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Clinical Research

Bioprosthetic leaflet thrombosis and reduced leaflet motion after transcatheter aortic valve replacement: A systematic review and meta-analysis☆

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A R T I C L E I N F O

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A B S T R A C T

Background: Leaflet thrombosis and reduced leaflet motion have become a concern with the expanding use of transcatheter aortic valve replacement in lower-risk patients.
Aims: To assess the proportions, predictors and clinical impact of leaflet thrombosis and reduced leaflet motion after transcatheter aortic valve replacement.
Methods: We performed a meta-analysis of studies assessing the proportions of and/or clinical outcomes according to the presence of leaflet thrombosis after transcatheter aortic valve replacement identified with computed tomography and/or echocardiography.
Results: Fifty-three studies, representing 25,258 patients undergoing transcatheter aortic valve replacement, were considered. The proportion of leaflet thrombosis was 5.2% overall, and was higher in computed tomography versus echocardiography (16.4% vs. 1.1%, respectively); reduced leaflet motion was identified in 11% of patients with four-dimensional computed tomography. Intra-annular bioprostheses were associated with a higher proportion of leaflet thrombosis, whereas chronic oral anticoagulation was protective for leaflet thrombosis in both computed tomography and echocardiographic studies (9.7% vs. 17.5%; relative risk [RR]: 0.51, 95% confidence interval [95% CI]: 0.37–0.71 and 0.9% vs. 2.7%; RR: 0.22, 95% CI: 0.06–0.79, respectively) and for reduced leaflet motion (2.5% vs. 12.4%; RR: 0.32, 95% CI: 0.13–0.76). Leaflet thrombosis was not associated with an increased risk of death, but with a higher risk of stroke in computed tomography studies (2.8% vs. 2.4%; RR: 1.63, 95% CI: 1.05–2.55), a difference more pronounced when considering reduced leaflet motion (3.5% vs. 1.7%; RR: 2.39, 95% CI: 0.63–8.34).
Conclusions: The proportion of leaflet thrombosis is highly variable according to the screening approach, the type of valve and the use of oral anticoagulation. The occurrence of cerebral events is increased when leaflet thrombosis and/or reduced leaflet motion are diagnosed, but leaflet thrombosis has no impact on survival.

1. Abbreviations

4D	four-dimensional
CI	confidence interval
CT	computed tomography
LT	leaflet thrombosis
RLM	reduced leaflet motion
RR	relative risk
TAVR	transcatheter aortic valve replacement

☆ Tweet: Leaflet thrombosis after TAVR was associated with a higher risk of stroke (without considering TIA) in computed tomography studies but has no impact on survival.

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TEE transoesophageal echocardiography

2. Background

Transcatheter aortic valve replacement (TAVR) is the preferred therapeutic procedure for severe aortic stenosis in inoperable and high-risk patients, and is now rapidly expanding as an alternative to surgical aortic valve replacement for intermediate- and low-risk categories, with established good short-term safety [1–4]. Attention is now focused on long-term durability and outcomes optimization.

Leaflet thrombosis (LT) is observed in 10–30% of individuals who undergo computed tomography after TAVR [5–7]; it has been reported as a potential and reversible cause of premature TAVR deterioration [8], but also as a substrate for thromboembolic complications, especially strokes. However, the clinical relevance of LT remains controversial [5,6,9,10]. Data are scarce, and subclinical LT has been associated with the occurrence of stroke and/or transient ischaemic attack [11], but not with stroke *per se*, which is more relevant [12]. The imaging diagnostic modality used to identify LT is key, as it is mostly subclinical, detected in asymptomatic individuals and has multiple modifiers, such as antithrombotic treatment and the type of valve prosthesis [6,9,13–15]. Four-dimensional computed tomography (4D-CT) is the gold standard technique to identify reduced leaflet motion (RLM), a more advanced phenomenon, but is not performed as a routine standard follow-up approach. We therefore conducted a systematic review and meta-analysis to assess the proportions, predictors and clinical impact of LT after TAVR in CT and echocardiographic studies, with a specific focus on RLM in 4D-CT studies.

3. Methods

3.1. Study selection

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for this systematic review and meta-analysis (see checklist, Table A.1). We conducted a systematic literature review by formal searches of the electronic MEDLINE database (source PubMed) and the Cochrane Central Register of Controlled Trials, as well as European Society of Cardiology, American Heart Association and American College of Cardiology annual meetings until 17 April 2022. The following search terms were used: “transcatheter aortic valve replacement” OR “TAVR” OR “transcatheter aortic valve implantation” OR “TAVI” AND “thrombosis” OR “leaflet thrombosis” OR “LT” OR “reduced leaflet motion” OR “hypo-attenuated leaflet thickening” OR “hypoattenuating leaflet thickening”. References from reviews and selected articles were also reviewed for potentially relevant citations. Two investigators (V. R. and P. G.) independently screened each title and abstract, excluding duplicates and studies not meeting the inclusion criteria. Discrepancies in the data collection were resolved by consensus.

We restricted our analysis to studies that met all of the following inclusion criteria: (1) reported data on proportions and/or outcomes associated with the presence/absence of LT; and (2) including ≥ 25 patients. Studies were excluded if any of the following criteria applied: (1) duplicate publication data; and (2) the outcome of interest was not clearly reported or was impossible to extract or calculate from the published results. Studies were divided into CT studies (when follow-up and LT diagnosis were systematically performed by CT) and echocardiographic studies (when LT diagnosis was assessed by echocardiography, with variable confirmation by transoesophageal echocardiography [TEE] and/or CT). This study has been registered in PROSPERO (CRD42021287183).

3.2. Outcomes

The primary endpoint was the presence of LT, defined as LT and/or RLM according to each study, and classified as grade 3 or 4 if specified [16]. Given the differences in the definitions of LT between CT and echocardiographic studies, all analyses are presented separately. Secondary endpoints were the proportion of stroke, stroke and/or transient ischaemic attack and death according to the presence of LT. Subgroup analyses were performed according to the valve characteristics (TAVR versus surgical aortic valve replacement, intra- vs. supra-annular valves, bovine versus porcine, self-versus balloon-expandable) and associated antithrombotic treatments. Specific analyses of RLM assessed by 4D-CT, with or without anticoagulation, and its association with stroke, with or without transient ischaemic attack, were also performed.

3.3. Assessment of risk of bias

We used the Newcastle-Ottawa Scale for assessment of risk of bias. This scale assesses risk of bias in the following three domains: selection of the study groups; comparability of groups; and ascertainment of exposure. Studies with scores of less than 4 were considered to have a high-risk of bias, those with scores of 4–6 an intermediate-risk of bias and those with scores of 7 or more a low-risk of bias.

3.4. Statistical analysis

The total number of patients experiencing or not the outcomes of interest in each arm extracted directly from the publications were used for the analyses. Results are presented as relative risks (RRs) with 95% confidence intervals (95% CIs). Outcomes from individual studies were combined using the Mantel–Haenszel random-effect model. Heterogeneity across studies was studied by the Cochran’s Q statistic, with a *P*-value set at 0.1. The I^2 was also considered, regardless of the *P*-value. An I^2 of ≥ 50% was prespecified as the threshold considered too high to provide consistent analysis. Tests were two-tailed, and a *P*-value of < 0.05 was considered statistically significant. Funnel plots, Egger’s regression tests and Harbord’s tests were used to assess publication bias. Analyses were conducted using Cochrane’s Review Manager (RevMan), version 5.4.1 (The Cochrane Collaboration, Copenhagen, Denmark).

4. Results

A total of 53 studies, representing 25,258 participants, were considered in this meta-analysis, of which 28 were classified as CT studies (*n* = 6803) and 25 as echocardiographic studies (*n* = 18,455) (Table A.2 and Table A.3). The review and selection process are depicted in Fig. 1.

4.1. Proportion of LT

The proportion of LT was 5.2% (1317/25,258), ranging from 0% to 78.4%, and mostly diagnosed using CT. Among echocardiographic studies, LT occurred in 1% (202/18,455; ranging from 0% to 12.6%), within a follow-up time window of 2 months up to 5 years (mostly at 1 year after TAVR). Among CT studies, the proportion of LT was 16.4% (1115/6803; ranging from 6.9% to 78.4%), within a follow-up time window of 3 days up to 19 months (mostly within 6 months). The proportion of RLM was 11% (443/4030) in 4D-CT studies.

4.2. Impact of valve type

The proportion of LT according to each valve type is detailed in Fig. 2. Intra-annular valves were associated with a higher

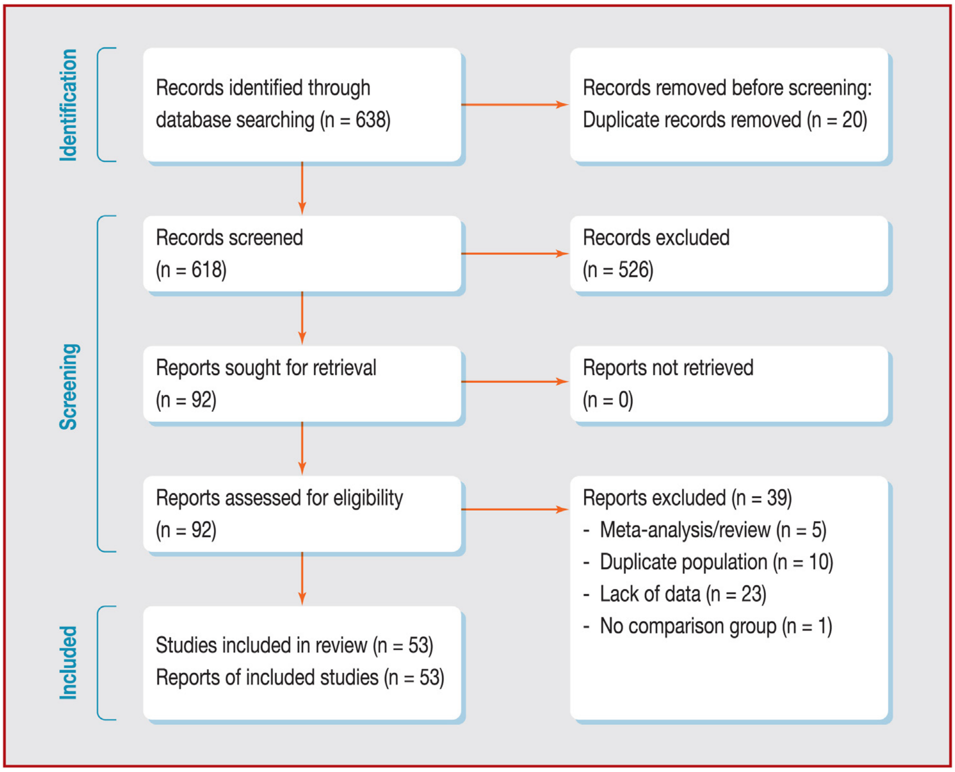


Fig. 1. Flow diagram selection.

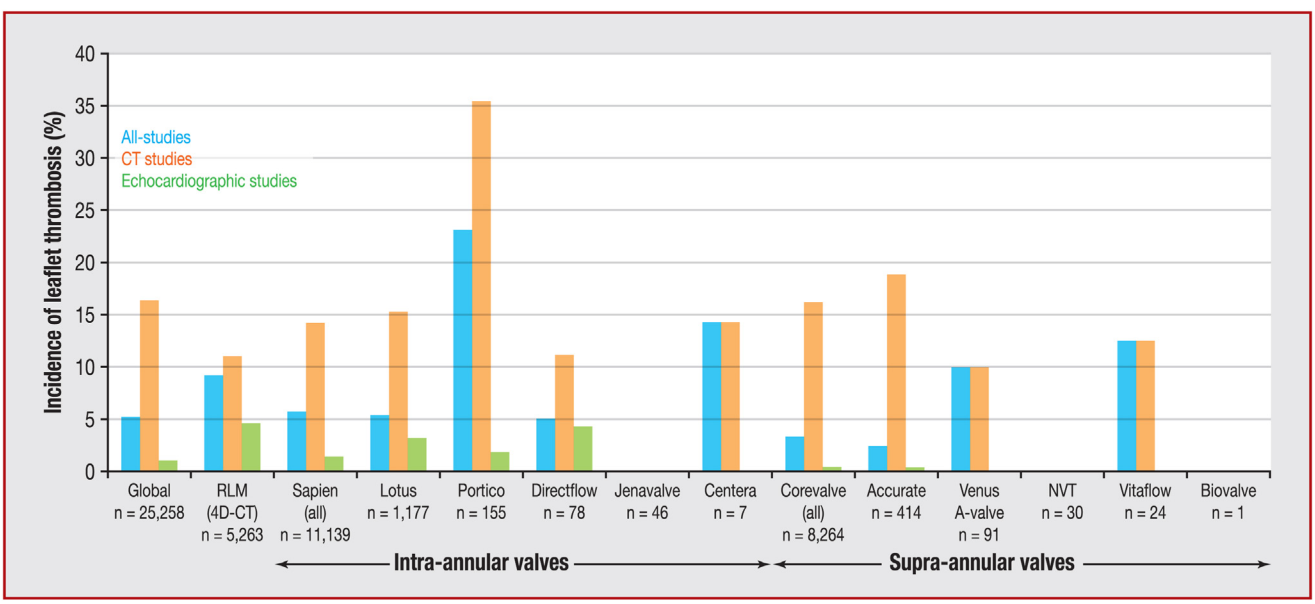


Fig. 2. Bar graph showing the incidence rates of leaflet thrombosis according to valve type. Rates of reduced leaflet motion (RLM) are also presented. 4D: four-dimensional; CT: computed tomography.

proportion of LT compared with supra-annular valves in CT studies (15.9% vs. 13.8%; RR: 1.39, 95% CI: 1.17–1.66; 16 studies including 4245 participants), a difference more pronounced in echocardiographic studies (1.8% vs. 0.5%; RR: 3.42, 95% CI: 2.12–5.54; nine studies including 11,463 participants) (Fig. 3). The proportion of LT did not differ significantly between TAVR and surgical aortic valve replacement (16.9% vs. 13.8%; RR: 1.46, 95% CI: 0.94–2.26; Fig. A.1A; four CT studies including 1628 participants). Participants treated with balloon-expandable valves had a higher proportion of LT compared with self-expandable valves in echocardiographic studies (1.5% vs. 0.6%; RR: 2.85, 95% CI: 1.53–5.31; eight studies including 10,122 participants; Fig. A.1B), but not in CT studies (14.5% vs. 12.2%; RR: 1.14, 95% CI: 0.96–1.36; 15 studies including 4277 participants). Participants treated with bovine valves had a higher proportion of LT compared with porcine valves, in CT studies (15.2% vs. 9.8%; RR: 1.37, 95% CI: 1.11–1.68; Fig. A.1C; 14 studies including 3836 participants) and echocardiographic studies (1.8% vs. 0.5%; RR: 3.40, 95% CI: 2.10–5.51; nine studies including 11,464 participants).

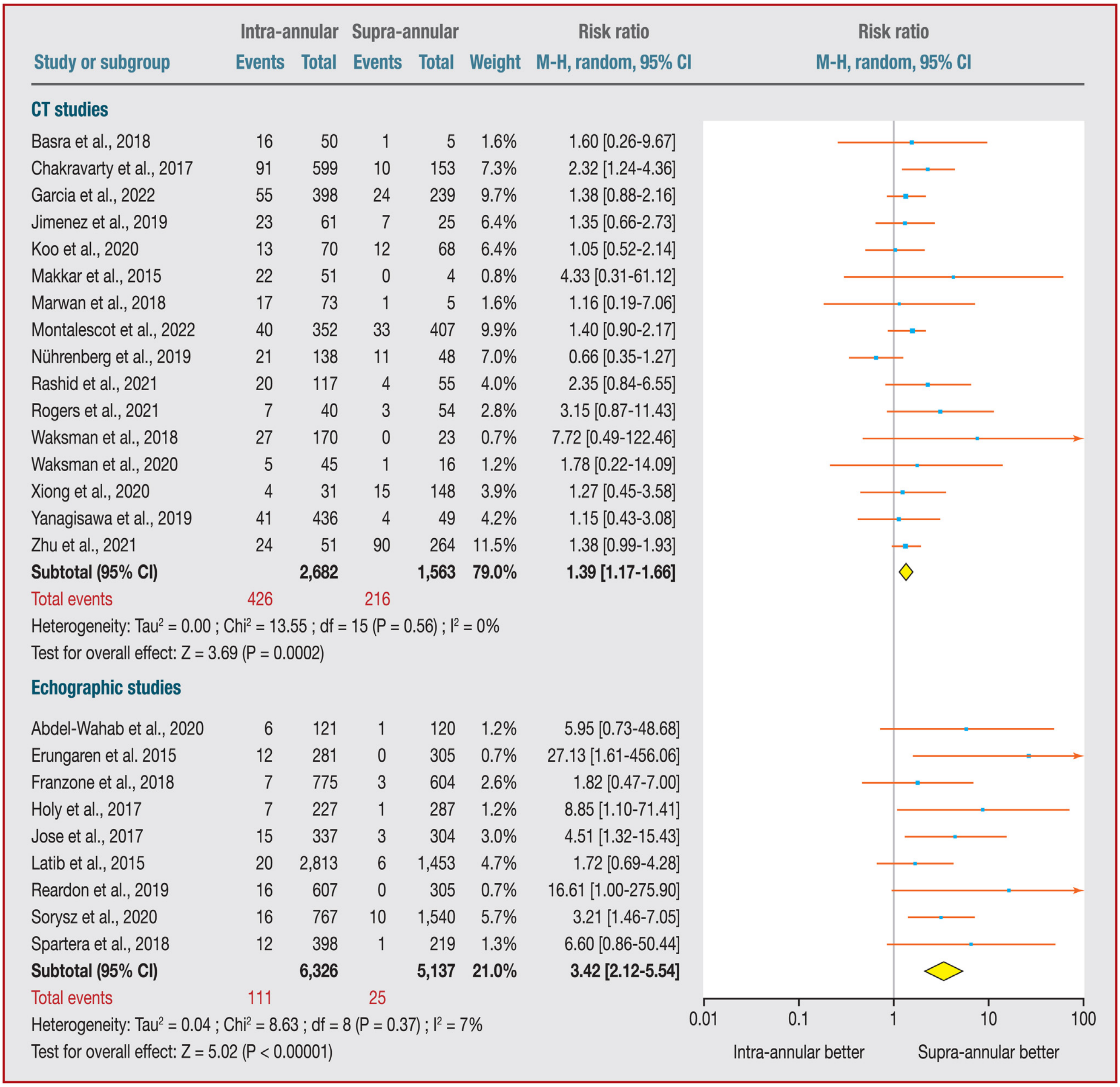


Fig. 3. Forest plot of selected studies comparing the effect of intra-annular versus supra-annular transcatheter aortic valve replacement on the occurrence of leaflet thrombosis.

4.3. *Impact of antithrombotic regimen at discharge*

Chronic oral anticoagulation was associated with a lower-risk of LT (9.7% vs. 17.5%; RR: 0.51, 95% CI: 0.37–0.71; 19 CT studies including 5882 participants; and 0.9% vs. 2.7%; RR: 0.22, 95% CI: 0.06–0.79; seven echocardiographic studies including 4163 participants; Fig. 4A), but with quantitative heterogeneity (I^2 = 76% and 61%, respectively). Chronic oral anticoagulation was also associated with a lower-risk of RLM (2.5% vs. 12.4%; RR: 0.32, 95% CI: 0.13–0.76; seven studies including 1465 participants; Fig. 4B), but with significant heterogeneity (I^2 = 60%). No significant differences in LT proportion were observed between vitamin K antagonists and non-vitamin K antagonist oral anticoagulants (3.3% vs. 3.9%; RR: 0.73, 95% CI: 0.43–1.23; 10 CT studies including 1151 participants), dual antiplatelet therapy and single antiplatelet therapy after TAVR (23% vs. 17%; RR: 1.08, 95% CI: 0.81–1.44; six CT studies including 1348 participants; and 1% vs. 0.8%, RR: 2.22, 95% CI: 0.60–8.20; three echocardiographic studies including 2000 participants; Fig. A.1D and Fig. A.1E).

4.4. *Clinical outcomes associated with LT and RLM (Central Illustration)*

LT was associated with a higher proportion of stroke in CT studies (2.8% vs. 2.4%; RR: 1.63, 95% CI: 1.05–2.55; 17 studies including 5553 participants), whereas echocardiographic studies were inconclusive because of a lack of data. RLM was associated with a higher but non-significant proportion of stroke (3.5% vs. 1.7%; RR: 2.29, 95% CI: 0.63–8.34; five studies including 1292 participants; Fig. 5A and B). Both LT, according to CT studies, and RLM were associated with higher rates of stroke and/or transient ischaemic attack (4.0% vs. 3.1%; RR: 1.86, 95% CI: 1.30–2.68; with 19 studies including 5701 participants; and 7.1% vs. 2.5%; RR: 3.31, 95% CI: 1.52–7.21; six studies including 1362 participants; Fig. A.1F, panels a and b, respectively). All-cause death did not differ between

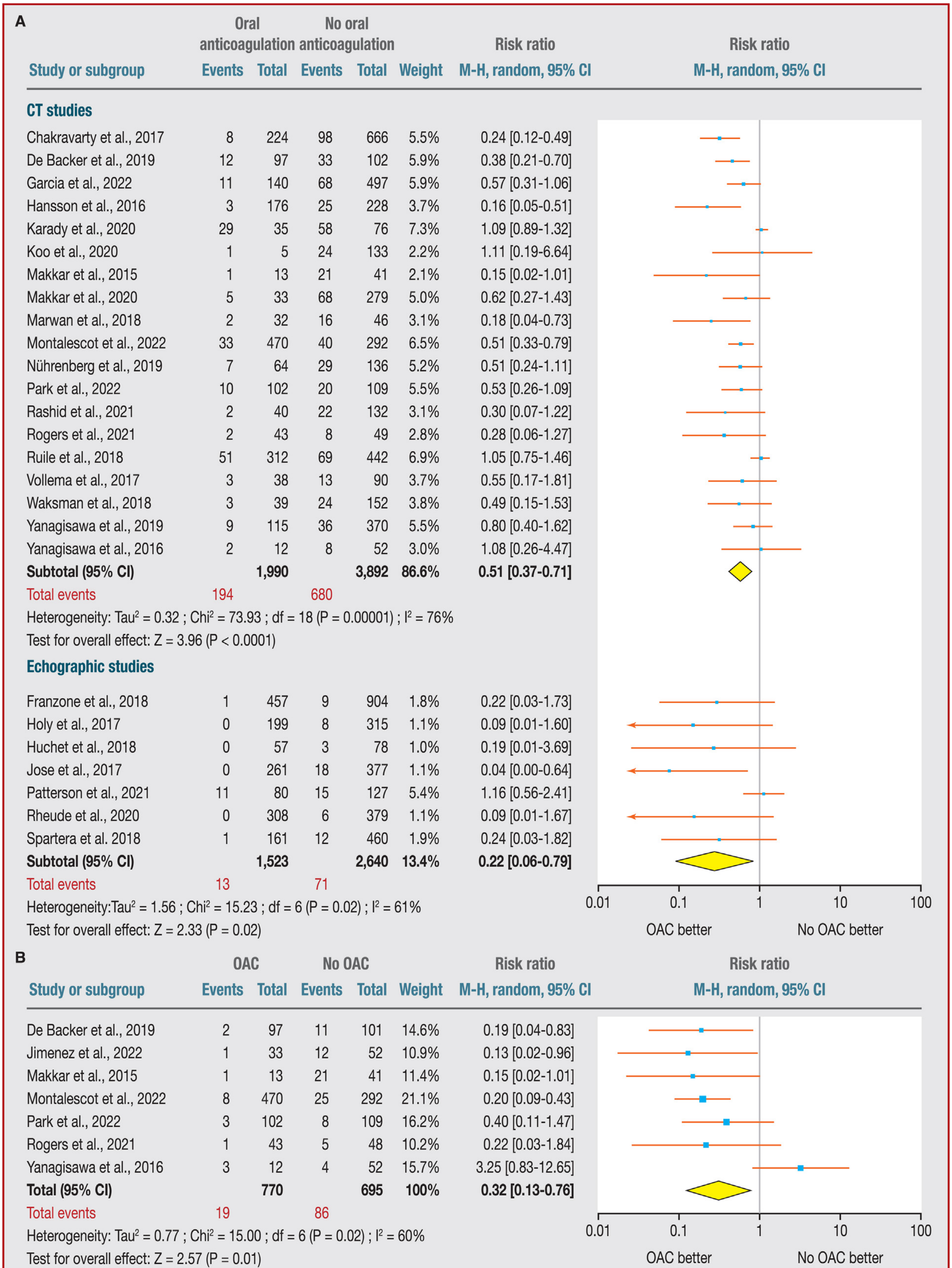


Fig. 4. A–B. Forest plots of selected studies comparing the occurrence of (A) leaflet thrombosis and (B) reduced leaflet motion according to the use or not of oral anticoagulation (OAC). CI: confidence interval; CT: computed tomography; M-H: Mantel–Haenszel.

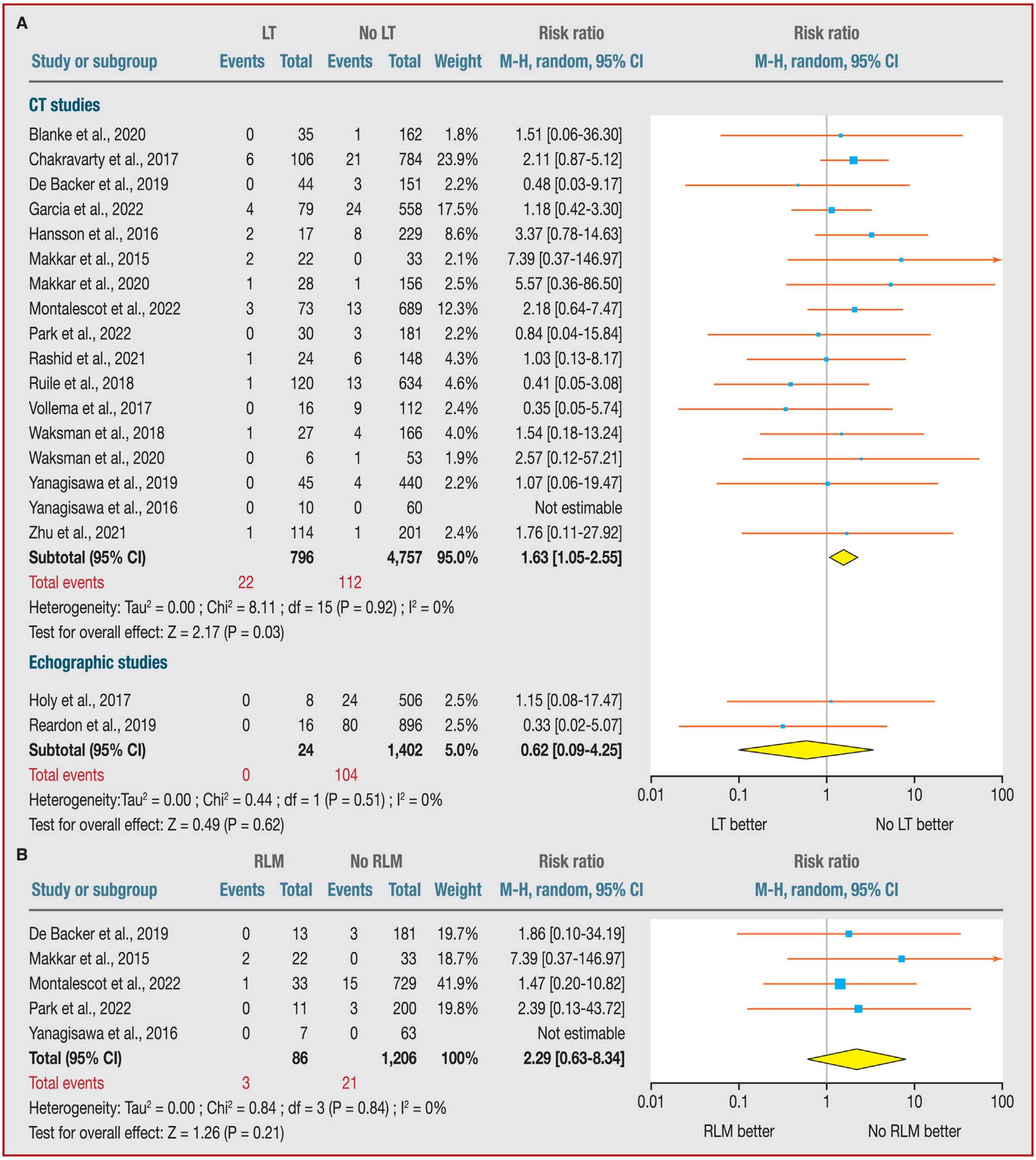


Fig. 5. A–B. Forest plots of selected studies comparing the occurrence of stroke according to the presence or not of (A) leaflet thrombosis (LT) and (B) reduced leaflet motion (RLM). CI: confidence interval; CT: computed tomography; M-H: Mantel–Haenszel.

participants with or without LT in CT studies (7.2% vs. 8.4%; RR: 1.13, 95% CI: 0.88–1.46; 18 studies including 5580 participants; Fig. A.1G). The studies were at intermediate or low risk of bias using the Newcastle-Ottawa Scale (Table A.4). Funnel plots are detailed in Fig. A.2. Egger's and Harbord's tests showed concordant publications bias when comparing intra-annular versus supra-annular valves ($P = 0.003$ and 0.062), self- vs. balloon-expandable valves ($P = 0.002$ and 0.020) and bovine versus porcine valves ($P = 0.005$ and 0.085, respectively).

5. Discussion

The present meta-analysis reports LT and RLM in almost two out of 10 patients after TAVR. Importantly, these cases of LT, which are mostly subclinical, were associated with a 1.63 RR increase in the proportion of stroke, without any increase in mortality. CT was more sensitive than transthoracic echocardiography in detecting subclinical LT. Chronic oral anticoagulation – either vitamin K antagonists or non-vitamin K antagonist oral anticoagulants –

was protective against LT, an effect even more pronounced when considering RLM.

The association between the occurrence of stroke (3.4% overall) and subclinical LT is striking, and is novel [11]. A previous report on this association was obtained from small subgroups with symptomatic valve thrombosis [17]. Stroke alone is obviously a more relevant concern than transient ischaemic attack, the major driver of previous investigations. Of note, the crude proportion of stroke almost doubled when RLM was identified, and additional investigations are needed, given the low event number. The more pronounced effect among participants with RLM than with LT supports a larger thrombus burden that is necessary to alter valve motion [18]. The lack of increase in mortality associated with subclinical LT may suggest that most of the reported strokes were not disabling [12], but raises the question of the optimal imaging follow-up after TAVR. Indeed, the vast majority of LT cases were subclinical, and it is likely that undiagnosed silent brain infarction, known to be associated with an increased risk of dementia and cognitive decline [19], may have occurred more frequently.

The definition of LT was highly variable among the included studies. CT studies used hypo-attenuated leaflet thickening, defined as an increased leaflet thickness with typical meniscal appearance on long-axis views [5,7], and quantified in four grades [16,18]. However, the presence or absence of hyp-oattenuated leaflet thickening was mainly considered, and accounts for the wide ranges in proportion of LT. Echocardiographic studies suspected LT if there was an increase in transprosthetic pressure gradient or a new more than mild regurgitation and/or worsening symptoms, eventually confirmed by CT, TEE [20,21] and/or response to anticoagulation [13]. Consequently, echocardiographic studies may have selected clinical and subclinical LT with haemodynamic compromise. Routine imaging follow-up after TAVR is usually performed using transthoracic echocardiography [22], which is available everywhere, but lacks diagnostic performance as a result of limited spatial resolution and valve stent frame artifacts [9,13]. Most echocardiographic studies [13,15,20,21,23] used increased aortic gradients as a surrogate marker of subclinical LT, although gradients lower than 20 mmHg have been evidenced in the vast majority of cases of subclinical LT or RLM in CT studies [6,7,24,25]. A 4D volume-rendered CT scan for an appropriate grading of both LT and RLM [26] is needed when there are abnormal TEE findings and/or thromboembolic events to guide the oral anticoagulation use [4]. Although CT is more accurate than TEE [27], resulting in a higher proportion of subclinical LT, the need for contrast administration, cost and radiation exposure are obvious limitations. This is why routine CT follow-up after TAVR is currently not recommended, but may be discussed in younger patients with longer life expectancy. Time delay from TAVR to CT ranged from 30 days up to 1 year, but was mainly less than 6 months, to allow the natural healing response after TAVR [27]. However, LT is a dynamic process, which may need serial assessment [6,8], raising the issue of radiation exposure. The timing of transthoracic echocardiography for LT identification appeared less clear, as it was rarely reported and follow-up intervals vary according to centre.

Several technical factors were associated with an increased risk of LT. Balloon-expandable valves interact more importantly with valve leaflets than self-expandable valves, causing traumatic injury [6,13]. Intra-annular design results in a larger neo-sinus with greater flow stasis [28] than supra-annular design. We found that the RR of LT was increased with bovine compared with porcine valves. Both tissues have different biophysical properties with various inflammation triggers [29,30]. These explanations remain interlinked, as most self-expandable valves are made of porcine leaflets and supra-annular design, and are therefore speculative. These results should be interpreted with caution knowing the observed publications bias.

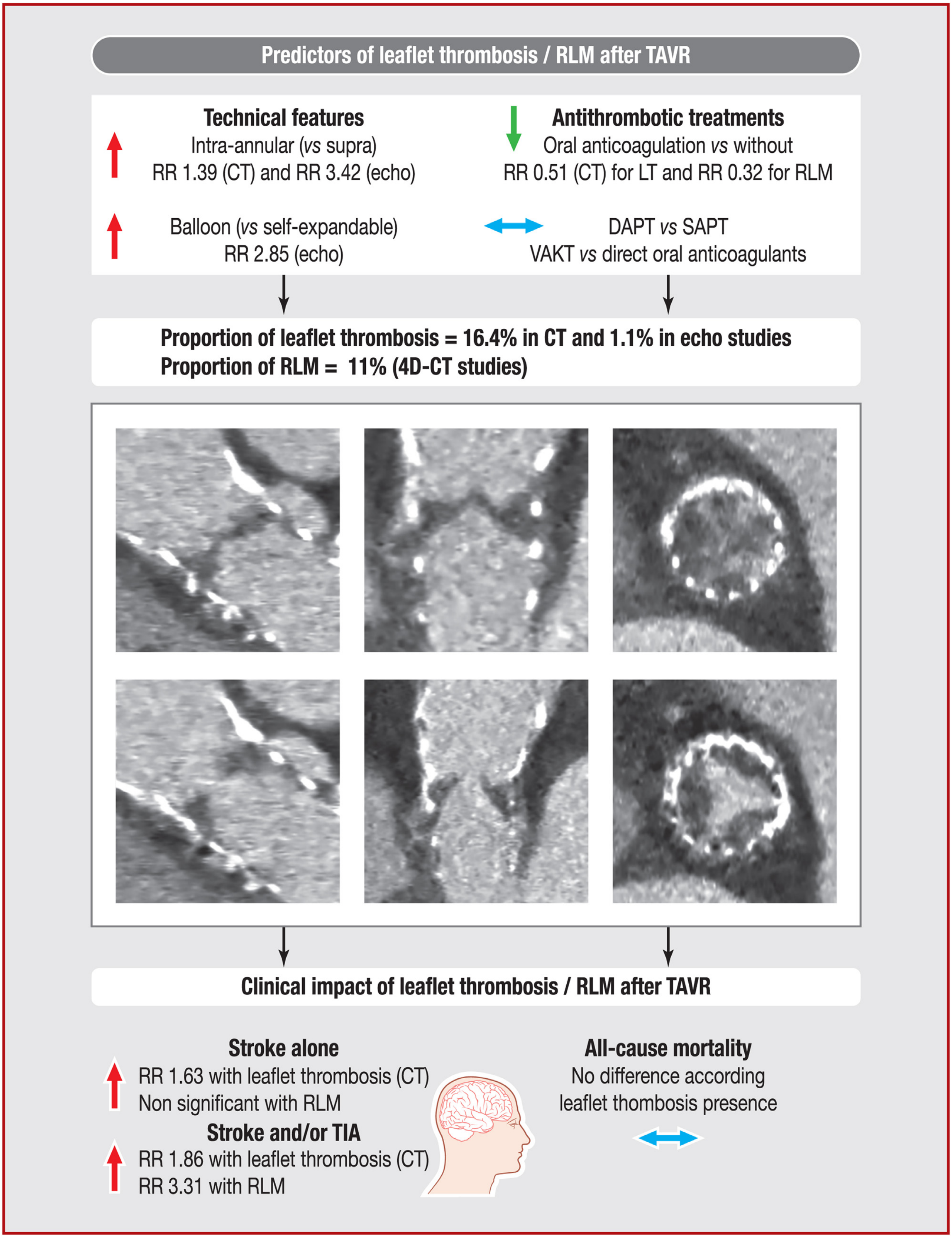
Oral anticoagulation halved the risk of LT and reduced the risk of RLM by nearly 70% according to CT studies. Non-vitamin K antagonist oral anticoagulants were as effective as vitamin K antagonists, and may appear as the preferred strategy to prevent LT when oral anticoagulation is needed for another indication, namely atrial fibrillation. When there is no other indication for long-term oral anticoagulation, the optimal antithrombotic treatment following TAVR remains challenging. In this setting, the 4D-CT substudies of the GALILEO and ATLANTIS trials [16,18] demonstrated that low-dose rivaroxaban plus aspirin and apixaban were associated with reduced rates of RLM and LT compared with antiplatelet therapy. However, these strategies are not recommended, given an excess of unexplained non-cardiovascular mortality and an unfavourable safety profile for rivaroxaban compared with antiplatelet therapy. Further research is needed to assess long-term clinical impact of LT/RLM and to test whether reduced doses of non-vitamin K antagonist oral anticoagulants would be beneficial in a low bleeding risk situation, together with long exposition to device complications.

5.1. Study limitations

We acknowledge several limitations. First, this post hoc analysis of LT subgroups should be considered as exploratory in nature. Second, the lack of individual patient data precludes any individual levels of risk assessment. Third, heterogeneity of LT definitions, time interval from TAVR to CT, follow-up durations and exclusion criteria may affect the interpretation of our results, as outlined by some publications bias. Finally, adverse outcome data were provided in a few studies, especially when considering echocardiographic studies.

6. Conclusions

LT and/or RLM are common after TAVR, with highly variable proportions according to the imaging modality used for screening. Valve characteristics and antithrombotic regimen are key players in the occurrence of LT and RLM, which are associated with an increased risk of stroke, without any impact on survival. Whether systematic identification of subclinical LT/RLM to adjust the antithrombotic regimen is a relevant approach warrants further investigation (Central Illustration).



Central Illustration. Predictors, proportions and clinical impact of leaflet thrombosis (LT) and reduced leaflet motion (RLM) after transcatheter aortic valve replacement (TAVR). Images in diastole (upper panel) and systole (lower panel) showing LT with hypo-attenuated leaflet thickening and reduced motion. 4D: four-dimensional; CT: computed tomography; DAPT: dual antiplatelet therapy; echo: echocardiography; RR: relative risk; SAPT: single antiplatelet therapy; TIA: transient ischaemic attack; VKA: vitamin K antagonist.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2023.10.003.

Disclosure of interest

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The other authors declare that they have no competing interest.

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