Current Cardiology Reports (2021) 23: 186
https://doi.org/10.1007/s11886-021-01614-z

VALVULAR HEART DISEASE (TL KIEFER, SECTION EDITOR)

Transcatheter Aortic Valve Leaflet Thrombosis: Prevalence, Management, and Future Directions

Makoto Nakashima[1] · **Hasan Jilaihawi**[1]

Accepted: 13 September 2021 / Published online: 11 November 2021

Abstract

Purpose of Review We review the pathology, prevalence, diagnosis, hemodynamics, risk factors, prognosis, and treatment of leaflet thrombosis (LT), and suggest future directions in this field.

Recent Findings The latest meta-analysis showed the prevalence of overall LT is 5.4% (clinical LT of 1.2% and subclinical LT of 15.1%). Either subclinical or clinical LT is not associated with risk of mortality; however, clinical LT is associated with increased risk of stroke. Although LT can be reduced by oral anticoagulation therapy (OAT), routine use of OAT as primary prevention for high-risk patients is not recommended due to increased risk of mortality.

Summary Four-dimensional computed tomography plays an important role in the diagnosis of LT and the accumulation of qualitative or qualitative assessments of hypoattenuated leaflet thickening would provide more clues to clarify effective OAT strategies. In addition, further studies are warranted to evaluate the efficacy of other anticoagulants in low-intermediate risk patients.

Keywords Aortic stenosis · Transcatheter aortic valve replacement · Hypoattenuated leaflet thickening · Prosthesis-patient mismatch · Anticoagulation

Abbreviations

CI	Confidence interval
CT	Computed tomography
DAPT	Dual antiplatelet therapy
DOAC	Direct oral anticoagulant
HALT	Hypoattenuated leaflet thickening
LT	Leaflet thrombosis
OAT	Oral anticoagulant therapy
OR	Odds ratio
RLM	Reduced leaflet motion
RR	Relative ratio
SAVR	Surgical aortic valve replacement
SVD	Structural valve deterioration
STS	Society of Thoracic Surgeons
TAVR	Transcatheter aortic valve replacement
THV	Transcatheter heart valve
TTE	Transthoracic echocardiography
VKA	Vitamin K antagonist

This article is part of the Topical Collection on *Valvular Heart Disease*

✉ Hasan Jilaihawi
hasanjilaihawi@gmail.com

[1] Heart Valve Center, NYU Langone Health, 530 1st Avenue, Suite 9V, New York, NY 10016, USA

Introduction

Transcatheter aortic valve replacement (TAVR) has become an established treatment option for patients with symptomatic severe aortic stenosis and has been a class I indication for high or prohibitive risk for surgical aortic valve replacement (SAVR) and class IIa for intermediate surgical risk patients [1]. Owing to the improvement of TAVR devices, the indications for TAVR have also been expanded to low surgical risk patients due to favorable trial results that compared TAVR with SAVR in such cohorts [2, 3]. However, the prevalence of leaflet thrombosis (LT) after TAVR is greater than with SAVR [2–6].

Most of LT cases are asymptomatic and incidentally detected by 4D computed tomography (CT) imaging after TAVR [7–9]. However, some cases have shown unpredictable catastrophic courses within a couple of days [10]. This review article summarizes the recently published papers about pathology, prevalence, diagnosis, hemodynamics, risk factors, prognosis, and treatment of LT, and suggests future directions in this field.

Pathology

The biomaterials of transcatheter heart valve (THV) are made of substances that are considered highly biocompatible such as bovine or porcine pericardial tissue, cobalt-chromium and nitinol frames, and polyethylene terephthalate sealing skirts to suppress inflammatory and immune reaction. Even though TAVR is minimally invasive, it is still an invasive procedure; thus, there is the potential for injury of tissue or biomaterials triggering inflammation and an immune response leading to thrombus formation [11]. The native endothelial layer throughout the cardiovascular system in human body offers an anticoagulant surface. Thus, building a monolayer of endothelial cells on the blood-contacting surfaces of cardiovascular devices is considered the most efficient means to solve this clot formation risk [12] but a bioprosthesis is not expected to be endothelialized immediately after TAVR procedure. Seller et al. investigated 23 explanted THVs after TAVR and reported that rapid early thrombus formation right after TAVR may occur before valve endothelialization and a combination of thrombus and fibrosis was seen beyond 60 days [13]. Histological studies using the explanted THVs from the autopsy cases showed that the rate of thrombus formation on the THV leaflets was high of 80–100% compared with the clinical diagnosis rate [13–16]. Thrombi were found as early as 1 day and as late as 2583 days [13]. Tissue histomorphometric findings and related time-dependent changes of prosthesis degeneration components such as fibrosis and calcification in their study suggest a continuous cascade of thrombus formation within hours, fibrosis after 60 days, and calcification after 4 years.

Prevalence

The LT is classified as subclinical or clinical types according to the presence of symptoms. Furthermore, based on the onset after TAVR, LT is classified as acute (0–3 days), subacute (3 days–3 months), late (3 months–1 year), and very late (> 1 year) [17]. According to the recent meta-analysis, the overall incidence of LT after TAVR was 5.4% (95% confidence interval [CI] 2.8–8.6), and clinical LT of 1.2% (95% CI 0.8–1.8) was less frequent than subclinical LT of 15.1% (95% CI 10.0–20.9) [2–4, 7, 8, 18–29, 30•, 31–33]. The prevalence of LT with specific devices was different among the available devices, and supra-annular valves such as Corevalve and Symetis had lower LT rate compared with intra-annular devices; 35.2% of Portico™ (37/105), 14.5% in Lotus™ (12/83), 14.2% in Centera™ (1/7), 11.6% in SAPIEN (148/1280), 0% in Direct Flow™ (0/6), 15.4% in Symetis Acurate Neo™ (2/13), and 6.2% in Corevalve (9/145) [5, 8, 22, 28, 29, 32–34].

With a view to comparing TAVR and SAVR, Chakravarty et al. analyzed two prospective single-center registries and found that subclinical LT was more frequent overall in TAVR vs SAVR (12% vs. 4%, $p = 0.001$) [5]; however, there were device-specific differences and the rate of subclinical LT with some TAVR devices was similar to SAVR. More in line with the latter observation, the sub-study of the Evolut Low Risk Trial showed the prevalence of hypoattenuated leaflet thickening (HALT) was similar in TAVR and SAVR groups at 30 days (17.3% vs.16.5%, $p = 0.856$) and at 1 year (30.9% vs. 28.4%, $p = 0.661$) [6]. The sub-study of PARTNER3 (The Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low-Risk Patients With Aortic Stenosis) also showed no significant differences of subclinical LT at 1 year between TAVR and SAVR (28% vs. 20%; $p = 0.19$) [4]. Since follow-up transthoracic echocardiography (TTE) is usually not routinely performed until 3 years after SAVR, the prevalence of LT after SAVR may have been underestimated in previous retrospective studies.

Diagnosis

The clinical diagnosis of LT is remains challenging as majority of LT are subclinical. Even when subclinical, LT may not result in hemodynamic sequelae. Echocardiography is essential for the initial and longitudinal assessment in patients with THV [35]. Follow-up TTE after TAVR procedure is recommended pre-discharge (or within 30 days after TAVR), at 6 and 12 months, and yearly thereafter [36]. The structural valve deterioration (SVD) staging and treatment strategy has recently been standardized to achieve consensus among the various subspecialties since different SVD criteria had been used in previous papers [37, 38]; this may be a metric for the more reliable documentation of durability comparisons of transcatheter and surgical bioprostheses, with not only LT but also pannus, fibrosis, and calcification contributing to SVD as underlying mechanisms.

The gold standard for diagnosing LT is 4D-CT angiography imaging. The imaging hallmarks of LT noted on CT are HALT and hypoattenuation affecting motion (HAM) defined by significant reduced leaflet motion (RLM) (≥ 50%) of 4D CT findings [9]. The advantages of multiphase CT are its high sensitivity in detecting leaflet morphology changes and early thrombotic changes, and its utility in assessing THV stent expansion and implantation depth [7, 29]; however, importantly, CT is not applicable for the direct assessment of hemodynamics, for which echocardiography remains the mainstay. A novel CT classification of bioprosthetic prosthetic valve degeneration may help better understand the relative contribution of HALT to various mechanisms driving SVD [39].

Furthermore, as pannus also shows similar hypoattenuating lesions below the leaflet [40], hypoattenuating lesions are not necessarily LT (Fig. 1). Cartlidge et al. reported that increased ^{18}F-fluoride PET uptake was seen in thrombotic, calcific degeneration, or pannus lesions corresponding with 4D CT imaging and was a predictor of late valve dysfunction. Their hypothesis that both thrombosis and pannus may be potential upstream triggers of prosthesis degeneration leading to calcific degeneration is consistent with pathological findings [13, 16, 41]. The co-existence of HALT and calcium is often seen on CT imaging; thus, HALT is not a specific finding for LT but may also be seen as fibrotic tissue during valve degeneration process.

Hemodynamics

In the SAPIEN 3 low-risk CT sub-study, HALT and RLM were associated with higher aortic valve mean gradient at 30 days and 1 year (17.8 ± 2.2 mm Hg vs. 12.7 ± 0.3 mm Hg; $p = 0.04$), as well as in patients with increasing severity of HALT [4]; however, no association was shown in the low-risk Evolut sub-study [6]. A meta-analysis showed the presence of LT was associated with higher aortic valve mean gradient at 30 days after TAVR, but not at discharge or at 1 year of follow-up (discharge, odds ratio [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, $p = 0.385$, $I^2 = 9.8\%$) [42]. The reason for contradictory results between two sub-studies is unclear, but the differences in valve specifications and structure may be contributory.

Risk Factors

Previous studies have reported many risk factors for LT such as male sex, low-flow low-gradient aortic stenosis, severe prosthetic-patient mismatch, and 29-mm balloon expandable valve, paravalvular leak less than mild, and stent frame under-expansion [18, 43, 44]. From a meta-analysis of 11,124 patients, a large valve diameter (> 28 mm) (OR 2.89; 1.55–5.8),

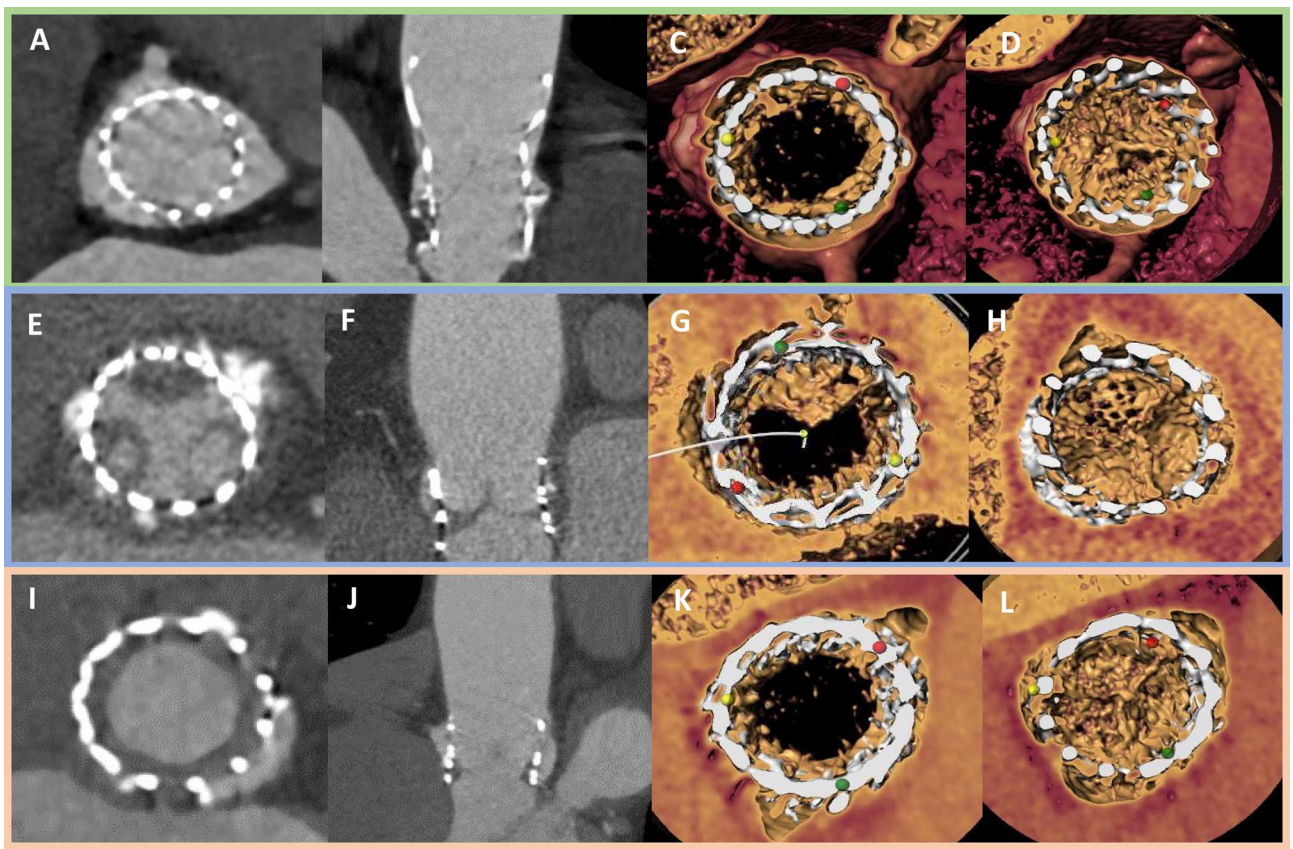

Fig. 1 4D CT observations in bioprostheses. **Top panel:** The appearance of a 26-mm Evolut Pro valve with no hypoattenuated leaflet thickening (HALT) or calcific degeneration at 6 months after TAVR (**A–D**). **Middle panel:** The appearance of HALT in patient with 29-mm SAPIEN 3 at 1 month after TAVR (**E–H**). HALT noted in 3 leaflets most prominent in the right coronary cusp (reduced leaflet motion+, immobile leaflet). **Lower panel:** The appearance of pannus proliferation in patient with 26-mm SAPIEN 3 at 13 months after TAVR (**I–L**). Hypoattenuated ring like tissue is seen below the transcatheter heart valve leaflets, but valve opening is preserved

balloon-expandable TAVR (OR 8; 2.1–9.7), or valve-in-valve procedures (OR 17.1; 3.1–84.9) were predictors of LT [45].

Oral anticoagulation therapy (OAT) heavily influences LT. Multiple studies have shown OAT reduced the prevalence of HALT compared with antiplatelet therapy [5, 25, 26, 46]. In addition, the GALILEO (Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes)-4D sub-study, which enrolled 231 TAVR patients and analyzed 4D CT at 3 months with the primary endpoint of ≥ grade 3 (> 50%) RLM, showed anticoagulation with rivaroxaban was associated with a lower incidence of RLM (difference, −8.8%, 95% CI −16.5 to −1.9%; $p = 0.01$) and HALT (difference, −20.0%, 95% CI −30.9 to −8.5%) compared with dual antiplatelet therapy (DAPT) [20]. However, the GALILEO main study showed that routine anticoagulation strategy was associated with a higher risk of all-cause death than antiplatelet therapy (hazard ratio for rivaroxaban, 1.69; 95% CI, 1.13–2.53) [47••], with increased bleeding noted. Interestingly, an in-depth analysis of GALILEO study showed the cause of increased death was not bleeding but non-cardiac mortality (cancer, respiratory failure, renal failure, and infection/sepsis) and occurred after discontinuation of rivaroxaban [19, 48]. The average age of 80 was also a concern of potential high bleeding risk in the study. Routine anticoagulation with rivaroxaban for elderly or bleeding high-risk patients is therefore not recommended at this time; however, the efficacy of other anticoagulants post-TAVR, especially in low-intermediate risk patients, is yet to be determined. The Anticoagulation versus Dual Antiplatelet Therapy for Prevention of Leaflet Thrombosis and Cerebral Embolisation after Transcatheter Aortic Valve Replacement (ADAPT-TAVR) trial is an ongoing international, multicenter, randomized, open-label, superiority trial comparing edoxaban mono-therapy strategy and DAPT (aspirin plus clopidogrel) strategy in patients without an indication for oral anticoagulation for 6 months [49]. Further studies are warranted to further delineate optimal anticoagulant therapy.

Prognosis

Regarding the prognosis of LT, some reports showed LT was related to increased death, stroke, and transient ischemic attack, while others showed no relationship between LT and cardiovascular events [6, 31]. Meta-analyses consistently showed that either clinical or subclinical LT was not associated with the increased risk of mortality [30•, 42, 45, 50, 51]; however, the risk of stroke was higher in patients with clinical LT (relative ratio [RR] 7.51; 95% CI 2.59–21.78, $p < 0.001$, $I^2 = 15\%$) [30•]. Similar to other arterial thromboses, urgent anticoagulation should be considered in patient with clinical LT.

Treatment

Current ESC and AHA guideline recommend DAPT with clopidogrel 75 mg and aspirin 100 mg for the first 6 months after TAVR and life-long aspirin 75 to 100 mg daily for prevention of LT [52, 53]. However, the POPular TAVI randomized trial (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic-Valve Implantation) showed that aspirin alone therapy was non-inferior, but not superior, to aspirin plus clopidogrel regarding bleeding (RR, 0.57; 95% CI 0.42–0.77, $p = 0.001$), and the composite of bleeding or thromboembolic events (RR, 0.74; 95% CI 0.57–0.95, $p = 0.04$) [54]. Although this study was not designed to evaluate LT by 4D CT, DAPT would not likely be useful as primary prevention of LT. Furthermore, single antiplatelet therapy seems to be appropriate in patients with high bleeding risk. On the other hand, anticoagulant is effective for primary prevention of LT as described above in one clinical trial. It may be also effective as secondary prevention by decreasing mean gradient in LT cases [45]. Vitamin K antagonist (VKA) has been the first choice in treatment of LT. Chakravarty et al. reported both 22 patients treated with VKAs and 12 patients treated with direct oral anticoagulants (DOACs) for 3 months were equally effective in prevention or treatment of subclinical LT [5]. On the other hand, Kawashima et al. compared VKA with DOAC after TAVR in patients with atrial fibrillation and showed the DOAC group had lower all-cause mortality than VKA group (10.3% vs. 23.3%; Cox-adjusted hazard ratio: 0.391; 95% CI: 0.204–0.749; $p = 0.005$) [55]. The choice of DOAC rather than VKA as an anticoagulant agent may thus be reasonable for easier management of medical therapy and could have a relative survival benefit, although this observation requires confirmation in future studies. However, so far routine OAT post-TAVR is not recommended. In summary, it may be reasonable to consider OAT as secondary prevention for subclinical LT or treatment for clinical LT.

Conclusions

Despite the improvement of TAVR devices and outcomes, the prevalence of LT of 5.4% (clinical LT of 1.2% and subclinical LT of 15.1%) remains a concern. Neither subclinical or clinical LT is associated with risk of mortality but clinical LT is associated with increased risk of stroke. Although HALT can be reduced by OAT, routine use of OAT as primary prevention for high-risk patients is not recommended due to increased risk of mortality. 4D CT plays an important role in the diagnosis of LT and the accumulation of qualitative or qualitative assessments of HALT could provide more clues to clarify effective OAT strategies (VKA

versus DOAC). In addition, further studies are warranted to evaluate the role of anticoagulants in low-intermediate risk patients.

Compliance with Ethical Standards

Conflict of Interest Dr. Jilaihawi is a consultant to Boston Scientific, Edwards Lifesciences, and Medtronic Inc. and has received grant/research support from Abbott Vascular, Edwards Lifesciences, and Medtronic Inc. Dr. Nakashima has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, 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. Circulation. 2017;135(25):e1159–95. https://doi.org/10.1161/CIR.0000000000000503.
2. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380(18):1695–705. https://doi.org/10.1056/NEJMoa1814052.
3. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med. 2019;380(18):1706–15. https://doi.org/10.1056/NEJMoa1816885.
4. Makkar RR, Blanke P, Leipsic J, Thourani V, Chakravarty T, Brown D, et al. Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves: PARTNER 3 cardiac computed tomography substudy. J Am Coll Cardiol. 2020;75(24):3003–15. https://doi.org/10.1016/j.jacc.2020.04.043.
5. Chakravarty T, Søndergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet (London, England). 2017;389(10087):2383–92. https://doi.org/10.1016/s0140-6736(17)30757-2.
6. Blanke P, Leipsic JA, Popma JJ, Yakubov SJ, Deeb GM, Gada H, et al. Bioprosthetic aortic valve leaflet thickening in the Evolut low risk sub-study. J Am Coll Cardiol. 2020;75(19):2430–42. https://doi.org/10.1016/j.jacc.2020.03.022.
7. Leetmaa T, Hansson NC, Leipsic J, Jensen K, Poulsen SH, Andersen HR, et al. Early aortic transcatheter heart valve thrombosis: diagnostic value of contrast-enhanced multidetector computed tomography. Circ Cardiovasc Interv. 2015;8(4). https://doi.org/10.1161/circinterventions.114.001596.
8. Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, De Backer O, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med. 2015;373(21):2015–24. https://doi.org/10.1056/NEJMoa1509233.
9. Jilaihawi H, Asch FM, Manasse E, Ruiz CE, Jelnin V, Kashif M, et al. Systematic CT methodology for the evaluation of subclinical leaflet thrombosis. JACC Cardiovasc Imaging. 2017;10(4):461–70. https://doi.org/10.1016/j.jcmg.2017.02.005.
10. Sakurai Y, Koide M, Okada H, Otsuki Y. Fatal leaflet thrombus following transcatheter aortic valve replacement during temporary anticoagulation withdrawal. JACC Cardiovasc Interv. 2019;12(16):1621–2. https://doi.org/10.1016/j.jcin.2019.04.050.
11. Liu JL, Zeng WN, Wang FY, Chen C, Gong XY, Yang H, et al. Effects of low-dose epinephrine on perioperative hemostasis and inflammatory reaction in major surgical operations: a randomized clinical trial. Journal of thrombosis and haemostasis : JTH. 2018;16(1):74–82. https://doi.org/10.1111/jth.13896.
12. Kaya H, Ozkan M, Yildiz M. Relationship between endothelial dysfunction and prosthetic heart valve thrombosis: a preliminary investigation. Eur Rev Med Pharmacol Sci. 2013;17(12):1594–8.
13. Sellers SL, Turner CT, Sathananthan J, Cartlidge TRG, Sin F, Bouchareb R, et al. Transcatheter aortic heart valves: histological analysis providing insight to leaflet thickening and structural valve degeneration. JACC Cardiovasc Imaging. 2019;12(1):135–45. https://doi.org/10.1016/j.jcmg.2018.06.028.
14. Yahagi K, Ladich E, Kutys R, Mori H, Svensson LG, Mack MJ, et al. Pathology of balloon-expandable transcatheter aortic valves. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2017;90(6):1048–57. https://doi.org/10.1002/ccd.27160.
15. Yahagi K, Torii S, Ladich E, Kutys R, Romero ME, Mori H, et al. Pathology of self-expanding transcatheter aortic valves: findings from the CoreValve US pivotal trials. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2018;91(5):947–55. https://doi.org/10.1002/ccd.27314.
16. Torii S, Romero ME, Kolodgie FD, Finn AV, Virmani R. Endothelial cell coverage on the leaflet after transcatheter aortic valve replacement. JACC Cardiovasc Imaging. 2019;12(3):566–7. https://doi.org/10.1016/j.jcmg.2018.12.027.
17. Dangas GD, Weitz JI, Giustino G, Makkar R, Mehran R. Prosthetic heart valve thrombosis. J Am Coll Cardiol. 2016;68(24):2670–89. https://doi.org/10.1016/j.jacc.2016.09.958.
18. Basra SS, Gopal A, Hebeler KR, Baumgarten H, Anderson A, Potluri SP, et al. Clinical leaflet thrombosis in transcatheter and surgical bioprosthetic aortic valves by four-dimensional computed tomography. Ann Thorac Surg. 2018;106(6):1716–25. https://doi.org/10.1016/j.athoracsur.2018.05.100.
19. Chakravarty T, Jilaihawi H, Rosa Adl, Makkar R. Anticoagulation therapy after transcatheter aortic valve replacement. Curr Cardiol Rep. 2020;22.
20. De Backer O, Dangas GD, Jilaihawi H, Leipsic JA, Terkelsen CJ, Makkar R, et al. Reduced leaflet motion after transcatheter aortic-valve replacement. N Engl J Med. 2020;382(2):130–9. https://doi.org/10.1056/NEJMoa1911426.
21. Franzone A, Pilgrim T, Haynes AG, Lanz J, Asami M, Praz F, et al. Transcatheter aortic valve thrombosis: incidence, clinical presentation and long-term outcomes. Eur Heart J Cardiovasc Imaging. 2018;19(4):398–404. https://doi.org/10.1093/ehjci/jex181.
22. Hansson NC, Grove EL, Andersen HR, Leipsic J, Mathiassen ON, Jensen JM, et al. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. J Am Coll Cardiol. 2016;68(19):2059–69. https://doi.org/10.1016/j.jacc.2016.08.010.
23. Holy EW, Kebernik J, Allali A, El-Mawardy M, Richardt G, Abdel-Wahab M. Comparison of dual antiplatelet therapy versus oral anticoagulation following transcatheter aortic valve replacement: a retrospective single-center registry analysis. Cardiol J. 2017;24(6):649–59. https://doi.org/10.5603/CJ.a2017.0050.

24. Huchet F, Letocart V, Guerin P, Cueff C, Roy-Giocosa J, Guyomarch-Delasalle B, et al. Could anticoagulation avoid bioprosthesis subclinical thrombosis in patients undergoing transcatheter aortic valve replacement? Arch Cardiovasc Dis. 2018;111(1):25–32. https://doi.org/10.1016/j.acvd.2017.03.006.
25. Jose J, Sulimov DS, El-Mawardy M, Sato T, Allali A, Holy EW, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. JACC Cardiovasc Interv. 2017;10(7):686–97. https://doi.org/10.1016/j.jcin.2017.01.045.
26. Latib A, Naganuma T, Abdel-Wahab M, Danenberg H, Cota L, Barbanti M, et al. Treatment and clinical outcomes of transcatheter heart valve thrombosis. Circ Cardiovasc Interv. 2015;8(4). https://doi.org/10.1161/circinterventions.114.001779.
27. Mangieri A, Jabbour RJ, Montalto C, Pagnesi M, Regazzoli D, Ancona MB, et al. Single-antiplatelet therapy in patients with contraindication to dual-antiplatelet therapy after transcatheter aortic valve implantation. Am J Cardiol. 2017;119(7):1088–93. https://doi.org/10.1016/j.amjcard.2016.11.065.
28. Marwan M, Mekkhala N, Göller M, Röther J, Bittner D, Schuhbaeck A, et al. Leaflet thrombosis following transcatheter aortic valve implantation. J Cardiovasc Comput Tomogr. 2018;12(1):8–13. https://doi.org/10.1016/j.jcct.2017.11.002.
29. Pache G, Schoechlin S, Blanke P, Dorfs S, Jander N, Arepalli CD, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. Eur Heart J. 2015;37(28):2263–71. https://doi.org/10.1093/eurheartj/ehv526.
30.• Rheude T, Pellegrini C, Stortecky S, Marwan M, Xhepa E, Ammon F, et al. Meta-analysis of bioprosthetic valve thrombosis after transcatheter aortic valve implantation. Am J Cardiol. 2021;138:92-9. https://doi.org/10.1016/j.amjcard.2020.10.018. **This recent meta-analysis showed the prevalence of subclinical or clinical LT and the increased stroke in patient with clinical LT; however, either subclinical or clinical LT was not associated with risk of mortality.**
31. Ruile P, Minners J, Breitbart P, Schoechlin S, Gick M, Pache G, et al. Medium-term follow-up of early leaflet thrombosis after transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2018;11(12):1164–71. https://doi.org/10.1016/j.jcin.2018.04.006.
32. Vollema EM, Kong WKF, Katsanos S, Kamperidis V, van Rosendael PJ, van der Kley F, et al. Transcatheter aortic valve thrombosis: the relation between hypo-attenuated leaflet thickening, abnormal valve haemodynamics, and stroke. Eur Heart J. 2017;38(16):1207–17. https://doi.org/10.1093/eurheartj/ehx031.
33. Yanagisawa R, Hayashida K, Yamada Y, Tanaka M, Yashima F, Inohara T, et al. Incidence, predictors, and mid-term outcomes of possible leaflet thrombosis after TAVR. JACC Cardiovasc Imaging. 2016. https://doi.org/10.1016/j.jcmg.2016.11.005.
34. Rashid HN, Nasis A, Gooley RP, Cameron JD, Brown AJ. The prevalence of computed tomography-defined leaflet thrombosis in intra- versus supra-annular transcatheter aortic valve prostheses. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2018;92(7):1414–6. https://doi.org/10.1002/ccd.27702.
35. Lancellotti P, Pibarot P, Chambers J, Edvardsen T, Delgado V, Dulgheru R, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian Department of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17(6):589–90. https://doi.org/10.1093/ehjci/jew025.
36. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document††The Valve Academic Research Consortium (VARC) consists of representatives from several independent Academic Research Organization, several Surgery and Cardiology Societies, members of the U.S. Food and Drug Administration (FDA), and several independents experts. However, it is not a society document. Neither the societies nor the FDA have been asked to endorse the document. J Am Coll Cardiol. 2012;60(15):1438–54. https://doi.org/10.1016/j.jacc.2012.09.001.
37. Capodanno D, Petronio AS, Prendergast B, Eltchaninoff H, Vahanian A, Modine T, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2017;38(45):3382–90. https://doi.org/10.1093/eurheartj/ehx303.
38. Dvir D, Bourguignon T, Otto CM, Hahn RT, Rosenhek R, Webb JG, et al. Standardized definition of structural valve degeneration for surgical and transcatheter bioprosthetic aortic valves. Circulation. 2018;137(4):388–99. https://doi.org/10.1161/CIRCULATIONAHA.117.030729.
39. Nakashima M, Williams M, He Y, Du R, Saric M, Staniloae C, et al. Novel computed tomography classification for bioprosthetic aortic valve degeneration. JACC: Cardiovascular Interventions.0(0). https://doi.org/10.1016/j.jcin.2020.12.023.
40. Koo HJ, Choe J, Kang D-Y, Ko E, Ahn J-M, Park D-W, et al. Computed tomography features of cuspal thrombosis and subvalvular tissue ingrowth after transcatheter aortic valve implantation. Am J Cardiol. 2020;125(4):597–606. https://doi.org/10.1016/j.amjcard.2019.11.015.
41. Cartlidge TRG, Doris MK, Sellers SL, Pawade TA, White AC, Pessotto R, et al. Detection and prediction of bioprosthetic aortic valve degeneration. J Am Coll Cardiol. 2019;73(10):1107–19. https://doi.org/10.1016/j.jacc.2018.12.056.
42. Sannino A, Hahn RT, Leipsic J, Mack MJ, Grayburn PA. Meta-analysis of incidence, predictors and consequences of clinical and subclinical bioprosthetic leaflet thrombosis after transcatheter aortic valve implantation. Am J Cardiol. 2020;132:106–13. https://doi.org/10.1016/j.amjcard.2020.07.018.
43. Andreas F, Ole De B, Matthew B, Martina Chantal de K, Gintautas B, Masanori Y, et al. Subclinical leaflet thickening and stent frame geometry in self-expanding transcatheter heart valves. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2017;13(9):e1067-e75.
44. Yanagisawa R, Tanaka M, Yashima F, Arai T, Jinzaki M, Shimizu H, et al. Early and late leaflet thrombosis after transcatheter aortic valve replacement. Circ Cardiovasc Interv. 2019;12(2): e007349. https://doi.org/10.1161/circinterventions.118.007349.
45. D'Ascenzo F, Salizzoni S, Saglietto A, Cortese M, Latib A, Franzone 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(3):488–94. https://doi.org/10.1093/ejcts/ezz099.
46. Jimenez C, Ohana M, Marchandot B, Kibler M, Carmona A, Peillex M, et al. Impact of antithrombotic regimen and platelet inhibition extent on leaflet thrombosis detected by cardiac MDCT after transcatheter aortic valve replacement. Journal of clinical medicine. 2019;8(4). https://doi.org/10.3390/jcm8040506.
47.•• Dangas GD, Tijssen JGP, Wöhrle J, Søndergaard L, Gilard M, Möllmann H, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. New England Journal of Medicine. 2019;382(2):120-9. https://doi.org/10.1056/NEJMoa1911425. **Findings from this study showed that routine anticoagulation**

with rivaroxaban after TAVR would not be recommended because of higher risk of death or thromboembolic complications and higher risk of bleeding.

48. Giustino G, Tijssen J, Windecker S, Dangas G. Rivaroxaban after transcatheter aortic valve replacement: the GALILEO trial. Cardiovasc Res. 2020;116(3):e39–41. https://doi.org/10.1093/cvr/cvaa026.
49. Park H, Kang DY, Ahn JM, Kim KW, Wong AYT, Lam SCC, et al. Rationale and design of the ADAPT-TAVR trial: a randomised comparison of edoxaban and dual antiplatelet therapy for prevention of leaflet thrombosis and cerebral embolisation after transcatheter aortic valve replacement. BMJ Open. 2021;11(1):e042587. https://doi.org/10.1136/bmjopen-2020-042587.
50. Kalra A, Raza S, Puri R, Deo SV, Auffret V, Khera S, et al. Subclinical leaflet thrombosis and clinical outcomes after TAVR: a systematic review and meta-analysis. Structural Heart. 2018;2(3):223–8. https://doi.org/10.1080/24748706.2018.1440678.
51. Rashid HN, Gooley RP, Nerlekar N, Ihdayhid AR, McCormick LM, Nasis A, et al. Bioprosthetic aortic valve leaflet thrombosis detected by multidetector computed tomography is associated with adverse cerebrovascular events: a meta-analysis of observational studies. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2018;13(15):e1748–55. https://doi.org/10.4244/eij-d-17-01062.
52. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739–91. https://doi.org/10.1093/eurheartj/ehx391.
53. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, 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(2):252–89. https://doi.org/10.1016/j.jacc.2017.03.011.
54. Brouwer J, Nijenhuis VJ, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, et al. Aspirin with or without clopidogrel after transcatheter aortic-valve implantation. N Engl J Med. 2020;383(15):1447–57. https://doi.org/10.1056/NEJMoa2017815.
55. Kawashima H, Watanabe Y, Hioki H, Kozuma K, Kataoka A, Nakashima M, et al. Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation after TAVR. JACC: Cardiovascular Interventions. 2020;13(22):2587–97. https://doi.org/10.1016/j.jcin.2020.09.013.