# Meta-analysis of Incidence, Predictors and Consequences of Clinical and Subclinical Bioprosthetic Leaflet Thrombosis After Transcatheter Aortic Valve Implantation

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**Leaflet thrombosis (LT) has been claimed as a potential cause of hemodynamic dysfunction or bioprosthetic valve degeneration of transcatheter heart valves. Sparse and contrasting evidence exists, however, regarding LT occurrence, prevention and treatment. MEDLINE, ISI Web of Science and SCOPUS databases were searched for studies published up to January 2020. Only studies reporting data on incidence and outcomes associated to the presence/absence of clinical or subclinical LT, detected or confirmed with a multidetector computed tomography exam were included. The study was designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) requirements. Two reviewers independently screened articles for fulfillment of inclusion criteria. Data were pooled using a random-effect model. The primary end point was the incidence of LT. Secondary outcomes included: stroke and transient ischemic attacks and mean transvalvular gradients at different time-points in patients with and without LT. Of the initial 200 studies, 22 were finally included with a total of 11,567 patients. LT overall incidence was 8% (95% Confidence Interval [CI]: 5% to 13%, $I^2 = 96.4\%$). LT incidence in patients receiving only antiplatelets was 13% (95% CI: 7% to 23%, p <0.0001); patients discharged on oral anticoagulants had a reported incidence of 4% (95% CI: 2% to 8%, p <0.0001). Patients with LT, either clinical or subclinical, were not at increased risk of stroke (OR 1.06, 95% CI: 0.75 to 1.50, p = 0.730, $I^2 = 0.0\%$) or transient ischemic attacks (Odds Ratio 1.01, 95% CI: 0.40 to 2.57, p = 0.989, $I^2 = 0.0\%$). LT was associated with higher mean transvalvular gradients compared with patients without LT at 30 days post-transcatheter implantation, but not at discharge or at 1 year. LT is a relatively common event that, even when clinically manifest, is not associated with an increased risk of cerebrovascular events. Although patients on anticoagulants appear to be at lower risk of LT, the available evidence does not allow formulation of recommendations for prophylactical anticoagulation nor routine computed tomography after transcatheter aortic valve replacement.**  **(Am J Cardiol 2020;132:106−113)**

The development of transcatheter aortic valve implanatation (TAVI) has revolutionized the treatment of severe aortic stenosis (AS). Originally shown to be effective for inoperable patients,[1] TAVI is now standard of care for patients at high or intermediate risk and even low risk for surgical valve replacement.[2] Despite proved safety and efficacy,[3,4] long-term durability of transcatheter heart valves (THVs) remains to be proved. Moreover, reports of early thrombosis of THV leaflets exist with a potential connection to embolic events and late structural valve deterioration (SVD).[5−17] The available literature on this topic is observational and conflicting. Therefore, we performed a systematic meta-analysis with the following aims: (1) to describe the incidence of leaflet thrombosis (LT), either clinical and subclinical; (2) to determine associated clinical sequelae of LT, and (3) to determine predisposing risk factors for THV thrombosis.

## Methods

The study was designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) requirements.[18] MEDLINE, ISI Web of Science and SCOPUS databases were searched for studies published up to January 2020. Studies were identified using the major medical subject heading "TAVI or transcatheter heart valve and LT or clot and stroke or TIA or mortality or outcome". English was set as a language restriction. Two authors (AS and PAG) independently examined the title and abstract of citations. The full texts of potentially eligible trials were obtained, and disagreements were resolved by discussion. To look for additional

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relevant studies, the full texts and bibliography of all potential articles were also retrieved in detail.

Studies were included if they reported data on incidence and outcomes associated with the presence/absence of LT.[19] Studies were excluded if any of the following criteria applied: (1) duplicate publication data; (2) lack of data on LT incidence and/or its correlation with outcomes; and (3) the outcome of interest was not clearly reported or was impossible to extract or calculate from the published results. Number of included patients and follow-up length was not set as a restriction.

Two reviewers independently screened articles for fulfillment of inclusion criteria (AS and PAG). Baseline characteristics, LT incidence and outcomes were abstracted. Reviewers compared selected trials and discrepancies were resolved by consensus.

The primary end point of this study was to evaluate the overall incidence of LT after TAVI . LT was defined as clinical when the typical finding of a mass/thrombous on a THV, visualized with echocardiography or CT, was associated with either new symptoms of heart failure or left-sided thromboembolic events, in the absence of endocarditis. LT was defined as subclinical when the "incidental" finding of THV leaflet thickening at CT was not associated with any clinically significant valve dysfunction or symptoms. As secondary end points, we analyzed: (1) Stroke and transient ischemic attack (TIA) in patients with and without LT; and (2) mean pressure gradients (MPG) difference in patients with and without LT at discharge, 30-day and 1-year post-TAVI.

Risk of bias for each included study was assessed using the Newcastle-Ottawa quality assessment scale, as previously described.[20] This scale allows the assessment of the internal validity of cohort studies included in meta-analysis on the basis of three main items: (1) Selection (adequate selection and definition of groups); (2) Comparability (comparability of two groups for a selected variable and comparability for other variables); and (3) Outcome (modality of assessment, enough length of follow-up and adequacy of follow-up). Based on the above criteria, studies with 4 stars for selection, 2 for comparability, and 3 for outcome were defined at low risk of bias. Studies with 2 or 3 stars for selection, 1 for comparability, and 2 for outcome were defined at medium risk. Any study with a score of 1 for selection or outcome ascertainment, or 0 for any of the three domains, was deemed at high risk of bias.

Two investigators independently extracted for each study the most comprehensively adjusted/unadjusted odds ratio (OR) and their 95% confidence intervals (CI) as well as means ± standard deviations. Estimates of effect were calculated with a random-effects model and expressed as OR or event rates. Statistical significance was set at $p \leq 0.05$ (2-tailed). Heterogeneity was assessed by a Q-statistic and $I^2$ test. Significant heterogeneity was considered present for p values <0.10 or an $I^2 > 50\%$. Meta-regression analysis was performed to assess the potentially important covariates (included in Supplementary Table 1) that might exert substantial impact on between-study heterogeneity (significance at $p \leq 0.05$).[21] A sensitivity analysis, that was conducted by removing one study at a time, was used to confirm the results in case of significant heterogeneity.[20]

Publication bias was assessed using funnel plots and when a significant publication bias was found, it was further explored by Egger's test, consisting in a linear regression of the intervention effect estimates on their standard errors, weighting by 1/(variance of the intervention effect estimate). All data analyses were performed using Prometa Software Version 2.[22,23]

## Results

The initial search of published articles identified 200 articles, of which 27 were retrieved for more detailed evaluation, and 22 were finally included in the meta-analysis, enrolling 11,567 subjects (Supplementary Table 1, Supplementary Figure 1).[5-12,14,16,17,24–34]

The overall incidence of LT was 8% (95% CI: 5% to 13%, $I^2 = 96.45\%$) (Figure 1). In the subgroup of studies assessing clinical LT. the incidence was estimated at 3% (9 studies, 95% CI: 1% to 8%, p <0.0001, $I^2 = 96.4\%$) . In the other studies (n = 13), where the CT scan was performed as part of the routine post-TAVI protocol, the incidence of subclinical LT was significantly higher (15%, 95% CI: 12% to 20%, p <0.0001, $I^2 = 88.53\%$; test for subgroup differences p = 0.001). Results were confirmed using a sensitivity analysis (Supplementary Figure 2A). In the subgroup of patients receiving only antiplatelet therapy without an oral anticoagulant at discharge, the overall incidence of LT was 14% (95% CI: 8% to 24%, $I^2 = 95.72\%$) (Figure 2). Conversely, in the subgroup of patients receiving an oral anticoagulant at discharge (with or without an antiplatelet agent), the overall LT incidence was 5% (95% CI: 3% to 8%, $I^2 = 80.59\%$) (Figure 2). Results were confirmed using a sensitivity analysis (Supplementary Figure 2B).

The incidence of stroke and TIA in patients with evidence of LT, either clinical or subclinical, was not significantly higher compared with patients without LT (OR 1.06, 95% CI: 0.75 to 1.5, p = 0.494, $I^2 = 0.0\%$; OR 1.01, 95% CI: 0.40 to 2.57, p = 0.989, $I^2 = 0\%$, respectively, Figure 3). The presence of LT was associated with higher MPG at 30 days post-TAVI, but not at discharge or at 1 year of follow-up (discharge, OR 0.97, 95% CI: 0.63 to 1.49, p = 0.887, $I^2 = 69.4\%$; 30 days, OR 1.91, 95% CI: 1.32 to 2.76, p = 0.001, $I^2 = 0.0\%$; 1 year, OR 1.26, 95% CI: 0.75 to 2.10, p = 0.385, $I^2 = 29.8\%$; Figure 4).

Heterogeneity assesses whether observed differences in results arise by chance alone. To assess the impact of study quality (bias) on heterogeneity, we applied the Newcastle-Ottawa quality assessment scale to the primary studies included in the meta-analysis. All included studies fell into the categories "low" or "medium" risk of bias (Supplementary Table 2).

To explore the potential impact of modifiers on the incidence of LT, we performed a meta-regression analysis of the baseline characteristics of the included studies. Meta-regression analysis showed no relationship between all the analyzed effect modifiers and the primary outcome of interest (all p values >0.05) (Supplementary Table 3). Supplementary Figure 3 reports results of meta-regression analysis for specific THV types. In particular, an inverse relation was found between the use of self-expandable valves and the incidence of LT, but it did not reach

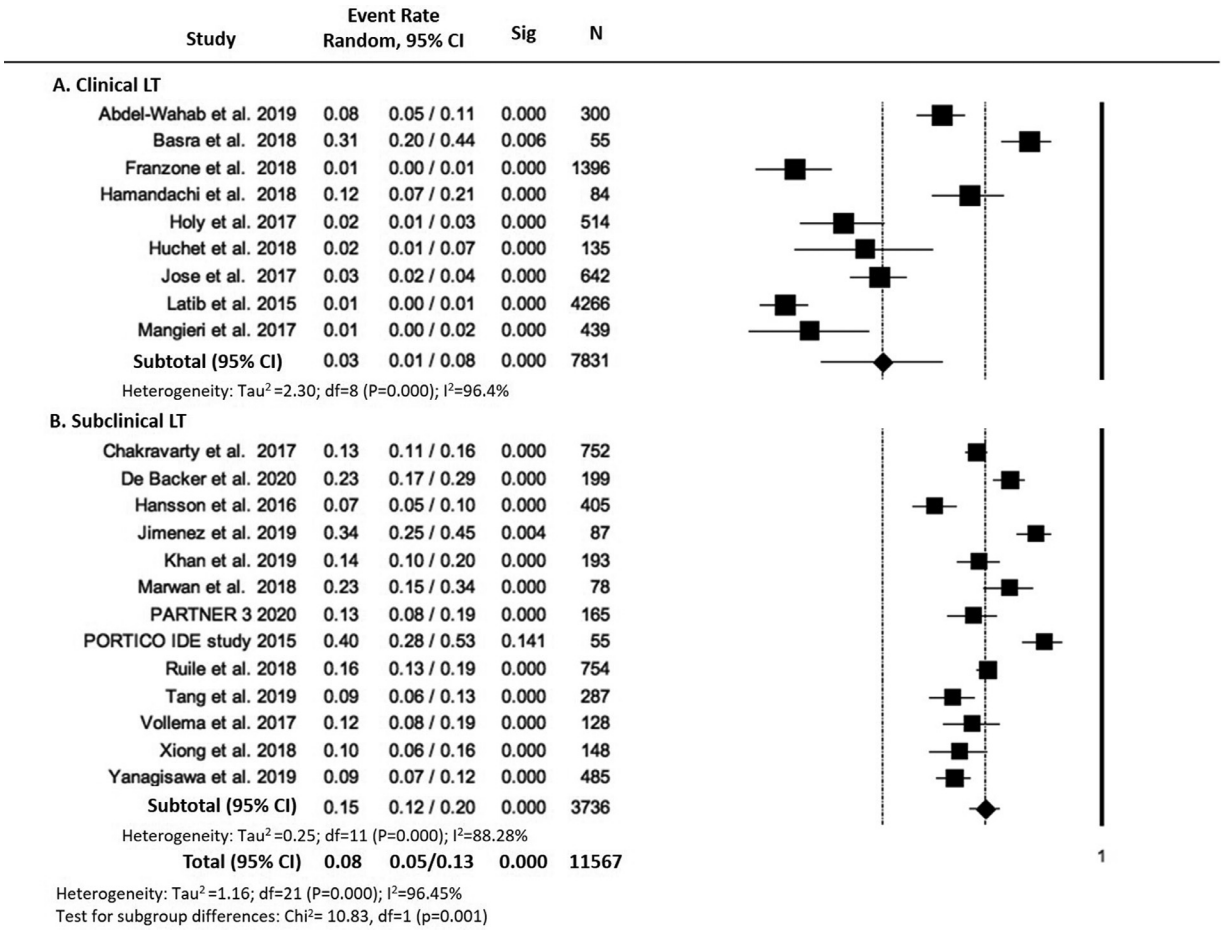


Figure 1. Forest plots for the incidence of THV thrombosis. (*A*) Incidence of Clinical LT. (*B*) Incidence of subclinical LT.

statistical significance. The funnel plots did not show any publication bias for all the analyses performed.

## Discussion

To the best of our knowledge, this is the first comprehensive meta-analysis including low-risk populations and assessing the incidence of LT after TAVI. The main results of this study are: (1) The overall incidence of THV thrombosis is 8% with a significant difference between clinical and subclinical LT. (2) The presence of LT, either clinical or subclinical, is not linked to the occurrence of cerebrovascular events. (3) The prevalence of LT post-TAVI is lower in patients on anticoagulant therapy compared with antiplatelet therapy. (4) There was no statistically significant difference in LT between different valves.

In the last decade, TAVI has been performed in over 400,000 patients worldwide and implantation rate continues to grow at 40% annually.[35] Compared with surgery, TAVI has demonstrated non-inferiority if not superiority across all risk categories.[3,4,36–39] As TAVI continues to expand to younger and healthier patients, the question of THV durability becomes more important. After TAVI, reports of early leaflet thickening and possible LT exist, with a concern that this may predispose toward SVD, although long-term follow-up of patients with LT is still lacking.[5–17]

The clinical diagnosis of LT can be challenging. Although transthoracic or transesophageal echocardiography may be able to identify other reasons for an increased THV gradient, such as a high flow state or prosthesis-patient mismatch, it lacks the resolution to identify small increases in valve thickening or motion, and cannot easily distinguish LT from pannus ingrowth.[24,19,40] Multidetector cardiac CT has, thus, become accepted as the gold-standard for identifying LT. Indeed, an actual correlation between hypo-attenuated leaflet thickening (HALT) seen at CT and thrombus at histopathology has been reported.[5,41] On CT, HALT appears meniscal-shaped on long axis reformats, following the curvi-linear shape of the neo-sinus, with greater thickness at the base than toward the center of the leaflet.[42,43] When HALT is associated with a significant reduction in leaflet motion on 4D assessment, it is defined as hypo-attenuation affecting motion which is considered highly specific for the presence of subclinical LT.[42]

The results of this meta-analysis of studies using CT for both surveillance and diagnosis, shows the prevalence of subclinical LT was significantly higher than clinical LT suggesting that perfoming a surveillance CT will significantly increase the detection of HALT. This may play a role in management decisions since a progression to SVD may begin with LT.[41] Observational data have consistently shown that anticoagulation is able to resolve HALT and restore proper leaflet motion, when

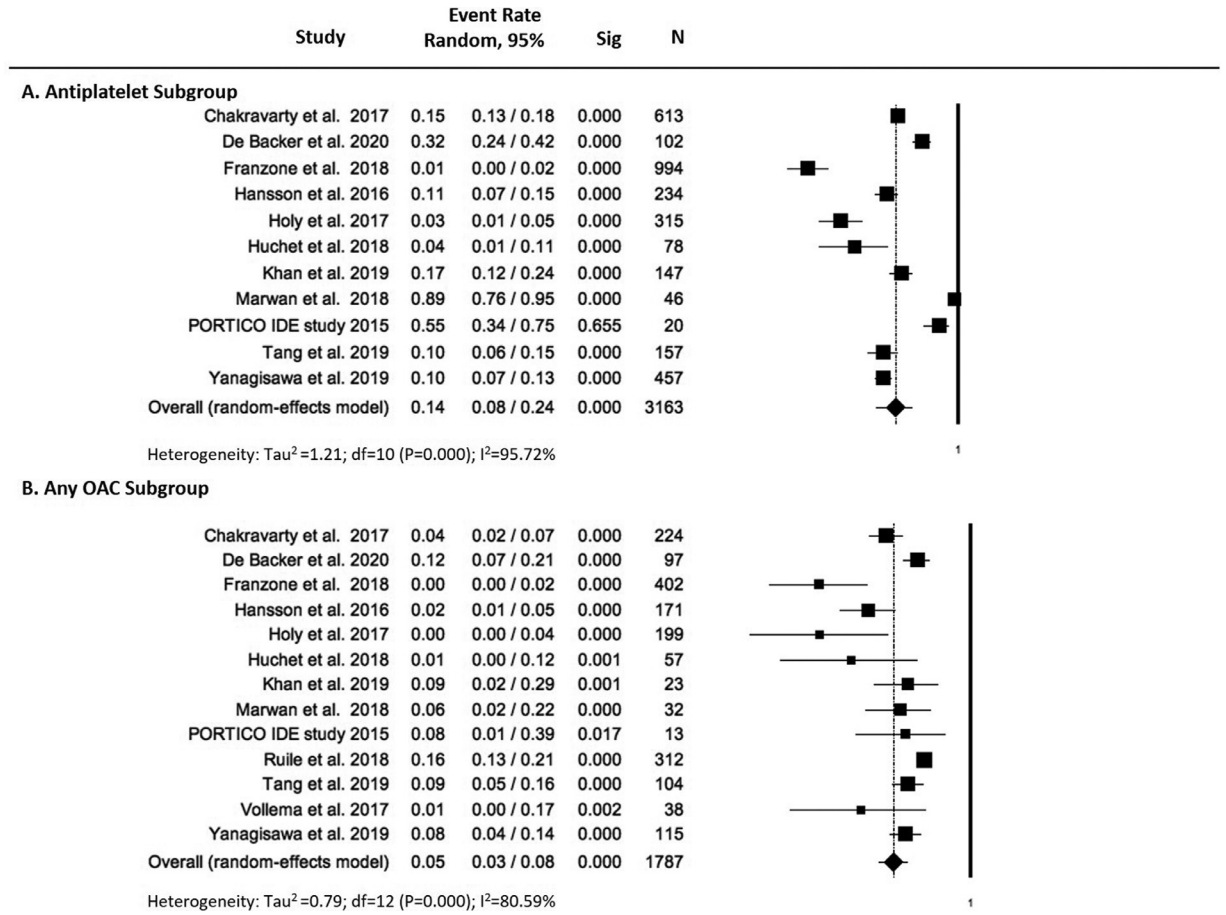


Figure 2. Forest plots for the incidence of LT according to antithrombotic therapy. (*A*) Subgroup analysis in patients discharge on antiplatelet therapy alone. (*B*) Subgroup analysis in patients discharge on oral anticoagulants (OAC).

reduction in leaflet motion is present.[6,9,10,12] However, minor degrees of HALT at the leaflet bases with normal leaflet mobility and no increase in gradient remains an area of uncertainty. Using a semi-quantitative HALT grading scheme proposed by the Society of Cardiovascular Computed Tomography,[43] data from the PARTNER 3 CT substudy was recently presented (Transcatheter Cardiovascular Therapeutics 2019, September 25) showing the 30 day incidence of HALT was 13.3% in TAVI, however 50% of these patients had resolution of the findings by 1 year in the absence of oral anticoagulation. In the current analysis, patients receiving only antiplatelet therapy without an oral anticoagulant at discharge had a higher overall incidence of LT (13% vs 8% for the overall cohort), suggesting a role for oral anticoagulation.

Although in this meta-analysis we observed that subclinical LT was detected at a median of 139.5 days after TAVI, it is not clear exactly when LT occurs. There is no definitive answer to how long anticoagulation therapy should be maintained after discovery of LT. Clinically, it is important to tailor the therapy to the patients' bleeding and thrombotic risk, but prospective clinical trials are needed. Unfortunately, whether LT is a predisposing factor to SVD in the long run is still uncertain. Thus, additional long-term studies are needed to shed further light on the prevalence of the disease and its relationship to procedural and pharmacology risks as well as SVD and clinical events. If future studies were to confirm a connection between LT and SVD, then how to treat LT before SVD happens will need to be investigated.

For the time being, anticoagulation with warfarin or unfractioned heparin is the treatment of choice in case of confirmed LT, as observational evidence has shown consistent resolution of HALT with restoration of leaflet mobility at follow-up CT after treatment. Indeed, both American College of Cardiology/American Heart Association and European Society of Cardiology and guidelines acknowledge the role of anticoagulation in this setting.[2,44] Some of the studies included in this meta-analysis reported data about the treatment of confirmed cases of LT; all used warfarin. Whether novel anticoagulants are as effective as warfarin in treatment of confirmed LT may never be tested given the results of the GALILEO trial.

The current analysis also shows no correlation between LT and cerebrovascular events (Figure 3). Thus, these results are in contrast with previous reports that suggested an association between LT and cerebrovascular events. The inclusion in our study of recent data coming from low-risk populations and the historically low incidence of stroke in this population, may explain this disparity. The lack of association with adverse outcomes raises further questions about the need for anticoagulation. There were no clinical predictors of LT in the current meta-analysis; importantly, there were no significant differences in LT associated with valve type.

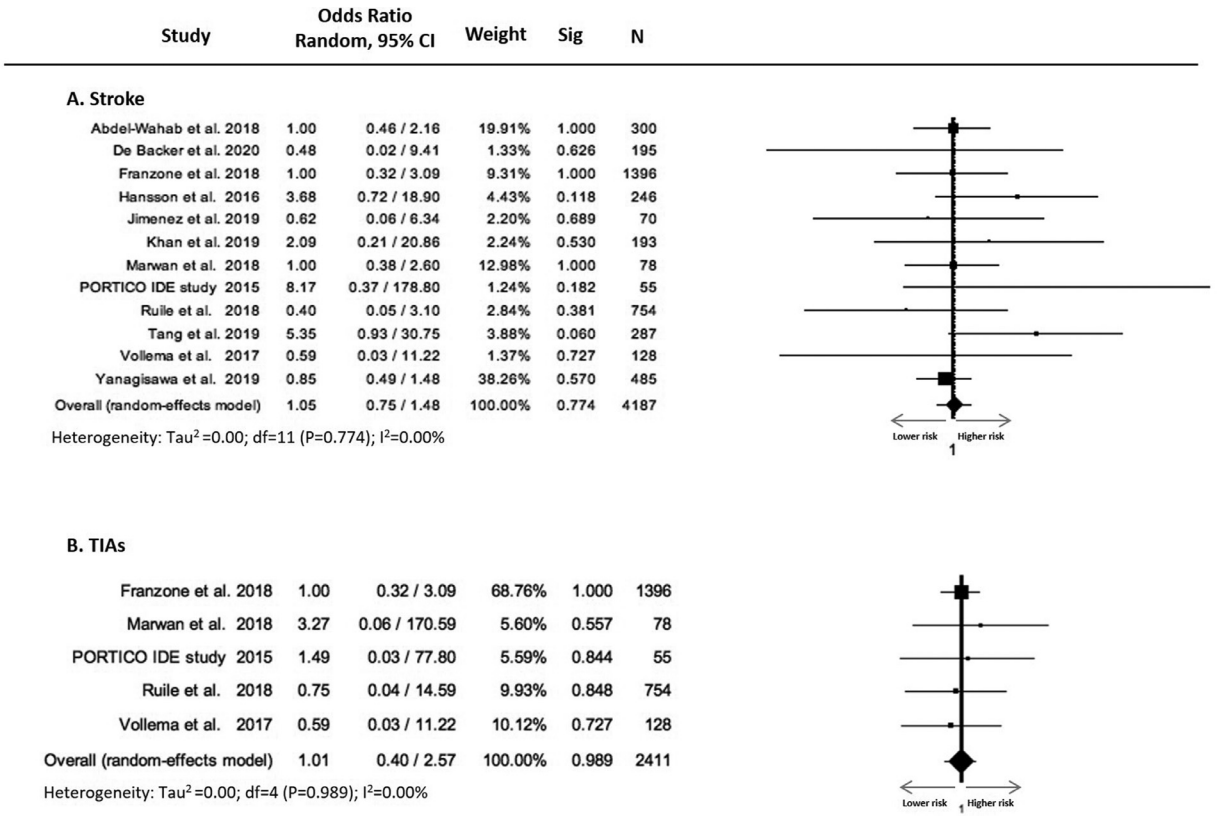


Figure 3. Forest plots for the clinical outcomes in patients with and without LT. (*A*) Stroke. (*B*) TIA.

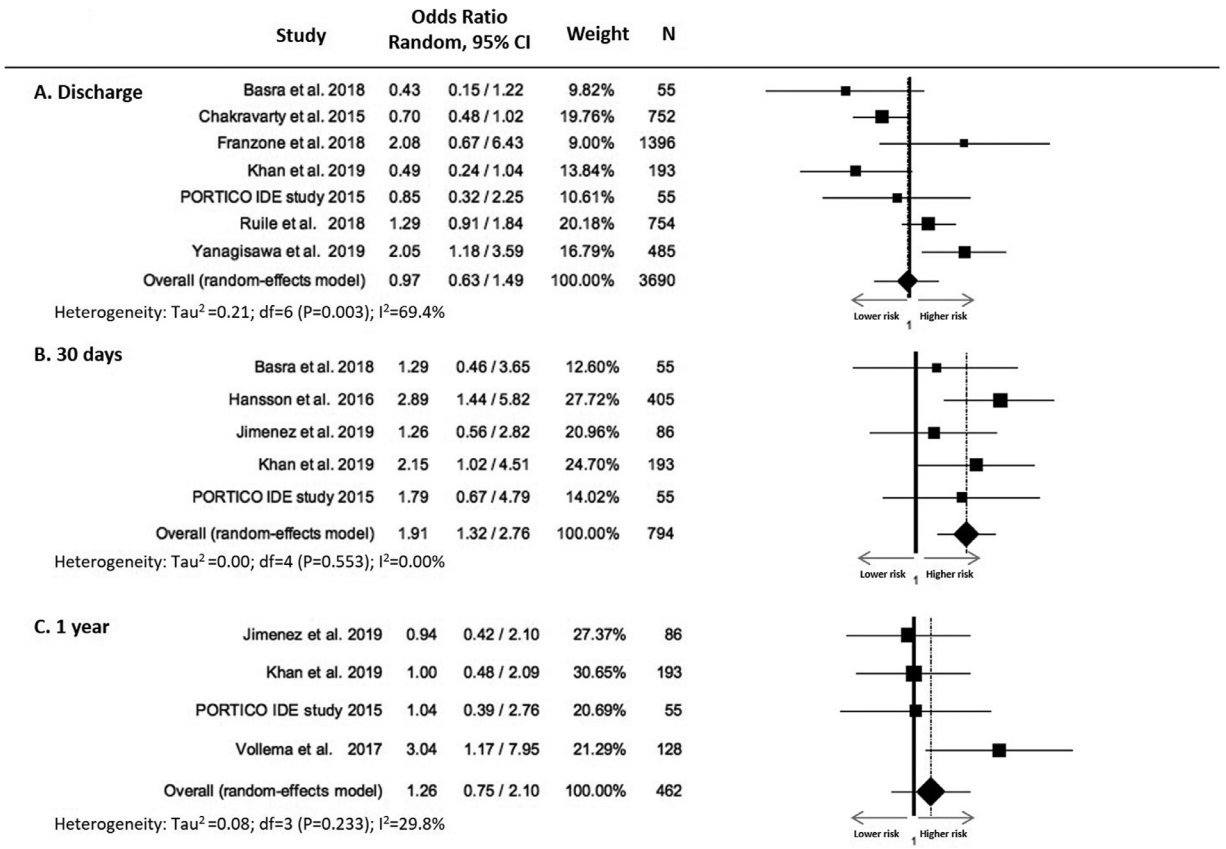


Figure 4. Forest plots for mean difference in mean pressure gradients (MPG) in patients with and without LT. (*A*) MPG at discharge. (*B*) MPG at 30 days. (*C*) MPG at 1 year.

This meta-analysis has several limitations. This study includes both randomized and observational studies, and this might have an impact on our results. However, even for randomized trials, only results from specific sub-studies were considered, therefore a sensitivity analysis for randomized and observational studies was not performed. Different populations with a wide range of surgical risk scores are involved in this meta-analysis, and this factor might account for the differences in outcomes as well as for a fairly high degree of heterogeneity in the performed analyses. However, the consistency of our results was confirmed using a sensitivity analysis for the primary outcome of interest.

In conclusion, THV thrombosis is common and probably the result of multiple factors. Although surveillance CT can detect subclinical LT, our meta-analysis suggests that there appears to be no increased risk for cerebrovascular events in patients with LT. In the absence of further evidence that specific medical treatment reduces the incidence of LT or LT-related adverse outcomes, CT evaluation at this time should be limited to those patients with an increase in peak velocity or mean gradient on follow-up echocardiography.

## Author contributions

Anna Sannino: Conceptualization; Methodology; Formal analysis; Investigation; Writing - Original Draft. Rebecca T. Hahn: Supervision; Writing - Review & Editing. Jonathon Leipsic: Supervision; Writing - Review & Editing. Michael J. Mack: Supervision; Writing - Review & Editing. Paul A. Grayburn: Conceptualization; Writing - Review & Editing; Supervision.

## Disclosure

Declaration of interests: The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this paper.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.07.018.


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