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CLINICAL RESEARCH
Atrial fibrillation

Role of pre-operative transthoracic echocardiography in predicting post-operative atrial fibrillation after cardiac surgery: a systematic review of the literature and meta-analysis

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Aims This systematic review and meta-analysis aims to evaluate the role of pre-operative transthoracic echocardiography in predicting post-operative atrial fibrillation (POAF) after cardiac surgery.

Methods and results Electronic databases were searched for studies reporting on pre-operative echocardiographic predictors of POAF in PubMed, Cochrane library, and Embase. A meta-analysis of echocardiographic predictors of POAF that were identified by at least five different publications was performed. Forty-three publications were included in this systematic review. Echocardiographic predictors for POAF included surrogate parameters for total atrial conduction time (TACT), structural cardiac changes, and functional disturbances. Meta-analysis showed that prolonged pre-operative PA-TDI interval [5 studies, Cohen's $d = 1.4$, 95% confidence interval (CI) 0.9–1.9], increased left atrial volume indexed for body surface area (LAVI) (23 studies, Cohen's $d = 0.8$, 95% CI 0.6–1.0), and reduced peak atrial longitudinal strain (PALS) (5 studies, Cohen's $d = 1.4$, 95% CI 1.0–1.8), were associated with POAF incidence. Left atrial volume indexed for body surface was the most important predicting factor in patients without a history of AF. These parameters remained important predictors of POAF in heterogeneous populations with variable age and comorbidities such as coronary artery disease and valvular disease.

Conclusion This meta-analysis shows that increased TACT, increased LAVI, and reduced PALS are valuable parameters for predicting POAF in the early post-operative phase in a large variety of patients.

Keywords Post-operative atrial fibrillation • Echocardiography • Cardiac surgery • Meta-analysis

Introduction

Post-operative atrial fibrillation (POAF) is the most common complication after cardiac surgery and up to 30% of patients without a history of AF develops POAF.[1,2] Historically POAF has been considered a transient arrhythmia resulting from triggers in the surgical aftermath. However, more recently POAF has been identified as an independent predictor of late AF development, early and long-term post-operative stroke, and increased all-cause mortality in the years following cardiac surgery, suggesting it may be an expression of an

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What's new?

- Increased preoperative total atrial conduction time (TACT, measured as PA- TDI interval), increased left atrial volume indexed for body surface area (LAVI), and reduced preoperative longitudinal strain (PALS), have a strong correlation with POAF incidence.
- These variables, which can be effectively measured by conventional bedside TTE, depict electrophysiological, structural, and functional cardiac changes associated with an arrhythmogenic substrate for POAF.
- Implementing measurements of preoperative TACT (measured as PA-TDI interval), LAVI, and PALS in the standard preoperative care might help to identify patients at risk for POAF.
- Using these parameters in the preoperative setting could result in a paradigm switch from "risk-factor-based" predictive models to "substrate-based" predictive models for POAF.

ingrained substrate.[2–4] In addition, identification of pre-existing clinical risk factors for POAF such as advanced age, hypertension, congestive heart failure, and its high incidence rate in valvular heart disease has emphasized the role of a pre-existing arrhythmogenic basis for POAF development.[5] Transthoracic echocardiography (TTE) is used to assess cardiac function in the pre-operative workup and several anatomical and functional echocardiographic parameters have been identified to be associated with POAF development.[6,7] These findings suggest that TTE has an important role in determining the pathophysiological changes, which may have already taken place in the atria prior to clinical manifestation of AF. In addition, novel echocardiographic techniques, such as strain analysis or the analysis of the atrial electrical conduction, offer new perspectives for quantification of the arrhythmogenic substrate in POAF patients.[8–12]. This systematic review aims to evaluate and classify these important echocardiographic parameters predicting POAF.

Methods

Literature search

For this systematic review, the 2009 PRISMA guidelines were followed.[13] In March 2020, a systematic literature search was conducted in PubMed, Cochrane database, and Embase (Supplementary material online, *Table S1*). Citation tracking was performed to identify additional publications.

Study selection

All identified studies were screened on their titles and abstracts. Two investigators were involved in identifying studies meeting criteria for inclusion (M.J.K. and M.G.). Studies with hybrid or catheter ablation as major intervention, studies not published in English, or studies without description of pre-operative echocardiographic workup and post-operative monitoring for POAF were excluded after screening the titles and abstracts. Full texts of the remaining articles were screened. The inclusion criteria for the systematic review were a pre-operative TTE evaluation of the cardiac function, cardiac surgery, and post-operative monitoring for POAF.

Quality assessment

The Downs and Black tool for quality assessment in non-randomized clinical trials was used to assess the quality of the studies included in the systematic review.[14] Additionally, description of TTE protocol and monitoring for POAF were added to the quality assessment.

Study outcomes

Primary outcomes were all pre-operative TTE parameters associated with the occurrence of POAF.

Statistical analysis

For echocardiographic variables that were identified by a minimum number of five publications as an independent predictor of POAF in a multivariable analysis, a meta-analysis was performed. A minimum amount of five publications was set to assess the effect of echocardiographic variables that showed a strong correlation with POAF.

Meta-analysis for continuous variables was performed to define the pooled standardized mean differences (SMD). To assess the SMD of the variables, Cohen's *d* was calculated. The following cut-offs for the interpretation of the SMD were selected: $0 < \text{Cohen's } d < 0.2$ = no effect, $0.2 \leq \text{Cohen's } d < 0.5$ = small effect, $0.5 \leq \text{Cohen's } d < 0.8$ = intermediate effect, $\text{Cohen's } d \geq 0.8$ = large effect. For the variables that were measured on the binary or categorical scale, a meta-analysis for binary groups was performed. Pooled results of the meta-analysis were visualized in a forest plot along with the standard deviations. Heterogeneity was assessed with the Cochrane Q-test and I^2 statistics with a significant cut-off value of $P < 0.10$ and $I^2 > 50\%$, respectively. To explore the patterns of heterogeneity, a Leave-one-out analysis or a Graphic Display of Heterogeneity (GOSH) plot was performed.[15] Subgroup analysis and meta-regression were performed to examine the between-study differences that might contribute to overall heterogeneity and different patterns of effect size distribution. The subgroups were defined based on the suspected contributors to between-study differences (patient characteristics, outcome measures and definitions, or interventions).

The publication bias was assessed in a funnel plot and by performing the Egger's test with a *P*-value <0.10 regarded as statistically significant.[16] Significant publication bias was explored using a Duval and Tweedie's trim-and-fill procedure to estimate the actual effect size.[17] All statistical values were computed with a 95% confidence interval (CI) in random-effects models. The two-tailed *P*-value cut-off for statistical significance was set at <0.05. All statistical models were created in 'Rstudio Version 1.2.1335' by using the 'meta', 'metafor', and 'dmetar' packages available for performing meta-analyses.[18,19]

Results

Study selection

After searching PubMed, Cochrane library, and Embase, 2531 citations were retrieved. After excluding 683 titles (duplicates, review articles, case reports, conference publications, and editorials), 1848 articles were screened for title and abstract according to the inclusion and exclusion criteria. We identified 94 studies that were eligible for the systematic review. After full-text evaluation, we excluded 51 articles based on various reasons (Supplementary material online, *Table S2*). Eventually, 43 publications were included in the systematic review and 23 studies in the meta-analyses of different echocardiographic variables. The summary of studies included in the meta-analysis is provided in Supplementary material online, *Table S3*. *Figure 1* depicts the study selection process for this systematic review.

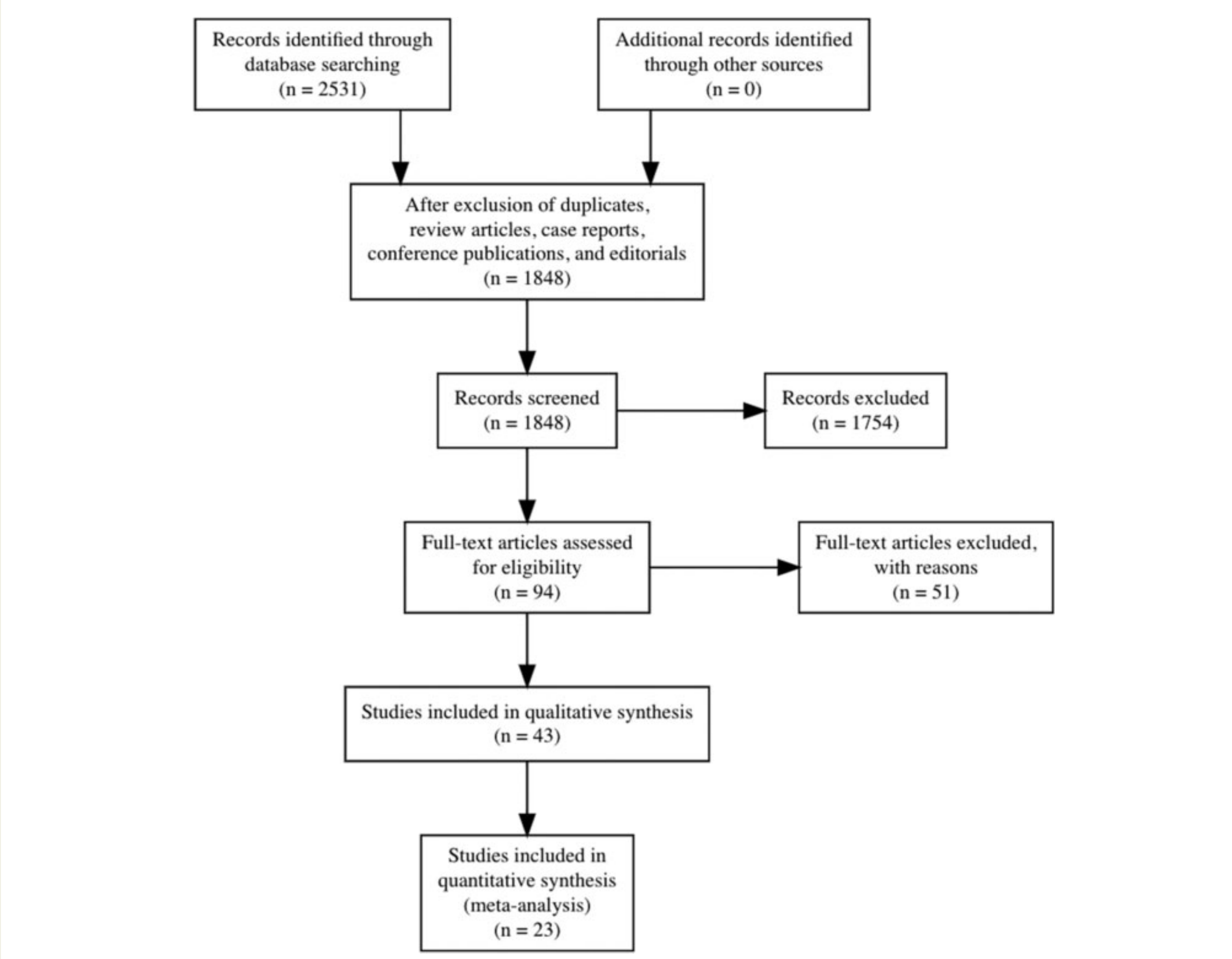

Figure 1 Study selection diagram.

Quality of studies

The quality of the studies included in the systematic review was high (Supplementary material online, *Table S4*). Objectives, outcomes, and main findings were clearly described in all studies. Most of the studies provided clear descriptions of imaging protocols, interventions, monitoring for POAF, and statistical analysis in the methods section. All studies clearly described whether patients with prior history of AF were included. In almost all studies, multivariable regression analysis was performed to adjust for potential confounders.

Study outcomes

Total atrial conduction time

Six studies found that a prolonged pre-operative total atrial conduction time (TACT), measured as atrial electromechanical interval (AEMI) or PA-TDI (interval between P-wave onset to peak A-wave measured with tissue Doppler imaging), was related to a higher incidence of POAF (*Table 1*).[20–25]

Meta-analysis for PA-TDI

Five studies were included in the continuous variables meta-analysis of PA-TDI using a random effects model (*Figure 2*).[20–24] One study was excluded from the meta-analysis, since the TACT was measured as the time interval from the start of the P-wave to the beginning of the A-wave, instead of the peak A-wave, which is a different technique compared to earlier mentioned studies.[25] *Figure 5A* demonstrates the average PA-TDI values calculated from the studies included in the meta-analysis. Patients developing POAF showed prolonged PA-TDI compared to patients without POAF (mean 151.3 vs. 127.8 ms, respectively). The cumulative Cohen's *d* obtained from the meta-analysis was 1.4 (0.9–1.9). The heterogeneity of the model was high $I^2 = 78\%$. Leave-one-out analysis for the meta-analysis of PA-TDI showed that omitting one study would reduce the I^2 to 40% without heavily influencing the overall SMD (1.2, 95% CI: 0.9–1.5) (Supplementary material online, *Figure S1*).[24]

Structural and functional parameters

Data on structural and functional risk factors and correlation with POAF are presented in*Tables 2 and 3*.[6–11,20–53] Several studies identified parameters representing left atrial (LA) structural remodelling, such as LA volume (LAV), LA diameter (LAD), LA area, and LA size, to be associated with POAF.[26,28–31,34–36,50], Also, diastolic dysfunction, reduced LA ejection fraction (LAEF), and reduced left

Table 1 Pre-operative electrophysiological disturbances identified by echocardiography as independent predictors of POAF

Study	Number of participants	Timing of pre-operative TTE	Type of surgery	POAF %	Predictors of POAF	Statistical value (95% CI)	Cut-off (ms)	Clinical value (%)
Prospective studies								
Roshanali *et al.*	355	<1 week prior to surgery	CABG	19.2	AEMI	OR = 1.37 (1.20–1.56)	>120	Sensitivity: 100 Specificity: 94.8 PPV: 81.9
Özlü *et al.*	128	NS	CABG	29.6	PA-TDI	HR = 1.03 (1.02–1.05)	>125.5	*N/A*
Muller *et al.*	60	1 day prior to surgery	CABG/AVR	38	PA-TDI	OR = 7.40 (5.90–9.30)	>133	Sensitivity: 100 Specificity: 86
Retrospective studies								
Takahashi *et al.* (2014)	63	<1 month prior to surgery	AVR	65	PA-TDI	OR = 1.07 (1.02–1.13)	>147.3	Sensitivity: 77.1 Specificity: 79.0 PPV: 79.0
Takahashi *et al.* (2016)	73	<1 month prior to surgery	MVR/MVP	60	PA-TDI	OR = 1.04 (1.01–1.07)	>159.4	Sensitivity: 55.8 Specificity: 84.6
Fujiwara *et al.*	88	<5 days prior to surgery	OPCAB	39.8	PA-TDI	OR = 1.11 (1.06–1.16)	>141	Sensitivity: 74.3 Specificity: 86.8

Cut-off and clinical values are shown for the electrophysiological parameters obtained from the studies.
AEMI, atrial electromechanical interval; AVR, aortic valve replacement; CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; ms, milliseconds; MVP, mitral valve plasty; MVR, mitral valve replacement; N/A, not available; NS, not specified; OPCAB, off-pump coronary artery bypass graft; OR, odds ratio; PA-TDI duration, total atrial conduction time; POAF, post-operative atrial fibrillation; TTE, transthoracic echocardiography.

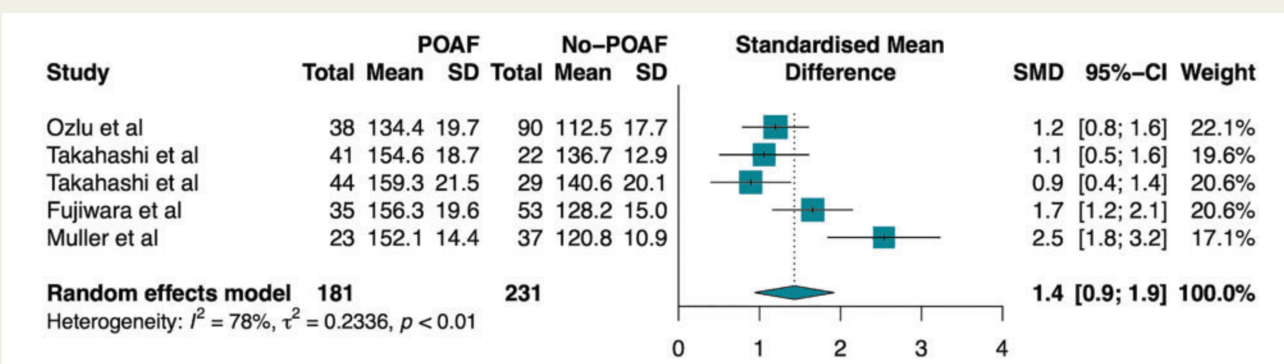

Figure 2 Forest plot depicting the meta-analysis of PA-TDI. Mean pre-operative PA-TDI for patients with and without POAF, along with the corresponding standard deviations, and the total amount of patients, are presented in this figure. Standardized mean differences are presented with the corresponding standard deviations. The overall effect estimate is presented in the diamond shape.

ventricular ejection fraction (LVEF) were independent predictors of POAF.[7,24,27,31–33,37,42,50] These variables were not assessed in a meta-analysis, since there were no more than five publications reporting them as independent predictors of POAF in multivariable analysis.

Meta-analysis for left atrial volume indexed for body surface

Twenty-seven studies investigated pre-operative left atrial volume indexed for body surface (LAVI) as a potential predictor of POAF (*Table 3*).[6–11,20–24,38–53] Twenty-three studies were included in the continuous variables meta-analysis using random effects model (*Figure 3*). Four studies were excluded from the meta-analysis because of insufficient data provided in the articles to perform a meta-analysis.[43,45–47]

The cumulative Cohen's *d* obtained from the meta-analysis was 0.8 (95% CI: 0.6–1.0). *Figure 5*B shows the average LAVI measured in the studies included in the meta-analysis. Average LAVI was higher in patients with POAF as compared to patients without POAF (41.1 vs.

Table 2 Pre-operative structural and functional disturbances identified by echocardiography as independent predictors of POAF

Study	Number of participants	Timing of pre-operative TTE	Type of surgery	POAF %	Predictors of POAF	Statistical value (95% CI)	Cut-off
Prospective studies							
Benedetto *et al.*	96	<1 week prior to surgery	CABG	25	LA-area	OR = 2.50 (1.60–5.10)	≥13 cm^2
					A-wave	OR = 1.80 (1.10–3.50)	≤9 cm/s
Haffajee *et al.*	101	<3 months prior to surgery	Diverse[a]	41	LAEF	OR = 6.89 (2.64–17.97)	<50%
					LAVminI	OR = 4.32 (1.57–11.90)	>13 mL/m^2
Muller *et al.*	66	1 day prior to surgery	CABG/AVR	38	LAEF	OR = 0.84 (0.77–0.91)	Per 1% increase
Lu *et al.*	126	NS	CABG/AVR	31.7	LA-diameter	OR = 1.12 (1.02–1.22)	Per 1 mm increase
Acil *et al.*	102	<2 days prior to surgery	CABG	18	LA-diameter	OR = 1.25 (1.06–1.56)	Per 1 mm increase
Melduni *et al.*	351	<3 months prior to surgery	CABG/valve surgery	38.5	LVDFG1	OR = 5.12 (1.60–16.38)	Impaired relaxation
					LVDFG2	OR = 9.87 (3.23–30.13)	Pseudo-normal filling
					LVDFG3	OR = 28.52 (7.11–114.44)	Restrictive filling
Roshanali *et al.*	355	<1 week prior to surgery	CABG	19.2	A-wave	OR = 0.84 (0.73–0.96)	Per 1 cm/s increase
Orowska-Baranowska *et al.*	423	NS	AVR	28.4	LVMI	OR = 0.93 (0.88–0.97)	Per 10 g/m^2 increase
Iribarren *et al.*	92	4 to 2 days prior to surgery	CABG	21	LA-size	OR = 2.23 (1.05–4.76)	Per 1 cm increase
					A-wave	OR = 0.70 (0.50–0.99)	Per 1 cm/s increase
Rostagno *et al.*	725	2 days prior to surgery	Diverse[c]	29.7	LA-diameter	OR = 4.18 (2.34–7.45)	>40 mm
Haghajoo *et al.*	302	NS	CABG/OPCAB	15	LA-diameter	OR = 1.07 (1.02–1.12)	Per 1 mm increase
Rizvi *et al.*	90	NS	CABG	37.7	LAEF	$P = 0.010$	<42%
Lisi *et al.*	36	1 day prior to surgery	MVR	32	LVMI	B = 0.36 ($P < 0.001$)	Per 1 g/m^2
Retrospective studies							
Aksu *et al.* (2019)	74	NS	CABG	–	RAVI	OR = 3.10 (2.20–6.30)	Per 1 mL/m^2 increase
Kernis *et al.*	762	NS	MV surgery	9	LVEF	OR = 1.04 (1.01–1.06)	Per 1% decline
Banach *et al.*	300	<2 days prior to surgery	AVR	43.7	LVEF	OR = 1.70 (1.10–2.70)	<50%
					LVESd	OR = 1.90 (1.20–3.00)	≥3.85 cm
					ESIVST	OR = 1.70 (1.10–2.70)	≥1.75 cm
Shimony *et al.*	768	<30 days prior to surgery	CABG	25.6	RVMPI	OR = 1.50 (1.01–2.24)	>0.4
Ismail *et al.*	252	NS	CABG	33.3	LA-volume	*N/A*	*N/A*
					LVEF	OR = 3.90 (3.32–4.71)	Per 1 mL increase
Barbara *et al.*	223	<1 year prior to surgery	Diverse[a]	40.8	LA-volume	OR = 1.01 (1.00–1.02)	Per 1 cc increase

AVR, aortic valve replacement; CABG, coronary artery bypass graft; CI, confidence interval; DD, diastolic dysfunction; HR, hazard ratio; LA, left atrium; LAEF, left atrial ejection fraction; LAVI, left atrial volume indexed for body area; LAVminI, left atrial volume minimum indexed; LVDFG, left ventricular diastolic function grade; LVEF, left ventricle ejection fraction; LVMI, left ventricular mass indexed; ms, milliseconds; MV, mitral valve; MVR, mitral valve replacement; N/A, not available; NS, not specified; OR, odds ratio; POAF, post-operative atrial fibrillation; RAVI, right atrial volume indexed for body surface; RVMPI, right ventricular myocardial performance index; TTE, transthoracic echocardiography.

[a]CABG, valvular surgery, myectomy, ventriculotomy, and aortic root repair.

[b]CABG, valvular surgery, aortic surgery, and combined surgery.

[c]CABG, OPCAB, valvular surgery, CABG + valvular surgery, Bentall procedure, and others.

Table 3 Pre-operative left atrium volume indexed for body surface (LAVI in mL/m^2) for predicting POAF

Study	Number of participants	Timing of pre-operative TTE	Type of surgery	POAF %	Statistical value (95% CI)	*P*-value	Statistical analysis
Prospective studies							
Candan *et al.*	53	2 days prior to surgery	MVR/MVP	28.3	OR = 1.10 (1.01–1.20)	0.04	Multivariate
Ozlu *et al.*	128	NS	CABG	29.6	HR = 1.03 (1.01–1.06)	0.03	Multivariate
Osranek *et al.*	203	NS	Diverse[a]	41.4	HR = 1.03 (1.01–1.04)	0.0001	Multivariate
Magne *et al.*	169	NS	CABG	38	OR = 1.12 (1.05–1.20)	<0.001	Multivariate
Mahmood *et al.*	169	Day of surgery	CABG/AVR	26	OR = 1.05 (1.01–1.09)	0.02	Multivariate
Ozben *et al.*	48	2 days prior to surgery	CABG	27.1	OR = 1.18 (1.02–1.36)	0.02	Multivariate
Tayyareci *et al.*	96	2 days prior to surgery	CABG	26	OR = 3.72 (3.32–4.63)	0.005	Multivariate
Haffajee *et al.*	101	<3 months prior to surgery	Diverse[b]	41	OR = 1.69 (0.70–4.08)	0.3	Multivariate
Muller *et al.*	66	1 day prior to surgery	CABG/AVR	38	OR = 0.90 (0.83–0.98)	<0.05	Multivariate
Her *et al.*	53	NS	CABG	25	OR = 1.01 (0.86–1.19)	0.9	Multivariate
Basaran *et al.*	90	<24 hours prior to surgery	CABG	25.6	OR = 1.06 (0.97–1.17)	0.21	Multivariate
Gabrielli *et al.*	70	NS	CABG	26	OR = 4.67 (1.50–19.20)	0.01	Multivariate
Hidayet *et al.*	66	NS	CABG	22.7	OR = 1.95 (1.16–3.28)	0.01	Multivariate
Cameli *et al.*	76	NS	AVR	19.7	HR = 1.03 (1.01–1.04)	0.05	Univariate
Pernigo *et al.*	60	1 day prior to surgery	AVR	43.3	OR = 1.04 (0.99–1.09)	0.10	Univariate
Imanishi *et al.*	27	NS	AVR	56	OR = 1.03 (0.98–1.07)	0.25	Univariate
Levy *et al.*	58	NS	AVR	48	*N/A*	0.88	Univariate
Melduni *et al.*	351	<3 months prior to surgery	CABG/Valve surgery	38.5	OR = 1.04 (1.01–1.06)	0.002	Univariate
Case–control studies							
Lisi *et al.*	74	1 day prior to surgery	MVR	32	B = 0.34	0.01	Multivariate
Retrospective studies							
Fujiwara *et al.*	88	<5 days prior to surgery	OPCAB	39.8	OR = 1.11 (1.02–1.20)	0.01	Multivariate
Aksu *et al.* (2017)	60	NS	CABG	32	OR = 1.20 (1.05–1.34)	0.008	Multivariate
Aksu *et al.* (2019)	74	NS	CABG	—	OR = 3.90 (2.60–7.21)	0.02	Multivariate
Avdic *et al.*	116	NS	CABG	31	OR = 1.05 (1.02–1.07)	0.0001	Multivariate
Shimony *et al.*	768	30 days prior to surgery	CABG	25.6	OR = 1.98 (1.36–2.87)	<0.001	Multivariate
Takahashi *et al.* (2014)	63	<1 month prior to surgery	AVR	65	OR = 1.05 (1.00–1.10)	0.05	Univariate
Takahashi *et al.* (2016)	73	<1 month prior to surgery	MVR/MVP	60	N/A	0.3	Univariate
Naito *et al.*	47	NS	AVR	42.6	LAVI > 52 mL/m^2	<0.01	Univariate

B, beta coefficient; CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; LAVI, left atrium volume indexed for body surface; MVP, mitral valve plasty; MVR, mitral valve replacement; N/A, not available; NS, not specified; OPCAB, off-pump coronary artery bypass; AVR, aortic valve replacement; OR, odds ratio; POAF, post-operative atrial fibrillation; TTE, transthoracic echocardiography.
[a]CABG, surgery of aortic valve, ascending aorta, tricuspid valve, pericardium, and myectomies.
[b]CABG, valvular surgery, myectomy, ventriculotomy, and aortic root repair.

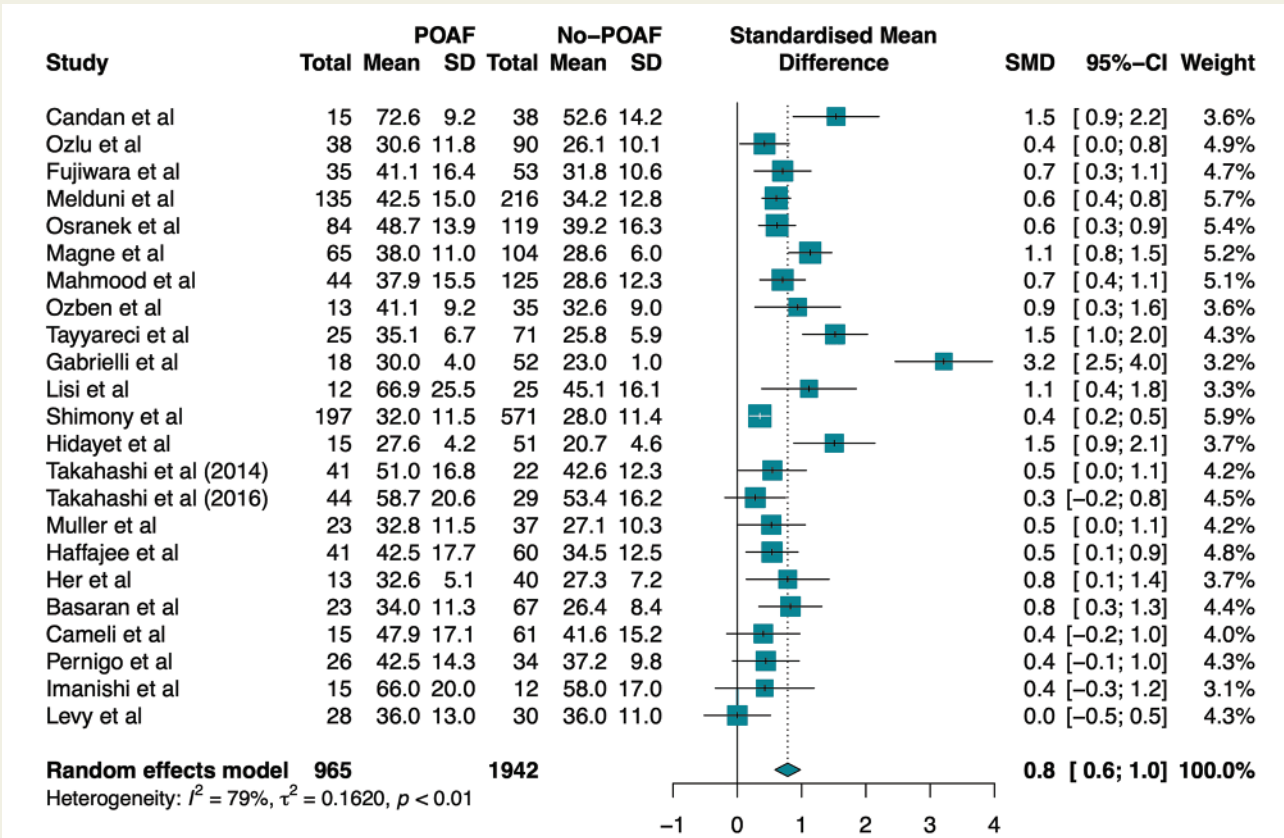

Figure 3 Forest plot depicting the meta-analysis of LAVI. Mean pre-operative LAVI for patients with and without POAF, along with the corresponding standard deviations, and the total amount of patients, are presented in this figure. Standardized mean differences are presented with the corresponding standard deviations. The overall effect estimate is presented in the diamond shape. LAVI, left atrial volume indexed for body surface; POAF, post-operative atrial fibrillation.

31.4 mL/m^2, respectively). Studies that included patients with a previous history of paroxysmal AF (PAF) showed a higher LAVI in POAF patients compared to studies excluding PAF patients (46.3 vs. 41.8 mL/m^2, respectively). The overall heterogeneity of the meta-analysis was high (I^2 = 79%). Therefore, a GOSH-analysis was performed to investigate the heterogeneity patterns (Supplementary material online, *Figure S2*). Three studies were identified as major contributors to the heterogeneity (Supplementary material online, *Figures S3–S5*).[40,41,44] After eliminating these studies from the analysis, a sensitivity analysis was performed, which showed that an increased SMD of LAVI was still associated with POAF (Cohen's *d* of 0.7, 95% CI: 0.5–0.8) with lower overall heterogeneity (I^2 = 49) (Supplementary material online, *Figure S6*).

Subgroup analysis and meta-regression for LAVI

Subgroup analysis and meta-regression were performed for the meta-analysis of LAVI (*Table 4*). Subgroup analysis on the type of surgery (coronary artery bypass grafting vs. aortic valve replacement vs. diverse vs. mitral valve surgery), %POAF in the study cohort (>30% or <30%), pre-operative history of PAF (yes vs. no), and type of study design (prospective, retrospective, or case-control) showed significant differences in the SMD of LAVI. (P = 0.02, 0.03, 0.006, and 0.001, respectively). Meta-regression showed that cohort age (beta = −0.04, P = 0.01) and percentage of male subjects in the study cohort (beta = 0.02, P = 0.04) were associated with the SMD of LAVI (Supplementary material online, *Figures S7 and S8*).

Strain analysis

Data obtained from the literature on the role of pre-operative strain analysis for predicting POAF are summarized in *Table 5*.[9–12,37,40–42,47,49,51–55]

Meta-analysis for peak atrial longitudinal strain

Five studies were included in the continuous variables meta-analysis of peak atrial longitudinal strain (PALS) using a random effects model (*Figure 4*).[10,11,42,49,51] One study was omitted from the meta-analysis since there was insufficient data presented in the article.[55] *Figure 5C* demonstrates the cumulative data of all five studies indicating low PALS values in POAF patients as compared to non-POAF patients (19.4% vs. 29.1%, respectively). The cumulative Cohen's *d* obtained from the meta-analysis was 1.4 (1.0–1.8). The heterogeneity of the model was acceptable at I^2 = 54%. Furthermore, LV contractile strain, LA contractile

Table 4 Subgroup analysis and meta-regression for left atrial volume indexed for body surface

Subgroups	Number of studies	SMD	95% CI	P-value
Study size (n)				
<100	16	0.90	0.57–1.22	0.14
>100	7	0.61	0.42–0.81	
Type of study				
Prospective cohort	18	0.86	0.62–1.09	**0.001**
Retrospective cohort	4	0.39	0.25–0.53	
Case–control study	1	1.12	0.38–1.85	
Type of surgery				
CABG	10	1.09	0.68–1.50	**0.02**
AVR	5	0.35	0.10–0.60	
Diverse[a]	5	0.61	0.47–0.75	
Mitral valve	3	0.95	0.15–1.75	
POAF %				
<30%	11	1.06	0.67–1.45	**0.03**
>30%	12	0.60	0.43–0.76	
Definition of POAF				
Any duration	5	0.79	0.34–1.24	0.17
Any duration + therapy	3	0.43	0.26–0.71	
>30 s	7	0.69	0.40–0.98	
At least >5 min	8	1.03	0.55–1.51	
Pre-operative history of paroxysmal AF				
No	17	0.92	0.67–1.18	**0.006**
Yes	6	0.47	0.28–0.67	
Meta-regression	**Number of studies**	**Beta**	**95% CI**	**P-value**
Age, per 1 year	23	−0.04	−0.07 to 0.01	**0.01**
Diabetes mellitus, per 1%	23	−0.03	−0.01 to 0.02	0.53
%Male, per 1%	22	0.02	0.001 to 0.03	**0.04**
Hypertension, per 1%	22	−0.01	−0.02 to 0.005	0.23
BSA, per 1 m^2	15	−0.19	−1.41 to 1.03	0.76
LVMi, g/m^2	15	−0.002	−0.02 to 0.01	0.77
E/e', per 1 unit	14	−0.07	−0.15 to 0.01	0.09
BMI, per 1 kg/m^2	13	−0.04	−0.15 to 0.08	0.54
E/A, per 1 unit	9	−0.23	−1.34 to 0.88	0.68

AVR, aortic valve replacement; Beta, beta coefficient; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; CI, confidence interval; LVMi, left ventricular mass indexed for body surface; POAF, post-operative atrial fibrillation; SMD, standardized mean difference.
The significance level was set at $p<0.05$ and all boldface values presented in the table are regarded as statistically significant.
[a]CABG, surgery of aortic valve, ascending aorta, tricuspid valve, pericardium, and myectomies.

strain, and LA global longitudinal strain were also impaired in POAF patients.[9,10,12,37,40,41,47,51–55]

Publication bias

The publication bias of the studies included in the different meta-analyses was explored in funnel plots (Supplementary material online, *Figures S9–S11*). Egger's test for LAVI showed significant publication bias ($P = 0.02$), whereas PA-TDI and PALS showed no significant publication bias ($P = 0.23$ and 0.45, respectively). To investigate the actual SMD in face of significant publication bias for LAVI, a trim-and-fill analysis was performed, showing an SMD of 0.5 (0.3–0.7), which might suggest an overestimation of the SMD obtained from the meta-analysis.

Discussion

This is to our knowledge the first systematic review and meta-analysis of the role of pre-operative TTE in predicting POAF. We found that increased pre-operative TACT (measured as PA-TDI interval), increased LAVI, and reduced PALS have a strong correlation with POAF incidence. These variables depict electrophysiological, structural, and functional cardiac changes associated with an arrhythmogenic substrate for POAF.

Total atrial conduction time

Intra-atrial conduction delay is one of the characteristics of LA electrical remodelling, resulting in AF.[56] TACT, measured as AEMI or PA-

Table 5 Pre-operative variables identified by strain analysis associated with a higher risk of POAF.

Study	Number of participants	Timing of pre-operative TTE	Type of surgery	POAF %	Predictors of POAF	Statistical value (95% CI)	Strain: cardiac function
Prospective studies							
Gabrielli *et al.*	70	NS	CABG	26	LASRa	OR = 2.40 (1.10–19.60)	Contractile
					LASRs	OR = 6.10 (1.30–15.20)	Reservoir
Her *et al.*	53	NS	CABG	25	LAGLS	OR = 1.12 (1.00–1.24)	Reservoir
Tayyareci *et al.*	96	2 days prior to surgery	CABG	26	LAGLS	OR = 3.82 (3.40–4.73)	Reservoir
					LASRs	OR = 3.92 (3.68–3.00)	Reservoir
					LAESRd	OR = 4.27 (3.25–6.72)	Conduit
Basaran *et al.*	90	NS	CABG	25.6	PALS	OR = 0.86 (0.75–0.98)	Reservoir
Rizvi *et al.*	90	NS	CABG	37.3	LAGLS	$P = 0.008$	Reservoir
Candan *et al.*	53	2 days prior to surgery	MVR/MVP	28.3	PALS	OR = 0.72 (0.55–0.95)	Reservoir
Sabry *et al.*	50	NS	MVR	44	LASs	OR = 0.15 (0.05–0.43)	Reservoir
					LVGLS	OR = 0.45 (0.22–0.93)	Contractile
Lisi *et al.*	36	1 day prior to surgery	MVR	32	PALS	B = −0.43 ($P < 0.001$)	Reservoir
Cameli *et al.*	76	NS	AVR	19.7	PALS	HR = 0.96 (0.94–0.98)	Reservoir
Pernigo *et al.*	60	1 day prior to surgery	AVR	43.3	PALS	OR = 0.73 (0.61–0.88)	Reservoir
					PACS	OR = 0.72 (0.59–0.87)	Contractile
Pessoa-Amorin *et al.*	115	NS	AVR	36.7	PALS	HR = 0.95 (0.91–0.98)	Reservoir
					PACS	HR = 0.93 (0.88–0.98)	Contractile
Imanishi *et al.*	27	NS	AVR	56	LASRa	HR = 0.005 (0.001–0.469)	Contractile
Levy *et al.*	58	NS	AVR	48	LVGLS	OR = 7.74 (1.15–52.03)	Contractile
Case–control studies							
Verdejo *et al.*	70	NS	CABG	38.5	LASs	OR = 1.63 (1.19–2.22)	Reservoir
Retrospective studies							
Aksu *et al.* (2019)	74	NS	CABG	50	RASr	OR = 0.82 (0.67–0.93)	Reservoir

AVR, aortic valve replacement; B, beta coefficient; CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; LAESRd, left atrial end diastolic strain rate; LAGLS, left atrial global longitudinal strain; LASRa, left atrial strain rate during atrial contraction; LASRs, left atrial strain rate during ventricular systole; LASs, left atrial strain during systole; LVGLS, left ventricular global longitudinal strain; MVP, mitral valve plasty; MVR, mitral valve replacement; N/A, not available; NS, not specified; OR, odds ratio; PACS, peak atrial contraction strain; PALS, peak atrial longitudinal strain; POAF, post-operative atrial fibrillation; RASr, right atrial strain reservoir; TTE, transthoracic echocardiography.
[a]CABG, mitral valve repair, mitral valve replacement, aortic valve replacement, tricuspid valve repair.

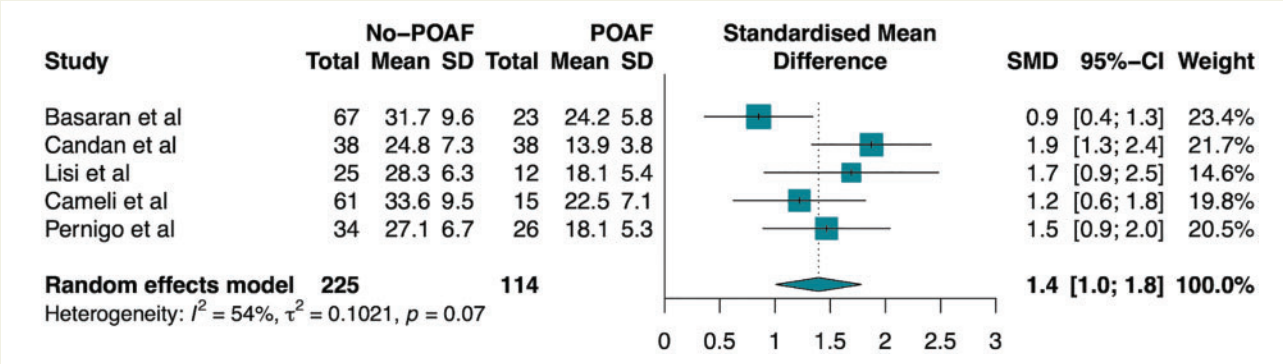

Figure 4 Forest plot depicting the meta-analysis of PALS. Mean pre-operative PALS for patients with and without POAF, along with the corresponding standard deviations, and the total amount of patients, are presented in this figure. Standardized mean differences are presented with the corresponding standard deviations. The overall effect estimate is presented in the diamond shape. PALS, peak atrial longitudinal strain; POAF, post-operative atrial fibrillation.

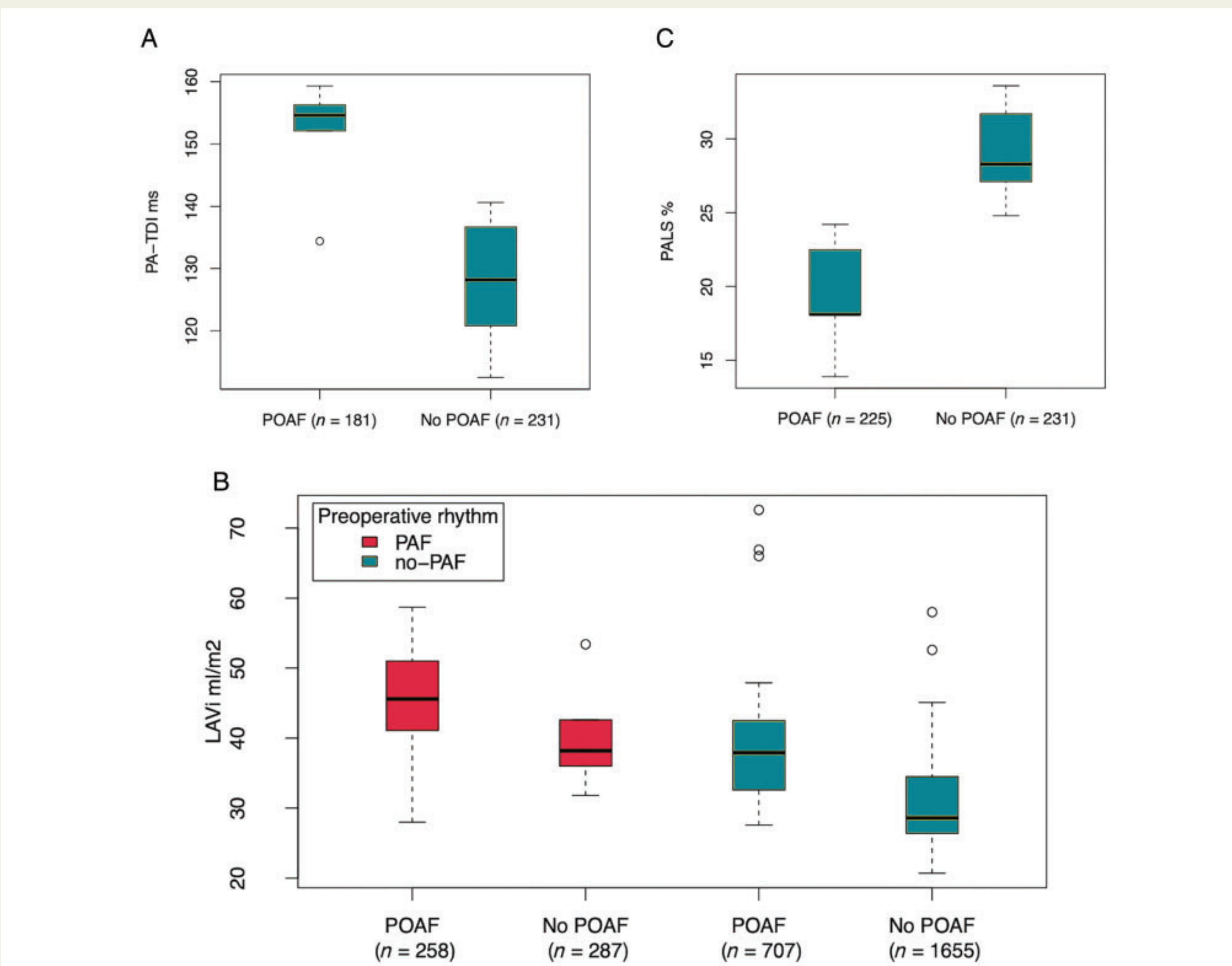

Figure 5 (A) Box plots depicting average difference between pre-operative PA-TDI for patients with POAF and no POAF. (*B*) Green box plots depict average difference between pre-operative LAVI for patients with POAF and no POAF in studies that excluded patients with history of PAF. Red box plots depict average difference between pre-operative LAVI for patients with POAF and no POAF in studies that included patients with history of PAF. (*C*) Box plots depicting average difference between pre-operative PALS for patients with POAF and no POAF. LAVI, left atrial volume indexed for body surface; PAF, paroxysmal AF; PALS, peak atrial longitudinal strain; POAF, post-operative atrial fibrillation.

TDI, is a non-invasive echocardiographic parameter reflecting the intra-atrial conduction delay. PA-TDI was previously validated as a technique for measuring TACT in patients with PAF.[57] Also, prolonged PA-TDI was linked to hypertension, increased age, diastolic dysfunction, and valvular incompetence in patients with PAF, suggesting a correlation between intra-atrial conduction delays and underlying heart disease.[58] Our results showed that TACT, measured as AEMI or PA-TDI, is also a useful parameter for identifying patients at risk for POAF. Prolonged pre-operative TACT is most likely the result of LA enlargement and it is associated with significantly higher rates of RA-fibrosis in samples that were obtained during surgery.[20,24] These structural changes play an important role in creating an arrhythmogenic basis for POAF development through re-entry mechanisms and multiple fibrillation waves in the atria.[59] Therefore, echocardiographic evaluation of TACT seems to be a promising parameter for detecting both the presence and severity of early electrophysiological changes of the atria predisposing to POAF.[20–25,57,60,61]

Structural and functional parameters

Structural echocardiographic parameters, such as increased LAV, LAD, and LA area, alongside lower LAEF and lower peak atrial systolic mitral annular velocity, were associated with POAF (*Table 2*). Our meta-analysis showed that patients developing POAF have an increased pre-operative LAVI as compared to patients that post-operatively remain in SR (*Figure 3*). These variables depict the early structural and functional alterations of the LA that are associated with LA dilatation, most likely caused by myocyte stretching and fibrosis.[62] LA enlargement is an important predictor of AF development and may be a consequence of volume overload resulting from mitral valve insufficiency or pressure overload due to diastolic dysfunction as a consequence of aortic valve stenosis, hypertension, or ageing. Also, progressive fibrosis of the myocardium causes stiffness of the LV and is responsible for disturbances in the diastolic function of the heart. Higher diastolic filling pressures in the LV increase the pressure in the LA and thereby distension of the pulmonary veins, which at their turn contribute to the arrhythmogenic substrate that is partly responsible for atrial arrhythmias.[7] In line with this statement, we found that diastolic dysfunction was independently associated with POAF development.

Notably, in the meta-analysis of LAVI, we found significant between-study-heterogeneity, which was further evaluated by subgroup analysis and meta-regression. We could attribute the degree of heterogeneity to differences in major interventions, cohort age, and different comorbidity profiles. Accordingly, we found that studies with older cohorts showed a lower effect size of LAVI suggesting a more complex risk profile of older patients when compared to younger individuals. Also, mean pre-operative LAVI of patients with a history of PAF developing POAF was higher compared to patients with POAF and no history of PAF (*Figure 5B*). In addition, studies that included patients with PAF were more frequently conducted in patients undergoing aortic or mitral valve surgery, which could explain the increased average LAVI in this population. However, the effect size and mean difference of LAVI appears to be lower in these studies, potentially resulting from pre-existing large atria as a consequence of AF history itself, as compared to studies which excluded patients with a history of AF (*Figure 5B*).

Strain analysis

PALS, which is a parameter depicting LA reservoir function, showed a large effect size in the meta-analysis (*Figure 4*), with an acceptable between-study-heterogeneity. Mean pre-operative PALS was lower in patients with POAF as compared to patients that remained in SR (*Figure 5C*). Decreased LA strain of the reservoir function depicts the disturbance of the myocardial passive stretching. A possible explanation for these changes is the induction of LA structural remodelling, which is associated with increased myocardial fibrosis and decreased atrial elasticity.[56,63]

Whereas PALS accounts for the amount of overall LA reservoir function, LA strain rate during ventricular systole (LASRs) depicts the velocity of shortening of the myocardial cells, providing information on the elasticity of the atrial wall.[40] We found that LASRs was also reduced in patients with POAF, suggesting impaired elasticity of the myocardium.[40,41] Besides reservoir function abnormalities, pre-operative LA contractile function seems to be impaired in patients that develop POAF. Reduced LA strain rate during atrial contraction (LASRa) and peak atrial contraction strain (PACS) are both associated with POAF, especially in patients with aortic valve stenosis.[53] These findings suggest that strain analysis is a useful imaging modality for detecting early structural alterations, such as atrial wall stiffness and reduced compliance potentially resulting in a substrate for POAF.[64]

Clinical implications

Prediction of POAF in a heterogeneous population undergoing cardiac surgery is limited by confounding factors such as type of underlying disease, types of surgery, age of the included population and definition of POAF. Therefore, pre-operative TTE is a promising tool in stratifying substrates in different underlying pathologies. Our meta-analyses show that POAF after cardiac surgery can be predicted by TTE parameters, despite inherently extensive heterogeneity within study populations and potential interobserver variability. Pre-operative electrophysiological disturbances of the atrial myocardium and LA dysfunction provide useful information for pre-operative risk stratification for POAF in patients undergoing cardiac surgery. Echocardiographic parameters depicting these functions are LAVI, PA-TDI interval, and PALS. These parameters indicate pathophysiological changes in the heart, which are associated with susceptibility to POAF, and implementing these measurements in the standard pre-operative care might help to identify patients at risk for POAF. Also, strain analysis provides useful insights into alterations in atrial reservoir, conduit, and contractile function, which are generally overlooked in conventional echocardiography. Furthermore, accurate identification of patients with a substrate for POAF could offer a more targeted deployment of preventive measures, such as pre-operative pharmacological prophylaxis or careful fluid balance management in the early post-operative setting.[5] Also, several studies have demonstrated the positive effect of beta-blockers, antiarrhythmic drugs (for example, sotalol and amiodarone), and magnesium in preventing POAF in the early post-operative phase.[5,65] Recent studies also showed a reduction in POAF incidence in patients who underwent Calcium-induced autonomic denervation of the major atrial ganglionated plexi or Botulinum toxin injection in epicardial fat pads, during cardiac surgery.[66,67] Moreover, precise identification of patients at high risk for POAF, based on their substrate, could in the future even result in deployment of more rigorous preventive measures, such as pre-emptive AF-ablation during the initial cardiac procedure.

Limitations

Our meta-analysis is limited, like all meta-analyses, by the quality of the studies included. Since the overall quality of the studies included was high, we believe that the data extracted from the original publications are also of high quality. The included studies showed marked heterogeneity, which was explored by several Influence Analyses (Supplementary material online, *Figures S1*–S6), and between-study differences, which were explored in several subgroup analyses and meta-regressions. In addition to the inherently heterogeneous population of patients undergoing cardiac surgery, TTE heavily depends on the expertise and experience of the observers. Furthermore, there was significant publication bias present in the meta-analysis for LAVI. The trim-and-fill procedure showed a lack of smaller studies reporting a lower Cohen's *d* for LAVI. Based on the results from this procedure, we see that the Cohen's *d* presented in our meta-analysis might be overestimated. Despite these limitations, we found a large effect size in all meta-analyses performed.

Conclusion

This systematic review of the literature and meta-analysis provides further evidence that a pre-existing substrate predisposes patients to POAF development. We found that pre-operative intra-atrial impulse conduction delays as well as, mostly LA and LV, pre-operative functional impairments, and structural alterations are important echocardiographic variables for predicting POAF. These variables can be effectively measured by conventional bedside TTE and using these parameters should result in a paradigm shift from 'risk-factor-based' predictive models to 'substrate-based' predictive models for POAF.

Supplementary material

Supplementary material is available at *Europace* online.

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