Systematic Review/Meta-analysis

Prevalence of Left Atrial Appendage Thrombus in Patients Anticoagulated With Direct Oral Anticoagulants: Systematic Review and Meta-analysis

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ABSTRACT

Background: Multiple studies have examined the prevalence of left atrial appendage thrombus (LAAT) in patients anticoagulated with direct oral anticoagulants (DOACs) and have reported conflicting results.

Methods: Studies reporting the prevalence of LAAT on transesophageal echocardiography (TEE) after 3 or more weeks of DOAC therapy were identified. The proportions of anticoagulated patients diagnosed with LAAT were pooled using random-effects models. Prespecified subgroup analyses by the indication of TEE (pre–atrial fibrillation [AF] ablation vs cardioversion) and TEE strategy (routine use vs selective) were conducted via stratification.

RÉSUMÉ

Introduction : De nombreuses études ont porté sur la prévalence des thrombi se formant dans l'appendice auriculaire gauche (TAAG) chez les patients qui reçoivent des anticoagulants oraux directs (AOD) et ont révélé des résultats contradictoires.

Méthodes : Nous avons recensé les études qui ont fait état de la prévalence des TAAG à l'échocardiographie transœsophagienne (ETO) trois semaines ou plus après le traitement par AOD. Les modèles à effets aléatoires ont permis de regrouper les patients qui prenaient des anticoagulants et avaient reçu un diagnostic de TAAG. Nous avons réalisé les analyses de sous-groupes prédéterminés par l'indication

Current guidelines allow for elective cardioversion of patients who are anticoagulated on direct oral anticoagulants (DOACs) for 3 or more weeks based on multiple randomized clinical trials (RCTs).[1] This has been extrapolated to atrial fibrillation (AF) ablation where pre-AF ablation transesophageal echocardiography (TEE) to rule out left atrial

appendage thrombus (LAAT) is felt to be optional in patients on DOACs.[2] In line with these recommendations, large observational studies have reported a low prevalence of LAAT in patients who were anticoagulated for at least 3 weeks and underwent TEE before AF ablation.[3,4] However, many other studies have reported conflicting results with an alarmingly high prevalence of LAAT despite appropriate anticoagulation.[5-8] Discerning the prevalence of LAAT has important clinical implications as it can inform on the appropriate use of TEE in this group of patients. Also, identifying factors associated with the higher prevalence of LAAT can help tailor the use of TEE in selected patients.

We sought to perform a systematic review and meta-analysis of studies that examined the prevalence of LAAT on TEE in patients anticoagulated with DOACs for 3 or more

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Results: Forty studies were identified: 22 full manuscripts and 18 abstracts. Only 11 studies performed TEE routinely. Most studies included patients with paroxysmal AF and low thromboembolic risk. The pooled prevalence of LAAT was 2.5% (95% confidence interval [1.6%-3.4%]). The prevalence of LAAT is lower in the pre-AF ablation group compared with pre-cardioversion (1.1% vs 4.0%, $P = 0.033$). Routine TEE strategy yielded a lower LAAT prevalence in both groups (0.1% vs 2.3%, $P = 0.002$ and 3.2% vs 5.8%, $P = 0.432$, respectively). **Conclusion:** The reported prevalence of LAAT on TEE in patients treated with DOACs is highly variable. Factors associated with a high LAAT prevalence were pre-cardioversion indication and selective TEE strategy. Routine use of TEE before AF ablation may not be warranted.

d'ETO (fibrillation auriculaire [FA] avant l'ablation *vs* FA avant la cardioversion) et la stratégie d'utilisation de l'ETO (systématique *vs* sélective) grâce à la stratification.
Résultats : Nous avons recensé 40 études : 22 manuscrits complets et 18 résumés. Seules 11 études portaient sur l'utilisation systématique de l'ETO. La plupart des études portaient sur des patients qui étaient atteints de FA paroxystique et exposés à un faible risque thromboembolique. La prévalence groupée de TAAG était de 2,5 % (intervalle de confiance à 95 % [1,6 %-3,4 %]). La prévalence de TAAG était plus faible dans le groupe de FA avant l'ablation que dans le groupe de FA avant la cardioversion (1,1 % *vs* 4,0 %, $P = 0,033$). La stratégie d'utilisation systématique de l'ETO a permis d'obtenir une prévalence plus faible de TAAG dans les deux groupes (0,1 % *vs* 2,3 %, $P = 0,002$ et 3,2 % *vs* 5,8 %, $P = 0,432$, respectivement). **Conclusion :** La prévalence de TAAG à l'ETO chez les patients traités par AOD varie beaucoup. Les facteurs associés à une prévalence élevée de TAAG étaient l'indication avant la cardioversion et la stratégie d'utilisation sélective de l'ETO. L'utilisation systématique de l'ETO avant l'ablation peut ne pas être justifiée.

weeks before either cardioversion or AF ablation to better define the prevalence of LAAT.

Methods

Literature search, study selection, and data collection

We performed a search of PubMed, Medline (via Ovid), Cochrane Central Register of Controlled Trials (via Ovid), Embase (via Ovid), and ISI Web of Science (Science Citation Index). The publication database search was executed by an academic librarian (LS). The literature search was supplemented by a manual search of bibliographies of published articles. See Supplemental Appendix S1 for details of search strategy. The search strategy focused on studies of human subjects with AF who underwent TEE after at least 3 weeks of anticoagulation on DOAC and reported the prevalence of LAAT. The search was conducted from the date of inception for each database until September 23, 2019. There were no language restrictions during the search; however, articles were screened for English language studies only. No exclusions were set. If a conference abstract was subsequently published in a full manuscript format, the latter was used for data extraction. Articles were independently screened by 2 authors (W.A. and E.G.) using a standard extraction form. Disagreements were resolved by consensus or adjudication (M.M.S.). We extracted all relevant details including indication for TEE, type of AF, comorbidities, specific type of anticoagulation used, and TEE strategy (whether TEE was performed routinely or for selected patients). The primary endpoint of the analysis was the prevalence of LAAT. Prespecified subgroup analyses based on indication of TEE (AF ablation vs cardioversion) and TEE strategy (whether TEE was performed routinely or selectively) were undertaken.

Risk of bias

The methodological quality of studies was assessed using the Grading of Recommendations Assessments, Development, and Evaluation (GRADE) guidelines.[9,10]

Analysis and synthesis of results

The proportions of anticoagulated patients diagnosed with LAAT were pooled using random-effects models according to the method described by DerSimonian and Liard.[11] Prespecified subgroup analyses by indication for TEE (ablation vs cardioversion) and routine vs selective TEE strategies were conducted via stratification. *Post hoc* subgroup analyses of LAAT incidences using routine vs selective TEE strategies, stratified by planned procedure (ablation or cardioversion), and sample size were also performed. Subgroup analyses by **C**ongestive Heart Failure, **H**ypertension, **A**ge ($\geq$ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female) (CHA_2DS_2-VASc) score and proportion of patients with persistent AF were planned but were not undertaken because of low numbers of relevant studies. Freeman-Tukey double arcsine transformation was used to stabilize the variances associated with extreme proportions (ie, 0%) in meta-analyses.[12] Statistical heterogeneity between studies was assessed using the I^2 statistic. Continuous or ordinal variables were analyzed both as such and as dichotomized variables for all analyses. Proportions are reported with 95% confidence intervals (CI). All analyses were performed using Stata 15 using a 2-tailed α level of 0.05 to define statistical significance.

Results

Synthesis of published reports

The systematic search identified 2636 citations. Of these, 40 met inclusion criteria: 22 full manuscripts and 18 abstracts (Supplemental Fig. S1).

Characteristics of included studies

All studies were published between 2013 and 2019. The populations studied were pre-AF ablation in 15 studies, pre-cardioversion in 10, and mixed population in 12 studies.

Table 1. Characteristics of studies included*

Study first author	Year published	Publication type	CHADS$_2$	CHA$_2$DS$_2$-VASc	Paroxysmal AF (%)	TEE strategy	Quality assessment
Preablation							
Alqarawi	2019	Manuscript	1 ± 1 (mean)	1.9 ± 1.4 (mean)	478 (72)	Routine	Low
Dzhioeva	2018	Abstract	Not reported	Not reported	Not reported	Selective	Low
Harada	2018	Manuscript	1.2 ± 1.2 (mean)	2.1 ± 1.6 (mean)	Not reported	Selective	Low
Wu	2018	Manuscript	1 (0-2) (median)	2 (1-3) (median)	367 (60)	Selective	Low
Atkinson	2017	Manuscript	1 (0-2) (median)	0 (0-1) (median)	227 (68)	Selective	Low
DaCosta	2017	Manuscript	Not reported	1.64 (1.46) (mean)	340 (59)	Selective	Low
Gunawardene	2017	Manuscript	Not reported	Not reported	804 (48)	Routine	Low
Tsyganov	2017	Manuscript	Not reported	2.09 (0.91) (mean)	71 (62)	Selective	Low
Wyrembak	2017	Manuscript	Not reported	3.1 ± 2 (mean)	385 (41)	Selective	Low
Yamashita	2017	Abstract	Not reported	Not reported	Not reported	Selective	Low
Atwater	2016	Abstract	Not reported	Not reported	Not reported	Routine	Low
Frenkel	2016	Manuscript	Not reported	2 (1-3.3) (median)	204 (53)	Selective	Very low
Sikorska	2015	Manuscript	1.1 (1.07) (mean)	1.54 (1.38) (mean)	117 (73)	Selective	Low
Somani	2014	Manuscript	0.74 (mean)	Not reported	140 (68)	Routine	Low
Riexinger	2013	Abstract	Not reported	Not reported	Not reported	Routine	Low
Precardioversion							
Kim	2018	Manuscript	Not reported	1.7 ± 1.3 (mean)	Not reported	Selective	Low
Russo	2018	Manuscript	Not reported	Not reported	0 (0)	Selective	Low
Schaeffer	2018	Manuscript	Not reported	3 (0-9)	Not reported	Selective	Low
Barysiene	2017	Manuscript	Not reported	3.5 (1.5) (mean)	0 (0)	Selective	Low
Merino	2017	Abstract	Not reported	Not reported	270 (12)	Selective	Low
Tint	2017	Manuscript	Not reported	Not reported	0 (0)	Routine	Low
Irmer	2016	Abstract	Not reported	2.9 (1.7) (mean)	0 (0)	Routine	Low
Reers	2016	Manuscript	Not reported	Not reported	172 (57)	Selective	Low
Stabile	2015	Manuscript	Not reported	2.37 (1.44) (mean)	Not reported	Selective	Low
Dizeo	2014	Abstract	Not reported	Not reported	Not reported	Routine	Low
Mixed							
Di Biase	2013	Abstract	Not reported	Not reported	Not reported	Selective	Low
Kelly	2018	Abstract	Not reported	4 (mean)	Not reported	Selective	Low
Minami	2018	Abstract	Not reported	Not reported	Not reported	Selective	Low
Al Rawahi	2017	Abstract	Not reported	Not reported	Not reported	Selective	Low
Alshoubaki	2017	Abstract	Not reported	Not reported	Not reported	Routine	Low
Bertaglia	2017	Manuscript	Not reported	2.6 (1.2) (median)	53 (13)	Selective	Low
Gawalko	2017	Manuscript	2 (2-3) (median)	2 (1-3) (median)	492 (57)	Routine	Low
Kawabata	2017	Manuscript	1.2 (1.1) (mean)	1.9 (1.5) (mean)	284 (51)	Selective	Low
Ito	2015	Abstract	Not reported	Not reported	Not reported	Routine	Low
Kishima	2015	Abstract	Not reported	Not reported	Not reported	Selective	Low
Zylla	2014	Manuscript	Not reported	4 (median)	210 (33)	Selective	Very low
Attenhofer Jost	2013	Abstract	Not reported	Not reported	Not reported	Selective	Low
Not reported							
Abdin	2018	Abstract	Not reported	4 (median)	Not reported	Selective	Low
Nazeri	2018	Abstract	Not reported	Not reported	Not reported	Selective	Low
Takahashi	2016	Abstract	Not reported	Not reported	Not reported	Selective	Low

AF, atrial fibrillation; CHADS$_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; CHA$_2$DS$_2$-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female); TEE, transesophageal echocardiography.

*More details about the studies are available in the Supplemental Table S1.

Eleven studies performed TEE routinely, whereas the remaining studies performed selectively. The mean or median **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack (CHADS$_2$) or CHA$_2$DS$_2$-VASc score was reported in 21 studies. Most studies (15 of 21, 71%) had a low predicted thromboembolic risk (CHADS$_2$ < 2 and/or CHA$_2$DS$_2$-VASc < 3). Paroxysmal AF was the most common AF type in all but 4 studies. Table 1 summarizes the study characteristics and risk of bias of all included studies. More details about the studies are available in the Supplemental Table S1.

Prevalence of LAAT

The pooled prevalence of LAAT was 2.5% (95% CI [1.6%-3.4%]) with a significant heterogeneity between studies (I^2 = 89.8%) (Fig. 1).

LAAT prevalence was lower in the pre-AF ablation group when compared with the pre-cardioversion group (1.1% vs 4.0%, P = 0.033) (Fig. 2). In the pre-AF ablation group, a routine TEE strategy yielded a very low LAAT prevalence at 0.1% (95% CI [0%-0.6%]) with no significant heterogeneity (I^2 = 46.6%), and was significantly lower than what was observed with the selective TEE strategy, which had a prevalence of 2.3% (95% CI [0.6%-4.7%], P = 0.002) (Fig. 3).

Similarly, the prevalence of LAAT in the pre-cardioversion group was lower in the routine TEE strategy compared with the selective strategy; however, this was not statistically significant (3.2% vs 5.8%, P = 0.432) (Fig. 4).

Supplemental Figure S2 shows the results stratified by study sample size. The prevalence of LAAT in studies with a large sample size (>1000 participants) was 0.06% with low heterogeneity between studies (I^2 = 40.2%) and 2.9% in
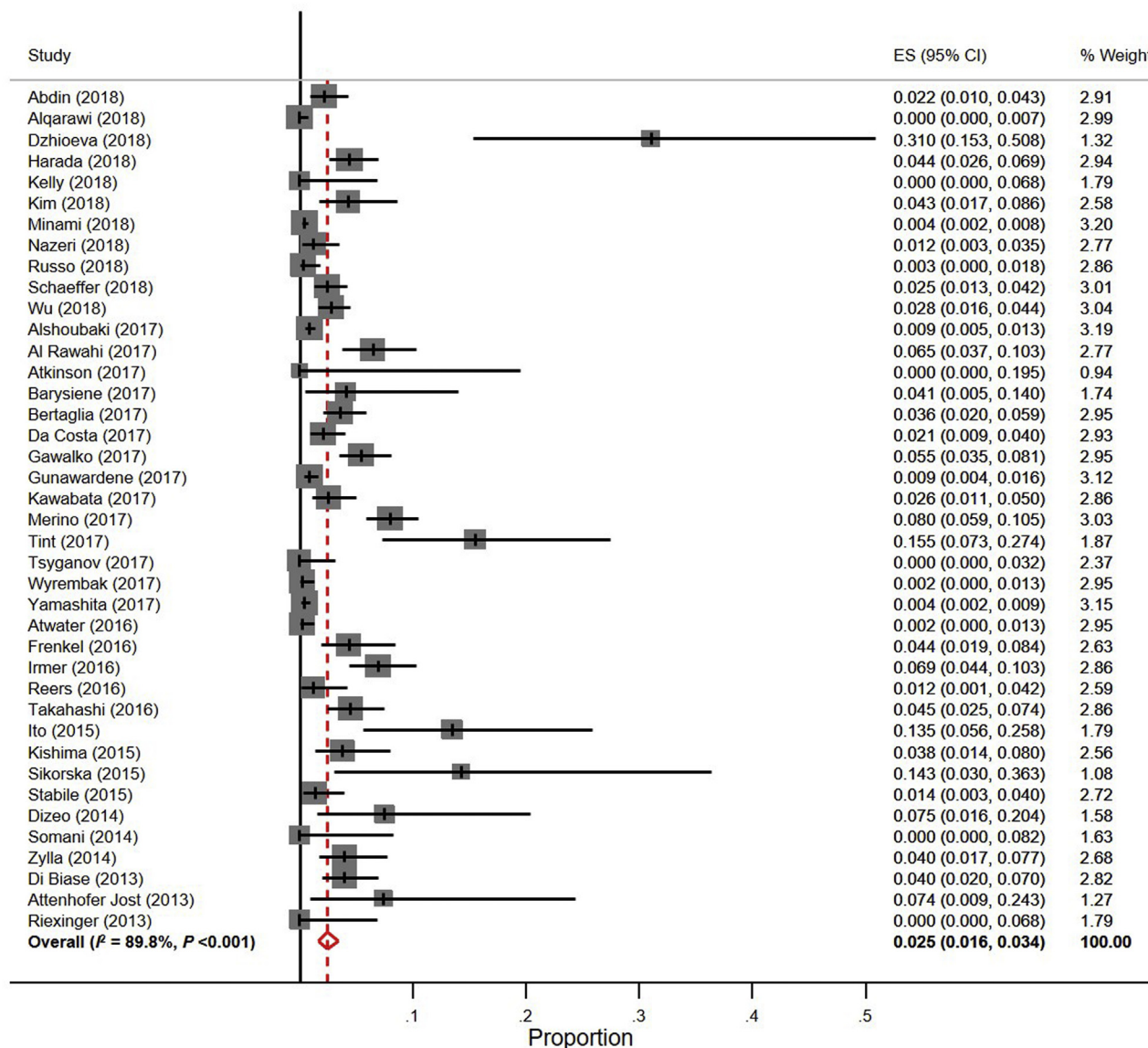
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Study	ES (95% CI)	% Weight
Abdin (2018)	0.022 (0.010, 0.043)	2.91
Alqarawi (2018)	0.000 (0.000, 0.007)	2.99
Dzhioeva (2018)	0.310 (0.153, 0.508)	1.32
Harada (2018)	0.044 (0.026, 0.069)	2.94
Kelly (2018)	0.000 (0.000, 0.068)	1.79
Kim (2018)	0.043 (0.017, 0.086)	2.58
Minami (2018)	0.004 (0.002, 0.008)	3.20
Nazeri (2018)	0.012 (0.003, 0.035)	2.77
Russo (2018)	0.003 (0.000, 0.018)	2.86
Schaeffer (2018)	0.025 (0.013, 0.042)	3.01
Wu (2018)	0.028 (0.016, 0.044)	3.04
Alshoubaki (2017)	0.009 (0.005, 0.013)	3.19
Al Rawahi (2017)	0.065 (0.037, 0.103)	2.77
Atkinson (2017)	0.000 (0.000, 0.195)	0.94
Barysiene (2017)	0.041 (0.005, 0.140)	1.74
Bertaglia (2017)	0.036 (0.020, 0.059)	2.95
Da Costa (2017)	0.021 (0.009, 0.040)	2.93
Gawalko (2017)	0.055 (0.035, 0.081)	2.95
Gunawardene (2017)	0.009 (0.004, 0.016)	3.12
Kawabata (2017)	0.026 (0.011, 0.050)	2.86
Merino (2017)	0.080 (0.059, 0.105)	3.03
Tint (2017)	0.155 (0.073, 0.274)	1.87
Tsyganov (2017)	0.000 (0.000, 0.032)	2.37
Wyrembak (2017)	0.002 (0.000, 0.013)	2.95
Yamashita (2017)	0.004 (0.002, 0.009)	3.15
Atwater (2016)	0.002 (0.000, 0.013)	2.95
Frenkel (2016)	0.044 (0.019, 0.084)	2.63
Irmer (2016)	0.069 (0.044, 0.103)	2.86
Reers (2016)	0.012 (0.001, 0.042)	2.59
Takahashi (2016)	0.045 (0.025, 0.074)	2.86
Ito (2015)	0.135 (0.056, 0.258)	1.79
Kishima (2015)	0.038 (0.014, 0.080)	2.56
Sikorska (2015)	0.143 (0.030, 0.363)	1.08
Stabile (2015)	0.014 (0.003, 0.040)	2.72
Dizeo (2014)	0.075 (0.016, 0.204)	1.58
Somani (2014)	0.000 (0.000, 0.082)	1.63
Zylla (2014)	0.040 (0.017, 0.077)	2.68
Di Biase (2013)	0.040 (0.020, 0.070)	2.82
Attenhofer Jost (2013)	0.074 (0.009, 0.243)	1.27
Riexinger (2013)	0.000 (0.000, 0.068)	1.79
Overall (I^2 = 89.8%, P <0.001)	**0.025 (0.016, 0.034)**	**100.00**

Figure 1. Pooled prevalence of left atrial appendage thrombi detected by transesophageal echocardiography in patients with atrial fibrillation on direct oral anticoagulants. CI, confidence interval; ES, effect size.

studies with a small sample size with substantial heterogeneity (I^2 = 85.5%).

Discussion

In this analysis, we found the prevalence of LAAT in patients anticoagulated for at least 3 weeks with DOACs to be highly variable depending on the TEE strategy used and the population studied. It ranges from 0.1% in patients who underwent TEE systematically before AF ablation to 5.8% in patients who underwent selective TEE before cardioversion. These observations suggest that routine TEE before AF ablation may not be necessary and that one needs to carefully review the TEE strategy used when interpreting studies that examined the prevalence of LAAT.

The variability in the prevalence of LAAT is not unique to patients anticoagulated on DOACs. Studies examining the prevalence of LAAT in patients anticoagulated with warfarin

also report a wide range, similar to our findings with DOACs.[3,13-16] There are multiple potential explanations for this variability. First, baseline characteristics are different among the studies included and are well known to predict the prevalence of LAAT.[15-17] $CHADS_2$ score was found to independently predict the LAAT prevalence in one study.[17] Moreover, Puwanant et al.[16] reviewed 1059 TEEs before AF ablation and found a graded prevalence of LAAT based on $CHADS_2$ score. Although the limited number of studies reporting the $CHADS_2$ score and the narrow range of $CHADS_2$ score between studies preclude any meaningful analysis in our study, we have found that the prevalence of LAAT in patients undergoing AF ablation is significantly lower than the prevalence of LAAT in patients undergoing cardioversion (1.1% vs 4.0%, P = 0.002). The difference in baseline characteristics between patients undergoing AF ablation vs those undergoing cardioversion is likely, at least in
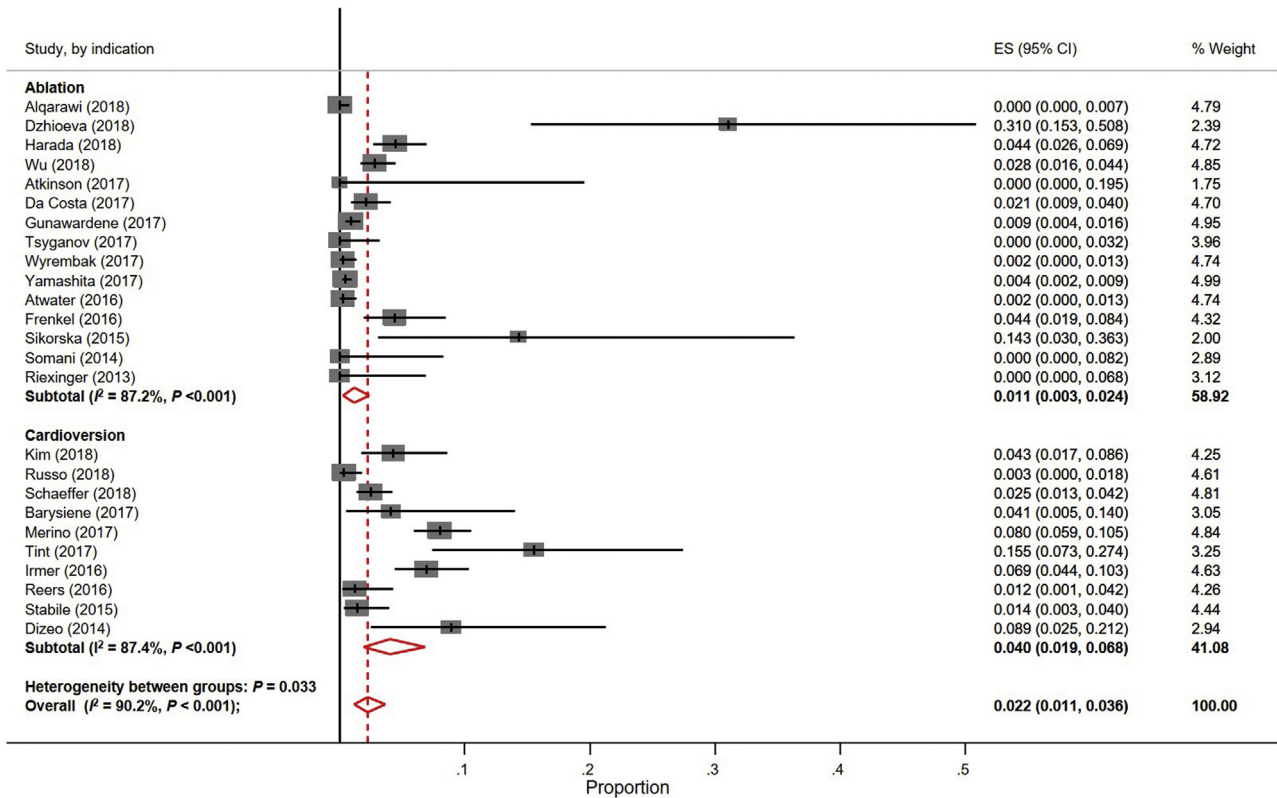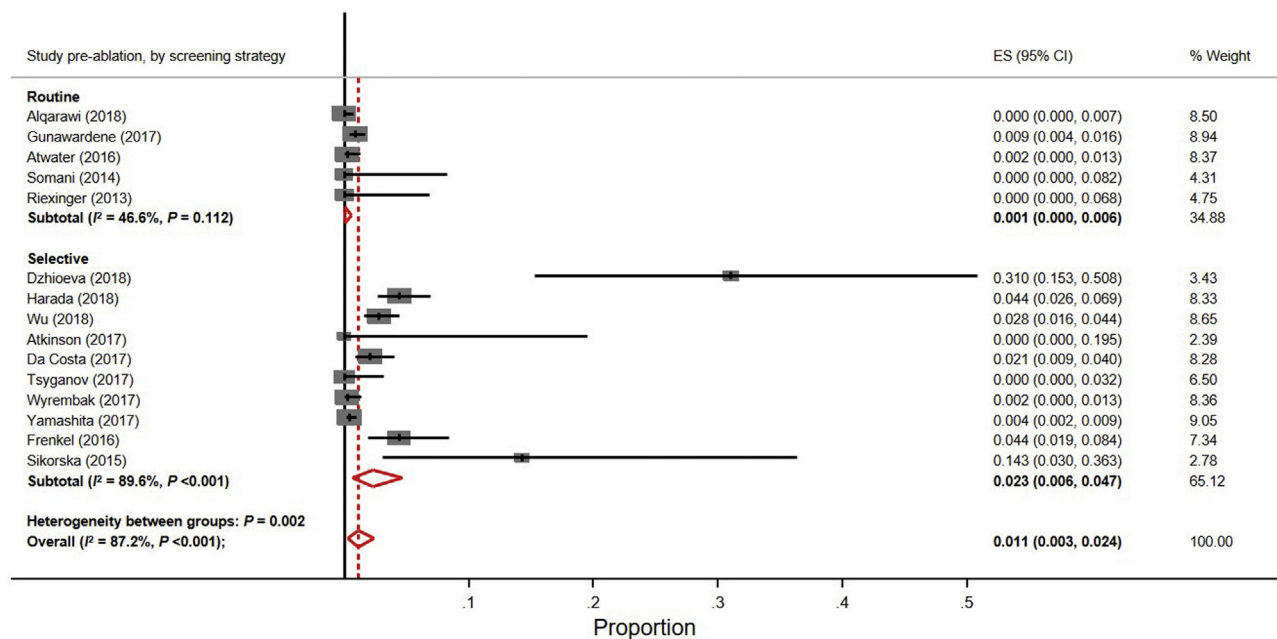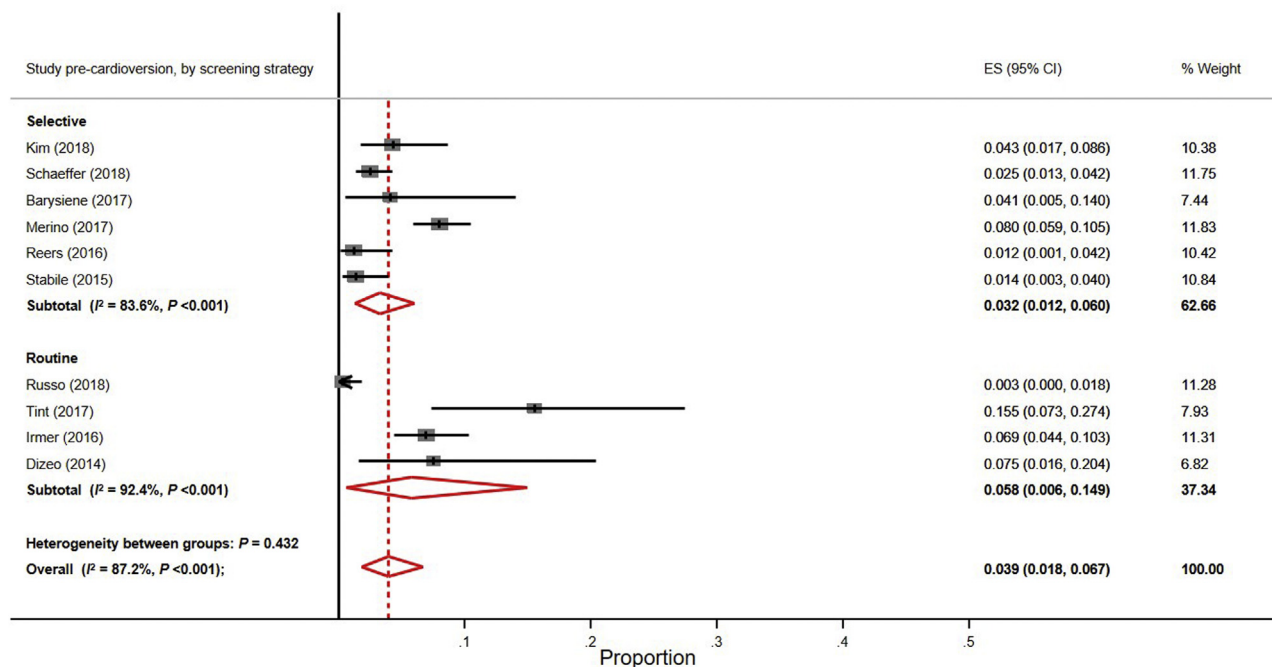
Figure 2. Prevalence of left atrial thrombi detected by transesophageal echocardiography in patients with atrial fibrillation (AF) on direct oral anticoagulants, stratified by indication for echocardiogram (pre-AF ablation or pre-cardioversion). CI, confidence interval; ES, effect size.

part, the reason for the difference in the prevalence of LAAT between the 2 groups. Second, the strategy of performing TEE before either cardioversion or AF ablation varies among different studies and is an important factor in the observed variability in the prevalence of LAAT. Most studies performed TEE only in selected patients, which introduces inherent bias

Figure 3. Prevalence of left atrial thrombi detected by transesophageal echocardiography (TEE) in patients with atrial fibrillation (AF) on direct oral anticoagulants pre-AF ablation, stratified by TEE strategy (routine or selective). CI, confidence interval; ES, effect size.

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Figure 4. Prevalence of left atrial thrombi detected by transesophageal echocardiography (TEE) in patients with atrial fibrillation on direct oral anticoagulants pre-cardioversion, stratified by TEE strategy (routine or selective). CI, confidence interval; ES, effect size.

that can artificially increase the prevalence of LAAT. This is because factors associated with selecting patients for TEE are likely associated with LAAT such as higher CHADS$_2$ and poor adherence to anticoagulation. Fewer studies performed TEE systematically but are likely more representative of the true prevalence of LAAT. Indeed, the prevalence of LAAT in patients undergoing AF ablation where all patients underwent TEE was significantly lower than the prevalence where TEE was selectively performed (0.1% vs 2.3%, $P = 0.002$). Third, interobserver variability in diagnosing LAAT by TEE is known and likely contributed to further variability in the reported LAAT prevalence. Schneider et al.[18] reported a 22% disagreement in diagnosing LAAT on TEEs by 2 experienced echocardiographers (Kappa = 0.5). Discrepant interpretations related to reverberation artefacts or difficulty differentiating LAAT from spontaneous echocardiographic contrast, echogenic atrioventricular groove, or pectinate muscles. Moreover, the operator's experience in obtaining and assessing echocardiographic images cannot be overstated.[19] It is likely that studies in this meta-analysis included TEE operators with different qualifications and levels of experience. Last, patient compliance is difficult to assess with DOAC therapy given the lack of a widely used objective measure of effect such as the international ratio for warfarin. It is conceivable that noncompliance might account for some of the differences.

The true prevalence of LAAT is likely overestimated in many studies. This is supported in our analysis by the lower prevalence of LAAT in studies that performed TEE systematically and the lower pooled prevalence of LAAT from studies with large same sizes, as pooling estimates from studies with large sample sizes are known to be more precise.[20,21] In addition, it is possible that small studies with high proportions were more likely to be published compared with those with small proportions (ie, publication bias). The safety of

withholding TEEs in patients undergoing cardioversion on uninterrupted anticoagulation has been shown in multiple large RCTs.[1,2,22,23] The discrepancy between the reported overall high prevalence of LAAT in patients undergoing cardioversion and the safety of withholding TEEs in these large RCTs supports our hypothesis that the true prevalence of LAAT may be lower than what is reported. Although it is true that patients enrolled in RCTs are likely different in regard to medication compliance and baseline characteristics, real-life data examining the safety of withholding TEE in patients appropriately anticoagulated on DOAC confirm RCT data.[24,25] Kaplan et al.[25] reviewed more than 600 patients who underwent cardioversion after 3 weeks of DOAC therapy and observed a low stroke rate at 30 days (2/600). It is important to note, however, that the safety of using DOAC in cardioversion is based on the low incidence of thromboembolic events rather than LAAT. It is conceivable that some patients with LAAT might not go on to have a thromboembolic event after cardioversion although the number is likely low.

Our study has important clinical implications. First, we have shown that the prevalence of LAAT in patients undergoing AF ablation after 3 weeks of DOAC therapy is very low when all patients are included (routine TEE strategy). This argues against the routine use of TEE before AF ablation if patients have received 3 weeks of DOAC therapy, notwithstanding that the threshold of the LAAT prevalence where withholding TEE is acceptable has not been established. Second, the prevalence of LAAT is dependent on the population studied. We have observed a significantly different LAAT prevalence between patients undergoing AF ablation and cardioversion. This is likely due to the difference in baseline characteristics; however, data were not available to test this hypothesis. Although we believe that the true

prevalence of LAAT is lower than reported for the reasons discussed above, it is possible that a subset of high-risk patients might benefit from a TEE-guided cardioversion even if they are on DOAC. This will need to be tested in future studies.

There are several limitations of our analysis. Most importantly, we found significant heterogeneity among studies included. The lack of a standardized definition of LAAT and information on the TEE operators' experience or qualifications limit the generalizability of our findings. Moreover, the inconsistency of reporting risk factors and the inability to access patient-level data precluded the identification of predictors of LAAT. Secondly, few studies reported the LAAT prevalence stratified by AF type (ie, paroxysmal vs persistent, etc.) precluding subgroup analysis for each type separately. Thirdly, the mean $CHADS_2$/CHA_2DS_2-VASc scores were low, and care should be taken when extrapolating the results of this review to higher-risk populations. Lastly, not all selective TEE strategies use the same criteria leading to further variations even within a selective strategy and could, in part, explain the difference in the prevalence of LAAT between pre-AF ablation and pre-cardioversion groups.

Conclusion

There is significant variability in the reported LAAT prevalence on TEE in patients anticoagulated with DOAC for 3 or more weeks. This is likely due to selection bias and differences in baseline risk factors. Systematic TEE use before AF ablation yielded a very low prevalence of LAAT. Further research is needed to discern whether a subset of patients on anticoagulation might benefit from TEE before undergoing cardioversion.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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