

Surgical Ablation for Atrial Fibrillation in Cardiac Surgery A Consensus Statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2009

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Objective: This purpose of this consensus conference was to determine whether surgical atrial fibrillation (AF) ablation during cardiac surgery improves clinical and resource outcomes compared with cardiac surgery alone in adults undergoing cardiac surgery for valve or coronary artery bypass grafting.

Methods: Before the consensus conference, the consensus panel reviewed the best available evidence, whereby systematic reviews, randomized trials, and nonrandomized trials were considered in descending order of validity and importance. Evidence-based statements were created, and consensus processes were used to determine the ensuing recommendations. The American Heart Association/

American College of Cardiology system was used to label the level of evidence and class of recommendation.

Results: The consensus panel agreed on the following statements in patients with AF undergoing cardiac surgery concomitant surgical ablation:

1. Improves the achievement of sinus rhythm at discharge and 1 year (level A); this effect is sustained up to 5 years (level B). Does not reduce the use of antiarrhythmic drugs at 12 months after surgery (level A; 36.0% vs. 45.4%), although trials were not designed to answer this question.
2. Does not increase the requirement for permanent pacemaker implantation (4.4% vs. 4.8%; level A).
3. Does not increase the risk of perioperative mortality (level A), stroke (level A), myocardial infarction (level B), cardiac tamponade (level A), reoperative bleeding (level A), esophageal injury (level B), low cardiac output (level A), intraaortic balloon (level B), congestive heart failure (level B), ejection fraction (EF; level B), pleural effusion (level A), pneumonia (level A), renal dysfunction (level B), and mediastinitis (level A). The incidence of esophageal injury remains to be low (level B).
4. Does not reduce mortality at 1 year (level A). There is a possible reduction in mortality beyond 1 year (level B), but no difference in stroke (level A), myocardial infarction (level A), and heart failure (level B). EF is increased (+4.1% more than control; level A).
5. Has been shown to improve exercise tolerance at 1 year (level A), but no impact on quality of life at 3 months and 1 year (level A); however, the methodology used and the number of trials studying these outcomes are insufficient.
6. Increases cardiopulmonary bypass and cross-clamp times (level A), with no difference in intensive care unit and hospital length of stay (level A). Overall costs were not reported.

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Conclusions: Given these evidence-based statements, the consensus panel stated that, in patients with persistent and permanent AF undergoing cardiac surgery, concomitant surgical ablation is recommended to increase incidence of sinus rhythm at short- and long-term follow-up (class 1, level A); to reduce the risk of stroke and thromboembolic events (class 2a, level B); to improve EF (class 2a,

level A); and to exercise tolerance (class 2a, level A) and long-term survival (class 2a, level B).

Atrial fibrillation (AF) is common in patients with mitral valve disease or coronary artery disease, and the role of surgical ablation of AF for patients undergoing surgical procedure for mitral valve repair/replacement and/or coronary artery bypass remains uncertain. An expert consensus statement, based on best available evidence, regarding the place of surgical ablation in practice should be undertaken, and the strength of evidence that form the basis for the statements should be made transparent. Statements based on strong evidence should be applied routinely, whereas statements based on low levels of evidence or opinion should be applied more flexibly after careful consideration of the tradeoffs in light of the lacking evidence base.^{1,2}

METHODS

Purpose of the Consensus Conference

This consensus conference was held to clarify, for clinical practitioners, researchers, and healthcare planners or administrators, the role of surgical AF ablation in adults undergoing cardiac surgery for valve or coronary artery bypass grafting (CABG). Increasing interest in surgical ablation of AF has drawn attention to the need for exhaustive review of the evidence for surgical AF ablation plus cardiac surgery, with careful deliberation of its relative merits and risks compared with cardiac surgery alone without ablation in patients who present with permanent or persistent AF and require open cardiac surgery. A secondary objective of this consensus conference was to identify the gaps in the evidence and suggest a future research agenda for surgical AF ablation.

Funding

Support for this consensus conference was provided by the International Society of Minimally Invasive Cardiothoracic Surgery, which has received unrestricted educational grants from industries that produce surgical technologies. Although International Society of Minimally Invasive Cardiothoracic Surgery receives industry funding, no specific industry was linked with this consensus conference, and it did not involve direct funding from manufacturers of devices related to AF ablation. Editorial independence was granted to the members of the expert panel, and the expectation was that the resulting consensus statements would be clearly based on the best available evidence, with explicit methodology to allow the reader/user to determine which aspects were informed by evidence and where evidence was lacking and opinion was required to create statements.

Selection of Panel Members

Members of the consensus panel were invited to participate by the chair and facilitator of the consensus process. Members included representation from four countries: eight cardiovascular surgeons, each with experience in cardiac surgery and AF ablation (two from Asia, two from Europe, and four from the USA), one cardiac anesthesiologist (Canada), and one methodologist with expertise in health technology assessment and meta-analysis (Canada).

Defining the Clinical Question

Before the consensus conference, the consensus panel was asked to define the clinical question, which involved defining the scope and depth of each of the following considerations: patient population of interest, intervention of interest, valid comparator groups, and outcomes of interest.³ The clinical question was developed collaboratively with input from all consensus panel members and was finally stated as follows:

In patients with AF undergoing cardiac surgery, does surgical AF ablation improve clinical outcomes, quality of life (QOL), and resource-related outcomes when compared with cardiac surgery without ablation?

Identifying Relevant Evidence

After the clinical questions had been defined, all published evidence with acceptable study designs was sought to maximally inform this clinical question. Acceptable study designs included any randomized or nonrandomized comparative trial comparing surgical AF ablation versus no surgical AF ablation in adults with AF undergoing cardiac surgery for valve repair or CABG. Because there was no comprehensive systematic review that included all relevant evidence to answer our clinical question, we conducted a full systematic review and meta-analysis of the evidence before the conference. The complete methodology and results of the systematic review has been described in another article in this issue of the *Journal*.⁴ In short, before the consensus conference, comprehensive searches of Cochrane, Medline, and other databases were conducted to identify all randomized and nonrandomized comparative trials of surgical AF ablation versus no ablation during cardiac surgery for valve replacement or CABG that reported clinical- or resource-related outcomes. Studies of catheter ablation were excluded. Studies of surgical ablation for lone AF were excluded. Potentially relevant trials were circulated to the consensus panel for review and to determine agreement with inclusion criteria and whether any relevant trials were missed. Information related to baseline characteristics and outcomes was extracted independently by at least two authors from each study that met prospectively defined inclusion criteria. When appropriate, data were synthesized by valid meta-analytic techniques to provide more precise aggregate outcome estimates. Data that were not appropriate for statistical synthesis across trials were summarized qualitatively in tables and text to ensure all relevant data were addressed in the systematic review. The results of the systematic review and meta-analysis⁴ were used to populate evidence tables and graphs to form the basis for discussions and support the decision making of the consensus panel.

Reviewing and Presenting the Evidence

Before the consensus conference, each member of the consensus panel received a copy of all identified randomized and nonrandomized clinical trials and relevant background literature related to the clinical question. During the consensus conference meeting, the panelists were divided into groups and asked to address the following subquestions with the best available evidence from the meta-analysis:

1. Does surgical ablation result in higher rates of sinus rhythm before discharge, and is the effect sustained long-term (6 months, 1 year, 3 years, and 5 years)?
2. Does ablation reduce the need for pharmacologic treatment of AF, DC cardioversion, or pacemaker insertion?
3. Does ablation reduce the risk of stroke, myocardial infarction (MI), heart failure, and other complications?
4. Does ablation improve QOL, functionality, or other patient-reported outcomes?
5. Does ablation reduce total costs, intensive care unit (ICU) and hospital length of stay, need for repeat cardiac surgery, readmissions, and cost-effective?

Applying the Evidence to Create Recommendations

Levels of Evidence and Grade of Recommendations

The best available evidence that was used to inform each clinical subquestion was classified according to the taxonomy suggested by American Heart Association (AHA)/American College of Cardiology (ACC), as outlined in Table 1. This classification categorizes the evidence based on study design and susceptibility to bias, wherein higher levels of evidence and grades are labeled to highlight their lesser likelihood for bias and increased confidence in “closeness to the truth.”^{5–8} Several systems of grading recommendations and labeling strength of the evidence exist. The AHA/ACC system was chosen for consistency with other guidelines [http://www.acc.org/clinical/manual/manual_index.htm (see Tables 1 and 2)]. As recommended by guidelines,⁹ classification of the evidence and labeling recommendations is best done by the group panel using a democratic voting process after group discussion of the strength of the evidence.

Members of the panel considered the highest possible level of evidence to inform their clinical subquestion, such that systematic reviews, meta-analyses, and randomized trials (level A evidence, see Table 1) were considered preferentially to nonrandomized clinical trials. If there was insufficient level A evidence to inform the question, members were encouraged to consult nonrandomized comparative trials (level B evidence, see Table 1). Only when level A and level B evidences failed to address the clinical question were noncomparative trials consulted to inform decisions (level C evidence) along with expert opinion. When evidence from published or unpublished clinical trials to address the question was nonexistent, expert opinion from the consensus panel members was consulted. In each case, the best available level of evidence was explicitly stated and interpreted in light of its methodological strengths and weaknesses before a statement of recommendation was made. It was agreed that recommendations

TABLE 1. Levels of Evidence

Level of evidence A	Data derived from multiple randomized clinical trials
Level of evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of evidence C	Consensus opinion of experts

TABLE 2. Classes of Recommendations

Class 1	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective
Class 2	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
IIb	Usefulness/efficacy is less well established by evidence/opinion
Class 3	Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful or effective and, in some cases, may be harmful

with higher levels of evidence should be interpreted with more confidence than recommendations based on lower levels of evidence, and that recommendations should be explicitly classified as per the ACC/AHA system (see Table 2). Each subgroup spent time discussing and critically evaluating the evidence they had reviewed for their preassigned subquestions. Subsequently, each subgroup prepared a proposed draft statement related to their assigned subquestion.

Consensus Process and the Role of Evidence versus Opinion

After each subgroup presented a proposed draft statement for their assigned subquestions to the entire consensus panel, further discussion of the strength, consistency, clinical significance, and relevance of the evidence occurred before final revisions, and final agreement was made to the consensus statement (along with its appropriate level of evidence and class of recommendation) for each of the subquestions.

When limited evidence was found to inform a clinical subquestion, it was explicitly recognized that scientific information would need to be supplemented by the interpretations and opinions of the experts. Legitimate conflicts over values and interpretations were resolved by discussion and majority vote. Therefore, it is important to note that consensus was not always unanimous. This is particularly true for the subquestions informed only by lower levels of evidence and expert opinion, where controversy was not allayed by clear evidence.

After each subquestion had been addressed, the entire consensus panel reviewed all of the recommendations and their assigned grades of recommendations and proposed levels of evidence to answer the overarching summary clinical question: Does surgical AF ablation versus cardiac surgery alone improve clinical and resource outcomes?

In summary, this consensus process sought to be primarily evidence based, whereas allowing for opinions to inform when the evidence was incomplete and requiring that the basis for the statement be labeled by a declarative level of evidence. Bringing selected experts together in a consensus process allowed for breadth of perspectives and representations of interpretations for a multidimensional and carefully considered judgment of the evidence along with its certainties and uncertainties.

RESULTS

The systematic review and meta-analysis of the evidence performed in consultation with the consensus panel was used as the basis for the discussion of the evidence and formation of the recommendations because all available randomized and nonrandomized comparative trials were included in the systematic review.⁴

The systematic review with meta-analysis identified 10 randomized trials (650 patients) and 23 nonrandomized trials (3997 patients) for a total of 36 trials involving 4647 patients comparing surgical AF ablation during cardiac surgery versus cardiac surgery alone.^{10–45} Most trials identified were published in English (1996–2009), and many were performed in the USA. Average age of patients at baseline was 64.6 years, ~50% of whom were men.

When heterogeneity was identified across studies for endpoints, much of the heterogeneity was found to be because of differences in definition of endpoints and differences in study design (especially for the nonrandomized studies). Heterogeneity was also likely related to the differences in techniques used for surgical AF ablation (ranging from cut-and-sew to radiofrequency ablation). Nevertheless, much of the heterogeneity was less concerning because it was driven by uncertainty about the size of effect and not the direction of effect and, therefore, did not put into question the presence of significant benefit (when detected).

The summary discussion and resulting statements with assignment of levels of evidence and class of recommendation are given below for each clinical subquestion and for the overarching clinical question. The aggregate results for randomized controlled trials (RCTs, level A) from the meta-analysis are preferentially relied on for the consensus statements; however, when randomized trials were unavailable, aggregate results from non-RCT evidence (level B) were considered. Readers may consult the original publication for comprehensive reporting of both randomized and nonrandomized trials for all endpoints. For discrete outcomes, odds ratios (ORs) and their 95% confidence intervals (95%CI) are reported. For continuous outcomes, the weighted mean difference (WMD, 95%CI) is reported.

Question 1: Does Surgical Ablation Result in Higher Rates of Sinus Rhythm Prior at Discharge and is the Effect Sustained Long-Term (6 Months, 1 Year, 3 Years, and 5 Years)?

Level A evidence shows that the number of patients achieving sinus rhythm was significantly improved in the surgical AF ablation group compared with the surgery alone group at discharge (59% vs. 14%) and during follow-up at 12 months (70% vs. 23%), and longer term beyond 1 year (63% vs. 20%). In the sole randomized trial that provided follow-up to 5 years, the proportion of patients with sinus rhythm remained significantly improved after surgical ablation compared with surgery alone (Table 3).⁴

Statement

In patients with AF undergoing cardiac surgery, surgical ablation improves the achievement of sinus rhythm at

TABLE 3. Sinus Rhythm Rates at Discharge and Follow-Up

	Design	Surgical AF Ablation	Cardiac Surgery Alone	OR
SR, at D/C	All	68.6	23.0	8.4 (4.9–14.4)
	8 RCT	59.3	14.3	10.1 (4.5–22.5)
	12 Non-RCT	72.7	26.9	7.2 (3.4–14.9)
SR, 3–6 mo	All	70.3	24.1	11.2 (7.5–16.7)
	9 RCT	63.0	23.0	6.7 (3.6–12.6)
	6 Non-RCT	81.8	25.1	15.9 (9.5–26.5)
SR, 1 yr	All	75.0	22.6	10.9 (7.4–16.0)
	8 RCT	70.0	23.0	9.6 (5.6–16.4)
	10 Non-RCT	77.2	22.3	12.4 (7.2–21.5)
SR, at latest follow-up (≥1 yr)	All	74.5	18.4	10.2 (5.5–18.7)
	10 RCT	62.5	20.0	6.7 (2.8–15.7)
	15 Non-RCT	76.6	18.3	15.5 (6.6–36.7)

discharge and 1 year (level A). This effect is sustained up to 5 years (level B).

Question 2: In Patients Undergoing Cardiac Surgery, Does Surgical AF Ablation Reduce the Need for Pharmacologic Treatment of AF, DC Cardioversion, or Pacemaker Insertion?

Although randomized trials did not show overall significant reduction in antiarrhythmic use, the studies were heterogeneous in their definition and protocols for antiarrhythmic use, and the results should be interpreted as nondefinitive. Only two randomized studies reported this outcome (involving only 130 patients). In these randomized trials, the study protocol mandated the use of antiarrhythmics postoperatively for a defined period, and this may have masked the ability to achieve a difference. In addition, it is important to note that these results simply describe the utilization of, and not necessarily the need for, antiarrhythmic drugs in these included studies. There was no intent within the studies to adequately study whether AF ablation can safely reduce the use of antiarrhythmics. Continuation of oral anticoagulants was also poorly reported in the trials and was not measured in our meta-analysis.

The incidence of permanent pacemaker insertion was not significantly different in randomized trials, although nonrandomized trials showed a trend for increased permanent pacemaker insertion in the surgical AF ablation group. The incidence of pacemaker insertion in these studies may be lower than that seen in practice, but the data are limited by the small number of studies reporting pacemaker insertion. In addition, procedures used for surgical ablation were heterogeneous across the studies (type of mapping, lesion sets, type of energy used, left atrial appendage excision, and biatrial vs. single atrial application varied), and clinical thresholds for insertion of pacemaker were generally not defined in the studies. The finding of increased need for pacemaker is congruent with the experience described in the Society for Thoracic Surgeons database.⁴⁶ Although incompletely understood and not adequately informed by the evidence, it remains possible that surgical ablation may increase the need

for pacemaker insertion and further understanding of whether differing lesion sets pose greater risk needs to be studied.

Statements

- i. In patients with AF undergoing cardiac surgery, surgical ablation did not reduce the use of antiarrhythmic drugs at 12 months after surgery (level A; 36.0% vs. 45.4%), although trials were not designed to answer this question.
- ii. In patients with AF undergoing cardiac surgery, surgical ablation did not increase the requirement for permanent pacemaker implantation (4.4% vs. 4.8%; level A), although level B evidence raises the possibility of increased need for pacemaker.

Question 3: In Patients Undergoing Cardiac Surgery, Does Surgical AF Ablation Reduce the Risk of Stroke, MI, Heart Failure, and Other Complications?

There was no significant difference in stroke or transient ischemic attack between groups for randomized studies (OR 0.92, 95%CI 0.20–4.32); however, there was significant reduction in nonrandomized studies (OR 0.25, 95%CI 0.14–0.46). When stroke or other thromboembolic events were considered in aggregate, the difference between groups did not reach significance for randomized studies (OR 0.35, 95%CI 0.09–1.32), but reached significance for nonrandomized studies (OR 0.28, 95%CI 0.15–0.52). Metaregression of risk of stroke over time for each group in randomized and nonrandomized studies showed that surgical ablation provided increasing protection from stroke with increasing length of follow-up.

In most trials, it was difficult to determine whether anticoagulants were continued indefinitely postoperatively in the surgical ablation group. The optimal duration of anticoagulant prophylaxis for patients who achieve normal sinus rhythm postablation is not yet known. If patients in the surgical ablation group were discontinued prematurely from anticoagulants, this may have predisposed to stroke.

Other clinical outcomes such as MI, low cardiac output syndrome, bleeding events, cardiac tamponade, reintervention for valvular leak, renal dysfunction, pneumonia, and pleural effusions did not differ between groups in randomized and nonrandomized studies. However, many of the studies failed to report on these outcomes, and the CIs remain wide.

Left ventricular ejection fraction (EF) slightly improved in randomized studies (WMD 4%, 95%CI 1%–7%), but not in nonrandomized studies (WMD –2, 95%CI +1% to –5%). The proportion of patients remaining in NYHA class III or IV was not different between groups in randomized and nonrandomized studies (8.3% vs. 12%).

All-cause mortality was not different between groups in randomized and nonrandomized studies at 30 days (3.7% vs. 2.8%) and 1 year (6.9% vs. 6.2%). In studies reporting all-cause mortality at 1 year or more (up to 5 years), all-cause mortality did not differ in randomized studies (7.7% vs. 6.0%; OR 1.21, 95%CI 0.59–2.51), but reached significant reduction in nonrandomized studies (5.4% vs. 13.5%; OR 0.54, 95%CI 0.31–0.96). However, there is risk of bias in

nonrandomized studies because of longer follow-up in the studies with historical control groups in some of the retrospective studies and potential for differential loss to follow-up between groups.

Statement

- i. In patients with AF undergoing cardiac surgery, surgical ablation does not increase the risk of perioperative mortality (level A), stroke (level A), MI (level B), cardiac tamponade (level A), reoperative bleeding (level A), esophageal injury (level B), low cardiac output (level A), intraaortic balloon (level B), congestive heart failure (level B), EF (level B), pleural effusion (level A), pneumonia (level A), renal dysfunction (level B), mediastinitis (level A). The incidence of esophageal injury remains low (level B).
- ii. In patients with AF undergoing cardiac surgery, surgical ablation does not reduce mortality at 1 year (level A). There is a possible reduction in mortality beyond 1 year (level B). There was no difference in stroke (level A), MI (level A), and heart failure (level B). EF is increased (+4.1% over control; level A).

Question 4: Does Ablation Improve QOL, Functionality, or Other Patient-Reported Outcomes?

The impact on functionality was inconsistently reported and was heterogeneous across the few trials that reported this outcome. The evidence for exercise testing was heterogeneous and did not provide definitive results. In most cases, only a subset of patients underwent testing, and in some cases, the endpoints are difficult to generalize to the real-life setting. Exercise testing was performed in two randomized trials. De Lima et al¹³ reported that the chronotropic response was significantly better in the surgical ablation group (PVI or maze) compared with control; however, in this study, only patients with normal sinus rhythm underwent testing, and this precludes generalization to the total study population. Deneke et al¹⁴ reported that although VO₂ max was not different between groups, the maximum workload was increased for surgical ablation versus control in 22 patients. Doukas et al¹⁵ reported that patients undergoing surgical ablation recorded longer distances than control patients on the shuttle walk test; although, when the change over baseline was compared, the significance did not remain.

QOL was reported in two randomized trials^{17,20} with no significant difference between surgical AF ablation and control patients on SF-36 domains at 3 months and 12 months.

Statement

In patients undergoing cardiac surgery, surgical AF ablation:

- i. Has been shown to improve exercise tolerance at 1 year (level A); however, the methodology used and the number of trials studying this outcome are insufficient.
- ii. Has not been shown to impact QOL at 3 months and 1 year (level A); however, the methodology used and number of trials studying this outcome are insufficient.

Question 5: In Patients Undergoing Cardiac Surgery, Does Surgical AF Ablation Reduce Total Costs, ICU and Hospital Length of Stay, Need for Repeat Cardiac Surgery, Readmissions, and Cost-Effective?

In the surgical AF ablation group compared with surgery alone group, cardiopulmonary bypass (CPB) time was significantly greater on average by 27 minutes in the randomized and 55 minutes in nonrandomized studies.⁴ Cross-clamp time was also significantly greater by a mean of 15 minutes in randomized and 41 minutes in nonrandomized studies.⁴ Operation time was not significantly longer in the single randomized trial that reported this outcome but was significantly longer on average by 166 minutes in nonrandomized studies. Length of stay in ICU was not significantly different between groups in the sole randomized trial reporting this outcome (WMD -0.5 , 95%CI -1.5 to 0.5), and was significantly increased by nearly 1 day in nonrandomized studies (WMD $+0.9$ days, 95%CI $+0.3$ to $+1.6$ days). Total hospital length of stay was not significantly different between groups for randomized studies (WMD 0.7 days, 95%CI -0.8 to 2.2 days) but was significantly increased by 1.5 days for nonrandomized studies (WMD 1.5 days, 95%CI $0.6-2.3$ days). The overall impacts of surgical AF ablation on resource utilization in hospital and over the longer term have not been reported in clinical trials to date. Whether longer term impacts on sinus rhythm and stroke may provide positive impacts on resource utilization and cost-effectiveness remains unstudied at this time.

Statement

In patients undergoing cardiac surgery, concomitant surgical ablation increases CPB and cross-clamp times (level A), with no difference in ICU and hospital length of stay (level A). Overall costs were not reported.

Question 6: In Patients With AF Undergoing Cardiac Surgery Plus Ablation, How Do Different Ablative Techniques Compare With Each Other for Conversion to Sinus Rhythm Cut-and-Sew, Cox Maze I, II, and III, Pulmonary Vein Isolation, Radiofrequency Ablation, Ultrasound Ablation, Laser Ablation, and Cryoablation?

Although a full systematic review of direct and indirect comparisons of different techniques for surgical ablation of AF was beyond the defined scope of our meta-analysis,⁴ we identified numerous studies (at least 2 RCTs, 51 non-RCTs) comparing two or more techniques or technologies for surgical ablation (Bilateral vs. left atrial [LA] lesions only, comparison between the following energy sources [cryothermal, radiofrequency {RA}, ultrasound, microwave and laser to the cut and sew technique; and comparison between different energy sources].) Because of heterogeneity in the techniques, technologies, and design bias of nonrandomized comparisons of prognostically disparate populations, it was not possible to aggregate data across studies to determine which factors were associated with greater success. In general, the studies showed similar rates of achievement of sinus

rhythm; however, the trials were individually underpowered to find differences between procedures and some studies used historical control groups using older surgical AF ablation techniques to indirectly compare the outcomes of newer surgical AF ablation techniques. Although indirect comparisons may help to guide future research, it would be premature to declare one technique superior to another without adequately powered direct comparative analyses in randomized trials. Assessment of the results of the trials suggests that, at the least, there are no clear differences in conversion to sinus rhythm. However, concerns over adverse effects were sometimes inferred but remain understudied. Similarly, because of their rarity, large comparisons would be needed to provide valid assessment of relative risks across different techniques and technologies used for surgical AF ablation.

Future systematic reviews should aim to systematically assess different lesion sets and differing energy modalities for AF ablation (or combinations of cutting and energy-mediated ablation), as well as the role of atrial appendage ligation and pulmonary vein isolation. Because prevention of AF over the longer term, along with stroke reduction and survival improvement, are the ultimate reasons to perform AF ablation, these studies should commit to long-term follow-up to determine the relative success of different techniques in achieving these ultimate goals.

DISCUSSION

After discussion of each of the substatements for the five subquestions, the consensus panel discussed what should be the overall role of surgical AF ablation in clinical practice to address the overarching question: Does surgical AF ablation compared with no ablation in adults undergoing cardiac surgery improve clinical and resource outcomes? Because there are no studies that examine a policy of surgical AF ablation versus none during cardiac surgery as standard of care, the maximal level of evidence for this recommendation is level B. However, because there was consistency of opinion across the consensus panel, the recommendation was designated as class I.

Recommendation

In patients with persistent and permanent AF undergoing cardiac surgery, concomitant surgical ablation is recommended to increase incidence of sinus rhythm at short- and long-term follow-up (class 1, level A); to reduce the risk of stroke and thromboembolic events (class 2a, level B); to improve EF (class 2a, level A); and to exercise tolerance (class 2a, level A) and long-term survival (class 2a, level B).

Statement on Future Research

A number of gaps in the evidence were identified throughout the consensus process. Based on discussion of the limitations of the evidence base, the following areas were suggested by the consensus panel as priority areas for future research:

Trial Design

Future trials should be designed to maximize validity, with incorporation of valid randomization processes, and

primary analysis by intention-to-treat, with subsequent subanalysis of patients who crossover.

Definitions

Efforts should be made to standardize definitions and reporting of lesion sets and technologies used. Definitions of AF should also adhere to the guidelines for reporting.^{47,48}

Outcomes

Although the evidence for benefits related to sinus rhythm consistently shows benefit over the short- to midterm, adequately powered studies randomized trials are urgently needed to address the more important following clinically relevant outcomes:

- stroke, symptomatic relief, QOL, and long-term mortality for concomitant AF surgical ablation and stand alone ablation;
- need for antiarrhythmics and anticoagulation agents in AF surgical ablation.

In addition, predictive factors for success should be evaluated, such as identifiable genomic factors that allow patient selection for the procedure based on markers for likelihood of success. Studies to define the relative roles of surgical AF ablation and catheter-based ablation for patients with lone AF are also required.

Despite increased CPB and cross-clamp times, the perioperative safety of surgical AF ablation seems acceptable with no proven increased risks of morbidity or mortality shown to date; however, further study with adequate power is required to confirm this. The cost effectiveness of surgical AF ablation should be considered, as the overall impact of the procedure on resource utilization is unknown. Although operating room time may increase, perhaps downstream costs may be prevented if surgical AF ablation prevents major morbidities (stroke, hospital admission) and premature death. A number of important clinical subgroups have not been studied (ie, elderly with low EF, patients undergoing repeat procedures for AF after failed catheter ablation or failed electrical cardioversion), and the generalizability of these findings to these subgroups is unknown.

The systematic approach to defining the research question, identifying all relevant published and unpublished evidence, and labeling that evidence based on its quality suggests that these statements represent the best available guideline for evidence-based clinical practice and resource decisions. These statements should be interpreted and applied with full acknowledgment of the level of evidence that informs that statement, whereby statements based on level A evidence are given more confidence than those of level B or less.^{1,2} Every effort was made throughout the consensus process and peer review process to ensure that the recommendations are clearly stated and their basis clearly documented.

Strengths and Limitations

This consensus statement is based on a current and comprehensive systematic review of the evidence, with formal consensus processes that limited the role of opinion

secondary to that of the evidence base. Care was taken to explicitly label the recommendations with the evidence available to inform it and, when evidence was unavailable, to apply considered expert judgment to provide perspective for potential users of the statement. With this explicit evidence-based consensus process, it is clear to the user how the recommendations were derived. The statements have also been exposed to the rigors of secondary panel review and subsequent external peer review before publication.

A notable strength of this consensus statement is its reliance on the evidence base, with comprehensive consideration of benefits, risks, and resource-related issues. The methodology undertaken and recommendations provided by this consensus conference are in agreement with current recommendations for developing consensus statements and guidelines.^{49,50} To self-appraise our consensus statement against current standards for valid guidelines, we subjected our consensus process and recommendations to quality assessment checklists and found that most indicators of high-quality were met or exceeded.^{50,51}

Although a wide range of health care professionals and methodological expertise was represented on the consensus panel, some stakeholders were not represented. In particular, patients were not invited to participate; however, patient-related outcomes including satisfaction and QOL were sought from published trials to address this perspective. It is unfortunate that patient satisfaction was infrequently reported in the studies. In addition, stakeholders from the manufacturing sector (ie, producers of technologies related to AF ablation) were not included in the consensus and review process to reduce the risk of bias that may result from direct manufacturer involvement.

Clinicians tend to overestimate the effectiveness of new interventions, especially if the intervention in question rests within the realm of their expertise. In addition, there is a tendency for group decision-making processes to experience “groupthink” with compromises made to come closest to pleasing all members of the panel, even for issues that start off greatly polarized. To mitigate these risks, experts in evidence-based methodology and health technology assessment from within and outside of the surgical field were invited to facilitate the discussion and to ensure that the best available evidence was the focus for discussion rather than opinions or political charges.

The scarcity of trials with longer term follow-up remains a limitation of the evidence. There is insufficient evidence with unbiased follow-up over the long-term to definitively rule out the possibility of clinically important differences in survival over the longer term. Nonrandomized data suggest that survival might be increased with surgical AF ablation compared with no ablation and that strokes may be reduced; however, caution is required in interpreting these findings because of potential differences in patient selection for the procedure and differential loss to follow-up in non-randomized trials. The potential for survival differences must be interpreted as a preliminary hypothesis, and randomized trials with long-term follow-up should be encouraged. It is hoped that future trials will be conducted to address these

areas where only lower levels of evidence are available or where trials have been underpowered.

Key Limitations in the Evidence

The following areas were identified by the consensus panel as limitations in the current studies that have been published:

- Few RCT and underpowered, design, techniques, and energy source;
- The studies reviewed had no uniform endpoints and definitions for success and failure;
- Modification of the maze technique and details of lesion sets or energy outputs inadequately described;
- Cardiac rhythm monitoring and surveillance was heterogeneous;
- Follow-up >1 years was incomplete, and differences in loss to follow-up occurred between groups in nonrandomized trials;
- Important clinical subgroups have not been studied (ie, extreme age and low EF);
- Importance ablation of LA appendices, importance of LA size (<6 cm);
- Incomplete follow-up;
- Use of oral anticoagulants postprocedure (ie, warfarin continuation?);
- Applicable to stand-alone AF ablation patient is not certain;
- This panel did not include an electrophysiologist.

These limitations should be borne in mind when interpreting the current evidence base and, also, should be mitigated when designing future research.

Feasibility and Training

Judgments about whether surgical AF ablation is feasible depends highly on the local context and setting. Feasibility issues worth considering include time, skills, staff, specific training under experienced guidance, and availability of supporting technologies necessary to perform the ablation lesions sets and mapping. Barriers to implementing these recommendations were not explicitly discussed during the consensus conference, because of the broad range of contexts represented by the consensus panel, but these considerations should not be minimized when choosing to undertake surgical ablation as a routine procedure for eligible patients.^{48,52} Guidelines for personnel requirements and proficiencies should be consulted. These guidelines define consistent set of guidelines for follow-up and definitions of various endpoints related to the nonmedical treatment of AF.⁵¹

Future Directions

These consensus statements will need to be revisited and updated as the technique and technologies evolve and when further evidence on the benefits, harms, and resource implications becomes available. Research efforts should be fully encouraged to address the gaps in the evidence as outlined in the statement for further research given above. This consensus statement is not intended to provide false assurance in the current state of the evidence and prematurely

TABLE 4. Summary Consensus Recommendations

Class of Recommendation and Level of Evidence	ISMICS Consensus Recommendations
	In patients with persistent and permanent atrial fibrillation undergoing cardiac surgery, concomitant surgical ablation is recommended:
Class 1, level A	To increase incidence of sinus rhythm at short- and long-term follow-up
Class 2a; level A	To improve ejection fraction and exercise tolerance
Class 2a; level B	To reduce the risk of stroke and thromboembolic events and to improve long-term survival

suggest that the evidence is sufficient. The recommendations are based on currently available evidence, with the hope that there will be parallel developments in the evidence base alongside practice that aligns with these recommendations.

SUMMARY AND CONCLUSIONS

After review and discussion of the best available evidence, the following summary consensus recommendations were delineated (Table 4):

Given these statements, it was the prevailing opinion of the consensus panel members that:

In patients with persistent and permanent AF undergoing cardiac surgery, concomitant surgical ablation is recommended to increase incidence of sinus rhythm at short- and long-term follow-up (class 1, level A); to reduce the risk of stroke and thromboembolic events (class 2a, level B); to improve EF (class 2a, level A); and to exercise tolerance (class 2a, level A) and long-term survival (class 2a, level B).

Future Research Efforts Should Address

In general future research should be focused on adequately power prospective randomized trial to focus on efficacy and safety. Success rate should be reported according to the new guidelines and relevant topics such as survival, strokes/transient ischemic attacks, and medications. Studies should be longitudinal with long-term follow-up.

There are specific subgroups of patients such as the elderly and the low EF group of patients should be investigated in a more detailed and defined way. The different lesion set should be compared prospectively and so do the various techniques to manage the left atrial appendage. In the coming years, a special focus should be given to the different energy sources in use (cryotherapy, RFA ultrasound, cut-and-sew, etc) and to studies specifically designed to compare and discuss the relative role of surgical- versus catheter-based AF ablation.

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REFERENCES

- Turner T, Misso M, Harris C, Green S. Development of evidence-based clinical practice guidelines (CPGs): comparing approaches. *Implement Sci.* 2008;3:45.
- Michie S, Berentson-Shaw J, Pilling S, et al. Turning evidence into recommendations: protocol for a study of guideline development groups. *Implement Sci.* 2007;2:29.
- Straus SE, Richardson WS, Glasziou P, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach EBM.* 3rd ed. Edinburgh: Churchill Livingstone; 2005.
- Cheng DCH, Ad N, Martin J, et al. Surgical ablation for atrial fibrillation in cardiac surgery: a meta-analysis and systematic review. *Innovations.* 2010;5:84–96.
- Colditz GA, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy. I: medical. *Stat Med.* 1989;8:441–454.
- Milz S, Colditz GA, Mosteller F. How study design affects outcomes in comparisons of therapy. II: Surgical. *Stat Med.* 1989;8:455–466.
- Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet.* 1998;22:609–613.
- Schulz KF, Chalmer I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA.* 1995;273:408–412.
- Shekelle PG, Woolf SH, Eccles M, et al. Clinical guidelines: developing guidelines. *BMJ.* 1999;318:593–596.
- Abreu Filho CA, Lisboa LA, Dallan LA, et al. Effectiveness of the maze procedure using cooled-tip radiofrequency ablation in patients with permanent atrial fibrillation and rheumatic mitral valve disease. *Circulation.* 2005;112:120–125.
- Akpınar B, Gudun M, Sagbas E, et al. Combined radiofrequency modified maze and mitral valve procedure through a port access approach: early and mid-term results. *Eur J Cardiothorac Surg.* 2003;24:223–230.
- Blomstrom-Lundqvist C, Johansson B, Berglin E, et al. A randomized double-blind study of epicardial left atrial cryoablation for permanent atrial fibrillation in patients undergoing mitral valve surgery: the SWEDish multicentre atrial fibrillation study (SWEDMAF). *Eur Heart J.* 2007;28:2902–2908.
- de Lima GG, Kalil RA, Leiria TL, et al. Randomized study of surgery for patients with permanent atrial fibrillation as a result of mitral valve disease. *Ann Thorac Surg.* 2004;77:2089–2094, discussion 2094–2095.
- Deneke T, Khargi K, Grewe PH, et al. Efficacy of an additional MAZE procedure using cooled-tip radiofrequency ablation in patients with chronic atrial fibrillation and mitral valve disease. A randomized, prospective trial. *Eur Heart J.* 2002;23:558–566.
- Doukas G, Samani NJ, Alexiou C, et al. Left atrial radiofrequency ablation during mitral valve surgery for continuous atrial fibrillation: A randomized controlled trial. *JAMA.* 2005;294:2323–2329.
- Khargi K, Deneke T, Haardt H, et al. Saline-irrigated, cooled-tip radiofrequency ablation is an effective technique to perform the maze procedure. *Ann Thorac Surg.* 2001;72:S1090–S1095.
- Jessurun ER, van Hemel NM, Defauw JJ, et al. A randomized study of combining maze surgery for atrial fibrillation with mitral valve surgery. *J Cardiovasc Surg (Torino).* 2003;44:9–18.
- Schuetz A, Schulze CJ, Sarvanakis KK, et al. Surgical treatment of permanent atrial fibrillation using microwave energy ablation: a prospective randomized clinical trial. *Eur J Cardiothorac Surg.* 2003;24:475–480, discussion 480.
- Srivastava V, Kumar S, Javali S, et al. Efficacy of three different ablative procedures to treat atrial fibrillation in patients with valvular heart disease: a randomised trial. *Heart Lung Circ.* 2008;17:232–240.
- von Oppell UO, Masani N, O'Callaghan P, et al. Mitral valve surgery plus concomitant atrial fibrillation ablation is superior to mitral valve surgery alone with an intensive rhythm control strategy. *Eur J Cardiothorac Surg.* 2009;35:641–650.
- Bai BJ, Zhong ZH, Xin LP, et al. The clinical study of circumferential ablation around orifice of pulmonary vein by radiofrequency energy with chronic atrial fibrillation undergoing rheumatic valvular heart surgery. *Zhonghua Wai Ke Za Zhi.* 2006;44:946–948.
- Bando K, Kasegawa H, Okada Y, et al. Impact of preoperative and postoperative atrial fibrillation on outcome after mitral valvuloplasty for nonischemic mitral regurgitation. *J Thorac Cardiovasc Surg.* 2005;129:1032–1040.
- Bando K, Kobayashi J, Hirata M, et al. Early and late stroke after mitral valve replacement with a mechanical prosthesis: risk factor analysis of a 24-year experience. *J Thorac Cardiovasc Surg.* 2003;126:358–364.
- Bando K, Kobayashi J, Kosakai Y, et al. Impact of Cox maze procedure on outcome in patients with atrial fibrillation and mitral valve disease. *J Thorac Cardiovasc Surg.* 2002;124:575–583.
- Chen MC, Chang JP, Guo GB, Chang HW. Atrial size reduction as a predictor of the success of radiofrequency maze procedure for chronic atrial fibrillation in patients undergoing concomitant valvular surgery. *J Cardiovasc Electrophysiol.* 2001;12:867–874.
- Damiano RJ Jr, Gaynor SL, Bailey M, et al. The long-term outcome of patients with coronary disease and atrial fibrillation undergoing the Cox maze procedure. *J Thorac Cardiovasc Surg.* 2003;126:2016–2021.
- Forlani S, De Paulis R, Guerrieri Wolf L, et al. Conversion to sinus rhythm by ablation improves quality of life in patients submitted to mitral valve surgery. *Ann Thorac Surg.* 2006;81:863–867.
- Gaita F, Gallotti R, Calo L, et al. Limited posterior left atrial cryoablation in patients with chronic atrial fibrillation undergoing valvular heart surgery. *J Am Coll Cardiol.* 2000;36:159–166.
- Guang Y, Zhen-jie C, Yong LW, et al. Evaluation of clinical treatment of atrial fibrillation associated with rheumatic mitral valve disease by radiofrequency ablation. *Eur J Cardiothorac Surg.* 2002;21:249–254.
- Handa N, Schaff HV, Morris JJ, et al. Outcome of valve repair and the Cox maze procedure for mitral regurgitation and associated atrial fibrillation. *J Thorac Cardiovasc Surg.* 1999;118:628–635.
- Itoh T, Okamoto H, Nimi T, et al. Left atrial function after Cox's maze operation concomitant with mitral valve operation. *Ann Thorac Surg.* 1995;60:354–359, discussion 359–360.
- Jatene MB, Marcial MB, Tarasoutchi F, et al. Influence of the maze procedure on the treatment of rheumatic atrial fibrillation—evaluation of rhythm control and clinical outcome in a comparative study. *Eur J Cardiothorac Surg.* 2000;17:117–124.
- Johansson B, Houltz B, Berglin E, et al. Short-term sinus rhythm predicts long-term sinus rhythm and clinical improvement after intraoperative ablation of atrial fibrillation. *Europace.* 2008;10:610–617.
- Kawaguchi AT, Kosakai Y, Sasako Y, et al. Risks and benefits of combined maze procedure for atrial fibrillation associated with organic heart disease. *J Am Coll Cardiol.* 1996;28:985–990.
- Kim HK, Kim YJ, Kim KI, et al. Impact of the maze operation combined with left-sided valve surgery on the change in tricuspid regurgitation over time. *Circulation.* 2005;112:114–119.
- Knaut M, Tugtekin SM, Matschke K. Pulmonary vein isolation by microwave energy ablation in patients with permanent atrial fibrillation. *J Card Surg.* 2004;19:211–215.
- Kobayashi J, Kosakai Y, Isobe F, et al. Rationale of the Cox maze procedure for atrial fibrillation during redo mitral valve operations. *J Thorac Cardiovasc Surg.* 1996;112:1216–1221, discussion 1222.
- Kobayashi J, Sasako Y, Bando K, et al. Eight-year experience of combined valve repair for mitral regurgitation and maze procedure. *J Heart Valve Dis.* 2002;11:165–171, discussion 171–172.
- Louagie Y, Buche M, Eucher P, et al. Improved patient survival with concomitant Cox maze III procedure compared with heart surgery alone. *Ann Thorac Surg.* 2009;87:440–446.
- Mantovan R, Raviele A, Buja G, et al. Left atrial radiofrequency ablation during cardiac surgery in patients with atrial fibrillation. *J Cardiovasc Electrophysiol.* 2003;14:1289–1295.
- Myrdko T, Sniezek-Maciejewska M, Rudzinski P, et al. Efficacy of intra-operative radiofrequency ablation in patients with permanent atrial fibrillation undergoing concomitant mitral valve replacement. *Kardiologia Pol.* 2008;66:932–938, discussion 939–940.
- Patwardhan AM, Dave HH, Tamhane AA, et al. Intraoperative radiofrequency microbipolar coagulation to replace incisions of maze III procedure for correcting atrial fibrillation in patients with rheumatic valvular disease. *Eur J Cardiothorac Surg.* 1997;12:627–633.
- Raanani E, Albage A, David TE, et al. The efficacy of the Cox/maze procedure combined with mitral valve surgery: a matched control study. *Eur J Cardiothorac Surg.* 2001;19:438–442.
- Tuinenburg AE, Van Gelder IC, Tieleman RG, et al. Mini-maze suffices as adjunct to mitral valve surgery in patients with preoperative atrial fibrillation. *J Cardiovasc Electrophysiol.* 2000;11:960–967.

45. Yuda S, Nakatani S, Kosakai Y, et al. Mechanism of improvement in exercise capacity after the maze procedure combined with mitral valve surgery. *Heart*. 2004;90:64–69.
46. Gammie JS, Haddad M, Milford-Feland S, et al. Atrial fibrillation correction surgery: lessons from the Society of Thoracic Surgeons National Cardiac Database. *Ann Thorac Surg*. 2008;85:909–914.
47. Shemin RJ, Cox JL, Gillinov AM, et al. Guidelines for reporting data and outcomes for the surgical treatment of atrial fibrillation. *Ann Thorac Surg*. 2007;83:1225–1230.
48. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257–e354.
49. Appraisal of Guidelines RaEiEACG. Guideline development in Europe. An international comparison. *Int J Technol Assess Health Care*. 2000; 16:1039–1049.
50. Cluzeau FA, Littlejohns P, Grimshaw JM, et al. Development and application of a generic methodology to assess the quality of clinical guidelines. *J Qual Health Care*. 1999;11:21–28.
51. European Heart Rhythm Association (EHRA); European Cardiac Arrhythmia Society (ECAS); American College of Cardiology (ACC); American Heart Association (AHA); Society of Thoracic Surgeons (STS), Calkins H, Brugada J, Paker 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. *Heart Rhythm*. 2007;4:816–861.
52. Ad N. How do we spell maze? A dialogue concerning definitions and goals. *J Thorac Cardiovasc Surg*. 2006;132:1253–1255.