broader surgical community. In this trial, we limited the number of devices with a radiofrequency energy source, including both bipolar and unipolar devices. In addition to the linear lesions created by unipolar or bipolar radiofrequency, additional spot lesions will be created at the mitral annulus and isthmus with either unipolar radiofrequency or cryotherapy. The cryoprobe is recommended for creating lesions near the mitral or tricuspid annulus; this enables incorporation of the coronary sinus. As such, this trial does not evaluate any specific device but rather a therapeutic approach, which is distinct from most industry-sponsored trials of new devices.

LAA Closure or Exclusion
Closure (amputation) of the LAA may be achieved by cut-and-sew technique or by application of a surgical stapler. Exclusion of the LAA may be accomplished by oversewing or stapling across its base.

Follow-up Medical Management
Unless contraindicated (hypotension or bradycardia with heart rate <60 beats/min), all patients will receive prophylactic class I or III antiarrhythmic drugs (amiodarone, sotalol, propafenone, procainamide) beginning within 24 hours of surgery and will be discharged while still receiving the agent. At 3 months, antiarrhythmic agents will be

terminated in all patients, and this recommendation will be communicated to the managing physician. Direct current cardioversion will be performed by managing physicians as clinically indicated. Unless contraindicated, warfarin sodium is prescribed for patients in both arms throughout the follow-up period.
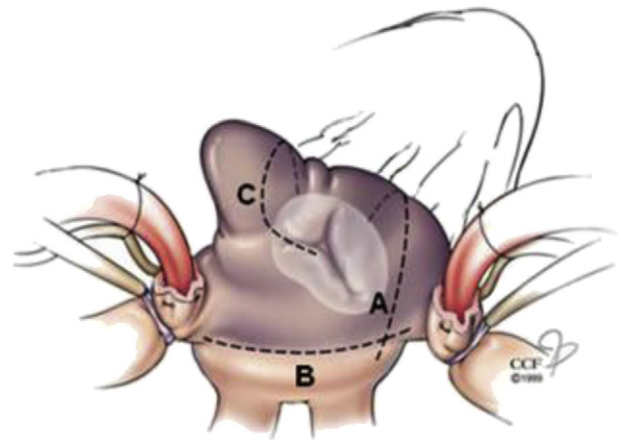

FIGURE E1. Right atrial lesions.