JACC: CARDIOVASCULAR INTERVENTIONS VOL. 14, NO. 24, 2021

PUBLISHED BY ELSEVIER

STATE-OF-THE-ART REVIEW

Subclinical Leaflet Thrombosis After Transcatheter Aortic Valve Replacement

A Meta-Analysis

Matthias Bogyi, MD,[a] Rüdiger E. Schernthaner, MD, PhD,[b] Christian Loewe, MD,[b] Gloria M. Gager, MD,[a,c] Al Medina Dizdarevic, MD,[a] Christina Kronberger, MD,[a] Marek Postula, MD, PhD,[d] Jacek Legutko, MD, PhD,[e] Poonam Velagapudi, MD,[f] Christian Hengstenberg, MD,[a] Jolanta M. Siller-Matula, MD, PhD[a,d]

ABSTRACT

This meta-analysis and systematic review was performed to evaluate the clinical relevance of subclinical leaflet thrombosis (SLT) following transcatheter aortic valve replacement. PubMed, Web of Science, and CENTRAL were searched for eligible randomized and nonrandomized studies until November 2020. Risk ratios (RRs) or odds ratios and 95% CIs were calculated, using a random-effects model. Overall, 25 studies were eligible for the analysis and comprised a total of 11,098 patients. The median incidence of SLT was 6% at a median follow-up of 30 days. Use of intra-annular valves was associated with 2-fold greater risk for the development of SLT compared with use of supra-annular valves. There was no difference in the risk for SLT (RR: 0.97; 95% CI: 0.72-1.29; $P = 0.83$) between single-antiplatelet therapy (SAPT) and dual-antiplatelet therapy (DAPT), whereas oral anticoagulation (OAC) was associated with a 58% relative risk reduction for SLT (RR: 0.42; 95% CI: 0.29-0.61; $P < 0.00001$) compared with SAPT and DAPT. In patients with diagnosed leaflet thrombosis at follow-up, the risk for stroke or transient ischemic attack was increased by 2.6-fold (RR: 2.56; 95% CI: 1.60-4.09; $P < 0.00001$) compared with patients without leaflet thrombosis. In patients diagnosed with SLT, the odds of SLT resolution increased by 99% after switch from antiplatelet agents to OAC (odds ratio: 0.01; 95% CI: 0.00-0.06; $P < 0.00001$). To summarize, indication-based use of OAC after transcatheter aortic valve replacement is associated with a lower risk for SLT compared with SAPT and DAPT. Switching to OAC seems to be effective for SLT resolution. As SLT increased the odds of stroke or transient ischemic attack in the included population, further studies are needed to investigate whether screening tests for SLT and appropriate antithrombotic therapy improve long-term valve functionality and clinical prognosis. (J Am Coll Cardiol Intv 2021;14:2643–2656) © 2021 by the American College of Cardiology Foundation.

Transcatheter aortic valve replacement (TAVR) has replaced surgical aortic valve replacement (SAVR) in patients at high risk for perioperative complications according to the 2017 European Society of Cardiology and the 2020 American College of Cardiology/American Heart Association valvular heart disease guidelines (1,2). TAVR is also an option for patients at intermediate

From the [a]Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria; [b]Division of Cardiovascular and Interventional Radiology, Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria; [c]Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria; [d]Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Center for Preclinical Research and Technology CEPT, Warsaw, Poland; [e]Jagiellonian University Medical College, Faculty of Medicine, Institute of Cardiology, Department of Interventional Cardiology, John Paul II Hospital, Krakow, Poland; and the [f]Division of Cardiovascular Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 3, 2021; revised manuscript received August 31, 2021, accepted September 7, 2021.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2021.09.019

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 14, NO. 24, 2021
DECEMBER 27, 2021:2643–2656

ABBREVIATIONS AND ACRONYMS

BEV = balloon-expandable valve

CT = computed tomography

DAPT = dual-antiplatelet therapy

HALT = hypoattenuated leaflet thickening

HAM = hypoattenuation affecting motion

MDCT = multidetector computed tomography

OAC = oral anticoagulation

OR = odds ratio

RELM = reduced leaflet mobility/motion

RR = risk ratio

SAPT = single-antiplatelet therapy

SAVR = surgical aortic valve replacement

SEV = self-expanding valve

SLT = subclinical leaflet thrombosis

TAVR = transcatheter aortic valve replacement

TIA = transient ischemic attack

risk for perioperative mortality (3,4). These trials in low-risk patients with severe aortic stenosis have indicated that TAVR is associated with better outcomes than SAVR, which suggests that the range of indications for TAVR might be expanded (5,6). The NOTION-2 (Comparison of Transcatheter Versus Surgical Aortic Valve Replacement in Younger Low Surgical Risk Patients With Severe Aortic Stenosis; NCT02825134) trial comparing TAVR versus SAVR in patients 75 years of age or younger with severe aortic valve stenosis is still ongoing. However, the long-term durability of TAVR valves remains an unanswered question (7), particularly in younger patients with longer life expectancy.

Although the durability issue remains unanswered, attention has been brought to the new phenomenon of subclinical leaflet thrombosis (SLT) (8). Recently, it has been shown that a large number of patients receiving bioprostheses for aortic stenosis develop SLT with or without reduced leaflet motion (15%-30%) (9-11). Isolated leaflet thrombosis is known as hypoattenuated leaflet thrombosis (HALT) on multidetector computed tomography (MDCT). A more serious form of leaflet pathology is reduced leaflet mobility/motion (RELM), if associated with HALT also called hypo-attenuation affecting motion (HAM). To evaluate the valve for RELM and HAM, retrospective electrocardiographically gated computed tomography (CT) is required, often referred to as 4-dimensional MDCT. Both phenomena have been described across different TAVR valves (first-generation CoreValve, Evolut R, Portico, Lotus, and SAPIEN 3) and surgical bioprostheses (Perimount and Trifecta). Three to 4 months after TAVR, leaflet thrombosis was present in 30% of transcatheter valves and 28% of the surgical valves (10,12-16).

To investigate the incidence, clinical impact, and predictors of SLT after TAVR, we performed a systematic review and meta-analysis. Furthermore, we aimed to assess the efficacy of treatment options for patients with SLT and to determine whether the presence of SLT has an impact on the incidence of adverse thrombotic events such as stroke or transient ischemic attack (TIA).

HIGHLIGHTS

- Intra-annular TAVR increases risk for SLT formation compared with supra-annular TAVR.
- SLT after TAVR is associated with increased risk for stroke or TIA.
- OAC reduces risk for SLT and leads to SLT resolution compared with DAPT/SAPT.

METHODS

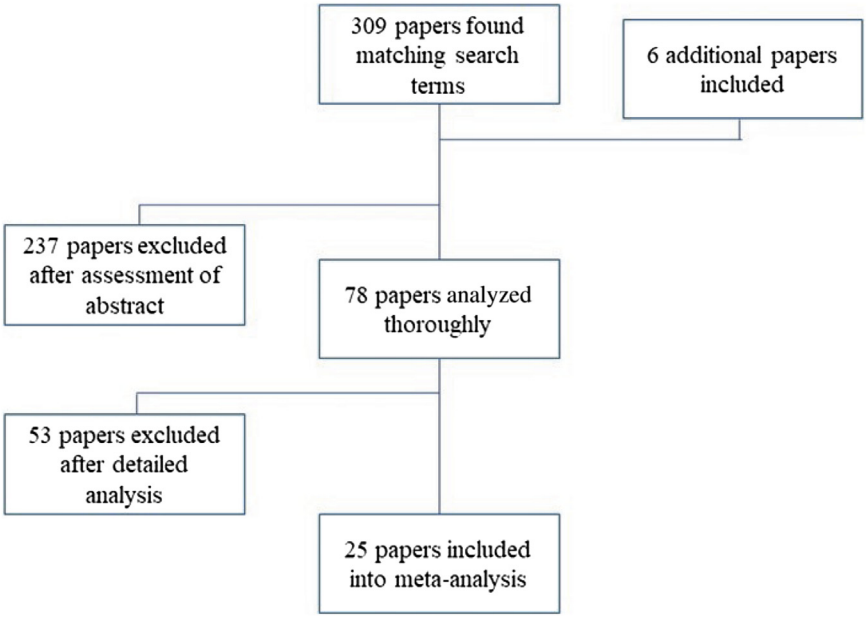
This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (17) guidelines as reported previously (5,18-22).

We searched PubMed, Web of Science, and CENTRAL (Cochrane Central Register of Controlled Trials) for the search terms "subclinical leaflet thrombosis" and "transcatheter aortic valve replacement" as well as different nomenclatures and abbreviations respectively: "(subclinical leaflet thrombosis OR SLT OR reduced leaflet motion OR [RELM] OR hypoattenuating leaflet thickening OR hypoattenuated leaflet thickening OR [HALT]) AND (transcatheter aortic valve insertion OR transcatheter aortic valve replacement OR TAVR OR TAVI)." We performed our search until November 30, 2020. There were no language restrictions. Titles and abstracts were screened for eligibility, and the full text was reviewed if the abstract met the criteria for inclusion. Papers without full text were excluded. We also included papers found in the reference lists of reviews found in our search if they met the criteria for inclusion; however, the reviews were not included. Studies reporting on SLT after TAVR diagnosed by CT and reporting at least 1 of the endpoints detailed as follows were included. Studies with fewer than 25 included patients were excluded.

The primary endpoint was the presence of SLT, as defined by the presence of HALT, HAM, or RELM. Secondary endpoints were the resolution of SLT and the incidence of stroke or TIA. A subgroup analysis regarding the most frequent types of valves inserted (SAPIEN, Medtronic, and Portico) was performed.

The meta-analysis were performed using Review Manager version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration). Data are reported as numbers and percentages. Risk ratios (RRs) or odds ratios (ORs) were calculated from individual studies and pooled according to the inverse-variance random-effect method with predetermined 95% CIs. The relative risk reduction was calculated as: 1 – RR. We checked for heterogeneity by calculating I^2 statistics, but random effects were used even if low

FIGURE 1 Selection of Papers for the Meta-Analysis



Flowchart showing the process of including and excluding papers from the meta-analysis.

heterogeneity was found. To check for potential bias, funnel plots were created for each analysis. Results with 2-sided P values < 0.05 were considered significant. A sensitivity analysis was conducted for the incidence of SLT depending on the type of procedure (TAVR vs SAVR).

STUDIES

Our initial search produced 309 papers reporting on this topic, and 6 additional papers were included. Of these papers, 237 were excluded after abstract review. Fifty-three papers were excluded after thorough analysis. Among the excluded papers, 2 were excluded because the full text could not be retrieved, and 2 further studies were excluded for not using MDCT at all in their search for SLT. Four papers were excluded because they reported on the same study populations as other included papers. However, we still included these papers in the systematic review. Two papers did not meet any exclusion criteria, but they failed to report any data for our calculations, so they were excluded. Overall, 25 studies were included in the meta-analysis. The study flow is shown in **Figure 1**, and details of the included studies are reported in **Tables 1 and 2**.

INCIDENCE OF SLT IN RELATION TO THE VALVE TYPE

Seventeen studies reported on the incidence of SLT by valve type (8,9,14,23-36). In total, 481 of 9,036 patients developed SLT. The reported incidence was low for the newer valves (JenaValve, Symetis, and Biovalve), but the number of the cases investigated was not sufficient to draw conclusions (**Figure 2**). The highest incidence was found for the Portico valve, at 22%. The median incidence was 6.0% (IQR: 0.1%-10.2%) during a median period of 30 days (IQR: 30-67.5 days; range 3-393 days) for post-TAVR CT.

EFFECT OF PROCEDURE TYPE (TAVR VERSUS SAVR) ON SLT

Four studies provided data on the incidence of SLT after TAVR compared with SAVR (9,24,25,29). Two hundred seven of 1,112 patients (18.6%) undergoing TAVR developed SLT, compared with 91 of 479 patients (19.0%) undergoing SAVR, with no difference in the occurrence of SLT after either procedure (RR: 1.38; 95% CI: 0.95-2.02; $I^2 = 54\%$; $P = 0.09$) (Supplemental Figure 1).

TABLE 1 Design, Time, and Size of Included Studies and Exclusion Criteria of the Respective Studies

First Author (Ref. #)	Study Design	Period of Recruitment	Study Population	Main Exclusion Criteria
Abdel-Wahab et al (23)	Randomized controlled trial	March 2012-December 2013	241	Aortic valve annulus <20 mm or >27 mm, previous AVR, endocarditis
Basra et al (24)	Prospective cohort study	October 2015-January 2017	101 (55 TAVR, 46 SAVR)	In-hospital stroke
Blanke et al (25)	Randomized controlled trial	November 2016-November 2018	375 (197 TAVR, 178 SAVR)	
Chakravarty et al (9)	Prospective registry study	December 2014-January 2017	890	GFR <30 mL/min
De Backer et al (12)	Randomized controlled trial	Before May 2018	231	
Erungaren et al (26)	Retrospective data analysis	September 2007-March 2015	588	
Franzone et al (27)	Prospective registry study	August 2007-February 2016	1,396	
Hansson et al (13)	Prospective cohort study	January 2011-January 2016	405	
Jimenez et al (37)	Prospective cohort study	August 2017-March 2018	90	GFR <30 mL/min
Jose et al (14)	Retrospective data analysis	September 2007-August 2015	642	Valve-in-valve
Khan et al (28)	Prospective cohort trial	February 2016-February 2018	170	Bicuspid aortic valve, GFR <20 mL/min, LVEF <20%, CAD, recent stroke or MI
Latib et al (41)	Retrospective data analysis	January 2008-September 2013	26	Endocarditis, other causes of valve failure
Makkar et al 2017 (8)	Prospective cohort study		55	
Makkar et al 2020 (29)	Randomized controlled trial	April 2016-March 2018	304	Bicuspid aortic valve, previous AVR, CAD, LVEF <30%, recent stroke or MI
Marwan et al (30)	Retrospective data analysis	October 2014-June 2016	78	
Nührenberg et al (38)	Prospective cohort study	January 2014-August 2017	200	$P2Y_{12}$ inhibitor therapy other than clopidogrel
Pache et al (40)	Prospective cohort study	February 2014-March 2015	156	GFR <30 mL/min, reduced general state of health
Reardon et al (31)	Randomized clinical trial	September 2014-December 2015	912	Bicuspid aortic valve, eGFR <20 mL/min, LVEF <20%, recent stroke or MI
Ruile et al (32)	Prospective cohort study	February 2012-March 2016	51	GFR <30 mL/min, reduced general state of health
Sorysz et al (33)	Retrospective data analysis	November 2008-November 2018	2,307	
Tang et al (39)	Prospective cohort study	July 2015-December 2017	287	
Vollema et al (34)	Retrospective data analysis	November 2007-June 2015	128	
Waksman et al 2018 (15)	Prospective cohort study	February 2016-February 2018	919 (200 TAVR, 719 SAVR)	Bicuspid aortic valve, GFR <20 mL/min, LVEF <20%, CAD, recent stroke or MI
Waksman et al 2020 (35)	Prospective cohort study	August 2016-September 2019	61	Tricuspid aortic valve, GFR <20 mL/min, LVEF <20%, CAD, recent stroke or MI
Yanagisawa et al (36)	Prospective registry study	October 2013-July 2016	485	

AVR = aortic valve replacement; CAD = coronary artery disease; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

EFFECT OF VALVE TYPE ON THE INCIDENCE OF SLT

Nineteen studies included data on the incidence of SLT in intra-annular valves compared with supra-annular valves (8,9,13,14,23,24,26-28,30-39). Four hundred thirty-three of 5,974 patients (7.2%) with intra-annular valves developed SLT. In comparison, 61 of 3,720 patients (1.6%) with supra-annular valves developed SLT. This shows a significant risk increase for SLT with intra-annular valves compared with supra-annular valves (RR: 2.03; 95% CI: 1.42-2.89; $I^2 = 29\%$; $P < 0.00001$) (Figure 3).

SUBGROUP ANALYSES. Edwards Lifesciences versus Medtronic valves. When comparing the incidence of SLT in SAPIEN (Edwards Lifesciences) valves (7.1% [293 of 4,151]) versus Medtronic valves (1.7% [55 of 3,273]), SAPIEN valves were associated with a 1.9-fold risk increase for SLT (RR: 1.94; 95% CI: 1.34-2.81; $I^2 = 27\%$; $P = 0.004$; Figure 3).

Lotus versus Medtronic valves. When comparing the incidence of SLT in Lotus valves (4.4% [45 of

TABLE 2 Endpoints, Types of Valves Used, Anticoagulation Regimens, and Timing of CT in Included Studies

First Author (Ref. #)	Main Endpoints	Type of Valve	Anticoagulation Regimen	Time Point of CT
Abdel-Wahab et al (23)	All-cause mortality, stroke	SAPIEN XT, CoreValve	DAPT or OAC plus SAPT	
Basra et al (24)	Reduced EF, thrombus seen on TTE, HALT, stroke, HF	SAPIEN,[a] Medtronic,[b] Direct Flow	DAPT or OAC plus DAPT	393 ± 315 d after procedure (TAVR), 5.8 y (mean) after insertion (SAVR)
Blanke et al (25)	HALT	Evolut R	DAPT or OAC plus SAPT	30 d after TAVR
Chakravarty et al (9)	Reduced leaflet motion	SAPIEN,[a] Medtronic,[b] Lotus, Portico, Symetis, Centera	SAPT or DAPT or OAC	Median 58 d after procedure (TAVR), median 163 d after insertion (SAVR)
De Backer et al (12)	Reduced leaflet motion		DAPT or OAC plus SAPT	3 mo after TAVR
Erungaren et al (26)	THVT	SAPIEN, CoreValve, Lotus	DAPT or SAPT or OAC	
Franzone et al (27)	THVT	SAPIEN,[a] Medtronic,[b] Lotus, Symetis, Portico	DAPT or OAC or OAC plus SAPT or OAC plus DAPT	Median 1 y after TAVR
Hansson et al (13)	HALT	SAPIEN[a]	DAPT or OAC or OAC plus SAPT	1-3 mo after TAVR
Jimenez et al (37)	THVT	SAPIEN,[a] Medtronic[b]	DAPT or OAC plus SAPT	Median 4 mo after TAVR
Jose et al (14)	THVT	SAPIEN,[a] Medtronic,[b] Biovalve, Jena, Symetis, Lotus	DAPT (TAVR), SAPT (SAVR), or OAC plus SAPT	Median 6 mo after TAVR
Khan et al (28)	HALT	SAPIEN 3, Evolut	APT or OAC	30 d after TAVR
Latib et al (41)	THVT	SAPIEN XT, CoreValve	DAPT or OAC	No CT performed regularly
Makkar et al 2017 (8)	THVT, major CV events	Portico	DAPT or OAC	30 d after TAVR
Makkar et al 2020 (29)	HALT	SAPIEN 3	DAPT or OAC	30 d and 1 y after TAVR
Marwan et al (30)	HALT	SAPIEN,[a] Portico, Symetis	DAPT or OAC	Median 4 mo after TAVR (IQR: 1 mo)
Nührenberg et al (38)	All-cause mortality, stroke		DAPT or OAC plus SAPT	5 d after TAVR
Pache et al (40)	HALT	SAPIEN 3	Before May 2014, MAPT; after June 2014, DAPT; or OAC plus SAPT	Median 5 d after TAVR
Reardon et al (31)	All-cause mortality, stroke	Lotus, Medtronic	DAPT or OAC plus SAPT	No CT performed
Ruile et al (32)	SLT resolution	SAPIEN,[a] Medtronic,[b] Lotus, Portico	DAPT or OAC plus SAPT	Median 5 d after TAVR
Sorysz et al (33)	THVT	SAPIEN,[a] Medtronic,[b] Lotus, Jena, Symetis, Portico, NVT	SAPT or DAPR or OAC or OAC plus SAPT	
Tang et al (39)	HALT	SAPIEN,[a] Medtronic[b]	DAPT or OAC plus SAPT	Before discharge or 30 d after TAVR
Vollema et al (34)	HALT, clinical events	SAPIEN,[a] CoreValve	DAPT or OAC plus clopidogrel	Median 35 d after TAVR
Waksman et al 2018 (15)	All-cause mortality, stroke, SLT (HALT)	SAPIEN 3, Medtronic[b]		30 d after TAVR
Waksman et al 2020 (35)	All-cause mortality	SAPIEN 3, Medtronic[b]		30 d after TAVR
Yanagisawa et al (36)	All-cause mortality, stroke, HF	SAPIEN,[a] CoreValve	SAPT or DAPT or OAC (plus APT)	3 d after TAVR

[a]Includes SAPIEN, SAPIEN 3, and SAPIEN XT. [b]Includes CoreValve, Evolut R, Evolut PRO, and Engager.

APT = antiplatelet therapy; CT = computed tomography; CV = cardiovascular; DAPT = dual-antiplatelet therapy; EF = ejection fraction; HALT = hypoattenuated leaflet thrombosis; HF = heart failure; OAC = oral anticoagulation; SAPT = single-antiplatelet therapy; SLT = subclinical leaflet thrombosis; THVT = transcatheter heart valve thrombosis; TTE = transthoracic echocardiography; other abbreviations as in Table 1.

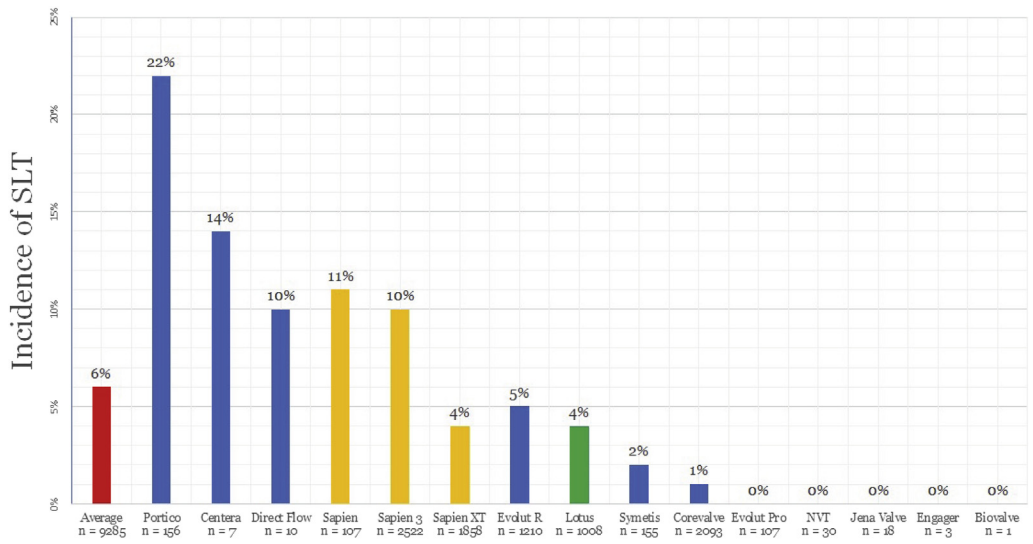
1,008]) versus Medtronic valves (0.9% [28 of 3,140]), Lotus valves were associated with a 4.6-fold risk increase for SLT (RR: 4.60; 95% CI: 2.48-8.54; $I^2 = 22\%$; $P < 0.00001$) (Figure 3).

EFFECT OF VALVE TYPE ON THE RISK OF SLT

Eighteen studies reported data on the occurrence of SLT in balloon-expandable valves (BEVs) compared with self-expanding valves (SEVs) (8,9,13,14,23,24,26-28,30,32-39). Among 4,745 patients receiving BEVs, 351 (7.4%) developed SLT. Ninety-five of 3,727 patients (2.5%) receiving any kind of SEV developed SLT. This indicates a statistically significant increase in the risk for developing SLT in the pooled analysis for BEVs (RR: 1.59; 95% CI: 1.15-2.20; $I^2 = 36\%$; $P = 0.005$) (Supplemental Figure 2).

SUBGROUP ANALYSIS. SAPIEN versus Portico. When comparing the incidences of SLT in SAPIEN valves (5.5% [139 of 2,520]) vs Portico valves (21.8% [34 of 156]), SAPIEN valves were associated with a lower risk for SLT (RR: 0.59; 95% CI: 0.41-0.85; $I^2 = 0\%$; $P = 0.005$) (Supplemental Figure 2).

FIGURE 2 Incidence of SLT According to Valve Type



Bar graph showing the various incidence rates of subclinical leaflet thrombosis (SLT) according to valve type. **Red**, average; **blue**, self-expanding valves; **yellow**, balloon-expandable valves; and **green**, mechanically expanding valves.

EFFECT OF ORAL ANTICOAGULATION THERAPY ON THE INCIDENCE OF SLT

Sixteen studies reported on the effect of oral anticoagulation (OAC) on the incidence of SLT (8,9,12-15,24,27,29,30,34,36-40). Of 1,751 patients receiving OAC after TAVR, 73 (4.2%) developed SLT, compared with 457 of 3,796 patients (12.0%) not receiving OAC (receiving dual-antiplatelet therapy [DAPT] or single-antiplatelet therapy [SAPT]). This results in a 58% relative risk reduction of SLT by OAC (RR: 0.42; 95% CI: 0.29-0.61; $I^2 = 47\%$; $P < 0.00001$) (**Figure 4A**).

EFFECT OF DAPT COMPARED WITH SAPT ON THE INCIDENCE OF SLT

Eight studies provided data on the incidence of SLT while on DAPT compared with SAPT (8,9,13,23,27,36,39,40). One hundred thirty of 1,801 patients (7.2%) receiving DAPT developed SLT, compared with 110 of 785 patients (14.0%) receiving SAPT, resulting in no difference in the risk for SLT between DAPT and SAPT (RR: 0.97; 95% CI: 0.72-1.29; $I^2 = 15\%$; $P = 0.83$) (**Figure 4B**).

EFFECT OF OAC ON THE RESOLUTION OF SLT

Fourteen papers reported data on the effect of initiation of OAC after the diagnosis of SLT and its impact on SLT resolution (8,9,13,14,23,24,27,30-33,37,39,41). Among 232 patients with SLT who received OAC, SLT resolution was confirmed in 219 patients (94%). Among patients with SLT who did not receive OAC after the diagnosis (and were treated according to the standard therapy), SLT resolved in 8 of 57 patients (14%). Therefore, treatment with OAC after SLT diagnosis was associated with a 99% increase in the odds of SLT resolution compared with no OAC treatment (OR: 0.01; 95% CI: 0.00-0.06; $I^2 = 36\%$; $P < 0.00001$) (**Figure 5A**).

ASSOCIATION OF SLT WITH THE RISK FOR STROKE OR TIA

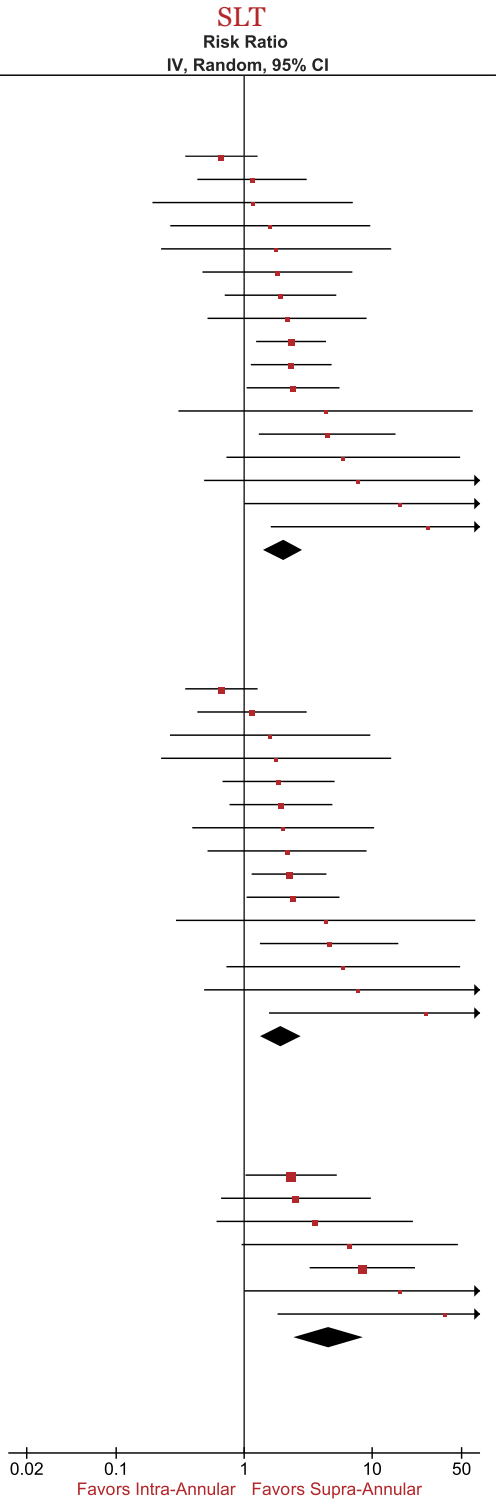
Twelve papers provided data (8,9,13,25,28-31,34,36,37,39) on the future risk for stroke or TIA associated with the presence of SLT. Twenty-two of 368 patients (6.0%) with SLT developed stroke or TIA during follow-up, compared with 152 of 3,253 patients (4.7%) without a diagnosis of SLT. Therefore, a diagnosis of SLT corresponds to a 2.6-fold relative risk increase for stroke or TIA (RR: 2.56; 95% CI: 1.60-4.09; $I^2 = 0\%$; $P < 0.00001$) (**Figure 5B**).

PREDICTORS OF LEAFLET THROMBOSIS

During the systematic review, we identified several predictors of SLT. Obesity (body mass index >30 kg/m^2) (OR: 4.6; 95% CI: 1.6-13.1; $P = 0.005$) (14),

FIGURE 3 Risk for SLT According to Valve Localization

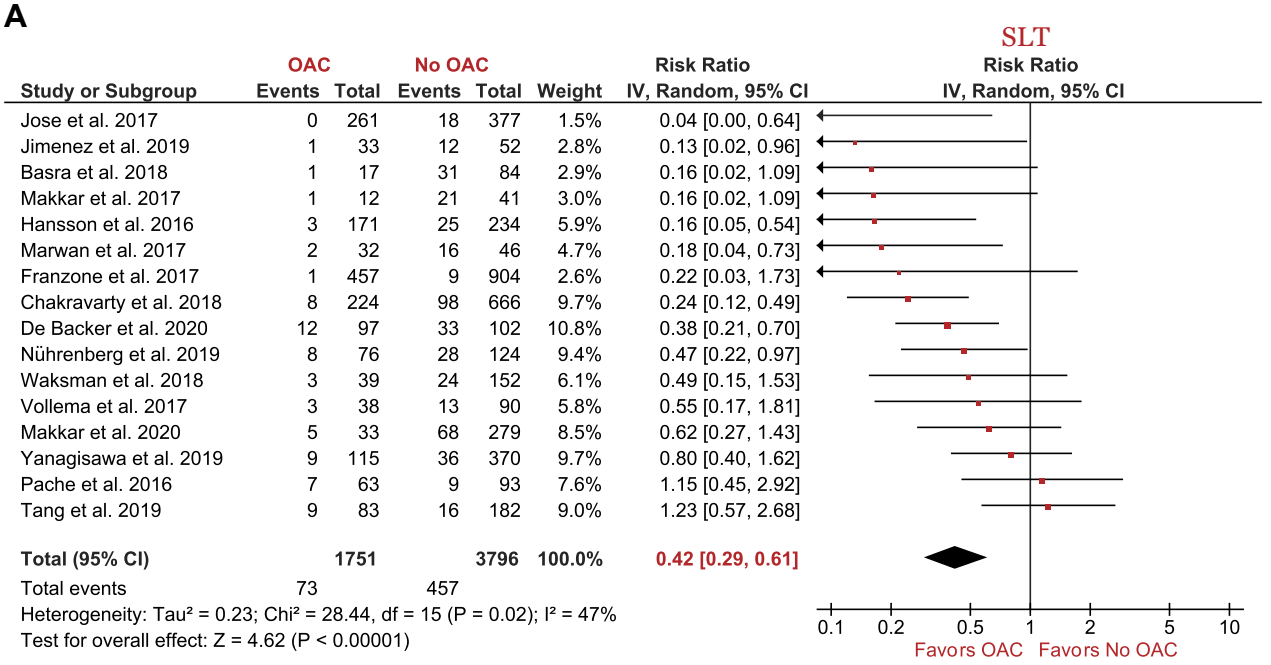
Study or Subgroup	Intra-Annular Events	Intra-Annular Total	Supra-Annular Events	Supra-Annular Total	Weight	Risk Ratio IV, Random, 95% CI
Intra-Annular vs Supra-Annular						
Vollema et al. 2017	16	128	0	0		Not estimable
Hansson et al. 2016	28	405	0	0		Not estimable
Nührenberg et al. 2019	21	138	11	48	13.2%	0.66 [0.35, 1.27]
Yanagisawa et al. 2019	41	436	4	49	8.4%	1.15 [0.43, 3.08]
Marwan et al. 2017	17	73	1	5	3.3%	1.16 [0.19, 7.06]
Basra et al. 2018	16	50	1	5	3.3%	1.60 [0.26, 9.67]
Waksman et al. 2020	5	45	1	16	2.6%	1.78 [0.22, 14.09]
Franzone et al. 2017	7	775	3	604	5.4%	1.82 [0.47, 7.00]
Ruile et al. 2017	47	776	4	127	8.2%	1.92 [0.71, 5.25]
Jimenez et al. 2019	11	61	2	24	4.9%	2.16 [0.52, 9.05]
Chakravarty et al. 2018	91	599	10	153	13.6%	2.32 [1.24, 4.36]
Sorysz et al. 2020	16	797	13	1510	11.9%	2.33 [1.13, 4.82]
Tang et al. 2019	19	152	7	135	10.3%	2.41 [1.05, 5.56]
Makkar et al. 2017	22	51	0	4	1.7%	4.33 [0.31, 61.12]
Jose et al. 2017	15	338	3	301	6.2%	4.45 [1.30, 15.23]
Abdel-Wahab et al. 2020	6	121	1	120	2.5%	5.95 [0.73, 48.68]
Khan et al. 2020	27	170	0	23	1.5%	7.72 [0.49, 122.46]
Reardon et al. 2019	16	578	0	291	1.5%	16.64 [1.00, 276.42]
Erungaren et al. 2015	12	281	0	305	1.5%	27.13 [1.61, 456.06]
Subtotal (95% CI)		**5974**		**3720**	**100.0%**	**2.03 [1.42, 2.89]**
Total events	433		61			
Heterogeneity: Tau² = 0.14; Chi² = 22.40, df = 16 (P = 0.13); I² = 29%						
Test for overall effect: Z = 3.90 (P < 0.0001)						
Edwards vs Medtronic valves						
Nührenberg et al. 2019	21	138	11	48	14.9%	0.66 [0.35, 1.27]
Yanagisawa et al. 2019	41	436	4	49	9.4%	1.15 [0.43, 3.08]
Basra et al. 2018	15	47	1	5	3.7%	1.60 [0.26, 9.67]
Waksman et al. 2020	5	45	1	16	2.9%	1.78 [0.22, 14.09]
Ruile et al. 2017	42	718	4	127	9.0%	1.86 [0.68, 5.09]
Sorysz et al. 2020	8	588	10	1425	10.1%	1.94 [0.77, 4.89]
Franzone et al. 2017	5	679	2	548	4.3%	2.02 [0.39, 10.36]
Jimenez et al. 2019	11	61	2	24	5.4%	2.16 [0.52, 9.05]
Chakravarty et al. 2018	64	460	9	145	14.4%	2.24 [1.14, 4.39]
Tang et al. 2019	19	152	7	135	11.5%	2.41 [1.05, 5.56]
Makkar et al. 2017	6	14	0	4	1.8%	4.33 [0.29, 64.00]
Jose et al. 2017	13	281	3	299	6.7%	4.61 [1.33, 16.01]
Abdel-Wahab et al. 2020	6	121	1	120	2.8%	5.95 [0.73, 48.68]
Khan et al. 2020	27	170	0	23	1.7%	7.72 [0.49, 122.46]
Erungaren et al. 2015	10	241	0	305	1.6%	26.55 [1.56, 450.88]
Subtotal (95% CI)		**4151**		**3273**	**100.0%**	**1.94 [1.34, 2.81]**
Total events	293		55			
Heterogeneity: Tau² = 0.13; Chi² = 19.17, df = 14 (P = 0.16); I² = 27%						
Test for overall effect: Z = 3.51 (P = 0.0004)						
Lotus vs Medtronic valves						
Chakravarty et al. 2018	12	83	9	145	30.5%	2.33 [1.02, 5.29]
Ruile et al. 2017	4	50	4	127	16.0%	2.54 [0.66, 9.77]
Jose et al. 2017	2	56	3	299	10.4%	3.56 [0.61, 20.82]
Franzone et al. 2017	2	82	2	548	8.8%	6.68 [0.95, 46.79]
Sorysz et al. 2020	7	119	10	1425	25.9%	8.38 [3.25, 21.62]
Reardon et al. 2019	16	578	0	291	4.5%	16.64 [1.00, 276.42]
Erungaren et al. 2015	2	40	0	305	4.0%	37.32 [1.82, 763.77]
Subtotal (95% CI)		**1008**		**3140**	**100.0%**	**4.60 [2.48, 8.54]**
Total events	45		28			
Heterogeneity: Tau² = 0.15; Chi² = 7.73, df = 6 (P = 0.26); I² = 22%						
Test for overall effect: Z = 4.83 (P < 0.00001)						
Test for subgroup differences: Chi² = 6.06, df = 2 (P = 0.05), I² = 67.0%						



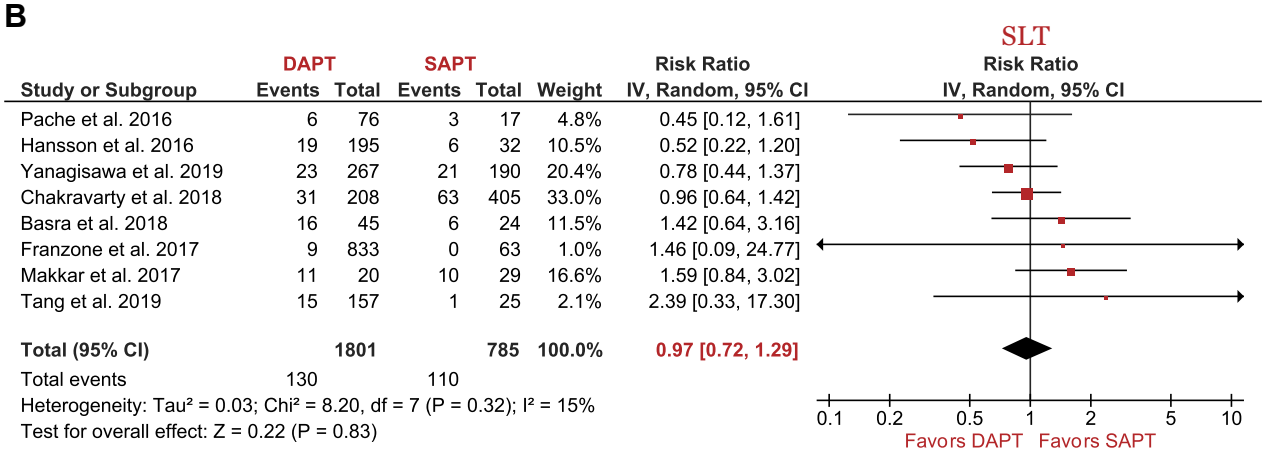
Forest plot showing risk ratios for subclinical leaflet thrombosis (SLT) according to valve localization: intra-annular compared with supra-annular valves. IV = inverse variance.

FIGURE 4 Risk for SLT According to Antithrombotic Strategy

A



B

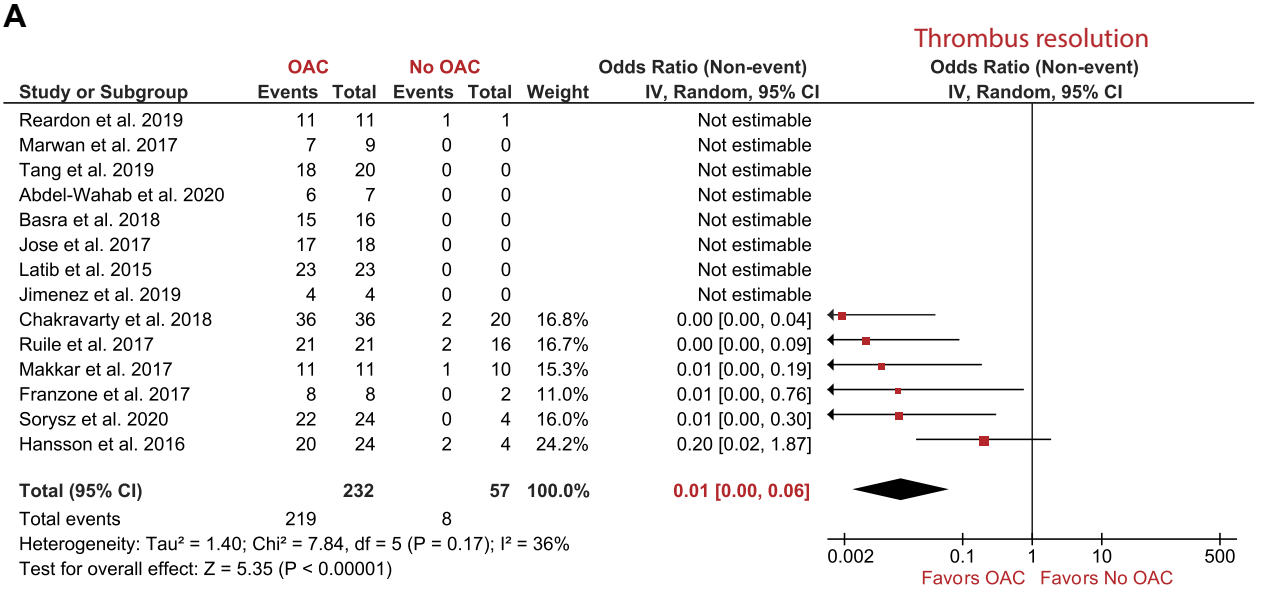


Forest plot showing risk ratios for SLT according to the antithrombotic strategy initiated after transcatheter aortic valve replacement: **(A)** oral anticoagulation (OAC) versus no OAC and **(B)** dual-antiplatelet therapy (DAPT) vs single-antiplatelet therapy (SAPT). Abbreviations as in Figure 3.

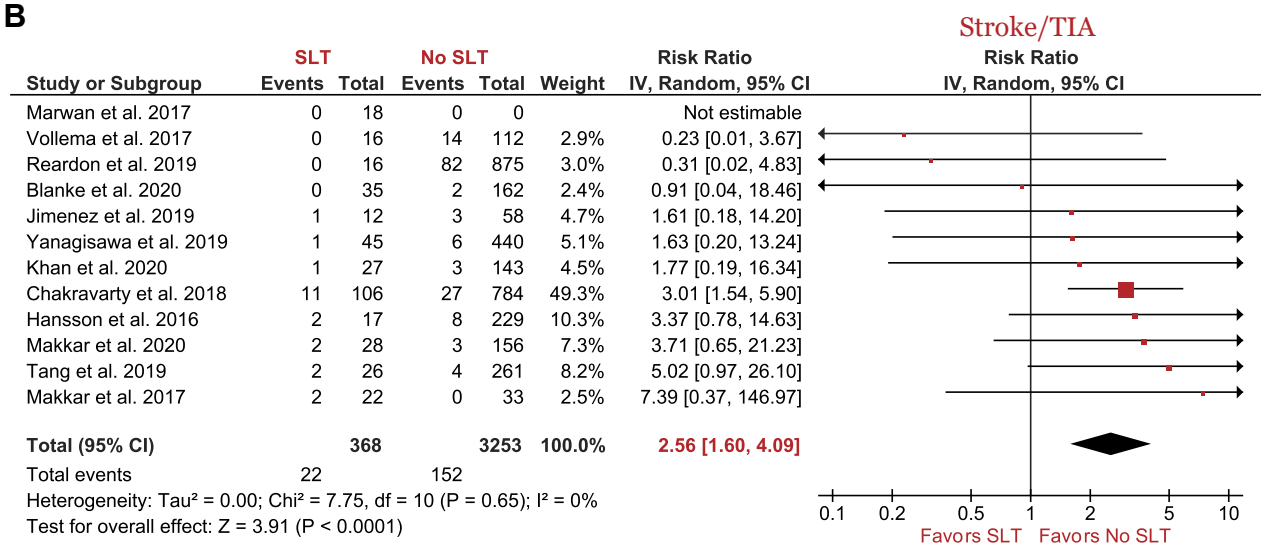
valve-in-valve TAVR (OR: 17.1; 95% CI: 3.4-84.9; $P = 0.001$) (14), male sex (RR: 2.06; 95% CI: 0.984.35; $P = 0.05$) (13,16), BEVs, and larger sinus of Valsalva or larger valves ($P = 0.005$) (16) were positive predictors of SLT (Figure 6). On the contrary, atrial fibrillation (associated with OAC use; $P = 0.003$) (9) (RR: 0.31; 95% CI: 0.13-0.76; $P = 0.006$) (13), heart failure (defined as New York Heart Association functional class III or IV, a CHA_2DS_2-VASc score variable, associated with OAC use; $P = 0.04$) (16), estimated glomerular filtration rate >30 mL/min/1.73 m^2 (RR: 2.49; 95% CI: 1.07-5.77; $P = 0.03$) (13), and diabetes (a CHADS-VASc score variable, associated with OAC use; $P = 0.033$) (34) were predictors of absence of SLT (Figure 6). While the data on the predictive properties of atrial fibrillation, renal insufficiency, obesity, and valve-in-valve procedures stem from multivariate analyses (9,13,14), the data on diabetes, heart failure, BEVs and larger sinus of Valsalva were calculated using univariate analyses (16,34).

FIGURE 5 **Impact of SLT on Incidence of Strokes and Treatment Options for SLT**

A



B



(A) Forest plot showing odds ratios for the resolution of SLT when switched from antiplatelet agents to OAC after SLT diagnosis compared with no switch. **(B)** Risk ratios for stroke or transient ischemic attack (TIA) according to diagnosis of SLT. Abbreviations as in Figure 3.

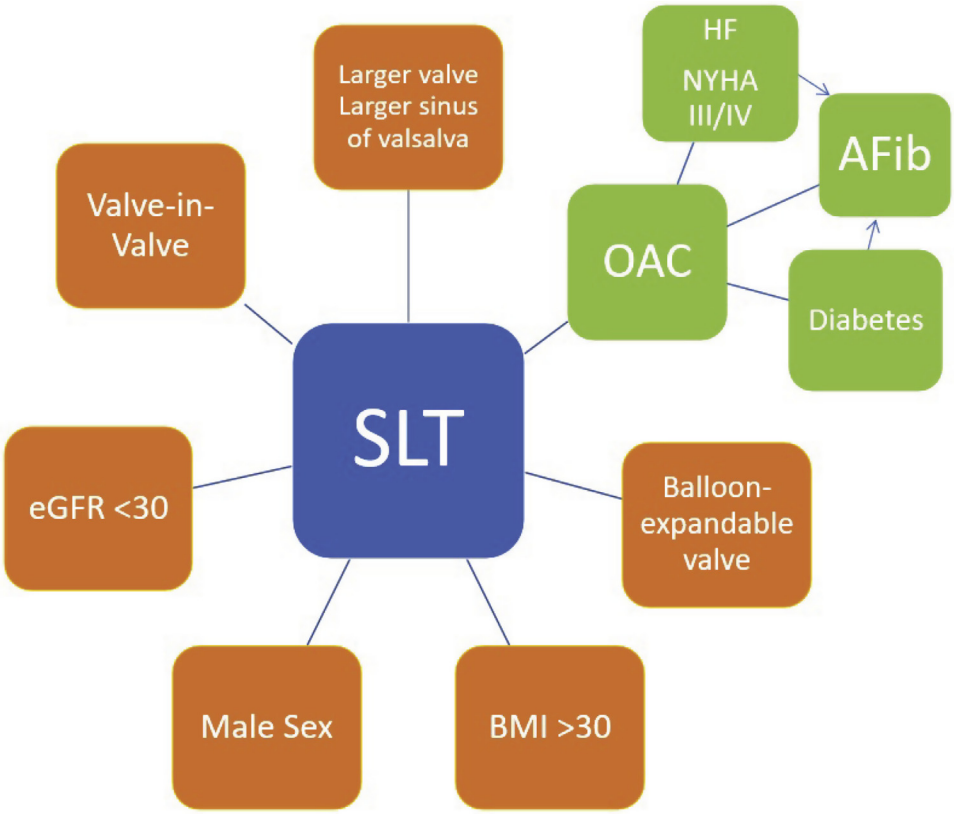
DISCUSSION

In our meta-analysis focusing on SLT, we included data from 25 studies in more than 11,000 patients. We described the incidence of SLT and its predictors and therapeutic options. We furthermore described the effect of SLT on the incidence of cerebral ischemic events.

We have shown that: 1) the presence of leaflet thrombosis without any clinical symptoms at the time of diagnosis was associated with a 2.6-fold risk increase for cerebral ischemic events such as stroke or TIA during the follow-up; 2) the risk for SLT was reduced by 58% under initial OAC in comparison with standard therapy with antiplatelet drugs, whereas there was no difference in the incidence of SLT between DAPT and SAPT; and 3) in patients diagnosed with SLT, switching to OAC resulted in 99% increased odds of SLT resolution (Central Illustration).

The most important finding in our meta-analysis is the fact that the phenomenon of subclinical (ie,

FIGURE 6 Risk Factors for SLT



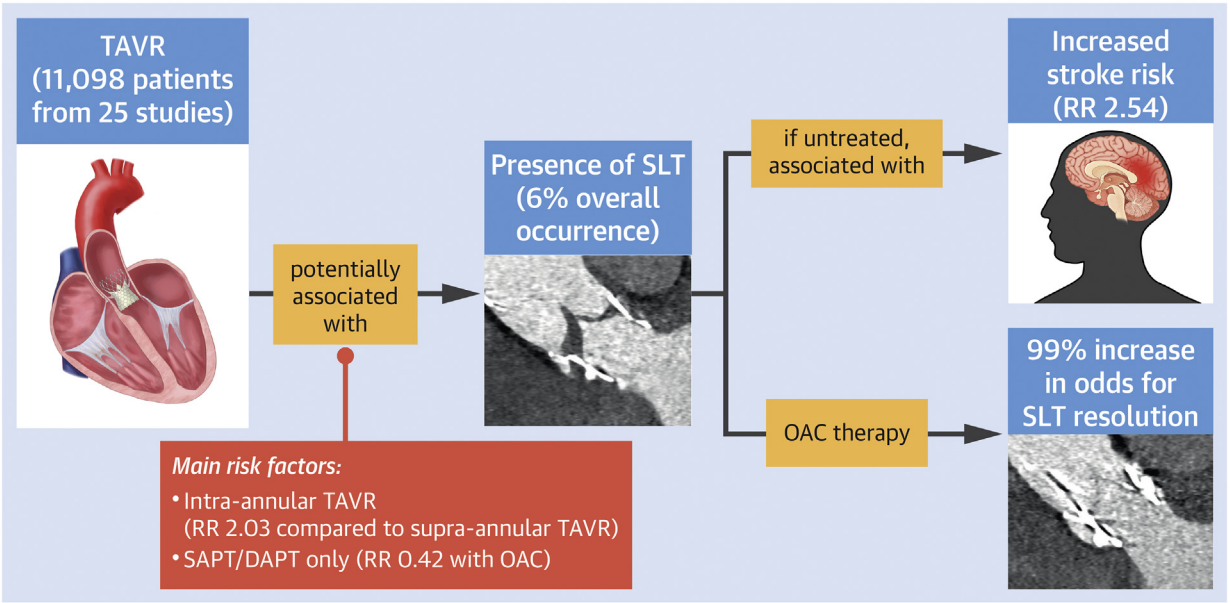
Positive **(orange)** and negative **(green)** predictors of SLT **(blue)** based on the systematic review of the literature (9,13,14,16,34). AFib = atrial fibrillation; BMI = body mass index; eGFR = estimated glomerular filtration rate; HF = heart failure; NYHA = New York Heart Association; other abbreviations as in Figure 4.

asymptomatic) leaflet thrombosis after TAVR is clinically relevant: SLT is associated with a markedly heightened risk for cerebral ischemic events during the period after SLT has been diagnosed. Our results regarding the SLT-associated risk for stroke (RR: 2.6) confirm the findings of a previous meta-analysis (OR: 4.2) focusing primarily on the incidence of clinical and SLT (incidence of 0.4% per month) (42). The main strength of our meta-analysis is the inclusion of a large number of recently published studies in the analyses on the impact of OAC, DAPT, and SAPT on SLT and stroke risk. Furthermore, we provide detailed analyses on the valve-related factors associated with SLT (valve type, procedure type).

As stroke is a deteriorating clinical condition associated with a high risk for mortality and morbidity (43-45), our meta-analysis implies that the diagnosis of SLT even in the absence of echocardiographic signs of leaflet dysfunction, and its subsequent treatment, needs to be addressed in clinical practice. This is particularly important, as silent cerebrovascular events following TAVR are frequent (46), and patients with silent brain infarcts have a 2-fold increased risk for dementia and a steeper decline in cognitive function than those without such lesions (47).

Therefore, a proper diagnosis of SLT seems to be increasingly relevant. The most established method to diagnose leaflet thrombosis and leaflet motion reduction after TAVR or SAVR is 4-dimensional CT (48). Although transthoracic echocardiography is a more readily available and feasible diagnostic tool, it has shown lower sensitivity in detecting SLT compared with CT (48). However, it is noteworthy that CT poses challenges as well: its higher cost, use of contrast media, and radiation exposure must be considered. In particular, retrospective electrocardiographically gated CT results in approximately twice the radiation exposure compared with other scanning techniques (49). This begs the question regarding the optimal

CENTRAL ILLUSTRATION **Subclinical Leaflet Thrombosis After Transcatheter Aortic Valve Replacement: Risk Factors, Effect on Outcome, and Treatment Options**



Bogyi, M. et al. J Am Coll Cardiol Intv. 2021;14(24):2643–2656.

Flowchart showing the risk factors leading to subclinical leaflet thrombosis (SLT) and the effect of SLT on the incidence of stroke and highlighting a treatment option for SLT. DAPT = dual-antiplatelet therapy; OAC = oral anticoagulation; RR = risk ratio; SAPT = single-antiplatelet therapy; SLT = subclinical leaflet thrombosis.

screening method for SLT. Although echocardiography can be easily performed during routine follow-up visits, leaflet thickening confirmed by CT rarely led to a change in transvalvular gradient and thereby would likely have been missed by echocardiography alone (48). However, it is unclear whether all patients should undergo postprocedural CT. Furthermore, the optimal timing of CT is difficult to determine, as the timing of CT in our analysis ranged from 3 days to more than 12 months, and SLT formation is possible at any time point within this range (32). A subgroup analysis for timing of CT was not performed because of the already high heterogeneity of the included studies and the high heterogeneity of the time point of CT within the included studies. Therefore, the ideal timing of CT for SLT should be analyzed in future studies. Finally, the feasibility of other scanning techniques for the detection of RELM and HAM, such as prospective electrocardiographically triggered scans with optimized timing, should be investigated in future trials (50).

The next logical question that should be addressed is the optimal antithrombotic strategy for the prevention and treatment of SLT. Our meta-analysis clearly indicates that OAC use was associated with a lower risk for SLT incidence and complete SLT resolution in 99% of cases if OAC was initiated after SLT was diagnosed. According to the current guidelines (1,2), DAPT is recommended for the first months after TAVR. Recently, the POPular-TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) trial showed that the use of clopidogrel in combination with aspirin leads to a significant increase in bleeding complications, while aspirin alone does not lead to an increase in thrombotic complications (51). Our meta-analysis also shows that regarding the incidence of SLT, DAPT and SAPT were equivalent. Therefore, future use of DAPT with aspirin and clopidogrel might be indicated only for TAVR patients undergoing percutaneous coronary intervention.

Not surprisingly, patients with atrial fibrillation and therefore on lifelong OAC therapy developed significantly less SLT in our meta-analysis. This begs the question of whether all patients should be routinely treated with OAC after TAVR and for how long. On the other hand, the GALILEO (Global Study

Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) trial showed that combined therapy of aspirin plus rivaroxaban 10 mg for 90 days followed by rivaroxaban 10 mg in patients without other pre-existing indications for OAC therapy led to both more deaths and more bleeding complications in comparison with DAPT consisting of aspirin and clopidogrel for 90 days, followed by aspirin monotherapy (52). Similarly, these results are supported by the POPular-TAVI trial subgroup analysis assessing the efficacy of OAC with and without clopidogrel in patients with permanent indication for OAC therapy. At the same time, OAC alone did not lead to worse outcomes regarding stroke or other thromboembolic events (53). This would suggest that although OAC reduces the incidence of SLT and thereby should also reduce the incidence of stroke and TIA after TAVR according to our meta-analysis, the bleeding complications seem to outweigh this benefit, if such a strategy is prescribed to all patients for a long period of time. Therefore, the GALILEO trial indicates that routine anticoagulation after TAVR should not be recommended for all patients.

Additionally, data from the ATLANTIS (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis) trial presented at the ACC.21 conference suggest that the routine use of apixaban reduced the incidence for SLT compared with the standard of care (SAPT or DAPT). However, as it is not clearly stated what exactly constituted the standard of care in both control groups, these data could not be included in our analysis before the full report has been published. Furthermore, data from the ATLANTIS trial failed to show an overall benefit when using apixaban routinely; moreover, the results suggested worse outcomes for the apixaban group (54).

Importantly, according to our meta-analysis, short-term treatment with OAC leads to a resolution of valve thrombosis in more than 94% of cases, as opposed to only a 14% success rate without the use of OAC in patients with confirmed leaflet thrombosis. This implicates that a short period of OAC only in patients with confirmed SLT is effective. Whether such a strategy is associated with a net clinical benefit remains to be proved in randomized clinical trials.

During the systematic review, we identified predictors of SLT from both univariate and multivariate analyses (9,13,14,16,34), while obesity (14), male sex (13), and larger valve sizes (16) were positive predictors of SLT, and systemic diseases such as heart failure (16), renal insufficiency (13), and diabetes mellitus (34), all associated with atrial fibrillation (9,13) and OAC use, were shown to be associated with the absence of SLT.

Of note, the incidence of SLT differed according to valve type. Patients receiving the Portico valve were more often diagnosed with SLT compared with those receiving the SAPIEN valve. Of great interest is the fact that the CoreValve and Evolut valves, from Medtronic, were reported to have the lowest incidence of SLT in observational analyses. However, the total number of Portico valves included in our analysis was significantly lower than other valve types used, which poses the question of whether the higher SLT incidence demonstrated in our meta-analysis might be due to the relatively smaller sample size and a systematic investigation of SLT in patients who received the Portico valve in the SAVORY and RESOLVED registries (8). Nevertheless, our meta-analysis suggests that the intra-annular TAVR prostheses might be associated with higher risk for SLT compared with supra-annular prostheses. This effect might be due to the formation of neosinuses after TAVR, which are located between the displaced diseased native valve leaflets (48). The aortic root morphology can affect blood flow behind the aortic prostheses, resulting in relative blood stasis behind the TAVR leaflets (55). The volume of these neosinuses also varies according to TAVR type: supra-annular TAVR deployment resulted in nearly a 7-fold reduction in the size of the stagnation zone within the neosinuses and shorter blood residence (56). Importantly, SLT was observed with a similar frequency after SAVR and TAVR in our meta-analysis, indicating that this phenomenon might be associated with biological prostheses independent of the type of procedure.

Another important concern regarding SLT is the question of whether this phenomenon might negatively influence valve durability and lead to early valve deterioration. Currently, long-term data are lacking, which would provide clarification of this issue. Importantly, 5-year follow-up data from several studies showed low rates of hemodynamic valve dysfunction or reintervention after TAVR procedures (57-60). However, these studies have not investigated whether redo procedures after TAVR could have been potentially due to SLT. Therefore, future prospective trials addressing this issue are urgently needed.

STUDY LIMITATIONS. The main limitation of our meta-analysis is the observational nature of the data on SLT. Moreover, the computed tomographic

examinations were performed at different time points in the included studies. Similarly, studies differed in the antithrombotic strategies used in the case of SLT: whereas in some studies the antithrombotic strategy remained unchanged, in other studies patients were switched from antiplatelet agents to OAC (direct oral anticoagulant agents or vitamin K antagonists). Therefore, this heterogeneity in the clinical data might be associated with some bias in our meta-analysis.

CONCLUSIONS

Our meta-analysis indicates that SLT is a frequent phenomenon of biological prostheses, regardless of whether TAVR or SAVR is performed. Of note, SLT, if untreated, is associated with unfavorable clinical outcomes such as higher risk for cerebral adverse ischemic events. It must be investigated in future trials whether SLT contributes to valve deterioration, which has been indicated by a mild increase in aortic gradients within months after procedure. Short-term anticoagulant treatment for SLT leads to resolution of leaflet thrombosis, but the question remains as to which drug should be administered and for how long. Likewise, more studies regarding the optimal time point of CT examinations and its frequency as a part of screening programs are urgently needed to ascertain the optimal clinical outcome after implantation of biological prostheses in the aortic position.

ACKNOWLEDGMENTS This paper was written by the members of the International Cardiovascular and Cardiometabolic Research Team.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Jolanta M. Siller-Matula, Department of Cardiology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria. E-mail: jolanta.siller-matula@meduniwien.ac.at. Twitter: @JSillerMatula.

REFERENCES

1. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791.

2. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017;70:252–289.

3. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–1620.

4. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376:1321–1331.

5. Hofer F, Hengstenberg C, Goliasch G, Grygier M, Mascherbauer J, Siller-Matula JM. Transcatheter versus surgical aortic valve replacement in low-risk patients: a meta-analysis of randomized trials. *Clin Res Cardiol*. 2020;109:761–775.

6. Komosa A, Perek B, Rzymski P, et al. Transcatheter aortic valve replacement is associated with less oxidative stress and faster recovery of antioxidant capacity than surgical aortic valve replacement. *J Clin Med*. 2019;8:1364.

7. Hengstenberg C, Siller-Matula JM. Coming closer to personalized medicine in transcatheter aortic valve replacement. *J Am Coll Cardiol Intv*. 2018;11:1730–1732.

8. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015–2024.

9. Chakravarty T, Sondergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383–2392.

10. Sondergaard L, De Backer O, Kofoed KF, et al. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. *Eur Heart J*. 2017;38:2201–2207.

11. Fuchs A, De Backer O, Brooks M, et al. Subclinical leaflet thickening and stent frame geometry in self-expanding transcatheter heart valves. *EuroIntervention*. 2017;13:e1067–e1075.

12. De Backer O, Dangas GD, Jilaihawi H, et al. Reduced leaflet motion after transcatheter aortic-valve replacement. *N Engl J Med*. 2020;382:130–139.

13. Hansson NC, Grove EL, Andersen HR, et al. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. *J Am Coll Cardiol*. 2016;68:2059–2069.

14. Jose J, Sulimov DS, El-Mawardy M, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *J Am Coll Cardiol Intv*. 2017;10:686–697.

15. Waksman R, Rogers T, Torguson R, et al. Transcatheter aortic valve replacement in low-risk patients with symptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2018;72:2095–2105.

16. Yanagisawa R, Hayashida K, Yamada Y, et al. Incidence, predictors, and mid-term outcomes of possible leaflet thrombosis after TAVR. *J Am Coll Cardiol Img*. 2017;10:1–11.

17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.

18. Eyileten C, Postula M, Jakubik D, et al. Non-vitamin K oral anticoagulants (NOAC) versus vitamin K antagonists (VKA) for atrial fibrillation with elective or urgent percutaneous coronary intervention: a meta-analysis with a particular focus on combination type. *J Clin Med*. 2020;9:1120.

19. Gue YX, Spinthakis N, Farag M, et al. Impact of preadmission morphine on reinfarction in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention: a meta-analysis. *Clin Pharmacol Ther*. 2020;108:54–62.

20. Gelbenegger G, Postula M, Pecen L, et al. Aspirin for primary prevention of cardiovascular disease: a meta-analysis with a particular focus on subgroups. *BMC Med*. 2019;17:198.

21. Komosa A, Lesiak M, Krasinski Z, et al. Optimal timing of $P2Y_{12}$ inhibitor loading in patients undergoing PCI: a meta-analysis. *Thromb Haemost*. 2019;119:1000–1020.

22. Siller-Matula JM, Petre A, Delle-Karth G, et al. Impact of preoperative use of $P2Y_{12}$ receptor inhibitors on clinical outcomes in cardiac and non-cardiac surgery: a systematic review and meta-analysis. *Eur Heart J Acute Cardiovasc Care*. 2017;6:753–770.

23. Abdel-Wahab M, Landt M, Neumann FJ, et al. 5-Year outcomes after TAVR with balloon-expandable versus self-expanding valves: results from the CHOICE randomized clinical trial. *J Am Coll Cardiol Intv*. 2020;13:1071–1082.

24. Basra SS, Gopal A, Hebeler KR, et al. Clinical leaflet thrombosis in transcatheter and surgical bioprosthetic aortic valves by four-dimensional computed tomography. *Ann Thorac Surg*. 2018;106:1716–1725.

25. Blanke P, Leipsic JA, Popma JJ, et al. Bioprosthetic aortic valve leaflet thickening in the Evolut low risk sub-study. *J Am Coll Cardiol*. 2020;75:2430–2442.

26. Erungaren JJ, Sulimov DS, El-Mawardy M, et al. Valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics and outcomes. *Am J Cardiol*. 2015;66:B46.

27. Franzone A, Pilgrim T, Haynes AG, et al. Transcatheter aortic valve thrombosis: incidence, clinical presentation and long-term outcomes. *Eur Heart J Cardiovasc Imaging*. 2018;19:398–404.

28. Khan JM, Rogers T, Waksman R, et al. Hemodynamics and subclinical leaflet thrombosis in low-risk patients undergoing transcatheter aortic valve replacement. *Circ Cardiovasc Imaging*. 2019;12:e009608.

29. Makkar RR, Blanke P, Leipsic J, et al. Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves: PARTNER 3 cardiac computed tomography substudy. *J Am Coll Cardiol*. 2020;75:3003–3015.

30. Marwan M, Mekkhala N, Goller M, et al. Leaflet thrombosis following transcatheter aortic valve implantation. *J Cardiovasc Comput Tomogr*. 2018;12:8–13.

31. Reardon MJ, Feldman TE, Meduri CU, et al. Two-year outcomes after transcatheter aortic valve replacement with mechanical vs self-expanding valves: the REPRISE III randomized clinical trial. *JAMA Cardiol*. 2019;4:223–229.

32. Ruile P, Jander N, Blanke P, et al. Course of early subclinical leaflet thrombosis after transcatheter aortic valve implantation with or without oral anticoagulation. *Clin Res Cardiol*. 2017;106:85–95.

33. Sorysz D, Dziewierz A, Bagienski M, et al. Early results of the ongoing Polish Registry on Valve Thrombosis After Transcatheter Aortic Valve Implantation (ZAK-POL TAVI). *Kardiol Pol*. 2020;78:681–687.

34. Vollema EM, Kong WKF, Katsanos S, et al. Transcatheter aortic valve thrombosis: the relation between hypo-attenuated leaflet thickening, abnormal valve haemodynamics, and stroke. *Eur Heart J*. 2017;38:1207–1217.

35. Waksman R, Craig PE, Torguson R, et al. Transcatheter aortic valve replacement in low-risk patients with symptomatic severe bicuspid aortic valve stenosis. *J Am Coll Cardiol Intv*. 2020;13:1019–1027.

36. Yanagisawa R, Tanaka M, Yashima F, et al. Early and late leaflet thrombosis after transcatheter aortic valve replacement. *Circ Cardiovasc Interv*. 2019;12:e007349.

37. Jimenez C, Ohana M, Marchandot B, et al. Impact of antithrombotic regimen and platelet inhibition extent on leaflet thrombosis detected by cardiac MDCT after transcatheter aortic valve replacement. *J Clin Med*. 2019;8:506.

38. Nuhrenberg TG, Hromek J, Kille A, et al. Impact of on-clopidogrel platelet reactivity on incidence of hypoattenuated leaflet thickening after transcatheter aortic valve replacement. *J Am Coll Cardiol Intv*. 2019;12:12–18.

39. Tang L, Lesser JR, Schneider LM, et al. Prospective evaluation for hypoattenuated leaflet thickening following transcatheter aortic valve implantation. *Am J Cardiol*. 2019;123:658–666.

40. Pache G, Schoechlin S, Blanke P, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. *Eur Heart J*. 2016;37:2263–2271.

41. Latib A, Naganuma T, Abdel-Wahab M, et al. Treatment and clinical outcomes of transcatheter heart valve thrombosis. *Circ Cardiovasc Interv*. 2015;8:e001779.

42. D'Ascenzo F, Salizzoni S, Saglietto A, et al. Incidence, predictors and cerebrovascular consequences of leaflet thrombosis after transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur J Cardiothorac Surg*. 2019;56:488–494.

43. Patti G, Pecen L, Manu MC, et al. Thromboembolic and bleeding risk in obese patients with atrial fibrillation according to different anticoagulation strategies. *Int J Cardiol*. 2020;318:67–73.

44. Renda G, Pecen L, Patti G, et al. Antithrombotic management and outcomes of patients with atrial fibrillation treated with NOACs early at the time of market introduction: Main results from the PREFER in AF Prolongation Registry. *Intern Emerg Med*. 2021;16:591–599.

45. Siller-Matula JM, Pecen L, Patti G, et al. Heart failure subtypes and thromboembolic risk in patients with atrial fibrillation: the PREFER in AF – HF substudy. *Int J Cardiol*. 2018;265:141–147.

46. Van Belle E, Hengstenberg C, Lefevre T, et al. Cerebral embolism during transcatheter aortic valve replacement: the BRAVO-3 MRI study. *J Am Coll Cardiol*. 2016;68:589–599.

47. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003;348:1215–1222.

48. Ng ACT, Holmes DR, Mack MJ, et al. Leaflet immobility and thrombosis in transcatheter aortic valve replacement. *Eur Heart J*. 2020;41:3184–3197.

49. Roos JE, Willmann JK, Weishaupt D, Lachat M, Marincek B, Hilfiker PR. Thoracic aorta: motion artifact reduction with retrospective and prospective electrocardiography-assisted multidetector row CT. *Radiology*. 2002;222:271–277.

50. Jurencak T, Turek J, Kietselaer BL, et al. MDCT evaluation of aortic root and aortic valve prior to TAVI. What is the optimal imaging time point in the cardiac cycle? *Eur Radiol*. 2015;25:1975–1983.

51. Brouwer J, Nijenhuis VJ, Delewi R, et al. Aspirin with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med*. 2020;383:1447–1457.

52. Dangas GD, Tijssen JGP, Wohrle J, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med*. 2020;382:120–129.

53. Nijenhuis VJ, Brouwer J, Delewi R, et al. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med*. 2020;382:1696–1707.

54. Collet JP. Oral anti-Xa anticoagulation after trans-aortic valve implantation for aortic stenosis: the randomized ATLANTIS trial. Presented at: American College of Cardiology (ACC) Virtual Annual Scientific Session; 2021.

55. Vahidkhah K, Azadani AN. Supra-annular valve-in-valve implantation reduces blood stasis on the transcatheter aortic valve leaflets. *J Biomech*. 2017;58:114–122.

56. Midha PA, Raghav V, Sharma R, et al. The fluid mechanics of transcatheter heart valve leaflet thrombosis in the neosinus. *Circulation*. 2017;136:1598–1609.

57. Kapadia SR, Leon MB, Makkar RR, et al. 5-Year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2485–2491.

58. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol*. 2014;63:1972–1981.

59. Mack MJ, Leon MB, Smith CR, et al. 5-Year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477–2484.

60. Gerckens U, Tamburino C, Bleiziffer S, et al. Final 5-year clinical and echocardiographic results for treatment of severe aortic stenosis with a self-expanding bioprosthesis from the ADVANCE study. *Eur Heart J*. 2017;38:2729–2738.

KEY WORDS aortic stenosis, oral anticoagulation, SAVR, subclinical leaflet thrombosis, TAVR, valve thrombosis

APPENDIX For supplemental figures, please see the online version of this paper.