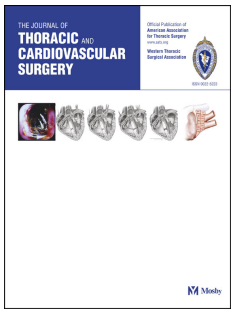
Accepted Manuscript



Expert Consensus Guidelines: Examining Surgical Ablation for Atrial Fibrillation

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PII: S0022-5223(17)30372-0

DOI: 10.1016/j.jtcvs.2017.02.027

Reference: YMTC 11275

To appear in: *The Journal of Thoracic and Cardiovascular Surgery*

Received Date: 21 December 2016

Revised Date: 27 January 2017

Accepted Date: 1 February 2017

Please cite this article as: Ad N, Damiano Jr RJ, Badhwar V, Calkins H, La Meir M, Nitta T, Holmes SD, Weinstein AA, Gillinov M, Expert Consensus Guidelines: Examining Surgical Ablation for Atrial Fibrillation, *The Journal of Thoracic and Cardiovascular Surgery* (2017), doi: 10.1016/j.jtcvs.2017.02.027.

Expert Consensus Guidelines: Examining Surgical Ablation for Atrial Fibrillation

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Word count: 8,967

Conflicts of Interest: Dr. Ad is a consultant for Medtronic, a member of the speaker's bureau for AtriCure, proctor and member of the speaker's bureau for LivaNova, on the advisory board for Nido Surgical, and co-owner for Left Atrial Appendage Occlusion, LLC. Disclosures of all other authors were made directly to the AATS Office and will be included in the JTCVS Disclosure Forms uploaded at the time of revision.

Source of Funding: No outside funding was received for this study.

Glossary of Abbreviations

AAD	antiarrhythmic drugs
AATS	American Association for Thoracic Surgery
ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
ATA	atrial tachyarrhythmias
DSWI	deep sternal wound infection
ICU	intensive care unit
LA	left atrium
LAA	left atrial appendage
LOS	length of stay
MCS	mental composite score
PCS	physical composite score
PVI	pulmonary vein isolation
RCT	randomized controlled trial
RF	radiofrequency
SF-12/SF-36	Medical Outcomes Study Short Form Health Survey
TIA	transient ischemic attack

Executive Summary

Research Question 1: Does concomitant surgical ablation for atrial fibrillation increase the incidence of perioperative morbidity?

Recommendation #1. Addition of a concomitant surgical ablation procedure for atrial fibrillation does not increase incidence of perioperative morbidity.

Class IIa: It is reasonable to choose to perform a concomitant surgical ablation procedure for patients with a history of atrial fibrillation over no treatment of atrial fibrillation because the incidence of perioperative morbidity is not increased by surgical ablation.

Level of Evidence:

- Level A for deep sternal wound infection, pneumonia, reoperation for bleeding, and renal failure requiring dialysis
- Level B-R for ICU length of stay and total hospital length of stay
- Level B-NR for readmission <30 days and renal failure

Research Question #2A: Does concomitant surgical ablation for atrial fibrillation reduce the incidence of early stroke/transient ischemic attack (TIA)?

Recommendation #2. Addition of a concomitant surgical ablation procedure for atrial fibrillation does not change the incidence of early stroke/TIA.

Class IIa: It is reasonable to choose to perform a concomitant surgical ablation procedure for patients with a history of atrial fibrillation over no treatment of atrial fibrillation because there is no increased risk of early stroke/TIA.

Level of Evidence: Level A

Research Question #2B. Does concomitant surgical ablation for atrial fibrillation reduce the incidence of late stroke/TIA?

Recommendation #3. Overall, addition of a concomitant surgical ablation procedure for atrial fibrillation does not change the incidence of late stroke/TIA, but subgroup analysis of non-randomized controlled trials (RCTs) found a significant reduction in late stroke/TIA incidence.

Class IIa: It is reasonable to choose to perform a concomitant surgical ablation procedure for patients with a history of atrial fibrillation over no treatment of atrial fibrillation because the incidence of late stroke/TIA is unaffected or decreased by surgical ablation.

Level of Evidence:

- Level A for no change in incidence of late stroke/TIA (up to 1 year of follow-up after surgery)
- Level B-NR for reduction in incidence of late stroke/TIA (>1 year of follow-up after surgery)

Research Question #3. Does concomitant surgical ablation for atrial fibrillation improve health-related quality of life and atrial fibrillation (AF)-related symptoms?

Recommendation #4. A surgical procedure that includes concomitant surgical ablation for AF does improve health-related quality of life, but this improvement is similar to that observed in patients who undergo cardiac surgery without surgical ablation. Addition of concomitant surgical ablation for atrial fibrillation does improve AF-related symptoms and this improvement is greater than in patients without surgical ablation.

Class IIa: It is reasonable to choose to perform a concomitant surgical ablation procedure for patients with a history of AF over no treatment of atrial fibrillation because there is significant improvement in health-related quality of life and AF-related symptoms associated with surgical ablation.

Level of Evidence:
- Level B-R for health-related quality of life
- Level C-LD for AF-related symptoms

Research Question #4A: Does concomitant surgical ablation for atrial fibrillation improve short-term survival?

Recommendation #5. Addition of concomitant surgical ablation for atrial fibrillation does improve 30-day operative mortality.

Class I: It is recommended to choose to perform a concomitant surgical ablation procedure for patients with a history of atrial fibrillation over no treatment of atrial fibrillation because there is significant improvement in operative survival associated with surgical ablation.

Level of Evidence: Level A

Research Question #4B: Does concomitant surgical ablation for atrial fibrillation improve long-term survival (>30 days)?

Recommendation #6. Overall, addition of a concomitant surgical ablation procedure for atrial fibrillation improves long-term survival, but subgroup analysis of RCTs found no significant improvement.

Class IIa: It is reasonable to choose to perform a concomitant surgical ablation procedure for patients with a history of atrial fibrillation over no treatment of atrial fibrillation because long-term survival is unaffected or improved by surgical ablation.

Level of Evidence:

- Level A for no change in long-term survival (up to 1 year after surgery)
- Level B-NR for improvement in long-term survival (>1 year after surgery)

Research Question #5: What are the indications for a hybrid ablation or stand alone off-pump epicardial ablation in patients with atrial fibrillation?

Recommendation #7. Overall, hybrid procedures have shown promising results compared to percutaneous catheter ablation in a subgroup of symptomatic patients with AF in which medical treatment and/or percutaneous catheter ablation have failed.

Class IIb: Hybrid procedures may be considered as a stand alone procedure in patients with appropriate indications and by an experienced heart team.

Level of Evidence: Level B-NR

Recommendation #8. Overall, minimally invasive approaches to isolate the pulmonary veins bilaterally have shown promising results compared to percutaneous catheter ablation in a subgroup of symptomatic patients with paroxysmal AF and a small left atrium in which medical treatment and/or percutaneous catheter ablation have failed.

Class IIa: It is reasonable to perform stand alone surgical ablation for pulmonary vein isolation in patients with symptomatic paroxysmal AF and small left atria.

Level of Evidence: Level B-R

Research Question #6: Which surgical ablation devices are associated with reliable transmural lesions?

Recommendation #9. The best evidence exists for the use of bipolar radiofrequency clamps and cryoablation devices, which have become integral parts of many procedures including pulmonary vein isolation and the Cox maze IV procedure. The use of epicardial unipolar radiofrequency ablation outside of clinical trials is not recommended, as its efficacy remains questionable.

a. Empty arrested or beating heart: recommended ablation devices for pulmonary vein isolation are bipolar radiofrequency clamps or reusable/disposable cryoprobes
b. Beating heart: bipolar radiofrequency clamps are effective to isolate pulmonary veins and recommended with mandatory testing for exit and/or entrance block
c. Beating heart: surface bipolar radiofrequency devices may be recommended for free wall linear ablation when lesion integrity can be tested and multiple applications are recommended to achieve adequate lesion depth
d. Beating heart: epicardial cryoablation is not recommended, but endocardial cryoablation is recommended for free wall linear ablation due to the high degree of transmurality
e. Clinical trials of hybrid procedures: only settings where epicardial unipolar radiofrequency devices may be applied provided it is accompanied by acute lesion integrity testing
f. When ablating with any device, coronary arteries should be identified and avoided

Research Question #7: What is the impact of surgeon experience with surgical ablation on return to sinus rhythm in patients with AF?

Recommendation #10. Training and education should be completed prior to the performance of surgical ablation. We highly recommend surgeons that are new to surgical AF be proctored by an experienced surgeon for 3-5 cases prior to performing surgical ablation alone.

Class I: Training and education should be considered prior to the performance of surgical ablation, but the effectiveness of a training program is unclear. More specific research needs to be conducted since there have been very limited populations evaluated.

Level of Evidence: Level C

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INTRODUCTION

The surgical treatment for atrial fibrillation is well established and performed. Atrial fibrillation (AF) is being treated as a stand alone procedure or concomitantly with valve, coronary bypass or other types of cardiac surgical procedures. This document was put together to serve as guidelines and provide recommendations related to the general outcomes associated with surgical ablation, the state of hybrid procedures, the optimal ablation tools available and recommendations for the appropriate education and training of surgeons in the field.

The Cox-Maze procedure was first performed in 1987 by Dr. James L. Cox and the report summarizing the experience with the Cox-Maze I procedure was published in 1991[1]. The original Cox-Maze was performed as a cut and sew procedure combined with focal cryoablations both in the right and the left atrium and evolved from the Cox-Maze I to III to address issues with sinus node function and right to left atrial conduction that resulted from the Cox-Maze I[2]. The Cox-Maze III procedure was then applied extensively in clinical practice[3].

Several modifications to the original lesion set have been introduced as well as the introduction of surgical ablation tools that utilize different energy sources (Figure 1)[4,5]. These different energy sources were applied both to perform lesion sets confined to the left atrium pulmonary vein isolation only or more extensive lesion set) or a full right and left atrial lesion set[6–8]. Despite the proven success of the Cox-Maze procedure and surgical ablation, referring general surgeons and physicians remain somewhat reluctant to adopt the procedure. A clear difference was documented for surgeon experience in the percent of AF patients treated concomitantly during cardiac surgical procedures[9]. The explanation for such a unique phenomenon in the surgical practice is not easy, but can probably be attributed to the perceived risk associated with the procedure, the level of training of the surgeons, and the lack of recognition of the clinical importance of atrial fibrillation.

These AATS guidelines are focused less on the efficacy of surgical ablation and more on the surgical outcomes, both short and long term. We also addressed the hybrid surgical ablation procedures that are performed together by electrophysiologists and cardiac surgeons. These new procedures may add to our ability to treat AF patients successfully.

It is clear that the success of any ablation procedure is dependent on the lesion pattern and the quality of the lesion. Surgeons should be familiar with the different lesion set options, and the efficacy of the ablation tool in use.

The AATS committee was tasked with the following:

I. To present a current analysis of the published literature and present a balanced view.
II. To provide evidence based clinical practice recommendations.
III. To address the quality and the effectiveness of the different energy sources.
IV. To discuss the education and the training requirement for surgeons that are

performing surgical ablation procedures

PREAMBLE

Our mission was to develop evidence-based guidelines on surgical ablation for the treatment of atrial fibrillation. Ten experts were invited by the American Association for Thoracic Surgery (AATS) leadership to participate in this effort: 6 cardiac surgeons, 1 electrophysiologist, and 2 biostatisticians.

Methods of Review

Members were tasked with making recommendation based on a review of the literature and meta-analyses of the literature (if it was possible). The task force panel graded the class of recommendation and the level of evidence for each of the research questions/recommendations according to the standards published by the Institute of Medicine. The five different classes of recommendation are: Class I (strong), IIa (moderate), IIb (weak), III (no benefit, moderate), and Class III (harm, strong). The five levels of evidence are: Level A, B-R (randomized), B-NR (non-randomized), C-LD (limited data), and Level C-EO (expert opinion).

Meta-analyses were conducted to investigate the four research questions within Aim 1 (safety and efficacy of surgical ablation). Relevant studies were identified through an electronic search of PubMed using comprehensive search terms for each of the relevant study questions (Supplemental Table 1). Reference lists of selected articles were reviewed for other potentially relevant citations as needed. The study period was confined to January 2000 through December 2015. Inclusion criteria comprised studies with concomitant surgical ablation procedures (full lesion set or limited) in the adult human population and a comparison group present. Only English language studies were included. There were no criteria limiting the type of lesion set performed or energy source used. Therefore, the included studies were variable on these components of surgical ablation.

For Research Question 1 (“Does concomitant surgical ablation for atrial fibrillation increase the incidence of perioperative morbidity?”) the outcome was operationalized as complications, excluding stroke and mortality within 30 days of surgery as these outcomes were examined in separate research questions. The following complications were included: deep sternal wound infection (DSWI), pneumonia, reoperation for bleeding, renal failure, renal failure requiring dialysis, readmission < 30 days, length of stay (LOS) in the intensive care unit (ICU), and total hospital LOS. A total of 905 studies were identified from the original PubMed search, of which 300 were reviewed in depth for inclusion, and 27 studies ultimately met all inclusion criteria[10–36]. The remaining 273 studies were excluded due to no comparison group (n = 245), case report (n = 7), no outcome data (n = 17), or duplicate data from the same investigators (n = 4).

For Research Question 2 ("Does concomitant surgical ablation for atrial fibrillation impact the incidence of early and late stroke/TIA?") the outcome was separated into early (in-hospital or <30 days) stroke and late or follow-up stroke. A total of 614 studies were identified through the PubMed search and an additional 20 studies were identified through review of reference lists of other articles. Of these studies, 87 were reviewed in depth for inclusion, and 20 ultimately met all inclusion criteria[13,18,22–24,26–28,30–33,35–42]. The remaining 67 studies were excluded due to no comparison group (n = 23), catheter ablation rather than surgical ablation (*n* = 17), duplicate data (*n* = 10), no ablation (*n* = 7), reviews (*n* = 6), and no outcome data (*n* = 4).

For Research Question 3 ("Does concomitant surgical ablation for atrial fibrillation improve health-related quality of life and AF-related symptoms?"), a standard meta-analysis was not feasible due to heterogeneity in methods, postoperative time points, and measures among studies. Therefore, a systematic review of the relevant studies was undertaken instead, which also allowed for inclusion of studies with no comparison group on these outcomes. From a total of 222 studies found through a PubMed search, 9 studies were selected for inclusion in the systematic review[10,24,33,39,43–47]. These included 4 RCT studies, 2 non-RCT studies, and 3 studies with no control group. All studies examined HRQL and 4 of the studies also investigated symptom status.

For Research Question 4 ("Does concomitant surgical ablation for atrial fibrillation improve perioperative and long-term survival?") the outcome was separated into short-term (<30 days) and long-term (≥12 months) mortality. A total of 905 studies were identified from the original PubMed search, of which 300 were reviewed in depth for inclusion, and 38 studies ultimately met all inclusion criteria[10–20,22–36,40,42,48–57]. The remaining 262 studies were excluded due to no comparison group (*n* = 245), case report (*n* = 7), no outcome (*n* = 6), or duplicate data from the same investigators (*n* = 4).

All meta-analyses were conducted using Comprehensive Meta-Analysis Version 2.2.064 (Biostat, Inc., Englewood, NJ). Effect sizes were able to be generated from studies with various outcome data presentations in order to combine the most studies possible for each question. Heterogeneity for each outcome was tested using Cochran's Q value and the I^2 statistic. Analyses with significant levels of heterogeneity were conducted using random effects models whereas all other analyses were conducted using fixed effects modeling. Forest plots were generated for each outcome and separately for RCT and non-RCT studies when necessary, which was identified as the most common source of heterogeneity for these analyses.

For Aims 2, 3, and 4, meta-analyses were not possible based on the current state of the literature. For these aims, literature summaries were conducted for each respective aim. Aim 3, which focuses on the evidence for devices, will not have class or level of evidence because the literature is based on animal data and is too unique for systematic combination. Then these summaries were submitted for full task force review and consideration. A consensus among the task force members was achieved prior to the adoption of the recommendations.

A final draft was prepared by authors N.A. and S.D.H. and this written draft was distributed to all members of the task force for final comments.

The following recommendations are based on the best available evidence from ablation surgery literature. This literature is relatively small in some areas and at those points, expert opinion was substituted for research literature in order to make recommendations. The recommendations are classified according to the AHA/ACC scheme[58] (Figure 2) and a summary of each can be found in Table 1.

Target Audience and the Patient Population

These guidelines are intended for cardiothoracic surgeons operating on patients with atrial fibrillation, as well as cardiologists and electrophysiologists who refer patients for surgical intervention.

EPIDEMIOLOGY OF ATRIAL FIBRILLATION, ITS IMPACT ON OUTCOMES, COST, AND MORBIDITY

Atrial fibrillation currently affects approximately 2.2 million patients in the United States and this figure is projected to at least double in the next 25 years[59]. Approximately, 2% of those younger than age 65 have atrial fibrillation, while that number increases to about 9% with those older than age 65[60]. African-Americans are less likely to experience atrial fibrillation than those of European descent.

Atrial fibrillation has a direct relationship to mortality and increased morbidity, especially for risk of stroke. Specifically, atrial fibrillation is associated with 1.5 to 1.9 increase in mortality risk, even after adjustment for many potential confounding variables including pre-existing cardiovascular conditions[61]. The age-adjusted incidence of stroke is five times greater when atrial fibrillation is present[62]. Hospitalizations with atrial fibrillation as the primary diagnosis exceed 460,000 each year and the hospitalization is the primary cost driver in the management of atrial fibrillation[63]. Medical costs are much higher (73% higher) in those with atrial fibrillation than in matched individuals without atrial fibrillation with approximately 6 billion dollars in medical costs spent on atrial fibrillation-related costs alone[63].

RECOMMENDATIONS AND REASONING

AIM 1. Safety and Efficacy of Surgical Ablation

Research Question 1: Does concomitant surgical ablation for atrial fibrillation increase the incidence of perioperative morbidity?

Recommendation #1.
Addition of a concomitant surgical ablation procedure for atrial fibrillation does not increase incidence of perioperative morbidity (Class IIa, Level A for deep sternal wound infection, pneumonia, reoperation for bleeding, and renal failure requiring dialysis, Level B-R for ICU length of stay and total hospital length of stay, and Level B-NR for readmission <30 days and renal failure).

Reasoning

Overall, the current literature demonstrates decreased incidence of perioperative morbidity, including reduced incidence of pneumonia in the perioperative time frame and decreased lengths of stay in the ICU. When exclusively examining RCTs, it was also found that total length of stay was increased with concomitant surgical ablation.

The meta-analysis for Research Question #1 investigated the potential increase in morbidity in concomitant surgical ablation examining the following outcome variables: pneumonia, deep sternal wound infection, length of stay in the ICU, total hospital stay, readmissions within 30 days, reoperation for bleeding, renal failure, and renal failure requiring dialysis. The evidence from this meta-analysis indicates that the only perioperative morbidity significantly associated with concomitant surgical ablation for atrial fibrillation was reduced incidence of pneumonia in the perioperative time frame (OR = 0.474, 95% CI = 0.262–0.857, $P = 0.013$; Figure 3). In fact, the surgical ablation group had 53% reduced odds for perioperative pneumonia. With 5 RCT and 3 non-RCT studies included in this analysis and no significant heterogeneity identified (I^2 = 12.621%, Q = 8.011, $P = 0.332$), the level of evidence is fairly strong to indicate that there is a benefit for the perioperative outcome of pneumonia associated with performing a concomitant surgical ablation procedure.

The evidence in this group of studies that met inclusion criteria showed no significant increase or reduction in the incidence of all other perioperative morbidities assessed, which included deep sternal wound infection (Figure 4), length of stay in the ICU (Figure 5), total hospital length of stay (Figure 6), readmissions within 30 days (Figure 7), reoperation for bleeding (Figure 8), renal failure (Figure 9), and renal failure requiring dialysis (Figure 10). The sample size was highest for reoperation for bleeding (n = 15) and total length of stay (n = 14) and lowest for readmissions within 30 days (n = 2), with all other analyses ranging from sample sizes of 4 to 9 studies. Publication bias was found to be low for pneumonia, deep sternal wound infection, reoperation for bleeding, renal failure, and renal failure requiring dialysis; moderate for ICU length of stay and total length of stay; undetermined for readmissions within 30 days due to small sample size.

The analyses of ICU length of stay (I^2 = 79.118%, Q = 38.311, $P < 0.001$) and total hospital length of stay (I^2 = 76.952%, Q = 56.404, $P < 0.001$) were the only two with a significant level of heterogeneity present and therefore the random effects results are reported. The fixed effects model results indicated a significant reduction in ICU and total length of stay associated with performing a concomitant surgical ablation procedure. It appears that separating the analyses by RCT and non-RCT studies shows a more consistent result in the length of stay outcomes for the RCT study subgroup analyses,

whereas more heterogeneity exists within the non-RCT study subgroup analyses. Within the RCT study subgroup analyses, ICU length of stay was reduced with a concomitant surgical ablation procedure (OR = 0.566, 95% CI = 0.346–0.925, *P* = 0.023), whereas total length of stay was increased with a concomitant surgical ablation procedure (OR = 1.452, 95% CI = 1.115–1.890, *P* = 0.006).

Research Question #2A: Does concomitant surgical ablation for atrial fibrillation reduce the incidence of early stroke/transient ischemic attack (TIA)?

Recommendation #2.
Addition of a concomitant surgical ablation procedure for atrial fibrillation does not change the incidence of early stroke/TIA (Class IIa, Level A).

Reasoning

The current literature demonstrates neither increase nor decrease of incidence of early stroke/TIA. Specifically, the meta-analysis indicates that there is no increase in the incidence of early stroke/TIA for surgical ablation (OR = 0.463, 95% CI = 0.212–1.011, *P* = 0.053; Figure 11). In fact, this combined effect appears to indicate that surgical ablation actually decreases the incidence of perioperative stroke/TIA, but the analysis did not reach statistical significance. Publication bias was found to be low for this analysis. With 6 RCT and 6 non-RCT studies included in this analysis, the level of evidence is fairly strong to indicate there is no perioperative safety issue, in regards to stroke/TIA, associated with performing a concomitant surgical ablation procedure.

Research Question #2B. Does concomitant surgical ablation for atrial fibrillation reduce the incidence of late stroke/TIA?

Recommendation #3.
Overall, addition of a concomitant surgical ablation procedure for atrial fibrillation does not change the incidence of late stroke/TIA, but subgroup analysis of non-randomized controlled trials (RCTs) found a significant reduction in late stroke/TIA incidence (Class IIa, Level A for no change in incidence of late stroke/TIA for up to 1 year of follow-up after surgery and
Level B-NR for reduction in incidence of late stroke/TIA greater than1 year of follow-up after surgery).

Reasoning

The overall evidence from a meta-analysis conducted to examine the incidence of late stroke/TIA following concomitant surgical ablation indicates that there is no significant decrease (or increase) in the incidence of late stroke/TIA for surgical ablation (OR = 0.505, 95% CI = 0.211–1.208, *P* = 0.125; Figure 12). However, further analyses found a significant level of heterogeneity present for the follow-up stroke/TIA analysis (I^2 = 48.29%, Q = 19.337, *P* = 0.036). Therefore, subgroup analyses by duration of follow-up were performed to evaluate this heterogeneity further. This research question was then examined separately for RCT and non-RCT studies because it was noted that all 6 RCT studies included a 12 month follow-up period, whereas the 5 non-RCT studies included varying follow-up time periods, but all were longer than 12 months. The RCT studies

showed a consistent pattern with no decrease in follow-up stroke/TIA incidence associated with surgical ablation during the first 12 months after surgery (OR = 1.014, 95% CI = 0.413–2.492, *P* = 0.976; Figure 13A). Conversely, the meta-analysis of non-RCT studies showed a significantly lower incidence of follow-up stroke/TIA for the patients with surgical ablation (OR = 0.269, 95% CI = 0.078–0.926, *P* = 0.037; Figure 13B). Neither subgroup analysis was found to have a significant level of heterogeneity, but the non-RCT analysis did show more heterogeneity than the RCT analysis, likely due to the varying follow-up time still present within the non-RCT analysis. Publication bias was found to be moderate for this outcome.

Research Question #3. Does concomitant surgical ablation for atrial fibrillation improve health-related quality of life and AF-related symptoms?

Recommendation #4.
A surgical procedure that includes concomitant surgical ablation for atrial fibrillation does improve health-related quality of life, but this improvement is similar to that observed in patients who undergo cardiac surgery without surgical ablation. Addition of concomitant surgical ablation for atrial fibrillation does improve AF-related symptoms and this improvement is greater than in patients without surgical ablation. (Class IIa, Level B-R for health-related quality of life and Level C-LD for AF-related symptoms).

Reasoning

Overall, the current literature demonstrates that surgical ablation patients have comparable improvements in HRQL post-surgery, as well as comparable post-surgery levels of HRQL. For AF-specific symptoms and AF-reported symptom frequency and severity after surgery, surgical ablation patients demonstrated more positive improvements than patients without surgical ablation.

Specifically, the evidence from the systematic review focusing on HRQL indicates that when measured before and after surgery, cardiac surgery with surgical ablation can improve HRQL, but these changes are similar for cardiac surgery patients without surgical ablation. When measured only after surgery, patients with and without surgical ablation can expect to report similar levels of HRQL.

All 4 RCT studies used a version of the Medical Outcomes Study Short Form Health Survey (SF-12 or SF-36) to measure HRQL. Two studies included preoperative and postoperative HRQL measures. Von Oppell and colleagues found that 5 of the 8 SF-36 subscale scores improved significantly between preoperative and postoperative measures, but improvement was similar between treatment groups. Similarly, Jessurun and colleagues found significant improvement from preoperative to postoperative measures on 2 of the 8 SF-36 subscales in patients with surgical ablation, but the group without surgical ablation also showed improvement in 2 of the 8 SF-36 subscales. The other two studies included postoperative HRQL measures only. Gillinov and colleagues found no significant difference in SF-12 mental composite score (MCS) or physical composite score (PCS) at 1 year after surgery between patients with and without surgical ablation. The study by Forlani and colleagues found that patients who underwent surgical ablation

were more likely to be in the "Good Quality of Life" group than the "Poor Quality of Life" group after surgery, but there were no analyses of the raw SF-36 scores by treatment group.
Both non-randomized controlled studies used matching techniques to select the control groups. The results from these studies were comparable to the RCT studies. In the study by Ad and colleagues, improvement in SF-12 PCS and MCS from preoperative to 6 months postoperative was similar for patients with and without surgical ablation. In addition, the study by Johansson and colleagues found no significant difference on any SF-36 scores between patients with and without surgical ablation when measured at long-term follow-up after surgery.

In the 3 studies that did not include a control group, the results showed a consistent message to the other controlled studies. Ad and colleagues found significant improvement from preoperative to 1 year postoperative in SF-12 PCS and MCS whereas Bakker and colleagues found no significant difference between their study sample and general population normal values in any of the SF-36 subscales at follow-up after surgery. The study by Grubitzsch and colleagues examined HRQL differently using the Minnesota Living with Heart Failure Questionnaire and comparisons by CHF and rhythm status after surgery. Patients with severe CHF who regained sinus rhythm after surgery had lower MLHF total score and MLHF physical component score compared to patients who did not regain SR, but no effect of rhythm status was found for patients with moderate CHF.

In contrast to the HRQL results, the evidence from this systematic review indicates that cardiac surgery with surgical ablation is associated with improvement in reported AF-specific symptoms and reduced AF-related symptom frequency and severity after surgery compared to patients without surgical ablation. Four studies examined the outcome of symptom status, mostly those specific to AF. The RCT by Gillinov and colleagues found that surgical ablation patients reported a significantly lower frequency of AF at 1 year after surgery compared to patients without surgical ablation. In a non-randomized controlled study, Johansson and colleagues found that severity but not frequency of AF-specific symptoms was lower in the surgical ablation group compared to the control group when measured at long-term follow-up. Similarly, in the study by Ad and colleagues without a control group, the frequency and severity of AF-specific symptoms decreased significantly from preoperative to 6 months postoperative. Using a different measure of symptoms, the RCT by Jessurun and colleagues found that patient-reported change in health was significantly improved from preoperative to 3 months after surgery in patients both with and without surgical ablation, but only the patients with surgical ablation had further significant improvement from 3 months to 12 months after surgery.

Research Question #4A: Does concomitant surgical ablation for atrial fibrillation improve operative survival (<30 days)?

Recommendation #5.
Addition of concomitant surgical ablation for atrial fibrillation does improve 30-day operative mortality (Class I, Level A).

Reasoning

The evidence indicates that surgical ablation is associated with improved survival in the perioperative time frame (OR = 0.643, 95% CI = 0.464–0.890, *P* = 0.008; Figure 14). In fact, the surgical ablation group had 36% reduced odds for perioperative mortality. With 10 RCT and 14 non-RCT studies included in this analysis, no heterogeneity identified (I^2 = 0%, Q = 18.135, *P* = 0.750), and low publication bias, the level of evidence is fairly strong to indicate that there is a benefit for short-term survival associated with performing a concomitant surgical ablation procedure.

Research Question #4B: Does concomitant surgical ablation for atrial fibrillation improve long-term survival (>30 days)?

> **Recommendation #6.**
> Overall, addition of a concomitant surgical ablation procedure for atrial fibrillation improves long-term survival, but subgroup analysis of RCTs found no significant improvement (Class IIa, Level A for no change in long-term survival of up to 1 year after surgery and Level B-NR for improvement in long-term survival of greater than 1 year after surgery).

Reasoning

The overall evidence indicates that there is a significant improvement in long-term survival for surgical ablation (OR = 0.486, 95% CI = 0.355–0.665, *P* < 0.001; Figure 15). However, further analyses found a significant level of heterogeneity present for the long-term survival analysis (I^2 = 40.41%, Q = 45.306, *P* = 0.015). Therefore, subgroup analyses by study design were performed to evaluate this heterogeneity further. Research Question 4B was examined separately for RCT and non-RCT studies because it was noted that all except for 3 of the 15 RCT studies included a 12-month follow-up period, whereas the 13 non-RCT studies included varying follow-up time periods, but all include more than 12 months of follow-up. The RCT studies showed a consistent pattern with no significant improvement in long-term survival associated with surgical ablation during approximately the first 12 months after surgery (OR = 0.910, 95% CI = 0.588–1.410, *P* = 0.673; Figure 16A). Conversely, the meta-analysis of non-RCT studies showed a significant improvement in long-term survival with concomitant surgical ablation (OR = 0.360, 95% CI = 0.248–0.522, *P* < 0.001; Figure 16B). The RCT analysis did not have significant heterogeneity (I^2 = 0%, *P* = 0.885), but the non-RCT analysis did identify significant heterogeneity (I^2 = 50.91%, *P* = 0.018), likely due to the varying follow-up times still present within the non-RCT analysis. Publication bias was found to be moderate for this outcome.

AIM 2. Indications for Surgical Ablation Using Hybrid Approaches

Research Question #5: What are the indications for a hybrid ablation or stand alone off-pump epicardial ablation in patients with atrial fibrillation?

Recommendation #7.
Overall, hybrid procedures have shown promising results compared to percutaneous catheter ablation in a subgroup of symptomatic patients with AF in which medical treatment and/or percutaneous catheter ablation have failed (Class IIb, Level B-NR).

Recommendation #8.
Overall, minimally invasive approaches to isolate the pulmonary veins bilaterally have shown promising results compared to percutaneous catheter ablation in a subgroup of symptomatic patients with paroxysmal AF and a small left atrium in which medical treatment and/or percutaneous catheter ablation have failed (Class IIa, Level B-R).

Reasoning

The improvement of ablation technology makes surgical approaches in patients with stand-alone atrial fibrillation less invasive. The hybrid AF surgical ablation procedure is defined, in the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, as a joint AF ablation procedure that is either a part of a single "joint" procedure or performed as two pre-planned separate ablation procedures separated by no more than six months of time[64]. Hybrid ablation procedures consist of epicardial surgical ablation combined with percutaneous endocardial ablation. This collaborative effort encompasses partnerships between electrophysiologists and cardiac surgeons in patient selection and treatment. The different hybrid ablation approaches provide an innovative solution for the treatment of atrial fibrillation that can be effective in experienced hands using refined techniques and energy source applications. However, the application of these technologies must be evaluated in the context of safety and the efficacy of alternative methods of surgical ablation, such as the Cox maze procedure. A recent thorough meta-analysis compared Cox maze and hybrid procedures to find that overall 1-year freedom from AF off AAD was 87 vs. 71%, respectively, but the complication rates were higher with hybrid procedures[65].

Based on current experience, the hybrid approach with the most effective outcomes and safety profile appears to be bilateral PVI procedures performed surgically with LAA management combined with different endocardial ablation protocols.

Hybrid approaches based upon the collaboration of the electrophysiologist and cardiac surgeon could expand the indications for more effective stand-alone interventions for AF in the future.

With current surgical ablation tools designed for beating heart AF ablation, technical difficulties are still a potential concern, especially with respect to transmurality of the lesion lines. To better understand the quality of the lesions that are created and the impact of the lesion set, a hybrid approach was designed. The principles of these approaches are based upon the understanding that it is possible to apply mapping techniques from electrophysiologists to surgical epicardial ablation techniques when performed on the beating heart. The add-on approach can potentially improve the quality of the lesion line and lesion set if necessary. In reality, hybrid procedures are often being performed in a

single stage procedure[66]. Currently there is not enough evidence to distinguish between the single or two stage approaches due to the lack of direct comparison and the significant variability in the procedure with regards to lesion set, energy sources, and procedural endpoints.

Different hybrid surgical ablation lesions sets are applied, usually in a manner less than the full Cox maze IV lesion set. They are performed epicardially via minimally invasive non-sternotomy approaches without cardiopulmonary bypass, followed by catheter-based endocardial mapping, and if necessary additional ablation. Within this category of surgical ablation therapy, there are three general categories of innovative procedures currently being performed:

I. Bilateral pulmonary vein isolation (PVI) procedures inclusive of left atrial appendage (LAA) management. This includes a bilateral thoracoscopic or thoracotomy approach to perform isolated right and left antral PVI pairs with or without additional linear lesions on the left and right atrium. An alternative approach is to perform a posterior PVI encircling box lesion.
II. Unilateral thoracoscopic PVI posterior encircling box lesion without management of the LAA.
III. Alternative approaches to posterior LA wall epicardial ablation lesion (i.e., pericardioscopic epicardial debulking ablation procedures “convergent method”) without management of the LAA.

The pathophysiologic basis behind the potential validity of targeted epicardial minimally invasive ablation, as a concept, may rest in the failures of catheter-based ablation and in the established AF mechanisms of macro-reentrant rotors degrading to include the complex foci of atrial wall fibrosis as AF duration and persistence increase[67–70]. This is further informed by anatomic substrates that could be the generation of AF as extrapulmonary triggers located in the superior vena cava, ligament of Marshall, and the epicardial ridge between the left pulmonary vein and the LAA[70].

Less often performed, stand-alone surgical ablations comprise only 8% of ablation procedures performed in the Society of Thoracic Surgeons Adult Cardiac Surgery Database[71]. Nevertheless, the ability to provide minimally invasive epicardial ablation procedures without the need for cardiopulmonary bypass or sternotomy remains an attractive option for patients and for electrophysiologists. In fact, a recent review demonstrated the Cox maze procedure is the most effective minimally invasive surgical strategy for the treatment of stand-alone AF[65]. Each of the three categories of hybrid ablation techniques will be briefly addressed and available data reviewed. In the future it will be necessary to compare these different techniques in order to create an evidence-based decision tree for the best surgical approach. However, currently there is not enough published data comparing these techniques to create such a decision tree.

Bilateral PVI and management of LAA

The technique of thoracoscopic port-only bilateral epicardial ablation was established a decade ago to be a safe and initially effective strategy to introduce the encircling PVI box lesion using alternative energy sources[72]. While energy sources such as microwave proved not to deliver effective lesions[73], several groups from around the world have since documented that RF ablation devices applied using this platform can result in good mid-term outcomes[74]. Similarly, the application of an RF clamp to create PVI antral pairs via bilateral thoracotomies has been established as a safe procedure with reasonable short term efficacy[75].

It was not until groups, such as those led by Damiano[76], began studying modes of failure of epicardial PVI ablation that we learned of the common occurrence of late gaps in ablation lines despite initial operative confirmation of pulmonary vein exit block. This information established a potential value for combining epicardial PVI with endocardial mapping and ablation. Early experiences with these so called "hybrid" approaches included immediate intraoperative or periprocedural catheter-based confirmation of lesions and the application of additional endocardial completion lesions as necessary[77]. Immediate EP lab assessments of epicardial lesions may not only provide logistical challenges, but may miss late ablation gaps that are electrically unmasked following resolution of the acute inflammatory process of surgical ablation. As such, early multi-author results assembled following hybrid ablation revealed freedom from AF off of AAD for paroxysmal AF of 75%, persistent AF of 67%, and long-standing AF of 43%[78].

Several authors have pursued hybrid AF ablation and epicardial LAA exclusion in combination with either immediate staged or interval staged EP catheter-based mapping and treatment. The majority of the available studies are single institution experiences describing cases of heterogeneous AF types.

The group from Maastricht, led by La Meir and Pison, has been a pioneer in this field[79–81]. Utilizing a bipolar RF clamp and a linear RF pen (AtriCure Inc., West Chester, OH), they diligently performed epicardial bilateral antral PVI, box lesion, mitral isthmus line, coronary sinus lesion, and SVC isolation concluding with LAA staple exclusion. This was followed by immediate staged catheter-based analysis using rapid atrial pacing induction. In their total of 78 patients from 2009 to 2012, 28 (36%) required endocardial completion of posterior LA lesions and 10 required mitral line adjustment. They had no 30-day mortality and 6 patients had major complications. Their 1-year freedom from AF and AAD measured by 7-day Holter was 87% overall, 87% (43/49) for persistent AF patients.

Mahapatra et al. reported on 15 persistent AF patients in whom they performed the same lesions with the same energy source (AtriCure Inc., West Chester, OH), but with a staged catheter-based assessment of 4-5 days[82]. They found that 4/15 (27%) had gaps in the roof line and mitral lines requiring endocardial consolidation as well as ablation of inducible flutter to result in a 1-year freedom from AF and AAD by 7-day Holter in 13 of the 14 patients followed (93%).

Kurfirst et al. performed bilateral PVI box lesion and an additional roof line with the bipolar clamp and RF pen (AtriCure Inc., West Chester, OH) and LAA exclusion with clips in 30 patients with persistent AF[83]. Importantly, they chose to perform the catheter-based component of the hybrid procedure at 3 months postoperatively and they found that gaps occurred in 77-87% of the PVI lesions, nearly 70% of the roof lines, and 40% of the floor lines requiring endocardial line consolidation. Nevertheless, they were able to obtain a 1-year freedom from AF and AAD by 7-day Holter of 90% (27/30).

Lee et al. applied a RF Cardioblate Gemini-X clamp (Medtronic, Minneapolis, MN) to perform bilateral PVI only and LAA staple exclusion in 25 patients[84]. Catheter-based assessment was performed only in 7 patients in a delayed interval of > 3 months based on recurrence of AF to find that all 7 had PV reconnection requiring endocardial ablation and completion of mitral lines. The 1-year freedom from AF and AAD by 7-day Holter was achieved in 12/23 (52%).

Unilateral thoracoscopic PVI encircling lesion without LAA exclusion

A unilateral thoracoscopic technique to encircle the pulmonary veins as a circumferential box lesion has been developed using the unipolar RF suction Estech Cobra Adhere XL device (AtriCure, Inc., West Chester, OH).

La Meir et al. applied this technique to 19 patients of mixed AF type followed by immediate staged hybrid catheter-based assessment to find that all 19 had gaps in the box lesion requiring ablation along with mitral line completion, and only 7/19 (36%) had 1-year freedom from AF and AAD[85].

Bisleri et al. utilized the same approach in 45 patients with persistent AF, but with a delayed staged hybrid catheter-based assessment at 30-45 days postoperatively[86]. They found PV reconnections in only 3/45 patients (7%). They measured 1-year freedom from AF and AAD with an implantable loop recorder defined as AF over 5 minutes or overall burden of over 0.5%, which occurred in 40/45 (89%) of their patients.

Epicardial Pericardioscopic Posterior LA ablation ("Convergent Procedure") without LAA exclusion

A novel approach to epicardial LA ablation has been recently explored with a vacuum irrigated unipolar RF device delivered via laparoscopic trans-diaphragmatic pericardioscopy using the Numeris Guided Coagulation System with VisiTrax (nContact Surgical Inc., Morrisville, NC). This technique avoids entry into the thoracic cavity altogether to provide non-encircling bilateral posterior antral lesions, a posterior box lesion, a mitral isthmus line, a coronary sinus lesion, and an additional roof line, but this does not permit LAA exclusion. The inferior and posterior left atrial surfaces may be well-visualized, but the superior and anterior lesions are applied without direct visualization, especially at the pericardial reflections. This "convergent" approach permits a debulking of the posterior left atrium.

Gehi et al. report a series of 101 patients with AF heterogeneity using this procedure followed by immediate staged catheter-based assessment and found PVI gaps in only 4%, but additional roof lines and completion lines to the mitral isthmus were required in 90% of patients[87]. They had 2 operative mortalities and 7 major complications and achieved a 24-hour Holter documented 1-year freedom from AF and AAD in 46/69 (67%). Gersak reported a multi-institutional European experience with the convergent procedure in 73 patients with persistent AF with mixed intervals of staged catheter-based assessment, but found PVI gaps in all patients at the pericardial reflections[88]. Edgerton applied this procedure to 24 patients with persistent AF and found that 19% were free of AF and AAD at 24 months, but 3 patients died (12.5%), 4.2% had an acute stroke, and one had an atrio-esophageal fistula. These results led them to conclude that this procedure does not improve outcomes in patients with larger LA and persistent AF and there was evidence that this combined surgical/endocardial ablation approach increased complication rates and did not improve outcomes when compared to extensive endocardial ablation only[89].

AIM 3. Ablation Tools

Research Question #6: Which surgical ablation devices are associated with reliable transmural lesions?

Recommendation #9.
The best evidence exists for the use of bipolar radiofrequency clamps and cryoablation devices, which have become integral parts of many procedures including pulmonary vein isolation and the Cox maze IV procedure. The use of epicardial unipolar radiofrequency ablation outside of clinical trials is not recommended, as its efficacy remains questionable.

Reasoning

Ablation devices have revolutionized the surgical treatment of atrial fibrillation. The best evidence exists for the use of bipolar radiofrequency clamps and cryoablation devices, which have become an integral part of many procedures including the Cox-Maze IV[90]. We do not recommend the use of epicardial unipolar radiofrequency ablation outside clinical trials, as its efficacy is questionable. Cryoablation is most effective when used on an empty heart, especially when it is applied endocardially. Full beating-heart epicardial cryoablation is not recommended, as the heat sink effect of circulating blood can render this technique ineffective[91]. Further research is necessary to produce devices that can complete a full Cox-Maze lesion set safely on the beating heart. The following general recommendations are given based on available experimental and clinical evidence:

a. Empty arrested or beating heart: recommended ablation devices for pulmonary vein isolation are bipolar radiofrequency clamps or reusable/disposable cryoprobes
b. Beating heart: bipolar radiofrequency clamps are effective to isolate pulmonary veins and recommended with mandatory testing for exit and/or entrance block

c. Beating heart: surface bipolar radiofrequency devices may be recommended for free wall linear ablation when lesion integrity can be tested and multiple applications are recommended to achieve adequate lesion depth
d. Beating heart: epicardial cryoablation is not recommended, but endocardial cryoablation is recommended for free wall linear ablation due to the high degree of transmurality
e. Clinical trials of hybrid procedures: only settings where epicardial unipolar radiofrequency devices may be applied provided it is accompanied by acute lesion integrity testing
f. When ablating with any device, coronary arteries should be identified and avoided

Reasoning

Over the last 15 years, the surgical treatment of atrial fibrillation (AF) has been transformed by the introduction of ablation devices to replace most of the incisions used in the original Cox-Maze procedure[6,7]. Numerous technologies have been developed and tested both in animal models and in prospective clinical trials and retrospective case series. Current clinically available ablation devices use either unipolar or bipolar radiofrequency energy or cryothermal energy. Of note, there is only one device which carries a specific indication for ablation of atrial fibrillation; the remainder are FDA approved only for ablation of cardiac tissue.

Current devices for surgical ablation of atrial fibrillation use either radiofrequency (RF) or cryothermal energy to ablate cardiac tissue. Radiofrequency ablation requires heating cardiac tissue to a temperature between 50 and 100 °C to cause coagulative necrosis. Both unipolar and bipolar radiofrequency devices are available. Cryoablation uses evaporative cooling to freeze cardiac tissue, leading to tissue necrosis. The available systems use nitrous oxide or argon as the refrigerant.

Bipolar RF Clamps

In these devices, the electrodes are embedded in the jaws of the clamp. There are also bipolar linear devices in which the electrodes are made to be placed on the endocardial or epicardial surface.

There are non-irrigated impedance-controlled dual electrode systems. It is the only device FDA approved with a specific indication for ablation of cardiac tissue for treatment of persistent or longstanding persistent AF during a concomitant procedure. Ablation should be performed until the audible tone becomes intermittent, which occurs when conductance reaches a stable minimal value. In a chronic porcine study, all lesions produced in this manner were transmural[92]. A version of this device has been modified for thoracoscopic use.

Care needs to be taken when using non-irrigated bipolar RF clamps. The electrodes need to be cleaned after every 2-3 ablations, as char decreases conductance which will result in

inadequate ablation. Other factors such as air, fat, intraluminal catheters or electrodes and other inanimate objects will also decrease conductance and limit ablation depth. These should all be avoided, and the electrodes need to firmly clamp the tissue without folding or imbricating the atria to be effective.

There are also irrigated impedance-controlled bipolar radiofrequency clamps. Irrigation is thought to increase the size of lesions by limiting char. These devices were evaluated in porcine models in two independent laboratories and showed a high rate of transmural lesion formation, up to 99% at 30 days[76,93]. Irrigated clamps do not need to be cleaned as the irrigation prevents char formation. However, the same precautions need to be taken to avoid factors which decrease conductance as stated above.

Surface Bipolar Devices

There are three surface bipolar radiofrequency devices available. These devices can be applied epicardially or endocardially. Ablation times range from 10-40 seconds per the manufacturer's instructions. Continuous lesions should be overlapped, as the highest risk of an ablation gap is at the end of the device. These devices have shown variable results. The Isolator® linear pen showed only a 64% overall rate of transmural lesion formation with an 11% rate of tissue perforation in an acute porcine model[94]. The Isolator® multifunctional pen showed transmural lesion formation in 10 seconds in tissues less than 4 mm thick but had a maximum depth of penetration of only 6.1 mm.[8] The Coolrail® linear pen produced transmurality in 76% of lesions at 4 weeks in a porcine beating-heart model[95,96], but was incapable of creating conduction block in a chronic animal model[96].

The COBRA Fusion™ 150 and 50 are suction-assisted temperature-controlled combined bipolar and unipolar radiofrequency devices. These should be applied with -500 mmHg vacuum and 60-120 s depending on the thickness of the tissue and the desired temperature per the manufacturer's instructions. This system was shown to produce transmural lesions in 94% of cross-sections evaluated in an acute porcine model, although only 68% of lesions were transmural throughout their length[97].

Unipolar RF Devices

In general, unipolar epicardial radiofrequency ablation has shown poor efficacy for the creation of transmural lesions. However, several devices remain on the market. The Cardioblate® irrigated pen; this device was evaluated in an *in vitro* model, which showed superior lesion size compared with conventional unipolar ablation, such as that found in the Cardioblate® MAPS device[98]. EPi-Sense® Coagulation System with VisiTrax® is another suction- and perfusion-assisted unipolar RF device. It is produced in three lengths, 1-3 cm. Results of animal studies with the nContact™ device have been variable. One acute ovine study showed a 100% rate of transmural lesions[99], but a porcine acute study showed only a 15% rate of transmural lesions[96].

Cryoablation Devices

Two manufacturers currently produce cryoablation devices for surgical cardiac ablation. The cryoICE® system uses nitrous oxide to freeze tissue with a minimal probe temperature of -50 to -70 °C. Nearly all (83/84) lesions produced using two minutes of cryoablation with this system were transmural in a chronic porcine study[100]. The Cardioblate® CryoFlex, CryoFlex 10-S, and CryoFlex Clamp all use argon as the refrigerant, reaching up to -160 °C. All are disposable. The CryoFlex clamp produced a 93% rate of transmural lesions in a chronic canine model[101]. The same study evaluated linear epicardial lesions produced using the CryoFlex system; only 84% of linear lesions were transmural after 180 s of ablation. Both technologies employ malleable disposable cryoprobes that can be shaped to facilitate minimally invasive use.

Ablation should be performed by surgeons with appropriate training and experience. Except within the context of clinical trials, only devices with proven efficacy should be used. When possible, the presence of acute conduction block should be used to confirm ablation efficacy. This is done by testing for exit and/or entrance block by pacing/sensing from the right and left pulmonary veins.

Ablation devices ideally should be evaluated prospectively in an independent laboratory with submission of results to peer-reviewed journals. Devices should be tested clinically using previously evaluated lesion sets to minimize confusion. Clinical follow-up data collected according to current guidelines should be the gold standard for evaluating a device's effectiveness. Ablation success is defined as freedom from atrial tachyarrhythmias (ATAs) and antiarrhythmic drugs at 12 months.[3]

AIM 4. Training

Research Question #7: Should surgeons performing surgical ablation be required to undergo basic training and education?

> **Recommendation #10.**
> Surgical ablation procedures should require basic training, proctoring, and education to improve surgeon understanding of atrial fibrillation, the surgical options and improved outcomes. Training and education should be completed prior to the performance of surgical ablation. We highly recommend surgeons that are new to surgical AF be proctored by an experienced surgeon for 3-5 cases prior to performing surgical ablation alone (Class I, Level C).

Reasoning

Currently there are no validated training plans or curricula for surgeons to complete before performing surgical ablation of AF. Although surgical procedures to treat AF were developed more than three decades ago, surgeons' approach to this problem has been widely varied. The introduction of new ablation technologies and the creation of a large number of different lesion sets have added to the complexity and confusion surrounding surgical ablation of AF. It is clear that training and surgical experience influence both the use of surgical ablation and the results[9,43,102]. With increasing experience, surgeons are

more likely to perform an ablation in patients with pre-existing AF. Like with any other cardiac surgical procedure, the percent of patients undergoing surgical ablation and the success of such procedures may be superior when performed by experienced and well-trained cardiac surgeons[9]. Optimization of patient outcomes requires a combination of education and formal training that incorporates understanding of 1) the risks associated with leaving AF untreated, 2) the risks associated with surgical ablation, 3) the recommended procedure, including choice of lesion set and ablation technologies, and 4) the results of surgical ablation.

Risks associated with untreated AF

It is axiomatic that surgeons should understand the conditions for which they are treating patients. Cardiac surgical patients with preexisting AF have reduced long-term survival if the AF is left untreated[45]. This holds true whether the patient's primary indication for surgery is valvular heart disease or coronary artery disease. Careful analysis of the results of surgical ablation of AF suggests that successful AF ablation may improve survival[103]. In addition, AF-related strokes are rare in patients who have undergone surgical ablation of AF. It has been argued that this finding could be related also to LAA ligation, which is anticipated to be addressed by the Left Atrial Appendage Occlusion Study (LAAOS) III that is currently underway[104]. Understanding the risks of untreated AF should prompt surgeons to consider AF ablation in all cardiac surgical patients presenting with AF.

Risks associated with treating AF

Our extensive summary indicates that perioperative morbidity including stroke is not increased with the addition of surgical ablation and we further found a short-term survival benefit. Surgeons must understand that the addition of surgical ablation does not increase the risk of major morbidity or mortality[10]. Multiple studies confirm that surgical ablation is safe[9,10,43,45,102,103,105]. Although surgical ablation does increase aortic cross-clamp and cardiopulmonary bypass times, this does not translate into increased patient risk. Surgical ablation may increase the risk of requiring a permanent pacemaker, but in most studies this risk is small[10,43,102].

Recommended ablation procedure

Results of the cut-and-sew Cox-Maze III procedure were excellent, and this procedure should therefore serve as the predicate for surgical ablation with new energy sources. All surgeons should understand the biatrial lesion sets of the Cox-Maze III and energy-assisted Cox-Maze IV procedures. Key components include isolation of the entire posterior left atrium (including the pulmonary veins), a connecting lesion to the mitral annulus that includes the coronary sinus, management of the left atrial appendage, and at least one right atrial lesion that reaches the tricuspid annulus.

While a recent randomized controlled clinical trial provided some data concerning the biatrial lesion set vs. a left atrial lesion set in patients with persistent and long-standing persistent AF, the trial was not powered to confirm that a left atrial lesion set alone is

equivalent to a biatrial lesion set in such patients[10]. It may be appropriate to employ a left atrial lesion set alone in selected patients with paroxysmal AF and normal left atrial size.

Once the surgeon is thoroughly versed in the choice of lesion set, he or she must understand appropriate use of ablation technology. This requires that the surgeon invest adequate time in understanding the technology and observe at least one surgical case employing the particular ablation technology. It is further advisable that the surgeon be proctored for his or her first ablation case. Surgeons should avail themselves of proctorship(s) made available by any company that has FDA-approved technology for AF ablation. The surgeon must understand proper lesion placement and pitfalls of ablation technologies (gaps, bunching of tissue, inadequate duration of freeze-thaw cycles, failure to clean the jaws of bipolar clamps, etc.). Once the surgeon has completed training, he/she may begin performing AF ablation. The surgeon should keep a log of AF ablation cases as this will aid in tabulating results (see below).

Results of surgical ablation

Before performing surgical ablation of AF, the surgeon must be well-versed in the expected results. In general, freedom from AF at one year should be 70% or greater; selected experts report success rates of 80% to 90%[9,43,45,102,103,105]. Surgeons should record their own results according to HRS guidelines; this requires long-term monitoring at the 12 month mark[60]. Surgeons should also record their rate for permanent pacemaker implantation after AF ablation. In order to achieve the best results, surgeons should be well-versed in the perioperative care of these patients. It is not enough to do a procedure and simply send the patient home. Successful ablation begins in the operating room but requires continued monitoring and medical management to achieve normal sinus rhythm. Many patients require postoperative antiarrhythmic therapy and electrical cardioversion. The surgeon must understand that successful ablation occurs over time and require effort.

Summary

Currently, there is no specific training that is required prior to a surgeon performing surgical ablation. It may be necessary to establish credentialing criteria for surgeons wanting to perform surgical ablation with novel technologies, including both proctoring and mentoring protocols in the operating room. Training and mentoring is essential for this technique to be implemented with the best possible outcomes for the patients. Therefore we recommend that training and education be completed prior to the performance of surgical ablation. This training and education should aim to provide surgeons with the following[64]:

1. Knowledge in atrial anatomy and appropriate patient selection
2. Basic understanding of the significance of the different lesion sets
3. Knowledge in the intraprocedural management of patients in terms of avoidance of complications and their treatment
4. Knowledge and understanding in post procedural management and follow up.

It is also highly recommended to include surgical AF ablation during training[106]. Previously, it has been recommended to include 30-50 ablation cases during training [64,106] We recommend that surgical training for surgical ablation should follow this same recommendation. We also highly recommend surgeons that are new to surgical AF be proctored by an experienced surgeon for 3-5 cases prior to performing surgical ablation alone. In terms of maintenance of proficiency level, surgeons with sufficient training should aim to routinely perform surgical ablation cases.

RECOMMENDATIONS FOR FUTURE AATS EFFORTS

The task force recommends the establishment of uniform definitions for time points and outcome measures so that systematic analyses can be conducted to more efficiently determine the effectiveness and safety of surgical ablation. In addition, it is recommended that more RCT trials are undertaken that are well-designed and well-controlled with regard to lesion set technology and outcomes.
The clinical areas and studies that are recommended are:

- Well-designed studies to address long term survival and embolic complications
- Well-designed studies to develop a better understanding on the cost effectiveness of surgical ablation
- Well-designed studies to assess the role of stand alone surgical ablation procedures to include a Cox-Maze procedure and off pump procedures to include the hybrid approach
- Training and education including surgical ablation should be included in the residency curriculum

RECOMMENDATIONS FOR THE USE OF THE GUIDELINES

These guidelines are best used as a guide for practice and teaching. The applicability of these recommendations to the individual patient should be evaluated on a case-by-case basis, and only applied when clinically appropriate. In addition, these guidelines can serve as a tool for uniform practices, to guide development of surgeon training protocols, and to form the basis of uniform time points and outcomes for the thoracic surgical community.

The task force received no financial support. AATS provided teleconferencing and covered the cost of a 1-day face-to-face conference for the participants. The members of this task force had no conflicts of interest related to any of the recommendations made here; all their other potential conflicts of interest were disclosed in writing.

SUMMARY

Surgical ablation is a safe and effective strategy for treatment of atrial fibrillation. It is important to consider the indications for hybrid ablation or the stand alone off bypass ablation. Bipolar radiofrequency clamps or reusable/disposable cryoprobes are the best ablation devices, but when ablating, coronary arteries should be avoided. Training and mentoring protocols for surgeons interested in performing surgical ablation need to be created to ensure patient safety and beneficial outcomes. Future studies should use

899 standardized time points and outcome measures to enhance the ability to compare
900 outcomes across different studies.

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TABLE 1.

Recommendation	Class	Level
#1: Perioperative Morbidity		
DSWI, pneumonia, bleeding reop, RF with dialysis	IIa	Level A
ICU stay, total LOS	IIa	Level B-R
Readmission <30 days, RF	IIa	Level B-NR
#2: Early stroke/TIA	IIa	Level A
#3: Late stroke/TIA		
Up to 1 year follow-up	IIa	Level A
>1 year follow-up	IIa	Level B-NR
#4: Quality of Life		
HRQL	IIa	Level B-R
AF-related symptoms	IIa	Level C-LD
#5: Short-term survival	I	Level A
#6: Long-term survival		
Up to 1 year follow-up	IIa	Level A
>1 year follow-up	IIa	Level B-NR
#7: Hybrid ablation	IIb	Level B-NR
#8: Stand alone off-pump epicardial ablation	IIa	Level B-R
#9: Surgical ablation device transmurality	N/A	N/A
#10: Surgeon Experience	I	Level C

SUPPLEMENTAL TABLE 1.

Research Question Search Terms
#1: Perioperative Morbidity ((((("atrial fibrillation" OR "AF" OR "afib") AND ("surgical ablation" OR "Maze" OR "Cox-Maze" OR "Cox maze" OR "ablation" OR "pulmonary vein isolation" OR "afib ablation" OR (afib AND ("therapy"[Subheading] OR "therapy" OR "treatment" OR "therapeutics"[MeSH Terms] OR "therapeutics")) OR "af ablation" OR "persistent af ablation")) AND ("cardiac surgery" OR "heart surgery" OR "surgery" OR "surgical" OR "median sternotomy" OR "mid-sternotomy" OR "mid sternotomy" OR "mid sternum" OR "minimally invasive" OR "right thoracotomy")) AND ("survival" OR "mortality" OR "death")
#2: Stroke/TIA (("cardiac surgery" OR "heart surgery" OR "surgery" OR "surgical" OR "median sternotomy" OR "mid-sternotomy" OR "mid sternotomy" OR "mid sternum" OR "minimally invasive" OR "right thoracotomy") AND ("surgical ablation" OR "Maze" OR "Cox-Maze" OR "Cox maze" OR "ablation" OR "pulmonary vein isolation" OR "afib ablation" OR "afib treatment" OR "af ablation" OR "persistent af ablation") AND ("atrial fibrillation" OR "AF" OR "afib") AND ("stroke" OR "embolic stroke" OR "embolic event" OR "TIA" OR "transient ischemic attack" OR transient ischaemic attack" OR "cerebrovascular accident" OR "CVA" OR "cerebrovascular insult" OR "CVI"))
#3: Quality of Life (((((("atrial fibrillation" OR "AF" OR "afib"))) AND (("surgical ablation" OR "Maze" OR "Cox-Maze" OR "Cox maze" OR "ablation" OR "pulmonary vein isolation" OR "afib ablation" OR (afib AND ("therapy"[Subheading] OR "therapy" OR "treatment" OR "therapeutics"[MeSH Terms] OR "therapeutics")) OR "af ablation" OR "persistent af ablation")))) AND (("cardiac surgery" OR "heart surgery" OR "surgery" OR "surgical" OR "median sternotomy" OR "mid-sternotomy" OR "mid sternotomy" OR "mid sternum" OR "minimally invasive" OR "right thoracotomy"))) AND (("HRQL" OR "health-related quality of life" OR "quality of life" OR "QOL" OR "health related quality of life" OR "SF-12" OR "Short Form 12" OR "SF-36" OR "Short Form 36"))
#4: Survival ((((("atrial fibrillation" OR "AF" OR "afib") AND ("surgical ablation" OR "Maze" OR "Cox-Maze" OR "Cox maze" OR "ablation" OR "pulmonary vein isolation" OR "afib ablation" OR (afib AND ("therapy"[Subheading] OR "therapy" OR "treatment" OR "therapeutics"[MeSH Terms] OR "therapeutics")) OR "af ablation" OR "persistent af ablation")) AND ("cardiac surgery" OR "heart surgery" OR "surgery" OR "surgical" OR "median sternotomy" OR "mid-sternotomy" OR "mid sternotomy" OR "mid sternum" OR "minimally invasive" OR "right thoracotomy")) AND ("survival" OR "mortality" OR "death")

FIGURE LEGENDS

Figure 1. Left atrial lesion sets for Cox maze IV procedure. (A) Most linear lesions are created with bipolar radiofrequency clamps; shaded in blue are cryolesions at the mitral isthmus (and left pulmonary veins for minimally invasive approach). (B) Linear lesions also can be created with cryoablation if required for minithoracotomies or reoperations. Right atrial lesion sets for Cox maze IV procedure. (A) Most linear lesions are created with bipolar radiofrequency clamps, and cryolesions are placed at two points on the tricuspid annulus through direct vision or small pursestring sutures (red arrows). (B) Linear lesions also can be created with cryoablation if required for minithoracotomies or reoperations. (Reprinted from The Annals of Thoracic Surgery, 103(1), Badhwar V, Rankin JS, Damiano RJ Jr, et al., The Society of Thoracic Surgeons 2017 Clinical Practice Guidelines for the Surgical Treatment of Atrial Fibrillation, pages 329–341, 2017. © [2014] Beth Croce)

Figure 2. Classification of recommendations and level of evidence using the ACC/AHA grading schema

Figure 3. Forest plot for pneumonia in the perioperative time frame (< 30 days) with concomitant surgical ablation

Figure 4. Forest plot for deep sternal wound infection in the perioperative time frame (< 30 days) with concomitant surgical ablation

Figure 5. Forest plot for length of stay in the ICU in the perioperative time frame (< 30 days) with concomitant surgical ablation

Figure 6. Forest plot for total hospital stay in the perioperative time frame (< 30 days) with concomitant surgical ablation

Figure 7. Forest plot for readmissions within 30 days with concomitant surgical ablation

Figure 8. Forest plot for reoperation for bleeding in the perioperative time frame (< 30 days) with concomitant surgical ablation

Figure 9. Forest plot for renal failure in the perioperative time frame (< 30 days) with concomitant surgical ablation

Figure 10. Forest plot for renal failure requiring dialysis in the perioperative time frame (< 30 days) with concomitant surgical ablation

Figure 11. Forest plot for incidence of early stroke/TIA (in-hospital or < 30 days) with concomitant surgical ablation

Figure 12. Forest plot for incidence of late stroke/TIA with concomitant surgical ablation

Figure 13. (A) Forest plot for incidence of late stroke/TIA with concomitant surgical ablation in randomized controlled studies. (B) Forest plot for incidence of late stroke/TIA with concomitant surgical ablation in non-randomized controlled studies

Figure 14. Forest plot for improved survival in the perioperative time frame (< 30 days) with concomitant surgical ablation

Figure 15. Forest plot for improved long-term survival with concomitant surgical ablation

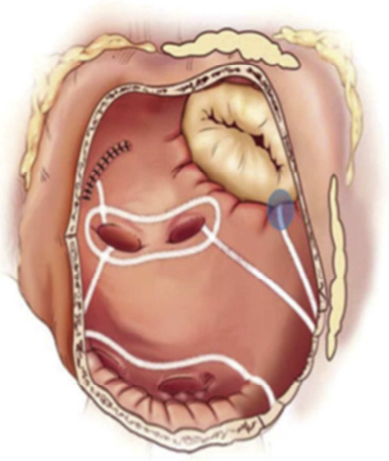
Figure 16. (A) Forest plot for long-term survival with concomitant surgical ablation in randomized controlled studies. (B) Forest plot for long-term survival with concomitant surgical ablation in non-randomized controlled studies

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be performed/ administered/ other is not useful/ beneficial/ effective COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

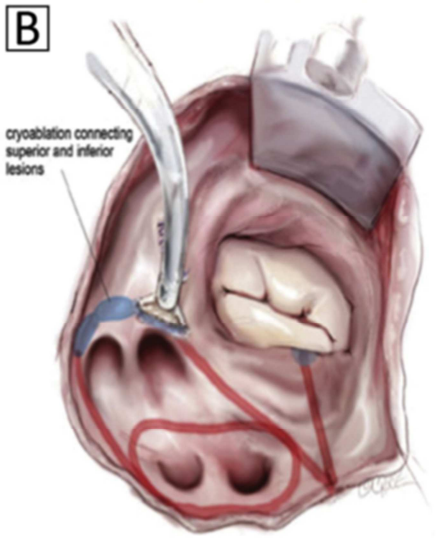
Left Atrial Lesion Set

A



Sternotomy

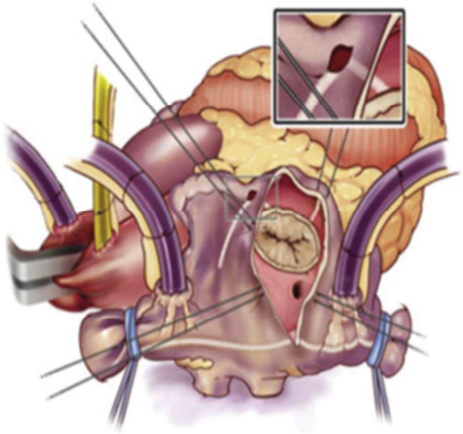
B



Right Mini-thoracotomy

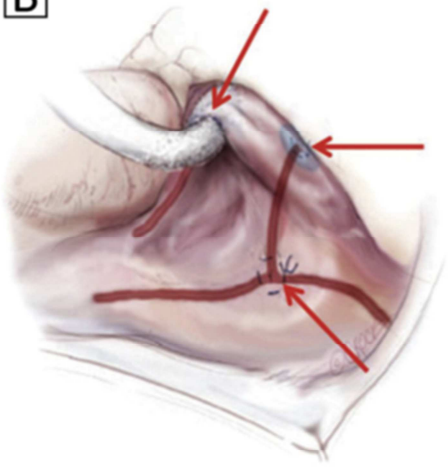
Right Atrial Lesion Set

A



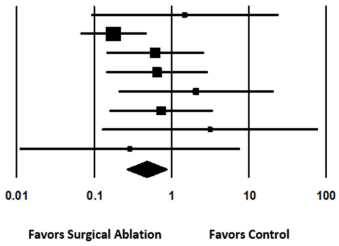
Sternotomy

B



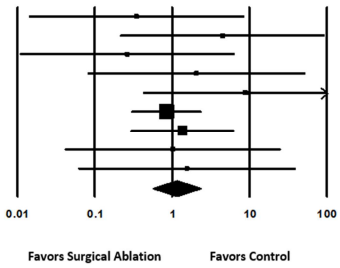
Right Mini-thoracotomy

Model	Study name	Subgroup within study	Outcome	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	82. Yoo	Non-RCT	Pneumonia	1.490	0.091	24.385	0.280	0.780
	134. Ad	Non-RCT	Pneumonia	0.178	0.066	0.477	-3.428	0.001
	139. Saint	Non-RCT	Pneumonia	0.618	0.144	2.653	-0.648	0.517
	251. Budera	RCT	Pneumonia	0.650	0.142	2.978	-0.554	0.579
	710. Abreu Filho	RCT	Pneumonia	2.077	0.205	21.045	0.619	0.536
	896. Liu	RCT	Pneumonia	0.735	0.156	3.456	-0.390	0.697
	902. Boersma	RCT	Pneumonia	3.149	0.126	78.801	0.698	0.485
	904. Vasconcelos	RCT	Pneumonia	0.290	0.011	7.737	-0.738	0.460
Fixed				0.474	0.262	0.857	-2.472	0.013



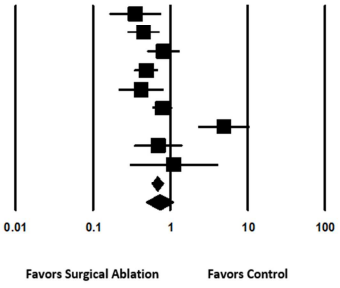
Meta Analysis

Model	Study name	Subgroup within study	Outcome	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	139. Saint	Non-RCT	DSWI	0.346	0.014	8.592	-0.647	0.517
	251. Budera	RCT	DSWI	4.476	0.212	94.327	0.964	0.335
	291. Kim JB	Non-RCT	DSWI	0.264	0.011	6.509	-0.814	0.415
	710. Abreu Filho	RCT	DSWI	2.060	0.081	52.392	0.438	0.662
	756. Nakajima	Non-RCT	DSWI	8.867	0.422	186.316	1.405	0.160
	893. Doukas	RCT	DSWI	0.846	0.296	2.412	-0.314	0.754
	896. Liu	RCT	DSWI	1.361	0.289	6.397	0.390	0.697
	898. Srivastava	RCT	DSWI	1.017	0.041	25.457	0.010	0.992
	900. Albrecht	RCT	DSWI	1.557	0.061	39.945	0.267	0.789
Fixed				1.133	0.561	2.288	0.348	0.728



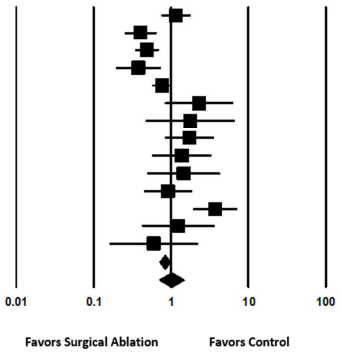
Meta Analysis

Model	Study name	Subgroup within study	Outcome	Statistics for each study				
				Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	93. Cherniavsky	RCT	ICU LOS	0.352	0.162	0.764	-2.641	0.008
	134. Ad	Non-RCT	ICU LOS	0.450	0.279	0.723	-3.294	0.001
	139. Saint	Non-RCT	ICU LOS	0.811	0.498	1.321	-0.843	0.399
	151. McCarthy	Non-RCT	ICU LOS	0.489	0.341	0.701	-3.892	0.000
	264. Malaisrie	Non-RCT	ICU LOS	0.420	0.213	0.825	-2.518	0.012
	312. Attaran	Non-RCT	ICU LOS	0.788	0.583	1.064	-1.555	0.120
	862. Raanani	Non-RCT	ICU LOS	4.922	2.284	10.609	4.068	0.000
	893. Doukas	RCT	ICU LOS	0.700	0.339	1.443	-0.968	0.333
	904. Vasconcelos	RCT	ICU LOS	1.111	0.296	4.163	0.156	0.876
Fixed				0.671	0.567	0.794	-4.652	0.000
Random				0.719	0.480	1.076	-1.603	0.109



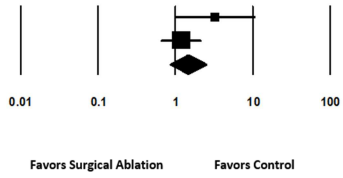
Meta Analysis

Model	Study name	Subgroup within study	Outcome	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	5. Gillinov	RCT	LOS	1.164	0.749	1.809	0.674	0.500
	134. Ad	Non-RCT	LOS	0.405	0.252	0.653	-3.714	0.000
	151. McCarthy	Non-RCT	LOS	0.489	0.341	0.701	-3.892	0.000
	264. Malaisrie	Non-RCT	LOS	0.378	0.192	0.744	-2.813	0.005
	312. Attaran	Non-RCT	LOS	0.771	0.571	1.041	-1.696	0.090
	525. von Oppell	RCT	LOS	2.307	0.824	6.458	1.592	0.111
	818. Jessurun	RCT	LOS	1.768	0.464	6.732	0.836	0.403
	862. Raanani	Non-RCT	LOS	1.731	0.828	3.620	1.459	0.145
	891. Blomstrom-Lundqvist	RCT	LOS	1.379	0.568	3.345	0.711	0.477
	892. Chevalier	RCT	LOS	1.457	0.491	4.323	0.679	0.497
	893. Doukas	RCT	LOS	0.918	0.446	1.889	-0.233	0.816
	902. Boersma	RCT	LOS	3.709	1.919	7.170	3.898	0.000
	903. Schuetz	RCT	LOS	1.246	0.418	3.715	0.394	0.694
	904. Vasconcelos	RCT	LOS	0.598	0.158	2.255	-0.760	0.447
Fixed				0.823	0.704	0.961	-2.467	0.014
Random				1.003	0.699	1.439	0.015	0.988



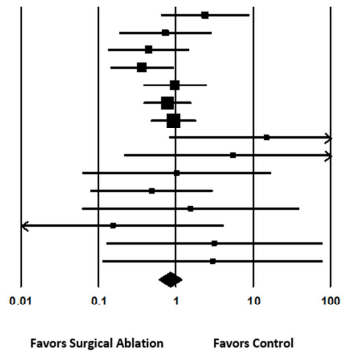
Meta Analysis

Model	Study name	Subgroup within study	Outcome	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	134. Ad	Non-RCT	Readmit <30 days	3.231	0.953	10.948	1.883	0.060
	151. McCarthy	Non-RCT	Readmit <30 days	1.184	0.645	2.170	0.545	0.586
Fixed				1.444	0.839	2.485	1.326	0.185

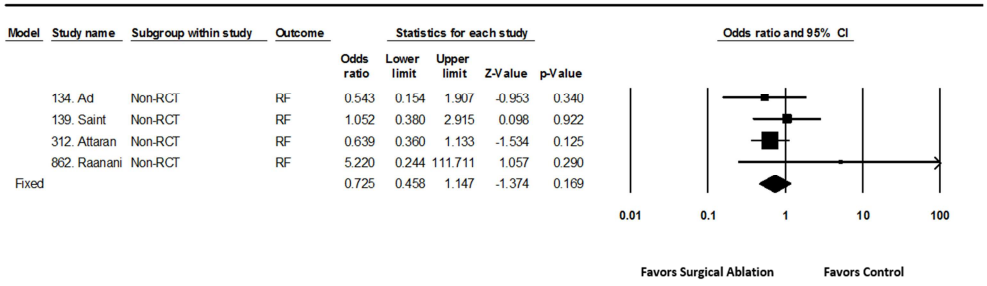


Meta Analysis

Model	Study name	Subgroup within study	Outcome	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	82. Yoo	Non-RCT	Reop for bleeding	2.386	0.637	8.934	1.291	0.197
	134. Ad	Non-RCT	Reop for bleeding	0.734	0.185	2.911	-0.441	0.660
	139. Saint	Non-RCT	Reop for bleeding	0.444	0.133	1.490	-1.314	0.189
	151. McCarthy	Non-RCT	Reop for bleeding	0.366	0.141	0.948	-2.069	0.039
	251. Budera	RCT	Reop for bleeding	0.975	0.380	2.502	-0.053	0.958
	291. Kim JB	Non-RCT	Reop for bleeding	0.784	0.384	1.601	-0.668	0.504
	312. Attaran	Non-RCT	Reop for bleeding	0.930	0.472	1.833	-0.208	0.835
	862. Raanani	Non-RCT	Reop for bleeding	14.880	0.813	272.168	1.821	0.069
	887. Jatene	Non-RCT	Reop for bleeding	5.462	0.212	140.565	1.024	0.306
	897. Akpinar	RCT	Reop for bleeding	1.031	0.062	17.200	0.021	0.983
	898. Srivastava	RCT	Reop for bleeding	0.487	0.078	3.026	-0.772	0.440
	900. Albrecht	RCT	Reop for bleeding	1.557	0.061	39.945	0.267	0.789
	901. de Lima	RCT	Reop for bleeding	0.154	0.006	4.154	-1.112	0.266
	902. Boersma	RCT	Reop for bleeding	3.149	0.126	78.801	0.698	0.485
	904. Vasconcelos	RCT	Reop for bleeding	3.000	0.113	79.914	0.656	0.512
Fixed				0.836	0.601	1.164	-1.061	0.289



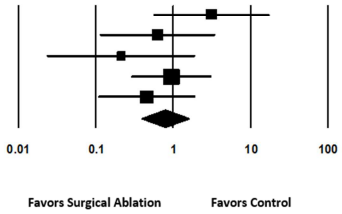
Meta Analysis



Model	Study name	Subgroup within study	Outcome	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	134. Ad	Non-RCT	RF	0.543	0.154	1.907	-0.953	0.340
	139. Saint	Non-RCT	RF	1.052	0.380	2.915	0.098	0.922
	312. Attaran	Non-RCT	RF	0.639	0.360	1.133	-1.534	0.125
	862. Raanani	Non-RCT	RF	5.220	0.244	111.711	1.057	0.290
Fixed				0.725	0.458	1.147	-1.374	0.169

Meta Analysis

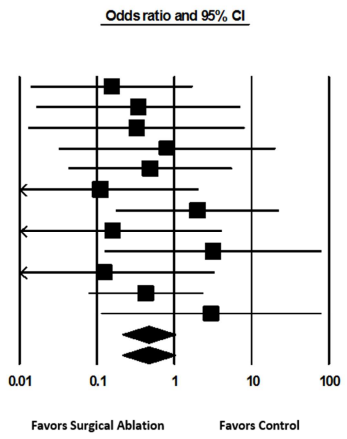
Model	Study name	Subgroup within study	Outcome	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	82. Yoo	Non-RCT	RF, dialysis	3.130	0.551	17.786	1.287	0.198
	134. Ad	Non-RCT	RF, dialysis	0.629	0.113	3.506	-0.528	0.597
	251. Budera	RCT	RF, dialysis	0.213	0.023	1.938	-1.373	0.170
	291. Kim JB	Non-RCT	RF, dialysis	0.953	0.287	3.160	-0.079	0.937
	893. Doukas	RCT	RF, dialysis	0.457	0.107	1.942	-1.062	0.288
Fixed				0.782	0.389	1.573	-0.690	0.490



Meta Analysis

Meta Analysis

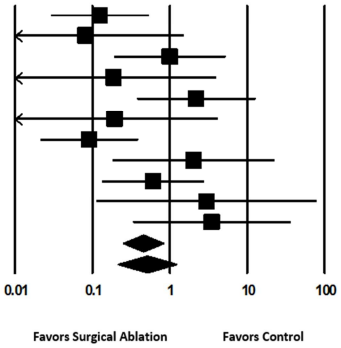
Model	Studyname	Time point	Statistics for each study				
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	77. Ad, N	Perioperative	0.155	0.014	1.738	-1.512	0.131
	713. Nakajima, H	Perioperative	0.345	0.016	7.249	-0.685	0.493
	711. Raanani, E	Perioperative	0.326	0.013	8.217	-0.680	0.496
	710. Mantovan, R	Perioperative	0.805	0.032	20.310	-0.132	0.895
	707. Johansson, B	Perioperative	0.487	0.042	5.601	-0.578	0.564
	706. Jatene, MB	Perioperative	0.111	0.006	2.075	-1.472	0.141
	704. Doukas, G	Perioperative	2.000	0.175	22.815	0.558	0.577
	802. Albrecht, A	Perioperative	0.160	0.006	4.122	-1.105	0.269
	702. Blomstrom-Lundqvist, C	Perioperative	3.179	0.125	80.789	0.701	0.483
	576. Jessurun, ER	Perioperative	0.124	0.005	3.321	-1.244	0.213
	193. Budera, P	Perioperative	0.430	0.077	2.397	-0.963	0.336
	801. Vasconcelos, JT	Perioperative	3.000	0.113	79.914	0.656	0.512
Fixed			0.463	0.212	1.011	-1.933	0.053



Meta Analysis

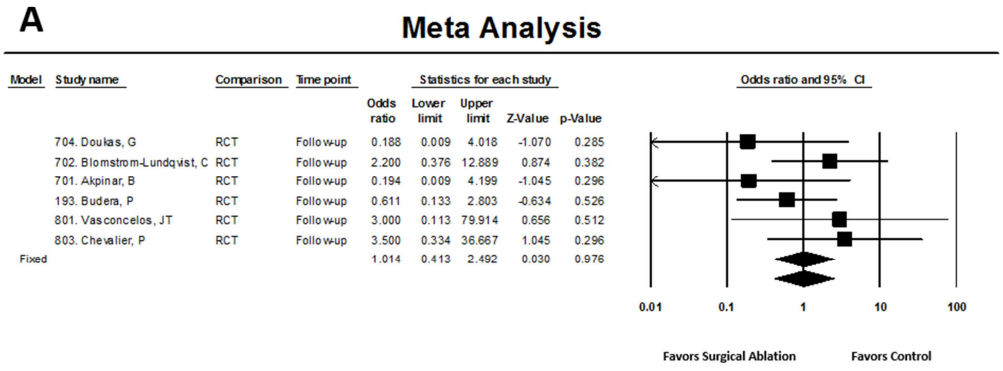
Meta Analysis

Model	Studyname	Time point	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	713. Nakajima, H	Follow-up	0.124	0.029	0.535	-2.800	0.005
	711. Raanani, E	Follow-up	0.081	0.004	1.515	-1.682	0.093
	707. Johansson, B	Follow-up	1.000	0.189	5.289	0.000	1.000
	704. Doukas, G	Follow-up	0.188	0.009	4.018	-1.070	0.285
	702. Blomstrom-Lundqvist, C	Follow-up	2.200	0.376	12.889	0.874	0.382
	701. Akpinar, B	Follow-up	0.194	0.009	4.199	-1.045	0.296
	515. Bando, K	Follow-up	0.091	0.021	0.392	-3.220	0.001
	268. Wang, J	Follow-up	2.025	0.180	22.770	0.571	0.568
	193. Budera, P	Follow-up	0.611	0.133	2.803	-0.634	0.526
	801. Vasconcelos, JT	Follow-up	3.000	0.113	79.914	0.656	0.512
	803. Chevalier, P	Follow-up	3.500	0.334	36.667	1.045	0.296
Random			0.505	0.211	1.208	-1.535	0.125



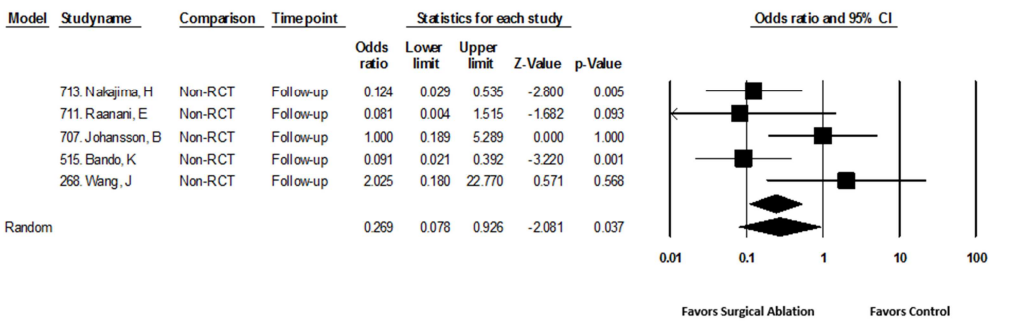
Meta Analysis

A



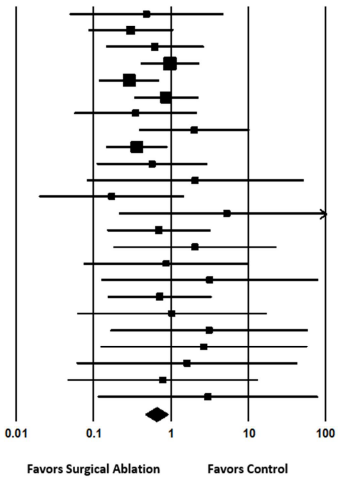
Meta Analysis

B



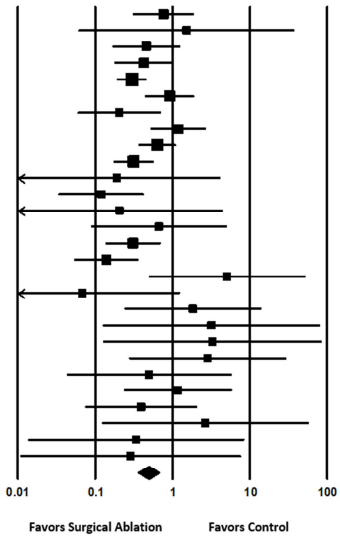
Meta Analysis

Model	Study name	Comparison	Time point	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	82. Yoo	Non-RCT	Operative	0.483	0.049	4.780	-0.622	0.534
	134. Ad	Non-RCT	Operative	0.303	0.085	1.077	-1.845	0.065
	139. Saint	Non-RCT	Operative	0.618	0.144	2.653	-0.648	0.517
	141. Kim HJ	Non-RCT	Operative	0.971	0.404	2.331	-0.066	0.947
	151. McCarthy	Non-RCT	Operative	0.288	0.117	0.709	-2.710	0.007
	251. Budera	RCT	Operative	0.869	0.331	2.281	-0.285	0.776
	264. Malaisrie	Non-RCT	Operative	0.350	0.056	2.182	-1.124	0.261
	291. Kim JB	Non-RCT	Operative	2.003	0.385	10.412	0.826	0.409
	312. Attaran	Non-RCT	Operative	0.364	0.146	0.908	-2.168	0.030
	528. Louagie	Non-RCT	Operative	0.571	0.109	2.986	-0.663	0.507
	710. Abreu Filho	RCT	Operative	2.060	0.081	52.392	0.438	0.662
	715. Knaut	Non-RCT	Operative	0.171	0.020	1.489	-1.600	0.110
	756. Nakajima	Non-RCT	Operative	5.273	0.213	130.519	1.016	0.310
	854. Chen	Non-RCT	Operative	0.698	0.149	3.264	-0.456	0.648
	862. Raanani	Non-RCT	Operative	2.044	0.179	23.348	0.576	0.565
	887. Jatene	Non-RCT	Operative	0.868	0.074	10.225	-0.112	0.911
	891. Blomstrom-Lundqvist	RCT	Operative	3.179	0.125	80.789	0.701	0.483
	893. Doukas	RCT	Operative	0.717	0.152	3.390	-0.419	0.675
	897. Akpinar	RCT	Operative	1.031	0.062	17.200	0.021	0.983
	898. Srivastava	RCT	Operative	3.129	0.165	59.393	0.759	0.448
	900. Albrecht	RCT	Operative	2.662	0.122	58.119	0.622	0.534
	901. de Lima	RCT	Operative	1.615	0.060	43.247	0.286	0.775
	903. Schuetz	RCT	Operative	0.783	0.046	13.390	-0.169	0.866
	904. Vasconcelos	RCT	Operative	3.000	0.113	79.914	0.656	0.512
Fixed				0.643	0.464	0.890	-2.664	0.008



Meta Analysis

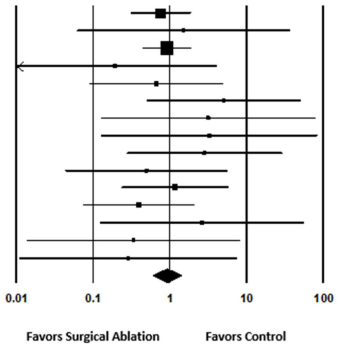
Model	Study name	Comparison	Time point	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	5. Gillinov	RCT	Follow-up	0.765	0.306	1.914	-0.572	0.568
	65. Wang	RCT	Follow-up	1.516	0.061	37.696	0.254	0.800
	82. Yoo	Non-RCT	Follow-up	0.457	0.166	1.256	-1.518	0.129
	134. Ad	Non-RCT	Follow-up	0.428	0.175	1.044	-1.865	0.062
	141. Kim HJ	Non-RCT	Follow-up	0.298	0.192	0.464	-5.369	0.000
	251. Budera	RCT	Follow-up	0.919	0.439	1.924	-0.223	0.823
	264. Malaisrie	Non-RCT	Follow-up	0.205	0.059	0.710	-2.499	0.012
	273. Araki	Non-RCT	Follow-up	1.190	0.519	2.731	0.412	0.681
	291. Kim JB	Non-RCT	Follow-up	0.634	0.362	1.108	-1.601	0.109
	312. Attaran	Non-RCT	Follow-up	0.315	0.172	0.576	-3.750	0.000
	525. von Oppell	RCT	Follow-up	0.192	0.009	4.210	-1.048	0.295
	528. Louagie	Non-RCT	Follow-up	0.120	0.033	0.430	-3.256	0.001
	563. Stulak	Non-RCT	Follow-up	0.207	0.010	4.491	-1.004	0.316
	710. Abreu Filho	RCT	Follow-up	0.667	0.088	5.035	-0.393	0.694
	715. Knaut	Non-RCT	Follow-up	0.309	0.135	0.708	-2.774	0.006
	721. Bando	Non-RCT	Follow-up	0.139	0.053	0.364	-4.026	0.000
	844. Deneke	RCT	Follow-up	5.091	0.496	52.285	1.369	0.171
	862. Raanani	Non-RCT	Follow-up	0.068	0.004	1.254	-1.808	0.071
	887. Jatene	Non-RCT	Follow-up	1.833	0.238	14.133	0.582	0.561
	891. Blomstrom-Lundqvist	RCT	Follow-up	3.179	0.125	80.789	0.701	0.483
	892. Chevalier	RCT	Follow-up	3.293	0.127	85.437	0.717	0.473
	894. Knaut	RCT	Follow-up	2.857	0.274	29.796	0.878	0.380
	897. Akpinar	RCT	Follow-up	0.500	0.043	5.803	-0.554	0.579
	898. Srivastava	RCT	Follow-up	1.177	0.234	5.911	0.198	0.843
	899. Van Breugel	RCT	Follow-up	0.394	0.074	2.106	-1.090	0.276
	900. Albrecht	RCT	Follow-up	2.662	0.122	58.119	0.622	0.534
	902. Boersma	RCT	Follow-up	0.339	0.014	8.478	-0.659	0.510
	904. Vasconcelos	RCT	Follow-up	0.287	0.011	7.704	-0.743	0.457
Random				0.486	0.355	0.665	-4.501	0.000



Meta Analysis

A

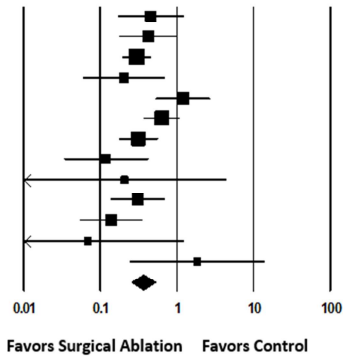
Model	Study name	Comparison	Time point	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	5. Gillinov	RCT	Follow-up	0.765	0.306	1.914	-0.572	0.568
	65. Wang	RCT	Follow-up	1.516	0.061	37.696	0.254	0.800
	251. Budera	RCT	Follow-up	0.919	0.439	1.924	-0.223	0.823
	525. von Oppell	RCT	Follow-up	0.192	0.009	4.210	-1.048	0.295
	710. Abreu Filho	RCT	Follow-up	0.667	0.088	5.035	-0.393	0.694
	844. Deneke	RCT	Follow-up	5.091	0.496	52.285	1.369	0.171
	891. Blomstrom-Lundqvist	RCT	Follow-up	3.179	0.125	80.789	0.701	0.483
	892. Chevalier	RCT	Follow-up	3.293	0.127	85.437	0.717	0.473
	894. Knaut	RCT	Follow-up	2.857	0.274	29.796	0.878	0.380
	897. Akpinar	RCT	Follow-up	0.500	0.043	5.803	-0.554	0.579
	898. Srivastava	RCT	Follow-up	1.177	0.234	5.911	0.198	0.843
	899. Van Breugel	RCT	Follow-up	0.394	0.074	2.106	-1.090	0.276
	900. Albrecht	RCT	Follow-up	2.662	0.122	58.119	0.622	0.534
	902. Boersma	RCT	Follow-up	0.339	0.014	8.478	-0.659	0.510
	904. Vasconcelos	RCT	Follow-up	0.287	0.011	7.704	-0.743	0.457
Fixed				0.910	0.588	1.410	-0.421	0.673



Meta Analysis

B

Model	Study name	Comparison	Time point	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	82. Yoo	Non-RCT	Follow-up	0.457	0.166	1.256	-1.518	0.129
	134. Ad	Non-RCT	Follow-up	0.428	0.175	1.044	-1.865	0.062
	141. Kim HJ	Non-RCT	Follow-up	0.298	0.192	0.464	-5.369	0.000
	264. Malaisrie	Non-RCT	Follow-up	0.205	0.059	0.710	-2.499	0.012
	273. Araki	Non-RCT	Follow-up	1.190	0.519	2.731	0.412	0.681
	291. Kim JB	Non-RCT	Follow-up	0.634	0.362	1.108	-1.601	0.109
	312. Attaran	Non-RCT	Follow-up	0.315	0.172	0.576	-3.750	0.000
	528. Louagie	Non-RCT	Follow-up	0.120	0.033	0.430	-3.256	0.001
	563. Stulak	Non-RCT	Follow-up	0.207	0.010	4.491	-1.004	0.316
	715. Knaut	Non-RCT	Follow-up	0.309	0.135	0.708	-2.774	0.006
	721. Bando	Non-RCT	Follow-up	0.139	0.053	0.364	-4.026	0.000
	862. Raanani	Non-RCT	Follow-up	0.068	0.004	1.254	-1.808	0.071
	887. Jatene	Non-RCT	Follow-up	1.833	0.238	14.133	0.582	0.561
Random				0.360	0.248	0.522	-5.401	0.000



Meta Analysis