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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Bleeding Events After Transcatheter Aortic Valve Replacement

JACC State-of-the-Art Review

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ABSTRACT

Transcatheter aortic valve replacement (TAVR) has gained over time a major reduction in procedural complications. Despite this, clinically relevant bleeding still occurs in a non-negligible proportion of patients and adversely affects prognosis. Patients with severe aortic stenosis are at heightened risk for spontaneous bleeding due to advanced age and a high comorbidity burden. Also, procedural factors and antithrombotic management contribute to define individual bleeding susceptibility. Bleeding prevention represents an emerging area for improving patient care. Because of the tight hemorrhagic/ischemic balance, a tailored approach based on individual bleeding-risk profile, such as a less invasive antithrombotic regimen or appropriate diagnostic preprocedural evaluation, should be pursued to avoid bleeding events. This review aims to provide an in-depth overview of bleeding events in the TAVR field, including definitions, timing and the extent of risk, and clinical impact, as well as updates on antithrombotic management and its potential influence on bleeding complications. (J Am Coll Cardiol 2023;81:684–702) © 2023 by the American College of Cardiology Foundation.

Transcatheter aortic valve replacement (TAVR) has led to a paradigm shift in the treatment of severe aortic stenosis, being a breakthrough treatment across the entire spectrum of surgical risk.[1,2] Advances in patient selection, device features, and procedural refinements have driven improvement in safety and reduction of procedural complications, explaining the TAVR-related survival benefit proved over time.[3-10] However, procedural complications with a detrimental impact on short- and long-term outcomes are still observed in a non-negligible proportion of patients.

Despite TAVR having been historically associated with lower rates of hemorrhagic events than conventional surgery, bleeding events in the context of TAVR have also been associated with poorer outcomes.[11] The complex balance between bleeding and thrombotic risks is strengthened in the TAVR setting as compared with other percutaneous interventions.[12] In fact, the 30-day rate of major and life-threatening bleeding ranged broadly between 2.4% and 41.7% in pivotal clinical trials, whereas the 30-day rate of major or disabling stroke ranged between 0% and 5%.[3-10]

Interestingly, the inclusion of major bleeding as part of the primary outcome in the recent largescale randomized clinical trials emphasizes the need to appropriately capture and report these complications. This review aims to provide an in-depth overview of bleeding events in the TAVR field, including definitions, timing and the extent of risk, and clinical impact, as well as updates on antithrombotic

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HIGHLIGHTS

- Despite improvement in outcomes, hemorrhagic complications of TAVR remain frequent and still have an important potential adverse impact.
- Preventive strategies are needed to reduce bleeding events and enhance the safety of TAVR procedures.
- Ongoing trials evaluating antithrombotic strategies after TAVR will refine postprocedural protocols to improve outcomes.

management and its potential influence on bleeding complications.

TAVR-RELATED BLEEDING EVENTS: COMMON ADOPTED CLASSIFICATIONS AND CHANGE OF INCIDENCE OVER TIME

Bleeding risk derives from a combination of procedural factors, medical treatment, and patient characteristics and comorbidities. In the TAVR setting, its definition is extremely heterogeneous, based on the time of occurrence (early, late), severity (type 1 to type 4, as per Valve Academic Research Consortium [VARC]-3 criteria), site (access-site, non-access-site), and source (overt, nonovert).

According to the time of occurrence, bleeding is commonly classified as early (within 30 days after TAVR) and late (after 30 days post-TAVR). Beyond the temporal patterns, these entities entail distinct underlying causes. Whereas early events are mainly related to periprocedural complications (access site, cardiac structure injuries), late-onset bleeding points to patient's bleeding susceptibility as well as long-term antithrombotic management and mostly correspond to non-access-site bleeding.

Early bleeding is 1 of the most common complications encountered after TAVR. In a meta-analysis including 3,519 patients, the reported rate of 30-day major and life-threatening bleeding was 22.3% and 15.5%, respectively.[13] Besides the periprocedural time frame, late-onset bleeding remains frequent, ranging from 5.9% (median time 132 days) among 2,401 patients in the PARTNER (Placement of Aortic Transcatheter Valve Trial) trial to 24% (median time 3 years) in a European cohort of 926 patients.[14,15]

During the last decade, technical refinements have been achieved in the field of transcatheter aortic valve therapy, overcoming some of the initial procedure-related drawbacks. Increased operator experience, reduction in sheath size (from more than 20-F in the initial TAVR experience up to 14-F in contemporary clinical practice), and widespread adoption of transfemoral access have translated into a progressive reduction in periprocedural bleeding rates. The latter was certainly facilitated also by the inclusion of patients with a lower risk profile. Nonetheless, despite these improvements enabling the expansion of the procedure to younger patients with longer life expectancies, bleeding risk remains relatively high even in low-risk patients, with a reported 1-year bleeding incidence up to 7.7% in the PARTNER 3 trial.[9] Actually, the risk is not diluted over time, and different factors delineate the lengthening of late bleeding, primarily nonaccess events. The incidence of major, life-threatening bleeding and major vascular complications in pivotal trials is reported in Figure 1.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
BARC = Bleeding Academic Research Consortium
DAPT = dual antiplatelet therapy
DOAC = direct oral anticoagulant
OAC = oral anticoagulation
PCI = percutaneous coronary intervention
PVL = paravalvular leak
SAPT = single antiplatelet therapy
TAVR = transcatheter aortic valve replacement
UFH = unfractionated heparin
VARC = Valve Academic Research Consortium
VKA = vitamin K antagonist
vWF = von Willebrand factor

UPDATES ON VARC-3 CRITERIA BLEEDING DEFINITION.

The VARC group has recently proposed updated standardized consensus definitions for relevant clinical endpoints in TAVR, providing an in-depth overview of procedural and long-term outcomes.[16] Bleeding definition has moved from a general grading of severity to a more descriptive classification scheme. Based on the Bleeding Academic Research Consortium (BARC) classification,[17] the prior VARC-2 consensus document classified bleeding as minor, major, and life-threatening or disabling.[18] The updated VARC-3, in a comprehensive fashion, characterizes bleeding severity as type 1 (minor: type BARC 2 and 3a), type 2 (major: type BARC 3a), type 3 (life-threatening: type BARC 3b, 3c, and 4), and type 4 (leading to death, either probable or definite: type BARC 5).[16] A summary of changes in VARC-3 bleeding definitions as compared with previous criteria is shown in Table 1.

VARC-3 document also defines "overt" bleeding as any event with a clinically obvious source or with a source identified after appropriate clinical and/or imaging testing. Notwithstanding, bleeding source could be indeterminate. A significant proportion of patients (≈14%) exhibit notable hemoglobin drops despite having no obvious source of bleeding after the procedure.[19] Hidden bleedings might be related to spontaneous "blood oozing," a clinically silent capillary hemorrhage (usually genitourinary or gastrointestinal) not directly related to the procedure.[20] This represents a potentially life-threatening complication due to lack of diagnosis and treatment, and should be

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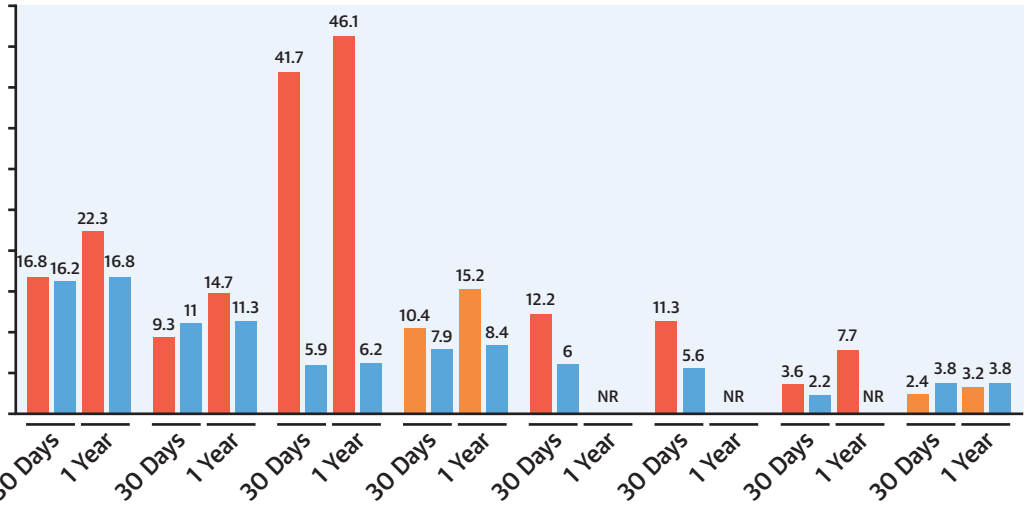
FEBRUARY 21, 2023:684–702

FIGURE 1 **Serious Bleeding and Major Vascular Complications in Pivotal Clinical Trials**



Age, Mean	83.1	83.6	83	81.5	80	79	73	74
STS Score, Mean (%)	11.2	11.8	7.3	5.8	4.4	2.9	1.9	1.9
Transfemoral Access, (%)	100	70.1	82.8	73.7	93.6	96.6	100	99
Sheath Size, F	22,24	22,24	18	16-20	18	18	14,16	14-18

Major, Life Threatening, or Disabling Bleeding
Life Threatening, or Disabling Bleeding
Major Vascular Complications

(Top) 30-day and 1-year rates of serious bleeding and major vascular complications in pivotal trials with balloon-expandable valves (PARTNER 1A, 1B, 2, and 3) and self-expanding valves (US CoreValve, SURTAVI, and Evolut Low Risk) across the entire spectrum of surgical risk. **(Bottom)** Key clinical (age, STS score) and technical features (% of transfemoral access, device sheath size) defying patient's and procedural risk. Serious bleeding refers to major, life-threatening, or disabling bleeding events. Rates of reported events are expressed in %. NOTION = Nordic Aortic Valve Intervention Trial; NR = not reported; PARTNER = Placement of Aortic Transcatheter Valve; STS = Society of Thoracic Surgeons; SURTAVI = Surgical Replacement and Transcatheter Aortic Valve Implantation.

suspected in case of unexplained and persistent new-onset anemia after TAVR. Furthermore, given the well-recognized adverse prognostic implications of blood transfusions[21] and to better reflect the severity and acuity of hemorrhagic events, indication, number of transfusions, and time to the index procedure should be reported, even if not associated with overt bleeding.

So far, VARC-3 bleeding endpoint definitions have not been validated in a real-world TAVR population, representing an emerging need. To evaluate the impact of bleeding according to the update definition on clinical outcomes and compare its predictive power with other established bleeding definitions would be interesting and deserves further investigations.

CLINICAL IMPACT: IS ALL THE BLEEDING THE SAME?

Bleeding events remain a significant source of morbidity and mortality. Their prognostic impact is related to severity. Multiple studies have demonstrated the negative clinical association of major and life-threatening bleeding post-TAVR with a significant increase in the risk of early and late mortality. Beyond the periprocedural period, the longitudinal detrimental effect of bleeding stands remarkable. As reported by Généreux et al,[14] late-onset bleeding is associated with a 4-fold increase in overall mortality at 1 year (HR: 3.91; 95% CI: 2.67-5.71; $P < 0.001$). In a recent report, major late bleeding events were

TABLE 1 Changes in the VARC-3 Bleeding Definition as Compared With Previous Criteria (VARC-2)

VARC-3				VARC-2			
	Type 1	Overt bleeding that does not require surgical or percutaneous intervention, but does require medical intervention, leading to hospitalization, an increased level of care, or medical evaluation	*BARC 2*	*BARC 2* *BARC 3a*	Any bleeding worthy of clinical mention	Minor	
		Overt bleeding that requires a transfusion of 1 U of whole blood/red blood cells	*BARC 3a*				
	Type 2	Overt bleeding that requires a transfusion of 2-4 U of whole blood/red blood cells	*BARC 3a*	*BARC 3a*	Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 U of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery	Major	
		Overt bleeding associated with a hemoglobin drop 3-5 g/dL	*BARC 3a*				
	Type 3	Overt bleeding requiring a transfusion of ≥5 U of whole blood/red blood cells	*BARC 3a*	*BARC 3b*	Overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells transfusion ≥4 U	Life-threatening or disabling	
		Overt bleeding associated with a hemoglobin drop ≥5 g/dL	*BARC 3b*				
		Overt bleeding causing hypovolemic shock or severe hypotension or requiring vasopressors or surgery	*BARC 3b*	*BARC 3b*	Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery		
		Overt bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardial, or intramuscular with compartment syndrome	*BARC 3b* *BARC 3c*	*BARC 3b* *BARC 3c*	Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome		
		Overt bleeding requiring reoperation, surgical exploration, or reintervention for the purpose of controlling bleeding	*BARC 3b* *BARC 4*				
		Post-thoracotomy chest tube output ≥2 L within 24 h	*BARC 4*				
	Type 4	Overt bleeding leading to death Probable: clinical suspicion BARC 5a Definite: confirmed by autopsy or imaging BARC 5b	*BARC 5*	*BARC 5*	Fatal bleeding		

BARC = Bleeding Academic Research Consortium; RBC = red blood cells; VARC = Valve Academic Research Consortium.

associated with an unfavorable impact on overall mortality (HR: 5.6; 95% CI: 3.10-10.31; $P < 0.001$), cardiac mortality (HR: 11.6; 95% CI: 4.59-29.37; $P < 0.001$), as well as transfusion and rehospitalization rates.[22] Among late events, gastrointestinal bleeding is the most common identifiable source of major bleeding (>40%).[14,15,22] Also, considering the gradual shift of TAVR candidates toward lower-risk patients, the prognostic yield of hemorrhagic events could be different in the near future.

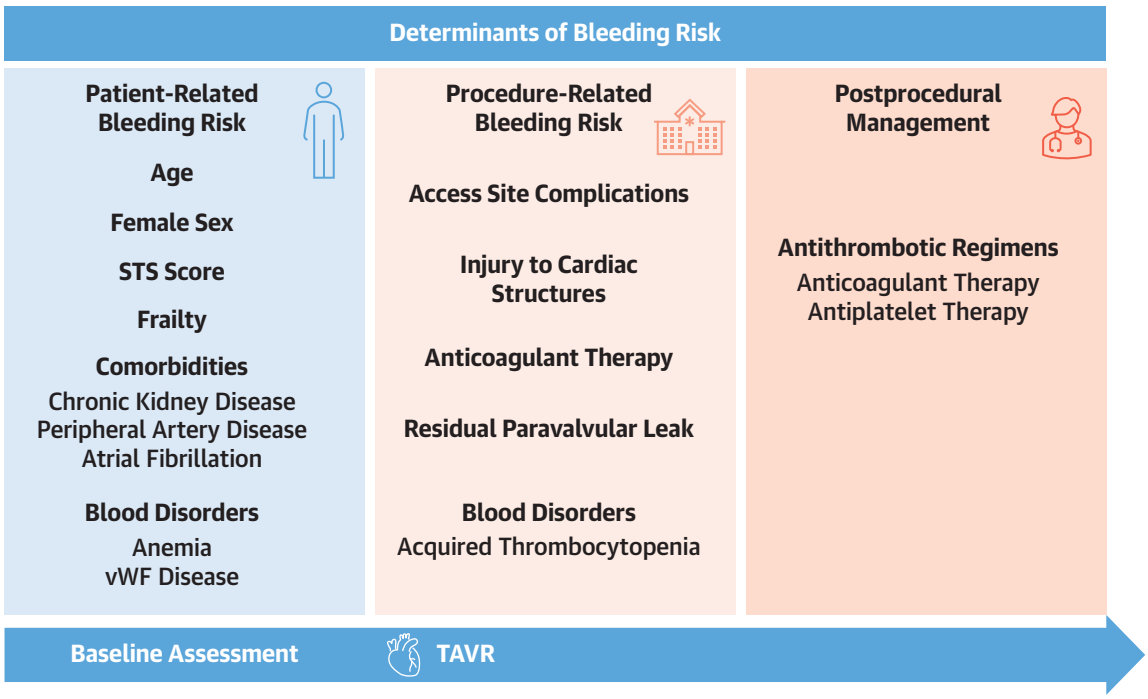
The site of bleeding differentially influences the prognosis in patients undergoing TAVR. Piccolo et al[15] showed that both access-site and non-access-site events are independently associated with an increased risk for mortality up to 5 years, with non-access-site bleeding linked to a significantly greater prognostic impact, resulting in a more than 2.5-fold higher risk of death in a transfemoral cohort (HR: 2.51; 95% CI: 1.84-3.43; $P < 0.001$). As hypothesized, the hazard of non-access-site bleeding is longitudinal and extends over time, highlighting the importance of the intensity and duration of antithrombotic therapy.

Notably, whereas the short-term impact is essentially tied to increased costs and impaired recovery after procedure, late bleeding events adversely impact survival and health status, potentially undermining the TAVR clinical benefit. As pointed out in a large study including 17,672 patients (18.2% TAVR patients), periprocedural bleeding occurring during interventions using large-bore catheters was associated with a more than 2-fold higher in-hospital mortality, longer hospitalization, and higher health care cost.[23] Moreover, life-threatening and major bleeding events have been associated with a decrement in quality of life at 1 year.[24,25] These findings confirm the unavoidable impact on patients' recovery after TAVR. Future efforts should aim to refine device iterations and periprocedural management to yield remarkable clinical benefits and improve the cost-effectiveness of the procedure.

PREDICTION OF BLEEDING EVENTS AFTER TAVR

The results of multiple studies highlight the need for continuous research into the factors that can

FIGURE 2 Determinants of Bleeding Risk in Patients Undergoing TAVR



Bleeding risk derives from a combination of procedural factors, medical treatment, and patient characteristics and comorbidities. Procedural aspects mainly impact early bleeding complications, while patient features, comorbidities, and long-term antithrombotic management usually outline susceptibility to late hemorrhagic events. STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; vWF = von Willebrand factor.

anticipate bleeding occurrence in order to improve risk stratification and allow preventive strategies. In view of this, preprocedural risk of bleeding is usually estimated considering both patient-related and procedure-related factors (Figure 2).

PATIENT-RELATED BLEEDING RISK. Advanced age is a variable with high statistical weight in most bleeding prediction risk scores. Consistently, frailty status, as a reflection of age burden and comorbidities, was found to be an independent predictor of post-procedural major bleeding and transfusions in an analysis from the FRAILTY-AVR (Frailty Assessment Before Cardiac Surgery & Transcatheter Interventions) study.[26]

The higher bleeding rate in women undergoing percutaneous cardiovascular procedures is well recognized. Vlastra et al[27] showed that female sex is associated with a substantially higher risk of early life-threatening or major bleeding after TAVR (6.7% vs 4.4%; $P < 0.01$). Despite early mortality rates being similar between women and men experiencing a bleeding event, the former had a noteworthy trend for higher mortality (20.1% vs 14.4%; $P = 0.09$). Procedural outcomes may have been influenced by different sex-related baseline characteristics, such as lower body mass index, older age, and smaller iliofemoral access with a subsequent larger sheath-to-femoral artery ratio, corroborating the known association between female sex and access-site bleeding.[15,28] Moreover, it has been shown that platelet-mediated bleeding times are higher in women, indicative of reduced platelet function as compared with men.[29]

Renal disease considerably weighs on the bleeding hazard. Patients with chronic kidney disease are at increased risk of major bleeding during index hospitalization (OR: 1.35; 95% CI: 1.27-1.44).[30] The risk for major or life-threatening events persists at 1 year after TAVR (HR: 1.91; 95% CI: 1.05-3.46), with a proven rise for each decrement in estimated glomerular filtration rate.[31] Also, given the risk factors overlap, peripheral artery disease is a frequent comorbidity in patients referred for TAVR. Data from STS/ACC TVT registry (Society of Thoracic Surgeons/American College of Cardiology Transcatheter Therapy Registry) reported a higher incidence of bleeding complication

at 1 year in patients with peripheral disease in both transfemoral and nontransfemoral cohorts.[32] In the PARTNER-1 trial, atrial fibrillation (AF) was identified as predictive of major late bleeding events.[14] In a recent meta-analysis including 158,220 patients, preexisting AF was linked to a higher risk of early bleeding complications after TAVR (OR: 2.06; 95% CI: 1.06-3.98).[33] However, only 1 of the 3 included studies[34] demonstrated a strong association between baseline AF and bleeding events, with the other 2 showing neutral results. Furthermore, patients with AF who experience a major bleeding are at a 2-fold higher risk of death at 1 year as compared with patients without AF. Undoubtedly, the use of long-term anticoagulation may contribute to these findings.

Additionally, hematologic disorders are relatively frequent in TAVR candidates. The prevalence of anemia in TAVR recipients across studies ranges from 45% to 64%, due to a multifactorial mechanism.[19] Chronic anemia may be a marker of frailty in patients with aortic stenosis. A higher comorbidity burden, including advanced age, chronic and inflammatory diseases, iron deficiency, and subclinical diathesis disorders, outlines the increased likelihood of anemia.[19] Baseline anemia correlates with worse outcomes after the procedure, including long-term mortality and increased risk of blood transfusions.[35-37] Likewise, preprocedural anemia has been associated with a longer hospital length and poorer functional status after TAVR.[38]

Aortic stenosis is also associated with acquired type 2A von Willebrand disease, with the shear stress triggered by stenotic valve inducing the cleavage of the von Willebrand factor (vWF). The resulting inactive fragments reduce the hemostasis cascade with a subsequent increasing risk of bleeding complications.[39] As a proof of this hypothesis, several studies showed that the TAVR procedure can resolve vWF defects, normalizing primary hemostasis dysfunction,[40] whereas residual significant paravalvular leak (PVL) negatively influences the normalization of vWF. Persistent increased flow turbulences and the high shear stress forces may promote vWF defects, predisposing patients to bleeding. In line with the previous findings from the PARTNER trial, update insights confirmed PVL as a predictor of late bleeding events.[14] Interestingly, the adenosine diphosphate (CT-ADP) test, as a sensitive marker of vWF defects, has proven to be predictive of residual PVL and 1-year mortality after TAVR.[41] Advocating this hypothesis, both moderate/severe PVL and prolonged CT-ADP (>180 seconds) were identified as strong predictors of late major and life-threatening bleeding events.[22] This finding reinforces the importance of optimizing valve implantation to minimize residual PVL, not only to avoid its detrimental hemodynamic effect, but also to restore a physiologic homeostasis to decrease the risk for subsequent bleeding events. Furthermore, vWF disease when associated with gastrointestinal angiodysplasia and aortic stenosis configures the Heyde's syndrome, reported in up to 6.3% in patients undergoing TAVR and associated with a nonnegligible rate of gastrointestinal bleeding.[42] Although the beneficial effect of surgical replacement was already known, Goltstein et al[42] recently highlighted that TAVR led to a large reduction in gastrointestinal bleedings after the procedure, and the beneficial effect was durable up to 5-year follow-up. The incremental value of vWF is emerging, and more studies are needed to confirm its role as a prognostic hemostatic marker of bleeding complications.

The clinical relevance of hematologic disorders remains high even in the postprocedural setting. Acquired thrombocytopenia is a common finding, carrying an increased risk of bleedings and transfusions.[43] Early platelet drop is usually related to periprocedural adverse events, such as vascular complication, bleeding, and blood transfusions, whereas inflammatory status and platelet activation on the surface of the bioprosthesis are the main determinants suggested as related to delayed nadir in platelet count. After TAVR, a significant proportion of patients exhibit drops in hemoglobin levels despite having no obvious source of bleeding.[20] Postprocedural hemoglobin drop is likely multifactorial. Hemodilution due to postoperative hydration may result in anemia detection without overt bleeding. Also, acute stress (with return of interstitial fluids) and catheter exchanges can lead to changes in volume status and consequent hemoglobin decrement.

Noteworthy, Nuis et al[35] evidenced that the indication of blood transfusion was unrelated to overt bleeding in more than one-half of TAVR patients with anemia. Several studies highlighted the harmful relationship between transfusions and patients' outcomes.[21,35] Blood transfusion was independently associated with increased 30-day mortality risk, regardless of the occurrence of major bleeding and vascular complications.[21] Many approaches could help to reduce the risk of transfusions, such as treating baseline anemia (iron supplement, epoetin), preventing access-site complications, avoiding excessive hemodilution after TAVR, and using a less invasive pharmacologic approach.[44] Moreover, a

TABLE 2 Predictors of Vascular Complications in Transfemoral TAVR Cohorts

First Author (Ref. #)	Predictors	OR/HR for Vascular Complications (95% CI)	*P* Value	HR for Mortality in Patients Who Experienced Vascular Complications (95% CI)	*P* Value
Sherwood[46] N = 34,893	Sex, female	1.97 (1.82-2.13)	<0.001	2.23 (1.80-2.77) 30 d 1.17 (1.05-1.30) 1 y	NR
	Sheath size, >17 F	1.28 (1.16-1.42)	<0.001		
	Peripheral artery disease	1.33 (1.22-1.46)	<0.001		
	BMI	1.11 (1.03-1.20)	0.009		
	Femoral cutdown vs femoral percutaneous access	1.24 (1.09-1.41)	0.001		
Piccolo[15] N = 926	Sex, female	2.59 (1.10-6.13)	0.030	1.33 (0.99-1.79)	0.056
van Wiechen[93] N = 512	Femoral artery diameter, per mm increase	0.81 (0.54-0.99)	0.015	–	–
	Femoral artery puncture height <0 cm, 0-2 cm as reference	3.47 (1.21-10.0)	0.002	–	–
	Femoral artery puncture height >2 cm, 0-2 cm as reference	2.43 (1.16-5.10)	0.002	–	–
Langouet[94] N = 479	Moderate-severe iliofemoral calcification	2.0 (1.29-3.10)	0.002	18.69 (5.7-61.1) 1 y (major vascular complications)	<0.001
	Moderate-severe iliofemoral tortuosity	2.36 (1.48-3.76)	<0.001		
	Sheath-to-iliofemoral artery ratio	6.52 (1.19-21.34)	0.002		
	Iliac morphology score	1.25 (1.08-1.46)	0.003		
van Kesteren[95] N = 400	Sheath-to-iliofemoral artery ratio	7.51 (1.61-34.95)	0.010	–	–
Batchelor[96] N = 303	Vessel tortuosity	3.1 (1.1-9.2)	0.04	–	–
	CAD	8.2 (1.8-37)	0.00	–	–

BMI = body mass index; CAD = coronary artery disease; TAVR = transcatheter aortic replacement.

restrictive threshold (hemoglobin <7-8 g/dL) should likely be implemented, especially in asymptomatic patients. Unlike the cardiac surgery setting, in which a more restrictive strategy was demonstrated to be noninferior to the liberal approach,[45] the optimal use and transfusion threshold in the TAVR context is not well established yet. Further research is needed to elucidate the complex interplay between the use of red blood cells and increased mortality risk, and to determine the safest transfusion strategy in patients with baseline anemia.

Additional preprocedural diagnostic tests (eg, gastroscopy and colonoscopy in patients with lower hemoglobin levels) and changes in medical therapy (eg, a widespread use of proton pump inhibition or a less aggressive antithrombotic strategy) in patients with a greater bleeding propensity should be carried out to reduce bleeding risks and improve long-term outcomes.

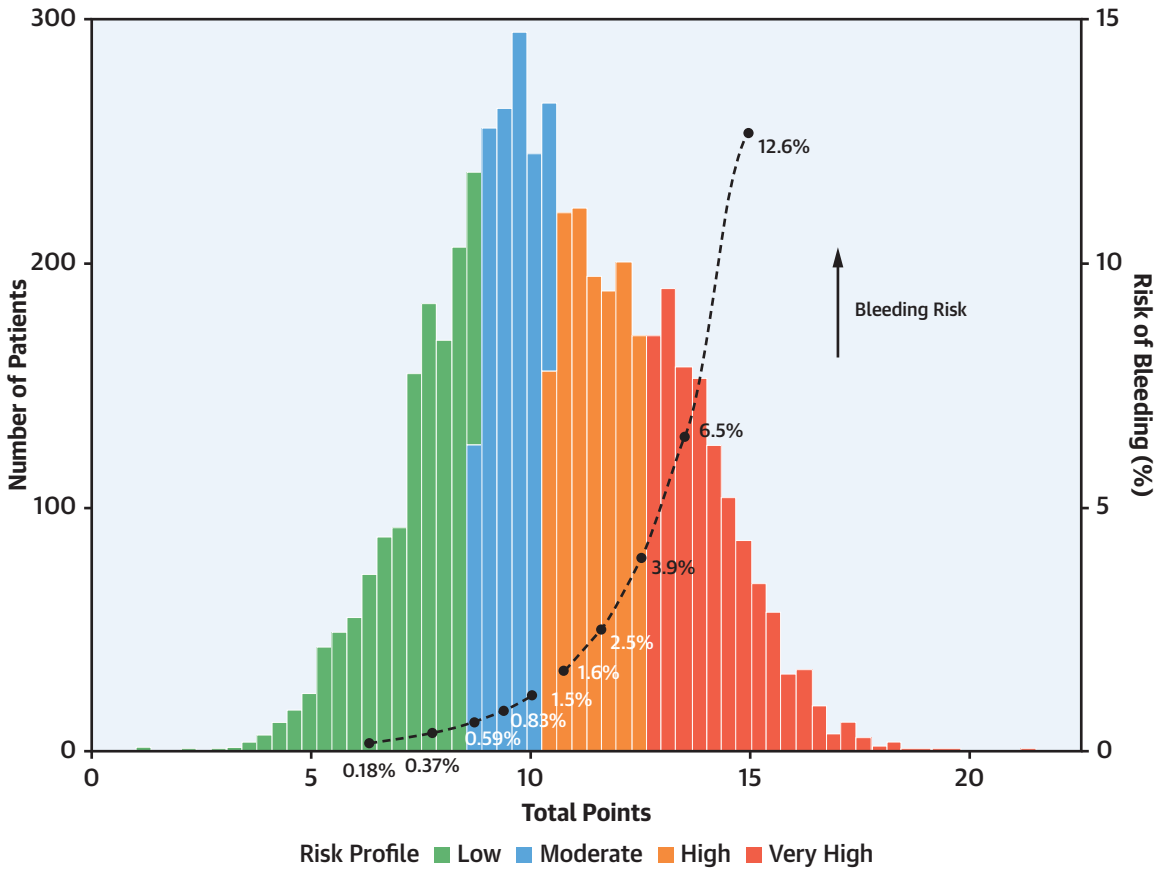
PROCEDURAL-RELATED BLEEDING RISK. Bleeding could be mechanically related to vascular complications, etiologically associated with access-site bleeding. These events are associated with increased morbidity, mortality, and the length of hospital stay, and likely predispose patients to antithrombotic therapy discontinuation, which may contribute to an increased risk of thrombotic events. The predictors of vascular complications are shown in Table 2.

In early TAVR experience, the use of large-bore catheters in elderly and high-risk patients initially translated into high rates (>15%) of major vascular complications.[3] Over the years, the increasing operator and center expertise, along with a progressive downsizing of sheath profile, and improvements on access hemostasis have translated into a significant reduction in vascular complications (Figure 1). However, the rate of major vascular complications remains relatively high. Data from the STS/ACC TVT Registry reported, in a contemporary cohort of 34,893 transfemoral TAVR recipients, a rate of vascular complications of 9.3%.[46]

Although transfemoral access is considered the default access strategy, 6% to 10% of TAVR candidates require an alternative access because of unfavorable iliofemoral anatomy. Historically, the adoption of nonarterial intrathoracic accesses (transaortic, transapical) has been associated with a major increase in bleeding complications. Thus, alternative arterial accesses expanded rapidly, due to their easier accessibility and the avoidance of thoracotomy. The preference toward a less invasive alternative approach was supported by superior outcomes in transcarotid access over transapical/transaortic, including major or life-threatening bleeding (4.3% vs 19.9%; $P = 0.002$).[47] Importantly, in a large meta-analysis including 79,426 patients, Faroux et al[48] reported that, despite

FIGURE 3 30-Day Bleeding Risk After Transcatheter Aortic Valve Replacement Across PREDICT-TAVR Quartiles

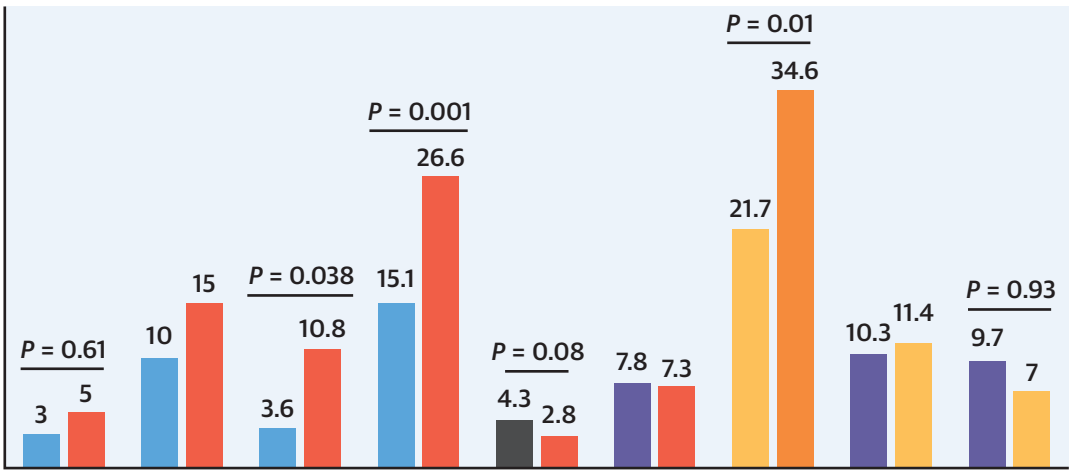
PREDICT-TAVR Score			
Variables	**Points**	**Total Score**	**Risk**
Oral anticoagulant therapy	0-2	≤8	Low
Hemoglobin	0-10		
Common femoral artery diameter	0-3	>8 and ≤10	Moderate
Dual antiplatelet therapy	0-2		
Serum Iron	0-5	>10 and ≤12	High
Creatinine clearance	0-3		
		>12	Very High



The PREDICT-TAVR is a bleeding risk model based on a 6-item score (blood hemoglobin, serum iron, creatinine clearance, common femoral artery diameter, dual antiplatelet therapy, and anticoagulant therapy). Bleeding rates were consistently separated by score quartiles (low risk ≤8; moderate risk >8 and ≤10; high risk >10 and ≤12; very high risk >12) with an exponential increase among top-quartile patients. Reproduced with permission from Navarese et al.[58]

nonfemoral access being associated with a higher risk of periprocedural stroke, the type of arterial approach (transcarotid/transsubclavian vs transfemoral) was not associated with increased risk of 30-day death, bleeding, or vascular complications. Finally, transcaval access is an emerging alternative approach, which has been associated with a comparable rate of bleeding and vascular complications as transaxillary access among experienced operators.[49] The choice of alternative access route should be individualized, considering patient's anatomy as well as bleeding/ischemic risk.

FIGURE 4 Major Bleeding Events in Randomized Trials on Antithrombotic Therapy After Transcatheter Aortic Valve Replacement



Treatment	Aspirin + Clopidogrel	Aspirin + Clopidogrel	Aspirin + Clopidogrel	Aspirin	Rivaroxaban + Aspirin	Apixaban	VKA	Apixaban	Edoxaban
Control	Aspirin	Aspirin	Aspirin	Aspirin + Clopidogrel	Aspirin + Clopidogrel	Aspirin ± Clopidogrel	Clopidogrel + VKA	VKA	VKA
N	79	120	222	665	1,644	1,049	313	451	1,426
Bleeding	=	=	X	✓	=	=	✓	=	X
Thrombosis	=	=	=	=	X	=	=	=	=

Aspirin DAPT DOAC + Aspirin DOAC VKA Clopidogrel + VKA

(Top) Rates of major bleeding events in clinical trials investigating antithrombotic strategies after transcatheter aortic valve replacement with and without indication for oral anticoagulation. **(Bottom)** Investigation strategy and control for each trial and respective sample size. Graphical representation of the results in terms of bleeding and thrombotic events. Rates of events are expressed in %. ARTE = Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation; ATLANTIS = Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis; DAPT = dual-antiplatelet therapy; DOAC = direct oral anticoagulant; ENVISAGE-TAVI AF = Edoxaban Versus Vitamin K Antagonist for Atrial Fibrillation After TAVI; GALILEO = Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes; OAC = oral anticoagulation; POPular-TAVI = Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation; SAT-TAVI = Single Antiplatelet Therapy for Transcatheter Aortic Valve Implantation; VKA = vitamin K antagonist.

Notably, the updated VARC document introduced the closure device failure endpoint in either major or minor vascular complications definitions.[16] The armamentarium of closure devices for large-bore access relies on multiple technologies, and their adoption has led to a significant decrease in vascular events. However, a learning curve process is mandatory, and TAVR operators should keep in mind anatomical variables guiding the choice (puncture site, common femoral artery diameter, posterior wall calcification), as well as acquire skills allowing to manage device failure (eg, crossover balloon techniques). In contrast to the previously published MASH (MANTA versus Suture-Based Vascular Closure After Transcatheter Aortic Valve Replacement) study,[50] in the CHOICE-CLOSURE (Randomized Comparison of Catheter-based Strategies for Interventional Access Site Closure during Transfemoral Transcatheter Aortic Valve Implantation) trial, the use of a pure plug-based technique (MANTA, Teleflex) was associated with an increase in access site or access-related vascular

complications compared with a double primary suture-based technique (ProGlide, Abbott Vascular) (19.4% vs 12.0%; $P = 0.029$).[51]

The adoption of techniques from the percutaneous coronary intervention (PCI) field may be of help in reducing vascular complications. First, a significant burden of bleeding events are related to secondary access. Rerouting the second vascular access from femoral to the radial artery has been demonstrated to significantly reduce vascular complications (4.7% vs 0.9%; $P < 0.001$) and periprocedural bleeding events (1.0% vs 0%; $P < 0.001$).[52] Therefore, the transradial approach as secondary access should probably be prioritized during TAVR.

There is no robust evidence supporting the routine use of ultrasound to guide femoral puncture. Whereas 2 single-center studies showed a significant reduction in vascular complications,[53,54] Witberg et al[55] reported that, compared with fluoroscopy and contralateral angiography, routine ultrasound guidance was not associated with a reduction of access complications in patients undergoing transfemoral TAVR. Despite this, ultrasound guidance remains an important tool in specific subgroups of patients at high risk of vascular complications (eg, small artery size, heavy calcification, higher sheath-to-vessel ratio, severe obesity).

Further delivery catheter design, optimizing preprocedural planning, and consolidating operator's experience with alternative access should be pursued to achieve additional reductions in vascular complications, which in turn will likely be linked with a decrease in severe bleeding events.

INDIVIDUALIZED ASSESSMENT OF THE BLEEDING RISK. Evidence on individualized bleeding prediction in the TAVR field is scarce. To date, few studies have applied existing bleeding risk scores developed in the PCI setting to TAVR patients, but their clinical impact remains confined.[56,57] Although most patient comorbidities and pharmacological regimens are in common with the PCI setting, certain procedural features closely contribute to enhance the TAVR-related bleeding risk. Recently, a dedicated bleeding risk score was developed and validated in 5,043 TAVR patients. The PREDICT-TAVR is a 6-item score (blood hemoglobin, serum iron, creatinine clearance, common femoral artery diameter, dual antiplatelet therapy [DAPT], and anticoagulant therapy) showing a high discriminative ability to predict bleeding events within the first 30 days after procedure (area under the curve: 0.80; 95% CI: 0.75-0.83), whereas no significant prediction was observed between 30 days and 1 year (**Figure 3**).[58] Its early bleeding risk assessment provided a consistent net benefit compared with other scores (PARIS and HAS-BLED scores). More research is needed to prospectively prove its reproducibility in defining patient risk, allowing avoidance strategies, such as a less intensive antithrombotic regimen.

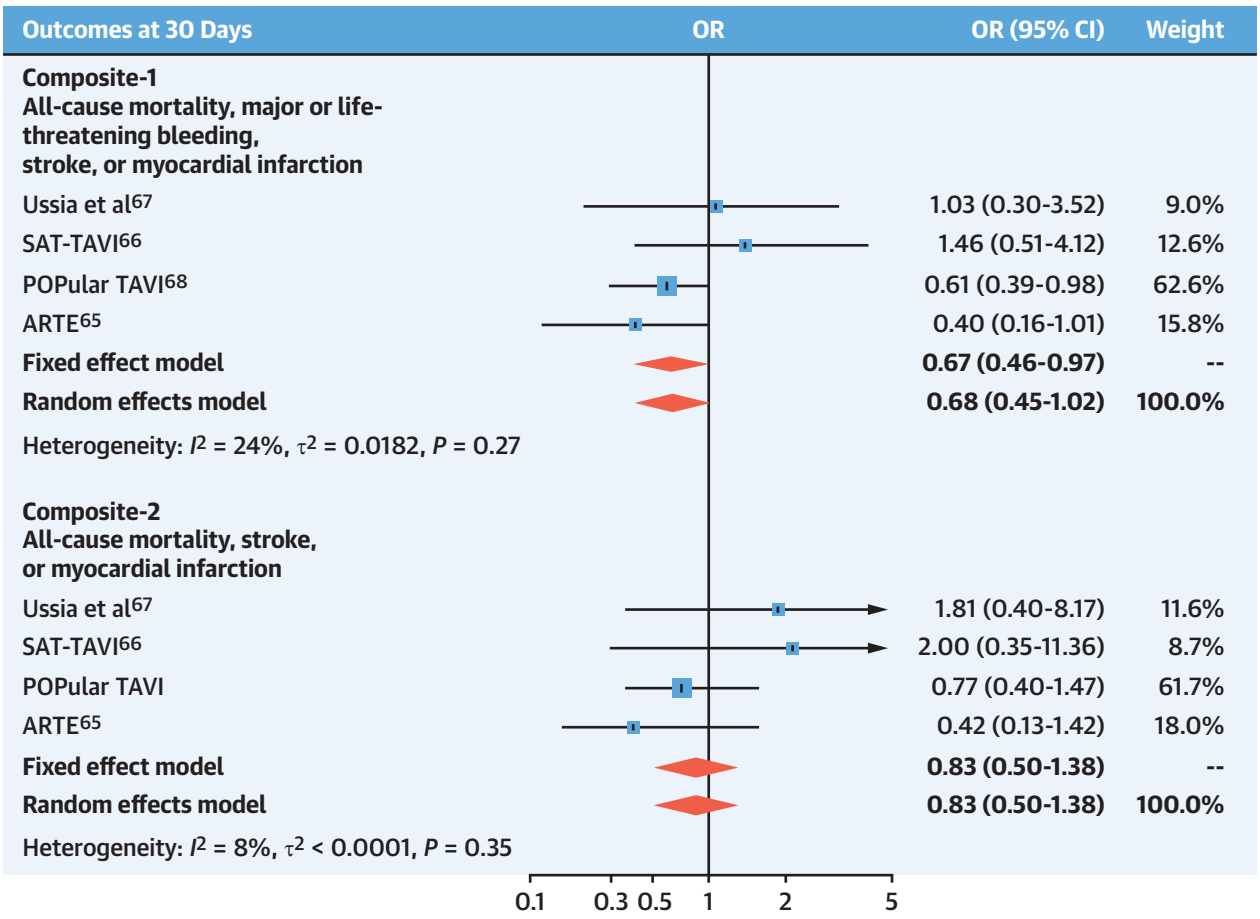
ANTITHROMBOTIC STRATEGIES DURING AND AFTER TAVR

The optimal antithrombotic regimen after TAVR remains an area of active debate. Since TAVR adoption, the use of antiplatelet therapy has been recommended because of the thrombogenicity of transcatheter heart valves. The anticoagulant agents have shown the potential of avoiding and treating valve leaflet thrombosis, potentially facilitating the preservation of long-term valve durability, raising at the same time different concerns on the inherent bleeding susceptibility. Indeed, each antithrombotic regimen unavoidably conveys an additional risk.[59] In view of this, the selection of a tailored treatment focusing on a balance between bleeding and ischemic risk plays a pivotal role to further improve patient outcomes. Bleeding events in clinical trials investigating the antithrombotic therapy in TAVR are reported in **Figure 4**.

PERIPROCEDURAL ANTITHROMBOTIC THERAPY. Periprocedural antithrombotic strategy is based on parental anticoagulation with unfractionated heparin (UFH) with a targeted activated clotting time between 250 and 300 seconds.[60] UFH has emerged as the anticoagulant of choice because of the close monitoring and immediate reversal ability by protamine. Indeed, a significant decrease of major and life-threatening bleeding has been associated with its reverse anticoagulation.[61] Furthermore, the direct thrombin inhibitor bivalirudin showed a similar risk for major bleeding after TAVR compared with UFH; its use is mainly limited to cases in which UFH is contraindicated (eg, heparin-induced thrombocytopenia).[62]

The time of administration of antithrombotic therapy may have an impact on bleeding events. In the BRAVO-3 (Effect of Bivalirudin on Aortic Valve Intervention Outcomes) trial, a preloading of clopidogrel (300 or 600 mg) on top of aspirin before the procedure was associated with a higher rate of vascular complications without protection from thromboembolic events.[63] However, after multivariable adjustment for baseline, procedural variables (including sheath size), and postprocedural anticoagulation, preloading dose was not associated with a higher risk of vascular complications. On the other

FIGURE 5 Clinical Outcomes in Trials Comparing Single vs Dual Antiplatelet Therapy



Meta-analysis of both primary outcomes at 30 days. The first primary outcome was the composite of all-cause mortality, major or life-threatening bleeding, stroke, or myocardial infarction. The second primary outcome was the composite of all-cause mortality, stroke, or myocardial infarction. Adapted from Brouwer et al.[69] Abbreviations as in Figure 4.

hand, one study suggested that in patients requiring anticoagulation therapy, its continuation throughout the procedure was not associated with an increase in bleeding or vascular complications rates.[64] The ongoing POPular PAUSE TAVI (Periprocedural Continuation Versus Interruption of Oral Anticoagulant Drugs During Transcatheter Aortic Valve Implantation; NCT04437303) trial will provide definite data on the safety of this strategy.

NO INDICATION FOR CONCOMITANT ORAL ANTICOAGULATION. The widely used DAPT strategy in TAVR recipients, mirroring PCI practice, was foremost empirical. Recent evidence has questioned this approach, suggesting that a DAPT strategy portends an enhanced bleeding risk without any significant ischemic protection. Randomized studies comparing single antiplatelet therapy (SAPT) and DAPT regimens reported no clinical benefit in terms of ischemic events prevention.[65-67] In the ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) trial, DAPT was associated with a 3-fold increase in major/life-threatening bleedings compared with a single antiplatelet strategy (10.8% vs 3.6% for DAPT and aspirin, respectively; OR: 3.22; 95% CI: 1.01-10.34; P = 0.038).[65] Along this line, the POPular-TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) trial (cohort A) confirmed that at 1-year, aspirin alone reduced bleeding events compared with DAPT (15.1% vs 26.6%, RR: 0.57; 95% CI: 0.42-0.77; P = 0.001), whereas the composite of cardiovascular death, stroke, or myocardial infarction was noninferior to

aspirin plus clopidogrel.[68] These results were corroborated in a meta-analysis reporting that aspirin alone significantly reduced the composite of thromboembolic and bleeding events after the procedure (**Figure 5**).[69]

Dual-pathway inhibition strategy might be an alternative approach to antiplatelet therapy.[70] The aforementioned effectiveness of oral anticoagulation (OAC) in preventing and treating leaflet thrombosis provided the rationale for its adoption in clinical practice. 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 trial reported that rivaroxaban was more effective in preventing subclinical leaflet-motion abnormalities than antiplatelet therapy, and similar results were observed in the ATLANTIS (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis) trial in which apixaban conferred a lower rate of valve thrombosis.[71,72] Hence, from a clinical standpoint, a clinical net benefit of OAC has not been proven in patients without an established indication for anticoagulation. In the GALILEO trial, the rivaroxaban-based strategy was associated with a higher risk of death or thromboembolic complications compared with the antiplatelet-based strategy, and the primary safety outcome of life-threatening, major, and minor bleeding complications tended to be more frequent in patients receiving rivaroxaban (HR: 1.50; 95% CI: 0.95-2.37; $P = 0.08$).[73] However, despite the higher number of deaths in the rivaroxaban group, a direct association with hemorrhagic events cannot be ascribed. Consistently, in the recently published ADAPT-TAVR (Anticoagulant Versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement) trial, the effect of edoxaban in reducing leaflet thrombosis was not associated with a reduction of neurological imaging and clinical assessment scales.[74] Safety concerns still arise, mainly related to the tradeoff between the potential benefit of prevention of subclinical leaflets thrombosis, an entity with uncertain clinical relevance, and the potential bleeding harm of OAC in patients without a clear indication.

Although evidence and current guidelines support a monotherapy approach over DAPT, whether aspirin or an oral $P2Y_{12}$ inhibitor should be used remains a matter of debate. In clinical practice, the use of other antiplatelet agents than aspirin is limited (eg, aspirin intolerance), and available data are limited to the OCEAN-TAVI (Optimized Transcatheter Valvular Intervention-Transcatheter Aortic Valve Implantation) registry in which clopidogrel was associated with a lower incidence of cardiovascular death compared with aspirin monotherapy during the 2-year follow-up after TAVR, without impact on bleeding events.[75] Few studies—the REAC-TAVI (Single Antiplatelet Treatment With Ticagrelor or Aspirin After Transcatheter Aortic Valve Implantation) and PTOLEMAIOS (A Trial to Assess the Safety and Efficacy of Prophylactic Ticagrelor With Acetylsalicylic Acid Versus Clopidogrel With Acetylsalicylic Acid in the Development of Cerebrovascular Embolic Events During TAVI) trials—have investigated the pharmacodynamic profile of $P2Y_{12}$ inhibitors, but the clinical correlate of the achieved platelet inhibition is still unknown.[76,77] Future randomized trials powered for clinical endpoints are warranted to better assess the optimal choice, timing of administration, and bleeding/ischemic risks related to these additional strategies.

INDICATION FOR CONCOMITANT OAC. Longstanding indication for OAC (mainly AF) turns pharmacological management more challenging in TAVR recipients. In this scenario, some questions remain: Is it safe to add an antiplatelet agent to OAC therapy? Among OAC, should we prefer a direct oral anticoagulant (DOAC) over a vitamin K antagonist (VKA)? Are all the DOACs the same?

The use of an antiplatelet agent on top of OAC leads to a higher rate of bleeding complications with no advantage in long-term thromboembolic events. The POPular-TAVI cohort B showed that supplementation of OAC (DOAC or VKA) with clopidogrel for 3 months after TAVR led to a significant increase of non-procedure-related bleeding (34.6% vs 21.7%; $P = 0.01$), whereas the composite endpoint of cardiovascular death, stroke, or myocardial infarction was similar between groups.[78] So far, these results represent the best evidence supporting an OAC-alone strategy after TAVR in patients with an established need for anticoagulation, without indications for additional antiplatelet agents.

Whether DOAC can be used instead of VKA is another controversial point. The choice of DOACs is appealing due to their favorable safety profile, especially in patients at high bleeding risk.[79] Compared with VKA, direct anticoagulation seems to provide a similar efficacy in stroke prevention, an advantage in mortality with a decrease in major bleeding rates (12.3% VKA vs 8.4% DOAC; $P < 0.005$).[79] To date, randomized data derived from the ATLANTIS 1st stratum trial and ENVISAGE-TAVI AF (Edoxaban Versus Vitamin K Antagonist for Atrial Fibrillation After TAVI) trial reported the noninferiority of

TABLE 3 Current Recommendations for Antithrombotic Strategies in TAVR

		ESC/EAPCI 2021[60]	ACC/AHA 2020[2]	CCS Statement 2019[97]
Preprocedural	**No indication for OAC**	Aspirin (or clopidogrel)	–	–
	Indication for OAC	OAC		
Procedural		Unfractionated heparin Goal ACT: 250-300 s Reversal with protamine recommended Bivalirudin in patients with contraindication to unfractionated heparin	–	–
Postprocedural	**No indication for OAC**	*Recent PCI (<3 mo)* 1-6 mo: aspirin + clopidogrel Lifelong: aspirin or clopidogrel *No recent PCI* Aspirin (or Clopidogrel)	Aspirin or 3-6 mo: aspirin + clopidogrel (Low bleeding risk) or 3 mo: VKA (Low bleeding risk)	*Recent PCI* Aspirin + clopidogrel As per treating physician *No recent PCI* Aspirin
	Indication for OAC	*Recent PCI (<3 mo)* 1-6 mo: OAC + aspirin (Or clopidogrel) Lifelong: OAC *No recent PCI* OAC	No specific recommendation	DOAC[a] + aspirin or OAC Avoid triple therapy in patients at increased bleeding risk

[a]Warfarin would be preferable for patients with contraindications to direct oral anticoagulants (DOACs) in the setting of mitral valve stenosis or mechanical valve replacement.

ACC = American College of Cardiology; ACT = activated clotting time; AHA = American Heart Association; CCS = Canadian Cardiovascular Society; EAPCI = European Association of Percutaneous Cardiovascular Interventions; ESC = European Society of Cardiology; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; TAVR = transcatheter aortic replacement; VKA = vitamin K antagonist.

apixaban and edoxaban, respectively, compared with VKA on the primary net composite endpoint.[72,80] Hence, whereas apixaban was associated with similar bleeding event rates as the standard of care, in the ENVISAGE-TAVI AF trial, edoxaban carried a higher risk of major bleeding (HR: 1.40; 95% CI: 1.03-1.91), mainly due to gastrointestinal bleeding.[80] Finally, in patients with relative contraindication for OAC, a nonpharmacological approach with left atrial appendage occlusion could be an attractive option. The ongoing WATCH-TAVR (WATCHMAN for Patients With Atrial Fibrillation Undergoing Transcatheter Aortic Valve Replacement; NCT03173534) study will reveal whether this combined strategy could minimize bleedings by discontinuing anticoagulation regimen while still guarding against stroke.

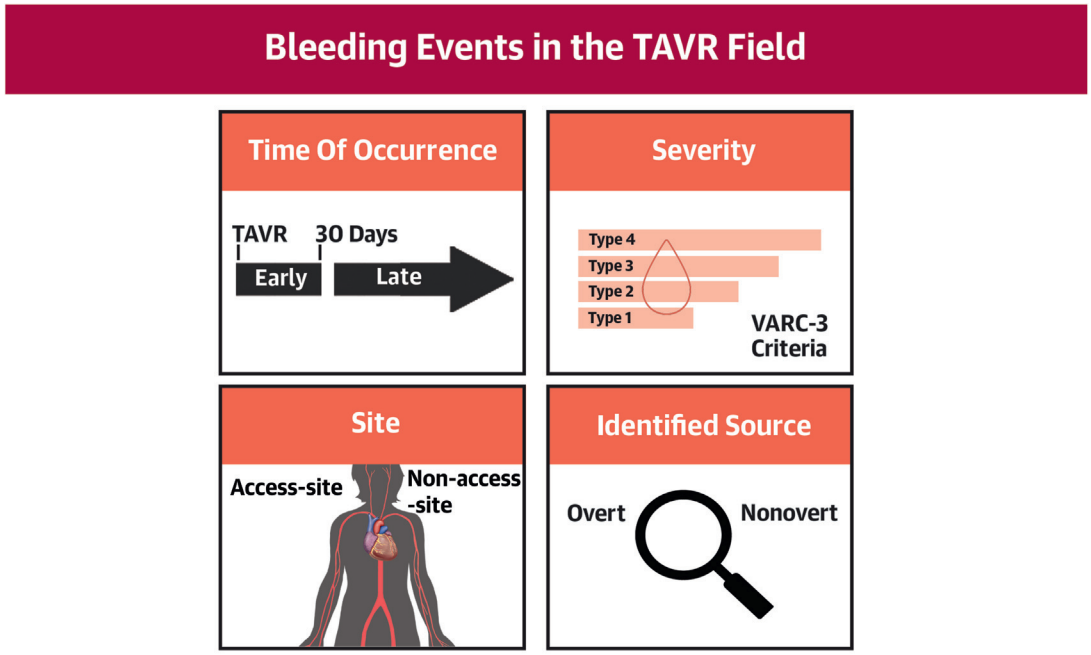
CURRENT GUIDELINES RECOMMENDATIONS. Although there is heterogeneity in accumulated evidence, SAPT seems to be an effective and safer therapeutic approach in TAVR patients with no indication for anticoagulation, whereas OAC alone is a reasonable strategy for those with chronic indications. To date, its role in preventing subclinical thromboembolic events remains still questionable. **Table 3** summarizes the current guideline recommendations, according to the presence of OAC indications and to recent coronary artery stenting.

BLEEDING AVOIDANCE STRATEGIES DURING AND AFTER TAVR

Bleeding avoidance should be intended as a systematic approach combining multiple preventive interventions (**Central Illustration**). In addition to strategies before TAVR, several options aim to reduce peri- and postprocedural bleeding.

The transfemoral route is the widely enshrined first-line approach. In view of this, technical optimization in obtaining vascular access, such as the adoption of ultrasound guidance, should probably be implemented, particularly in specific subgroups of patients at high risk of vascular complications (eg, small artery size, heavy calcification, higher sheath-to-vessel ratio, severe obesity).[81] The radial artery approach should probably be selected as the default option for secondary arterial access, whereas the contralateral femoral access should be promptly available in case of failure or emergent need for crossover. Some studies have shown a lower incidence of access-site complications and bleeding events with the use of the crossover balloon occlusion technique to facilitate vascular hemostasis, particularly in obese patients.[82,83] Although the contralateral femoral access has been commonly used for the crossover technique, some studies have shown its feasibility through the radial access.[84]

CENTRAL ILLUSTRATION **Bleeding Events in the Transcatheter Aortic Valve Replacement Field and Bleeding Avoidance Strategies**



Strategies For Preventing Bleeding Events in TAVR

Before TAVR

Bleeding Risk Stratification

Avoid Routine Pretreatment with $P2Y_{12}$

Assess Presence and Severity of Blood Disorders
In patients with anemia at baseline consider:

- Use of PPI
- Blood transfusions
- Epoetin administration
- Diagnostic tests (gastroscopy, colonoscopy)
- Less intensive antithrombotic therapy

During TAVR

First Access → Transfemoral
Transcarotid/Transsubclavian → Transcaval → Transaortic/Transapical

Second Access → Radial Artery

Ultrasound Guidance Crossover Balloon Occlusion
Patients at high risk of vascular complications

Weight Adjusted Unfractionated Heparin Dosage Reversal (UFH) With Protamine

Valve Post-Dilation
In patients with significant paravalvular leak (PVL)

Left Atrial Appendage Occlusion
AF patients at high bleeding risk

After TAVR

Tailored Antithrombotic Strategy

- No oral anticoagulation (OAC) indication → single antiplatelet therapy (SAPT)
- OAC indication → OAC alone

Assess Presence and Severity of Blood Disorders

- Systematic evaluation during hospitalization and after discharge in selected patients

Avvedimento M, et al. J Am Coll Cardiol. 2023;81(7):684–702.

(Top) Bleeding events can be defined according to time of occurrence, severity, site, and source (overt, nonovert). **(Bottom)** Summary of bleeding avoidance strategies proposed to reduce the risk of bleeding in patients undergoing transcatheter aortic valve replacement (TAVR). These actions should be intended as a systematic approach combining multiple preventive interventions before, during, and after transcatheter aortic valve replacement. PPI = proton pump inhibitors; VARC = Valve Academic Research Consortium.

TABLE 4 Ongoing Randomized Studies on Antithrombotic Therapy After TAVR

Study ClinicalTrials.gov Identifier	Experimental Arm	Comparison Arm	Primary Endpoint	Population	Sample Size	Follow-Up
Recruiting						
AVATAR NCT02735902	OAC (VKA or DOAC)	Aspirin + OAC	Composite of death from any cause, myocardial infarction, stroke, valve thrombosis and hemorrhage ≥2 as defined by the VARC 2	Indication for OAC	170	12 mo
REAC-TAVI2 NCT05283356	Ticagrelor 60 mg	Aspirin	Composite of all-cause mortality, transient ischemic attack or stroke, myocardial infarction, angina, rehospitalization or new coronary angiography, valve thrombosis, claudication, acute limb ischemia, any bleeding	All TAVR patients	1,206	12 mo
ACASA-TAVI NCT05035277	DOAC	Aspirin	Hypoattenuated leaflet thickening, composite of VARC-3 bleeding events, thromboembolic events (myocardial infarction or stroke), and all-cause mortality	All TAVR patients	360	12 mo
REDOX-TAVI NCT04171726	Edoxaban	VKA	Incidence of aortic valve leaflet thickening after TAVI as assessed by cardiac 4D CT	All TAVR patients	100	3 mo
PTOLEMAIOS NCT02989558	Ticagrelor + Aspirin	Clopidogrel + Aspirin	The number of HITS as assessed with transcranial Doppler on middle cerebral arteries	All TAVR patients	90	3 mo
Not yet recruiting						
Antithrombotic Strategy Based on Clinical Events and 4D-CT for Patients After TAVR NCT05375474	OAC (VKA)	Clopidogrel + Aspirin	Composite of all-cause mortality, myocardial infarction, stroke, TIA, peripheral artery thrombosis, disabling, life-threatening and major bleeding Rates of prosthetic valve thrombosis detected by 4D-CT	All TAVR patients	420	12 mo
ACLO-TAVR NCT05493657	Aspirin	Clopidogrel	Leaflet thrombosis on cardiac CT	No indication for OAC	230	3 mo

4D = 4-dimensional; ACASA-TAVI = Anticoagulation Versus Acetylsalicylic Acid After Transcatheter Aortic Valve Implantation; ACLO-TAVR = Aspirin vs Clopidogrel After TAVR; AVATAR = Anticoagulation Alone Versus Anticoagulation and Aspirin Following Transcatheter Aortic Valve Interventions (1:1); CT = computed tomography; DOAC = direct oral anticoagulant; HITS = high intensity transient signals; PTOLEMAIOS = A Trial to Assess the Safety and Efficacy of Prophylactic Ticagrelor With Acetylsalicylic Acid Versus Clopidogrel With Acetylsalicylic Acid in the Development of Cerebrovascular Embolic Events During TAVI; REAC-TAVI2 = Single Antiplatelet Treatment With Ticagrelor or Aspirin After Transcatheter Aortic Valve Implantation; REDOX-TAVI = Rotterdam Edoxaban Leaflet Evaluation in Patients After Transcatheter Aortic Valve Implantation; TIA = transient ischemic attack; other abbreviations as in Tables 1 and 3.

Weight-adjusted UFH dosage and its reversal with protamine administration represents the most common anticoagulation strategy during the TAVR procedures. Furthermore, several studies and a recent patient-level meta-analysis have shown a reduction in bleeding events with the use of SAPT vs DAPT in TAVR candidates, and the benefits of such a strategy seem to start in the periprocedural period.[65,68,69] A nonpharmacological stroke protection with left atrial appendage occlusion combined with TAVR may represent an attractive treatment in patients at increased bleeding risk with relative contraindication for OAC.[85] Also, percutaneous techniques to preventing PVL (eg, adequate implantation height and valve sizing, valve postdilation) could have a positive effect on homeostasis balance, decreasing the risk of bleeding events.[86]

Endeavors in the TAVR field are affording an increasingly less invasive approach. Recently, the use of a left ventricular pacing technique has facilitated a minimalist approach by avoiding the accessory venous access for right ventricular pacing,[87,88] and this may also contribute to reduce vascular and bleeding events. Moreover, a novel technology able to detect the onset and the severity of internal bleed (Early Bird Bleed Monitoring System, Saranas) has been shown to be an accurate system for the early recognition of access-site bleedings, mitigating their baleful impact.[89,90] Its application could be helpful in high-risk procedures (eg, large-bore catheter, additional antithrombotic agents, suboptimal access or closure).

Meticulous patient selection and risk stratification stand as key factors in identifying high-risk bleeding features and defining appropriate bleeding-avoidance strategies, whose application in clinical practice would improve procedural effectiveness and safety.

FUTURE DIRECTIONS AND GAPS IN KNOWLEDGE

The potential areas of investigation may be summarized as follows:

1. The optimal antithrombotic treatment after procedure in different clinical scenarios remains a matter of debate. The main gaps in knowledge are regarding the equivalence between aspirin or an oral $P2Y_{12}$ inhibitor as single antiplatelet agent, the preference of DOACs over VKA in patients with an indication for OAC therapy, the choice between double or triple therapy (in patients with AF), and its duration in TAVR candidates requiring concomitant PCI. Future research will help to address this unmet need. Ongoing studies in the field of antithrombotic therapy after TAVR are shown in **Table 4**.
2. The duration of antithrombotic treatment after TAVR has not been evaluated yet. The recommendation of lifelong SAPT (mainly aspirin) remains empirical, and it is likely to be associated with an increased risk of bleeding events,[91,92] with doubtful benefits regarding ischemic events. Further studies are needed to elucidate the optimal duration of antithrombotic treatment following TAVR.
3. A tailored antithrombotic therapy according to a careful weighing of individual bleeding and thrombotic risk is an overworked focus in PCI setting. However, this approach is still underused in TAVR and may stimulate further studies in the near future.
4. In current standardized TAVR endpoints, a detailed classification of non-access-site bleedings is still missing, and more data are needed to reclassify these events into a well-defined category.
5. Due to the gradual shift of TAVR patients toward a lower risk profile, future studies are needed to redefine predictors of bleeding complications and their impact on the extent of bleeding risk over time.

CONCLUSIONS

An assumption for TAVR to become an undisputed alternative to surgical aortic valve replacement in younger and lower risk patients regardless of age would be a further reduction in procedural complications. Bleeding represents one of the common TAVR complications, outweighing the deleterious impact of ischemic events. The impact of patient's predisposing factors and antithrombotic management in defying hemorrhagic risk is extensively defined. New evidence points toward the role of the pathophysiological interaction between the implanted bioprosthesis and stenotic valve, as well as the impact of the hemodynamic results, on bleeding susceptibility. Although device technology and pharmacotherapy strategies continue to be refined, unmet needs in the TAVR setting remain. First, an individual bleeding risk stratification represents a warranted area of investigation. Furthermore, a tailored antithrombotic approach may mitigate bleeding risks. Finally, future studies focusing on preventive strategies are warranted to further enhance the safety profile of TAVR and improve patients' outcomes.

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