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Original Article

Factors associated with maintenance of sinus rhythm after surgical ablation in patients with concomitant atrial fibrillation: a systematic review and meta-analysis

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Abstract: Objective: The treatment efficacy of surgical ablation in patients with atrial fibrillation (AF) remains controversial. It is currently difficult to identify what kinds of AF patients may benefit most from this surgical strategy. The present meta-analysis systematically reviewed relevant clinical trials to identify the factors that affect sinus rhythm maintenance after surgical AF ablation (SAFA). Methods: From their inception to Mar 2015, the trials that discuss multiple risk factor interventions for sinus rhythm maintenance after SAFA were retrieved from the MEDLINE, PubMed, Cochrane Library, and EMBASE databases. Study characteristics included 11 factors related to the demographics, cardiac conditions, cardiac morbidity, and comorbidities. Results: According to the inclusion and exclusion criteria, 11 trials that involved 1099 patients were screen out from 2431 studies for meta-analysis. Of the 12 potential risk factors, 3 showed significant associations with sinus rhythm maintenance and AF recurrence, i.e., duration of AF (mean difference: 2.05; 95% confidence interval: 0.29-3.80; P=0.0005), left atrial diameter (mean difference: 6.24; 95% confidence interval: 4.85-7.62; P<0.0001), and tricuspid valve disease (odds ratio: 2.95; 95% confidence interval: 1.66-5.23; P=0.0002). Other factors had no significant associations with sinus rhythm maintenance. Conclusions: Duration of AF, left atrial diameter, and tricuspid valve disease are the main factors affecting sinus rhythm maintenance after SAFA. Patients with long-standing AF, large left atrial diameter, and/or tricuspid valve disease are more likely to fail in sinus rhythm maintenance and suffer from recurrent AF after SAFA.

Keywords: Atrial fibrillation, surgical ablation, cardiac function, statistics, meta analysis, postoperative care

Introduction

Atrial fibrillation (AF) is the most common tachyarrhythmia encountered in clinical practice. There are over 2.3 million people suffering from AF in the United States, and this population is expected to reach 5.6 million by 2050 [1]. A report has shown that surgical ablation is more effective than catheter ablation in preventing recurrent arrhythmias in AF patients after unsuccessful medical therapy [1]. Surgical treatment of AF has evolved from a cut-and-saw technique to ablation using alternative energy sources, e.g., cryotherapy and radiofrequency [3, 4]. With the continuous advance of operative techniques, a minimally invasive approach for surgical AF ablation (SAFA) has been developed as an alternative to the open-heart Cox maze procedure [2]. Clinically, AF may occur in patients with coronary artery disease or vascular heart disease and an indication for cardiac surgery. In such patients, concomitant SAFA in the cardiac surgery should be considered [3].

Presently, worldwide clinical trials of treatment for AF are mainly focused on the effectiveness of different interventions. Although several small-scale prospective cohort studies have assessed the efficiency of SAFA with different risk factors, the conclusions are inconsistent primarily due to limited datasets [3, 7-16]. To date, there has been no consensus on the selection process of patients who may benefit the most from SAFA treatment. Therefore, our meta-analysis was performed for systematically reviewing SAFA-related clinical trials in order to identify the factors that affect sinus rhythm maintenance after SAFA.

Table 1. Quality assessment of the studies included in the present meta-analysis

Reference	Randomization	Allocation concealment	Blinding	Follow-up time (yr)	Loss to follow-up	Intention to treat analysis	Grade
Chen [7]	Unclear	Unclear	Unclear	3.8±2.0	Yes	Yes	B
Funatsu [8]	Adequate	Adequate	Adequate	~3.8	Yes	Yes	A
Houltz [9]	Adequate	Adequate	Adequate	2.3±0.4	Yes	Yes	A
Katritsis [10]	Adequate	Unclear	Unclear	1–3	Yes	Yes	B
Kim [3]	Unclear	Unclear	Unclear	1.9±1.0	Yes	Yes	B
Klinkenberg [11]	Unclear	Unclear	Unclear	1.3±0.6	Yes	Yes	B
Letsas [12]	Adequate	Adequate	Unclear	1.0±0.5	Yes	Yes	B
Liu [13]	Unclear	Unclear	Unclear	0.8±0.4	Yes	Yes	B
MacDonald [14]	Adequate	Adequate	Adequate	≥0.5	Yes	Yes	A
Ngaage [15]	Adequate	Unclear	Unclear	~4.5	Yes	Yes	B
Wang [16]	Unclear	Unclear	Unclear	0.5	Yes	Yes	B

Materials and methods

Literature search

From their inception to Mar 2015, all randomized, controlled trials that discuss the efficacy of SAFA were reviewed. Computerized literature searches of the MEDLINE, PubMed, Cochrane Library, and EMBASE databases were accomplished using the search terms “surgical ablation”, “atrial fibrillation”, and “treatment” in different combinations. Reference lists of the original articles and relevant reviews on the same topic were examined to identify additional eligible trials. Two investigators performed the literature search independently.

Inclusion criteria

(1) Full-length peer-reviewed articles; (2) Postoperative follow-up for more than 6 months; (3) References provide numeric measures of clinical outcomes on each possible factor that may influence the success of the surgery; and (4) Case-control clinical trials.

Exclusion criteria

Abstracts, SAFA trials without follow-up, questionnaires, surveys, case reports, and catheter ablation studies were excluded. Multiple studies published by the same author or institution were carefully evaluated to include only the study reporting the most complete dataset.

Data extraction

The trials that met the inclusion criteria were independently identified by 2 co-authors and checked by an independent reviewer. The consistency of trial selection was evaluated by the Kappa test. When it was difficult to reach an agreement on an article due to lack of information, we moved it into the wait-for-assessment team, contacted its corresponding author for more information, and then decided whether to include it in the meta-analysis or not.

The included studies were reviewed based on randomization, allocation concealment, blinding, loss of follow-ups, and intention to treat analysis, then scored to 3 grades according to the Cochrane System Evaluation Handbook (Grade A, cases met all evaluation standards and used correct methodologies with a low risk of bias; Grade B, cases did not describe one or several standards and had a moderate risk of bias; and Grade C, cases had one or several incorrect standards and had a high risk of bias) (**Table 1**).

Outcomes

The primary outcome was the recurrence of AF after SAFA during the follow-up period. Study characteristics included demographics (age; gender; AF type and duration of AF), cardiac conditions (left atrial diameter, LAD; left ventricular ejection fraction, LVEF; left ventricular end-diastolic diameter, LVEDD; left ventricular end-systolic diameter, LVESD; and New York Heart Association classification, NYHA class), cardiac morbidity (tricuspid valve disease, TVD), and comorbidities (hypertension and diabetes mellitus).

Statistical analysis

Statistical analyses were performed using Review Manager (RevMan 5.2; Cochrane

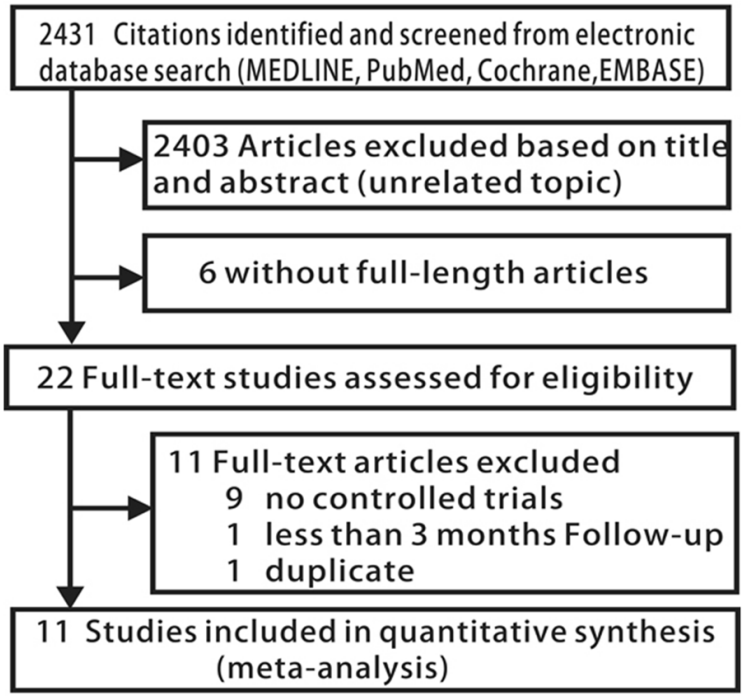


Figure 1. Process of study selection. Eleven articles were excluded, including 9 without controlled trials, 1 with less than 1-year follow-up, and 2 from a single author with duplicate patients, of which only the study with a larger patient group was included.

Collaboration. Oxford, United Kingdom). Continuous descriptive data were reported as *mean* ± standard deviation (*SD*), and dichotomous data were recorded as the case number (*n*).

The heterogeneity of the selected studies was tested using the Mantel-Haenszel Q statistic, and the proportion of total variation in the estimation results related to the heterogeneity was examined using the I^2 statistic. $P>0.10$ or $P\leq0.10$, $I^2\leq50\%$ indicates no significant heterogeneity between the trials and the fixed-effects model, and $P\leq0.10$, $I^2>50\%$ indicates significant heterogeneity between the random-effect models. $P\leq0.05$ was considered statistically significant.

Extensive effort was made to remove duplicated data and to include all relevant studies published up to Mar 2015. Publication bias in the outcomes was assessed and treated by Egger's test and Begg's test. Funnel plots were prepared for visual inspection of the relationship between the sample size and treatment effects of each potential risk factor. Means, SDs, and 95% confidence intervals (CIs) were computed for continuous demographic factors, and event rates, standard errors, and 95% CIs were computed for the remaining demographic factors to describe the proportion of samples with varying comorbidities.

Results

Search results

A total of 2431 SAFA-related articles were retrieved from the MEDLINE, PubMed, Cochrane Library, and EMBASE databases. Of these, 2403 articles irrelevant to the purpose of the present meta-analysis were excluded after scanning the titles and abstracts. Full-length articles were not obtained for 6 trials. In the remaining 22 articles, 11 eligible controlled trials [3, 7-16] of 1099 patients were identified by full text assessment (**Figure 1**) and finally included in the meta-analysis.

Study characteristics

The odds ratio (OR) and mean difference (MD) were summarized for potential risk factors reported in at least 3 studies (**Table 2**).

Factors in Demographics

The demographics-related potential risk factors of sinus rhythm maintenance after SAFA are summarized in Supplementary Table 1. Nine studies including 817 cases [3, 7, 10-16] and nine studies including 1049 cases [3, 7, 8, 10, 12-16] indicated that age and gender were not strongly associated with sinus rhythm maintenance after SAFA (Age-MD: 1.45, 95% *CI*: -1.44-4.33; Gender-OR: 0.95, 95% CI: 0.71-1.27) (**Figure 2A** and **2B**). As for AF types, the analysis results of three studies [11-13] indicated that AF type was not the risk factor (OR: 1.82, 95% *CI*: 0.76-4.36) (**Figure 2C**). However, Six studies including 389 cases [3, 7, 12-14] suggested that duration of AF was strongly associated with recurrence of AF after SAFA (MD: 2.05; 95% *CI*: 0.29-3.80) and longer duration of AF may indicate high risk of recurrent AF after SAFA (**Figure 2D**).

Table 2. Study characteristics included in the present meta-analysis

Reference	Year	Number of patients		Demographics						Cardiac Conditions										Morbidity	Comorbidities	
				Age (Year)		Gender		AF type		Duration of AF (Yrs)		LAD (mm)		LVEF (cm^2)		LVEDD (mm)		LVSD (mm)		NYHA class		TVD	Hypertension	Dm
				Mean	SD	Male	Female	Persistent	Paroxysmal	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	n	n	N
Chen [7]	2005	16	Group 1	48.2	8.2	6	10	---	---	8	4.25	61.9	10.2	60.9	10.8	54.4	9.2	36.1	7.9	3.06	0.44	14	3	2
		83	Group 2	51.8	11.7	38	45	---	---	3	3.75	51.7	8.5	62.1	12.3	54.6	9.8	35.5	8.5	2.89	0.58	2	11	11
Funatsu [8]	2009	43	Group 1	---	---	19	24	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
		204	Group 2	---	---	111	93	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Houltz [9]	2010	11	Group 1	---	---	---	---	---	---	---	---	---	---	49	15	50	5	---	---	---	---	---	---	---
		24	Group 2	---	---	---	---	---	---	---	---	---	---	56	9	48	7	---	---	---	---	---	---	---
Katritsis [10]	2005	16	Group 1	45.31	10.26	15	1	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
		16	Group 2	40.5	7.66	13	3	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Kim [3]	2011	20	Group 1	62.2	7.1	6	14	---	---	10.6	6.6	63.9	14.6	---	---	---	---	---	---	---	---	12	---	---
		72	Group 2	54	10.4	27	72	---	---	6.5	6	60.7	10.8	---	---	---	---	---	---	---	---	8	---	---
Klinkenberg [11]	2009	3	Group 1	46	10.54	---	---	1	2	----	----	----	----	---	---	50	1.73	35.67	1.53	---	---	---	---	---
		12	Group 2	46.83	10.22	---	---	3	9	----	----	----	----	---	---	51.58	5.57	34	5.33	---	---	---	---	---
Letsas [12]	2009	28	Group 1	53.3	7.8	24	4	12	16	5.7	3.1	42.9	6.1	54.9	10.2	53.5	4.9	33.6	6.4	---	---	---	9	5
		44	Group 2	55.8	9.4	34	10	14	30	5.3	2.9	39.2	4.9	59.6	7.4	50.3	5.4	31.4	4.9	---	---	---	5	11
Liu [13]	2009	3	Group 1	68	9.9	2	1	2	1	15.5	20.5	46.5	4.9	64.67	6.51	52	6	---	---	---	---	---	1	---
		5	Group 2	55.8	17.5	3	2	1	4	3	6.3	41.7	4.2	57	12.75	49.4	5.59	---	---	---	---	---	2	---
MacDonald [14]	2011	28	Group 1	63.9	8	22	6	---	---	4.83	3.83	---	---	39.2	10.4	---	---	---	---	2.89	0.31	---	18	6
		10	Group 2	60.7	6.7	7	3	---	---	2.87	2.19	---	---	38.2	14.7	---	---	---	---	2.9	0.32	---	6	4
Ngaage [15]	2006	129	Group 1	74	10	87	42	---	---	---	---	---	---	56	16	---	---	---	---	2.57	0.83	16	---	22
		252	Group 2	73	9	166	86	---	---	---	---	---	---	56	16	---	---	---	---	2.72	0.7	113	---	35
Wang [16]	2012	24	Group 1	52.17	12.31	8	24	---	---	2.54	1.96	57.08	3.53	60.58	5.63	49.75	5.17	---	---	2.5	0.52	---	---	---
		56	Group 2	53.96	9.27	22	34	---	---	2.46	1.54	49.82	4.36	59.07	8.99	52.61	6.73	---	---	2.29	0.46	---	---	---

Group 1 = Recurrence of AF; Group 2 = No recurrence of AF; LAD = left atrial diameter; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; NYHA class = New York Heart Association classification; TVD = tricuspid valve disease; and DM = diabetes mellitus.

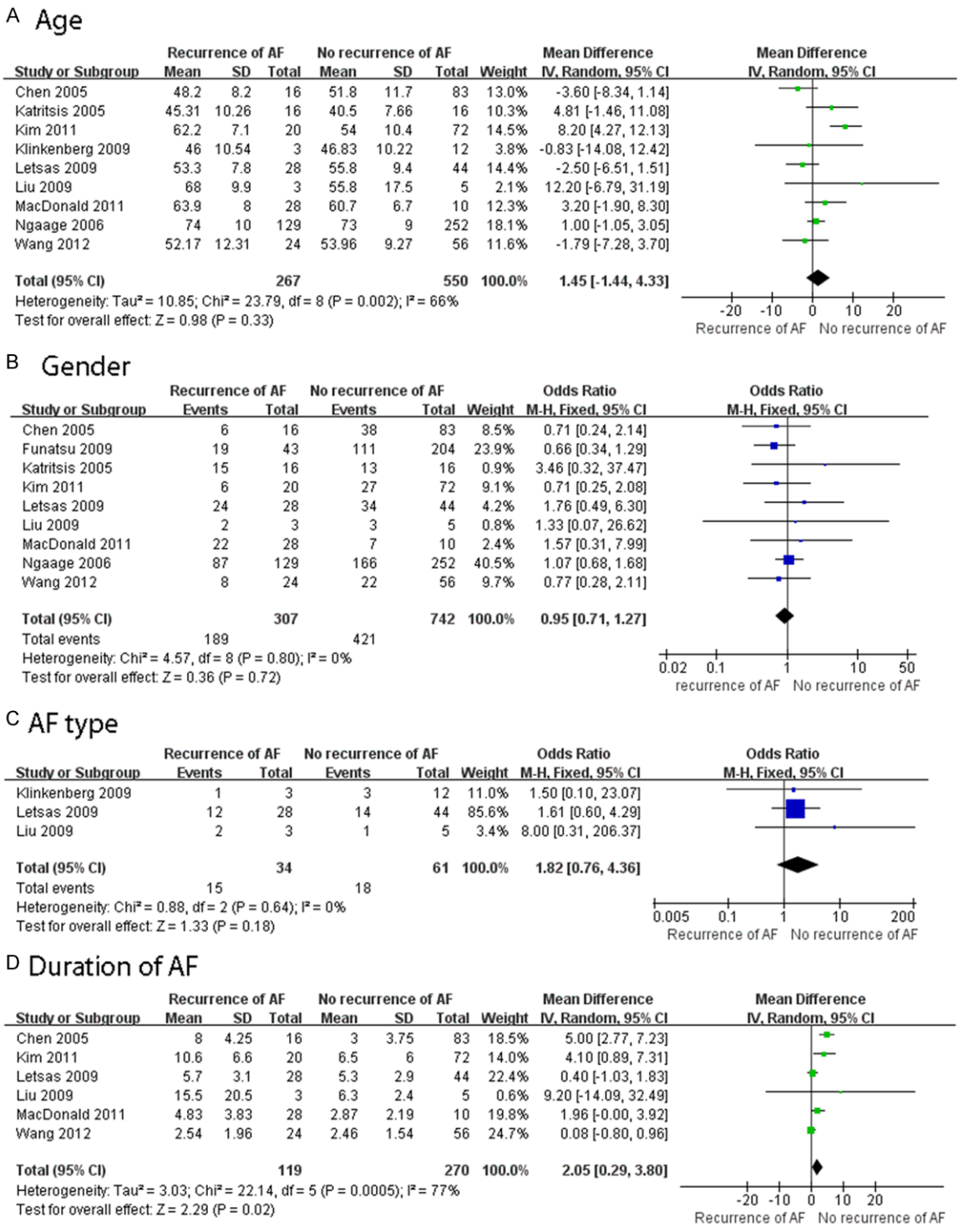


Figure 2. Effect estimates and 95% confidence intervals (CIs) of AF recurrence odds ratio (OR) associated with demographics. The ORs are shown as diamonds, with the middle corresponding to the point estimate and the width representing the 95% CI.

Factors in cardiac conditions

The cardiac condition-related factors potentially affecting sinus rhythm maintenance after SAFA are summarized in Supplementary Table 2. Five studies including 351 cases [3, 7, 12, 13, 16] indicated that large LAD was associated with increased AF prevalence after SAFA

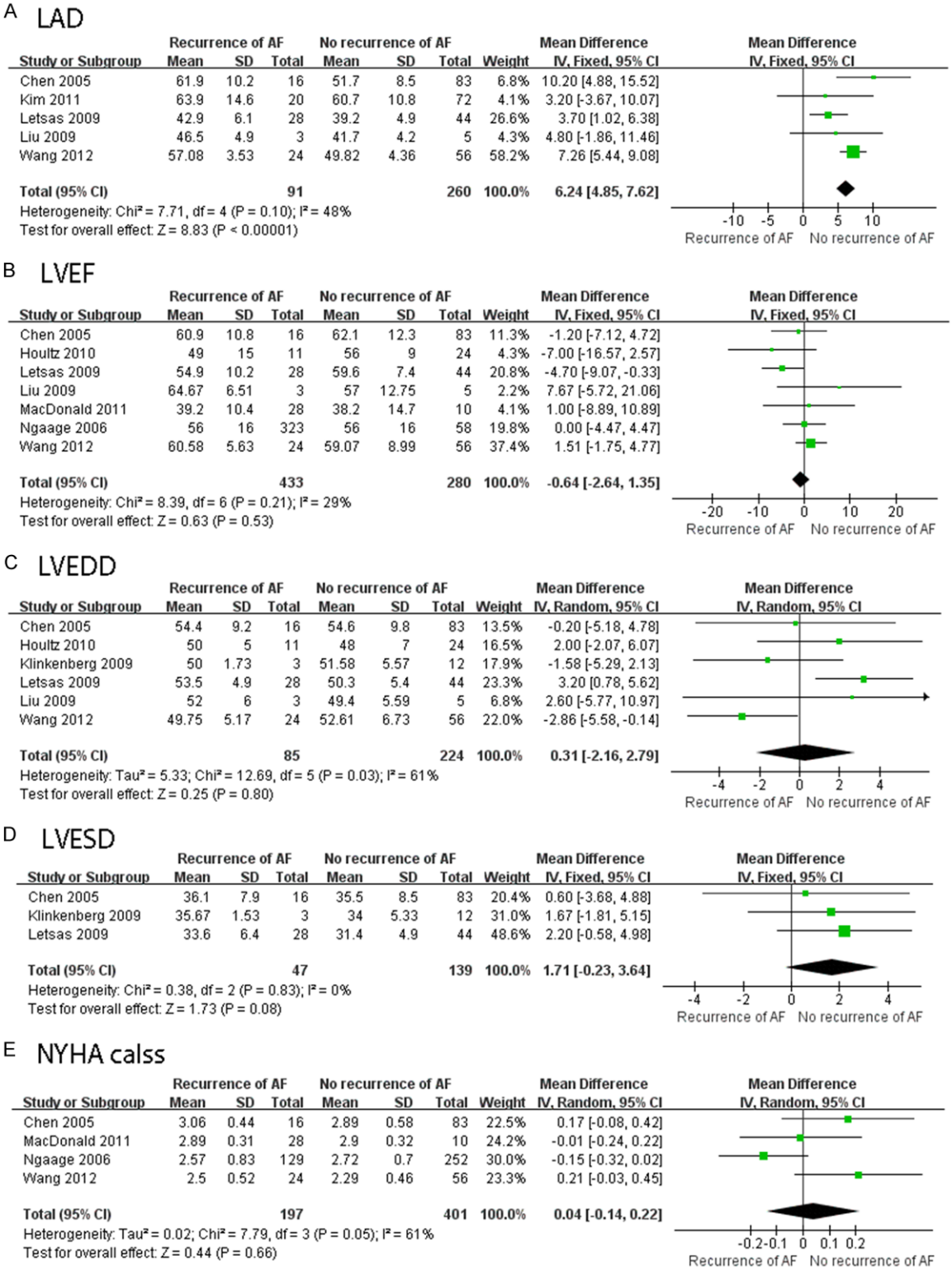


Figure 3. Effect estimates and 95% confidence intervals of AF recurrence odds ratio (OR) associated with cardiac conditions.

(OR: 6.24, 95% CI: 4.85-7.62) (**Figure 3A**). Seven studies [7, 9, 12-16] focused on LVEF, six studies [7, 9, 11-13, 16] focused on LVEDD, three studies [7, 11, 12] focused on LVESD and

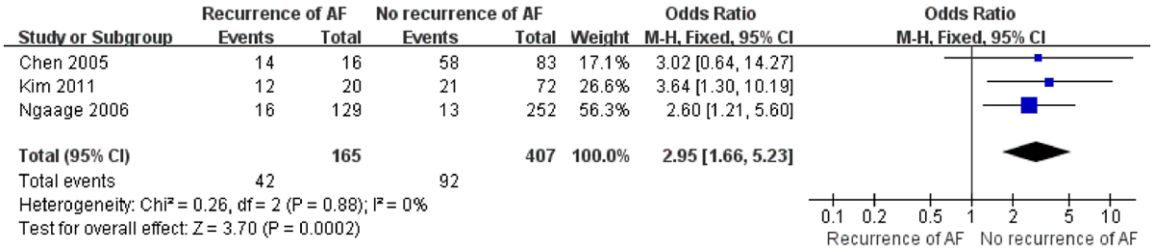


Figure 4. Effect estimates and 95% confidence intervals of AF recurrence odds ratio (OR) associated with cardiac morbidity.

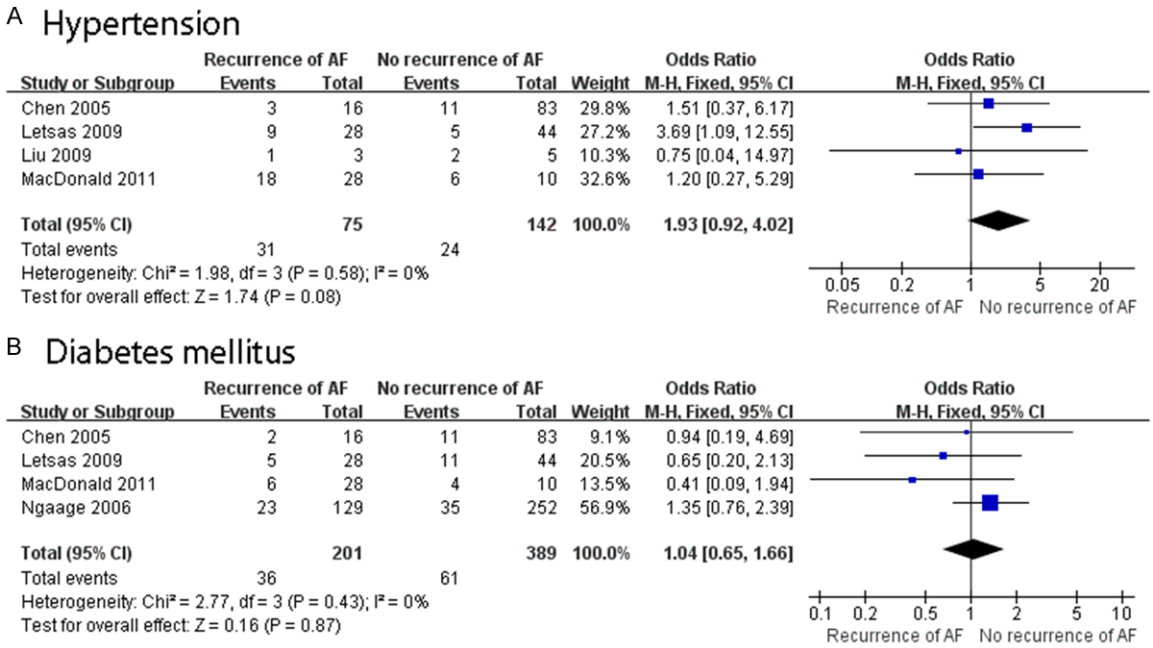


Figure 5. Effect estimates and 95% confidence intervals of AF recurrence odds ratio (OR) associated with comorbidities.

four studies [7, 14-16] focused on NYHA class. However, the potential factors mentioned above had not been found significant associations with sinus rhythm maintenance up till now based on our meta-analysis (LVEF-OR: -0.64, 95% CI: -2.64-1.35, **Figure 3B**; LVEDD-MD: 0.31, 95% CI: -2.16-2.79, **Figure 3C**; LVESD-MD: 1.71, 95% CI: -0.23-3.64, **Figure 3D**; NYHA class-MD: 0.04, 95% CI: -0.14-0.22, **Figure 3E**).

Factors in cardiac morbidity

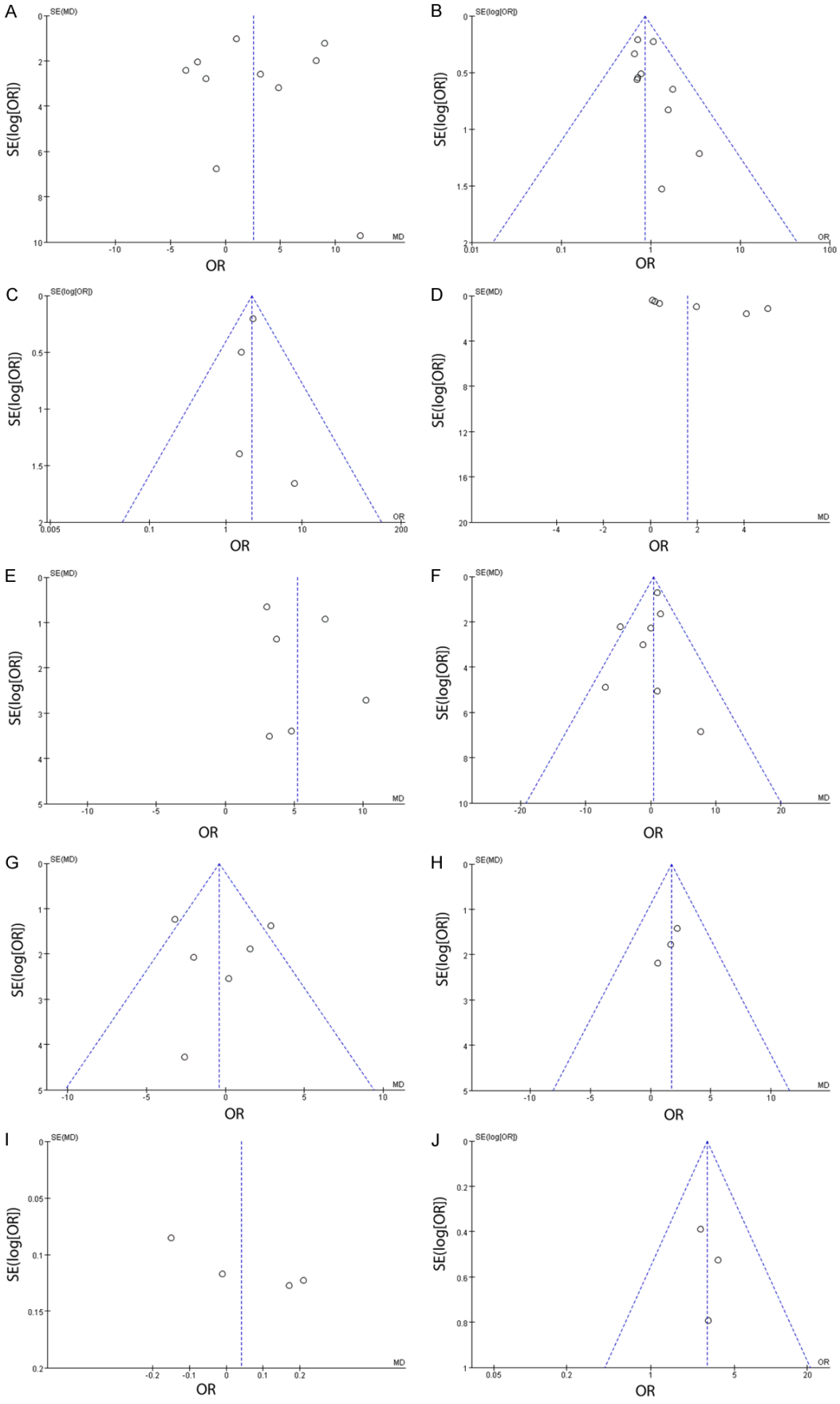
As for factors in Cardiac Morbidity, three studies including 572 cases [3, 7, 15] indicate that patients with TVD were more likely to have recurrent AF after SAFA (OR: 2.95, 95% CI: 1.66-5.23) (**Figure 4**; Supplementary Table 3).

Factors in comorbidities

The comorbidity-related factors potentially affecting sinus rhythm maintenance after SAFA are summarized in Supplementary Table 4. Four studies including 217 cases [7, 12-14] indicate that hypertension was not a risk factor to sinus rhythm maintenance after SAFA (OR: 1.93, 95% CI: 0.92-4.02, **Figure 5A**) while diabetes mellitus was also judged as a no-related factor to sinus rhythm maintenance after SAFA based on four studies including 590 cases [7, 12, 14, 15] (OR: 1.04, 95% CI: 0.65-1.66, **Figure 5B**).

Sensitivity analysis and publication bias

The test of each potential risk factor with the fixed- and random-effect models produced con-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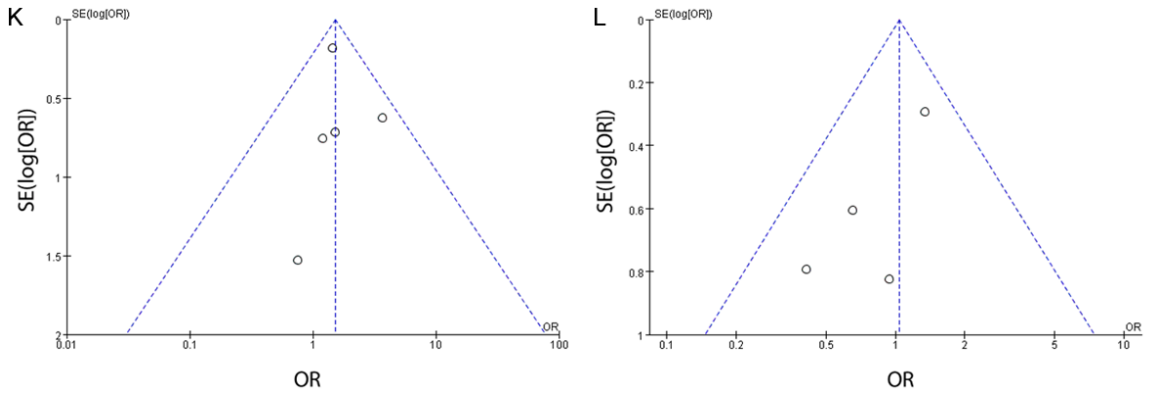

Figure 6. Funnel plot for each comparison. A. Age; B. Gender; C. AF type; D. Duration of AF; E. Left atrial diameter; F. Left ventricular ejection fraction (LVEF); G. Left ventricular end-diastolic dimension (LVEDD); H. Left ventricular end systolic diameter (LVESD); I. New York Heart Association classification (NYHA class); J. Tricuspid valve disease; K. Hypertension; and L. Diabetes mellitus.

sistent results. Funnel plot for each comparison shows an inverted funnel shape with bilateral symmetry (**Figure 6**), indicating the lack of publication bias and the reliability of our results.

Conclusions

Major findings

Major factors that affect sinus rhythm maintenance and AF recurrence after SAFA include duration of AF as well as LAD and TVD. AF patients with long-standing AF, large LAD, and/or TVD are more likely to have recurrent AF after SAFA.

Previous studies has mentioned the association between duration of AF and relapse of AF [4, 17, 18], and this meta-analysis has proved this conclusion more persuasively (P=0.02). The duration of AF is indicative of the exposure time of a patient to AF-inducing organic stress. Long duration of AF is commonly associated with fibrosis and decrease in the elasticity of the atrial wall [19], accounting for the high possibility of AP recurrence.

However, our results first provide strong evidences for the associations of LAD and TVD with recurrent AF after SAFA, which may help cardiac surgeons to evaluate the condition of SAFA patients accurately. AF itself may cause structural changes in atrium and result in structural remodeling [6], furthermore, it may also increase the rate and organization of depolarization waves emanating from focal sources [20] and promote the formation of intra-atrial rotors [21]. As we know, LAD reflects the preexisting AF burden, so our findings indicate that large LAD may directly contributes to SA failure. As for TVD, preoperative moderate-to-severe tricuspid regurgitation is related to left-sided cardiac problems and can lead to right ventricular dilatation. Moderate-to-severe tricuspid regurgitation occurs due to functional regurgitation, whereas long-standing AF or pulmonary hypertension can cause considerable tricuspid valve regurgitation. Dreyfus et al. [22] commented that tricuspid anuloplasty should be diagnosed based on the presence of annular dilatation, rather than the degree of regurgitation, in functional tricuspid regurgitation [7].

Clinical relevance

A significant proportion of recurrent AF events are classified as apparently unprovoked in the absence of major known risk factors, e.g., prolonged duration of AF [23, 24]. Recognition of other potential risk factors relevant to recurrent AF after SAFA will substantially lower the incidence of recurrent AF and support new strategy development for prevention of AF recurrence. In addition to long-standing AF, large LAD and TVD were found negatively affecting sinus rhythm maintenance and strongly associated with recurrent AF after SAFA. Thus, clinicians can immediately predict a high probability of procedural SAFA failure based on the identification of large LAD and/or TVD. Under such circumstances, the therapy can be modified for maximizing the success rate of SAFA. In order to minimize AF recurrence rate, patients with large LAD require routine detailed mapping of the scar with ablation of all potential isthmuses that can cause intra-atrial re-entry postoperation [25].

Study limitations

A meta-analysis has inherent weaknesses in combining heterogeneous datasets. As the present meta-analysis was performed by necessity restricted to individual risk factors, there is a distinct possibility that the strength of the association between specific risk factors and AF recurrence after SAFA is weaker with a multi-factorial regression analysis.

The potential factors reported in less than 3 studies were not evaluated due to lack of clinical data. Future studies are needed to examine the effects of other risk factors on sinus rhythm maintenance, e.g., BMI [12, 15], LAA [7, 9]; RAA [7, 9], SHD [12, 16]; CHD [7, 14]; RHD [3, 7], and renal dysfunction [8, 15].

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Demographics-related factors potentially affecting sinus rhythm maintenance after surgical ablation of atrial fibrillation

Risk factor	Number of cases	OR/MD [95% CI]	p_Q for heterogeneity	I^2 for heterogeneity, %	P for overall effect
Age	817	1.45 [-1.44,4.33]	P=0.002	66	0.33
Gender	1049	0.95 [0.71, 1.27]	P=0.80	0	0.72
AF type	95	1.82 [0.76, 4.36]	P=0.64	0	0.18
Duration of AF	389	2.05 [0.29, 3.80]	P=0.0005	77	0.02

Supplementary Table 2. Cardiac condition-related factors potentially affecting sinus rhythm maintenance after surgical ablation of atrial fibrillation

Risk factor	Number of cases	OR/MD [95% CI]	p_Q for heterogeneity	I^2 for heterogeneity, %	P for overall effect
LAD	351	6.24 [4.85, 7.62]	P=0.10	48	0.00001
LVEF	713	-0.64 [-2.64, 1.35]	P=0.21	29	0.53
LVEDD	309	0.31 [-2.16, 279]	P=0.03	61	0.80
LVESD	186	1.71 [-0.23, 3.64]	P=0.83	0	0.08
NYHA class	598	0.04 [-0.14, 0.22]	P=0.05	61	0.66

Supplementary Table 3. Cardiac morbidity-related factors potentially affecting sinus rhythm maintenance after surgical ablation of atrial fibrillation

Risk factor	Number of cases	OR/MD [95% CI]	p_Q for heterogeneity	I^2 for heterogeneity, %	P for overall effect
Tricuspid valve disease	572	2.95 [1.66, 5.23]	P=0.88	0	0.0002

Supplementary Table 4. Comorbidity-related factors potentially affecting sinus rhythm maintenance after surgical ablation of atrial fibrillation

Risk factor	Number of cases	OR/MD [95% CI]	p_Q for heterogeneity	I^2 for heterogeneity, %	P for overall effect
Hypertension	217	1.93 [0.92, 4.02]	P=0.58	0	0.08
Diabetes mellitus	590	1.04 [0.65, 1.66]	P=0.43	0	0.87