SYSTEMATIC REVIEW

Cardiovascular Therapeutics

Surgical Maze Procedure as a Treatment for Atrial Fibrillation: A Meta-Analysis of Randomized Controlled Trials

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Surgical or modified Maze procedures have been promoted to treat atrial fibrillation (AF); however, few randomized controlled clinical trials (RCTs) examine their outcomes. The purpose of this meta-analysis is to compare the efficacy of surgical Maze procedures performed concomitantly with referral cardiac surgery versus pharmacologic therapy for the treatment of AF. We searched MEDLINE, Cochrane database, FDA web-portal, and clinicaltrials.gov for all RCTs comparing surgical Maze procedures with medical therapy for sinus rhythm maintenance. Primary outcomes were either freedom from AF within 12 months postprocedure off antiarrhythmic drug (AAD), or freedom from AF while taking an AAD. Secondary outcomes included operative mortality, all-cause mortality, hospital length of stay, and postoperative complications. Both fixed- and random-effects models were used for a meta-analysis of 9 randomized controlled trials (n = 472, of which 249 underwent a Maze procedure and 213 underwent referral surgery alone). The surgical Maze procedure significantly increased the odds of freedom from AF within 12 months compared with cardiac surgery alone (OR 5.22, 95% CI 1.71–15.88). There was significant heterogeneity among the trials for freedom from AF (chi-square = 15.98 for 4 degrees of freedom, $P = 0.003$). Among the two studies that fully reported AAD use, there was no evidence of improved survival free from AF and AAD therapy (OR 1.78, 95% CI 0.73–4.34). Among patients with valvular AF, surgical Maze procedures are associated with a decrease in AF one year postprocedure without significant increase in mean length of hospital stay, perioperative complications, operative, or all-cause mortality. Large RCTs defining rates of freedom from AF without AADs postprocedure, are still needed to evaluate outcomes and determine the appropriate role for surgical Maze procedures in the management of AF.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice, accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances [1]. AF causes significant morbidity and mortality, particularly in elderly patients and patients with significant valvular disease. It is estimated that over half of all patients undergoing valve repair or replacement also have AF. Even after mitral valve surgery, those patients who remain in AF have lower 3- and 5-year survival rates compared with those in sinus rhythm [2].

The increasing prevalence of AF coupled with the limited efficacy and safety profile of current antiarrhythmic medications has encouraged the continued development of nonpharmacologic procedures like surgical ablation [1,3–5]. Although the Cox-Maze III procedure is recognized as the standard for the surgical treatment of medically refractory AF, the traditional cut-and sew Maze has been increasingly supplanted by modified procedures designed to minimize technical complexity and

invasiveness, decrease cardiopulmonary bypass times, and reduce the risk of surgical complications while maintaining procedural efficacy [6–8]. These modifications include simpler lesion sets such as ablation limited to the left atrium, epicardial rather than endocardial lesion applications, and replacement of the cut-and-sew lesions with radiofrequency, microwave, and cryothermy tissue ablation. However, few randomized studies of the safety and efficacy of modified Maze procedures for treatment of AF are available. Furthermore, the success rates associated with these procedures have varied widely from 60% to 85% of patients free from AF at one year of follow-up [9–11].

To assess the efficacy and safety of the surgical Maze and modified Maze procedures for the elimination of AF, we performed a meta-analysis of randomized clinical trials comparing the surgical Maze or modified Maze procedure in the setting of cardiac surgery with nonablative, medical therapy for the treatment of AF.

Methods

Data Sources and Searches

A systematic search of MEDLINE was conducted with the following MeSH terms: "atrial fibrillation" AND "clinical trial [Publication Type]" AND "ablation OR maze." The query was limited to studies involving humans >19 years of age; written in English; and published since January 1, 1993. The same query was conducted in (1) the Cochrane database; (2) the FDA web-portal; and (3) clinicaltrials.gov. The bibliographies of the identified studies were also reviewed for additional studies meeting the inclusion criteria.

Study Selection

We included trials in which patients with AF referred for primary cardiac or valvular surgery were randomized to undergo the initial referral cardiac surgery alone versus the cardiac surgery in addition to a traditional Maze or modified Maze operation using alternative energy sources. Additional inclusion criteria included follow-up ≥6 months, and full-length peer-reviewed publication. Trials with surgical ablation in both treatment arms, with follow-up <6 months, or with a control group of <10 patients, were excluded.

Data Extraction and Quality Assessment

All studies that met the inclusion and exclusion criteria were independently reviewed with standardized data abstraction by two of the investigators (MHK and JPP). A third investigator (SMA) adjudicated any discrepancies. The results of the MEDLINE query included those reports identified by the other search methods (www.fda.gov, clinicaltrials.gov, Cochrane database, and bibliographies). Abstracted data included eligibility criteria, study population demographics, baseline characteristics, study design (including the treatment and control arms), follow up, and outcomes.

The primary outcomes of interest were: (1) freedom from AF within 12 months and (2) the composite endpoint of freedom from AF and freedom from an antiarrhythmic drug within 12 months postprocedure. When available, data were also abstracted on prespecified secondary measures of the efficacy and safety of the surgical ablation procedure including: survival (operative mortality and all-cause mortality); surgical revision; operative time including total time on bypass and duration of aortic cross-clamp; perioperative complications (pericardial effusion, tamponade, chest/sternal wound infection, endocarditis, mediastinitis, pneumothorax, pneumonia, sepsis, bleeding; thromboembolic events (transient ischemic attack, cerebrovascular accident, non-CNS embolism); left atrial diameter; improvement in left ventricular ejection fraction; hospital length of stay; postoperative rhythm status (AF, atrial flutter, atrial tachycardia, junctional rhythm) at time points immediately postoperatively, at discharge, and at 3-, 6-, 12-months postoperatively; use of AADs postoperatively; need for drugs to control ventricular response rate postoperatively; number of cardioversions; and need for postoperative pacemaker implantation. Outcomes were analyzed according to intention-to-treat. The study selection process according to QUOROM guidelines is outlined in Figure 1.

Data Synthesis and Analysis

Both fixed and random effects models were used to evaluate the effects of surgical ablation on the primary and secondary outcomes. Heterogeneity between studies was determined using Cochrane's Q statistic. Statistical testing was two-tailed, and statistical significance was declared when $\alpha < 0.05$. Although several methods can be used to combine the results of 2×2 contingency tables assuming a fixed effects model, we chose the method of Mantel-Haenszel [12]. For the random effects model, the estimates of the odds ratios were combined using an empirical Bayes estimator as described by Hedges and Olkin in 1985 [13]. This estimator has the property that it reduces to a fixed effects estimator if no heterogeneity is present. The estimates were computed using the FAST*PRO Software [14].

Because the mortality event rates were so small, conventional meta-analysis methods combining odds ratios

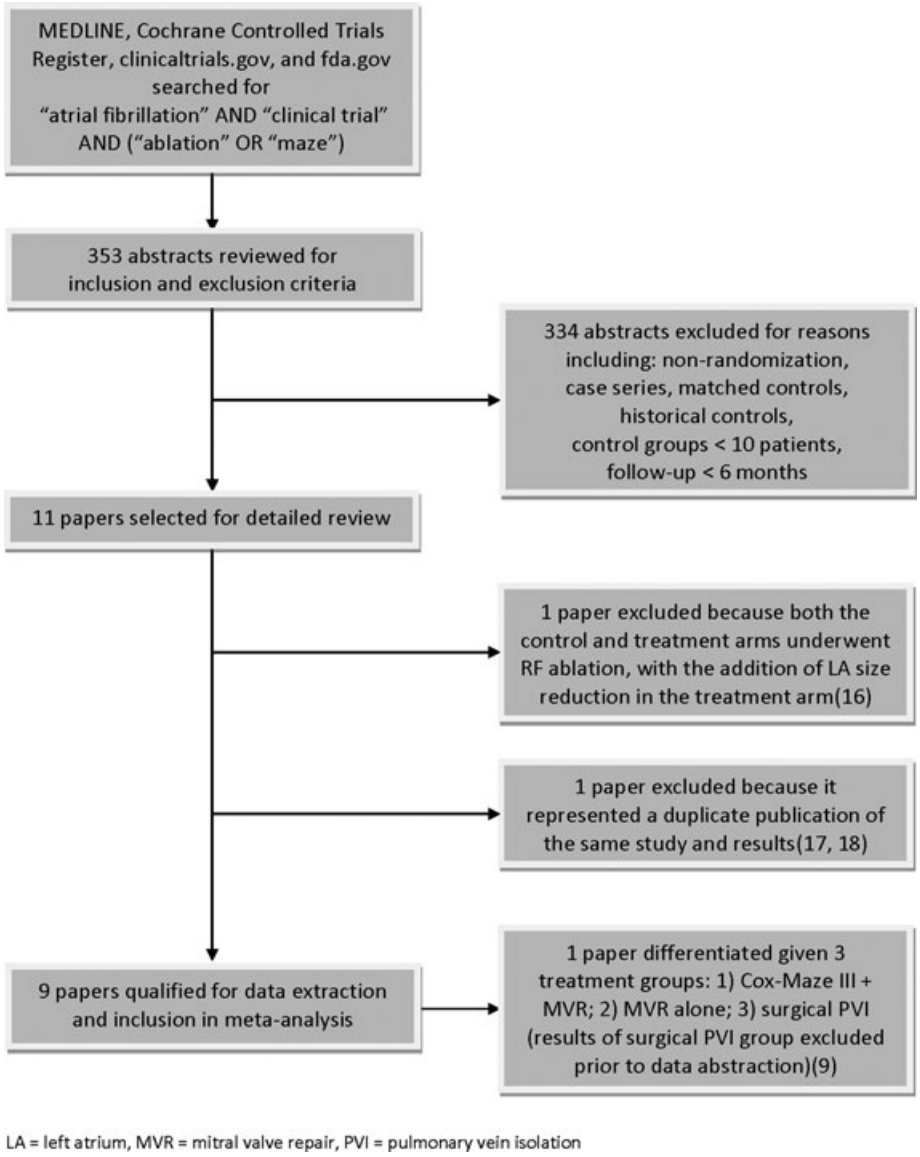

Figure 1 Flowchart of surgical Maze procedure trials used for the meta-analysis.

could not be used for such rare events. For example, the Jessurun et al. study reported 0/35 deaths in the surgical Maze arm and 0/10 in the control arm [15]. Although the result is informative with respect to the difference in rates, it does not provide an estimate of the odds ratio. The likelihood function for the difference is shown in Figure 2A. Note that 95% likelihood ratio confidence intervals for the difference in rates can be constructed from this study alone, giving values of −0.17 to 0.06.

For very small counts, the usual normal approximation to the likelihood function will not work and it is necessary to compute the exact likelihood function for the difference. If we denote the true rate in experimental group as θ_t and the true rate in the control group as θ_{nt}. The likelihood for a single study is proportional to:

$$L(\theta_t, \theta_{nt}) \propto \theta^{s_t}(1-\theta)^{n_t - s_t}\,\theta^{s_{nt}}(1-\theta_{nt})^{n_{nt} - s_{nt}}.$$

It is possible to numerically calculate the marginal likelihood function for the difference, $\theta_t - \theta_{nt}$, for each study. These likelihood functions can then be combined numerically to give maximum likelihood estimates and confidence intervals, or to give a posterior distribution [14]. We combined the results from all studies by combining their likelihoods (fixed effects model).

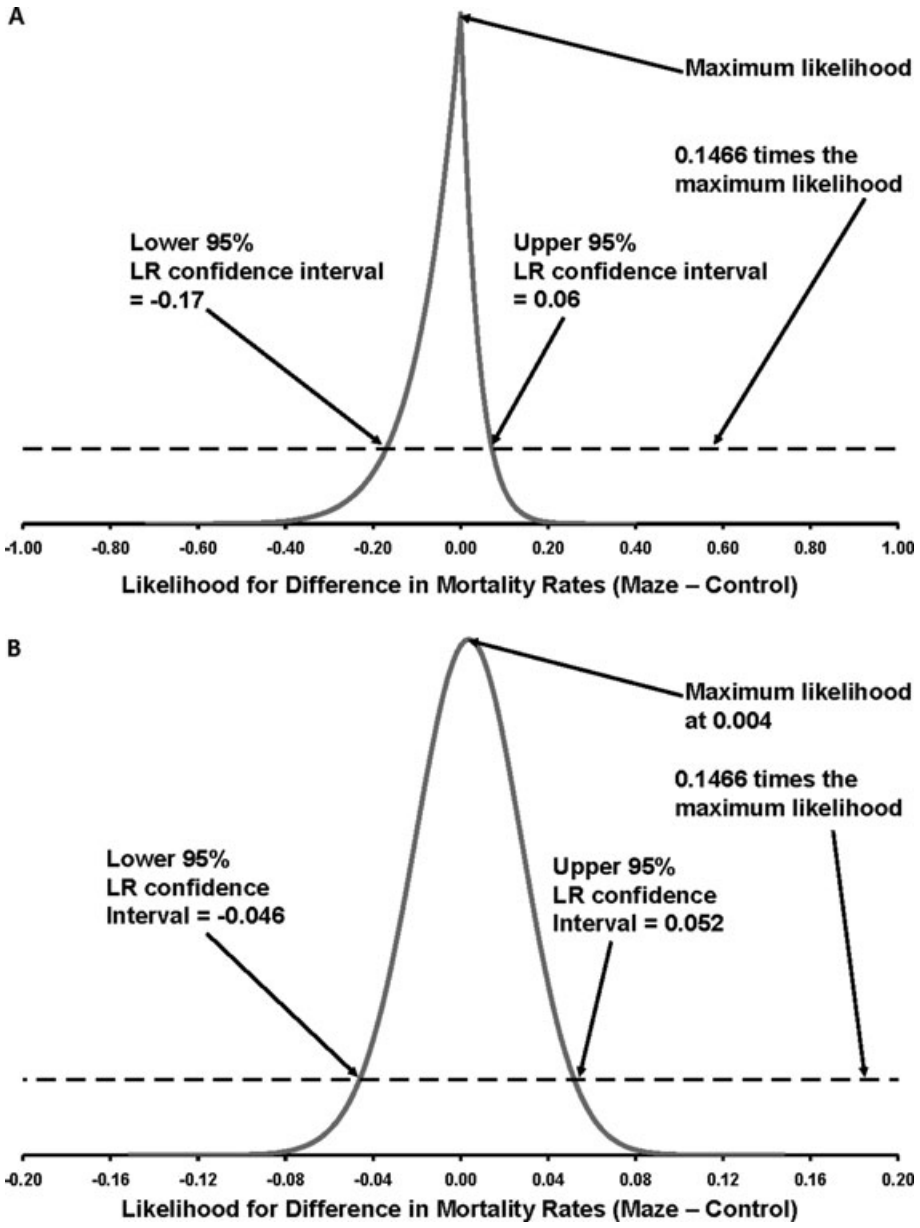

Figure 2 (**A**) Example of the likelihood function using the Jessurun et al. study (**B**) likelihood function for all studies combined.

Results

Search Results

A total of 353 abstracts were identified and reviewed for the inclusion and exclusion criteria (Figure 1). From this initial pool of abstracts, 342 abstracts were excluded for the following reasons: study of therapy other than surgical Maze, e.g., catheter ablation, imaging, drug therapy, device therapy, or other (n = 281); study of arrhythmia other than AF, e.g., atrial flutter, atrioventricular nodal reentrant tachycardia (n = 4); nonrandomized design (n = 39); control groups consisting of fewer than 10 patients or using historical or matched controls (n = 2); study was not a clinical trial (n = 16). Of the 11 remaining studies, one randomized study was excluded because the focus was on efficacy of left atrial size reduction surgery in addition to endocardial pulmonary vein isolation with radiofrequency ablation and thus both the treatment and control arms included ablation [16]. Another study was excluded because it was a duplicate publication with identical results [17,18]. The remaining 9 studies were included in this analysis (Table 1).

Table 1 Summary of randomized controlled trials included in meta-analysis

Study	Journal	Center	Total n	Inclusion criteria	Exclusion criteria	Control arm	Specified primary endpoint	Follow-up monitoring protocol	Anticoagulation postprocedure
Abreu Filho et al. [19]	Circulation (2005)	single	70	Permanent AF preexisting for more than 1 year; rheumatic MV disease	NR	Amiodarone (900–1200 mg/day postop); 200 mg/day after discharge from ICU	Cumulative frequencies of SR	12-lead EKG, Holter, TTE at 3, 6, 12 months	Minimum 3–6 months
Akpinar et al. [10]	Eur J Cardio-thorac Surg (2003)	single	67	History of persistent AF >6 months in patients undergoing minimally invasive MV surgery	Severe chest wall deformities (pectus excavatum); significant CAD; aortic valve insufficiency; lung adhesions; iliac artery disease	Amiodarone 150 mg IV postop then 0.5 mcg/kg/ min × 24 hrs, then 200 mg daily × 12 months	Freedom from AF	72 hr Holter during index hospitalization; 12-lead EKG at 6, 12, 12+ months	Mechanical valves anticoagulated indefinitely; otherwise, if pt in SR, then anticoagulation discontinued after 6 months
Blomstrom-Lundqvist et al. [20]	Eur Heart J (2007)	multi-center	71	Aged 18 to 80 years with permanent AF (≥3 months with failed or not attempted cardioversion); MV disease requiring MV surgery	NYHA class IV; previous cardiac surgery other than CABG; planned MV surgery combined with cardiac surgery other than CABG; tricuspid valvuloplasty; conditions imposing increased risk for a prolonged surgical procedure; permanent pacemaker secondary to AV block; hyperthyroidism; geographical reasons; unwillingness to participate	Prophylactic AAD (sotalol, flecainide, propafenone, disopyramide, amiodarone) ×3 months, then discontinued if no AF recurrence	Regained SR without AF recurrence 6 months postoperatively	12-lead EKG, medical history, physical exam, history of DCCV at 1, 2, 3, 6, 12 months postoperatively; no continuous rhythm monitoring performed	Minimum 3 months
de Lima et al. [9]	Ann Thorac Surg (2004)	single	30	Age 18 to 75 years with permanent AF lasting >6 months before surgery	Previous cardiac surgery; pregnancy; LVEF <20%	Pharmacologic or electrical cardioversion with maintenance of SR by use of amiodarone ×30 days	Maintenance of SR after mitral surgery	12-lead EKG at 2, 4, 6, 18, 24 months; exercise treadmill test and Holter at 6 months	Not fully reported or required by study

Table 1 Continued

Study	Journal	Center	Total n	Inclusion criteria	Exclusion criteria	Control arm	Specified primary endpoint	Follow-up monitoring protocol	Anticoagulation postprocedure
Doukas et al. [11]	JAMA (2005)	single	97	Required MV surgery and also had a history of continuous AF (defined as presence of uninterrupted AF for >6 months without evidence of spontaneous reversibility to SR and that was not possible to revert with medications or direct current cardioversion	Sick sinus syndrome; uncontrolled hyperthyroidism; permanent pacemaker; previous cardiac surgery	Amiodarone (or sotalol if intolerant to amiodarone)	Presence of SR at 12 months	48 hrs continuous monitoring; then daily 12-lead EKG during index hospitalization and 12-lead EKG at 3, 6, 12 months and 12-lead EKG and Holter if symptoms	3 months
Jessurun et al. [15]	J Cardiovasc Surg (2003)	single	35	Age <75 years selected for MV surgery with symptomatic AF, irrespective of type and duration of arrhythmia	Aged >75 or <18 years; concomitant cardiac surgery of aortic valve disease; congenital malformations; CABG with >3 distal anastomoses; vascular surgery; prior MV surgery; LVEF < 25%; PAP > 75% of systemic pressure; PVR > 5 Wood units; factors negatively interfering with cardiac surgical outcomes including severe lung disease; impaired renal function (creatinine >150 μmol/L); limited life expectancy (<2 years) for all causes; pregnancy; unwillingness to participate; or inability to understand or sign the written informed consent	Sotalol, digitalis, or quinidine were prescribed	SR without AF following mitral surgery	Holter and bicycle stress testing at 3 and 12 months	3 months (if evidence of persistent SR)
Khargi et al. [17]	Ann Thorac Surg (2001)	single	30	Documented chronic AF, preexisting for more than 1 year, and MV disease	NR	Sotalol 40 mg bid on POD #1; increased to 80 mg bid on POD#3; increased to 160 mg bid if no bradycardia × 6 months; then metoprolol	Cumulative frequency of SR	DCCV if AF in 1st 24 hrs; if AF after POD#12, or after 3 or 6 months, then DCCV × 2; EKG at 3, 6, 9, 12 months; 24 hr Holter and TTE at 6 and 12 months	Warfarin started on POD#1 and continued for 6 months

Table 1 Continued

Study	Journal	Center	Total n	Inclusion criteria	Exclusion criteria	Control arm	Specified primary endpoint	Follow-up monitoring protocol	Anticoagulation postprocedure
Schuetz et al. [21]	Eur J Cardio-thorac Surg (2003)	single	43	Permanent AF, who had been unsuccessfully treated previously, presented to clinic for surgical treatment of valve disease and/or required CABG	NR	Amiodarone or sotalol ×3 months if SR restored	Not formally stated	Continuous monitoring until ICU discharge; then 24 hr Holter and 12-lead EKG prior to hospital discharge; repeat EKG at 3, 6, 12 months w/ 24 hr Holter at 12 months	Minimum 3 months
Vasconcelos et al. [22]	Arq Bras Cardiol (2004)	single	29	Diagnosis of chronic rheumatic heart disease–established according to clinical and echo criteria; persistent AF (at least 6 months prior to study); important MV disease with indication of surgical treatment; LA diameter ≤65 mm established on M-mode echo; age ≤ 60 years	Antecedents of acute MI; atherosclerotic coronary lesions of any vessel > 50%; important tricuspid insufficiency (established by clinical, echo and hemodynamic criteria); tricuspid stenosis; important pulmonary hypertension (established by hemodynamic or echo criteria defined as systolic PAP ≥ 60 mmHg; significant LV dysfunction (LVEF by echo ≤ 30% and/or LV diameter ≥70 mm; idiopathic dilated cardiomyopathy; hypertrophic cardiomyopathy; Chagasic cardiomyopathy; collagenoses; COPD; chronic renal insufficiency requiring dialysis; primary thyroid disease; contraindications to the use of amiodarone	Amiodarone for postoperative AF or recurrence	Not formally stated	During hospitalization: daily EKG or cardiac monitoring w/ portable device. After discharge: clinical and EKG assessment monthly w/ TTE after second postoperative month	NR

AAD, antiarrhythmic drug; AF, atrial fibrillation; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DCCV, direct-current cardioversion; EF, ejection fraction; EKG, electrocardiogram; LA, left atrial; LV, left ventricular; MI, myocardial infarction; MV, mitral valve; NR, not reported; NYHA, New York Heart Association; PAP, pulmonary artery pressure; POD, postoperative day; PVR, pulmonary vascular resistance; SR, sinus rhythm; TTE, transthoracic echocardiogram.

Trial Characteristics and Study Quality

The nine randomized controlled trials included in this analysis were studies of Cox-Maze III or modified Maze ablation procedures and enrolled a total of 472 patients (Table 1) [9–11,15,17,19–22]. Eight trials were single center and none of the trials was performed in the United States. Five studies explicitly excluded patients with paroxysmal AF; however, eight of the nine studies enrolled only patients with persistent/permanent AF. Only one study included both patients with paroxysmal AF (n = 15) and persistent/permanent AF (n = 20) [15]. Although all nine trials randomized patients to the surgical Maze or a modified Maze procedure versus a nonablation treatment strategy, significant variation existed among the control arm strategies (Table 1). Of note, deLima et al. randomized 30 patients to one of 3 treatment groups: Cox-Maze III plus mitral valve repair/replacement; mitral valve correction alone; or surgical pulmonary vein isolation; however, the results of the 10 patients randomized to the surgical pulmonary vein isolation group were excluded prior to data abstraction and were not included in this analysis. There was also substantial variation in reported primary endpoints among the nine trials with 2 studies reporting only "cumulative frequencies of sinus rhythm" at 12 months as opposed to freedom from AF within 12 months [17,19]. Although 3 additional studies did not specify an *a priori* endpoint of freedom from AF within 12 months, these studies still reported these data for analysis [20–22]. Finally, although all nine studies were randomized, none of them had blinded postprocedure follow-up. Postprocedure follow-up monitoring protocols and anticoagulation regimens varied widely among the nine trials (Table 1).

Baseline Patient Characteristics

Across the nine trials, only limited baseline and demographic characteristics were uniformly reported. Combined, the nine trials enrolled 227 (48.1%) males, of which 122 underwent a surgical Maze procedure and 245 females (59.1%), of whom 127 underwent a surgical Maze procedure. Averaged across all nine trials, mean age of the patients who underwent a concomitant surgical Maze procedure was 61.2 years, versus 60.4 years old in the control groups (Table 2).

The mean duration of AF among patients in the surgical Maze treatment arms was reported in 7 studies and ranged considerably from 3.8 ± 2.84 months in the Schuetz et al. study to 66.1 ± 57.4 months in the Abreu Filho et al. study (Table 2). None of the trials reported baseline antiarrhythmic drug therapy status prior to enrollment. The mean LA diameter of the patients who underwent a surgical maze procedure was 58.7 mm versus 59.7 mm in the control arms. The mean LVEF was 57.3% in the surgical Maze arm versus 58.8% in patients randomized to the control arms.

Surgical Maze Ablation Techniques

The surgical ablation techniques varied among the nine studies in terms of lesion sets, epicardial versus endocardial approaches, and left atrial versus biatrial patterns, energy sources, and technical equipment (Table 3). Only one study performed the classic Cox-Maze III cut-and-sew operation [15]. A single study used cryoablation [20], and a single study used microwave ablation [21].

Among the 3 trials that reported total procedure time, the mean total duration of the combined Maze plus the referral cardiac surgery was 226.1 minutes compared with a total operative time of 198.6 minutes in the control groups [10,17,21]. The mean cardiopulmonary bypass time across all nine trials was 128.3 minutes for the patients who underwent a concomitant Maze procedure compared with only 103.8 minutes for the patients in the control groups. Mean cross clamp time was 42.9 minutes among patients in the treatment groups versus only 32.3 minutes among patients in the control groups (Table 3).

Efficacy of the Surgical Maze

After excluding the 3 studies that did not report freedom from AF within 12 months as well as the single study that enrolled patients with paroxysmal AF, significant heterogeneity persisted amongst the remaining 5 studies using Cochrane's Q-statistic (chi-square = 15.98 for 4 degrees of freedom, $P = 0.003$). We combined the results using both fixed effects (Mantel-Haenszel) and random effects (empirical Bayes) models (Table 4A). The combined results are shown in Figure 3A. Both models suggest that a surgical Maze procedure greatly increases the odds of freedom from AF within 12 months postprocedure. Note that the combined effect based on the random effects model is larger and wider than the fixed effects model. The estimated odds ratio for the random effects model is 5.22 (95% CI 1.71 to 15.88).

Only 2 studies provided information on the combined endpoint of freedom from both AF and from an AAD within 12 months (Table 4B). The combined results are presented in Figure 3B. The estimated combined odds ratio for the empirical Bayes model was 1.78 (95% CI 0.73 to 4.34).

The mean length of hospital stay was reported in five studies [11,15,20–22]. Combined across studies, patients in the treatment groups were hospitalized for a

Table 2 Baseline patient characteristics in randomized controlled trials

Study	Patients n	Mean age years	Males	Duration of AF months	LA diameter mm	LVEF%
Abreu Filho et al.						
Maze	42	55.4 ± 12.8	14	66.1 ± 57.4	61.1 ± 7.9	64.2 ± 8.8
Control	28	50.7 ± 9.7	12	43.8 ± 28.5	58.8 ± 4.7	66.6 ± 10.5
Akpinar et al.						
Maze	33	53 ± 10	13	19.87 ± 10.6	62.45 ± 10.5	55.19 ± 6.3
Control	34	50 ± 8	9	21.97 ± 13.9	66.66 ± 9.0	55.03 ± 8.1
Blomstrom-Lundqvist et al.						
Maze	36	69.5 ± 7.9	25	26 ± 33 (3–120)[a]	61 ± 11 (41–94)	53.6 ± 9.1 (29–67)
Control	35	65.6 ± 8.8	26	33 ± 54 (3–240)	58 ± 7 (43–75)	57 ± 12 (20–77)
de Lima et al.						
Maze	10	50.1 ± 15.3	3	14 (9–63)[b]	60 ± 16	0.643 ± 0.1
Control	10	50.1 ± 15.4	6	16.5 (13–24)	62 ± 12	0.64 ± 0.1
Doukas et al.						
Maze	49	67.2 ± 9	31	57 ± 55.1	58 ± 0.7	57 ± 6
Control	48	67 ± 8	24	46.7 ± 64.3	60 ± 1.1	58 ± 7
Jessurun et al.						
Maze	25	64 ± 12	14	NR	53 ± 9 (38.5–71.2)	45 ± 15 (25–66)
Control	10	64 ± 9	5	NR	56 ± 7 (49–68)	45 ± 6 (37–51)
Khargi et al.						
Maze	15	64.7	6	NR	NR	NR
Control	15	69.7	3	NR	NR	NR
Schuetz et al.						
Maze	24	64.57 ± 10.0	12	3.8 ± 2.84	54.9 ± 11	NR
Control	19	70.21 ± 7.9	14	9.21 ± 9.24	54.37 ± 17.1	NR
Vasconcelos et al.						
Maze	15	49.40 ± 10.1	4	23.80 ± 19.9	55.27 ± 5.02	68.33 ± 8.8
Control	14	50.79 ± 9.7	6	33.85 ± 28.5	55.86 ± 4.74	66.07 ± 10.6

AF, atrial fibrillation; LA, left atrial; LVEF, left ventricular ejection fraction; NR, not reported; SD, standard deviation.
[a]Mean ± 1 SD with range in brackets.
[b]Median (25^{th}–75^{th} percentiles).

mean of 13.7 days, which was similar to patients in the control groups, who were hospitalized for a mean of 13.6 days.

Mortality and Complications of the Surgical Maze

All-cause mortality was reported in all but one trial [20]. Based on the eight trials that reported all-cause mortality, of 213 patients in the treatment groups, 14 patients died (6.6%) and of 178 patients in the control groups, 11 died (6.2%) [9–11,15,17,19,21,22]. Combining the estimates for the difference in mortality rates resulted in a maximum likelihood estimate of 0.004 (slightly higher rates for the Maze group) with 95 percent likelihood ratio confidence intervals of −0.046 to 0.052 (Figure 2B). There was no evidence of a significant difference in mortality between the two groups. All studies reported operative mortality rates: 4.0% in the treatment groups (n = 10/249) and 3.3% in the control groups (n = 7/213). Rates of surgical revision were not different between the treatment and control groups in the studies that reported this measure.

For the purpose of this analysis, we defined major complications as any chest/sternal infections, mediastinitis, endocarditis, tamponade, pericardial effusion, pneumonia, sepsis, bleeding, thromboembolic events, and the need for permanent pacing postoperatively. Although these were the major complications most often reported in the literature, not all studies reported event rates for each of these complications (Table 5). The overall rate of major complications in the treatment groups was 24.4% (61 events per 249 patients), which was comparable to the rate in the control groups of 24.9%. Likewise, thromboembolic events occurred with similar frequency between the treatment and control groups. However, there was a preponderance of thromboembolic events in the treatment group of the Blomquist et al. study. Although not all studies reported the incidence of patients requiring permanent pacemaker implantation, of the 7 studies that provided these data, 12 patients in the surgical ablation group and 11 patients in the control arm required implantation of a permanent pacemaker within

Table 3 Characteristics of the surgical Maze treatment arms

Study	Energy Source	Description of Maze Procedure and Modifications		Mean Operation Time minutes	Mean CPB Time minutes	Mean Cross-Clamp Time minutes
Abreu Filho et al.	SICTRA set-up consisting of a RF generator (CardioRhythm-ATAKR, Medtronic, Minneapolis, MN) and a unipolar catheter (Cardioblate, Medtronic, Minneapolis, MN)	Modified CM III procedure using biatrial endocardial intra-atrial transmural lesions; all atrial incisions used in CM III replaced by ablation lines except for incisions to enter right and left atrial cavities; both atrial appendages excised	Maze	NR	107.2 ± 21.1	67.5 ± 13.5
			Control	NR	78.2 ± 24.4	47.1 ± 15.8
Akpinar et al.	Unipolar RF catheter and power generator (Cardioblate, Medtronic, Minneapolis, MN)	Modified CM III procedure with either LA only or biatrial endocardial Maze; biatrial procedure only performed in patients needing tricuspid valve or ASD repair or in patients with history of atrial flutter; LAA oversewn from inside the LA; epicardial ablation lines performed around base of RAA	Maze	192.5 ± 20.4	140.5 ± 34.3	88.5 ± 13.4
			Control	185.4 ± 25.5	128.3 ± 28.3	78.9 ± 9.4
Blomstrom-Lundqvist et al.	Cryoablation (SurgiFrost™ CryoAblation System, CryoCath Technologies Inc., Quebec, Canada)	LA epicardial cryoablation lesions created around each pair of PVs, between the left and right pairs and connecting the LUPV to the LAA	Maze	NR	146.6 ± 27.9 (95–215)[a]	87.4 ± 95.2 (53–181)
			Control	NR	119.2 ± 33.0 (73–193)	84.4 ± 23.3 (52–142)
de Lima et al.	Cut & sew + electrocoagulation	Modified CM III procedure with all of the standard cut & sew CM III lesions performed, except that the terminal points of the incision were performed by electrocoagulation instead of cryoablation	Maze	NR	115.3 ± 25	NR
			Control	NR	68.3 ± 22	49.1 ± 19
Doukas et al.	Monopolar RF catheter ((EP Technologies, Boston Scientific Corp, San Jose, CA)	LA endocardial RF lesions isolating left PVs, semilunar RF line isolating right PVs, RF line connecting the 2 encircling lines, the obliterated LAA, and the mitral valve annulus; LAA oversewn from inside the LA	Maze	NR	106 (34)[b]	70 (26)
			Control	NR	99 (37)	64 (28)
Jessurun et al.	Cut & sew	Unmodified CM III	Maze	NR	155 ± 27 (118–234)	90 ± 24 (66–145)
			Control	NR	97 ± 27 (71–155)	60 ± 18 (37–88)
Khargi et al.	SICTRA set-up consisting of a SICTRA catheter (Sprinklr; Medtronic, Minneapolis, MN) and a RF generator (CardioRhythm-ATAKR, Medtronic, Minneapolis, MN)	Modified CM III procedure combining both cut & sew lesions and epicardial and endocardial RF lesions; both RAA and LAA were excised, except that LAA was occasional ablated if adhesions prevented resection	Maze	270 (232–323)[c]	188 (165–230)	103 (86–134)
			Control	190 (128–314)	127 (60–197)	84 (38–112)

Table 3 Continued

Study	Energy Source	Description of Maze Procedure and Modifications		Mean Operation Time minutes	Mean CPB Time minutes	Mean Cross-Clamp Time minutes
Schuetz et al.	Microwave ablation system (AFx Inc., Fremont, CA) consisting of a surgical ablation probe (FLEX 2) connected by a coaxial cable to a microwave generator	LA endocardial microwave ablation starting at the mural mitral annulus, continuing between the orifices, ending at the mural annulus connecting completed circles within the PVs; LAA oversewn from inside LA; excluded LAA surrounded by another continuous ablation line starting from LUPV	Maze	244.73 ± 63.1	120.59 ± 24.8	99.59 ± 24.8
			Control	228.95 ± 62.4	103.79 ± 45.1	77 ± 44.3
Vasconcelos et al.	Cut & sew	Left atrial cut & sew lesions isolating the LA posterior wall encompassing the ostia of the PVs; LAA was sectioned and sutured at its base; two additional incision performed uniting the isolated area to the mitral ring and to the base of the LAA	Maze	NR	106 ± 17.3 (60–124)	NR
			Control	NR	78.2 ± 24.4 (35–120)	NR

ASD, atrial septal defect; CM III, Cox Maze III; CPB, cardiopulmonary bypass; LA, left atrium; LAA, left atrial appendage; LUPV, left upper pulmonary vein; NR, not reported; PV, pulmonary vein; RAA, right atrial appendage; RF, radiofrequency; SD, standard deviation.
[a]Mean ±1 SD with range in parentheses.
[b]Mean with 1SD in parentheses.
[c]Mean with range in parentheses.

Table 4A Randomized controlled trials reporting results on freedom from AF within 12 months

Study	Maze		Control	
	Free from AF	Total n	Free from AF	Total n
Akpinar et al.[a]	28	33	3	34
Blomstrom-Lundquist et al.	22	36	15	35
de Lima et al.[b]	6	10	3	10
de Vasconcelos et al.[c]	12	15	5	14
Schuetz et al.	15	24	9	19
COMBINED	83	118	35	112

AF, atrial fibrillation.
[a]Median follow-up was 10 months.
[b]Reported follow-up at 10 months.
[c]Mean follow-up was 10.3 months in Maze group and 11.5 months in control group.

12 months postprocedure [9–11,17,19,20,22]. The rate of adverse events associated with antiarrhythmic drug therapy was not uniformly reported. None of the 9 RCTs included quality of life data.

Discussion

To define the safety and efficacy of surgical ablation for the treatment of AF, we conducted a meta-analysis of 9 randomized controlled trials. There are three main findings in our analysis. First, when performed in addition to cardiac surgery, the Maze procedure is associated with a significant increase in the odds of freedom from AF at 12 months of follow-up. Secondly, the Maze procedure is not associated with a significant increase in morbidity or mortality. Finally, despite an increased odds of freedom from AF, the limited available data suggest that the Maze procedure does not provide an incremental advantage over nonablative therapy in the combined endpoint of freedom from antiarrhythmic drug therapy and AF within one year.

Given the increasing prevalence of AF, its associated morbidity and mortality, and the disappointing efficacy and toxicity of available pharmacologic therapies, procedural therapies have become more attractive options for patients with long-standing, symptomatic, medically refractory AF. In the U.S., roughly 12,000 patients undergo catheter ablation for AF and 2000 patients undergo a

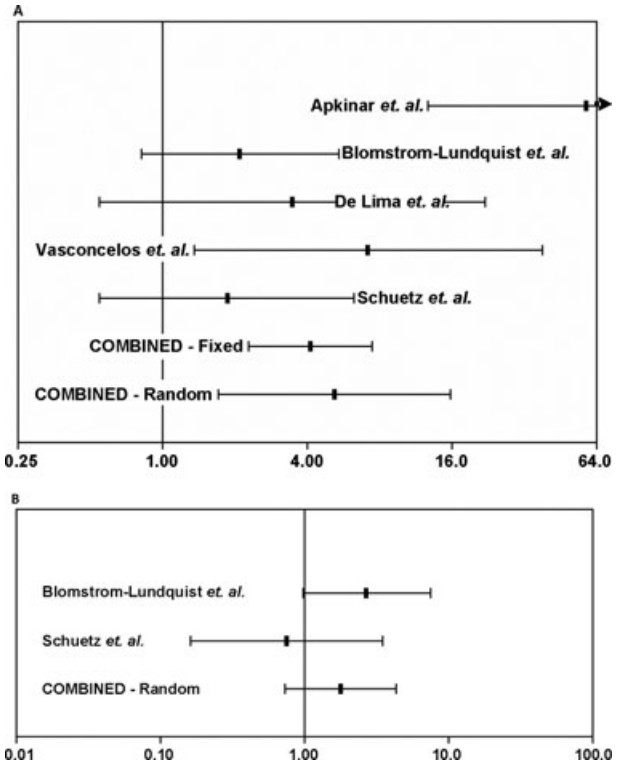

Figure 3 (**A**) Odds ratio for freedom from AF within 12 months postsurgical Maze (**B**) Odds ratio for freedom from both AF and AADs within 12 months postsurgical Maze.

Table 4B Randomized controlled trials reporting results on freedom from AF within 12 months

Study	Maze		Control	
	Free from AF & AAD	Total n	Free from AF & AAD	Total n
Blomstrom-Lundquist et al.	16	36	8	35
Schuetz et al.	4	24	4	19
COMBINED	20	60	12	54

AAD, antiarrhythmic drug; AF, atrial fibrillation.

surgical procedure for AF annually [23]. The Cox-Maze III operation has been promoted as the gold standard surgical ablation for the treatment of AF and has been reported in multiple case series to successfully eliminate AF in over 90% of patients, many of whom had already failed multiple AADs [24–27]. However, despite this reported efficacy, the widespread adoptability has been limited due to the technical complexity of the standard procedure and its attendant operative risks and possible complications like mediastinitis, thromboembolic events, and the need for permanent pacing postoperatively. Additionally, acceptance of a surgical ablation for patients with isolated AF is often precluded due to the required sternotomy and cardiopulmonary bypass time. As a result, a plethora of modifications to the traditional Cox-Maze III procedure have evolved with a wide range of reported efficacies [11].

The studies that have examined the outcomes of the surgical Maze or a modified Maze procedure with respect to the type of AF or the type of patient have been mostly case series with no controls, using diverse patient populations, and using different surgical techniques, approaches, tools, lesion sets, and energy sources. The lack of randomized trials with concurrent control groups limits interpretation of the effects of corrected valvular disease relative to rhythm-control [20]. This difficulty is further compounded by the fact that the published studies of the surgical Maze or modified Maze procedure are very heterogeneous in terms of patient selection including factors such as the earlier timing for valve interventions relative to disease progression; reliability of lesion transmurality, different techniques, approaches, tools, and lesion sets; thoroughness/extent of follow-up and intensity of the postoperative treatment strategy; methods of rhythm assessment and unknown burden of AF given lack of continuous rhythm monitoring; and terminology and methods of reporting success in AF elimination [28].

In the absence of data from large randomized clinical trials, meta-analyses may inform decision making in relation to surgical ablation of AF. Although other groups have performed systematic reviews and meta-analyses of published studies, these analyses did not exclude studies on the basis of study methods, sample size, degree of follow-up, patient selection, definitions of AF, or definition of successful AF elimination and have often pooled extremely heterogeneous studies [29–31]. This extreme heterogeneity among the pooled studies coupled with the disparate methods used to collect and report arrhythmia suppression outcomes has hampered interpretation of those meta-analyses [23,32].

Unlike other meta-analyses, our meta-analysis included only those randomized trials with a control arm that enrolled patients with persistent or permanent AF and reported the primary endpoint of freedom from AF within 12 months postprocedure. Using the more widely reported endpoint of "freedom from AF" defines any recurrence as a procedural failure and may underestimate clinical efficacy; however, although many studies describe "cumulative incidence of sinus rhythm," this reporting measure underestimates recurrence rates and overestimates procedural success. This approach reduces heterogeneity and facilitates interpretation of our findings. It is noteworthy that although,

Table 5 Secondary outcomes and perioperative complications

Study	Patients n	All-Cause Mortality	Operative Mortality	Surgical Revision	Total Hospital Stay days	Thromboembolic Events	Permanent Pacemaker
Abreu Filho et al.							
Maze	42	2	1	NR	NR	0	1
Control	28	2	1	NR	NR	0	1
Akpinar et al.							
Maze	33	2	1	1	NR	0	1
Control	34	3	1	1	NR	2	0
Blomstrom-Lundqvist et al.							
Maze	36	NR	1	2	8.0 ± 7.0 (4–44)[a]	4	7
Control	35	NR	0	2	8.0 ± 3.9 (4–22)	1	4
de Lima et al.							
Maze	10	1	0	0	NR	0	0
Control	10	0	0	1	NR	1	0
Doukas et al.							
Maze	49	3	3	2	11.9 ± 5.5	2	0
Control	48	4	4	0	12.2 ± 7.1	1	1
Jessurun et al.							
Maze	25	0	0	NR	15.7 ± 5.7	0	2
Control	10	0	0	NR	14.1 ± 2.9	1	4
Khargi et al.							
Maze	15	4	2	NR	NR	NR	NR
Control	15	1	0	NR	NR	NR	NR
Schuetz et al.							
Maze	24	1	1	NR	21.5 ± 13.3	1	1
Control	19	1	1	NR	20 ± 11.2	0	1
Vasconcelos et al.							
Maze	15	1	1	1	17.8 ± 10.2 (7–42)	1	NR
	14	0	0	1	23 ± 24.2 (7–92)	0	NR
Control							

Study	Chest/Sternal Infection	Mediastinitis	Endocarditis	Tamponade	Pericardial Effusion	Pneumonia	Sepsis	Bleeding
Abreu Filho et al.								
Maze	4	1	0	NR	1	3	1	NR
Control	0	0	1	NR	3	1	0	NR
Akpinar et al.								
Maze	0	NR	0	1	NR	1	NR	1
Control	1	NR	0	2	NR	0	NR	1
Blomstrom-Lundqvist et al.								
Maze	1	NR	NR	0	NR	1	1	3
Control	1	NR	NR	1	NR	0	1	3
de Lima et al.								
Maze	NR	NR	NR	0	0	NR	NR	NR
Control	NR	NR	NR	1	1	NR	NR	NR
Doukas et al.								
Maze	8	NR	NR	NR	NR	NR	3	NR
Control	9	NR	NR	NR	NR	NR	2	NR
Jessurun et al.								
Maze	NR	NR	NR	NR	NR	NR	NR	NR
Control	NR	NR	NR	NR	NR	NR	NR	NR

Table 5 Continued

Study	Chest/Sternal Infection	Mediastinitis	Endocarditis	Tamponade	Pericardial Effusion	Pneumonia	Sepsis	Bleeding
Khargi et al.								
Maze	4	1	NR	NR	NR	NR	NR	1
Control	1	0	NR	NR	NR	NR	NR	0
Schuetz et al.								
Maze	NR	NR	NR	NR	NR	NR	NR	NR
Control	NR	NR	NR	NR	NR	NR	NR	NR
Vasconcelos et al.								
Maze	NR	NR	0	1	NR	0	1	1
Control	NR	NR	1	4	NR	1	1	0

NR, not reported

[a]Reported mean ±1 SD with range in brackets.

we did not detect a significant difference in freedom from both AF and AADs between patients who underwent cardiac surgery alone (51.9%) versus those who underwent cardiac surgery and a concurrent Maze procedure (53.3%), the number of studies that included data on the freedom from antiarrhythmic drug therapy was extremely limited. Thus, this issue deserves further study.

Given the growing numbers of patients with AF, its associated morbidity and mortality, escalating health care costs associated with hospitalizations, outpatient care and medical therapy for AF, and the lack of consistent efficacy and safety of currently available antiarrhythmic medications, more invasive management strategies including surgical, catheter- and device-based therapies are emerging as acceptable alternatives [33,34]. As such, the most recent ACC/AHA guidelines were expanded to now include catheter ablation as a Class IIa recommendation for second line treatment in selected AF patients [1]. Recently published meta-analyses evaluating the efficacy of percutaneous pulmonary vein isolation compared to AADs for the treatment of AF have shown rates of freedom from AF (defined as no AF recurrence at 12 months postprocedure) ranging from 65% to 75%, which are comparable to the 70% rate of freedom from AF at 1 year for the surgical Maze procedures performed in the RCTs included in this meta-analysis [35–37]. At this time there are no RCTs comparing surgical ablation with percutaneous catheter ablation.

Substantial research and development efforts continue to focus on novel techniques and tools for improving procedural time, efficacy, safety, and durability of both surgical (open-chest as well as minimally-invasive, closed chest procedures) and catheter ablations. These innovations have resulted in an accelerated growth and interest in surgical ablation and catheter ablation as treatment options for a larger proportion of the AF patient population. Highlighting the rapid advancement of non-pharmacologic therapies for AF, the FDA's Circulatory System Medical Devices advisory panel has convened multiple meetings to discuss issues relating to the regulation of devices intended for the treatment of AF as well as how to design clinical trials to evaluate such therapies [38,39].

Study Limitations

Our study has some limitations. As with any meta-analysis, we cannot exclude the possibility of publication bias and our inclusion of only randomized controlled trials may not reflect the experience of patients treated in general clinical practice. Due to relatively small sample sizes of the individual studies and the few randomized clinical trials, we combined studies of the classic Cox-Maze III surgery with modified Maze procedures using alternative ablative energy sources—each of which affect atrial tissue differently in ways that may not be captured quantitatively—and several of which were combined in a single modified procedure. Furthermore, the umbrella of modified surgical Maze procedures included both left atrial and biatrial lesion sets. Finally, as we did not have access to the original data, our findings may be affected by errors from extrapolation of data and combination of data from multiple control groups into one group through weighting. To minimize such errors, we double-adjudicated all data abstraction and unclear cases were adjudicated by a third reviewer. Although the studies we included were all published between 2001 and 2007, surgical ablation expertise, techniques, and tools have changed over time and may have further contributed to differences in the reported survival and freedom from AF between studies.

Conclusions

Compared with a nonablative treatment strategy, among patients with persistent AF and underlying valvular disease, surgical ablation is associated with a markedly increased freedom from AF within one year postprocedure without a significant increase in the mean length of hospital stay, all-cause mortality, operative mortality, or perioperative complications. Large, multicenter, randomized trials are still needed to assess the long-term efficacy and safety of surgical Maze procedures for the maintenance of sinus rhythm. Our study also highlights the need for improved standardization and uniformity of reporting to enable more reliable evaluations of these surgical procedures.

Conflict of Interest

Melissa H. Kong has no disclosures, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Vic Hasselblad has no disclosures and also had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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