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EXPERT CONSENSUS

Defining high bleeding risk in patients undergoing transcatheter aortic valve implantation: a VARC-HBR consensus document

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ABSTRACT

The identification and management of patients at high bleeding risk (HBR) undergoing transcatheter aortic valve implantation (TAVI) are of major importance, but the lack of standardised definitions is challenging for trial design, data interpretation, and clinical decision-making. The Valve Academic Research Consortium for High Bleeding Risk (VARC-HBR) is a collaboration among leading research organisations, regulatory authorities, and physician-scientists from Europe, the USA, and Asia, with a major focus on TAVI-related bleeding. VARC-HBR is an initiative of the CERC (Cardiovascular European Research Center), aiming to develop a consensus definition of TAVI patients at HBR, based on a systematic review of the available evidence, to provide consistency for future clinical trials, clinical decision-making, and regulatory review. This document represents the first pragmatic approach to a consistent definition of HBR evaluating the safety and effectiveness of procedures, devices and drug regimens for patients undergoing TAVI.

KEYWORDS: bleeding, outcomes, risk, survival, TAVI, valves

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The Academic Research Consortium (ARC) is a collaborative forum of clinical, scientific, industry and regulatory stakeholders founded in 2006 to develop and disseminate consensus definitions for pivotal clinical trials of medical devices[1]. The Valve Academic Research Consortium (VARC) is an ARC derivative initiated in 2010 and devoted to the field of heart valve interventions. Recently, the VARC-3 collaboration provided an update on emerging clinical research issues in transcatheter aortic valve intervention (TAVI), including a clarification and redirection of endpoint definitions for future clinical trials[2]. VARC-3 also provided an overview of risk assessment after TAVI that included definitions of bleeding, but factors contributing to this risk were not sufficiently discussed. Standardised bleeding definitions for cardiovascular clinical trials were first introduced in 2011 by the Bleeding Academic Research Consortium (BARC)[3]. In addition to the BARC bleeding definitions, the ARC introduced a consensus document on factors defining high bleeding risk (HBR) in percutaneous coronary intervention (PCI) patients in 2019[4].

Although less prevalent compared with after surgical aortic valve replacement, major bleeding remains a frequent serious adverse event after TAVI that has been consistently and independently associated with an increased risk of early and late mortality[5,6], longer periprocedural hospitalisation, higher healthcare costs, and worse quality of life at 1 year[7,8]. Compared to PCI, TAVI is more invasive and typically applied to elderly patients with more comorbidities and concomitant disease such as atrial fibrillation that increase bleeding risk. Medical conditions and risk factors for bleeding related to PCI were defined by the ARC-HBR initiative in 2019[4], with validation of such definitions in several contemporary groups of PCI patients[9-11], but they remain insufficiently explored in the context of TAVI. A recent *post hoc* analysis of the SCOPE II trial demonstrated that patients with and without HBR, according to the ARC-HBR criteria for PCI, experienced similar rates of BARC Type 3 or 5 bleeding[12], and similar findings were observed in a large Japanese registry[13]. The fact that HBR definitions for TAVI and PCI might differ is not surprising: in transradial PCI, most major bleeding is not access site-related, whereas in TAVI, access site and procedural bleeding are far more prevalent. Known predictors of major bleeding in TAVI patients are conspicuously absent from the ARC-HBR definitions for PCI; however, predictors of PCI-related bleeding have not demonstrated an adverse bleeding risk after TAVI. HBR criteria should, therefore, be defined in a way that is specific to TAVI patients, especially for risk assessment prior to the selection of the TAVI procedural strategy and for the selection of post-TAVI antithrombotic regimens based on individualised bleeding risk profiles.

Given the complexity of bleeding pathophysiology, clear and standardised classifications and definitions of bleeding predictors are essential to reporting the outcomes of studies on heart valve diseases. Though there is extensive literature on the risk of bleeding after such interventions, there is still a lack of uniform definitions and reporting. To better characterise the profile of HBR patients with valve disease, VARC-HBR, a new ARC initiative, was designed, combining the contributions of experts from the VARC, BARC and ARC-HBR groups, including worldwide physicians, regulators, and industry representatives. A kick-off meeting of the consortium, organised by the Cardiovascular European Research Center (CERC), was held in Barcelona, Spain, in August 2022. The meeting included representatives of the U.S. Food and Drug Administration and the Japanese Pharmaceuticals and Medical Devices Agency, as well as observers from the pharmaceutical and medical device industries. Two additional meetings took place in February and April 2023 in order to reach consensus on the criteria for the VARC-HBR definition and their relative significance.

Landmark TAVI clinical trials have used heterogeneous bleeding definitions that may challenge the comparison of bleeding rates among studies. The rates of periprocedural and non-periprocedural bleeding in contemporary trials are provided in **Supplementary Appendix 1** and **Supplementary Table 1**[6, 14-24]. In addition, bleeding rates in contemporary trials in TAVI patients with or without a clinical indication of oral anticoagulation are available in **Supplementary Appendix 2** and **Supplementary Table 2**[25-31]. There are few data on factors that promote HBR in TAVI patients. Given the advanced age and comorbidities of these patients, HBR criteria as defined in the literature of PCI are frequently observed, but these criteria do not discriminate the risk of BARC Type 3 or 5 bleeding (**Supplementary Appendix 3**)[12,32,33]. The risk of bleeding after TAVI varies over time. A recent report from 10 clinical studies indicated that the increase in mortality risk associated with major bleeding was observed both at 30-day and at 1-year follow-up[34]. An assessment for bleeding risk should be encouraged prior to the procedure, but also at 30 days after TAVI, as early severe bleeding may be associated with higher rates of 1-year bleeding events.

Defining the VARC-HBR criteria

The VARC-HBR task force agreed to define a "very high" bleeding risk as a BARC 3-5 bleeding risk at 1 year of ≥8%, a "high" bleeding risk as a BARC 3-5 risk of ≥4% and <8%, and a "moderate" bleeding risk as a BARC 3-5 risk of <4%.

The cutoff value of 8% for BARC 3-5 bleeding was based on the consensus of the participants, considering that 1-year major bleeding rates in recent TAVI trials, which largely

Abbreviations

ARC	Academic Research Consortium
BARC	Bleeding Academic Research Consortium
CKD	chronic kidney disease
DAPT	dual antiplatelet therapy
HBR	high bleeding risk
OAC	oral anticoagulation
PCI	percutaneous coronary intervention
TAVI	transcatheter aortic valve implantation
TCVT	TransCatheter Valve Treatment
VARC-HBR	Valve Academic Research Consortium for High Bleeding Risk

excluded intermediate- and high-risk patients, were ≤8% and that, in TAVI trials enrolling all-comer patients, 1-year BARC Type 3-5 bleeding rates were in the range of 7% to 9% (e.g., 7.2% in SCOPE II, 8.0% in POPular TAVI, and 8.5% in ENVISAGE-TAVI AF where patients required long-term oral anticoagulation [OAC] for atrial fibrillation). These rates were mitigated when drug combinations and drug intensity were reduced. The bleeding rates observed in trials published between 2010 and 2016 largely exceeded 10%, but this was most likely related to the effects of operator learning curves, outdated technologies, and a highly selected population of very high-risk patients deemed not suitable for surgery, which represent a smaller proportion in current real-world practice.

VARC-HBR DEFINITION

Twenty-one clinical, anatomical, or procedural criteria were identified as major or minor by consensus, supported by published evidence **(Table 1)**.

Patients are considered at very high risk of bleeding if at least two major or three minor criteria are met, at high risk if one major or two minor criteria are met, and at moderate risk if only one minor criterion is met. It is recognised that the coexistence of increasing numbers of risk factors for bleeding is associated with a stepwise increase in the risk of BARC 3-5 bleeding; therefore, as opposed to the ARC-HBR definition, the proposed consensus-based definition takes into account three levels of risk to better characterise the bleeding risk of patients undergoing TAVI. The risk stratification is proposed as a three-level scale, since sufficient data are not currently available to create a point-based score considering the relative weight of each criterion.

The proposed consensus-based definition considers the available evidence for patients at HBR undergoing TAVI and is pragmatic for application to clinical trials supporting clinical practice recommendations and regulatory review. The criteria establishing the definition are discussed below, categorised as patient-, anatomy-, or procedure-related factors **(Figure 1)**. Associated BARC 3-5 bleeding rates at 1 year are provided when available. Since periprocedural and non-periprocedural bleeding risks have different risk factors, some predictors may only apply in the early term. Therefore, the participants decided to consider periprocedural and non-periprocedural bleeding events that impact both clinical outcomes and patient survival, with a clear identification of factors impacting mostly periprocedural or non-periprocedural bleeding risk, or both **(Figure 1)**.

PATIENT-RELATED FACTORS

AGE

Age ≥90 years is considered a minor VARC-HBR criterion **(Table 1)**. Although the age and surgical risk of patients undergoing TAVI have decreased over the last decade, many patients are still over 80[35]. In PARTNER 3, the rate of BARC 3-5 bleeding was 3.6%, whereas it was 10.4% in PARTNER 2, where patients were 10 years older on average[17,19]. Indeed, elderly patients undergoing TAVI have more comorbidities and coexisting risk factors compared to younger patients, including comorbidities that require long-term OAC and other conditions that require antiplatelet therapy[17]. Advanced age has generally persisted as an independent predictor of bleeding after adjustment for coexisting risk factors in current bleeding risk scores for patients undergoing TAVI. However, machine learning analysis did not identify age as a significant clinical variable for the 6-item PREDICT-TAVR score (available at: https://predict-tavr.shinyapps.io/dynnomapp/)[33].

LOW BODY MASS INDEX

A body mass index (BMI) <20 is considered a major VARC-HBR criterion **(Table 1)**. In order to reflect ethnical specificities, the group of participants decided to exclude Asian patients with a BMI <20 and no obvious frailty, who should not be considered at HBR. Vascular complications and BARC 3-5 bleeding are more frequent in low-BMI patients[36-39]. Although BMI ≤20 should be considered a frailty marker, clinical frailty is not routinely used in clinical practice due to the cumbersome nature of its assessment. An easily measurable surrogate, a product of BMI and serum albumin (i.e., modified BMI), has been shown to be associated with increased events, including severe bleeding events and mortality at 1 year[38]. Due to a lack of consensus on how frailty is best assessed and the paucity of data demonstrating a causative role in bleeding in patients undergoing TAVI, the use of a frailty score was not selected as a criterion. Nevertheless, the inclusion of advanced age and coexisting VARC-HBR criteria may account, to some degree, for frailty.

CHRONIC KIDNEY DISEASE

Severe or end-stage chronic kidney disease (CKD, defined as an estimated glomerular filtration rate [eGFR] <30 mL/min or patients requiring dialysis) is considered a major VARC-HBR criterion **(Table 1)**. Severe CKD is an important factor for severe bleeding after TAVI[40], and the bleeding risk increases incrementally with worsening CKD[41-44]. The reduced clearance of certain antithrombotic medications, related anaemia and inherent platelet dysfunction contribute to explaining the increased risk of CKD patients[45]. In the majority of studies, eGFR <30 mL/min in isolation places patients in the highest quartile for bleeding risk, whereas milder CKD is associated with a slightly to moderately increased bleeding risk[42,46-48]. In the PREDICT-TAVR score, creatinine clearance was one of the six strongest elements for identifying bleeding risk at 30 days after TAVI[33].

LIVER CIRRHOSIS WITH PORTAL HYPERTENSION

The presence of cirrhosis with portal hypertension is considered a major VARC-HBR criterion **(Table 1)**. The reported prevalence of cirrhosis in patients undergoing TAVI in the USA is 3%, and this increased 3-fold between 2003 and 2014[6,49-50]. The bleeding risk in patients with chronic liver disease may be related to impaired haemostasis (resulting from coagulation factor deficiency, thrombocytopaenia, platelet dysfunction, or increased fibrinolysis)[51] or to oesophageal varices in the presence of portal hypertension. Data from the National Inpatient Sample (NIS) registry (n=34,752) from the years 2015 to 2018 showed liver disease to be an independent predictor of in-hospital major bleeding in patients undergoing TAVI (adjusted odds ratio [OR] 1.96, 95% confidence interval [CI]: 1.61-2.39)[49]. In addition, 1% of patients had in-hospital gastrointestinal bleeding after TAVI, and the presence of liver disease was associated with one of the highest odds

Table 1. Major and minor criteria for HBR at the time of TAVI.

Major	Minor
	Age >90 years
BMI <20, cachexia (except for Asian patients)	
End-stage CKD (eGFR <30 mL/min), dialysis	
Liver cirrhosis with portal hypertension	
Active stage III and IV malignancies	
Haemoglobin <11 g/dL	
Severe baseline thrombocytopaenia (platelet count <50×10^9/L)	Moderate baseline thrombocytopaenia (platelet count ≥50 and <100×10^9/L)
Previous intracranial haemorrhage	
Moderate or severe ischaemic stroke (National Institutes of Health Stroke Scale score ≥5 on presentation) in the past 6 months	
Chronic bleeding diathesis, coagulopathy, Heyde's syndrome	
Spontaneous (non-intracranial) bleeding requiring hospitalisation or transfusion in the past 6 months (or at any time if recurrent)	First spontaneous (non-intracranial) bleed requiring hospitalisation or transfusion >6 and <12 months before TAVI
Need for long-term OAC combined with at least one antiplatelet agent	Need for long-term OAC
	Need for DAPT/concurrent PCI
Non-deferrable major surgery	
Sheath-to-femoral artery ratio >1	
Severe calcifications and tortuous iliac and/or femoral arteries (peripheral artery disease)	
	Non-transfemoral access
Immediate conversion to open heart surgery	

BMI: body mass index; CKD: chronic kidney disease; DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; OAC: oral anticoagulation; PCI: percutaneous coronary intervention; TAVI: transcatheter aortic valve implantation

of having a gastrointestinal bleed[52]. Among 2,401 patients who underwent TAVI within the randomised cohorts and continued access registries in the PARTNER trial and who survived to 30 days, severe liver disease was more frequently associated with the presence of late bleeding complications (5.0%) compared to an absence (2.4%) (p=0.09)[6]. In a recent meta-analysis, of 1,476 patients undergoing TAVI, 41% were affected by severe chronic liver disease. In this report, in-hospital major bleeding was 9.25%[53]. Although Child-Pugh and Mayo End-Stage Liver Disease criteria were used as exclusion criteria in some TAVI trials, such scores have been validated for predicting mortality in end-stage liver disease but not for predicting bleeding risk[54,55].

ACTIVE ADVANCED STAGE MALIGNANCY (STAGE III, IV)

Active malignancy (excluding non-melanoma skin cancer) is considered a major VARC-HBR criterion **(Table 1)**. Active malignancy is defined as a diagnosis within the previous 12 months or ongoing active cancer treatment (surgery, radiotherapy, chemotherapy, or immunotherapy). Cancer that is considered to be in complete remission or that requires only maintenance therapy (e.g., tamoxifen for breast cancer) is not considered active. The reported prevalence of active cancer in patients undergoing TAVI was 5.6% in Japan and 4% in the USA and European Union; this increased 7-fold between 2008 and 2016[56,58]. Active cancer was associated with a higher rate of periprocedural major bleeding (8.6% vs 3.1% for patients with or without cancer; p<0.0001), despite a similar rate of major vascular complications. In contrast, most of the reports indicate that severe bleeding and associated rates of mortality are similar between cancer and non-cancer patients undergoing TAVI[58-62]. The likely mechanisms for this finding are the impossibility to differentiate active malignancies from a history of malignancy and the variability in cancer type and stage[63], as "bleeding cancers" accounted for very low rates in some cohorts (i.e., 3.2% of colorectal and 3.6% of urinary and bladder cancers in reports from the US National Readmission Database)[57]. Besides the presence of a potentially bleeding tumour, patients with advanced cancer are often anaemic, have thrombocytopaenia, and clotting diathesis, which place them at higher risk of both bleeding and thromboembolic complications[63].

ANAEMIA

A haemoglobin (Hb) level <11 g/dL is considered a minor VARC-HBR criterion **(Table 1)**. Preoperative anaemia defined by World Health Organization criteria (Hb <13 g/dL in men and <12 g/dL in women) is frequently encountered in patients undergoing TAVI, with a reported prevalence of 57% in the Rotterdam[64] and 59% in the Hamburg registries[65]. Preoperative anaemia, a marker of chronic bleeding and impaired haemostasis, correlates with the risk of 30-day life-threatening bleeding in patients undergoing TAVI, and this risk increases incrementally from 5% to 8% in patients with mild to severe anaemia[66]. In addition, baseline anaemia is a predictor of impaired 3-year survival after TAVI, and its effect is surpassed by the adverse impact of periprocedural complications[65]. Despite their lower risk of mortality at 1 year compared to men, women more frequently have baseline anaemia and a higher risk of vascular/bleeding complications

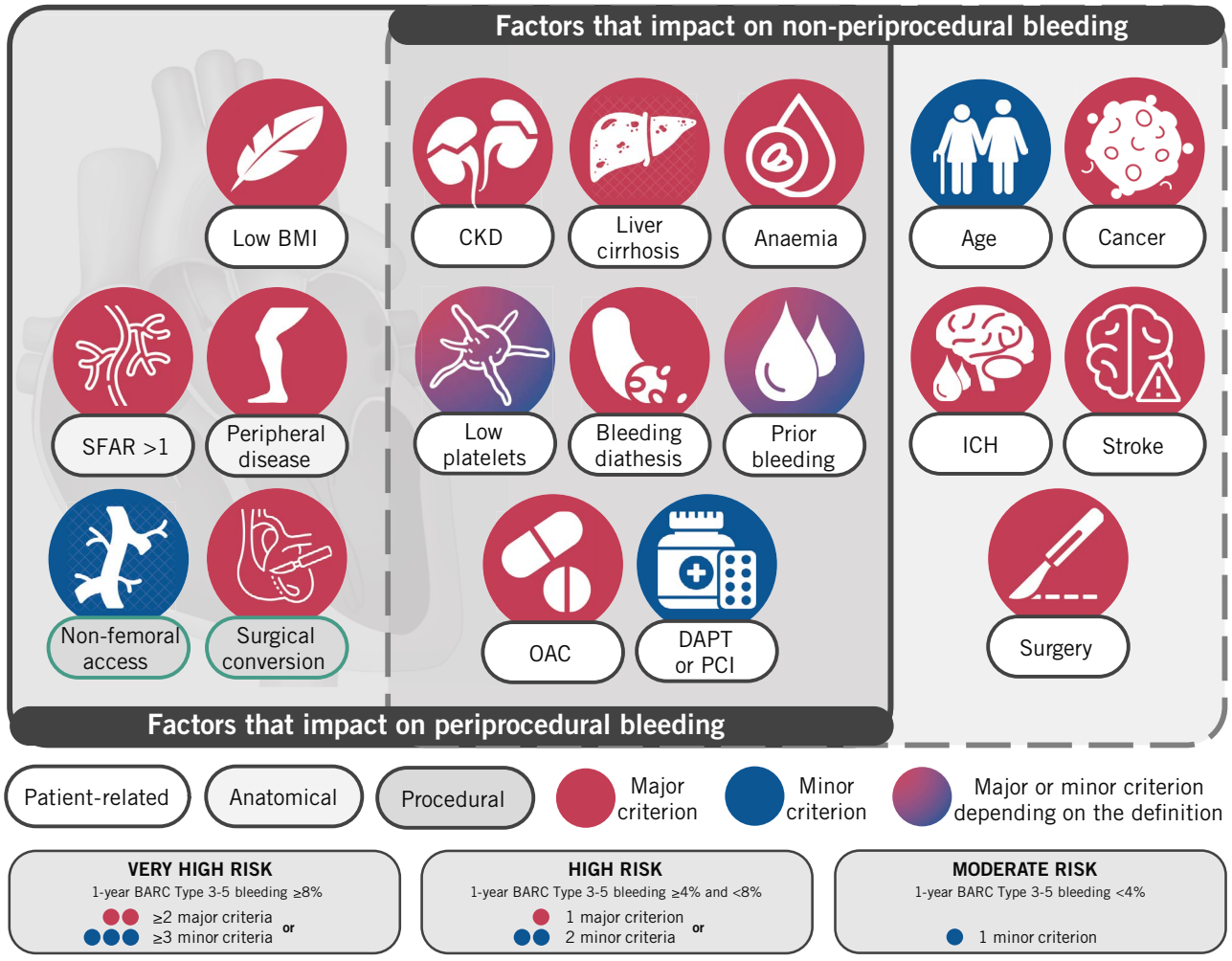

Figure 1. *VARC-HBR criteria. BARC: Bleeding Academic Research Consortium; BMI: body mass index; CKD: chronic kidney disease; DAPT: dual antiplatelet therapy; ICH: intracranial haemorrhage; OAC: oral anticoagulation; PCI: percutaneous coronary intervention; SFAR: sheath-to-femoral artery ratio; VARC-HBR: Valve Academic Research Consortium for High Bleeding Risk*

and mortality at 30 days[67]. Anaemia is an important part of the essential frailty toolset, a practical frailty scale that also includes physical weakness, cognitive impairment, and malnutrition. Compared to other frailty scores, it is a more robust predictor of adverse outcomes after TAVI or surgical aortic valve replacement[68]. This frailty scale is an independent predictor of bleeding and red cell transfusion early after TAVI[68] and is also associated with a greater risk of late (up to 2 years) bleeding events, even after adjusting for age, sex, and other clinical covariates[69]. The detrimental effect of bleeding complications on survival after TAVI has been reported[6,65,70], and a postprocedural Hb drop resulting from bleeding, inflammation, and haemodilution has been associated with an increased incidence of acute kidney injury and 1-year mortality[66].

THROMBOCYTOPAENIA

Severe baseline thrombocytopaenia (platelet count <50×10^9/L) is considered a major VARC-HBR criterion, while moderate baseline thrombocytopaenia (platelet count ≥50 and <100×10^9/L) is considered a minor VARC-HBR criterion **(Table 1)**. Baseline thrombocytopaenia refers to thrombocytopaenia that is present before TAVI and is distinct from acquired thrombocytopaenia. The reported prevalence of baseline thrombocytopaenia in patients undergoing TAVI is 20% to 40%[71-74], and the incidence of post-TAVI thrombocytopaenia ranges from 69% to 87%[75-77]. Patients with thrombocytopaenia are underrepresented in randomised trials of TAVI, and those who are enrolled generally have no more than mild thrombocytopaenia, because a platelet count of <100×10^9/L is a common exclusion criterion. Thrombocytopaenia is a risk factor for both bleeding and ischaemic complications. In an analysis from the NIS database, 9.3% of patients had in-hospital major or life-threatening bleeding, and patients presenting with baseline thrombocytopaenia had higher adjusted rates of such bleeding events (OR 1.47, 95% CI: 1.36-1.59)[52]. In another report from the same database, in the propensity-matched cohort, patients with baseline thrombocytopaenia

had higher rates of vascular complications and severe bleeding requiring blood transfusion, compared to those without thrombocytopaenia[71]. Notably, the bleeding risk appears to be proportional to the degree of thrombocytopaenia[74,78]. An analysis of the Japanese multicentre OCEAN-TAVI registry including patients with baseline thrombocytopaenia undergoing TAVI (n=2,588) showed increased rates of BARC 3-5 bleeding at 3 years in patients with baseline mild thrombocytopaenia (7.3% vs 3.6%, adjusted hazard ratio [HR] 2.10, 95% CI: 1.36-2.21) and moderate/severe thrombocytopaenia (14.1% vs 3.6%, adjusted HR 2.66, 95% CI: 1.35-4.88; p=0.006), compared to those without thrombocytopaenia[74].

PREVIOUS INTRACRANIAL HAEMORRHAGE

Previous intracranial haemorrhage (ICH) at any time is considered a major VARC-HBR criterion **(Table 1)**. In the SWEDEHEART registry, approximately 1% of patients undergoing TAVI reported a prior ICH[79]. A medical history of previous ICH was present in 2.7% of the patients with postprocedural haemorrhagic stroke compared to 0.4% in patients without a haemorrhagic stroke. Patients with a prior ICH were also prone to more frequent non-cerebral major bleeding events (0.7% vs 0.4% for patients without a major bleeding event). In the METHYSTROKE study (ClinicalTrials.gov: NCT02972008), 26% of unselected patients requiring TAVI had preprocedural cerebral microbleeds. Within 3 days after TAVI, a total of 40% of the patients had a cerebral microbleed, with 23% of these patients exhibiting new haemorrhagic lesions. Associations with a new postprocedural cerebral microbleed included a history of previous bleeding (including gastrointestinal and cerebral bleeding; p=0.03), a longer procedure (p=0.02), and a higher total dose of heparin (p=0.03)[80].

STROKE

A moderate or severe ischaemic stroke (National Institutes of Health Stroke Scale score ≥5 on presentation) within 6 months prior to TAVI is considered a major VARC-HBR criterion **(Table 1)**. The reported prevalence of a history of stroke in patients undergoing TAVI in the USA from 2011 to 2017 is ~15%[81]. The authors reported that patients with prior stroke were more prone to have a post-TAVI recurrent stroke, but the rates of bleeding were not captured in this analysis. In the ENVISAGE-TAVI AF trial, 17% of patients had a history of cerebrovascular events, and the rate of post-TAVI life-threatening bleeding was ~2 per 100 person-years, which was higher than the 1.5 per 100 person-years observed in the GALILEO trial, where only 5.2% of the patients had a history of stroke[26,31].

CHRONIC BLEEDING DIATHESIS, COAGULOPATHY, HEYDE'S SYNDROME

The presence of a clinically significant chronic bleeding diathesis is considered a major VARC-HBR criterion **(Table 1)**. Chronic bleeding diatheses include inherited or acquired conditions known to be associated with increased bleeding risk such as platelet dysfunction, von Willebrand factor (vWF) disease, inherited or acquired clotting factor deficiencies or acquired antibodies to clotting factors[82,83]. For the purpose of the current VARC-HBR definition, thrombocytopaenia is discussed separately. Data on bleeding rates after TAVI in patients with bleeding diatheses are scarce, because such patients have generally been excluded from trials. The most important and reliable predictor of bleeding in patients with bleeding diatheses is a personal history of bleeding, which may be assessed with a bleeding questionnaire[84]. Aortic stenosis is associated with acquired type 2A vWF disease[85]. Heyde's syndrome refers to the association between aortic valve stenosis and gastrointestinal bleeding from angiodysplasia[85]. Among patients undergoing TAVI, Godino et al reported a 1.7% rate of Heyde's syndrome[86]. Spangenberg et al identified the presence of abnormal vWF multimers in 42% of TAVI candidates, with 18% and 3.2% of patients with bleeding episodes and proven Heyde's syndrome, respectively[87]. High-molecular-weight multimers increase proportionally to the drop in the mean pressure gradient after TAVI and return to a normal value in most patients[87,88]. Residual paravalvular leaks after TAVI, however, negatively influence the normalisation of vWF levels[87]. Godino et al showed that preprocedural bleeding disorders resolved in all patients after TAVI during 2 years of follow-up[86]. Hence, TAVI could have a positive impact on haemostasis and type 2A vWF disease. Moreover, all patients exhibiting bleeding complications during the TAVI procedure were diagnosed with subclinical vWF dysfunction[88]. These data suggest that vWF monitoring could be useful to predict procedural bleeding, but further studies are warranted. Ishii et al demonstrated significant decreases in total thrombogenic activity, measured by the Total Thrombus-formation Analysis System (Fujimori Kogyo Co.), and platelet count after TAVI despite the improvement in vWF multimers[89]. This phenomenon might explain the high risk of complications after TAVI.

PRIOR BLEEDING AND TRANSFUSION

Spontaneous (non-intracranial) bleeding requiring hospitalisation or transfusion in the past 6 months (or at any time if recurrent) is considered a major VARC-HBR criterion, and a first spontaneous (non-intracranial) bleed requiring hospitalisation or transfusion >6 and <12 months before PCI is considered a minor VARC-HBR criterion **(Table 1)**. Information on the risk of subsequent bleeding in patients with a prior bleeding event who undergo TAVI is scarce. Long-term bleeding and related mortality after TAVI are unlikely to be related to the TAVI procedure itself but are more likely to be driven by underlying pre-existing comorbidities. Notably, bleeding beyond 30 days after the procedure was not carefully tracked nor uniformly defined in most TAVI trials. In an analysis from the NIS database from 2011 to 2018, 1% of patients undergoing TAVI had gastrointestinal bleeding, and they had higher mortality rates than those without gastrointestinal bleeding (12.1% vs 3.2%; p<0.01)[63]. The presence of peptic ulcer disease was associated with an 8-fold increased risk of bleeding. In patients presenting with peptic ulcer bleeding on aspirin monotherapy randomised to treatment with clopidogrel versus aspirin plus esomeprazole after confirmed ulcer healing, the respective 1-year rates of recurrent ulcer bleeding were 8.6% versus 0.7% (p=0.001)[90]. In another small randomised trial in patients with acute peptic ulcer bleeding on aspirin monotherapy, recurrent ulcer bleeding at 30 days occurred in 10.3% versus 5.4% of patients allocated

to aspirin plus pantoprazole versus aspirin discontinuation (HR 1.9, 95% CI: 0.6-6.0; p=0.25)[91]. Data on the association between previous blood transfusion and subsequent bleeding risk in patients undergoing TAVI are scarce. The value of blood transfusions in managing life-threatening bleeding is undisputed. However, transfusions are used for indications with less clear benefit and are pre-emptively indicated in stable patients with low baseline Hb levels and multiple comorbidities such as chronic anaemia, older age, chronic kidney disease, malnutrition, changes in volume status, or subclinical bleeding diathesis. Zimarino et al examined the use of transfusions and outcomes in the TRITAVI registry including 2,587 patients undergoing transfemoral TAVI[92]. Transfusions were used in 16% of the patients. Transfusion use was associated with a 2-fold increase in 30-day mortality regardless of blood loss (Hb drop of <3 g/dL or ≥3 g/dL), or absolute Hb nadir after the procedure (<7.5 g/dL, 7.5-9.5 g/dL, or >9.5 g/dL)[93]. Yet, transfusions may just be a marker of multimorbidity and higher mortality risk.

NEED FOR LONG-TERM ORAL ANTICOAGULATION

The need for long-term OAC after TAVI is considered a minor VARC-HBR criterion, and the need for long-term OAC combined with an antiplatelet agent is considered a major VARC-HBR criterion **(Table 1)**. The need for long-term OAC is more common in TAVI patients (approximately 40% of them) compared to PCI patients (<10%). The VARC-HBR participants decided to discriminate the bleeding risk associated with different intensity antithrombotic treatments. Randomised trials have consistently demonstrated the detrimental excess of bleeds in patients on oral anticoagulation with antiplatelet therapy versus anticoagulation alone (GALILEO, POPular cohort B and ENVISAGE-TAVI AF). The negative results of GALILEO highlight the challenge of antithrombotic therapy in TAVI patients who are elderly, potentially frail, or affected by multiple coexisting conditions associated with an increased risk of both bleeding and thromboembolic events[26]. In this context, the lack of benefit of rivaroxaban occurred despite evidence from an imaging substudy that the OAC strategy was associated with a lower incidence of subclinical valve thrombosis. The ATLANTIS study also demonstrated an unfavourable risk-benefit ratio for apixaban compared to standard antiplatelet therapy in patients without an indication for OAC[27]. In those with an indication for OAC, bleeding rates were higher compared to those without an indication for OAC, and the net clinical benefit of apixaban was not better than vitamin K antagonists (VKA)[27]. In ENVISAGE-TAVI AF, although edoxaban plus antiplatelet drugs was non-inferior for the primary efficacy outcome in approximately 60% of patients with a baseline indication to OAC, it was associated with higher rates of major bleeding, especially gastrointestinal, compared to VKA[31].

DUAL ANTIPLATELET THERAPY/CONCURRENT PCI

The need for dual antiplatelet therapy (DAPT)/concurrent PCI (within 1 month of the TAVI procedure) is considered a minor VARC-HBR criterion **(Table 1)**. Both access site and non-access site bleeding have potential adverse consequences[94]. The need for DAPT is no longer perceived as a major concern by most participants in the era of short (1 to 3 months) DAPT. Most randomised studies of antiplatelet regimens in TAVI included pre-TAVI loading with clopidogrel, and therefore did not specifically study the antiplatelet regimen after successful TAVI. This is the most common situation in many centres where PCI is performed upstream of TAVI, which implies a TAVI procedure under a DAPT regimen that may increase the complication rates. Several studies have shown the feasibility and safety of TAVI and concomitant PCI[95,96]. In the POPular TAVI trial, aspirin alone was associated with a lower incidence of bleeding (HR 0.57, 95% CI: 0.42-0.77) and the composite of bleeding or thromboembolic events (HR 0.74, 95% CI: 0.57-0.95) at 1 year, compared to aspirin plus clopidogrel administered for 3 months[25]. Similarly, the ARTE Trial reported a higher rate of major or life-threatening bleeding events within 3 months following the TAVI procedure in patients receiving DAPT, compared to those allocated to aspirin alone (10.8% vs 3.6%, respectively; p=0.038)[25]. These two trials highlighted the potential role of DAPT on the consequences of bleeding after TAVI.

NON-DEFERRABLE MAJOR SURGERY

Planned non-deferrable major surgery in patients on DAPT after TAVI is considered a major VARC-HBR criterion **(Table 1)**. After TAVI, up to 10% of patients undergo a non-cardiac surgery within 1 year, with a 30-day incidence of major or life-threatening bleeding of 11.3%[97]. TAVI and non-cardiac surgery have the potential to increase the risk of bleeding, especially while on antithrombotic medications. Available evidence on the safety of non-cardiac surgery after TAVI is scarce, often limited to small case series, and does not provide guidance on the timing of non-cardiac surgery or factors associated with procedural risk[98]. The increased risk of bleeding in a patient on antiplatelet therapy undergoing major surgery must be balanced against the potential risks of discontinuing DAPT in the potentially prothrombotic perioperative setting[99]. Important considerations include (i) the temporal relationship between TAVI and surgery, (ii) whether the surgery is deferrable, (iii) the anticipated bleeding risk specific to the surgical procedure, and (iv) the anticipated bleeding/thrombotic risk as defined by patient and procedural characteristics[63,99]. Although clinical practice guidelines provide recommendations on the perioperative management of antithrombotic therapy, they do not define the perioperative bleeding risk of different surgical procedures[100,101]. In summary, DAPT at the time of or shortly after surgery increases bleeding risk. Most elective surgery can be deferred beyond the proposed DAPT duration. For urgent or non-deferrable surgery, the risk of bleeding is much higher during the first month after TAVI compared with subsequent months.

ANATOMY-RELATED FACTORS

SHEATH-TO-FEMORAL ARTERY RATIO >1

A sheath-to-femoral artery ratio >1 is considered a major VARC-HBR criterion **(Table 1)**. In early TAVI clinical trials with first-generation devices and 22 Fr and 18 Fr sheath calibre delivery systems, vascular complications were reported in nearly 15% of patients[14,18]. The rates of both vascular complications and bleeding have decreased significantly since 2011[21]. Several studies showed that larger sheath sizes are significantly associated with vascular complications

(arterial rupture, perforation, or dissection) and bleeding events[21,102]. The rates of vascular and bleeding complications seemed to decrease in the clinical trials of second- and third-generation systems that used smaller sheath sizes (18 Fr, 16 Fr, and 14 Fr)[16,103,104]. In an analysis of 34,893 patients included in the Transcatheter Valve Therapy (TVT) registry, a few important patient factors were associated with a greater risk for vascular complications and bleeding events on multivariable modelling. Female sex, a smaller common femoral artery diameter, peripheral artery disease (PAD), sheath size >17 Fr, and open surgical cutdown were independently associated with a significantly greater risk[21]. This is supported by studies examining vascular complications and bleeding in clinical trial populations and in observational studies[105-108]. However, these complications were also associated with sheath oversizing, as measured by differences between the sheath's outer diameter and minimal iliofemoral vessel diameters. The sheath-to-femoral artery ratio was first described in 2011[102] and was shown, along with the presence of femoral calcifications and the experience of the operators, to predict the occurrence of VARC major vascular complications. Using the smallest possible delivery system may be associated with less risk for vascular complications. The sheath-to-artery ratio has not been validated in the context of expandable sheaths, whose diameters transiently exceed the nominal sheath size during delivery of the transcatheter heart valve (THV) (by up to 6 Fr).

SEVERELY CALCIFIED AND TORTUOUS ILIOFEMORAL ARTERIES (I.E., PERIPHERAL ARTERY DISEASE)

The association of severe arterial calcifications and tortuosity is considered a major VARC-HBR criterion **(Table 1)**. The reported rates of major vascular complications in transfemoral TAVI range from 2% to 15% and are more frequent compared with surgery (3%)[22], particularly in patients with PAD, owing to the large diameter of current devices and generalised atherosclerotic disease in patients with PAD. Indeed, multiple reports demonstrated that the prevalence of PAD in patients referred for TAVI ranged from 20% to 30% in the early 2010s and has decreased to between 10% and 20% in present practice[26,109,110]. Using the data of 2,167 patients, Yamawaki et al showed that the 2-year incidence of major or life-threatening bleeding tended to be higher in patients with PAD (p=0.06)[111]. In an analysis from the NIS database, 3,930/42,215 (9.3%) patients had PAD, and they had higher rates of severe bleeding requiring transfusion after transfemoral TAVI (14.2% vs 11.7%, OR 1.23, 95% CI: 1.12-1.35; p<0.001) compared to patients without PAD[110]. In an analysis of the Society of Thoracic Surgeons/American College of Cardiology TVT Registry, PAD was associated with increased rates of vascular (adjusted OR 1.33, 95% CI: 1.22-1.46; p<0.001) and in-hospital severe bleeding (adjusted OR 1.37, 95% CI: 1.25-1.50; p<0.001) complications[21]. Percutaneous closure devices are used to obtain femoral access haemostasis after large-bore arteriotomy[112]. Upfront combined strategies using an adjunctive non-suture-based device on top of a suture-based device may have the potential to reduce major vascular complications and major or life-threatening bleeding due to closure system failure, particularly in calcified femoral arteries[113,114].

PROCEDURE-RELATED FACTORS

NON-TRANSFEMORAL ROUTES

The use of non-transfemoral access is considered a minor VARC-HBR criterion **(Table 1)**. Despite improvements in TAVI techniques and device profiles, 10% to 15% of patients are still denied transfemoral access because of unfavourable anatomy due to iliofemoral arteriopathy, tortuosity, severe calcifications, aortic aneurysm, or previous vascular surgery[115-117]. Several alternatives have been developed to address the limitations of transfemoral TAVI, including surgical approaches, such as transapical, transaortic and transcarotid, and more recently, percutaneous techniques, such as transaxillary/subclavian and transcaval. In a report from the TransCatheter Valve Treatment (TCVT) Sentinel Registry Investigators of the EURObservational Research Programme (EORP) of the European Society of Cardiology enrolling 4,571 patients from 2011 to 2012, non-femoral access was an independent predictor of 1-year mortality (HR 1.32, 95% CI: 1.04-1.66; p<0.0001 for non-femoral vs femoral access, and HR 1.64, 95% CI: 1.36-1.98; p<0.01 for apical vs femoral access)[118,119]. In high-risk patients, non-femoral access was associated with higher rates of death up to 1 year, and this was also associated with a 2-fold increase in major and life-threatening bleeding[119]. In a large meta-analysis involving 49 studies and 828,528 TAVI patients, Patel et al showed that in-hospital life-threatening bleeding and non-femoral access were among the most frequent predictors for 30-day and 1-year readmission after TAVI[117]. More recently, a propensity-matched analysis from 3,226/21,611 patients demonstrated that non-transfemoral access for TAVI is associated with similar outcomes (including severe bleeding events) compared with transfemoral TAVI, except for 2-fold lower rates of major vascular complications and unplanned vascular repairs. Similar results were reported from a large German registry including 1,000 patients with similar rates of death and of major and life-threatening bleeding (6.1% vs 6.5%, and 10.9% vs 11.9% for apical vs femoral access, respectively)[120].

CONVERSION TO OPEN HEART SURGERY

Conversion to open heart surgery during TAVI procedures is considered a major VARC-HBR criterion **(Table 1)**. Approximately 0.2% to 2% of patients undergoing transfemoral TAVI may require immediate conversion to open heart surgery because of device embolisation, coronary obstruction, annulus rupture and ventricular perforation causing tamponade[16,17,121-124]. Interestingly, they found that female sex was associated with more frequent conversion to surgery, which might be explained by a slightly higher risk of ventricular perforation and pericardial effusion due to smaller left ventricles. The 1-year survival of patients surviving the in-hospital period is 40% to 50%[121].

The principles of trial design for VARC-HBR trials of TAVI including outcomes of interest, patient risk profile and age, medical history and endpoint definitions are provided in **Supplementary Appendix 4**[2,26,31,125-131]. Several conditions were not identified as major or minor criteria by consensus and are discussed in **Supplementary Appendix 5**. The present article reflects the consensus views of the VARC-HBR group and does not necessarily represent the recommendations of

the regulatory agencies or a regulatory requirement from the agencies **(Supplementary Appendix 6)**.

Conclusions

The VARC-HBR group hereby provides a uniform definition of HBR for patients undergoing TAVI with the goal of guiding the assessment and reporting of current data, as well as the generation of new data. Through this effort, the VARC-HBR group aims at improving the efficiency and validity of investigations in the field of heart valve bleeding risk and ensures that interventions performed on patients undergoing transcatheter interventions are effective, safe and durable.

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Guest Editor

This paper was guest edited by Franz-Josef Neumann, MD, PhD; *Department of Cardiology and Angiology, University Heart Centre Freiburg • Bad Krozingen, Medical Centre – University of Freiburg, Freiburg, Germany.*

Conflict of interest statement

In accordance with the ARC charter, none of the participants received fees or honoraria for their participation in the meeting or their contribution to this document. P. Garot reports receiving speaker and consulting honoraria from Abbott, Biosensors, Boston Scientific, Edwards Lifesciences, GE HealthCare, and Terumo; serves as medical co-director at the Cardiovascular European Research Center, the contract research organisation organising the not-for-profit VARC-HBR initiative; and he is a shareholder of Electroducer and Basecamp Vascular companies. M-C. Morice is the chief executive officer of the Cardiovascular European Research Center, the contract research organisation organising the not-for-profit VARC-HBR initiative; and she is a shareholder of Electroducer and Basecamp Vascular companies. D.J. Angiolillo declares that he has received consulting fees or honoraria from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Daiichi Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, Novartis, PhaseBio, PLx Pharma, Pfizer, Sanofi, and Vectura; he also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi Sankyo, Eisai, Eli Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, and the Scott R. MacKenzie Foundation. J. Rodés-Cabau has received institutional research grants and consultant/speaker fees from Edwards Lifesciences and Medtronic. D-W. Park reports grants from Daiichi Sankyo, ChongKunDang Pharm, and Daewoong Pharm; personal fees from Edwards Lifesciences and Medtronic; and grants and personal fees from Abbott Vascular, outside the submitted work. N.M. Van Mieghem has received research grant support from Abbott Vascular, Biotronik, Boston Scientific, Medtronic, Edwards Lifesciences, PulseCath BV, Daiichi Sankyo, and AstraZeneca; he has received consultancy fees from Abbott Vascular, Biotronik, Boston Scientific, Medtronic, Anteris, JenaValve, Amgen, Abiomed, PulseCath BV, Daiichi Sankyo, and AstraZeneca. J-P. Collet reports grants for the institution, honoraria, or research fees from BMS Pfizer, Medtronic, Boston Scientific, and AstraZeneca. G. Sengottuvelu has received consulting honoraria from Abbott Vascular, Medtronic, Boston Scientific, and Meril Life Sciences. M.B. Leon reports institutional clinical research support from Abbott, Abiomed, Boston Scientific, Edwards Lifesciences, and Medtronic. J.M. ten Berg reports receiving institutional research grants from ZonMw and Daiichi Sankyo as well as speaker and consulting honoraria from Ferrer, CeleCor, and Daiichi Sankyo. D. Mylotte has received research grant support from Medtronic and Boston Scientific. He has received

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References

1. Krucoff MW, Mehran R, van Es GA, Boam AB, Cutlip DE. The academic research consortium governance charter. *JACC Cardiovasc Interv.* 2011;4:595-6.
2. VARC-3 WRITING COMMITTEE:; Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, Bax JJ, Leipsic JA, Blanke P, Blackstone EH, Finn MT, Kapadia S, Linke A, Mack MJ, Makkar R, Mehran R, Popma JJ, Reardon M, Rodes-Cabau J, Van Mieghem NM, Webb JG, Cohen DJ, Leon MB. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. *J Am Coll Cardiol.* 2021;77:2717-46.
3. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736-47.
4. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson CM, Gregson J, Haude M, James SK, Kim HS, Kimura T, Konishi A, Laschinger J, Leon MB, Magee PFA, Mitsutake Y, Mylotte D, Pocock S, Price MJ, Rao SV, Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhoevel U, Yeh RW, Krucoff MW, Morice MC. Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention. *Circulation.* 2019;140:240-61.
5. Rodés-Cabau J, Dauerman HL, Cohen MG, Mehran R, Small EM, Smyth SS, Costa MA, Mega JL, O'Donoghue ML, Ohman EM, Becker RC. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. *J Am Coll Cardiol.* 2013;62:2349-59.
6. Généreux P, Cohen DJ, Mack M, Rodes-Cabau J, Yadav M, Xu K, Parvataneni R, Hahn R, Kodali SK, Webb JG, Leon MB. Incidence, predictors, and prognostic impact of late bleeding complications after transcatheter aortic valve replacement. *J Am Coll Cardiol.* 2014;64:2605-15.
7. Redfors B, Watson BM, McAndrew T, Palisaitis E, Francese DP, Razavi M, Safirstein J, Mehran R, Kirtane AJ, Généreux P. Mortality, Length of Stay, and Cost Implications of Procedural Bleeding After Percutaneous Interventions Using Large-Bore Catheters. *JAMA Cardiol.* 2017;2:798-802.
8. Arnold SV, Zhang Y, Baron SJ, McAndrew TC, Alu MC, Kodali SK, Kapadia S, Thourani VH, Miller DC, Mack MJ, Leon MB, Cohen DJ. Impact of Short-Term Complications on Mortality and Quality of Life After Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv.* 2019;12:362-9.
9. Cao D, Mehran R, Dangas G, Baber U, Sartori S, Chandiramani R, Stefanini GG, Angiolillo DJ, Capodanno D, Urban P, Morice MC, Krucoff M, Goel R, Roumeliotis A, Sweeny J, Sharma SK, Kini A. Validation of the Academic Research Consortium High Bleeding Risk Definition in Contemporary PCI Patients. *J Am Coll Cardiol.* 2020;75:2711-22.
10. Corpataux N, Spirito A, Gragnano F, Vaisnora L, Galea R, Svab S, Gargiulo G, Zanchin T, Zanchin C, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Räber L, Capodanno D, Urban P, Pocock S, Heg D, Windecker S, Valgimigli M. Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. *Eur Heart J.* 2020;41:3743-9.
11. Ueki Y, Bär S, Losdat S, Otsuka T, Zanchin C, Zanchin T, Gragnano F, Gargiulo G, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Heg D, Valgimigli M, Windecker S, Räber L. Validation of the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores. *EuroIntervention.* 2020;16:371-9.
12. Garot P, Neylon A, Morice MC, Tamburino C, Bleiziffer S, Thiele H, Scholtz S, Schramm R, Cockburn J, Cunnington M, Wolf A, Barbanti M, Tchetché D, Pagnotta P, Gilard M, Bedogni F, Van Belle E, Vasa-Nicotera M, Chieffo A, Bogaerts K, Hengstenberg C, Capodanno D. Bleeding risk differences after TAVR according to the ARC-HBR criteria: insights from SCOPE 2. *EuroIntervention.* 2022;18:503-13.
13. Mizutani K, Nakazawa G, Yamaguchi T, Ogawa M, Okai T, Yashima F, Naganuma T, Yamanaka F, Tada N, Takagi K, Yamawaki M, Ueno H, Tabata M, Shirai S, Watanabe Y, Yamamoto M, Hayashida K. Academic Research Consortium High Bleeding Risk Criteria associated with 2-year bleeding events and mortality after transcatheter aortic valve replacement discharge: a Japanese Multicentre Prospective OCEAN-TAVI Registry Study. *Eur Heart J Open.* 2021;1:oeab036.
14. Adams DH, Popma JJ, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med.* 2014;371:967-8.
15. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP; SURTAVI Investigators. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med.* 2017;376:1321-31.
16. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL 3rd, Forrest JK, Tchétché D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ; Evolut Low Risk Trial Investigators. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med.* 2019;380:1706-15.
17. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR; PARTNER 3 Investigators. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med.* 2019;380:1695-705.
18. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE,

Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187-98.

19. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG; PARTNER 2 Investigators. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med*. 2016;374:1609-20.

20. Abdel-Wahab M, Hartung P, Dumpies O, Obradovic D, Wilde J, Majunke N, Boekstegers P, Müller R, Seyfarth M, Vorpahl M, Kiefer P, Noack T, Leontyev S, Sandri M, Rotta Detto Loria J, Kitamura M, Borger MA, Funkat AK, Hohenstein S, Desch S, Holzhey D, Thiele H; CHOICE-CLOSURE Investigators. Comparison of a Pure Plug-Based Versus a Primary Suture-Based Vascular Closure Device Strategy for Transfemoral Transcatheter Aortic Valve Replacement: The CHOICE-CLOSURE Randomized Clinical Trial. *Circulation*. 2022;145:170-83.

21. Sherwood MW, Xiang K, Matsouaka R, Li Z, Vemulapalli S, Vora AN, Fanaroff A, Harrison JK, Thourani VH, Holmes D, Kirtane A, Pineda AM, Peterson ED, Rao SV. Incidence, Temporal Trends, and Associated Outcomes of Vascular and Bleeding Complications in Patients Undergoing Transfemoral Transcatheter Aortic Valve Replacement: Insights From the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies Registry. *Circ Cardiovasc Interv*. 2020;13:e008227.

22. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597-607.

23. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, Hermiller J Jr, Hughes GC, Harrison JK, Coselli J, Diez J, Kafi A, Schreiber T, Gleason TG, Conte J, Buchbinder M, Deeb GM, Carabello B, Serruys PW, Chenoweth S, Oh JK; CoreValve United States Clinical Investigators. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol*. 2014;63:1972-81.

24. Thyregod HG, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrøm T, Clemmensen P, Hansen PB, Andersen LW, Olsen PS, Søndergaard L. Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis: 1-Year Results From the All-Comers NOTION Randomized Clinical Trial. *J Am Coll Cardiol*. 2015;65:2184-94.

25. Brouwer J, Nijenhuis VJ, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, Frambach P, De Bruyne B, van Houwelingen GK, Van Der Heyden JAS, Toušek P, van der Kley F, Buysschaert I, Schotborgh CE, Ferdinande B, van der Harst P, Roosen J, Peper J, Thielen FWF, Veenstra L, Chan Pin Yin DRPP, Swaans MJ, Rensing BJWM, van 't Hof AWJ, Timmers L, Kelder JC, Stella PR, Baan J, Ten Berg JM. Aspirin with or without Clopidogrel after Transcatheter Aortic-Valve Implantation. N Engl J Med. 2020;383:1447-57.

26. Dangas GD, Tijssen JGP, Wöhrle J, Søndergaard L, Gilard M, Möllmann H, Makkar RR, Herrmann HC, Giustino G, Baldus S, De Backer O, Guimarães AHC, Gullestad L, Kini A, von Lewinski D, Mack M, Moreno R, Schäfer U, Seeger J, Tchétché D, Thomitzek K, Valgimigli M, Vranckx P, Welsh RC, Wildgoose P, Volkl AA, Zazula A, van Amsterdam RGM, Mehran R, Windecker S; GALILEO Investigators. A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement. *N Engl J Med*. 2020;382:120-9.

27. Collet JP, Van Belle E, Thiele H, Berti S, Lhermusier T, Manigold T, Neumann FJ, Gilard M, Attias D, Beygui F, Cequier A, Alfonso F, Aubry P, Baronnet F, Ederhy S, Kasty ME, Kerneis M, Barthelemy O, Lefèvre T, Leprince P, Redheuil A, Henry P, Portal JJ, Vicaut E, Montalescot G; ATLANTIS Investigators of the ACTION Group. Apixaban vs. standard of care after transcatheter aortic valve implantation: the ATLANTIS trial. *Eur Heart J*. 2022;43:2783-97.

28. Guedeney P, Roule V, Mesnier J, Chapelle C, Portal JJ, Laporte S, Ollier E, Zeitouni M, Kerneis M, Procopi N, Barthelemy O, Sorrentino S, Mihalovic M, Silvain J, Vicaut E, Montalescot G, Collet JP. Antithrombotic therapy and cardiovascular outcomes after transcatheter aortic valve implantation in patients without indications for chronic oral anticoagulation: a systematic review and network meta-analysis of randomized controlled trials. *Eur Heart J Cardiovasc Pharmacother*. 2023;9:251-61.

29. Kobari Y, Inohara T, Tsuruta H, Yashima F, Shimizu H, Fukuda K, Naganuma T, Mizutani K, Yamawaki M, Tada N, Yamanaka F, Shirai S, Tabata M, Ueno H, Takagi K, Watanabe Y, Yamamoto M, Hayashida K. No Antithrombotic Therapy After Transcatheter Aortic Valve Replacement: Insight From the OCEAN-TAVI Registry. *JACC Cardiovasc Interv*. 2023;16:79-91.

30. Nijenhuis VJ, Brouwer J, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, Frambach P, De Bruyne B, van Houwelingen GK, Van Der Heyden JAS, Toušek P, van der Kley F, Buysschaert I, Schotborgh CE, Ferdinande B, van der Harst P, Roosen J, Peper J, Thielen FWF, Veenstra L, Chan Pin Yin DRPP, Swaans MJ, Rensing BJWM, van 't Hof AWJ, Timmers L, Kelder JC, Stella PR, Baan J, Ten Berg JM. Anticoagulation with or without Clopidogrel after Transcatheter Aortic-Valve Implantation. *N Engl J Med*. 2020;382:1696-707.

31. Van Mieghem NM, Unverdorben M, Hengstenberg C, Möllmann H, Mehran R, López-Otero D, Nombela-Franco L, Moreno R, Nordbeck P, Thiele H, Lang I, Zamorano JL, Shawl F, Yamamoto M, Watanabe Y, Hayashida K, Hambrecht R, Meincke F, Vranckx P, Jin J, Boersma E, Rodés-Cabau J, Ohlmann P, Capranzano P, Kim HS, Pilgrim T, Anderson R, Baber U, Duggal A, Laeis P, Lanz H, Chen C, Valgimigli M, Veltkamp R, Saito S, Dangas GD; ENVISAGE-TAVI AF Investigators. Edoxaban versus Vitamin K Antagonist for Atrial Fibrillation after TAVR. *N Engl J Med*. 2021;385:2150-60.

32. Honda Y, Yamawaki M, Araki M, Tada N, Naganuma T, Yamanaka F, Watanabe Y, Yamamoto M, Shirai S, Hayashida K; OCEAN-TAVI investigators. Impact of HAS-BLED score to predict trans femoral transcatheter aortic valve replacement outcomes. *Catheter Cardiovasc Interv*. 2018;92:1387-96.

33. Navarese EP, Zhang Z, Kubica J, Andreotti F, Farinaccio A, Bartorelli AL, Bedogni F, Rupji M, Tomai F, Giordano A, Reimers B, Spaccarotella C, Wilczek K, Stepinska J, Witkowski A, Grygier M, Kukulski T, Wanha W, Wojakowski W, Lesiak M, Dudek D, Zembala MO, Berti S; a Joint Effort of the Italian and Polish Cardiac Interventional Societies. Development and Validation of a Practical Model to Identify Patients at Risk of Bleeding After TAVR. *JACC Cardiovasc Interv*. 2021;14:1196-206.

34. van Nieuwkerk AC, Aarts HM, Hemelrijk KI, Cantón T, Tchétché D, de Brito FS Jr, Barbanti M, Kornowski R, Latib A, D'Onofrio A, Ribichini F, Maneiro Melón N, Dumonteil N, Abizaid A, Sartori S, D'Errigo P, Tarantini G, Fabroni M, Orvin K, Pagnesi M, Vicaino Arellano M, Dangas G, Mehran R, Voskuil M, Delewi R. Bleeding in Patients Undergoing Transfemoral Transcatheter Aortic Valve Replacement: Incidence, Trends, Clinical Outcomes, and Predictors. *JACC Cardiovasc Interv*. 2023;16:2951-62.

35. ten Berg J, Rocca B, Angiolillo DJ, Hayashida K. The search for optimal antithrombotic therapy in transcatheter aortic valve implantation: facts and uncertainties. *European Heart Journal*. 2022;43:4616-34.

36. Seiffert M, Conradi L, Terstesse AC, Koschyk D, Schirmer J, Schnabel RB, Wilde S, Ojeda FM, Reichenspurner H, Blankenberg S, Schäfer U, Treede H, Diemert P. Blood transfusion is associated with impaired outcome after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv*. 2015;85:460-7.

37. Wenaweser P, Pilgrim T, Roth N, Kadner A, Stortecky S, Kalesan B, Meuli F, Büllesfeld L, Khattab AA, Huber C, Eberle B, Erdös G, Meier B, Jüni P, Carrel T, Windecker S. Clinical outcome and predictors for adverse events after transcatheter aortic valve implantation with the use of different devices and access routes. *Am Heart J*. 2011;161:1114-24.

38. Driggin E, Gupta A, Madhavan MV, Alu M, Redfors B, Liu M, Chen S, Kodali S, Maurer MS, Thourani VH, Dvir D, Mack M, Leon MB, Green P. Relation between Modified Body Mass Index and Adverse Outcomes after Aortic Valve Implantation. *Am J Cardiol*. 2021;153:94-100.

39. Koifman E, Kiramijyan S, Negi SI, Didier R, Escarcega RO, Minha S, Gai J, Torguson R, Okubagzi P, Ben-Dor I, Satler LF, Pichard AD, Waksman R. Body mass index association with survival in severe aortic stenosis patients undergoing transcatheter aortic valve replacement. *Catheter Cardiovasc Interv*. 2016;88:118-24.

40. Rodés-Cabau J. Transcatheter aortic valve implantation: current and future approaches. *Nat Rev Cardiol.* 2011;9:15-29.

41. Sinning JM, Ghanem A, Steinhäuser H, Adenauer V, Hammerstingl C, Nickenig G, Werner N. Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. *JACC Cardiovasc Interv.* 2010;3:1141-9.

42. Dumonteil N, van der Boon RM, Tchetche D, Chieffo A, Van Mieghem NM, Marcheix B, Buchanan GL, Vahdat O, Serruys PW, Fajadet J, Colombo A, de Jaegere PP, Carrié D. Impact of preoperative chronic kidney disease on short- and long-term outcomes after transcatheter aortic valve implantation: a Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC-Plus) initiative substudy. *Am Heart J.* 2013;165:752-760.

43. Yamamoto M, Hayashida K, Mouillet G, Hovasse T, Chevalier B, Oguri A, Watanabe Y, Dubois-Randé JL, Morice MC, Lefèvre T, Teiger E. Prognostic value of chronic kidney disease after transcatheter aortic valve implantation. *J Am Coll Cardiol.* 2013;62:869-77.

44. D'Ascenzo F, Moretti C, Salizzoni S, Bollati M, D'Amico M, Ballocca F, Giordana F, Barbanti M, Ussia GP, Brambilla N, Bedogni F, Biondi Zoccai G, Tamburino C, Gaita F, Sheiban I. 30 days and midterm outcomes of patients undergoing percutaneous replacement of aortic valve according to their renal function: a multicenter study. *Int J Cardiol.* 2013;167:1514-8.

45. Ullah W, Zahid S, Hamzeh I, Birnbaum Y, Virani SS, Alam M. Trends and Predictors of Transcatheter Aortic Valve Implantation Related In-Hospital Mortality (From the National Inpatient Sample Database). *Am J Cardiol.* 2021;143:97-103.

46. Allende R, Webb JG, Munoz-Garcia AJ, de Jaegere P, Tamburino C, Dager AE, Cheema A, Serra V, Amat-Santos I, Velianou JL, Barbanti M, Dvir D, Alonso-Briales JH, Nuis RJ, Faqiri E, Imme S, Benitez LM, Cucalon AM, Al Lawati H, Garcia del Blanco B, Lopez J, Natarajan MK, DeLarochellière R, Urena M, Ribeiro HB, Dumont E, Nombela-Franco L, Rodés-Cabau J. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. *Eur Heart J.* 2014;35:2685-96.

47. Grundmann D, Linder M, Goßling A, Voigtländer L, Ludwig S, Waldschmidt L, Demal T, Bhadra OD, Schäfer A, Schirmer J, Reichenspurner H, Blankenberg S, Westermann D, Schofer N, Conradi L, Seiffert M. End-stage renal disease, calcification patterns and clinical outcomes after TAVI. *Clin Res Cardiol.* 2022;111:1313-24.

48. Levi A, Codner P, Masalha A, Gargiulo G, Praz F, Hayashida K, Watanabe Y, Mylotte D, Debry N, Barbanti M, Lefèvre T, Modine T, Bosmans J, Windecker S, Barbash I, Sinning JM, Nickenig G, Barsheshet A, Kornowski R. Predictors of 1-Year Mortality After Transcatheter Aortic Valve Implantation in Patients With and Without Advanced Chronic Kidney Disease. *Am J Cardiol.* 2017;120:2025-30.

49. Khan H, Gilani A, Qayum I, Khattak T, Haq F, Zahid Anwar M, Khan MA, Asjad SJ, Abbas S, Inayat A. An Analysis of the Predictors of Major Bleeding After Transcatheter Aortic Valve Transplantation Using the National Inpatient Sample (2015-2018). *Cureus.* 2021;13:e16022.

50. Alqahtani F, Aljohani S, Ghabra A, Alahdab F, Kawsara A, Holmes DR, Alkhouli M. Outcomes of Transcatheter Versus Surgical Aortic Valve Implantation for Aortic Stenosis in Patients With Hepatic Cirrhosis. *Am J Cardiol.* 2017;120:1193-7.

51. Mitchell O, Feldman DM, Diakow M, Sigal SH. The pathophysiology of thrombocytopenia in chronic liver disease. *Hepat Med.* 2016;8:39-50.

52. Zahid S, Ullah W, Khan MU, Abbas S, Ud Din MT, Uddin MF, Inayat A, Ubaid A, Salman F, Thakkar S, Salama A, Khan MZ. Trends, predictors, and outcomes of major bleeding after transcatheter aortic valve implantation, from national inpatient sample (2011-2018). *Expert Rev Cardiovasc Ther.* 2021;19:557-63.

53. Ma X, Zhao D, Li J, Wei D, Zhang J, Yuan P, Kong X, Ma J, Ma H, Sun L, Zhang Y, Jiao Q, Wang Z, Zhang H. Transcatheter aortic valve implantation in the patients with chronic liver disease: A mini-review and meta-analysis. *Medicine (Baltimore).* 2020;99:e19766.

54. Child CG, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg.* 1964;1:1-85.

55. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg.* 1973;60:646-9.

56. Landes U, Iakobishvili Z, Vronsky D, Zusman O, Barsheshet A, Jaffe R, Jubran A, Yoon SH, Makkar RR, Taramasso M, Russo M, Maisano F, Sinning JM, Shamekhi J, Biasco L, Pedrazzini G, Moccetti M, Latib A, Pagnesi M, Colombo A, Tamburino C, D' Arrigo P, Windecker S, Pilgrim T, Tchetche D, De Biase C, Guerrero M, Iftikhar O, Bosmans J, Bedzra E, Dvir D, Mylotte D, Sievert H, Watanabe Y, Søndergaard L, Dagnegård H, Codner P, Kodali S, Leon M, Kornowski R. Transcatheter Aortic Valve Replacement in Oncology Patients With Severe Aortic Stenosis. *JACC Cardiovasc Interv.* 2019;12:78-86.

57. Jain V, Saad AM, Gad MM, Bansal A, Abdelfattah O, Farwati M, Ahuja KR, Yun J, Krishnaswamy A, Kapadia SR. Outcomes of Cancer Patients Undergoing Transcatheter Aortic Valve Replacement. *JACC CardioOncol.* 2020;2:506-8.

58. Kojima Y, Higuchi R, Hagiya K, Saji M, Takamisawa I, Iguchi N, Takanashi S, Doi S, Okazaki S, Sato K, Tamura H, Takayama M, Ikeda T, Isobe M. Prognosis of patients with active cancer undergoing transcatheter aortic valve implantation: An insight from Japanese multicenter registry. *Int J Cardiol Heart Vasc.* 2022;40:101045.

59. Song Y, Wang Y, Wang Z, Xu C, Dou J, Jiang T. Comparing Clinical Outcomes on Oncology Patients With Severe Aortic Stenosis Undergoing Transcatheter Aortic Valve Implantation: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med.* 2022;9:890082.

60. Siddiqui MU, Yacob O, Junarta J, Pasha AK, Mookadam F, Mamas MA, Fischman DL. Mortality after transcatheter aortic valve replacement for aortic stenosis among patients with malignancy: a systematic review and meta-analysis. *BMC Cardiovasc Disord.* 2022;22:210.

61. Watanabe Y, Kozuma K, Hioki H, Kawashima H, Nara Y, Kataoka A, Shirai S, Tada N, Araki M, Takagi K, Yamanaka F, Yamamoto M, Hayashida K. Comparison of Results of Transcatheter Aortic Valve Implantation in Patients With Versus Without Active Cancer. *Am J Cardiol.* 2016;118:572-7.

62. Mędrek S, Szmit S. Are cardiovascular comorbidities always associated with a worse prognosis in patients with lung cancer? *Front Cardiovasc Med.* 2022;9:984951.

63. Zahid S, Khan MZ, Bapaye J, Altamimi TS, Elkhapery A, Thakkar S, Nepal M, Rai D, Ullah W, Patel HP, Sattar Y, Khan MU, Ur Rahman A, Balla S. Outcomes, Trends, and Predictors of Gastrointestinal Bleeding in Patients Undergoing Transcatheter Aortic Valve Implantation (from the National Inpatient Sample). *Am J Cardiol.* 2022;170:83-90.

64. Nuis RJ, Sinning JM, Rodés-Cabau J, Gotzmann M, van Garsse L, Kefer J, Bosmans J, Yong G, Dager AE, Revilla-Orodea A, Urena M, Nickenig G, Werner N, Maessen J, Astarci P, Perez S, Benitez LM, Amat-Santos IJ, López J, Dumont E, van Mieghem N, van Gelder T, van Domburg RT, de Jaegere PP. Prevalence, factors associated with, and prognostic effects of preoperative anemia on short- and long-term mortality in patients undergoing transcatheter aortic valve implantation. *Circ Cardiovasc Interv.* 2013;6:625-34.

65. Seiffert M, Conradi L, Gutwein A, Schön G, Deuschl F, Schofer N, Becker N, Schirmer J, Reichenspurner H, Blankenberg S, Treede H, Schäfer U. Baseline anemia and its impact on midterm outcome after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv.* 2017;89:E44-E52.

66. Arai T, Morice MC, O'Connor SA, Yamamoto M, Eltchaninoff H, Leguerrier A, Leprince P, Laskar M, Iung B, Fajadet J, Prat A, Lièvre M, Donzeau-Gouge P, Chevreul K, Teiger E, Lefèvre T, Gilard M; FRANCE 2 Registry Investigators. Impact of pre- and post-procedural anemia on the incidence of acute kidney injury and 1-year mortality in patients undergoing transcatheter aortic valve implantation (from the French Aortic National CoreValve and Edwards 2 [FRANCE 2] Registry). *Catheter Cardiovasc Interv.* 2015;85:1231-9.

67. Rodriguez-Gabella T, Zimarino M, Barbanti M, Testa L, Capodanno D, Stefanini GG, Radico F, Fabbiocchi F, Piva T, Saia F, Biancari F, Eskola M, Niemelä M, Airaksinen J, Valtola A, Raivio P, Reimers B, Picci A, Nicolini E, Olivares P, Moretti C, Maddestra N, Bedogni F, Gallina S, Tamburino C, Amat-Santos IJ. Sex based analysis of the impact of red

blood cell transfusion and vascular or bleeding complications related to TAVI - The TRITAVI-Women Study. *Int J Cardiol.* 2021;333:69-76.

68. Afilalo J, Lauck S, Kim DH, Lefèvre T, Piazza N, Lachapelle K, Martucci G, Lamy A, Labinaz M, Peterson MD, Arora RC, Noiseux N, Rassi A, Palacios IF, Généreux P, Lindman BR, Asgar AW, Kim CA, Trnkus A, Morais JA, Langlois Y, Rudski LG, Morin JF, Popma JJ, Webb JG, Perrault LP. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. *J Am Coll Cardiol.* 2017;70:689-700.

69. Tsujimoto S, Yamamoto M, Kagase A, Tokuda T, Koyama Y, Shimura T, Adachi Y, Yamaguchi R, Otsuka T, Yashima F, Watanabe Y, Tada N, Naganuma T, Yamawaki M, Yamanaka F, Mizutani K, Tabata M, Ueno H, Takagi K, Shirai S, Hayashida K; OCEAN-TAVI Investigators. The Usefulness of the Modified Essential Frailty Toolset to Predict Late Bleeding Events after Transcatheter Aortic Valve Implantation. *Am J Cardiol.* 2022;184:111-9.

70. Tamburino C, Capodanno D, Ramondo A, Petronio AS, Ettori F, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, Antoniucci D, Napodano M, De Carlo M, Fiorina C, Ussia GP. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation.* 2011;123:299-308.

71. Saad M, Mahmoud AN, Barakat AF, Mentias A, Elbadawi A, Elgendy IY, Abuzaid A, Elgendy AY, Jneid H. In-Hospital Outcomes After Transcatheter Aortic Valve Implantation in Patients With Versus Without Chronic Thrombocytopenia. *Am J Cardiol.* 2019;124:1106-12.

72. Shokr M, Adegbala O, Elmoghrabi A, Saleh M, Ajam M, Ali A, Yassin AS, Ando T, Eperjesiova B, Aly A, Pahuja M, Ashraf S, Abubakar H, Ahmed A, Subahi A, Lieberman R, Afonso L. Impact of Chronic Thrombocytopenia on Outcomes After Transcatheter Valvular Intervention and Cardiac Devices Implantation (From a National Inpatient Sample). *Am J Cardiol.* 2019;124:1601-7.

73. De Larochellière H, Puri R, Eikelboom JW, Rodés-Cabau J. Blood Disorders in Patients Undergoing Transcatheter Aortic Valve Replacement: A Review. *JACC Cardiovasc Interv.* 2019;12:1-11.

74. Ito S, Taniguchi T, Shirai S, Ando K, Watanabe Y, Yamamoto M, Naganuma T, Takagi K, Yamawaki M, Tada N, Yamanaka F, Tabata M, Ueno H, Yashima F, Hayashida K. The Impact of Baseline Thrombocytopenia on Late Bleeding and Mortality After Transcatheter Aortic Valve Implantation (From the Japanese Multicenter OCEAN-TAVI Registry). *Am J Cardiol.* 2021;141:86-92.

75. Flaherty MP, Mohsen A, Moore JB 4th, Bartoli CR, Schneibel E, Rawasia W, Williams ML, Grubb KJ, Hirsch GA. Predictors and clinical impact of pre-existing and acquired thrombocytopenia following transcatheter aortic valve replacement. *Catheter Cardiovasc Interv.* 2015;85:118-29.

76. McCabe JM, Huang PH, Riedl LA, Devireddy SR, Grondell J, Connors AC, Davidson MJ, Eisenhauer AC, Welt FG. Incidence and implications of idiopathic thrombocytopenia following transcatheter aortic valve replacement with the Edwards Sapien(©) valves: a single center experience. *Catheter Cardiovasc Interv.* 2014;83:633-41.

77. Sexton TR, Wallace EL, Chen A, Charnigo RJ, Reda HK, Ziada KM, Gurley JC, Smyth SS. Thromboinflammatory response and predictors of outcomes in patients undergoing transcatheter aortic valve replacement. *J Thromb Thrombolysis.* 2016;41:384-93.

78. Kalińczuk Ł, Zieliński K, Chmielak Z, Mintz GS, Dąbrowski M, Pręgowski J, Proczka M, Michałowska I, Czerwińska-Jelonkiewicz K, Łazarczyk H, Demkow M, Hryniewiecki T, Witkowski A. Effect on Mortality of Systemic Thromboinflammatory Response After Transcatheter Aortic Valve Implantation. *Am J Cardiol.* 2019;124:1741-7.

79. Christersson C, Ståhle E, Lindhagen L, James S. Haemorrhagic stroke and major bleeding after intervention with biological aortic valve prosthesis: risk factors and antithrombotic treatment. *Eur Heart J Suppl.* 2020;22:C26-C33.

80. Van Belle E, Debry N, Vincent F, Kuchcinski G, Cordonnier C, Rauch A, Robin E, Lassalle F, Pontana F, Delhaye C, Schurtz G, JeanPierre E, Rousse N, Casari C, Spillemaeker H, Porouchani S, Pamart T, Denimal T, Neiger X, Verdier B, Puy L, Cosenza A, Juthier F, Richardson M, Bretzner M, Dallongeville J, Labreuche J, Mazighi M, Dupont-Prado A, Staels B, Lenting PJ, Susen S. Cerebral Microbleeds During Transcatheter Aortic Valve Replacement: A Prospective Magnetic Resonance Imaging Cohort. *Circulation.* 2022;146:383-97.

81. Huded CP, Tuzcu EM, Krishnaswamy A, Mick SL, Kleiman NS, Svensson LG, Carroll J, Thourani VH, Kirtane AJ, Manandhar P, Kosinski AS, Vemulapalli S, Kapadia SR. Association Between Transcatheter Aortic Valve Replacement and Early Postprocedural Stroke. *JAMA.* 2019;321:2306-15.

82. Sellers SL, Gulsin GS, Zaminski D, Bing R, Latib A, Sathananthan J, Pibarot P, Bouchareb R. Platelets: Implications in Aortic Valve Stenosis and Bioprosthetic Valve Dysfunction From Pathophysiology to Clinical Care. *JACC Basic Transl Sci.* 2021;6:1007-20.

83. Franchini M, Coppola A. Atherothrombosis in von Willebrand disease: an analysis of the literature and implications for clinical management. *Semin Thromb Hemost.* 2012;38:185-99.

84. Federici AB, Bucciarelli P, Castaman G, Mazzucconi MG, Morfini M, Rocino A, Schiavoni M, Peyvandi F, Rodeghiero F, Mannucci PM. The bleeding score predicts clinical outcomes and replacement therapy in adults with von Willebrand disease. *Blood.* 2014;123:4037-44.

85. Baliga RR. From clinical observation to mechanism--Heyde's syndrome. *N Engl J Med.* 2013;368:579.

86. Godino C, Lauretta L, Pavon AG, Mangieri A, Viani G, Chieffo A, Galaverna S, Latib A, Montorfano M, Cappelletti A, Maisano F, Alfieri O, Margonato A, Colombo A. Heyde's syndrome incidence and outcome in patients undergoing transcatheter aortic valve implantation. *J Am Coll Cardiol.* 2013;61:687-9.

87. Spangenberg T, Budde U, Schewel D, Frerker C, Thielsen T, Kuck KH, Schäfer U. Treatment of acquired von Willebrand syndrome in aortic stenosis with transcatheter aortic valve replacement. *JACC Cardiovasc Interv.* 2015;8:692-700.

88. Sedaghat A, Kulka H, Sinning JM, Falkenberg N, Driesen J, Preisler B, Hammerstingl C, Nickenig G, Pötzsch B, Oldenburg J, Hertfelder HJ, Werner N. Transcatheter aortic valve implantation leads to a restoration of von Willebrand factor (VWF) abnormalities in patients with severe aortic stenosis - Incidence and relevance of clinical and subclinical VWF dysfunction in patients undergoing transfemoral TAVI. *Thromb Res.* 2017;151:23-8.

89. Ishii M, Kaikita K, Mitsuse T, Nakanishi N, Oimatsu Y, Yamashita T, Nagamatsu S, Tabata N, Fujisue K, Sueta D, Takashio S, Arima Y, Sakamoto K, Yamamoto E, Tsujita K. Reduction in thrombogenic activity and thrombocytopenia after transcatheter aortic valve implantation - The ATTRACTIVE-TTAS study. *Int J Cardiol Heart Vasc.* 2019;23:100346.

90. Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN, Hui AJ, Wu JC, Leung WK, Lee VW, Lee KK, Lee YT, Lau JY, To KF, Chan HL, Chung SC, Sung JJ. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med.* 2005;352:238-44.

91. Sung JJ, Lau JY, Ching JY, Wu JC, Lee YT, Chiu PW, Leung VK, Wong VW, Chan FK. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med.* 2010;152:1-9.

92. Zimarino M, Barbanti M, Dangas GD, Testa L, Capodanno D, Stefanini GG, Radico F, Marchioni M, Amat-Santos I, Piva T, Saia F, Reimers B, De Innocentiis C, Picchi A, Toro A, Rodriguez-Gabella T, Nicolini E, Moretti C, Gallina S, Maddestra N, Bedogni F, Tamburino C. Early Adverse Impact of Transfusion After Transcatheter Aortic Valve Replacement: A Propensity-Matched Comparison From the TRITAVI Registry. *Circ Cardiovasc Interv.* 2020;13:e009026.

93. Costa F, Cohen MG. Transfusion and Mortality After Transcatheter Aortic Valve Replacement: Association or Causation? *Circ Cardiovasc Interv.* 2020;13:e010225.

94. Piccolo R, Pilgrim T, Franzone A, Valgimigli M, Haynes A, Asami M, Lanz J, Räber L, Praz F, Langhammer B, Roost E, Windecker S, Stortecky S. 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;10:1436-46.

95. Wenaweser P, Pilgrim T, Guerios E, Stortecky S, Huber C, Khattab AA, Kadner A, Buellesfeld L, Gloekler S, Meier B, Carrel T, Windecker S. Impact of coronary artery disease and percutaneous coronary intervention on outcomes in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *EuroIntervention.* 2011;7:541-8.

96. Barbanti M, Buccheri S, Capodanno D, D'Errigo P, Ranucci M, Rosato S, Santoro G, Fusco D, Tamburino C, Biancari F, Seccareccia F; OBSERVANT Research Group. Transcatheter or surgical treatment of severe aortic stenosis and coronary artery disease: A comparative analysis from the Italian OBSERVANT study. *Int J Cardiol*. 2018;270:102-6.

97. Okuno T, Demirel C, Tomii D, Erdoes G, Heg D, Lanz J, Praz F, Zbinden R, Reineke D, Räber L, Stortecky S, Windecker S, Pilgrim T. Risk and Timing of Noncardiac Surgery After Transcatheter Aortic Valve Implantation. *JAMA Netw Open*. 2022;5:e2220689.

98. Omoto T, Aoki A, Maruta K, Masuda T, Horikawa Y. Influence of transcatheter aortic valve replacement on patients with severe aortic stenosis undergoing non-cardiac surgery. *J Cardiothorac Surg*. 2020;15:198.

99. Capodanno D, Collet JP, Dangas G, Montalescot G, Ten Berg JM, Windecker S, Angiolillo DJ. Antithrombotic Therapy After Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv*. 2021;14:1688-703.

100. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, De Hert S, de Laval I, Geisler T, Hinterbuchner L, Ibanez B, Lenarczyk R, Mansmann UR, McGreavy P, Mueller C, Muneretto C, Niessner A, Potpara TS, Ristić A, Sade LE, Schirmer H, Schüpke S, Sillesen H, Skulstad H, Torracca L, Tutarel O, Van Der Meer P, Wojakowski W, Zacharowski K; ESC Scientific Document Group. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing noncardiac surgery. *Eur Heart J*. 2022;43:3826-924.

101. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation*. 2016;134:e123-55.

102. Hayashida K, Lefèvre T, Chevalier B, Hovasse T, Romano M, Garot P, Mylotte D, Uribe J, Farge A, Donzeau-Gouge P, Bouvier E, Cormier B, Morice MC. Transfemoral aortic valve implantation new criteria to predict vascular complications. *JACC Cardiovasc Interv*. 2011;4:851-8.

103. Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, Smalling R, Lim S, Malaisrie SC, Kapadia S, Szeto WY, Greason KL, Kereiakes D, Ailawadi G, Whisenant BK, Devireddy C, Leipsic J, Hahn RT, Pibarot P, Weissman NJ, Jaber WA, Cohen DJ, Suri R, Tuzcu EM, Svensson LG, Webb JG, Moses JW, Mack MJ, Miller DC, Smith CR, Alu MC, Parvataneni R, D'Agostino RB Jr, Leon MB. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet*. 2016;387:2218-25.

104. Popma JJ, Reardon MJ, Khabbaz K, Harrison JK, Hughes GC, Kodali S, George I, Deeb GM, Chetcuti S, Kipperman R, Brown J, Qiao H, Slater J, Williams MR. Early Clinical Outcomes After Transcatheter Aortic Valve Replacement Using a Novel Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis Who Are Suboptimal for Surgery: Results of the Evolut R U.S. Study. *JACC Cardiovasc Interv*. 2017;10:268-75.

105. Van Mieghem NM, Tchetche D, Chieffo A, Dumonteil N, Messika-Zeitoun D, van der Boon RM, Vahdat O, Buchanan GL, Marcheix B, Himbert D, Serruys PW, Fajadet J, Colombo A, Carrié D, Vahanian A, de Jaegere PP. Incidence, predictors, and implications of access site complications with transfemoral transcatheter aortic valve implantation. *Am J Cardiol*. 2012;110:1361-7.

106. Généreux P, Webb JG, Svensson LG, Kodali SK, Satler LF, Fearon WF, Davidson CJ, Eisenhauer AC, Makkar RR, Bergman GW, Babaliaros V, Bavaria JE, Velazquez OC, Williams MR, Hueter I, Xu K, Leon MB; PARTNER Trial Investigators. Vascular complications after transcatheter aortic valve replacement: insights from the PARTNER (Placement of AoRTic TraNscathetER Valve) trial. *J Am Coll Cardiol*. 2012;60:1043-52.

107. Généreux P, Cohen DJ, Williams MR, Mack M, Kodali SK, Svensson LG, Kirtane AJ, Xu K, McAndrew TC, Makkar R, Smith CR, Leon MB. Bleeding complications after surgical aortic valve replacement compared with transcatheter aortic valve replacement: insights from the PARTNER I Trial (Placement of Aortic Transcatheter Valve). *J Am Coll Cardiol*. 2014;63:1100-9.

108. Fanaroff AC, Manandhar P, Holmes DR, Cohen DJ, Harrison JK, Hughes GC, Thourani VH, Mack MJ, Sherwood MW, Jones WS, Vemulapalli S. Peripheral Artery Disease and Transcatheter Aortic Valve Replacement Outcomes: A Report From the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Therapy Registry. *Circ Cardiovasc Interv*. 2017;10:e005456.

109. Didier R, Lhermusier T, Auffret V, Eltchaninoff H, Le Breton H, Cayla G, Commeau P, Collet JP, Cuisset T, Dumonteil N, Verhoye JP, Beurtheret S, Lefèvre T, Teiger E, Carrié D, Himbert D, Albat B, Cribier A, Sudre A, Blanchard D, Bar O, Rioufol G, Collet F, Houel R, Labrousse L, Meneveau N, Ghostine S, Manigold T, Guyon P, Delepine S, Favereau X, Souteyrand G, Ohlmann P, Doisy V, Beygui F, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Iung B, Gilard M; STOP-AS and France-TAVI. TAVR Patients Requiring Anticoagulation: Direct Oral Anticoagulant or Vitamin K Antagonist? *JACC Cardiovasc Interv*. 2021;14:1704-13.

110. Darmoch F, Alraies MC, Al-Khadra Y, Pacha HM, Soud M, Kaki A, Rab T, Grines CL, Bagur R, Kwok CS, Mamas M, Banerjee S, AlJaroudi W, Pinto DS. Outcome of Transcatheter Aortic Valve Implantation in Patients with Peripheral Vascular Disease. *Am J Cardiol*. 2019;124:416-22.

111. Yamawaki M, Honda Y, Makino K, Nakano T, Iida Y, Yashima F, Ueno H, Mizutani K, Tabata M, Tada N, Takagi K, Yamanaka F, Naganuma T, Watanabe Y, Yamamoto M, Shirai S, Hayashida K; OCEAN-TAVI registry. Influence of polyvascular disease on clinical outcome in patients undergoing transcatheter aortic valve implantation via transfemoral access. *PLoS One*. 2021 Dec 2;16(12):e0260385.

112. Maniotis C, Andreou C, Karalis I, Koutouzi G, Agelaki M, Koutouzis M. A systematic review on the safety of Prostar XL versus ProGlide after TAVR and EVAR. *Cardiovasc Revasc Med*. 2017;18:145-50.

113. Costa G, Valvo R, Picci A, Criscione E, Reddavid C, Motta S, Strazzieri O, Deste W, Giuffrida A, Garretto V, Cannizzaro MT, Inserra C, Veroux P, Giaquinta A, Sgroi C, Tamburino C, Barbanti M. An upfront combined strategy for endovascular haemostasis in transfemoral transcatheter aortic valve implantation. *EuroIntervention*. 2021;17:728-35.

114. Gmeiner JMD, Linnemann M, Steffen J, Scherer C, Orban M, Theiss H, Mehilli J, Sadoni S, Peterß S, Joskowiak D, Hagl C, Tsilimparis N, Curta A, Maurus S, Doldi PM, Löw K, Haum M, Roden D, Hausleiter J, Massberg S, Rizas K, Deseive S, Braun D. Dual ProGlide versus ProGlide and FemoSeal for vascular access haemostasis after transcatheter aortic valve implantation. *EuroIntervention*. 2022;18:812-19.

115. Biasco L, Ferrari E, Pedrazzini G, Faletra F, Moccetti T, Petracca F, Moccetti M. Access Sites for TAVI: Patient Selection Criteria, Technical Aspects, and Outcomes. *Front Cardiovasc Med*. 2018;5:88.

116. Beurtheret S, Karam N, Resseguier N, Houel R, Modine T, Folliguet T, Chamandi C, Com O, Gelisse R, Bille J, Joly P, Barra N, Tavildari A, Commeau P, Armero S, Pankert M, Pansieri M, Siame S, Koning R, Laskar M, Le Dolley Y, Maudiere A, Villette B, Khanoyan P, Seitz J, Blanchard D, Spaulding C, Lefevre T, Van Belle E, Gilard M, Eltchaninoff H, Iung B, Verhoye JP, Abi-Akar R, Achouh P, Cuisset T, Leprince P, Marijon E, Le Breton H, Lafont A. Femoral Versus Nonfemoral Peripheral Access for Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol*. 2019;74:2728-39.

117. Patel JS, Krishnaswamy A, Svensson LG, Tuzcu EM, Mick S, Kapadia SR. Access Options for Transcatheter Aortic Valve Replacement in Patients with Unfavorable Aortoiliofemoral Anatomy. *Curr Cardiol Rep*. 2016;18:110.

118. Gilard M, Schlüter M, Snow TM, Dall'Ara G, Eltchaninoff H, Moat N, Goicolea J, Ussia GP, Kala P, Wenaweser P, Zembala M, Nickenig G, Price S, Alegria Barrero E, Iung B, Zamorano P, Schuler G, Corti R, Alfieri O, Prendergast B, Ludman P, Windecker S, Sabate M, Witkowski A, Danenberg H, Schroeder E, Romeo F, Macaya C, Derumeaux G, Laroche C, Pighi M, Serdoz R, Di Mario C. The 2011-2012 pilot European Society of Cardiology Sentinel Registry of Transcatheter Aortic Valve Implantation: 12-month clinical outcomes. *EuroIntervention*. 2016;12:79-87.

119. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetche D, Carrié D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Van Belle E, Laskar M; FRANCE 2 Investigators. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med*. 2012;366:1705-15.

120. Schymik G, Würth A, Bramlage P, Herbinger T, Heimeshoff M, Pilz L, Schymik JS, Wondraschek R, Süselbeck T, Gerhardus J, Luik A, Gonska BD, Posival H, Schmitt C, Schröfel H. Long-term results of transapical versus transfemoral TAVI in a real world population of 1000 patients with severe symptomatic aortic stenosis. *Circ Cardiovasc Interv*. 2014;8:e000761.

121. Arsalan M, Kim WK, Van Linden A, Liebetrau C, Pollock BD, Filardo G, Renker M, Möllmann H, Doss M, Fischer-Rasokat U, Skwara A, Hamm CW, Walther T. Predictors and outcome of conversion to cardiac surgery during transcatheter aortic valve implantation. *Eur J Cardiothorac Surg*. 2018;54:267-72.

122. Eggebrecht H, Vaquerizo B, Moris C, Bossone E, Lämmer J, Czerny M, Zierer A, Schröfel H, Kim WK, Walther T, Scholtz S, Rudolph T, Hengstenberg C, Kempfert J, Spaziano M, Lefevre T, Bleiziffer S, Schofer J, Mehilli J, Seiffert M, Naber C, Biancari F, Eckner D, Cornet C, Lhermusier T, Philippart R, Siljander A, Giuseppe Cerillo A, Blackman D, Chieffo A, Kahlert P, Czerwinska-Jelonkiewicz K, Szymanski P, Landes U, Kornowski R, D'Onofrio A, Kaulfersch C, Søndergaard L, Mylotte D, Mehta RH, De Backer O; European Registry on Emergent Cardiac Surgery during TAVI (EuRECS-TAVI). Incidence and outcomes of emergent cardiac surgery during transfemoral transcatheter aortic valve implantation (TAVI): insights from the European Registry on Emergent Cardiac Surgery during TAVI (EuRECS-TAVI). *Eur Heart J*. 2018;39:676-84.

123. Eggebrecht H, Mehta RH, Kahlert P, Schymik G, Lefèvre T, Lange R, Macaya C, Mandinov L, Wendler O, Thomas M. Emergent cardiac surgery during transcatheter aortic valve implantation (TAVI): insights from the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry. *EuroIntervention*. 2014;10:975-81.

124. Griese DP, Reents W, Kerber S, Diegeler A, Babin-Ebell J. Emergency cardiac surgery during transfemoral and transapical transcatheter aortic valve implantation: incidence, reasons, management, and outcome of 411 patients from a single center. *Catheter Cardiovasc Interv*. 2013;82: E726-33.

125. Capodanno D, Morice MC, Angiolillo DJ, Bhatt DL, Byrne RA, Colleran R, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson CM, Gregson J, Haude M, James SK, Kim HS, Kimura T, Konishi A, Leon MB, Magee PFA, Mitsutake Y, Mylotte D, Pocock SJ, Rao SV, Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhovel U, Krucoff MW, Urban P, Mehran R. Trial Design Principles for Patients at High Bleeding Risk Undergoing PCI: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2020;76:1468-83.

126. De Backer O, Dangas GD, Jilaihawi H, Leipsic JA, Terkelsen CJ, Makkar R, Kini AS, Veien KT, Abdel-Wahab M, Kim WK, Balan P, Van Mieghem N, Mathiassen ON, Jeger RV, Arnold M, Mehran R, Guimarães AHC, Nørgaard BL, Kofoed KF, Blanke P, Windecker S, Søndergaard L; GALILEO-4D Investigators. Reduced Leaflet Motion after Transcatheter Aortic-Valve Replacement. *N Engl J Med*. 2020;382:130-9.

127. Makkar RR, Blanke P, Leipsic J, Thourani V, Chakravarty T, Brown D, Trento A, Guyton R, Babaliaros V, Williams M, Jilaihawi H, Kodali S, George I, Lu M, McCabe JM, Friedman J, Smalling R, Wong SC, Yazdani S, Bhatt DL, Bax J, Kapadia S, Herrmann HC, Mack M, Leon MB. Subclinical Leaflet Thrombosis in Transcatheter and Surgical Bioprosthetic Valves: PARTNER 3 Cardiac Computed Tomography Substudy. *J Am Coll Cardiol*. 2020;75:3003-15.

128. Urban P, Gregson J, Owen R, Mehran R, Windecker S, Valgimigli M, Varenne O, Krucoff M, Saito S, Baber U, Chevalier B, Capodanno D, Morice MC, Pocock S. Assessing the Risks of Bleeding vs Thrombotic Events in Patients at High Bleeding Risk After Coronary Stent Implantation: The ARC-High Bleeding Risk Trade-off Model. *JAMA Cardiol*. 2021;6:410-9.

129. Jørgensen TH, Thyregod HGH, Ihlemann N, Nissen H, Petursson P, Kjeldsen BJ, Steinbrüchel DA, Olsen PS, Søndergaard L. Eight-year outcomes for patients with aortic valve stenosis at low surgical risk randomized to transcatheter vs. surgical aortic valve replacement. *Eur Heart J*. 2021;42:2912-9.

130. Greco A, Spagnolo M, Capodanno D. Antithrombotic therapy after transcatheter aortic valve implantation. *Expert Rev Med Devices*. 2022;19: 499-513.

131. Sinning JM, Horack M, Grube E, Gerckens U, Erbel R, Eggebrecht H, Zahn R, Linke A, Sievert H, Figulla HR, Kuck KH, Hauptmann KE, Hoffmann E, Hambrecht R, Richardt G, Sack S, Senges J, Nickenig G, Werner N. The impact of peripheral arterial disease on early outcome after transcatheter aortic valve implantation: results from the German Transcatheter Aortic Valve Interventions Registry. *Am Heart J*. 2012;164: 102-10.e1.

Supplementary data

Supplementary Appendix 1. Bleeding in contemporary clinical trials.

Supplementary Appendix 2. Trials of antithrombotic strategies for TAVI.

Supplementary Appendix 3. Limitations of existing definitions and scores.

Supplementary Appendix 4. Principles of trial design for VARC-HBR trials of TAVI.

Supplementary Appendix 5. Open areas and unknown factors.

Supplementary Appendix 6. Regulatory considerations.

Supplementary Table 1. Risk for major bleeding events in landmark trials of transcatheter aortic valve implantation.

Supplementary Table 2. Design and rates of life-threatening bleeding in clinical trials of antithrombotic therapy for transcatheter aortic valve implantation.

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Supplementary data

Supplementary Appendix 1. Bleeding in contemporary clinical trials.

Periprocedural bleeding

Landmark TAVI clinical trials have used heterogeneous bleeding definitions that may challenge the comparison of bleeding rates among studies. Refinements in procedural technique and iterative development of transcatheter heart valve and delivery system technology have substantially reduced procedure-related bleeding, but they further hamper a fair comparison across trials and eras. According to the risk-category of TAVI recipients, life-threatening bleeding rates, which are typically related to the periprocedural period, have fallen from 16.6% among high-risk patients treated with first generation self-expanding valves to 11.3% in intermediate risk patients, and to 3.2% among low-risk cases with contemporary devices and techniques. Similar reductions were reported among trials using balloon-expanding valves (**eTable 1**). The temporal reduction in the rates of major bleeding has been similarly remarkable: major bleeding occurred in 14.7% of patients in the PARTNER 1A trial and in 4.9% in the PARTNER 3 trial. The rates of minor bleeding have been infrequently reported but occurred in 7.7% among TAVI patients in PARTNER 3. In the contemporary CHOICE-Closure trial, life-threatening bleeding occurred in only 0.8% of patients treated with suture-based closure. Real-world data from the STS/TVT registry have also documented significant reductions in in-hospital bleeding events over the last decade. Peri-procedural bleeding is inextricably linked to vascular complications, classified as major or minor, and can relate to both primary and secondary access sites. The rates of major vascular complications have fallen in line with bleeding events over time: major vascular complications occurred in 11.3% in PARTNER 1A and in 2.8% in PARTNER 3.

Non-periprocedural bleeding

Although definitions of major bleeding were not uniformly defined in most TAVI trials, patients at high or prohibitive surgical risk experienced the highest bleeding rates in the pivotal TAVI trials (9.3%-36.7% at 30 days and 14.7%-42.8% at 1 year), whereas patients at low surgical risk experienced the lowest early and late bleeding rates both at 30 days (2.4%-11.3%) and at one year (3.2%-7.7%). Although the precise incidence of procedural bleeding events was not uniformly reported among these studies, the difference between bleeding rates at 30 days and one year gives a rough estimate of the large relative contribution of non-

periprocedural bleeding to the overall bleeding risk of TAVI (**eTable 1**). In the PARTNER 1 trial and its continued-access registry, major late-onset bleeding (>30 days after TAVI) occurred in 5.9% at a median time of 132 days after the index procedure and was represented mainly by gastrointestinal bleeding (40.8%), neurological bleeding (15.5%), and bleeding due to traumatic falls (7.8%).

Supplementary Appendix 2. Trials of antithrombotic strategies for TAVI.

Patients without a clinical indication of oral anticoagulation

Single antiplatelet therapy (i.e., aspirin) is the current standard treatment for TAVI patients without an established indication for oral anticoagulation (OAC). In the POPular TAVI trial, periprocedural and post-intervention life-threatening or major bleeding occurred in 5.1% and 10.8% of patients without OAC randomized to aspirin alone or aspirin plus three months of clopidogrel, respectively (**eTable 2**). The primary endpoint of any VARC-2 major bleeding was lower with aspirin only, with no apparent increase in thrombotic events. The approach of using a novel anticoagulant in patients with no baseline indication for OAC was not supported by the GALILEO trial, which was prematurely stopped due to an increase in all-cause mortality and major bleeding (2.8% vs 1.4%) with rivaroxaban 10 mg daily plus aspirin for three months versus aspirin plus clopidogrel for three months, followed by aspirin monotherapy. In the ATLANTIS trial, two thirds of patients had no indication for OAC after successful TAVI. The primary net benefit endpoint did not differ between apixaban and standard of care, and there was no interaction between the treatment effect of apixaban and the clinical indication for OAC. In the stratum of patients without an indication for OAC, the rate of life-threatening or major bleeding did not differ between apixaban versus standard of care (7.8% vs 7.3%) but an excess of non-cardiovascular death was noted in apixaban-treated patients. In a recent review and meta-analysis of trials evaluating post-TAVI antithrombotic regimens in patients without an indication for OAC, single antiplatelet therapy was associated with a significant reduction of life-threatening or major bleeding compared to DAPT (relative risk 0.45; 95% confidence interval 0.29-0.70 without significant ischemic offset. Furthermore, a recent multicenter observational Japanese registry reported a lower incidence of bleeding without increased risk of adverse cardiovascular events in 8.2% of patients receiving no antithrombotic therapy, compared to those receiving single or dual antiplatelet treatment.

Patients requiring OAC for other clinical conditions

In the cohort B of the POPular TAVI trial, including patients on OAC, patients were randomized before the TAVI procedure to OAC monotherapy or OAC in combination with clopidogrel. The primary endpoint of any bleeding at one year occurred less frequently in the OAC alone versus OAC plus clopidogrel arm (21.7% vs. 34.6%; p=0.01), with most bleeding events located at the large bore access site; life-threatening or major bleeding did not differ, although it was numerically higher with OAC combined with clopidogrel (8.9% vs 16.7%) (**Table 2**). ENVISAGE TAVI AF randomized patients to the direct oral anticoagulant edoxaban or vitamin K antagonists. There was no difference between the two OAC treatment regimens in the primary net clinical benefit endpoint (i.e., non-inferiority met); however, edoxaban was associated with significantly more major bleeding events (9.7% vs 7.0%) driven by more gastrointestinal bleeding. In the stratum #1 of the ATLANTIS trial, patients with an indication for OAC (n=451) were randomized to either apixaban twice daily or vitamin K antagonists. There was no difference in the primary efficacy endpoint or in major bleeding (10.3% vs 11.4%) between the two regimens.

Supplementary Appendix 3. Limitations of existing definitions and scores.

There are few data on factors that promote HBR in TAVI patients, especially when compared to the PCI or atrial fibrillation populations. Given the advanced age and comorbidities of a typical TAVI population, HBR criteria as defined in the literature of PCI are frequent. For example, in SCOPE-2, over 80% of the population was considered at HBR using the ARC-HBR criteria.

The HAS-BLED score used to estimate bleeding risk for an atrial fibrillation population on vitamin K antagonists was applied to a TAVI population in the OCEAN TAVI registry. A threshold score of four predicted severe bleeding and mortality in a transfemoral population, independent of the presence of atrial fibrillation, but this finding has yet to be validated in other cohorts.

Recently, machine learning was used to develop the PREDICT-TAVR model, which is made of six items (hemoglobin, serum iron concentration, common femoral artery diameter, creatinine clearance, DAPT, OAC therapy). In a validation cohort, the score successfully predicted events in the first 30 days, with good discrimination (area under the curve, 0.80 95% CI, 0.75 to 0.83). While this score is an important step towards profiling risk in the early phase post TAVI where bleeding events are highest, it did not show any significant prediction

for non-procedural events between 30 days and one year and it was unable to distinguish between major and minor bleeding events.

Supplementary Appendix 4. Principles of trial design for VARC-HBR trials of TAVI.

Trials testing antithrombotic strategies after TAVI have shown two important lessons. Firstly, that a 'one size fits all' strategy is unlikely to provide answers in a very complex and diverse population. Secondly, although questions that need to be answered are generally of pragmatic nature, future trial design may benefit from selecting precise cohorts that address one question at the time. With this background, we provide a series of consensus recommendations for future trials designs.

Outcomes of interest

In trials addressing bleeding risk, outcomes of interest may be divided into ischemic events and bleeding events. Among ischemic events after TAVI, myocardial infarction, cerebrovascular events (CVEs), and valve thrombosis are of highest interest. Other thrombotic events potentially occurring post-TAVI, such as peripheral thrombotic events or pulmonary embolism, are less frequent and relevant from a clinical trial perspective. Besides mechanical coronary obstruction or valve thrombosis-related myocardial infarction, a TAVI implantation is not *per se* a mechanistic factor increasing the risk of myocardial infarction in the long term. Thus, experimental antithrombotic strategies may reasonably target the former rare, but serious events. Similarly, CVEs related to TAVI occur primarily as a consequence of physical manipulation during transcatheter heart valve delivery due to embolization of debris to the brain, or potentially due to valve thrombosis. The latter is likely the most relevant target of antithrombotic therapies post-TAVI and can be divided into subclinical leaflet thrombosis and overt valve thrombosis. A sensitive approach to investigate valve thrombosis requires precision in cohort selection in addition to well-designed imaging trials. Additional high-quality mechanistic data linked to clinical outcomes may further identify sub-groups potentially benefiting from a large-scale antithrombotic clinical trial. The trade-off of increasing antithrombotic potency to reduce ischemic events, is the inevitable increased risk of bleeding events. Major or more severe bleeding events (VARC-3-BARC types 2, 3 and 4) are associated with increased risk of fatalities at long-term; thus, balancing the potential benefit of reducing ischemic events but increased bleeding events is the most important consideration when designing HBR trials. Given the different pathophysiology of events

occurring at either the time of the procedure, early after the procedure, or at long term, it is important to standardize these time points. We suggest reporting events as in-hospital, at 30 days, and at 1 year, as minimum, and following timing recommendations of VARC-3 for specific endpoints.

Patient risk profile and age

TAVI cohorts are traditionally classified according to the surgical risk of mortality, as low, intermediate, and high surgical risk. This risk classification directly correlates with the risk of bleeding as well as with age. The higher the surgical risk, the higher the average age, and the risk of bleeding. It is advisable to carefully consider the risk profile population to be addressed in a particular trial.

Medical history

Coronary artery disease is highly prevalent in patients undergoing TAVI, affecting two thirds, and with one fourth having undergone PCI or presented a myocardial infarction. Similarly, atrial fibrillation affects one third of patients planned for TAVI and up to two thirds after TAVI. Study cohorts could be divided as those with existing (and de-novo) indication of oral anticoagulation, largely driven by atrial fibrillation, and those with no indication of anticoagulation. Additional factors are the co-existence of coronary artery disease and the indication of SAPT or DAPT. Naturally, the surgical risk profile may be taken into consideration, and for the purpose of investigating antithrombotic strategies, the bleeding risk profile adds significant precision to the cohort selection. It must be emphasized as well that one fourth of patients planned for TAVI may present with co-existent PAD, which in severe cases poses challenges to vascular access, and have been associated with increased peri-procedural bleeding risk. Thus, vascular access information should ideally be captured in the trial database as well, when performing trials investigating bleeding events.

Endpoint definitions

The VARC-HBR committee aligns fully with the VARC-3 endpoint definitions and recommendations for clinical events classification. When testing therapies to reduce ischemic events, a composite of ischemic events to include death, myocardial infarction, and stroke may be considered for the primary endpoint. However, even when using composite endpoints, the expected event rates will be low and will require large sample sizes, unless novel composites including quantitative parameters are utilized. It is likely, based on the risk factors for HBR, that non-cardiovascular mortality will be a key outcome and it is crucial to report

all-cause mortality, as well as sub-classifications to further understand the risks in patients undergoing TAVI being treated with various antithrombotic or anti-ischemic strategies. Among subjects at HBR, a primary endpoint driven by bleeding events with a secondary endpoint that excludes a significant increase in ischemic events may be preferred. Depending on the clinical trial, a composite to include ischemic and bleeding events, or net clinical benefit, may also be reasonable; although the analysis plan will need to exclude that the average effect does not include a significant increase in risk for either ischemia or bleeding. However, given the overall rates of major bleeding usually surpass the rates of major ischemic events, interpretation and clinical application of net clinical benefit should be carefully considered. Moreover, well-designed imaging trials may address directly the most relevant question, which relates to the optimal management of valve thrombosis at its different stages, and in different risk profile populations.

Pragmatic considerations

Due to the relatively simple nature of the questions that need an answer (e.g., one versus another antithrombotic strategy, different duration of antithrombotic strategy, reduced intensity of antithrombotic strategy) the execution of pragmatic trials would be a possible approach to consider for this field. A pragmatic trial design may include the use of national registries, commercially-available drugs, lack of blinding, and simplified study procedures; however, adequate data and site monitoring remains paramount to maintain the quality and completeness of trial data. Comparative approaches using the win ratio or Bayesian analyses may also be seen as a way to increase the efficiency and pragmatism of trials in the field.

Supplementary Appendix 5. Open areas and unknown factors.

We acknowledge that the selection process of criteria associated with a higher rate of bleeding after TAVI is, despite an extensive and systematic lecture of the literature subject to some uncertainties. We have decided not to select frailty as a criterion for reasons that have been mentioned in the manuscript. Although poorly detailed in the TAVI literature, the role of frailty in predicting bleeding events may be underestimated and some centers may use appropriate scales to better identify frailty. Among them, the comprehensive geriatric assessment (CGA) is one of the cornerstones of modern geriatric care helping to develop a coordinated and integrated plan for treatment and follow-up. Nonetheless, CGA is resource intensive and is difficult to interpret and use for risk stratifications or frailty classifications.

Frailty assessment using the frailty phenotype-5 items validated by the Cardiovascular health study (CHS) is less time-consuming in assessing frailty and its severity. However, because only limited items are evaluated it lacks information to build strategy for frailty intervention.

Serum concentrations of antithrombotic drugs may be associated with increased risk of bleeding. Conditions leading to higher serum concentrations of these drugs are multifactorial, including Kidney or liver diseases, drug and food interactions, patient's non-adherence with overexposure related to excessive intake. Available data on serum concentration in the TAVI literature is scarce and, although this may be associated with increased bleeding in a given patient, we did not consider this to be an established criterion defining HBR in patients undergoing TAVI.

TAVI is mostly an elective procedure. However, TAVI may be performed in emergency in a patient with decompensated cardiac failure, impaired hemodynamics and shock. Ischemia-induced multiple organ failure may occur as a consequence of shock with subsequent hepatic damage leading to coagulation disorders that may further increase the risk and severity of bleeding. Although this may significantly impact the prognosis and bleeding risk of a given patient, this situation is rare. Because of the paucity of clinical data in the literature, the consensus of the VARC-HBR board was that TAVI performed in an emergency or semi-emergency setting may not be considered a criterion for HBR.

Female gender is usually associated with some of the criteria (low body mass index, anemia, smaller common femoral artery diameter) that have been selected to define a high-risk population for bleeding after TAVI. The VARC-HBR Board considered that adding female gender as a criterion to define a HBR population after TAVI may be redundant as these factors are differently distributed between sexes. Defining female gender as a VARC-HBR criterion may imply underuse of TAVI in women because of a pretended too high risk for bleeding and account for potential loss of opportunity for women to be treated with current standard of care.

Finally, some patients may cumulate >3 or 4 major VARC-HBR criteria with an expected "excessive" or "prohibitive" risk of bleeding associated with a TAVI procedure. Several cardiac and extra-cardiac conditions and frailty increase the risk of mortality despite TAVI. Among the survivors, these comorbidities can inhibit improvements in quality of life. This confers to the definition of "futile TAVI" resulting in the unnecessary exposure of risk for patients and inefficient resource utilization for healthcare services, a well-known concept that overcomes the risk of bleeding and is usually well considered by heart teams. The

decision not to perform the TAVI procedure is multifactorial, considering bleeding and other risks, and should remain the prerogative of local heart teams. Therefore, we decided not to introduce a fourth level scale that would consider the bleeding risk as too high or excessive.

Supplementary Appendix 6. Regulatory considerations.

Studies of patients at HBR have intrinsic public health value and support the mission of regulatory bodies. Consensus definitions are necessary to improve the efficiency and predictability of study design and quality and can assist regulatory decision-making for safe and effective drugs and devices for patients at HBR in a timely fashion. Sex, nationality, and ethnic differences in bleeding risk may also be important considerations in trial design and the interpretation of study outcomes. This article reflects the consensus views of the VARC-HBR consortium and does not necessarily represent the practices, policies, requirements, or recommendations of the US Food and Drug Administration or the Japanese Pharmaceuticals and Medical Devices Agency. Furthermore, the recommendations in this document do not represent a regulatory requirement from either agency. Although regulators consider it acceptable to propose and justify alternative definitions and HBR criteria, they encourage investigators to discuss any proposed trial-specific definitions of HBR prospectively with the relevant regulatory bodies before study initiation.

Supplementary Table 1. Risk for major bleeding events in landmark trials of transcatheter aortic valve implantation.

Trials (N, TAVI Arm)	Antithrombotic regimen		Access Site				Major or Life-threatening Bleeding (%)	
	Default strategy	History of AF and OAC (%)	PAD (%)	TF (%)	Sheath size	30-day major vascular complications (%)	30-day	1-year
High or prohibitive surgical risk								
PARTNER 1A High risk (N = 348)	DAPT 6 mo, then ASA	40.8	43.0	70.1	22-24 F	11.0	9.3	14.7
PARTNER 1B Prohibitive risk (N = 179)	DAPT 6 mo, then ASA	32.9	30.3	100	22-24 F	16.2	16.8	22.3
US CoreValve Prohibitive risk TF access (N = 489)	DAPT 3 mo, then ASA or clopidogrel	46.8	35.2	100	18-20 F	8.2	36.7	42.8
US CoreValve High risk (N =394)	DAPT 3 mo, then ASA or clopidogrel	41.0	41.7	82.8	18-20 F	5.9	28.1	29.5
REPRISE 2 (N=120)	DAPT 1 mo, then ASA	40.8	NA	100	22-24 F	2.5	17.6	21.0
CHOICE (N=241)	DAPT 3 mo, then ASA	28.2	17.4	100	18-20 F	10.4	16.6	17.8
Intermediate surgical risk								
PARTNER 2 (N = 994)	DAPT 1 mo, then ASA	31.0	27.9	76.7	16-20 F	7.9	10.4	15.2
SURTAVI (N = 858)	DAPT 3 mo, then ASA or clopidogrel	28.1	30.8	93.6	16-20 F	6.0	12.2	13.0
PORTICO-1 (N=941)	NA	30.0	6.3	100	18-19 F	5.5	8.5	8.7
SCOPE 1 (N=739)	DAPT 3 mo, then ASA or clopidogrel	36.4	11.6	100	14-20 F	6.6	10.0	NA

Low surgical risk								
PARTNER 3 (N = 496)	DAPT 1 mo, then ASA	15.7	6.9	100	14-16 F	2.2	3.6	7.7
Evolut Low Risk (N = 725)	DAPT 1 mo, then ASA	15.4	7.5	99.0	16-20 F	3.8	2.4	3.2
NOTION (N = 142)	DAPT 3 mo, then ASA	27.8	4.1	96.5	18-20 F	**5.6**	11.3	NA
SCOPE 2 (N=796)	DAPT 3 mo, then ASA or clopidogrel	33.2	8.9	100	16-20 F	7.2	2.1	3.0

Abbreviations; AF, atrial fibrillation; ASA, aspirin; DAPT, dual antiplatelet therapy; F, French; mo, month; NA, not available; OAC, oral anticoagulation; PAD, peripheral artery disease; TF, transfemoral.

Supplementary Table 2. Design and rates of life-threatening bleeding in clinical trials of antithrombotic therapy for transcatheter aortic valve implantation.

Trials (N)	Antithrombotic regimen		Patient characteristics					Follow-up	Major or life-threatening bleeding, %	
	Treatment arm	Control arm	Age	Females, %	Prior stroke, %	PAD			Treatment arm	Control arm
	Patients with no need for chronic anticoagulation									
ARTE (N=222)	Clopidogrel + ASA 3 mo	ASA 3 mo	79	41.9	NA	NA		3 mo	10.8	3.6
GALILEO (N=1644)	Rivaroxaban + ASA for 3 mo	ASA + clopidogrel for 3 mo	81	49.5	5.2	10.0		17 mo	5.6	3.8
POPular TAVI Cohort A (N=665)	ASA 3 mo	ASA + clopidogrel 3 mo	80	48.7	4.5	17.3		12 mo	5.1	10.8
ATLANTIS 2nd stratum (N=1049)	Apixaban (alone 75%, with SAPT 25%)	SAPT/DAPT (22%/78%)	NA	NA	NA	NA		12 mo	7.8	7.3
	Patients with need for chronic anticoagulation									
ENVISAGE-TAVI AF (N=1426)	Edoxaban (with SAPT in 60%)	VKA (with SAPT in 60%)	82	47.5	16.8	NA		18 mo	9.7	7.0
POPular TAVI Cohort B (N=313)	VKA 12 mo	VKA 12 mo + clopidogrel for 3 mo	81	45.4	9.6	18.5		12 mo	8.9	16.7
ATLANTIS 1st stratum (N=451)	Apixaban (with SAPT in 25%)	VKA (with SAPT in 25%)	NA	NA	NA	NA		12 mo	10.3	11.4

Definitions for major bleeding were VARC-2 in ARTE, GALILEO, ATLANTIS; VARC, BARC, TIMI and GUSTO in POPular TAVI; ISTH, BARC, TIMI and GUSTO in ENVISAGE-TAVI AF. Abbreviations: ASA, aspirin; DAPT, dual antiplatelet therapy; mo, month; PAD; peripheral artery disease; SAPT, single antiplatelet therapy; VKA, vitamin-K antagonist.