Strait Circulation Journal
海峽循環學雜誌

Mini Review

The Challenges of TAVR: HALT and Antithrombotic Therapy

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Accepted 28 June 2021; Volume: 3; Issue: 2; Pages: 4-10; DOI: 10.6907/SCJ.202104_3(2).0002

Abstract:
Transfemoral transcatheter aortic valve replacement (TAVR) has become an established therapeutic option for symptomatic AS patients at the age over 65 years old regardless of their surgical risk. With the expansion of treatment candidates into younger and lower-risk patients, valve durability and thrombosis stay in the center of discussion. Even though hypo-attenuating leaflet thickening (HALT), the hallmark of subclinical leaflet thrombosis (SLT), is prevalent, its clinical implication and the effect of corresponding treatment to lower thromboembolic events are still uncertain. In addition, antithrombotic therapy after TAVR aims to prevent valve thrombosis, but the ideal regimen and treatment duration are still under debate. In this review article, we aim to summarize the current evidence on HALT, discuss the current treatment options of antithrombotic therapy post-TAVR and future aspects to understand the optimal antiplatelet/antithrombotic strategies after TAVR.

Citation: str.circ.j., 2021, 3, 2, 2, 4-10

1. Review

Since its first description by Cribier and his colleagues in 2002 [1], transcatheter aortic valve replacement (TAVR) has undergone an accelerated period of development, revolutionizing the treatment of patients with severe symptomatic aortic valve stenosis (AS). As supporting data emerging, TAVR was proven to be as effective as or superior to surgery in the short- to medium-term in patients at all levels of surgical risk [2–7]. The new ACC/AHA guideline recommends TAVR for symptomatic AS patients who are over 65 years old and have anatomic suitability for transfemoral TAVR regardless of surgical risk [8]. This renders TAVR as a treatment option for younger and lower-risk patients, therefore, valve durability and thrombosis have become an important concern. Studies have reported good durability of TAVR prostheses, for both balloon- and self-expandable valves, up to 5 years follow-up using transthoracic echocardiography [9–12]. Five-year follow-up data from the Placement of Aortic Transcatheter Valves (PARTNER) trial have shown stable valve hemodynamics in 348 high-risk patients (mean transvalvular gradient was 10.7 mmHg and aortic valve area was 1.6cm2)

without occurrence of structural valve deterioration requiring surgical valve replacement (SAVR) [12,13]. As result, the valve durability of TAVR prostheses achieves at least comparable to SAVR prostheses. Even so, bioprosthetic valve thrombosis to cause future thromboembolic event and valve dysfunction still remains a huge concern in TAVR patients. The preparation of bioprostheses and procedures of TAVR could contribute the occurrence of Virchow's triad, ie. hemodynamic changes, endothelial injury/dysfunction, and hypercoagulability. Low cardiac output, creation of another periprosthetic spaces [14], local flow disturbance due to large prosthetic size [15,16], and valve-in-valve deployment [17] could cause hemodynamic flow alteration. The valve crimping [18], valve deployment (especially in balloon-expandable valves) [19], post-dilatation in underexpanded valves [20] and the process of recapturing and resheathing in repositionable valves could lead to irregular leaflet surfaces and further leaflet damage. Underlying comorbidities of the patients, especially those with older age, and degenerated/calcified aortic valve could lead to hypercoagulable state [15,21]. Therefore, early and prompt detection of subclinical leaflet thrombosis (SLT) seem crucial to prevent possible clinical sequelae, specifically the cerebrovascular events.

SLT, characterized by hypo-attenuated leaflet thickening (HALT) and reduced leaflet motion (RLM) observed on computed tomography (CT), may represent a form of bioprosthetic valve dysfunction [22–25]. The two phenomena of hypoattenuating material and significant (>50%) RLM on 4D-CT assessment formed the bases of the definition for SLT [25]. HALT is the hallmark of SLT and involves the periphery and base of the leaflet and extend to varying degrees to the edges of the leaflet in the center of the bioprosthetic frame. Due to its possible clinical relevance to systemic thromboembolic events, the clinical implication of HALT caught the attention yet remained unsettled.

While surgical prosthetic aortic valve thrombosis is associated with an increased risk of stroke [26,27], this association is not consistently observed with the presence of HALT on TAVR prostheses [23, 24,28]. The reported rates of stroke and transient ischemic accident (TIA) in the PARTNER trial-Cohort A ranged from 5.5% to 8.3% at 30 days and 1-year follow-up, respectively, and to 15.9% at 5 years follow-up [4,12]. In the NOTION (Nordic Aortic Valve Intervention) trial, randomizing low surgical risk patients to TAVR or SAVR, the rates of stroke and TIA were 2.9% and 2.1% at 1- year follow-up, respectively [29]. Meanwhile, the incidence of HALT was 10-16% at one month, and increased to 24% at 1 year [30–32], demonstrating the discrepancy of clinical incidence between HALT and stroke/TIA. In addition, the clinical implications of HALT, including prognostic and therapeutic, are still unsettled. In the CT substudy of PARTNER3 trial, the presence of HALT didn't affect aortic valve mean gradients at 30 days or 1 year, but associated with increased pooled thromboembolic event rates of stroke, TIA and renal artery occlusion [32]. Another observational study, combining RESOLVE registry and SAVORY registry, demonstrated SLT (HALT+RLM) was associated with increased rates of TIA and all strokes or TIA [22]. However, other studies didn't show the same correlation [15,16,31,33]. Therefore, these results suggest that the source of stroke/TIA may not primarily be related to the transcatheter valve or that the CT findings may not be sensitive enough to detect early structural changes of the valve that can cause embolic events. As result, even though treatment with anticoagulants could alleviate or resolve HALT, the uncertainty surrounding the clinical sequelae of HALT has led to ambiguity in its management.

With regards to the ideal antithrombotic therapy post-TAVR, both the ESC/EACTS and AHA/ACC guideline recommend dual-antiplatelet therapy with clopidogrel and aspirin for 3–6 months, followed by aspirin alone [34,35], though these recommendations are based on regimens used in initial TAVR trials (Table. 1). Therefore, multiple clinical trials were conducted to answer this important unsettled question (Table 2). Recently, both the cohort A and B of POPular TAVI trial demonstrated regardless of the indication for oral anticoagulation (OAC), the addition of 3-month clopidogrel on either OAC or aspirin had higher rates of bleeding without a clear benefit in terms of reducing ischemic events after TAVR [36,37]. In the pooled cohort RARTNER2 trial, including randomized trials and nonrandomized registries, early OAC in intermediate– or higher–surgical risk patients after TAVR did not change rates of stroke or major bleeding after TAVR at 1 year, but

Table 1. Current AHA/ACC and ESC/EACTS guidelines on antithrombotic therapy with TAVR

Guideline	AHA/ACC 2021	ESC/EACTS 2017
Antiplatelet recommendation	Dual antiplatelet therapy with aspirin 75 to 100 mg and clopidogrel 75 mg may be reasonable for 3 to 6 months, followed by lifelong aspirin use, in patients with low risk of bleeding (Class IIb, LOE B-NR)	Dual-antiplatelet is recommended for 3–6 months then lifelong single-antiplatelet therapy (Class IIa, LOE C) Single-antiplatelet may be considered in patients with high bleeding risk (Class IIb, LOE C)
Anticoagulation recommendation	Anticoagulation with VKA to achieve an INR of 2.5 may be reasonable for at least 3 months, followed by lifelong aspirin or OAC (with OAC indication) use, in patients with low bleeding risk (Class IIb, LOE B-NR)	Oral anticoagulation is recommended lifelong in patients with other indications for anticoagulation (Class I, LOE C)
Subclinical leaflet thrombosis or clinical valve thrombosis	Initial treatment with VKA is reasonable in patients with stable hemodynamics and without contraindications to anticoagulation (Class IIa, LOE B-NR)	Anticoagulation using VKA and/or UFH is recommended in bioprosthetic valve thrombosis before considering reintervention. (Class I, LOE C)

OAC: oral anticoagulant, UFH: unfractionated heparin, VKA: vitamin-K antagonist

was associated with a lower incidence of an increase in mean gradient >10 mm Hg over the first year after implantation [38]. However, the GALILEO trial failed to demonstrate the clinical benefit of add-on OAC. In this trial, treatment with medium-dose rivaroxaban plus aspirin was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than dual antiplatelet therapy after TAVR [39]. Another ATLANTIS trial, which compared standard-dose apixaban with dual-antiplatelet therapy or vitamin K antagonist (VKA) as post-TAVR treatment, was recently presented in 2021 Conference of American College of Cardiology and demonstrated similar result as GALILEO trial, showing apixaban use resulted in higher non-cardiovascular mortality compared with antiplatelet use (both single and dual) among patients without an indication for oral anticoagulant, but supporting the use of apixaban instead of warfarin among patients requiring long-term OAC (data not published yet). Therefore, single antiplatelet or anticoagulation therapy stays the cornerstone of antithrombotic therapy after TAVR. However, the choice of antiplatelet or anticoagulant therapy after TAVR remains unclear in patients without indication for anticoagulant use.

Even though the causal relationship between HALT and ischemic events still needs further investigation, this has led to ongoing debate on how to follow-up patients after TAVR and which antiplatelet/anticoagulation regime would be more appropriate. Treatment with OAC has been shown to be effective in treating or preventing HALT [15,23,40], whereas dual antiplatelet therapy didn't achieve as effective as OAC use [22]. The progression of HALT to Hypo-Attenuation affecting Motion (HAM) didn't occur in patients on OAC, but was reported in 22% of patients on antiplatelet therapy [25]. In addition, HALT relapsed in half of the patients when OAC was interrupted [23]. Therefore, according to above findings, current guideline recommended OAC, particularly VKA, is recommended for 1-6 months with close follow-up in the patients with HALT or clinical valve thrombosis if no contraindication is present [8,41]. In patients receiving TAVR who experience a stroke or systemic embolic event while on antiplatelet therapy, VKA anticoagulation, instead of antiplatelet therapy may be considered after assessment of bleeding risk [8]. However, the debate of post-TAVR antiplatelet/anticoagulation is not settled, and a patient-tailored antithrombotic therapy is suggested.

Table 2. List of current antiplatelet/antithrombotic trials after TAVR

Trial	Study population	Duration, months	Treatment strategy	Outcome	Anticipated completion date
ARTE	222	3	ASA vs DAPT	Aspirin arm had less major/life threatening bleeding	Completed
AUREA	124	3	VKA vs DAPT	No differences in hemodynamics, MACCE, TIA, stroke, and death; less major or life-threatening events in ASA alone group (3 months)	Completed
GALILEO	1644	25	Rivaroxaban 10mg + ASA (3 months), followed by rivaroxaban alone vs. DAPT (3 months), followed by ASA alone	Stopped prematurely because of increased bleeding and mortality in the rivaroxaban group	Completed
ATLANTIS	1510	13	Apixaban 5 mg twice daily vs standard of care (VKA or DAPT)	No OAC indication: Apixaban resulted in higher non-cardiovascular mortality With OAC indication: similar efficacy and safety between apixaban and VKA	Completed, not published yet
POPular-TAVI (cohort A-no OAC indication)	665	12	ASA vs DAPT (3 months), followed by ASA alone	ASA has less bleeding and MACCE+bleeding	Completed
POPular-TAVI (cohort B- OAC indication)	313	12	VKA vs VKA+clopidogrel (3 months), followed by VKA alone	VKA alone has lower incidence of serious bleeding VKA alone has less MACCE+ bleeding	Completed
AVATAR (OAC indication)	170	12	VKA vs VKA+ASA	Pending	Completed, no results coming yet
ENVISAGE-TAVI AF (OAC indication)	1400	36	VKA vs Edoxaban	Pending	June 2021
ADAPT-TAVI (no OAC indication)	245	6	Edoxaban vs DAPT (min. 6 months)	Pending	December 20211

AF: atrial fibrillation, ASA: aspirin, DAPT: dual-antiplatelet therapy, MACCE: major adverse cardiovascular and cerebrovascular events (composed of death from cardiovascular causes, stroke from any cause, transient ischemic attack or myocardial infarction), OAC: oral anticoagulant (either vitamin K antagonist or direct acting oral anticoagulant), TIA: transient ischemic attack, VKA, vitamin-K antagonist

2. Conclusion

The mid-term durability of TAVR bioprostheses have been proved and the rate of possible valve thrombosis is low. However, the incidence of SLT, particularly HALT, is relatively high. Current evidences are insufficiently powered to demonstrate its relationship to hemodynamic and clinical

endpoints, particularly cerebrovascular events. Although much uncertainty still exists in this field, current guideline recommends treatment with OAC for clinical valve thrombosis and SLT, but the optimal medical treatment and duration is not clear yet. Future studies are needed to address several key clinical questions, including predictors of SLT, strategies for prevention and optimal treatment regimens.

Conflicts of Interest:
The authors declare no conflict of interest.

References

1. Cribier, A.; Eltchaninoff, H.; Bash, A.; Borenstein, N.; Tron, C.; Bauer, F.; Derumeaux, G.; Anselme, F.; Laborde, F.; Leon, M.B. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation* **2002**, *106*, 3006–3008.
2. Leon, M.B.; Smith, C.R.; Mack, M.; Miller, D.C.; Moses, J.W.; Svensson, L.G.; Tuzcu, E.M.; Webb, J.G.; Fontana, G.P.; Makkar, R.R.; others. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *New England Journal of Medicine* **2010**, *363*, 1597–1607.
3. Popma, J.; Adams, D.; Reardon, M.; Yakubov, S.; Kleiman, N.; Heimansohn, D.; Hermiller Jr, J.; Hughes, G.; Harrison, J.; Coselli, J.; others. CoreValve United States Clinical Investigators 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.
4. Smith, C.R.; Leon, M.B.; Mack, M.J.; Miller, D.C.; Moses, J.W.; Svensson, L.G.; Tuzcu, E.M.; Webb, J.G.; Fontana, G.P.; Makkar, R.R.; others. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *New England Journal of Medicine* **2011**, *364*, 2187–2198.
5. Reardon, M.J.; Van Mieghem, N.M.; Popma, J.J.; Kleiman, N.S.; Søndergaard, L.; Mumtaz, M.; Adams, D.H.; Deeb, G.M.; Maini, B.; Gada, H.; others. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *New England Journal of Medicine* **2017**, *376*, 1321–1331.
6. Mack, M.J.; Leon, M.B.; Thourani, V.H.; Makkar, R.; Kodali, S.K.; Russo, M.; Kapadia, S.R.; Malaisrie, S.C.; Cohen, D.J.; Pibarot, P.; others. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *New England Journal of Medicine* **2019**, *380*, 1695–1705.
7. Popma, J.J.; Deeb, G.M.; Yakubov, S.J.; Mumtaz, M.; Gada, H.; O'Hair, D.; Bajwa, T.; Heiser, J.C.; Merhi, W.; Kleiman, N.S.; others. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *New England Journal of Medicine* **2019**, *380*, 1706–1715.
8. Otto, C.M.; Nishimura, R.A.; Bonow, R.O.; Carabello, B.A.; Erwin III, J.P.; Gentile, F.; Jneid, H.; Krieger, E.V.; Mack, M.; McLeod, C.; others. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology* **2021**, *77*, 450–500.
9. Gleason, T.G.; Reardon, M.J.; Popma, J.J.; Deeb, G.M.; Yakubov, S.J.; Lee, J.S.; Kleiman, N.S.; Chetcuti, S.; Hermiller, J.B.; Heiser, J.; others. 5-year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. *Journal of the American College of Cardiology* **2018**, *72*, 2687–2696.
10. Douglas, P.S.; Leon, M.B.; Mack, M.J.; Svensson, L.G.; Webb, J.G.; Hahn, R.T.; Pibarot, P.; Weissman, N.J.; Miller, D.C.; Kapadia, S.; others. Longitudinal hemodynamics of transcatheter and surgical aortic valves in the PARTNER trial. *JAMA cardiology* **2017**, *2*, 1197–1206.
11. Barbanti, M.; Petronio, A.S.; Ettori, F.; Latib, A.; Bedogni, F.; De Marco, F.; Poli, A.; Boschetti, C.; De Carlo, M.; Fiorina, C.; others. 5-year outcomes after transcatheter aortic valve implantation with CoreValve prosthesis. *JACC: Cardiovascular interventions* **2015**, *8*, 1084–1091.
12. Mack, M.; Leon, M.; Smith, C.; Miller, D.; Moses, J.; Tuzcu, E.; Webb, J.; Douglas, P.; Anderson, W.; Blackstone, E.; others. PARTNER 1 trial investigators. 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.
13. Kapadia, S.R.; Leon, M.B.; Makkar, R.R.; Tuzcu, E.M.; Svensson, L.G.; Kodali, S.; Webb, J.G.; Mack, M.J.; Douglas, P.S.; Thourani, V.H.; others. 5-year outcomes of transcatheter aortic valve replacement compared

with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *The Lancet* **2015**, *385*, 2485–2491.

14. Midha, P.A.; Raghav, V.; Sharma, R.; Condado, J.F.; Okafor, I.U.; Rami, T.; Kumar, G.; Thourani, V.H.; Jilaihawi, H.; Babaliaros, V.; others. The fluid mechanics of transcatheter heart valve leaflet thrombosis in the neosinus. *Circulation* **2017**, *136*, 1598–1609.
15. Hansson, N.C.; Grove, E.L.; Andersen, H.R.; Leipsic, J.; Mathiassen, O.N.; Jensen, J.M.; Jensen, K.T.; Blanke, P.; Leetmaa, T.; Tang, M.; others. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. *Journal of the American College of Cardiology* **2016**, *68*, 2059–2069.
16. Yanagisawa, R.; Hayashida, K.; Yamada, Y.; Tanaka, M.; Yashima, F.; Inohara, T.; Arai, T.; Kawakami, T.; Maekawa, Y.; Tsuruta, H.; others. Incidence, predictors, and mid-term outcomes of possible leaflet thrombosis after TAVR. *JACC: Cardiovascular Imaging* **2017**, *10*, 1–11.
17. Jose, J.; Sulimov, D.S.; El-Mawardy, M.; Sato, T.; Allali, A.; Holy, E.W.; Becker, B.; Landt, M.; Kebernik, J.; Schwarz, B.; others. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *JACC: Cardiovascular Interventions* **2017**, *10*, 686–697.
18. Alavi, S.H.; Groves, E.M.; Kheradvar, A. The effects of transcatheter valve crimping on pericardial leaflets. *The Annals of thoracic surgery* **2014**, *97*, 1260–1266.
19. de Buhr, W.; Pfeifer, S.; Slotta-Huspenina, J.; Wintermantel, E.; Lutter, G.; Goetz, W.A. Impairment of pericardial leaflet structure from balloon-expanded valved stents. *The Journal of Thoracic and Cardiovascular Surgery* **2012**, *143*, 1417–1421.
20. Hahn, R.T.; Pibarot, P.; Webb, J.; Rodes-Cabau, J.; Herrmann, H.C.; Williams, M.; Makkar, R.; Szeto, W.Y.; Main, M.L.; Thourani, V.H.; others. Outcomes with post-dilation following transcatheter aortic valve replacement: the PARTNER I trial (placement of aortic transcatheter valve). *JACC: Cardiovascular Interventions* **2014**, *7*, 781–789.
21. Luszczak, J.; Undas, A.; Gissel, M.; Olszowska, M.; Butenas, S. Activated factor XI and tissue factor in aortic stenosis: links with thrombin generation. *Blood coagulation & fibrinolysis: an international journal in haemostasis and thrombosis* **2011**, *22*, 473.
22. Chakravarty, T.; Søndergaard, L.; Friedman, J.; De Backer, O.; Berman, D.; Kofoed, K.F.; Jilaihawi, H.; Shiota, T.; Abramowitz, Y.; Jørgensen, T.H.; others. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *The Lancet* **2017**, *389*, 2383–2392.
23. Makkar, R.R.; Fontana, G.; Jilaihawi, H.; Chakravarty, T.; Kofoed, K.F.; De Backer, O.; Asch, F.M.; Ruiz, C.E.; Olsen, N.T.; Trento, A.; others. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *New England Journal of Medicine* **2015**, *373*, 2015–2024.
24. Pache, G.; Schoechlin, S.; Blanke, P.; Dorfs, S.; Jander, N.; Arepalli, C.D.; Gick, M.; Buettner, H.J.; Leipsic, J.; Langer, M.; others. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. *European heart journal* **2016**, *37*, 2263–2271.
25. Sondergaard, L.; De Backer, O.; Kofoed, K.F.; Jilaihawi, H.; Fuchs, A.; Chakravarty, T.; Kashif, M.; Kazuno, Y.; Kawamori, H.; Maeno, Y.; others. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. *European heart journal* **2017**, *38*, 2201–2207.
26. Jander, N.; Sommer, H.; Pingpoh, C.; Kienzle, R.P.; Martin, G.; Zeh, W.; Pache, G.; Siepe, M.; Beyersdorf, F.; Schumacher, M.; others. The porcine valve type predicts obstructive thrombosis beyond the first three postoperative months in bioprostheses in the aortic position. *International journal of cardiology* **2015**, *199*, 90–95.
27. Puvimanasinghe, J.; Steyerberg, E.; Takkenberg, J.; Eijkemans, M.; Van Herwerden, L.; Bogers, A.; Habbema, J. Prognosis after aortic valve replacement with a bioprosthesis: predictions based on meta-analysis and microsimulation. *Circulation* **2001**, *103*, 1535–1541.
28. Leetmaa, T.; Hansson, N.C.; Leipsic, J.; Jensen, K.; Poulsen, S.H.; Andersen, H.R.; Jensen, J.M.; Webb, J.; Blanke, P.; Tang, M.; others. Early aortic transcatheter heart valve thrombosis: diagnostic value of contrast-enhanced multidetector computed tomography. *Circulation: Cardiovascular Interventions* **2015**, *8*, e001596.
29. Thyregod, H.G.H.; Steinbrüchel, D.A.; Ihlemann, N.; Nissen, H.; Kjeldsen, B.J.; Petursson, P.; Chang, Y.; Franzen, O.W.; Engstrøm, T.; Clemmensen, P.; others. Transcatheter versus surgical aortic valve

replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *Journal of the American College of Cardiology* **2015**, *65*, 2184–2194.

30. Ruile, P.; Neumann, F.J. Hypo-attenuated leaflet thickening of transcatheter aortic valves: jeopardy or epiphenomenon? *European heart journal* **2017**, *38*, 1218–1221.
31. Khan, J.M.; Rogers, T.; Waksman, R.; Torguson, R.; Weissman, G.; Medvedofsky, D.; Craig, P.E.; Zhang, C.; Gordon, P.; Ehsan, A.; others. Hemodynamics and subclinical leaflet thrombosis in low-risk patients undergoing transcatheter aortic valve replacement. *Circulation: Cardiovascular Imaging* **2019**, *12*, e009608.
32. Makkar, R.R.; Blanke, P.; Leipsic, J.; Thourani, V.; Chakravarty, T.; Brown, D.; Trento, A.; Guyton, R.; Babaliaros, V.; Williams, M.; others. Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves: PARTNER 3 cardiac computed tomography substudy. *Journal of the American College of Cardiology* **2020**, *75*, 3003–3015.
33. Vollema, E.M.; Kong, W.K.; Katsanos, S.; Kamperidis, V.; van Rosendael, P.J.; van der Kley, F.; de Weger, A.; Ajmone Marsan, N.; Delgado, V.; Bax, J.J. Transcatheter aortic valve thrombosis: the relation between hypo-attenuated leaflet thickening, abnormal valve haemodynamics, and stroke. *European heart journal* **2017**, *38*, 1207–1217.
34. Baumgartner, H.; Falk, V.; Bax, J.J.; De Bonis, M.; Hamm, C.; Holm, P.J.; Iung, B.; Lancellotti, P.; Lansac, E.; Munoz, D.R.; others. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Kardiologia Polska (Polish Heart Journal)* **2018**, *76*, 1–62.
35. Members, W.C.; Otto, C.M.; Nishimura, R.A.; Bonow, R.O.; Carabello, B.A.; Erwin III, J.P.; Gentile, F.; Jneid, H.; Krieger, E.V.; Mack, M.; others. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology* **2021**, *77*, e25–e197.
36. Brouwer, J.; Nijenhuis, V.J.; Delewi, R.; Hermanides, R.S.; Holvoet, W.; Dubois, C.L.; Frambach, P.; De Bruyne, B.; van Houwelingen, G.K.; Van Der Heyden, J.A.; others. Aspirin with or without clopidogrel after transcatheter aortic-valve implantation. *New England Journal of Medicine* **2020**, *383*, 1447–1457.
37. Nijenhuis, V.J.; Brouwer, J.; Delewi, R.; Hermanides, R.S.; Holvoet, W.; Dubois, C.L.; Frambach, P.; De Bruyne, B.; van Houwelingen, G.K.; Van Der Heyden, J.A.; others. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. *New England Journal of Medicine* **2020**, *382*, 1696–1707.
38. Chakravarty, T.; Patel, A.; Kapadia, S.; Raschpichler, M.; Smalling, R.W.; Szeto, W.Y.; Abramowitz, Y.; Cheng, W.; Douglas, P.S.; Hahn, R.T.; others. Anticoagulation after surgical or transcatheter bioprosthetic aortic valve replacement. *Journal of the American College of Cardiology* **2019**, *74*, 1190–1200.
39. Dangas, G.D.; Tijssen, J.G.; Wöhrle, J.; Søndergaard, L.; Gilard, M.; Möllmann, H.; Makkar, R.R.; Herrmann, H.C.; Giustino, G.; Baldus, S.; others. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *New England journal of medicine* **2020**, *382*, 120–129.
40. Ruile, P.; Jander, N.; Blanke, P.; Schoechlin, S.; Reinöhl, J.; Gick, M.; Rothe, J.; Langer, M.; Leipsic, J.; Buettner, H.J.; others. Course of early subclinical leaflet thrombosis after transcatheter aortic valve implantation with or without oral anticoagulation. *Clinical Research in Cardiology* **2017**, *106*, 85–95.
41. Rosseel, L.; De Backer, O.; Søndergaard, L. Clinical valve thrombosis and subclinical leaflet thrombosis following transcatheter aortic valve replacement: is there a need for a patient-tailored antithrombotic therapy? *Frontiers in cardiovascular medicine* **2019**, *6*, 44.