

Evolving concepts in the management of antithrombotic therapy in patients undergoing transcatheter aortic valve implantation

Dirk Jan van Ginkel^{a,1}, Willem L. Bor^{a,1}, Leo Veenstra^{b,c,d}, Arnoud W.J. van 't Hof^{b,c,d}, Enrico Fabris^{e,*}

^a Department of Cardiology, St. Antonius Hospital, Nieuwegein, the Netherlands

^b Department of Cardiology, Zuyderland Medical Centre, Heerlen, the Netherlands

^c Department of Cardiology, Maastricht University Medical Centre, Maastricht, the Netherlands

^d Cardiovascular Research Institute Maastricht (CARIM), Maastricht, the Netherlands

^e Cardiothoracovascular Department, University of Trieste, Trieste, Italy

ARTICLE INFO

Keywords:

TAVI
Antithrombotic therapy
DAPT
Anticoagulation
Aortic stenosis
Valve disease

ABSTRACT

Thromboembolic and bleeding complications negatively impact recovery and survival after transcatheter aortic valve implantation (TAVI). Particularly, there is a considerable risk of ischaemic stroke and vascular access related bleeding, as well as spontaneous gastro-intestinal bleeding. Therefore, benefit and harm of antithrombotic therapy should be carefully balanced. This review summarizes current evidence on peri- and post-procedural antithrombotic treatment. Indeed, in recent years, the management of antithrombotic therapy after TAVI has evolved from intensive, expert opinion-based strategies, towards a deescalated, evidence-based approach. Besides per procedural administration of unfractionated heparin, this encompasses single antiplatelet therapy in patients without a concomitant indication for oral anticoagulation (OAC); and OAC monotherapy in patients with such indication, mainly being atrial fibrillation. Combination therapy should generally be avoided to reduce bleeding risk, except after recent coronary stenting where a period of dual antiplatelet therapy (aspirin plus P2Y12-inhibitor) or P2Y12-inhibitor plus OAC (in patients with an independent indication for OAC) is recommended to prevent stent thrombosis. This new paradigm in which reduced antithrombotic intensity leads to improved patient safety, without a loss of efficacy, may be particularly suitable for elderly and fragile patients. Whether this holds in upcoming populations of younger and lower-risk patients and in specific populations as patients with subclinical valve thrombosis, is yet to be proven. Finally, whether less intensive or alternative approaches should be also applied for the periprocedural management of the antithrombotic therapy, has to be determined by ongoing and future studies.

1. Introduction

Transcatheter aortic valve implantation (TAVI) is an effective and less invasive treatment option compared with conventional surgical aortic valve replacement (SAVR), and is the standard of care for patients with severe aortic stenosis considered inoperable or at high surgical risk [1,2]. Currently, the indication for TAVI is shifting towards younger and lower risk patients [3–6]. Although TAVI techniques and the risk level of the treated population have improved over time, thromboembolic and bleeding complications are still frequent and negatively impact recovery and survival after TAVI.[7] To prevent thromboembolic, in particular

cerebrovascular events, antithrombotic therapy is recommended in all TAVI patients.[1,2] However, recent evidence underlines to be cautious with intensive antithrombotic treatment, given the associated risk of bleeding in the current TAVI population [8–10]. This poses a challenge on clinical practise, especially in the elderly TAVI population, to strike the optimal balance between thromboembolic and bleeding risk. Therefore, in this review we provide an overview of the most recent evidence regarding the optimal antithrombotic therapy in patients undergoing TAVI.

* Corresponding author.

E-mail address: enrico.fabris@hotmail.it (E. Fabris).

¹ These authors contributed equally to this article.

2. Thromboembolic risk and bleeding risk

The incidence of thromboembolic events varies between 3 and 15% within the first year following TAVI, depending on the risk level of the treated population [3–16]. This involves the occurrence of ischaemic stroke and transient ischaemic attack (~1–7%), myocardial infarction (~0.5–2%), systemic thromboembolism (~0.5–2%), intra-cardiac thrombus (0.5–1%) and obstructive valve thrombosis (~0.5–3%) [3–14]. These complications have devastating effects, especially ischaemic stroke, leading to permanent disability or death in many of the affected patients [7,11]. Most of the thromboembolic events occur within the first 48 hours, followed by an ongoing increased incidence in the first months with a gradual decrease thereafter [3–6,11–14,16]. The underlying pathophysiological mechanism is assumed to be multifactorial and is related to both patient- and procedure-related characteristics. Procedural factors explain most of the events in the acute periprocedural phase, caused by the interaction between the device and the calcified aortic valve, with debris dislodgment due to the placement of wires and catheters, valve deployment and pre- and post-dilatation [17]. Histopathologic studies on periprocedural emboli demonstrated that embolization occurs in the majority of patients, including thrombus, calcium, tissue fragments, and foreign material [18,19]. New-onset atrial fibrillation (NOAF) explains part of the thromboembolic events during the early postprocedural phase [11,20]. A meta-analysis (n=14,078; 26 trials) regarding this issue reported an incidence of 17.5% NOAF after TAVI. Although very common, pre-existing atrial fibrillation did not, but NOAF did increase the risk of stroke significantly in the short-term [20]. Furthermore, the early high-risk period might be caused by the lack of endothelialisation of the newly implanted transcatheter valve [21]. The native anatomy of the patient and the deployed TAVI valve together create a unique anatomic geometry, which can lead to stagnant blood flow in the neo-sinus (region between the native and transcatheter aortic valve leaflet) [17,22]. This stagnant flow may allow blood to stay in prolonged contact with the foreign surface of the transcatheter heart valve and result in thrombosis [22]. Finally, thromboembolic risk is also enhanced by coexisting atherosclerotic disease. TAVI patients often suffer from coronary, cerebrovascular and peripheral artery disease, which increase the risk of subsequent thromboembolic events until in the late postprocedural phase [23]. In the elderly, the CHA2DS2-VASc score may help to quantify thromboembolic risk and give an indication of frailty status [24]. Also, specific frailty assessment tools, like the Edmonton Frail Scale, may identify individuals at highest risk of a poor outcome [7,24,25].

The incidence of major bleeding varies between 3 and 17% in the first year after TAVI and consists of periprocedural (mainly vascular access related) bleeding and spontaneous bleeding [3–10,12–14,26,27]. Most spontaneous bleeding events occur in the gastro-intestinal or urogenital tract [9,10]. Vascular access related bleeding has decreased over time, due to routine contrast-enhanced CT assessment of vascular anatomy, ultrasound-guided vascular puncture, smaller bore catheters and the use of better closure devices. Still, vascular access related bleeding accounts for half of all major bleeding events. Non-transfemoral access and sheath diameter have been reported as procedural risk factors [28]. Patient related risk factors include higher age, frailty and frequent comorbidities like renal insufficiency, anaemia and atrial fibrillation [28–32]. Furthermore, aortic stenosis related conditions like acquired type 2A von Willebrand factor (vWF) defect, angiodysplasia, (transient) thrombocytopenia and Heyde's syndrome increase the hazards of bleeding [33,34]. This complex bleeding diathesis is further amplified by the use of antithrombotic drugs, especially in elderly patients who are frequently affected by multimorbidity and subsequent polypharmacy which expose them to potential pharmacological interactions [35].

3. Periprocedural antithrombotic therapy

Before TAVI, a loading dose of aspirin is usually administered to patients without a pre-existent indication for antiplatelet therapy [36]. In patients already on antiplatelet therapy this is often continued during TAVI as single antiplatelet therapy (SAPT), except for patients with recent coronary stenting in whom dual antiplatelet therapy (DAPT) is indicated [36,37]. Several studies have shown that adding clopidogrel before TAVI, either using a loading dose or as maintenance therapy, is not associated with any patient benefit [10,38,39]. However, the optimal timing of administration (before or after TAVI) and type of SAPT (Aspirin or a P₂Y₁₂ inhibitor) still lacks of supporting evidence.

Periprocedural practice differs widely in patients with OAC (e.g. for atrial fibrillation). Studies report perioperative interruption of OAC 2-7 days prior to TAVI, as well as full continuation of OAC [40–45]. Also, some clinics use unfractionated heparin, low molecular weight heparin or aspirin for bridging in patients in whom OAC is interrupted, whereas others do not [40–45]. Interestingly, a recent observational study (n = 1317) reported that continuation of OAC was associated with a similar rate of major or life-threatening bleeding and major vascular complications compared with interruption. Stroke rates were numerically higher in patients with interruption of OAC, but this did not reach statistical significance [40]. However, considering the numerous limitations associated with this retrospective analysis [46], these results need robust confirmation before they can inform clinical practice. The results of the 'Periprocedural Continuation Versus Interruption of Oral Anticoagulant Drugs During Transcatheter Aortic Valve Implantation (POPular PAUSE TAVI) trial' (NCT04437303) will provide more evidence on this topic.

Per procedural, parenteral anticoagulation is administered to prevent catheter thrombosis and possibly reduce periprocedural thromboembolism [36]. The BRAVO 3 Trial (n = 802) demonstrated non-inferiority, but not superiority of bivalirudin versus unfractionated heparin in the occurrence of major bleeding and net adverse cardiovascular events (all-cause mortality, myocardial infarction, stroke or major bleeding) within 30 days after TAVI [47]. Because bivalirudin is more expensive and requires continuous infusion, unfractionated heparin remains the first-line drug [48]. Bivalirudin serves as a valuable alternative in the presence of contraindications like heparin-induced thrombocytopenia [36,48]. Furthermore, unfractionated heparin can be reversed using protamine sulphate in order to reduce bleeding complications. This has been adopted from its use in cardiac surgery and is supported by low-level evidence [49–51]. One retrospective study (n=873) reported that heparin reversal by protamine administration resulted in significantly lower rates of life-threatening and major bleeding complications compared with patients without heparin reversal. No signs of a prothrombotic effect were observed [49]. More recent, the PS TAVI trial, a small single-centre randomized clinical trial (n=100) reported a non-significant but substantial reduction in major or life-threatening bleeding with protamine versus placebo [50]. The numerous limitations of both studies warrant larger trials, since protamine can cause allergic reactions including anaphylaxis, hypotension, bronchospasm and skin reactions in 1-10% of patients [52]. Moreover, at higher doses, protamine may have significant anticoagulant and antiplatelet side effects [53]. The results of the 'Effect of routine versus selective protamine administration on bleeding in patients undergoing transcatheter aortic valve implantation' trial (ACTRN12621001261808) will provide more evidence on this topic.

4. Postprocedural antithrombotic therapy

4.1. In the absence of an indication for oral anticoagulation

After TAVI, lifelong SAPT is recommended in patients with no indication for OAC (Fig. 1) [2]. This is distilled from several large randomized trials which investigated different antithrombotic strategies

	No indication for OAC	Indication for OAC
No recent PCI	Single Antiplatelet Therapy (Aspirin or P2Y12-inhibitor)	OAC monotherapy (NOAC or VKA)
Recent PCI	1-6 months Dual Antiplatelet Therapy (Aspirin + P2Y12-inhibitor) followed by Single Antiplatelet Therapy (Aspirin or P2Y12-inhibitor)	1-6 months Dual Antithrombotic Therapy (P2Y12-inhibitor + OAC) followed by OAC monotherapy (NOAC or VKA)

Fig. 1. Preferred antithrombotic regimen according to the clinical setting
VKA= vitamin-K antagonist, NOAC= non-vitamin-K antagonist oral anticoagulants, OAC=oral anticoagulation, PCI=percutaneous coronary intervention.

after TAVI (Table 1). In the GALILEO trial (n=1644), patients were randomized after TAVI to low-dose rivaroxaban plus aspirin for three months, followed by rivaroxaban alone; versus aspirin plus clopidogrel for 3 months, followed by aspirin alone. The trial was prematurely terminated, because the rivaroxaban-based strategy was associated with a higher risk of death or thromboembolic events and a higher risk of bleeding than the antiplatelet-based strategy [8]. Notably, a significant reduction in subclinical leaflet thrombosis was observed in the rivaroxaban group [54]. In stratum 2 of the ATLANTIS trial (n = 1049), patients were randomized after TAVI to full-dose apixaban monotherapy versus standard care antiplatelet therapy (majority DAPT) [55]. Apixaban monotherapy was not superior to antiplatelet therapy in terms of net clinical benefit (mortality, thromboembolic and bleeding events) [56]. Although subclinical leaflet thrombosis was lower with apixaban compared with antiplatelet therapy, this did not lead to an improvement in clinical outcomes [56,57]. In fact, in line with the results of GALILEO (8), more non-cardiovascular deaths occurred in the apixaban group as compared to the antiplatelet group [51]. In contrary to GALILEO and ATLANTIS, cohort A of the POPular TAVI trial (n=690) investigated a deescalated antithrombotic strategy and randomized patients to aspirin monotherapy versus three months of aspirin plus clopidogrel, followed by aspirin alone [10,58]. Significantly lower rates of bleeding were observed in the aspirin alone group without an increase in thromboembolic events [10]. Meta-analyses have substantiated this finding [59–61]. Based on these studies (Table 1), clinical practice has shifted from DAPT in the first 3–6 months after TAVI to lifelong SAPT in patients without coexisting conditions necessitating OAC or DAPT [2,36].

4.2. In the presence of an indication for oral anticoagulation

In patients with an indication for OAC, OAC monotherapy is recommended after TAVI (Fig. 1) [2,36]. This is supported by the results of cohort B of the POPular TAVI trial (n=326), which randomized patients with a long-term indication for OAC to OAC alone versus OAC plus three months clopidogrel, followed by OAC alone (Table 1) [9,58]. In line with the results of cohort A, significantly lower rates of bleeding were observed in the OAC alone group without an increase in thromboembolic events [9]. Whether vitamin-K antagonist (VKA) or non-vitamin-K antagonist oral anticoagulants (NOAC) are preferred after TAVI is still unclear. Observational studies are contradictory on this topic [62–64]. In stratum 1 of the ATLANTIS trial (n=451), patients with an indication for OAC were randomized to apixaban versus VKA [55,56]. Similar rates of mortality, thromboembolic and bleeding events were observed between the study groups, consequently the trial failed its primary hypothesis of superiority of apixaban over VKA [56]. However, since the number of OAC patients was too small to provide sufficient evidence for this hypothesis, definitive conclusions on the safety and efficacy of apixaban as compared to VKA cannot be drawn from this trial. The ENVISAGE-TAVI AF trial (n = 1426), randomized patients to edoxaban versus VKA [65,66]. Similar rates of the primary composite outcome including mortality, thromboembolic and major bleeding events occurred between the trial arms and non-inferiority of edoxaban as compared to VKA was proven. Nevertheless, major bleeding was significantly higher in the edoxaban group, mainly due to an increase in gastro-intestinal bleeding [66]. This was not observed in patients who

Table 1

Overview of randomized clinical trials investigating the effect of different antithrombotic strategies after TAVI on clinical endpoints.

Study	Year	N	Comparison	Main endpoints	Main results
Randomized clinical trials including patients without an indication for oral anticoagulation:					
Ussia et al. [86]	2011	79	SAPT (aspirin) vs. 3 months DAPT (aspirin + clopidogrel) followed by SAPT	Composite of all-cause mortality, MI, major stroke, or life-threatening bleeding or urgent conversion to surgery at 6 months.	No significant difference in the primary composite endpoint (15% vs 18% respectively, p=0.85)
SAT-TAVI [87]	2014	120	SAPT (aspirin) vs. 6 months DAPT (aspirin + clopidogrel or ticlopidine)	All-cause mortality, major vascular complications, life-threatening or disabling bleeding, acute kidney injury stage 3, major stroke, MI, repeat procedure or valve related dysfunction according to VARC-2 at 30 days.	No significant differences in VARC-2 endpoints, except more vascular complications in the DAPT compared to SAPT group (13.3% vs 5%, p<0.05)
ARTE [88]	2017	222	SAPT (aspirin) vs. 3 months DAPT (aspirin + clopidogrel)	Primary composite of all-cause mortality, MI, stroke or TIA, or major or life-threatening bleeding according to VARC-2 at 3 months.	The primary composite endpoint was numerically higher in the DAPT group (15.3% vs. 7.2%, p=0.065). DAPT was associated with a higher rate of major or life-threatening bleeding (10.8% vs. 3.6%; p=0.038). There were no differences in the occurrence of death, MI, stroke or TIA.
GALILEO [8]	2020	1644	3 months rivaroxaban 10mg + SAPT (aspirin) followed by rivaroxaban 10 mg vs. 3 months DAPT (aspirin + clopidogrel) followed by SAPT	Composite of all-cause death or thromboembolic events and the composite of life-threatening, disabling or major bleeding according to VARC-2 after a median of 17 months	Higher rate of all-cause death or thromboembolic events (9.8 vs. 7.2 per 100 person-years, HR 1.35, p=0.04) and bleeding (4.3 vs. 2.8 per 100 person-years, HR 1.5, p=0.08) in the rivaroxaban group.
POPular TAVI [10] (cohort A)	2020	665	SAPT (aspirin) vs. 3 months DAPT (aspirin + clopidogrel) followed by SAPT	All bleeding, non-procedure-related bleeding, the composite of cardiovascular mortality, non-procedural bleeding, stroke, or MI and the composite of cardiovascular mortality, ischaemic stroke, or MI at one year.	Lower risk of all bleeding (15.1% vs. 26.6%, RR 0.57, p=0.001), non-procedure-related bleeding (15.1% vs 24.9%, RR 0.61, P=0.005), and the composite of cardiovascular mortality, non-procedural bleeding, stroke, or MI (23.0% vs. 31.1%, RD -8.2, p=0.04) in the SAPT group. No difference in the composite of cardiovascular mortality, ischaemic stroke, or MI.
ATLANTIS [56] (stratum 2)	2021	1049	Apixaban monotherapy vs. standard of care antiplatelet therapy (majority DAPT)	Efficacy outcome: death, MI, stroke, intracardiac or valve thrombosis, systemic emboli, deep vein thrombosis or pulmonary embolism. Safety outcome: life-threatening, disabling or major VARC-2 bleeding at one year.	No significant difference in the efficacy outcome (16.9% vs. 19.3%, HR 0.88, 95% CI 0.66-1.17) and the safety outcome (7.8% vs. 7.3%, HR 1.09, 95% CI 0.69-1.69) between the study groups. Higher risk of non-cardiovascular mortality (2.66% vs. 0.96%) in the apixaban group.
Randomized clinical trials including patients with an indication for oral anticoagulation:					
POPular TAVI [9] (cohort B)	2020	313	OAC monotherapy vs. OAC + 3 months SAPT (clopidogrel) followed by OAC alone	All bleeding, non-procedure-related bleeding, the composite of cardiovascular mortality, non-procedural bleeding, stroke, or MI and the composite of cardiovascular mortality, ischaemic stroke, or MI at one year.	Lower risk of all bleeding (21.7% vs. 34.6%, RR 0.63, p=0.01), non-procedure-related bleeding (21.7% vs 34.0%, RR 0.64, P=0.02), and the composite of cardiovascular mortality, non-procedural bleeding, stroke, or MI (31.2% vs. 45.5%, RR 0.69, 95% CI for superiority 0.51 to 0.92) in the OAC monotherapy group. No difference in the composite of cardiovascular mortality, ischaemic stroke, or MI.
ATLANTIS [56] (stratum 1)	2021	451	Apixaban vs VKA	Efficacy outcome: death, MI, stroke, intracardiac or valve thrombosis, systemic emboli, deep vein thrombosis or pulmonary embolism. Safety outcome: life-threatening, disabling or major VARC-2 bleeding at one year.	No significant difference in the efficacy outcome (21.9% vs. 21.9%, HR 1.02, 95% CI 0.68-1.51) and the safety outcome (10.3% vs. 11.4%, HR 0.92, 95% CI 0.52-1.60) between the study groups.
ENVISAGE-TAVI AF [66]	2021	1426	Edoxaban vs VKA	Efficacy outcome: composite of all-cause death, MI, ischaemic stroke, systemic thromboembolism, valve thrombosis, or ISTH major bleeding. Safety outcome: ISTH major bleeding at a median follow-up of 554 vs. 530 days, respectively.	Edoxaban was non-inferior to VKA regarding efficacy outcome (17.3 vs 16.5 per 100 person-years, p=0.01 for non-inferiority). Significantly higher rates of ISTH major bleeding occurred in the edoxaban group (9.7 vs. 7.0 per 100 person-years; hazard ratio, 1.40; 95% CI, 1.03 to 1.91).

CI=Confidence interval, DAPT=Dual antiplatelet therapy, HR=Hazard ratio, ISTH=International Society on Thrombosis and Haemostasis, MI=Myocardial Infarction, RD=Risk difference, RR=Risk ratio, SAPT=Single antiplatelet therapy, TIA=Transient ischaemic attack, VARC=Valve Academic Research Consortium, VKA=Vitamin K antagonist.

met the dose reduction criteria for edoxaban. So, these criteria should be carefully followed, especially in patients with renal insufficiency. Patients with severe renal insufficiency should be switched to VKA to avoid accumulation and bleeding [30,67]. For clinical practice the results of the ENVISAGE-TAVI AF trial are reassuring with respect to the efficacy of NOACs after TAVI, but do not support proactive postprocedural switching of VKA to NOAC until more evidence on their safety is available.

4.3. After recent coronary stenting

In patients with coronary stenting before or after TAVI, DAPT is

recommended in the absence of an indication for OAC to prevent stent thrombosis. The duration of DAPT depends on the indication, being either chronic (CCS) or acute coronary syndrome (ACS), and the bleeding risk of the individual patient. Since TAVI patients are generally at high bleeding risk, as discussed above, the duration of DAPT can be 1-3 months for CCS and 3-6 months for ACS in most cases [36,37]. Accordingly, in patients with an indication for OAC, dual antithrombotic therapy (DAT; i.e. P₂Y₁₂ inhibitor plus OAC) is recommended for the same duration [36,37]. Of note, these recommendations are based primarily on studies in patients with coronary artery disease only, because direct evidence in patients undergoing percutaneous coronary intervention before or after TAVI is scarce.

4.4. In patients with (subclinical) valve thrombosis

The incidence of obstructive valve thrombosis, recently defined as clinically significant valve thrombosis [68], varies between 1-3% after TAVI [15,69]. Remarkably, an incidence of 7.6% has been reported in patients after valve-in-valve TAVI, which represents an important risk factor [70]. Obstructive valve thrombosis may lead to symptoms of heart failure or presents as a source of thromboembolism [71]. Therefore, treatment with OAC using a VKA and/or unfractionated heparin is recommended [2].

Subclinical valve thrombosis is more frequent and has been reported in up to 32% of the patients undergoing computed tomography (CT) early after TAVI [54,57,71–74]. This predominantly involves the leaflet (s) of the bioprosthetic valve, without apparent clinical symptoms and is often referred to as subclinical leaflet thrombosis (SCLT) [71]. SCLT seems associated with an increased rate of thromboembolic events, however this association is inconsistent and possibly biased [54,57, 71–82]. Due to the dynamic nature of SCLT - it can occur early or later after TAVI and may resolve spontaneously - it is hard to establish a true causal relationship with the occurrence of thromboembolic events [73]. Furthermore, SCLT may also affect valve durability based on thrombus calcification leading to bioprosthetic valve degeneration [83–85]. However, this link is largely unexplored and even more challenging to investigate. Given the limited evidence of clinically relevant consequences, there is currently no consensus that routine four-dimensional CT screening should be used for diagnosis of SCLT. Although OAC has been proven more effective than antiplatelet therapy in the prevention and treatment of SCLT (see also section *Postprocedural Antithrombotic Therapy - In the absence of an indication for oral anticoagulation*), it is uncertain whether this also translates into improved clinical outcomes. Taking into account the associated risks of OAC exposure in the current frail TAVI population, this warrants further investigation. Meanwhile, recent ESC guidelines state that anticoagulation should be considered in patients with leaflet thickening and reduced leaflet motion leading to elevated gradients, at least until resolution [2].

5. Conclusions

The management of antithrombotic therapy after TAVI has evolved from rather intensive, expert opinion-based strategies, towards a deescalated, evidence-based approach. This new paradigm in which reduced antithrombotic intensity leads to improved patient safety, without a loss of efficacy, may be particularly suitable for elderly and fragile patients. Whether this holds in upcoming populations of younger and lower-risk patients and in specific populations as patients with subclinical valve thrombosis, is yet to be proven. Finally, whether a less intensive or alternative approaches should be also applied for the periprocedural management of the antithrombotic therapy, has to be determined by ongoing and future studies.

Declaration of Competing Interest

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

References

- [1] Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology, 143. *Circulation: American Heart Association Joint Committee on Clinical Practice Guidelines*; 2021. Feb 2.
- [2] Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2022;43(7):561–632. Feb 12.

- [3] Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374(17):1609–20. Apr 28.
- [4] Reardon MJ, van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;376(14):1321–31. Apr 6.
- [5] 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. May 2.
- [6] 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. May 2.
- [7] van Ginkel DJ, Brouwer J, van Hemert ND, Kraaijeveld AO, Rensing BJWM, Swaans MJ, et al. Major threats to early safety after transcatheter aortic valve implantation in a contemporary cohort of real-world patients. *Neth Heart J* 2021; 29(12):632–42. Dec 1.
- [8] Dangas GD, Tijssen JGP, Wöhrle J, Søndergaard L, Gilard M, Möllmann H, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med* 2020;382(2):120–9. Jan 9.
- [9] Nijenhuis VJ, Brouwer J, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, et al. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med* 2020;382(18):1696–707. Apr 30.
- [10] 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. Oct 8.
- [11] Patel PA, Patel S, Feinman JW, Gutsche JT, Vallabhajosyula P, Shah R, et al. Stroke after transcatheter aortic valve replacement: incidence, definitions, etiologies and management options. *J Cardiothorac Vasc Anesth* 2018;32(2):968–81. Apr.
- [12] Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363(17):1597–607. Oct 21.
- [13] Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364(23):2187–98. Jun 9.
- [14] Thyregod HGH, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petrusson P, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis. *J Am Coll Cardiol* 2015;65(20):2184–94. May.
- [15] Jose J, Sulimov DS, El-Mawardi M, Sato T, Allali A, Holy EW, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2017;10(7):686–97. Apr.
- [16] Vlastra W, Jimenez-Quevedo P, Tchéhécé D, Chandrasekhar J, de Brito FS, Barbanti M, et al. Predictors, incidence, and outcomes of patients undergoing transfemoral transcatheter aortic valve implantation complicated by stroke, 12. *Circulation: Cardiovascular Interventions*; 2019. Mar.
- [17] Greco A, Capodanno D. Anticoagulation after transcatheter aortic valve implantation: current status. *Interventional Cardiology Review*; 2020. p. 15. Apr 23.
- [18] van Mieghem NM, el Faquir N, Rahhab Z, Rodríguez-Olivares R, Wilschut J, Ouhlous M, et al. Incidence and predictors of debris embolizing to the brain during transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2015;8(5): 718–24. Apr.
- [19] Seeger J, Virmani R, Romero M, Gonska B, Rottbauer W, Wöhrle J. Significant differences in debris captured by the sentinel dual-filter cerebral embolic protection during transcatheter aortic valve replacement among different valve types. *JACC Cardiovasc Interv* 2018;11(17):1683–93. Sep.
- [20] Sannino A, Gargiulo G, Schiattarella GG, Perrino C, Stabile E, Losi MA, et al. A meta-analysis of the impact of pre-existing and new-onset atrial fibrillation on clinical outcomes in patients undergoing transcatheter aortic valve implantation. *EuroIntervention* 2016;12(8):e1047–56. Oct.
- [21] Vranckx P, Windecker S, Welsh RC, Valgimigli M, Mehran R, Dangas G. Thromboembolic prevention after transcatheter aortic valve implantation. *Eur Heart J* 2017; 38(45):3341–50. Dec 1.
- [22] Midha PA, Raghav V, Sharma R, Condado JF, Okafor IU, Rami T, et al. The fluid mechanics of transcatheter heart valve leaflet thrombosis in the neosinus. *Circulation* 2017;136(17):1598–609. Oct 24.
- [23] Mangieri A, Montalto C, Poletti E, Sticchi A, Crimi G, Giannini F, et al. Thrombotic versus bleeding risk after transcatheter aortic valve replacement. *J Am Coll Cardiol* 2019;74(16):2088–101. Oct.
- [24] Fumagalli S, Pelagalli G, Montorzi RF, Marozzi I, Migliorini M, D'Andrea MF, et al. The CHA2DS2-VASc score and geriatric multidimensional assessment tools in elderly patients with persistent atrial fibrillation undergoing electrical cardioversion. A link with arrhythmia relapse? *Eur J Intern Med* 2020;82:56–61. <https://linkinghub.elsevier.com/retrieve/pii/S0953620520302934>.
- [25] Koizia L, Khan S, Frame A, Mikhail GW, Sen S, Ruparelia N, et al. Use of the reported Edmonton frail scale in the assessment of patients for transcatheter aortic valve replacement: a possible selection tool in very high-risk patients? *J Geriatr Cardiol [Internet]* 2018;15(6):463–6. <http://www.ncbi.nlm.nih.gov/pubmed/30108620>.
- [26] Piccolo R, Pilgrim T, Franzone A, Valgimigli M, Haynes A, Asami M, et al. Frequency, timing, and impact of access-site and non-access-site bleeding on mortality among patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2017;10(14):1436–46. Jul.
- [27] Zahid S, Ullah W, Khan MU, Abbas S, Ud Din MT, Uddin MF, et al. Trends, predictors, and outcomes of major bleeding after transcatheter aortic valve implantation, from national inpatient sample (2011–2018). *Expert Rev Cardiovasc Ther* 2021;19(6):557–63. Jun 3.

- [28] Sun Y, Liu X, Chen Z, Fan J, Jiang J, He Y, et al. Meta-analysis of predictors of early severe bleeding in patients who underwent transcatheter aortic valve implantation. *Am J Cardiol* 2017;120(4):655–61. Aug.
- [29] Bendayan M, Messas N, Perrault LP, Asgar AW, Lauck S, Kim DH, et al. Frailty and bleeding in older adults undergoing TAVR or SAVR. *JACC Cardiovasc Interv* 2020;13(9):1058–68. May.
- [30] Sgura FA, Arrotti S, Magnavacchi P, Monopoli D, Gabbieri D, Banchelli F, et al. Kidney dysfunction and short term all-cause mortality after transcatheter aortic valve implantation. *Eur J Intern Med* 2020;81:32–7.
- [31] Waduud MA, Giannoudi M, Drozd M, Sucharitkul PPJ, Slater TA, Blackman DJ, et al. Morphometric and traditional frailty assessment in transcatheter aortic valve implantation. *J Cardiovasc Med (Hagerstown)* 2020;21(10):779–86. Oct.
- [32] Mach M, Okutucu S, Kerbel T, Arjomand A, Fatihoglu SG, Werner P, et al. Vascular complications in TAVR: incidence, clinical impact, and management. *J Clin Med* 2021;10(21). Oct 28.
- [33] de Larocheillère H, Puri R, Eikelboom JW, Rodés-Cabau J. Blood disorders in patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2019;12(1):1–11. Jan.
- [34] Vincentelli A, Susen S, le Tourneau T, Six I, Fabre O, Juthier F, et al. Acquired von willebrand syndrome in aortic stenosis. *N Engl J Med* 2003;349(4):343–9. Jul 24.
- [35] Schneider KL, Kastenmüller K, Weckbecker K, Bleckwenn M, Böhme M, Stingl JC. Potential Drug-Drug Interactions in a Cohort of Elderly, Polymedicated Primary Care Patients on Antithrombotic Treatment. *Drugs Aging* 2018;35(6):559–68. Jun 8.
- [36] ten Berg J, Sibbing D, Rocca B, van Belle E, Chevalier B, Collet JP, et al. Management of antithrombotic therapy in patients undergoing transcatheter aortic valve implantation: a consensus document of the ESC working group on thrombosis and the European association of percutaneous cardiovascular interventions (EAPCI), in collaboration with the ESC Council on Valvular Heart Disease. *Eur Heart J* 2021;42(23):2265–9. Jun 14.
- [37] Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J* 2018;39(3):213–60. Jan 14.
- [38] Rodés-Cabau J, Masson JB, Welsh RC, Garcia del Blanco B, Pelletier M, Webb JG, et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve. *JACC Cardiovasc Interv* 2017;10(13):1357–65. Jul.
- [39] Nijenhuis VJ, ten Berg JM, Hengstenberg C, Lefèvre T, Windecker S, Hildick-Smith D, et al. Usefulness of clopidogrel loading in patients who underwent transcatheter aortic valve implantation (from the BRAVO-3 Randomized Trial). *Am J Cardiol* 2019;123(9):1494–500. May.
- [40] Mangner N, Crusius L, Haussig S, Woitek FJ, Kiefer P, Stachel G, et al. Continued versus interrupted oral anticoagulation during transfemoral transcatheter aortic valve implantation and impact of postoperative anticoagulant management on outcome in patients with atrial fibrillation. *Am J Cardiol* 2019;123(7):1134–41. Apr.
- [41] Brinkert M, Mangner N, Moriyama N, Keller LS, Hagemeyer D, Crusius L, et al. Safety and efficacy of transcatheter aortic valve replacement with continuation of vitamin K antagonists or direct oral anticoagulants. *JACC Cardiovasc Interv* 2021;14(2):135–44. Jan.
- [42] D'Ascenzo F, Benedetto U, Bianco M, Conrotto F, Moretti C, D'Onofrio A, et al. Which is the best antiaggregant or anticoagulant therapy after TAVI? A propensity-matched analysis from the ITER registry. The management of DAPT after TAVI. *EuroIntervention* 2017;13(12):e1392–400. Dec.
- [43] Seeger J, Gonska B, Rodewald C, Rottbauer W, Wöhrle J. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement. *JACC Cardiovasc Interv* 2017;10(1):66–74. Jan.
- [44] Geis NA, Kiriakou C, Chorianopoulos E, Uhlmann L, Katus HA, Bekeredjian R. NOAC monotherapy in patients with concomitant indications for oral anticoagulation undergoing transcatheter aortic valve implantation. *Clin Res Cardiol* 2018;107(9):799–806. Sep 11.
- [45] Nijenhuis VJ, Stella PR, Baan J, Brueren BRG, de Jaegere PP, den Heijer P, et al. Antithrombotic therapy in patients undergoing TAVI: an overview of Dutch hospitals. *Neth Heart J* 2014;22(2):64–9. Feb 28.
- [46] Auffret V, Leurent G, le Breton H. Oral anticoagulation continuation throughout TAVR. *JACC Cardiovasc Interv* 2021;14(2):145–8. Jan.
- [47] Dangas GD, Lefèvre T, Kupatt C, Tchetché D, Schäfer U, Dumonteil N, et al. Bivalirudin versus heparin anticoagulation in transcatheter aortic valve replacement. *J Am Coll Cardiol* 2015;66(25):2860–8. Dec.
- [48] Rao Sv. *The Multidimensionality of Cardiovascular Procedures*, Vol. 66. USA: Journal of the American College of Cardiology. Elsevier; 2015. p. 2869–71.
- [49] Al-Kassou B, Kandt J, Lohde L, Shamekhi J, Sedaghat A, Tabata N, et al. Safety and efficacy of protamine administration for prevention of bleeding complications in patients undergoing TAVR. *JACC Cardiovasc Interv* 2020;13(12):1471–80. Jun.
- [50] Zbroński K, Grodecki K, Gozdowska R, Ostrowska E, Wysińska J, Rymuza B, et al. Protamine sulfate during transcatheter aortic valve implantation (PS TAVI) — a single-center, single-blind, randomized placebo-controlled trial. *Kardiol Pol* 2021;79(9):995–1002. Sep 30.
- [51] Zbroński K, Grodecki K, Gozdowska R, Jędrzejczyk S, Ostrowska E, Wysińska J, et al. Use of protamine sulfate during transfemoral transcatheter aortic valve implantation – a preliminary assessment of administration rate and impact on complications. *Adv Interv Cardiol* 2020;16(3):306–14.
- [52] Makris M, van Veen JJ, Tait CR, Mumford AD, Laffan M. Guideline on the management of bleeding in patients on antithrombotic agents. *Br J Haematol* 2013;160(1):35–46. Jan.
- [53] Boer C, Meesters MI, Veerhoek D, Vonk ABA. Anticoagulant and side-effects of protamine in cardiac surgery: a narrative review. *Br J Anaesth* 2018;120(5):914–27. May.
- [54] 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. Jan 9.
- [55] Collet JP, Berti S, Cequier A, van Belle E, Lefevre T, Leprince P, et al. Oral anti-Xa anticoagulation after trans-aortic valve implantation for aortic stenosis: The randomized ATLANTIS trial. *Am Heart J* 2018;200:44–50. Jun.
- [56] Collet JP. Anti-thrombotic strategy to lower all cardiovascular and neurologic ischemic and hemorrhagic events after trans-aortic valve implantation for aortic stenosis : a randomized, open-label. phase 3 trial. Presented online at ACC congress; 2021.
- [57] Montalescot G. Apixaban and valve thrombosis after transcatheter aortic valve implantation: The ATLANTIS-4D-CT substudy. Presented online at ACC congress; 2021.
- [58] Nijenhuis VJ, Bennaghmouch N, Hassell M, Baan J, van Kuijk JP, Agostoni P, et al. Rationale and design of POPular-TAVI: antiPlatelet therapy fOr Patients undergoing Transcatheter Aortic Valve Implantation. *Am Heart J* 2016;173:77–85. Mar.
- [59] Brouwer J, Nijenhuis VJ, Rodés-Cabau J, Stabile E, Barbanti M, Costa G, et al. Aspirin alone versus dual antiplatelet therapy after transcatheter aortic valve implantation: a systematic review and patient-level meta-analysis. *J Am Heart Assoc* 2021;10(8). Apr 20.
- [60] Kuno T, Yokoyama Y, Briasoulis A, Mori M, Iwagami M, Ando T, et al. Duration of antiplatelet therapy following transcatheter aortic valve replacement: systematic review and network meta-analysis. *J Am Heart Assoc* 2021;10(9). May 4.
- [61] Zhang Y, Shen L, Yang W, He B. Dual Antiplatelet Therapy vs. single antiplatelet therapy after transcatheter aortic valve replacement: an updated systematic review and meta-analysis. *8. Frontiers in Cardiovascular Medicine*; 2021. Jun 21.
- [62] Jochheim D, Barbanti M, Capretti G, Stefanini GG, Hapfelmeier A, Zadrozny M, et al. Oral anticoagulant type and outcomes after transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2019;12(16):1566–76. Aug.
- [63] Butt JH, de Backer O, Olesen JB, Gerdts TA, Havers-Borgersen E, Gislason GH, et al. Vitamin K antagonists vs. direct oral anticoagulants after transcatheter aortic valve implantation in atrial fibrillation. *Eur Heart J Cardiovasc Pharmacother*. 2021;7(1):11–9. Jan 16.
- [64] 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 Cardiovasc Interv* 2020;13(22):2587–97. Nov.
- [65] van Mieghem NM, Unverdorben M, Valgimigli M, Mehran R, Boersma E, Baber U, et al. Edoxaban Versus standard of care and their effects on clinical outcomes in patients having undergone Transcatheter Aortic Valve Implantation in Atrial Fibrillation—Rationale and design of the ENVISAGE-TAVI AF trial. *Am Heart J* 2018;205:63–9. Nov.
- [66] van Mieghem NM, Unverdorben M, Hengstenberg C, Möllmann H, Mehran R, López-Otero D, et al. Edoxaban versus Vitamin K Antagonist for Atrial Fibrillation after TAVR. *N Engl J Med* 2021;385(23):2150–60. Dec 2.
- [67] Lutz J, Jurk K, Schinzel H. Direct oral anticoagulants in patients with chronic kidney disease: patient selection and special considerations. *Int J Nephrol Renovasc Dis* 2017;10:135–43. Jun;Volume.
- [68] Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, et al. Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. *Eur Heart J* 2021;42(19):1825–57. May 14.
- [69] 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). Apr.
- [70] Abdel-Wahab M, Simonato M, Latib A, Galeski PJ, Allali A, Kaur J, et al. Clinical valve thrombosis after transcatheter aortic valve-in-valve implantation. *Circ Cardiovasc Interv* 2018;11(11). Nov.
- [71] 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?, 6. *Frontiers in Cardiovascular Medicine*; 2019. Apr 18.
- [72] 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. Jan 9.
- [73] Makkar RR, Blanke P, Leipsic J, Thourani V, Chakravarty T, Brown D, et al. Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves. *J Am Coll Cardiol* 2020;75(24):3003–15. Jun.
- [74] Blanke P, Leipsic JA, Popma JJ, Yakubov SJ, Deeb GM, Gada H, et al. Bioprosthetic aortic valve leaflet thickening in the evolutive low risk sub-study. *J Am Coll Cardiol* 2020;75(19):2430–42. May.
- [75] 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. Sep 1.
- [76] Rashid H, Gooley R, Nerlekar N, Ihdayhid A, McCormick L, 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* 2018;13(15):e1748–55. Feb.
- [77] Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofeod KF, de Backer O, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med* 2015;373(21):2015–24. Nov 19.

- [78] Hansson NC, Grove EL, Andersen HR, Leipsic J, Mathiassen ON, Jensen JM, et al. Transcatheter aortic valve thrombosis. *J Am Coll Cardiol* 2016;68(19):2059–69. Nov.
- [79] 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* 2016;37(28):2263–71. Jul 21.
- [80] 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. Apr 21.
- [81] 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 North Am Ed* 2017;389(10087):2383–92. Jun.
- [82] 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. Jan.
- [83] Doris MK, Dweck MR. Is bioprosthetic leaflet thrombosis a trigger to valve degeneration?, 104. *Heart*; 2018. p. 792–3. May.
- [84] 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, 91. *Catheterization and Cardiovascular Interventions*; 2018. p. 947–55. Apr 12.
- [85] Yahagi K, Ladich E, Kutys R, Mori H, Svensson LG, Mack MJ, et al. Pathology of balloon-expandable transcatheter aortic valves, 90. *Catheterization and Cardiovascular Interventions*; 2017. p. 1048–57. Nov 15.
- [86] Ussia GP, Scarabelli M, Mulè M, Barbanti M, Sarkar K, Cammalleri V, et al. Dual antiplatelet therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation. *Am J Cardiol* 2011;108(12):1772–6. Dec.
- [87] Stabile E, Pucciarelli A, Cota L, Sorropago G, Tesorio T, Salemm L, et al. SAT-TAVI (single antiplatelet therapy for TAVI) study: a pilot randomized study comparing double to single antiplatelet therapy for transcatheter aortic valve implantation. *Int J Cardiol* 2014;174(3):624–7. Jul.
- [88] Rodés-Cabau J, Masson JB, Welsh RC, Garcia del Blanco B, Pelletier M, Webb JG, et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve. *JACC Cardiovasc Interv* 2017;10(13):1357–65. Jul.