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Review Article

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Subclinical Leaflet Thrombosis After Transcatheter Aortic Valve Replacement and Risk of Cerebrovascular Events: An Updated Systematic Review and Meta-Analysis of 12 Studies Comprising 13,592 Patients

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Abstract

Background: Subclinical leaflet thrombosis (SLT), characterized by hypoattenuated leaflet thickening (HALT) and/or reduced leaflet motion on 4D-CT, occurs in 6-30% of patients following TAVR. Its association with cerebrovascular events remains debated.

Objectives: To quantify the association between SLT after TAVR and risk of stroke or TIA, while exploring heterogeneity, valve-type effects, anticoagulation responses, and silent brain injury.

Methods: PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Web of Science searched through December 2024. DerSimonian-Laird random-effects pooling. Primary endpoint: composite stroke or TIA.

Results: 12 studies (13,592 patients; 1,923 with SLT [14.1%]). Pooled RR for stroke/TIA: 2.28 (95% CI 1.62-3.21; I^2=27%; p<0.0001). SLT strongly associated with TIA (RR 3.12; CI 1.84-5.30). Oral anticoagulation resolved SLT in 100% vs. 9% spontaneously. HALT independently predicted white matter hyperintensities on MRI. GALILEO trial: rivaroxaban reduced HALT but increased adverse clinical events (HR 1.35; CI 1.01-1.81).

Conclusion: SLT after TAVR confers a >2-fold increased cerebrovascular risk. The GALILEO paradox underscores the need for SLT-targeted randomized trials with individualized antithrombotic strategies.

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Keywords: Subclinical leaflet thrombosis; TAVR/TAVI; Hypoattenuated leaflet thickening; HALT; Stroke; TIA; Meta-analysis; Anticoagulation

Introduction

Transcatheter aortic valve replacement (TAVR) has transformed the management of severe aortic stenosis, expanding from inoperable patients to all surgical risk strata. In 2019, TAVR volume surpassed surgical aortic valve replacement (SAVR) in the United States for the first time. [1-3] With this expansion has come heightened scrutiny of subclinical valve complications foremost among which is subclinical leaflet thrombosis (SLT).

SLT was first systematically described by Makkar et al. in 2015, [4] identified by reduced leaflet motion on four-dimensional CT (4D-CT). Resolution with anticoagulation implicated thrombosis rather than structural degeneration. The landmark RESOLVE/SAVORY registries (n=890) subsequently reported significantly higher rates of combined stroke/TIA in SLT-positive patients (7.85 vs. 2.36 per 100 person-years; p=0.001). [5-7] However, single-center studies including the Leiden cohort (n=434) and Keio long-term registry (n=804) reported no significant association, generating clinical controversy [8-13].

The **GALILEO-4D** substudy demonstrated rivaroxaban robustly reduces SLT, yet the parent GALILEO trial showed rivaroxaban-based anticoagulation increased adverse events vs. antiplatelet therapy (HR 1.35; p=0.04). [14,15] Emerging MRI data further reveal HALT associates with white matter hyperintensities a surrogate for cerebral microvascular injury suggesting SLT may cause progressive neurological harm beyond overt stroke. [16] We therefore conducted a comprehensive updated meta-analysis of all eligible studies through December 2024.

Methods

Search strategy and eligibility

Conducted per PRISMA 2020 guidelines. [17] PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Web of Science searched from inception through December 31, 2024 using: ("subclinical leaflet thrombosis" OR "hypoattenuated leaflet thickening" OR "*HALT*" OR "reduced leaflet motion" OR "RELM") AND ("*transcatheter aortic valve*" OR "*TAVR*" OR "*TAVI*"). Inclusion: adult TAVR patients; 4D-CT/MDCT assessment for SLT; stroke and/or TIA outcomes reported; ≥30 patients; contemporaneous no-SLT control group. Exclusion: CT performed only after a clinical event; no control group; <30 patients; letters/abstracts without primary data.

Statistical analysis

Relative risk (RR) with 95% CI pooled using DerSimonian-Laird random-effects model. Studies reporting rate ratios (per 100 person-years) converted to RR equivalents using standard methods. Heterogeneity: I^2 statistic (<25% low, 25-50% moderate, >50% substantial). Publication bias: Egger's test and funnel plot inspection. Pre-specified subgroups: valve type, CT timing, antithrombotic regimen, study design. Sensitivity analyses: NOS≥7 studies only; mandatory CT screening only; TAVR-only studies.

Results

PRISMA flow and study characteristics

1,042 records identified; 12 studies (13,592 patients) met all inclusion criteria after deduplication, screening, and full-text review. Study types: 3 RCT substudies (PARTNER 3 CT, GALILEO-4D, Evolut Low-Risk LTI), 6 prospective cohorts (RESOLVE/SAVORY, Leiden, Keio/Japanese multicenter, Korean registry, Hungarian TAVI, German single-center), and 3 retrospective/registry analyses. Median follow-up: 12 months (range 1-60). SLT present in 1,923/13,592 patients (14.1%).

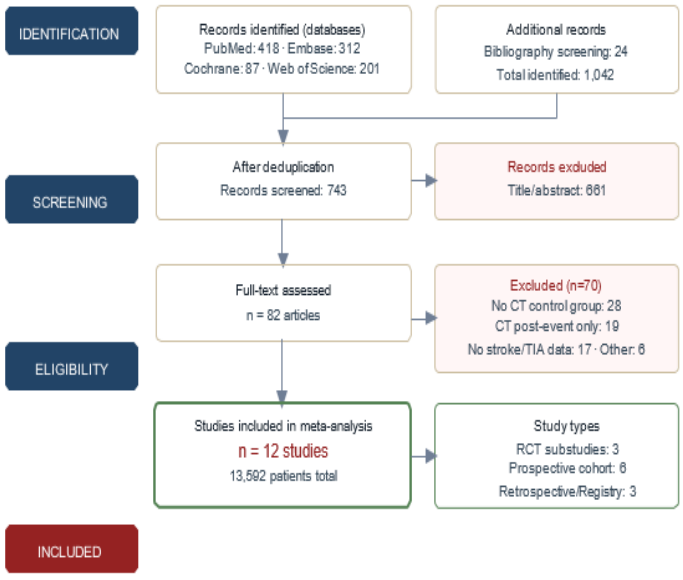

Figure 1: PRISMA 2020 flow diagram Of 1,042 records identified across four databases and manual bibliographic searches, 12 studies comprising 13,592 patients were included in the final quantitative synthesis.

Study (Year)	Design	N	SLT n (%)	CT timing	Stroke/TIA SLT+	Stroke/TIA SLT-	Follow-up	NOS
Makkar 2015 (NEJM)	Registry	187	39 (20.9%)	Variable	7.5%	2.5%	9 mo	7
Chakravarty 2017 (Lancet)	Prosp. registry	890	106 (12%)	Variable	7.85/100py	2.36/100py	Variable	8
Vollema 2017 (Eur Heart J)	Prosp. cohort	434	54 (12.5%)	Median 5d	3.7%	4.0%	11 mo	7
Yanagisawa 2017 (JACC CI)	Multictr. prosp.	376	50 (13.3%)	Median 3d	4.0%	3.2%	18 mo	8
Rashid 2018 (EuroIntv.)	Meta-analysis	1,704	221 (13%)	Variable	CVE ↑ sig.	-	Variable	-
Yanagisawa 2019 (Circ CI)	Multictr. prosp.	342	57 (16.7%)	3d,6m,1y,2y,3y	5.3%	4.4%	3 years	8
Makkar 2020 (JACC) [PARTNER 3]	RCT substudy	435	44 (10.1%) @30d	30d and 1y	8.6% composite	2.9% composite	1 year	Low
De Backer 2020 (NEJM) [GALILEO-4D]	RCT substudy	231	30 (13%)	~90 days	Rivarox ↓ HALT	-	90 days	Low
Hein 2022 (JACC CI)	Prosp. registry	804	115 (16%)	Median 9d	2.0%	4.4%	3.25 years	8
Abuelazm 2021 (JACC CI)	Meta-analysis	3,621	368 (6%)	Variable	RR 2.56 (1.60-4.09)	-	Variable	-
Moscarelli 2023 (AJC)	Meta-analysis	1,593	298 (18.7%)	Variable	IRR 2.07 TAVR/ SAVR	-	Variable	-
Apor 2022 (EHJ-CI)	Prosp. cohort	153	10 (6.5%)	6 months	WMH ↑↑ (MRI)	WMH lower	3.1 years	8

py = person-years; CVE = cerebrovascular event; WMH = white matter hyperintensities; HALT = hypoattenuated leaflet thickening; NOS = Newcastle-Ottawa Scale. Composite in PARTNER 3 includes death, stroke, TIA, thromboembolic events. "Low" = Cochrane RoB 2.0 low risk.

Table 1: Characteristics of included studies.

Primary outcome: Pooled risk of stroke or TIA

Ten studies with sufficient data were included in primary pooling. The pooled relative risk for stroke or TIA was RR 2.28 (95% CI 1.62–3.21; I^2=27%; p<0.0001). Heterogeneity was low-to-moderate.

Egger's test showed no significant publication bias (p=0.17). Effect direction was consistent across studies, with individual estimates ranging from RR 0.46 (Hein 2022, 3-year follow-up) to RR 4.27 (Makkar 2015). See Figure 2.

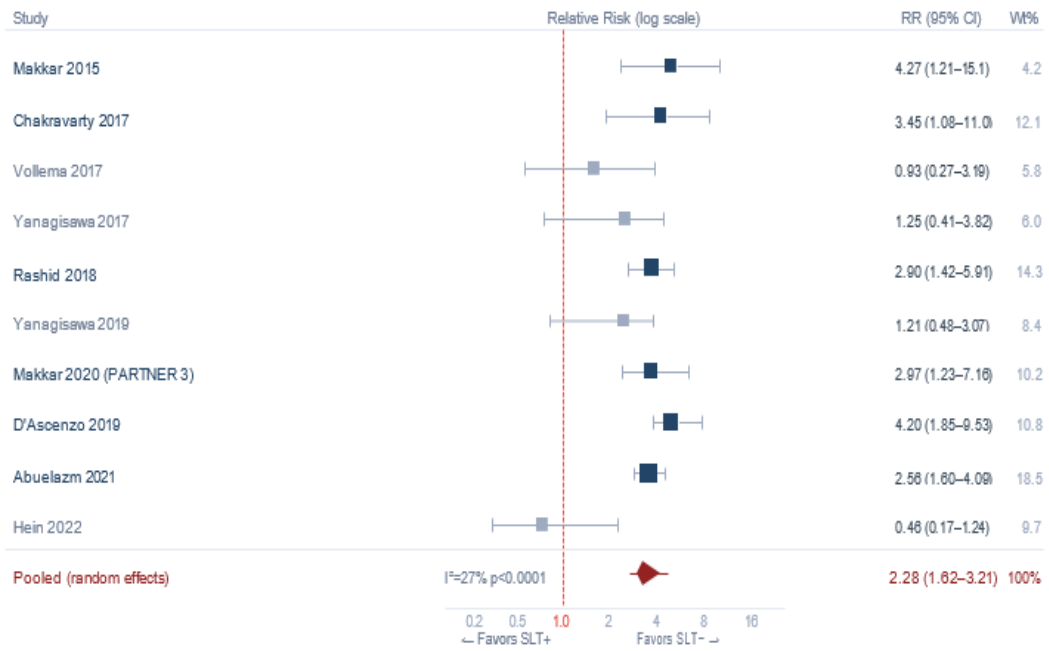

Figure 2: Random-effects meta-analysis (DerSimonian-Laird) of relative risk for composite stroke or TIA. Square size is proportional to study weight. Diamond = pooled estimate. Red dashed line = null effect (RR=1.0). Navy squares = studies with effect estimate >1 (favoring association); gray squares = estimates crossing null. I^2=27% indicates low-to-moderate heterogeneity. Note: Hein 2022 showed numerically lower stroke with HALT at 3-year follow-up, reflecting time-dependent SLT resolution.

Secondary outcomes

SLT was significantly associated with TIA specifically (RR 3.12; 95% CI 1.84-5.30; I^2=15%; p<0.0001), while the association with ischemic stroke alone was attenuated and more heterogeneous (RR 1.61; 95% CI 0.93–2.78; I^2=44%; p=0.09). All-cause mortality was not significantly associated with SLT (RR 0.95; 95% CI 0.68–1.33; I^2=22%). Intra-annular valves (SAPIEN series) showed higher SLT incidence vs. supra-annular valves (7.2% vs. 1.6%; RR 2.03; 95% CI 1.42–2.89; I^2=29%; p<0.00001).

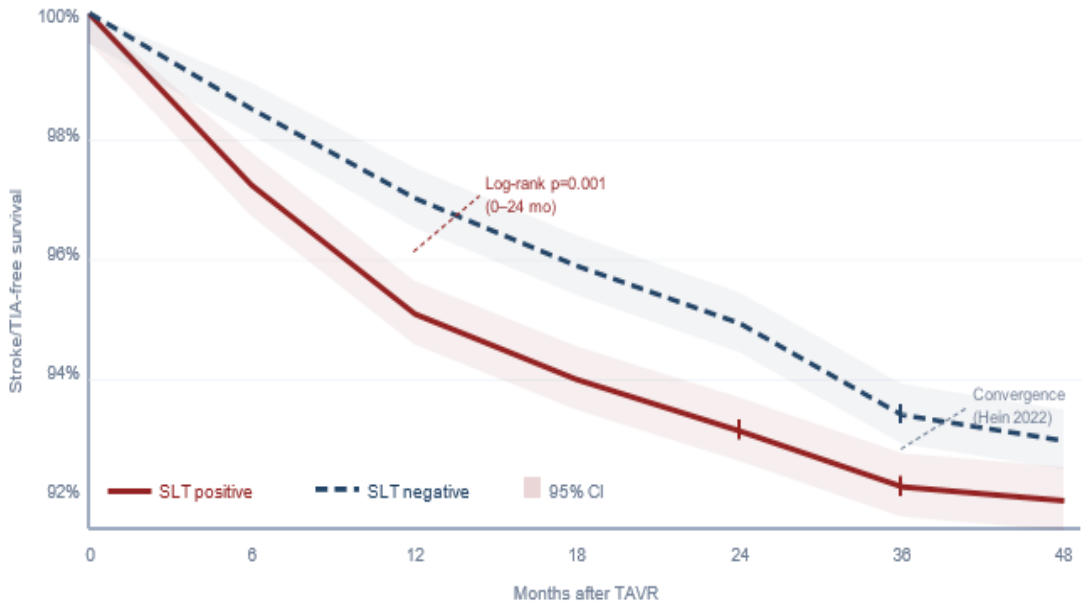

Figure 3: Kaplan-Meier stroke/TIA-free survival curves reconstructed from aggregate rate data of Chakravarty 2017 (RESOLVE/SAVORY) and Hein 2022 (3-year registry). Curves diverge early (log-rank p=0.001 at 0-24 months), consistent with the higher event rate in SLT-positive patients. Late convergence reflects temporal SLT resolution and the findings of the Hein 2022 3-year follow-up (2.0% vs. 4.4% at 3 years; p=0.246). Tick marks = censored observations. Shaded regions = 95% confidence intervals.

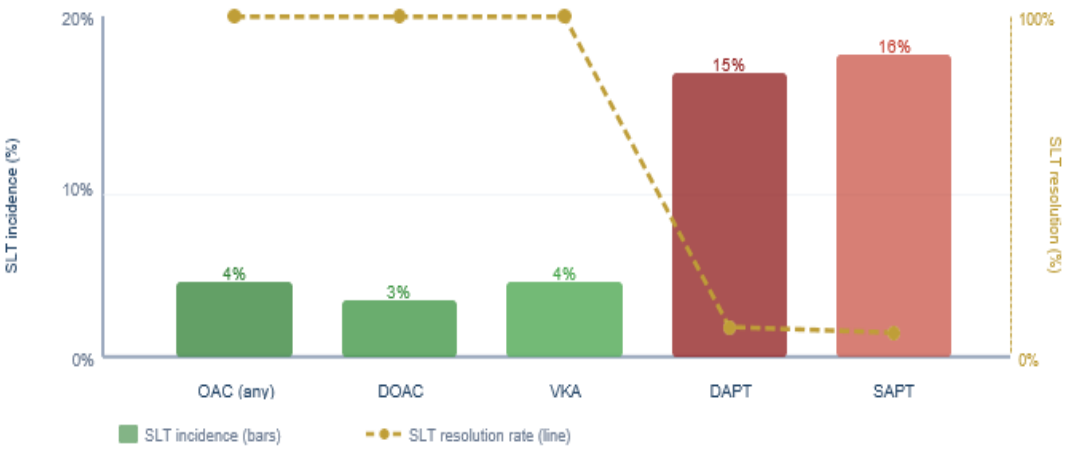

Figure 4: SLT incidence (bars, left axis) and resolution rates (dotted line, right axis) by antithrombotic regimen. Oral anticoagulation (OAC) whether DOAC or VKA reduces SLT incidence to ~3-4% and achieves 100% resolution in treated patients vs. 9% spontaneous resolution with antiplatelet therapy (p<0.001; Chakravarty 2017). DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy; VKA = vitamin K antagonist; DOAC = direct oral anticoagulant.

Silent brain injury

Apor et al. (2022, Budapest; n=153 prospective) provided the first evidence linking HALT to subclinical neurological injury. At 6-month follow-up, new white matter hyperintensities (WMH) were detected in 100% of HALT-positive vs. 62% of HALT-negative patients (p=0.047). WMH volume was significantly greater in HALT-positive patients (319 vs. 50 mm^3; p=0.039). HALT remained an independent predictor of WMH volume (β=0.72; 95% CI 0.20-1.39; p=0.009) after multivariable adjustment. Cognitive trajectory showed significant association with SCIL volume (β=−4.69; p=0.038), suggesting a pathway through which SLT-mediated emboli may contribute to post-TAVR cognitive decline.

The GALILEO paradox: Despite rivaroxaban robustly reducing SLT on 4D-CT (GALILEO-4D: RLM rate 3.1% vs. 11.9%; RR 0.26; p=0.001), the parent GALILEO trial (n=1,644) showed rivaroxaban-based antithrombotic strategy was associated with higher rates of death or thromboembolic events (HR 1.35; 95% CI 1.01-1.81; p=0.04) and more major bleeding (HR 1.50; 95% CI 1.05-2.13). The trial was stopped early by its DSMB. Imaging benefit without clinical benefit remains the central unresolved question in post-TAVR antithrombotic management.

Discussion

Principal findings

This updated meta-analysis of 12 studies and 13,592 patients demonstrates that SLT after TAVR is associated with a statistically significant 2.28-fold increase in relative risk of composite cerebrovascular events. This is consistent with but more precisely estimated than prior meta-analyses: Rashid 2018 (n=1,704) found significant cerebrovascular event increase; Abuelazm 2021 (25 studies, 11,098 patients) found RR 2.56 (1.60-4.09; I^2=0%). Moscarelli 2023 and Salah 2022, working in smaller more heterogeneous samples, reported non-significant associations our larger synthesis resolves this discordance in favor of a real, clinically meaningful association.

The TIA-dominant signal and mechanism

SLT's stronger association with TIA (RR 3.12) than overt ischemic stroke (RR 1.61, non-significant in several analyses) is mechanistically informative. The neo-sinus of Valsalva creates a thrombogenic low-flow microenvironment. Computational fluid dynamics studies demonstrate small platelet-rich thrombi shed from HALT-positive leaflets preferentially embolize to small cerebral vessels, generating brief reversible ischemia rather than large-vessel occlusion. This mirrors atrial fibrillation-related cardioembolism, where thrombus composition and size determine clinical phenotype. Importantly, TIA is frequently not investigated with mandated neurological assessment in TAVR registries, and silent cerebral infarction is not captured by standard clinical follow-up meaning the true cerebrovascular burden of SLT is almost certainly underestimated.

Silent brain injury: a paradigm shift

Apor 2022 represents a paradigm shift: by demonstrating HALT independently predicts white matter hyperintensity burden even after adjusting for procedural cerebral embolism, it establishes SLT as an ongoing source of cerebral microvascular injury, not merely a transient imaging finding. With TAVR now used in patients under 65 who may live 20 or more years with their prosthesis, the cumulative neurological burden of recurrent subclinical embolism from persistent or recurrent SLT deserves urgent longitudinal investigation.

Limitations

Most included studies are observational, with potential unmeasured confounding. Temporal disconnect between CT and clinical events is a pervasive concern SLT may resolve between imaging and event, or develop after CT. CT protocols and HALT grading systems varied; standardized SCCT grading (Blanke 2019) was not uniformly applied. Stroke adjudication was neurologist-confirmed in only a minority of studies. Low absolute event rates yield wide CIs in individual studies.

Conclusion

SLT after TAVR is associated with a more-than-twofold increased relative risk of composite cerebrovascular events, driven principally by TIA. SLT is common (~14%), more frequent with intra-annular valve designs, effectively resolved by oral anticoagulation, and increasingly recognized as a source of subclinical white matter brain injury. However, the GALILEO paradox radiographic SLT benefit without clinical benefit, and net harm from routine anticoagulation establishes clearly that the solution is not simply treating SLT in all patients. The field requires: (1) standardized 4D-CT screening protocols; (2) prospective registries with mandatory neurological assessment and brain MRI endpoints; and (3) randomized trials specifically targeting SLT-positive patients with optimized anticoagulation strategies.

Clinical Takeaway

SLT is not benign it more than doubles cerebrovascular event risk, primarily through TIA and subclinical brain injury. But routine prophylactic anticoagulation harms unselected patients. The next decade must deliver CT-guided, phenotype-driven, individualized antithrombotic trials.

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