JACC: CARDIOVASCULAR INTERVENTIONS VOL. 17, NO. 19, 2024

STATE-OF-THE-ART REVIEW

Antithrombotic Therapy in High Bleeding Risk, Part I

Percutaneous Cardiac Interventions

Mattia Galli, MD, PhD,[a,b,*] Felice Gragnano, MD, PhD,[c,d,*] Martina Berteotti, MD, PhD,[d,*] Rossella Marcucci, MD,[e] Giuseppe Gargiulo, MD, PhD,[f] Paolo Calabrò, MD, PhD,[c,d] Fabrizia Terracciano, MD,[c,d] Felicita Andreotti, MD, PhD,[g,h] Giuseppe Patti, MD,[i] Raffaele De Caterina, MD, PhD,[j] Davide Capodanno, MD, PhD,[k] Marco Valgimigli, MD, PhD,[l,m] Roxana Mehran, MD,[n] Pasquale Perrone Filardi, MD, PhD,[f] Plinio Cirillo, MD, PhD,[f] Dominick J. Angiolillo, MD, PhD,[o] the Working Group of Thrombosis of the Italian Society of Cardiology

ABSTRACT

Antithrombotic therapy after cardiac percutaneous interventions is key for the prevention of thrombotic events but is inevitably associated with increased bleeding, proportional to the number, duration, and potency of the antithrombotic agents used. Bleeding complications have important clinical implications, which in some cases may outweigh the expected benefit of reducing thrombotic events. Because the response to antithrombotic agents varies widely among patients, there has been a relentless effort toward the identification of patients at high bleeding risk (HBR), in whom modulation of antithrombotic therapy may be needed to optimize the balance between safety and efficacy. Among patients undergoing cardiac percutaneous interventions, recent advances in technology have allowed for strategies of de-escalation to reduce bleeding without compromising efficacy, and HBR patients are expected to benefit the most from such approaches. Guidelines do not extensively expand upon the topic of de-escalation strategies of antithrombotic therapy in HBR patients. In this review, we discuss the evidence and provide practical recommendations on optimal antithrombotic therapy in HBR patients undergoing various cardiac percutaneous interventions. (JACC Cardiovasc Interv. 2024;17:2197–2215) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

From the [a]GVM Care & Research, Maria Cecilia Hospital, Cotignola, Italy; [b]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; [c]Department of Translational Medical Sciences, University of Campania Luigi Vanvitelli, Caserta, Italy; [d]Division of Clinical Cardiology, A.O.R.N. Sant'Anna e San Sebastiano, Caserta, Italy; [e]Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy; [f]Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy; [g]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [h]Catholic University Medical School, Rome, Italy; [i]Department of Cardiology, Ospedale Maggiore della Carità di Novara, University of Piemonte Orientale, Novara, Italy; [j]Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Pisa, Italy; [k]Division of Cardiology, Azienda Ospedaliero Universitaria Policlinico G. Rodolico-San Marco, University of Catania, Catania, Italy; [l]Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, Lugano, Switzerland; [m]Department of Biomedical Sciences, University of Italian Switzerland, Lugano, Switzerland; [n]Icahn School of Medicine at Mount Sinai, New York, New York, USA; and the [o]Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida, USA. *Drs Galli, Gragnano, and Berteotti contributed equally to this work.

H. Vernon "Skip" Anderson, MD, served as Guest Editor for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 28, 2023; revised manuscript received August 15, 2024, accepted August 16, 2024.

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2024.08.022

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

BARC = Bleeding Academic Research Consortium

DAPT = dual antiplatelet therapy

DAT = dual antithrombotic therapy

HBR = high bleeding risk

OAC = oral anticoagulation

PCI = percutaneous coronary intervention

SAPT = single antiplatelet therapy

TAT = triple antithrombotic therapy

Antithrombotic therapy plays a key role in preventing local and systemic thrombotic events after percutaneous cardiac interventions.[1,2] Specifically, antithrombotic therapy reduces the risk of stent thrombosis (ST) and subsequent ischemic events (ie, spontaneous myocardial infarctions or stroke) in patients undergoing percutaneous coronary interventions (PCIs), and prevents thrombotic complications on the surface of devices implanted for cardiac structural interventions before endothelization.[1,2] Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor represents the standard of care for patients undergoing PCI, and has been often empirically used after other percutaneous cardiac interventions, such as transcatheter aortic valve replacement (TAVR), left atrial appendage closure (LAAC), or transcatheter mitral and tricuspid valve interventions.[1-3] However, compared with single antiplatelet therapy (SAPT) or no antiplatelet treatment, DAPT is associated with increased bleeding, which may outweigh its ischemic benefits.[4,5] Indeed, the clinical effectiveness of antithrombotic therapy depends on multiple factors (eg, clinical, procedural, demographic, genetic) that vary widely among patients.[6] Although DAPT increases the risk of bleeding in all patients, there are certain subjects, categorized as high bleeding risk (HBR), who are particularly susceptible to this adverse outcome.[4,5]

The ever-growing recognition that the occurrence of a bleeding event among patients treated with antithrombotic therapy negatively impacts prognosis has prompted numerous investigations aimed at identifying patients at HBR and in whom modulation of antithrombotic therapy by using treatment regimens associated with reduced antithrombotic potency, known as de-escalation, can be implemented.[7] Indeed, such de-escalation strategies represent an attractive approach for HBR patients, as they can reduce the risk of bleeding without any trade-off in efficacy. De-escalation strategies include shortening the duration of DAPT, switching to a less potent drug or reducing the dose of a drug have been associated with reduced bleeding.[7-9] Percutaneous cardiac interventions, either coronary or structural, are often performed instead of surgery in patients at high surgical risk (eg, advanced age, multiple comorbidities) and who may thus also be at increased risk of bleeding.[10] Importantly, mortality related to bleeding may be increased in HBR patients with multiple comorbidities. Technological advancements leading to devices (ie, coronary stent platforms) with reduced thrombogenicity have prompted the adoption of less potent antithrombotic strategies.[2,8] In this review, we discuss the latest evidence and provide practical recommendations on the optimal antithrombotic therapy in HBR patients undergoing various cardiac percutaneous interventions.

HIGHLIGHTS

- Percutaneous cardiac interventions, whether coronary or structural, require antithrombotic therapy to prevent thrombotic events. However, antithrombotic therapy is associated with an increased risk of bleeding, which may outweigh its benefits, particularly in patients at HBR.
- The broad variability in individual response to antithrombotic agents and the associated risk of bleeding, which carries significant prognostic implications, underscores the need for tailored antithrombotic strategies to optimize the risk/benefit ratio in patients undergoing various cardiac interventions. These strategies are particularly important among patients at HBR.
- In this review, we appraise and discuss the clinical relevance of bleeding, definition of HBR, and evidence supporting the implementation of dedicated antithrombotic regimens in HBR patients, providing practical recommendations across the spectrum of various cardiac interventions.

PERCUTANEOUS CORONARY INTERVENTIONS

BLEEDING RISK IN PATIENTS UNDERGOING PCI.

Bleeding is common among PCI patients, with risk proportional to the intensity, duration, and number of antithrombotic agents.[4] The prognostic implications of bleeding are well established and vary according to the timing and severity of the event as well as the definition used, as described elsewhere.[4,11] Early studies showed that adding a thienopyridine (ie, ticlopidine or clopidogrel) to aspirin (ie, DAPT) decreased the rate of ST and other ischemic events

but increased the risk of major bleeding by 38% to 83% compared with aspirin alone.[12] Moreover, compared with clopidogrel, the use of the pharmacodynamically more effective $P2Y_{12}$ receptor inhibitors (ie, prasugrel or ticagrelor) further reduced thrombotic complications, particularly in specific subsets of patients such as those presenting with an acute coronary syndrome (ACS), but at the cost of a 25% to 30% relative increase in major bleeding.[13,14] With regard to DAPT duration, 12-month DAPT was associated with a 40% relative increase in major bleeding compared with short (1-3 months) DAPT, whereas longer DAPT durations (>12 months) were associated with a 60% relative increase in major bleeding compared with 12-month DAPT.[15,16] Importantly, the number of antithrombotic agents used has a major impact on the risk of major bleeding. The incidence per 100 person-years, indeed, raises from 2% to 3% in patients on SAPT to 3% to 4% and 4% to 5%, respectively, in patients on DAPT and dual antithrombotic therapy (DAT) with SAPT plus oral anticoagulation (OAC), and becomes highest (8%-10%) with triple antithrombotic therapy (TAT) (ie, DAPT plus OAC).[17,18]

Among patients with ACS, Bleeding Academic Research Consortium (BARC)-2 and -3 bleeds are associated with increased mortality, the extent of which was similar to the mortality rate associated with myocardial infarction (MI) for BARC 3b bleeding, and greater than that associated with MI for BARC 3c bleeding.[5] Importantly, bleeding and ischemic risks vary over time: ischemic risk is highest in the first few months after PCI and decreases thereafter, while bleeding risk tends to remain steadily elevated over time, underlying the rationale for de-escalating the potency of antiplatelet treatment regimens after an initial period of more intense treatment.[1]

HBR DEFINITIONS IN PATIENTS UNDERGOING PCI. Several scores and classifications have been proposed to define HBR patients and standardize their identification across studies (**Table 1**). The PRECISE-DAPT score was developed to predict the risk of out-of-hospital TIMI major or minor bleeding at 1 year in patients receiving DAPT using 5 items (hemoglobin, age, white blood cell count, creatinine clearance, and previous bleeding).[19] In patients at HBR (score ≥25 points), prolonged DAPT (12-24 months) is associated with increased bleeding without a reduction in ischemic events.[20] A recent meta-analysis including 67,283 patients found HBR defined by the PRECISE-DAPT score to be as frequent as 24.7% among PCI patients and associated with a 2.7-fold increase in any bleeding and a 3.5-fold increase in major bleeding compared with patients without HBR.[21] The PRECISE-DAPT score has also shown to inform decision making on the duration of DAPT.[20]

More recently, the Academic Research Consortium for High Bleeding Risk (ARC-HBR) defined HBR patients as those having a BARC 3 or 5 bleeding risk ≥4% or an intracranial hemorrhage (ICH) risk ≥1% at 1 year.[22] A total of 14 major and 6 minor criteria, including clinical and laboratory variables, were identified. A major criterion is defined as any criterion that, in isolation, confers a BARC 3 or 5 bleeding risk ≥4% or an ICH risk ≥1% at 1 year. A minor criterion is defined as any criterion that, compared with its absence, confers an increased risk of BARC 3 or 5 bleeding <4% at 1 year. Several studies have validated the ARC-HBR definition in contemporary PCI settings.[23] However, a recent study found that 5 out of the 6 minor criteria actually identify in isolation patients with a BARC 3 or 5 bleeding risk ≥4%, resembling in magnitude the risk of bleeding originally associated with major criteria, suggesting that further investigations are required to refine the accuracy of different criteria in the ARC-HBR definition.[24] Recently, the ARC developed a trade-off model predicting the absolute and relative risks of bleeding and ischemic events at the time of PCI, to guide clinical decision making.[25]

In addition to risk algorithms, all of which include age, additional individual demographic (eg, East Asian ethnicity), clinical (eg, ACS, renal dysfunction, cardiogenic shock, cardiac arrest, frailty), and procedural (eg, nonradial access, periprocedural antithrombotic therapy, use of mechanical support) features have been associated with bleeding and should be considered to increase the accuracy by which patients are stratified for their bleeding risk.[26,27] However, it should be acknowledged that the clinical utility of using scores and classifications to guide antithrombotic therapy among PCI patients is limited by the fact that thrombotic and bleeding risks frequently coexist, with HBR patients being often also at increased risk of thrombotic events.[1,6] Moreover, whether scores designed to predict the benefit of prolonged DAPT after PCI (ie, DAPT score) also apply to the subgroup of HBR patients remains to be determined.

ANTITHROMBOTIC STRATEGIES AFTER PCI IN HBR PATIENTS. Patients without an indication for OAC. The evidence on antithrombotic treatment options for HBR-PCI patients without an indication to be on an OAC not only derives from dedicated studies selectively including HBR patients, but also indirectly derives from randomized controlled trials (RCTs)

TABLE 1 Main HBR Classification Tools Among the Spectrum of Cardiac Percutaneous Interventions

	Bleeding Definition	Score Range	Score Threshold	Bleeding Risk Score Factors	Performance
Percutaneous coronary intervention					
PRECISE-DAPT	TIMI major and minor	0-100	Score ≥25	Age, previous bleed, WBC, Hb, Cr clearance	C_{stat}: 0.71
ARC-HBR	BARC major bleeding	Qualitative	1 major criterion or 2 minor criteria	OAC, CKD, Hb, previous bleeding, PLT, bleeding diathesis, liver, malignancy, ICH, bAVM, recent or nondeferrable surgery, age, NSAID use, stroke	C_{stat}: 0.69
Transcatheter aortic valve replacement					
PREDICT-TAVR	VARC-2 bleeding	0-25	Score ≤8 = low risk Score ≥12 = very high risk	Hb, serum iron, creatinine clearance, OAC, DAPT, common femoral artery diameter	C_{stat}: 0.78
ARC-HBR[a]	BARC major bleeding	Qualitative	1 major criterion or 2 minor criteria	OAC, CKD, Hb, previous bleeding, PLT, bleeding diathesis, liver, malignancy, ICH, bAVM, recent or nondeferrable surgery, age, NSAID use, stroke	N/A
VARC-HBR	BARC major bleeding	Qualitative	2 major criteria or 3 minor criteria (very high bleeding risk); 1 major criterion or 2 minor criteria (high bleeding risk); 1 minor criteria (moderate risk)	Clinical: age, BMI, CKD, liver, active malignancies, Hb, PLT, ICH, stroke, bleeding diathesis, coagulopathy, Heyde's syndrome, spontaneous bleeding, OAC, DAPT, nondeferrable major surgery Procedural: sheath-to-femoral artery ratio >1, nontransfemoral access, conversion to open heart surgery Anatomical: severe calcifications and tortuous iliac and/or femoral arteries	N/A
Left atrial appendage closure					
HAS-BLED[a]	Major bleeding (intracranial, hospitalization, Hb decrease >2 g/L, and/or transfusion)	0-9	Score ≥3	Hypertension, liver, stroke, bleeding, INR, age, drugs, alcohol	N/A

[a]Limited evidence (not validated in this population).

ARC-HBR = Academic Research Consortium for High Bleeding Risk; BARC = Bleeding Academic Research Consortium; bAVM = brain arteriovenous malformation, BMI = body mass index; CKD = chronic kidney disease; C_{stat} = C-statistic; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; HAS-BLED = hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; Hb = hemoglobin; HBR = high bleeding risk; ICH = intracranial hemorrhage; INR = international normalized ratio; N/A = not available; NSAID = nonsteroidal anti-inflammatory drug; OAC = oral anticoagulation; PLT = platelet; VARC = Valve Academic Research Consortium; VARC-HBR = Valve Academic Research Consortium for High Bleeding Risk; VKA = vitamin K antagonist; WBC = white blood cell.

testing de-escalation strategies among all-comer patients with ACS and/or PCI (Table 2). De-escalation strategies associated with a reduction in potency of platelet inhibition achieved can occur by shortening DAPT duration, reducing the dose of a given agent or switching to less a potent agent. More specifically, shortening DAPT duration may be achieved by either discontinuing aspirin or the $P2Y_{12}$ inhibitor after a brief course of DAPT (eg, 1-3 months). De-escalation of $P2Y_{12}$ inhibitory effects can be achieved by lowering the dose of a drug (eg from prasugrel 10 mg to 5 mg or ticagrelor 90 mg to 60 mg) or switching to a less potent agent (eg, from ticagrelor or prasugrel to clopidogrel).[7,8] The latter (ie, de-escalation by switching) may be either guided or unguided depending on whether platelet function or genetic testing are used or not to guide the selection of $P2Y_{12}$ inhibitor therapy.[26]

Among studies testing bleeding reduction strategies in HBR patients, several registries have investigated shortened (eg, 1-3 months) DAPT in HBR patients undergoing PCI with specific drug-eluting stent platforms, suggesting that shortened DAPT is associated with a reduced risk of bleeding without a meaningful trade-off in ischemic events.[28,29] However, such single-arm registries used historical cohorts or objective performance goals as reference, and the nonrandomized design does not allow to draw definitive conclusions regarding the optimal DAPT duration in HBR-PCI patients.

MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated vs. Standard DAPT Regimen) was the first trial to compare abbreviated vs standard DAPT in HBR-PCI patients.[30] Specifically, 4,434 HBR patients (~50% with ACS and ~32% with

TABLE 2 Antithrombotic Therapy for Bleeding Reduction According to Different Cardiac Percutaneous Interventions and Main Supporting Studies

Randomized Controlled Trial	Treatment Arms	Patients (Follow-Up)	Primary Endpoint	Safety/Secondary Endpoint
Percutaneous coronary intervention[a]				
Patients without an indication for OAC				
De-escalation strategy among HBR patients[b]				
Abbreviated DAPT				
MASTER DAPT	1 vs >3 mo DAPT	4,434 (335 d)	Noninferior for death, MI, stroke, or major bleeding and MACCE	Superior for major or CRNM bleeding
De-escalation strategies among all-comers[c]				
Abbreviated DAPT				
EXCELLENT	6- vs 12-mo DAPT	1,443 (12 mo)	Noninferior for cardiac death, MI, or ischemia-driven TVR	No difference in major bleeding
RESET	3- vs 12-mo DAPT	2,117 (12 mo)	Noninferior for CV death, MI, ST, TVR, or bleeding	No difference in major bleeding
OPTIMIZE	3- vs 12-mo DAPT	3,119 (12 mo)	Noninferior for death, MI, stroke, or major bleeding	No difference in major bleeding
SECURITY	6- vs 12-mo DAPT	1,339 (12 mo)	Noninferior for cardiac death, MI, stroke, ST, or major bleeding	No difference in major bleeding
ISAR-SAFE	6- vs 12-mo DAPT	4,000 (9 mo)	Noninferior for death, MI, ST, stroke, or major bleeding	No difference in TIMI major bleeding
I-LOVE-IT 2	6- vs 12-mo DAPT	1,829 (12 mo)	Noninferior for cardiac death, TV-MI, or clinically indicated TVR	No difference in major bleeding
NIPPON	6- vs 18-mo DAPT	3,773 (18 mo)	Noninferior for death, MI, stroke, and major bleeding	No difference in major bleeding
DAPT-STEMI	6- vs 12-mo DAPT	870 (18 mo)	Noninferior for death, MI, revascularization, stroke, and major bleeding	No difference in major bleeding
SMART-DATE	6- vs 12-mo DAPT	2,712 (18 mo)	Noninferior for death, MI, or stroke; increased rate of MI	No difference in major bleeding
OPTIMA-C	6- vs 12-mo DAPT	1,368 (12 mo)	Noninferior for cardiac death, MI, or ischemia-driven TVR	No difference in major bleeding
REDUCE	3- vs 12-mo DAPT	1,496 (12 mo)	Noninferior for death, MI, ST, stroke, TVR, or CRNM or major bleeding	No difference in CR bleeding
One-mo DAPT	1- vs 6- to 12-mo DAPT	3,020 (12 mo)	Noninferior for cardiac death, MI, TVR, stroke, or major bleeding	No difference in major bleeding
Aspirin-free strategies				
GLOBAL-LEADERS	Ticagrelor monotherapy for 23 mo after 1-mo ticagrelor-based DAPT vs 12-mo DAPT followed by 12-mo ASA	15,968 (24 mo)	Not superior for all-cause death or new Q-wave MI	No difference in major bleeding
TWILIGHT	Ticagrelor monotherapy vs DAPT from 3 mo after PCI	7,119 (12 mo)	Superior for CRNM or major bleeding and noninferior for death, MI, or stroke	Reduced BARC ≥3 bleeding
SMART-CHOICE	P2Y12 inhibitor monotherapy vs DAPT after 3-mo DAPT	2,993 (12 mo)	Noninferior for death, MI, or stroke	Reduced CRNM or major bleeding
STOPDAPT-2	Clopidogrel monotherapy vs DAPT after 1-mo DAPT	3,045 (12 mo)	Superior for CV death, MI, stroke, ST, or major or minor bleeding	Reduced major and minor bleeding
TICO	Ticagrelor monotherapy vs DAPT after 3-mo DAPT	3,056 (12 mo)	Superior for major bleeding, death, MI, ST, stroke, or TVR; MACCE not significantly different	Reduced major bleeding
STOPDAPT-2 ACS	Clopidogrel monotherapy vs standard DAPT after 1-2-mo DAPT	4,169 (12 mo)	Not noninferior; higher rate of MI	Reduced major or minor bleeding
STOPDAPT-3	Prasugrel (3.75 mg/d) monotherapy vs prasugrel-based DAPT	5,966 (1 month)	Noninferior for CV death, MI, ST, ischemic stroke	Not superior for major bleeding
Unguided de-escalation				
TOPIC	Clopidogrel-based DAPT vs standard DAPT after 1-mo DAPT	646 (12 mo)	Superior for CV death, urgent coronary revascularization, stroke, and CRNM or major bleeding	Reduced CRNM or major bleeding

Continued on the next page

TABLE 2 Continued

Randomized Controlled Trial	Treatment Arms	Patients (Follow-Up)	Primary Endpoint	Safety/Secondary Endpoint
HOST-REDUCE POLYTECH-ACS	Prasugrel 5 mg based DAPT vs prasugrel 10 mg based DAPT after 1-mo DAPT	2,338 (12 mo)	Noninferior for death, MI, ST, revascularization, stroke, and CRNM or major bleeding.	Reduced CRNM or major bleeding
TALOS-AMI	Clopidogrel-based DAPT vs ticagrelor-based DAPT after 1-mo DAPT	2,697 (12 mo)	Superior for CV death, MI, stroke, or major bleeding	Reduced CRNM or major bleeding
Guided de-escalation				
ANTARTIC	PFT-guided de-escalation vs standard DAPT	877 (12 mo)	Not superior for CV death, MI, ST, stroke, urgent revascularization, and CRNM or major bleeding	No difference in CRNM or major bleeding
TROPICAL-ACS	PFT-guided de-escalation vs standard DAPT	2,610 (12 mo)	Noninferior for CV death, MI, stroke or CRNM or major bleeding; no increase in risk of CV death, MI, or stroke	No difference in CRNM or major bleeding
POPular Genetics	Genotype guided de-escalation vs standard DAPT	2,488 (12 mo)	Noninferior for death, MI, ST, stroke, or major bleeding.	Reduced major or minor bleeding
Patients with an indication for OAC				
De-escalation strategies among all-comers[c]				
Abbreviated DAPT				
PIONEER AF-PCI	Dual (clopidogrel+rivaroxaban 15 mg) vs 8 mo triple (ASA+clopidogrel+VKA) therapy	2,124 (12 mo)	Superior for major or minor bleeding	No difference in rates of CV death, MI, or stroke
RE-DUAL PCI	Dual (clopidogrel+dabigatran 110 mg twice daily or 150 mg twice daily) vs 2.7 mo triple (ASA+clopidogrel+VKA) therapy	2,725 (14 mo)	DAT with dabigatran 110 mg superior to TAT and DAT with dabigatran 150 mg noninferior to TAT for CRNM or major bleeding.	Noninferior for the composite efficacy endpoint
AUGUSTUS	Dual (clopidogrel+apixaban 5 mg twice daily/VKA) vs 6 mo triple (ASA+clopidogrel+ apixaban 5 mg twice daily/ VKA) therapy	4,614 (6 mo)	Superior for clinically relevant or major bleeding	No difference in death or hospitalization and ischemic events
ENTRUST-AF-PCI	Dual (clopidogrel+edoxaban 60 mg) vs 2 mo triple (ASA+clopidogrel+VKA) therapy	1,506 (12 mo)	Noninferior for clinically relevant or major bleeding.	No difference in rates of CV death, stroke, systemic embolic event, MI, or ST
Transcatheter aortic valve replacement[a]				
Patients without an indication for OAC				
De-escalation strategies among all-comers[c]				
SAPT vs DAPT				
Ussia et al[131]	ASA alone vs 3-mo DAPT	79 (6 mo)	No significant difference in death, MI, major stroke, urgent or emergency conversion to surgery, or life-threatening bleeding	No difference in life-threatening bleeding
SAT-TAVI	ASA alone vs 6-mo DAPT	120 (1 mo)	No significant difference in the safety endpoints, all-cause and CV mortality	Reduced vascular complications
ARTE	ASA alone vs 3-mo DAPT	222 (3 mo)	No significant difference in death, MI, stroke or TIA, or major or life-threatening bleeding	Reduced rate of major or life-threatening bleeding
POPular TAVI (cohort A)	ASA alone vs 3-mo DAPT	665 (12 mo)	Superior for all bleeding and non-procedure-related bleeding	Superior for CV death, non-procedure-related bleeding, stroke, or MI and noninferior for CV death, MI, or ischemic stroke
Patients with an indication for OAC				
De-escalation strategy among all-comers[c]				
OAC vs OAC plus SAPT				
POPular TAVI (cohort B)	OAC alone vs OAC + clopidogrel for 3 mo	313 (12 mo)	Superior for all bleeding and non-procedure-related bleeding	Superior for CV death, non-procedure-related bleeding, stroke, or MI and noninferior for CV death, MI, or ischemic stroke

Continued on the next page

TABLE 2 Continued

Randomized Controlled Trial	Treatment Arms	Patients (Follow-Up)	Primary Endpoint	Safety/Secondary Endpoint
Left atrial appendage closure[a]				
De-escalation strategies among all-comers[c]				
1) OAC-based vs DAPT-based regimens				
Amulet IDE	DAPT (Amulet) vs 45-d OAC+ASA followed by 6-mo DAPT (WATCHMAN)	1,878 (18 mo)	Noninferior for stroke, systemic embolism, or CV/unexplained death	Noninferior procedure-related complications, all-cause death, or major bleeding at 12 mo
2) Low-dose vs full-dose DOACs				
Della Rocca et al[115,d]	Full-dose DOAC+ASA for 45 d followed by 6-monht DAPT and ASA alone vs half-dose DOAC+ASA for 45 d followed by half-dose DOAC alone	555 (13 mo)	DRT occurred in 2.1% of patients, all in the standard therapy group with full-dose DOAC; the rate of ischemic stroke, TIA, and peripheral thromboembolism was significantly lower in the half-dose DOAC group	Major bleeding was significantly lower in the half-dose DOAC group
3) SAPT or no antiplatelet therapy				
Patti et al[126,d]	SAPT vs DAPT	610 (12 mo)	No significant difference in ischemic events and DRT	Reduced major bleeding

[a]Percutaneous intervention. [b]Focus on HBR patients. [c]All-comer patients. [d]Nonrandomized trial.

APT = antiplatelet therapy; ASA = aspirin; CRNM = clinically relevant nonmajor; CV = cardiovascular; DAT = dual antithrombotic therapy; DRT = device-related thrombosis; MACCE = major adverse cardiac or cerebral event(s); MASTER DAPT = Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated vs. Standard DAPT Regimen; MI = myocardial infraction; PFT = platelet function test; RR = risk ratio; SAPT = single antiplatelet therapy; ST = stent thrombosis; TAT = triple antithrombotic therapy; TIA = transient ischemic attack; TV-MI = target vessel myocardial infarction; TVR = target vessel revascularization; VKA = vitamin K antagonist; other abbreviations as in Table 1.

atrial fibrillation [AF]) undergoing PCI and without ischemic or active bleeding events in the first month were randomized to abbreviated (mean duration 34 days) or standard (mean duration 193 days) DAPT.[30] At 335 days, noninferiority of the abbreviated antiplatelet regimen was met for the primary endpoints of net adverse clinical events (a composite of all-cause death, MI, stroke, or major bleeding) or major adverse cardiac and cerebrovascular events. There was a reduction in major or clinically relevant nonmajor bleeding favoring short DAPT (from 9.4% to 6.5%; $P < 0.0001$) but no significant difference in major bleeding between groups.[30] A recent meta-analysis of RCTs including 9,006 HBR patients found that abbreviated (1-3 months) DAPT reduced bleeding and cardiovascular (CV) mortality, without increasing ischemic events, compared with standard (≥6 months) DAPT.[31] Limitations of this analysis include the fact that DAPT entailed different types of SAPT after DAPT discontinuation (ie, aspirin, clopidogrel, prasugrel, or ticagrelor monotherapy), it included subgroup analyses of RCTs, and many of the included studies focused on East Asian patients, known to exhibit different ischemic and bleeding risk profiles compared with other ethnicities.[6]

Regarding RCTs testing different bleeding reduction strategies in all-comer ACS/PCI patients without an indication to be on an OAC, ranging from shortening DAPT duration followed by aspirin or $P2Y_{12}$ monotherapy to guided or unguided de-escalation of the $P2Y_{12}$ inhibitor intensity, these strategies reduced bleeding without a meaningful trade-off in ischemic events (Table 2).[7,8] However, there are some limitations on the supporting evidence for the use of these strategies, such as the noninferiority design using a composite of ischemic and bleeding events as primary endpoint in many of the RCTs. This translates into low statistical power for hard ischemic or bleeding endpoints assessed individually. In addition, there is lack of solid evidence on the comparative efficacy of various de-escalation strategies and there is a need to better define the differential clinical impact of the specific $P2Y_{12}$ inhibitor used (ie, clopidogrel vs prasugrel or ticagrelor) or the population being tested (ie, East Asian vs non-East Asian).[7,8,32] Indeed, the prevalence of loss-of-function alleles in the gene encoding cytochrome P450 (CYP)2C19—the most important enzyme responsible for the transformation of clopidogrel into its active metabolite—varies according to ethnicity, ranging from 20% to 60% and being highest among East Asians.[33] In fact, the safety and efficacy of these strategies was found to be significantly influenced by ethnicity, reflecting the different ischemic and bleeding risk profiles as well as the different response to antiplatelet agents some populations may exhibit

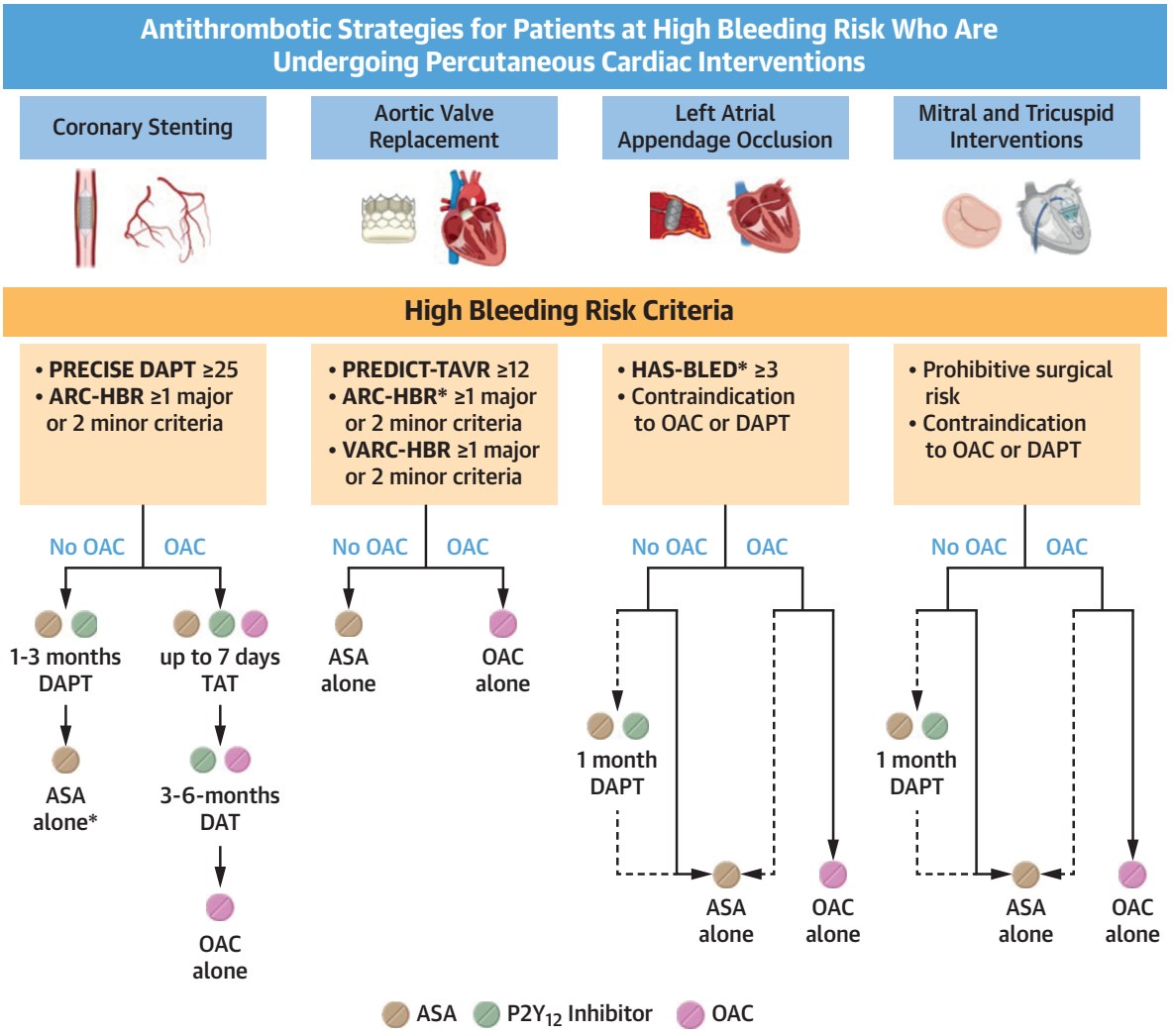
compared with others.[6,34] Although validation studies are warranted in this specific setting, these bleeding reduction strategies are expected to be at least as safe and effective in the subgroup of HBR-PCI compared with the all-comer PCI population.

The results of RCTs on bleeding reduction strategies in HBR and all-comer PCI patients have led to current guidelines recommending DAPT duration may be shortened up to 1 month post-PCI irrespective of clinical presentation.[35-37] Collectively, although the comparative safety and efficacy of different strategies remains to be determined, antiplatelet strategies for bleeding reduction are to be considered in HBR-PCI patients, particularly shortening of DAPT duration (**Central Illustration**).[38] With regard to the SAPT to be used in HBR-PCI patients, whether clopidogrel monotherapy could be safely and effectively used in lieu of aspirin requires further investigations given the large interindividual variability in its pharmacodynamic response.

Patients with an indication for OAC. The need for long-term OAC carries relevant implications for bleeding, to the point that it is a major criterion in the ARC-HBR framework.[22] DAPT is theoretically needed on top of OAC early after PCI, a regimen known as TAT, which confers a very high risk of bleeding.[18] AF is the most common indication for OAC in PCI cohorts, found in approximately 10% of PCI cases. The antithrombotic agents to be used in this setting have been a source of debate, with guidelines providing changes in recommendations over the past decade.[39] The availability of 4 RCTs comparing TAT using aspirin, clopidogrel, and a vitamin K antagonist (VKA) lasting an average of 4.7 months (2, 2.7, 6, and 8 months in ENTRUST-AF-PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention), RE-DUAL PCI (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting), AUGUSTUS (The Open-Label, 2 × 2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention), and PIONEER AF-PCI (An Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention), respectively) vs DAT with a $P2Y_{12}$ inhibitor (clopidogrel in >90% of cases) plus each of the 4 available direct oral anticoagulants (DOACs) after a short course of TAT lasting an average of 4 days (2, 3, 5, and 6 days in ENTRUST-AF-PCI, PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS, respectively) has provided important evidence for shortening DAPT by stopping aspirin in these patients (**Table 2**).[40] Overall, these studies included a total 10,234 subjects with AF, including both stable patients undergoing PCI (44%) and ACS (56%), and found a 36% reduction in major bleeding and a 49% reduction in ICH with shorter DAPT duration without a meaningful trade-off in major adverse cardiovascular events (MACE) compared with TAT.[41-43] However, an increased risk of ST was found in the DAT vs TAT group, the occurrence of which was nevertheless rare (number needed to treat: 274).[41,42,44] Furthermore, a subanalysis of the MASTER DAPT trial focusing on OAC-treated patients found no difference in MACE and net adverse clinical events between abbreviated (average duration 33 days) and prolonged TAT (average duration 96 days), providing evidence in support of shortening DAPT duration in this setting.[45] This study also supports the maintenance of DAT with SAPT plus OAC for 6 months after PCI followed by OAC alone in HBR-PCI patients, although limitations should be acknowledged including the short-term follow-up of the trial and the lack of data on compliance to antiplatelet therapy 12 months after PCI preventing a precise assessment of the clinical safety and efficacy of long-term antithrombotic therapy in these patients.[45]

Although some concerns remain about the efficacy of such an early shortening of DAPT duration in patients at high ischemic risk due to clinical or procedural characteristics, 1-week TAT followed by 6-month DAT using clopidogrel and a DOAC is recommended by current guidelines as default strategy for most PCI patients, including those at HBR (**Central Illustration**).[35,40,46] An emerging alternative antithrombotic regimen that could be of interest for HBR patients in this clinical setting is represented by the omission of OAC and the use of DAPT or ticagrelor monotherapy in the first month after ACS/PCI followed by SAPT + OAC.[47] The rationale for this strategy is represented by the fact that the vast majority of STs (~80%) occur during the first month after ACS/PCI and that the overall risk of thromboembolic events in patients treated with DAPT for 1 month, particularly if at low risk (ie, low CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category] score), is relatively small, with a risk of ST of 1% to 2% at 1 year.[47,48] Ongoing trials (NCT04436978 and NCT05955365) will provide

CENTRAL ILLUSTRATION **Antithrombotic Treatment Strategies in Patients Undergoing Percutaneous Cardiac Interventions at High Bleeding Risk**



- For patients undergoing coronary stenting who do not have an indication for OAC: de-escalation and short DAPT strategies should be considered; for those who have an indication for OAC: evidence suggests up to 1 week TAT followed by 3-6 months DAT using clopidogrel and a DOAC as the default strategy
- For patients undergoing aortic valve replacement who do not have an indication for OAC: SAPT is considered to be safer and similarly effective to DAPT after TAVR; for those who have an indication for OAC: OAC monotherapy should be the first-line therapy, but whether DOACs or VKAs should be preferred is less defined
- For patients undergoing LAAO who do not have an indication for OAC: clopidogrel-based DAPT for 1 month followed by aspirin alone, alternatively aspirin alone may be used; for those who have an indication for OAC: OAC alone is recommended; aspirin is reserved for patients with a contraindication to OAC
- For patients undergoing mitral or tricuspid interventions who do not have an indication for OAC: clopidogrel-based DAPT for 1 month followed by aspirin alone, alternatively aspirin alone may be used; for those who have an indication for OAC: OAC alone is recommended; aspirin is reserved for patients with a contraindication to OAC

Galli M, et al. JACC Cardiovasc Interv. 2024;17(19):2197–2215.

*$P2Y_{12}$ inhibitor monotherapy may be considered in lieu of aspirin (see text). ARC-HBR = Academic Research Consortium for High Bleeding Risk; ASA = aspirin; DAPT = dual antiplatelet therapy, DAT = double antithrombotic therapy; HAS-BLED = hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; OAC = oral anticoagulation; TAT = triple antithrombotic therapy; VARC-HBR = Valve Academic Research Consortium for High Bleeding Risk; VKA = vitamin K antagonist.

evidence on the safety and efficacy of this strategy. Finally, although HBR patients are typically at higher risk of perioperative complications, including bleeding and need for transfusions, coronary artery bypass grafting may be used in selective patients instead of PCI to allow for the use of SAPT rather than DAPT after revascularization. However, AF necessitating OAC may also occur following cardiac surgery, resulting in an increased risk of bleeding. Finally a surgical approach may allow for the surgical closure of the left atrial appendage in AF patients, exempting the patient from the chronic use of OAC.[49]

PATIENTS UNDERGOING CORONARY ARTERY BYPASS STENTING. The evidence on the incidence and prognostic implications of bleeding as well as on HBR classifications in patients undergoing stenting of coronary artery bypasses is scarce. Indeed, these patients are typically excluded or represent a minority of those included in the overall cohort of patients undergoing PCI. Stenting of coronary artery bypasses is associated with increased periprocedural (ie, slow- and no-reflow phenomenon) and long-term adverse MACE including mortality, compared with patients undergoing PCI of the native vessels.[50-53] Of note, PCI of a venous graft is also included in the DAPT score, designed to predict the benefit or harm of prolonged (>12 months) DAPT after PCI, as a factor in favor of prolonged DAPT.[54]

No RCT has been specifically designed to assess the optimal antithrombotic regimen to be used in this subgroup of patients, particularly among those at HBR. A prospective study including 603 patients who underwent PCI of a venous graft found that discontinuation of clopidogrel within 3 months after PCI was associated with increased death and MI compared with longer (91-365 days) DAPT durations.[55] With regard to a strategy of short DAPT followed by $P2Y_{12}$ inhibitor monotherapy, a post hoc analysis of the TWILIGHT trial (TWILIGHT-CABG study) compared aspirin or placebo, in addition to ticagrelor, after 3 months of ticagrelor plus aspirin, in 703 ACS patients with prior coronary artery bypass grafting (CABG).[56] The authors found that ticagrelor monotherapy reduced bleeding events compared with ticagrelor plus aspirin without any increase in ischemic events, irrespective of prior CABG status, including the subgroup of patients who underwent of PCI a coronary artery bypass.[56]

A strategy of dual pathway inhibition, consisting of the association of SAPT or DAPT with low-dose OAC—typically a DOAC—may represent an interesting option in patients with CABG, including those undergoing PCI of a coronary artery bypass, given that coronary artery bypasses, particularly saphenous veins, are characterized by larger conduits that potentially enhance blood stasis compared with arterial conduits.[57,58] However, a prespecified substudy of the COMPASS trial including 1,448 patients randomized within 4 to 14 days after CABG to rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily, rivaroxaban 5 mg twice daily, or aspirin 100 mg daily found no difference in the rate of both arterial and venous bypass failure between groups, at 1 year.[58] These results were consistent with the older Post CABG trial published in 1999, in which low-dose anticoagulation with VKA on top of aspirin did not improve clinical and angiographic outcomes in 1,351 diabetic patients with a history of CABG (1-11 years prior).[59]

Collectively, international guidelines recommend that patients undergoing PCI of coronary artery bypasses are treated the same as patients undergoing PCI (**Central Illustration**).[35-37]

TRANSCATHETER AORTIC VALVE REPLACEMENT

BLEEDING RISK IN PATIENTS UNDERGOING TAVR. Because aortic stenosis is the most common valvular heart disease in the elderly, often associated with frailty and high comorbidity burden, patients undergoing TAVR are often at high risk for bleeding.[60] Bleeding events after TAVR can occur early (within 30 days) or late (beyond 30 days). Early bleeding events account for approximately 80% of all bleeding events and are mainly access site related (60%-65%).[60-62] Although both access site- and non-access site-related events are associated with increased mortality, nonaccess bleeding showed a 2-fold increase compared with patients without bleeding and a 56% relative increase compared with patients with access site bleeding. The rates of early major and life-threatening bleeding approximate 22% and 15%, respectively.[62,63]

Late bleeding events are often gastrointestinal (>40% of bleeds) and primarily related to the patient's risk profile and use of long-term antithrombotic therapy.[60] The rate of late events varies widely among studies reaching 24% at 3 years in TAVR registries, and their occurrence has been associated with a 5-fold increased risk of death at 383 days compared with that of patients without bleeding.[61,64]

HBR DEFINITIONS IN PATIENTS UNDERGOING TAVR. Appropriate identification of HBR patients undergoing TAVR is critical for their management. Patient- and procedure-related factors have been associated

with bleeding in TAVR recipients, and their identification may improve risk stratification.[60]

Among patient-related factors, older age, frailty status, female sex, chronic kidney disease, and concomitant AF have been associated with increased bleeding.[65-68] Blood disorders are also common in TAVR patients.[69] Chronic anemia affects approximately 50% of cases and has been associated with worse health status and higher mortality risk.[70] Importantly, in patients with aortic stenosis, shear stress leads to an acquired type 2A von Willebrand disease predisposing to gastrointestinal bleeding, a condition known as Heyde's syndrome, which is observed in approximately 6% of TAVR candidates.[70] This bleeding diathesis is corrected by TAVR but may persist in case of significant paravalvular leaks.[64,71] Procedure-related risk factors mainly predispose to access site-related bleeding and include operator/center experience, sheath size, access site selection, and hemostasis technique.[60] Of note, access site-related bleeding in the setting of TAVR has unique features compared with those observed in PCI, given the specific characteristics of the vascular access, the preprocedural assessment of vessel anatomy, the much larger devices used, and the variable use of different closure techniques among centers/operators.[60,61]

Bleeding risk algorithms developed for PCI cohorts have been provisionally applied to the TAVR setting, but they experience from several limitations due to the inadequate assessment of the unique characteristics of TAVR cohorts.[24,72] In particular, the ARC-HBR was observed to exhibit poor performance in identifying HBR patients undergoing TAVR, indicating the possible need for the use of different thresholds in HBR classification.[72] Notably, most TAVR patients fulfill the HBR definitions due to their advanced age and frailty status, the prevalence of which is significantly higher than in the PCI setting,[23,50] thus making discrimination of bleeding risk in the TAVR population more difficult. A dedicated risk score for post-TAVR bleeding was developed in 5,185 patients from the RISPEVA registry and validated in 5,043 patients from the POL-TAVI database (Table 1).[73] The novel 6-item PREDICT-TAVR score (hemoglobin, serum iron, creatinine clearance, oral anticoagulation, DAPT, common femoral artery diameter) showed good discrimination for 30-day bleeding in the derivation cohort (area under the curve: 0.80; 95% CI: 0.75 to 0.83) and in external validation (area under the curve: 0.78; 95% CI: 0.72 to 0.82).[73] According to score quartiles, 30-day bleeding rate ranged from 0.8% in the low-risk group (≤8 points) to 8.5% in the very high-risk group (>12 points). Notably, no significant prediction was observed from 30 days to 1 year, probably due to the low number of events collected in this time frame.[73] Recently, the Valve Academic Research Consortium for High Bleeding Risk (VARC-HBR) task force developed a consensus definition of TAVR patients at HBR which will enable consistency for future clinical trials, clinical decision making, and regulatory review.[74] The VARC-HBR definition defines a very high bleeding risk as a BARC 3 to 5 risk at 1 year of ≥8%, a high bleeding risk as a BARC 3 to 5 risk of ≥4% and <8%, and a moderate bleeding risk as a BARC 3 to 5 risk of <4%.[74] Twenty-one clinical, anatomical, or procedural criteria were identified as major or minor.[74] Patients are considered at very high risk of bleeding if at least 2 major or 3 minor criteria are met, at high risk if 1 major or 2 minor criteria are met, and at moderate risk if only 1 minor criterion is met.[74] The proposed definition is based on consensus and warrants validation in contemporary real-world cohorts.

ANTITHROMBOTIC STRATEGIES AFTER TAVR IN HBR PATIENTS. Antithrombotic therapy is empirically used in patients undergoing TAVR with the rationale of reducing the risk of clinical and subclinical thrombotic complications of the prosthetic valve (eg, leaflet and frame thrombosis), which can lead to leaflet immobility and valve dysfunction and adversely affect valve durability.[75] In addition, clinically indicated antiplatelet therapy or anticoagulation is required to prevent MI or stroke/systemic embolism in patients with concomitant coronary artery disease or AF, respectively, which are common comorbidities in the TAVR population.[2] To date, no RCT has assessed the use of different antithrombotic agents in the specific setting of HBR-TAVR patients. However, similar to HBR-PCI patients, evidence in this setting may be derived from RCTs testing antithrombotic regimens of reduced intensity following de-escalation in all-comer TAVR patients (Table 2). Antithrombotic therapies in HBR-TAVR patients may be classified whether there is an indication or not to be on OAC.

Patients without an indication for OAC. The use of DAPT with aspirin and clopidogrel in pivotal TAVR studies was empirically derived from PCI practice, and early trials recommended 3 or 6 months of DAPT after self-expanding or balloon-expandable TAVR.[76,77] Recent evidence, however, challenged this approach, suggesting that SAPT could be safer and similarly effective to DAPT after TAVR.[2] The ARTE trial was the first to compare aspirin alone vs clopidogrel-based DAPT in 222 TAVR patients, showing a trend toward a reduced composite endpoint of death, MI, stroke, or transient ischemic

attack, and major or life-threatening bleeding at 3 months in the SAPT compared with DAPT group (7.2% vs 15.3%; $P = 0.065$).[78] Similarly, the POPular TAVI trial (cohort A) showed aspirin alone to reduce the rate of the 2 primary endpoints of all bleeding (15.1% vs 26.6%; $P = 0.001$) and non-procedure-related bleeding (15.1% vs 24.9%; $P = 0.005$) at 1 year, compared with DAPT. Notably, the bleeding benefit was driven by a reduction in major bleeding and occurred without a signal of increased ischemic events.[79] The superiority of SAPT over DAPT after TAVR has been confirmed in a patient-level meta-analysis of 4 trials, supporting current guideline recommendations.[80-82]

Whether aspirin or $P2Y_{12}$ inhibitor monotherapy should be the preferred long-term strategy in HBR-TAVR patients (with or without concomitant coronary artery disease) remains unclear.[83-85] In the Japanese multicenter OCEAN-TAVI registry, clopidogrel was associated with a lower risk of 2-year CV death after TAVR compared with aspirin in 196 propensity-matched patients, possibly because of lower rates of stroke and sudden cardiac death.[83] However, East Asians exhibit a different response to antiplatelet agents compared with other ethnicities, preventing from generalizing these findings. More recently, the REAC-TAVI (Assessment of platelet REACtivity after Transcatheter Aortic Valve Implantation) and PTOLEMAIOS (A Trial to Assess the Safety and Efficacy of Prophylactic TicagrelOr With Acetylsalicylic Acid Versus CLopidogrel With Acetylsalicylic Acid in the Development of Cerebrovascular EMbolic Events During TAVI) trials evaluated the effects of ticagrelor vs aspirin or clopidogrel, respectively, after TAVR.[86,87] In both trials, ticagrelor achieved greater platelet inhibition than the comparator, but the lack of powered clinical outcome analyses precludes conclusions on the potential implications in practice.

The use of a reduced dose of DOACs on top of SAPT or DAPT in TAVR patients without an indication for long-term OAC was investigated in the GALILEO (rivaroxaban 10 mg once daily), ATLANTIS (apixaban 5 mg twice daily), and ADAPT-TAVR (edoxaban 60 mg once daily) trials.[88-90] Although this strategy showed to consistently reduce leaflet thrombosis, these trials raised safety concerns primarily related to the increase in major bleeding rates and mortality without a clear benefit in ischemic events, with a trade-off that could be more unfavorable in HBR patients.[88-90]

Collectively, in HBR-TAVR patients without concomitant indication to be on OAC, SAPT with aspirin appears as the most appropriate option to minimize bleeding without incurring a significant trade-off in thrombotic risk. However, it is important to note that this evidence comes from studies underpowered for ischemic events. DAPT should be used in the subset of patients with recent ACS/PCI in whom DAPT duration should not exceed 1 month (**Central Illustration**).[30] Of note, the extent by which findings from earlier studies of antithrombotic therapy in high-risk TAVR recipients apply to contemporary TAVR populations, which include younger and lower-risk patients, remains to be determined.[2]

Patients with an indication for OAC. A significant proportion of HBR-TAVR candidates have comorbidities requiring long-term OAC (eg, AF), which makes their antithrombotic management more challenging. In the POPular TAVI trial (cohort B), 326 patients with an indication for long-term OAC were randomized before TAVR to receive or not clopidogrel for 3 months.[91] At 1 year, OAC alone was associated with a lower risk of the 2 primary endpoints of bleeding (21.7% vs 34.6%; $P = 0.01$) and non-procedure-related bleeding (21.7% vs 34.0%; $P = 0.02$) compared with OAC plus clopidogrel, with no difference in thromboembolic events.[91] These results are consistent with previous observational studies.[91,92]

The comparative efficacy and safety of DOACs vs VKAs after TAVR remains controversial. In a pooled analysis of the France-TAVI and FRANCE-2 registries, including 8,962 patients on OAC, there was a 37% increase in long-term mortality and a 64% increase in major bleeding with VKA compared with DOACs.[93] In the ATLANTIS trial (stratum 1), there was no difference between apixaban 5 mg twice daily and VKAs in the primary net clinical endpoint or the composite safety endpoint of major, disabling, or fatal bleeding.[89] In the ENVISAGE-TAVI AF (Edoxaban versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation-Atrial Fibrillation) trial, the incidence of the primary endpoint of thrombotic events and bleeding was similar between edoxaban 60 mg once daily and VKAs, but there was a 49% relative increase in major bleeding with edoxaban, mainly gastrointestinal.[94] This harm with edoxaban may appear to be in contrast to previous trials, which showed a better benefit-risk profile with DOACs than with VKAs in patients with nonvalvular AF.[69] Yet, several differences between the populations of the ENVISAGE-TAVI AF trial and other trials, such as a mean age that was approximately 1 decade older and a higher prevalence of heart failure, and the concomitant use of antiplatelet therapy, and presumed Heyde's syndrome, may help explain the excess of gastrointestinal bleeding with edoxaban compared with VKAs in patients with severe aortic stenosis.[69]

The recent WATCH-TAVR (WATCHMAN for Patients with AF Undergoing TAVR) trial explored the safety and efficacy of concomitant WATCHMAN left atrial appendage obstruction (LAAO) + TAVR vs TAVR + medical therapy in 349 AF patients.[95] Patients undergoing LAAO + TAVR showed longer procedure time (38 minutes) and increased intraprocedural median contrast volume (119 mL vs 70 mL). At 24-month follow-up, LAAO + TAVR patients were treated more often (82.5% vs 50.8%) with antiplatelet therapy and less often (13.9% vs 66.7%) with OAC and was noninferior to TAVR + medical therapy for the primary endpoint of all-cause mortality, stroke, and major bleeding.[95]

Overall, the available evidence suggests that OAC alone should be the first-line therapy in HBR-TAVR patients who have an indication to be on long-term OAC, but whether a DOAC or VKA should be preferred is less defined (**Central Illustration**).

Patients with subclinical or clinical valve thrombosis. In patients undergoing TAVR, OAC with either a VKA or a DOAC is the therapy of choice for the treatment of clinical or subclinical valve thrombosis and hypoattenuated leaflet thickening (HALT). In particular, HALT occurs in 10% to 25% of patients undergoing TAVR at 1 year and may be diagnosed using transthoracic echocardiography (ie, mean transaortic gradient ≥20 mm Hg or an increase in >50% from baseline and/or leaflet thickening), transesophageal echocardiography (TEE), or the gold standard computed tomography (CT). HALT is identified at CT as increased leaflet thickness with the typical meniscal appearance on long-axis view and can be graded into a 4-tier scale (≤25%, 26%-50%, 51%-75%, >75%).[96]

In the GALILEO-4D trial, rivaroxaban 10 mg daily was superior to antiplatelet therapy in reducing the incidence of HALT on 4-dimensional computed tomography (12.4% vs 32.4%; difference: −20.0%; 95% CI: −30.9% to −8.5%).[97] In the ATLANTIS and ADAPT-TAVR trials, which used apixaban and edoxaban, respectively, valve leaflet thrombosis was consistently reduced compared with antiplatelet therapy, but this effect did not translate into improved clinical outcomes or neurological function.[89,90] Therefore, the association between HALT hemodynamic valve deterioration, stroke and long-term mortality is still debated, and OAC should not be considered to improve prognosis.[98,99] A threshold for the treatment of HALT has not yet been established, but a selective strategy of OAC in patients with a marked increase in transvalvular gradient with or without evidence of HALT on CT may be considered. However, among HBR patients, OAC for patients with HALT should be approached cautiously, as the elevated risk of bleeding may outweigh any potential clinical benefit.

Clinical valve thrombosis is a rare but life-threatening event after TAVR and should be suspected in the setting of early valve dysfunction.[2,100] Treatment with a VKA is usually effective to improve prosthesis function, although in some cases thrombolytics may be required for treatment.[2,100]

LEFT ATRIAL APPENDAGE CLOSURE

BLEEDING RISK IN PATIENTS UNDERGOING LAAC. Transcatheter LAAC is appropriate for patients with nonvalvular AF at high risk of thromboembolism and who are not suited for long-term OAC. In current practice, approximately 80% of LAAC recipients are classified as HBR.[101,102] In patients undergoing LAAC, the 1-year major bleeding rate is high, ranging from 6% to 12%, with most events occurring within 45 days post-LAAC (when anticoagulation is generally recommended).[103-106] The high bleeding rate is largely due to the numerous bleeding risk factors that enrich this population, including advanced age and multiple comorbidities, typically history of stroke, coronary artery disease, renal dysfunction (including end-stage renal disease contraindicating DOAC), blood disorders, and cancer.[103-108] Many patients undergoing LAAC have a history of clinically relevant bleeding (around 70%-80%, with >10% being intracranial), which is associated with a >2-fold increased risk of major postprocedural bleeding.[103-109] Similar to PCI and TAVR, bleeding after LAAC has detrimental prognostic effects, being associated with a 3-fold increased mortality risk.[61,107,110]

HBR CLASSIFICATION IN PATIENTS UNDERGOING LAAC. Dedicated risk scores for LAAC patients are lacking, and in general patients undergoing LAAC are deemed to be at HBR (**Table 1**).[111]

ANTITHROMBOTIC STRATEGIES AFTER LAAC IN HBR PATIENTS. Several antithrombotic strategies for bleeding reduction have been tested in LAAC patients, although specific evidence in HBR-LAAC patients is lacking (**Table 2**).

Anticoagulation-based regimens after LAAC. Anticoagulation with VKA plus aspirin is a well-established strategy after WATCHMAN implantation based on the PROTECT AF and PREVAIL trials and Food and Drug Administration–mandated registries.[112-114] In these studies, after a 45-day therapy with warfarin plus aspirin, TEE was performed

and patients were continued on warfarin and aspirin if a peridevice leak >5 mm was shown, otherwise patients were switched to DAPT with clopidogrel 75 mg/d plus aspirin until 6 months after LAAC, and then to aspirin alone. The recent PINNACLE FLX study used a similar protocol but first showed that DOACs (preferably with apixaban or rivaroxaban) may be safely used after WATCHMAN FLX placement.[104]

Recently, an observational study in 555 patients undergoing LAAC with WATCHMAN suggested improved safety and efficacy of a regimen with half-dose DOACs (apixaban 2.5 mg twice daily or rivaroxaban 10 mg/d plus aspirin for the first 45 days) compared with full-dose DOAC.[115] Although preliminary results appear promising, further evidence is needed to support this approach in clinical practice, particularly for HBR-LAAC patients. Finally, the phase IIb ADRIFT trial randomizing 105 patients after successful LAAC to either rivaroxaban 10 mg, rivaroxaban 15 mg, or DAPT with aspirin and clopidogrel 75 mg found reduced thrombin generation with rivaroxaban-based compared with DAPT strategy and no difference in clinical outcomes at 3 months.[116]

Ongoing studies, including the ANDES (Short-Term Anticoagulation Versus Antiplatelet Therapy for Preventing Device Thrombosis Following Left Atrial Appendage Closure; NCT03568890) trial and the FADE-DRT (Efficacy of Different Anti-Thrombotic Strategies on Device-Related Thrombosis Prevention After Percutaneous Left Atrial Appendage Occlusion; NCT04502017) trial, will provide additional evidence on the efficacy and safety of full-dose and half-dose DOACs after LAAC.

DAPT-based regimens after LAAC. One- to 6-month clopidogrel-based DAPT is the standard regimen after LAAC with Amulet and an alternative to OAC after WATCHMAN implantation.[117,118] This treatment option has been proposed to reduce bleeding compared with a strategy of OAC plus SAPT and also to overcome the fact that LAAC recipients often have relative/absolute contraindications to long-term OAC, as supported by registry data showing that only 12.2% actually received the full antithrombotic treatment used in RCTs.[119] In 2022, the U.S. Food and Drug Administration also expanded the WATCHMAN FLX device label to include a 45-day DAPT regimen as an alternative to 45 days of OAC plus aspirin for post-procedural treatment.[120]

The randomized Amulet IDE trial compared patients undergoing LAAC with Amulet Occluder (75.7% discharged on DAPT) or WATCHMAN 2.5 (95.8% discharged on OAC), showing similar rates of stroke and major bleeding at 1 year.[105] No other RCT has evaluated DAPT-based strategies after LAAC, and observational studies reported contrasting results on the safety and effectiveness of DAPT vs OAC plus aspirin.[119,121,122]

SAPT or no antithrombotic therapy after LAAC. In real-world practice, nearly 20% of LAAC candidates are at prohibitive risk of major or disabling bleeding, resulting in the use of SAPT or no antithrombotic therapy after LAAC.[119,121-123] Particular caution is warranted in patients at extreme risk of bleeding, such as those with coexisting conditions predisposing to intracranial (untreatable vascular malformations, amyloid angiopathy) or gastrointestinal diseases (severe angiodysplasia, inoperable cancer).[117] The available studies are observational and have reported mixed results, with some suggesting a significant increase in the incidence of embolic events and device-related thrombosis and others indicating a higher net clinical benefit with SAPT.[109,119,123-126] Therefore, further research is needed to clarify whether a strategy of SAPT may be a safe option for HBR-LAAC patients. The ongoing ARMYDA-AMULET trial (NCT02879448) is directly comparing clopidogrel-based DAPT vs aspirin alone after LAAC, whereas the ASPIRIN LAAO trial (NCT03821883) will provide additional insight into the risks and benefits of discontinuing aspirin starting 6 months after LAAC.

Among HBR patients, current guidelines recommend the use of clopidogrel-based DAPT for 1 to 6 months followed by aspirin alone, regardless of the device used (**Central Illustration**).[127]

TRANSCATHETER MITRAL AND TRICUSPID VALVE INTERVENTIONS

Several transcatheter approaches have been developed for the treatment of mitral or tricuspid valve regurgitation as an alternative to surgery when surgical risk is prohibitive.[81] Transcatheter edge-to-edge mitral valve repair (mTEER) is an established strategy in high-risk patients with primary mitral regurgitation (MR) and in selected cases of secondary MR.[81] Transcatheter mitral valve replacement (TMVR) is increasingly used to treat severe MR because of potential advantages over mTEER, including a more consistent MR reduction and feasibility in high-risk anatomies, such as severe mitral annular calcification and degenerated bioprostheses.[81] Transcatheter tricuspid valve intervention is an emerging approach for patients with severe tricuspid regurgitation to reduce the severity of regurgitation and improve quality of life.[128]

Because the introduction of transcatheter mitral and tricuspid valve interventions is relatively recent and mostly limited to patients with prohibitive

surgical risk at an advanced stage of disease, there is paucity of evidence on the bleeding risk prevalence and HBR definitions. Moreover, a substantial number of patients undergoing such interventions are at high risk for bleeding due to the presence of frailty and significant comorbidities, making antithrombotic treatment decisions challenging.[81]

In patients undergoing mTEER, the most commonly used therapeutic regimens in clinical practice are derived from the protocol of trials evaluating these devices.[129] Antithrombotic therapy primarily consists of 1 to 6 months of DAPT with aspirin plus clopidogrel, the duration of which should be tailored to the thromboembolic and bleeding risk of the individual patient, followed by aspirin monotherapy. Similar to surgical valve procedures, patients undergoing TMVR should receive OAC with a VKA to achieve an international normalized ratio of 2.5 for 3 to 6 months (Class IIa).[81] DOACs may also be an alternative to VKAs, although their role remains uncertain due to the paucity of data. To this extent, the RIVER trial showed noninferiority of rivaroxaban 20 mg daily vs warfarin (international normalized ratio 2.0-3.0) in 1,005 patients with AF and a surgical bioprosthetic mitral valve for the primary outcome of all-cause death, MACE, and major bleeding at 12 months.[130] In HBR patients, antiplatelet therapy may represent an alternative to anticoagulation TMVR (**Central Illustration**); however, these patients should receive careful imaging surveillance for early detection of signs of bioprosthesis thrombosis or dysfunction (ie, increased transvalvular gradients, thickened leafets, reduced mobility, or thrombus visualization).[2] OAC alone remains the strategy of choice for AF patients undergoing transcatheter mitral interventions (**Central Illustration**). For long-term treatment, guidelines recommend lifelong low-dose aspirin for all patients with a bioprosthetic mitral valve.[81]

Because no randomized evidence for patients with transcatheter tricuspid valve interventions is yet available, the antithrombotic therapy to be used in these patients reflects that of patients undergoing mitral valve procedures. Further research is necessary to deepen our understanding in this domain.

CONCLUSIONS

A growing number of patients undergoing cardiac percutaneous interventions are at HBR. Prompt identification of HBR status and the implementation of tailored antithrombotic treatment regimens is of utmost importance to optimize the balance between bleeding and thrombotic risk in these patients. Dedicated trials are warranted to best define the optimal antithrombotic strategy in HBR patients undergoing cardiac percutaneous interventions for coronary and structural heart diseases.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Galli has received consulting fees or honoraria from Terumo, outside the present work. Dr Andreotti has received speaker or consultancy fees from Amgen, Bayer, BMS/Pfizer, Daiichi-Sankyo, and Servier, outside the present work. Dr Capodanno has received personal honoraria from Novo Nordisk, Sanofi, and Terumo; and payment to his institution from Medtronic, outside the present work. Dr Valgimigli has received personal fees from AstraZeneca, Alvimedica/CID, Abbott Vascular, Daiichi-Sankyo, Bayer, CoreFLOW, Idorsia Pharmaceuticals, Universität Basel | Dept. Klinische Forschung, Bristol-Myers Squibb SA, Medscape, Biotronik, and Novartis, outside the submitted work; and grants and personal fees from Terumo. Dr Mehran has received institutional research payments from Abbott, Abiomed, Affluent Medical, Alleviant Medical, Amgen, AM-Pharma, Applied Therapeutics, Arena, AstraZeneca, AtriCure Inc., Biosensors, Biotronik, Boston Scientific, Bristol Myers Squibb, CardiaWave, CeloNova, Chiesi, Concept Medical, CSL Behring, Cytosorbents, Daiichi-Sankyo, Duke, Element Science, Faraday, Humacyte, Idorsia, I-Laser, Janssen, Magenta, MedAlliance, Medscape, Mediasphere, Medtelligence, Medtronic, MJH Healthcare, Novartis, OrbusNeich, Penumbra, PhaseBio, Philips, Pi-Cardia, PLx Pharma, Protembis, RenalPro, RM Global, Shockwave, Transverse Medical, Vivasure, and Zoll; has received personal fees from Affluent Medical, the Cardiovascular Research Foundation, Daiichi-Sankyo Brasil, E.R. Squibb & Sons, Esperion Science/Innovative Biopharma, Europa Group/Boston Scientific, Gaffney Events, Educational Trust, Ionis Pharmaceuticals, J-CalC, Novartis, Novo Nordisk, Vectura, VoxMedia, IQVIA, McVeigh Global, Overcome, Primer Healthcare of New Jersey, Radcliffe, SL Solutions, TARSUS Cardiology, and WebMD, outside the submitted work; owns equity (<1%) in Applied Therapeutics, Elixir Medical, Stel, ControlRad (via her spouse); and has received no fees from the American Medical Association (Scientific Advisory Board) and the Society of Cardiovascular Angiography and Interventions (Women in Innovations Committee Member); has served on the faculty of the Cardiovascular Research Foundation; and has received honoraria from *JAMA Cardiology* (Associate Editor) and the American College of Cardiology (Board of Trustees Member, Member Clinical Trials Research Program). Dr Angiolillo has received consulting fees or honoraria from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Faraday, Haemonetics, Janssen, Merck, Novartis, Novo Nordisk, PhaseBio, PLx Pharma, Pfizer, Sanofi, and Vectura, outside the submitted work; and his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Faraday, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, and the Scott R. MacKenzie Foundation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Rossella Marcucci, Department of Experimental and Clinical Medicine, University of Florence, Largo Brambilla, 50134 Florence, Italy. E-mail: rossella.marcucci@unifi.it.

REFERENCES

1. Angiolillo DJ, Galli M, Collet JP, Kastrati A, O'Donoghue ML. Antiplatelet therapy after percutaneous coronary intervention. *EuroIntervention*. 2022;17:e1371–e1396.

2. Calabrò P, Gragnano F, Niccoli G, et al. Antithrombotic therapy in patients undergoing transcatheter interventions for structural heart disease. *Circulation*. 2021;144:1323–1343.

3. Savarese G, Reiner MF, Uijl A, et al. Antithrombotic therapy and major adverse limb events in patients with chronic lower extremity arterial disease: systematic review and meta-analysis from the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy in Collaboration with the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases. *Eur Heart J Cardiovasc Pharmacother*. 2020;6:86–93.

4. Galli M, Laborante R, Andreotti F, et al. Bleeding complications in patients undergoing percutaneous coronary intervention. *Rev Cardiovasc Med*. 2022;23(8):286.

5. Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J*. 2017;38:804–810.

6. Galli M, Ortega-Paz L, Franchi F, Rollini F, Angiolillo DJ. Precision medicine in interventional cardiology: implications for antiplatelet therapy in patients undergoing percutaneous coronary intervention. *Pharmacogenomics*. 2022;23:723–737.

7. Capodanno D, Mehran R, Krucoff MW, et al. Defining strategies of modulation of antiplatelet therapy in patients with coronary artery disease: a consensus document from the Academic Research Consortium. *Circulation*. 2023;147:1933–1944.

8. Galli M, Angiolillo DJ. De-escalation of antiplatelet therapy in acute coronary syndromes: why, how and when? *Front Cardiovasc Med*. 2022;9:975969.

9. Capodanno D, Bhatt DL, Gibson CM, et al. Bleeding avoidance strategies in percutaneous coronary intervention. *Nat Rev Cardiol*. 2022;19:117–132.

10. Reinöhl J, Kaier K, Reinecke H, et al. Effect of availability of transcatheter aortic-valve replacement on clinical practice. *N Engl J Med*. 2015;373:2438–2447.

11. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736–2747.

12. Galli M, Andreotti F, D'Amario D, et al. Antithrombotic therapy in the early phase of non-ST-elevation acute coronary syndromes: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother*. 2020;6:43–56.

13. Navarese EP, Khan SU, Kołodziejczak M, et al. Comparative efficacy and safety of oral P2Y(12) inhibitors in acute coronary syndrome: network meta-analysis of 52 816 patients from 12 randomized trials. *Circulation*. 2020;142:150–160.

14. Galli M, Benenati S, Franchi F, et al. Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials. *Eur Heart J*. 2022;43:959–967.

15. Navarese EP, Andreotti F, Schulze V, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. *BMJ (Clin Res Ed)*. 2015;350:h1618.

16. Benenati S, Galli M, De Marzo V, et al. Very short vs. long dual antiplatelet therapy after second generation drug-eluting stents in 35 785 patients undergoing percutaneous coronary interventions: a meta-analysis of randomized controlled trials. *Eur Heart J Cardiovasc Pharmacother*. 2021;7:86–93.

17. van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy. *Circulation*. 2019;139:775–786.

18. Lamberts M, Olesen JB, Ruwald MH, et al. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. *Circulation*. 2012;126:1185–1193.

19. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017;389:1025–1034.

20. Costa F, Van Klaveren D, Feres F, et al. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. *J Am Coll Cardiol*. 2019;73:741–754.

21. Munafò AR, Montalto C, Franzino M, et al. External validity of the PRECISE-DAPT score in patients undergoing PCI: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother*. 2023;9(8):709–721.

22. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. *Circulation*. 2019;140:240–261.

23. Gargiulo G, Esposito G. Consolidating the value of the standardised ARC-HBR definition. *EuroIntervention*. 2021;16:1126–1128.

24. Corpataux N, Spirito A, Gragnano F, et al. Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. *Eur Heart J*. 2020;41:3743–3749.

25. Urban P, Gregson J, Owen R, et al. 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;6:410–419.

26. Galli M, Franchi F, Rollini F, Angiolillo DJ. Role of platelet function and genetic testing in patients undergoing percutaneous coronary intervention. *Trends Cardiovasc Med*. 2023;33:133–138.

27. Kim HK, Tantry US, Smith SC Jr, et al. The East Asian paradox: an updated position statement on the challenges to the current antithrombotic strategy in patients with cardiovascular disease. *Thromb Haemost*. 2021;121:422–432.

28. Mehran R, Cao D, Angiolillo DJ, et al. 3- or 1-Month DAPT in patients at high bleeding risk undergoing everolimus-eluting stent implantation. *JACC Cardiovasc Interv*. 2021;14:1870–1883.

29. Kandzari DE, Kirtane AJ, Windecker S, et al. One-month dual antiplatelet therapy following percutaneous coronary intervention with zotarolimus-eluting stents in high-bleeding-risk patients. *Circ Cardiovasc Interv*. 2020;13:e009565.

30. Valgimigli M, Frigoli E, Heg D, et al. Dual antiplatelet therapy after PCI in patients at high bleeding risk. *N Engl J Med*. 2021;385:1643–1655.

31. Costa F, Montalto C, Branca M, et al. Dual antiplatelet therapy duration after percutaneous coronary intervention in high bleeding risk: a meta-analysis of randomized trials. *Eur Heart J*. 2022;44:954–968.

32. Galli M, Laudani C, Occhipinti G, et al. P2Y12 inhibitor monotherapy after short DAPT in acute coronary syndrome: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother*. Published online July 25, 2024. https://doi.org/10.1093/ehjcvp/pvae057

33. Galli M, Franchi F, Rollini F, et al. Genetic testing in patients undergoing percutaneous coronary intervention: rationale, evidence and practical recommendations. *Expert Rev Clin Pharmacol*. 2021;14:963–978.

34. Galli M, Laborante R, Occhipinti G, et al. Impact of ethnicity on antiplatelet treatment regimens for bleeding reduction in acute coronary syndromes: a systematic review and pre-specified subgroup meta-analysis. *Eur Heart J Cardiovasc Pharmacother*. 2024;10(2):158–169.

35. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC guidelines for the management of acute coronary syndromes: developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2023;44(38):3720–3826.

36. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407–477.

37. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2023;82:833–955.

38. Kuno T, Watanabe A, Shoji S, et al. Short-term DAPT and DAPT de-escalation strategies for patients with acute coronary syndromes: a systematic review and network meta-analysis. *Circ Cardiovasc Interv*. 2023;16:e013242.

39. Angiolillo DJ, Galli M, Alexopoulos D, et al. International consensus statement on platelet function and genetic testing for guiding oral P2Y12 inhibitor treatment in percutaneous coronary intervention: 2024 update. *JACC Cardiovasc Interv*. 2024.

40. De Caterina R, Agewall S, Andreotti F, et al. Great debate: triple antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting should be limited to 1 week. *Eur Heart J*. 2022;43:3512–3527.

41. Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J*. 2019;40:3757–3767.

42. Galli M, Andreotti F, Porto I, Crea F. Intracranial haemorrhages vs. stent thromboses with direct oral anticoagulant plus single antiplatelet agent or triple antithrombotic therapy: a meta-analysis of randomized trials in atrial fibrillation and percutaneous coronary intervention/acute coronary syndrome patients. *Europace*. 2020;22:538–546.

43. Galli M, Andreotti F, D'Amario D, et al. Randomised trials and meta-analyses of double vs triple antithrombotic therapy for atrial fibrillation-ACS/PCI: a critical appraisal. *Int J Cardiol Heart Vasc*. 2020;28:100524.

44. Galli M, Andreotti F, D'Amario D, et al. Dual therapy with direct oral anticoagulants significantly increases the risk of stent thrombosis compared with triple therapy. *Eur Heart J Cardiovasc Pharmacother*. 2020;6:128–129.

45. Smits PC, Frigoli E, Tijssen J, et al. Abbreviated antiplatelet therapy in patients at high bleeding risk with or without oral anticoagulant therapy after coronary stenting: an open-label, randomized, controlled trial. *Circulation*. 2021;144:1196–1211.

46. Angiolillo DJ, Bhatt DL, Cannon CP, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update. *Circulation*. 2021;143:583–596.

47. Limbruno U, Goette A, De Caterina R. Commentary: Temporarily omitting oral anticoagulants early after stenting for acute coronary syndromes patients with atrial fibrillation. *Int J Cardiol*. 2020;318:82–85.

48. Lopes RD, Leonardi S, Wojdyla DM, et al. Stent thrombosis in patients with atrial fibrillation undergoing coronary stenting in the AUGUSTUS trial. *Circulation*. 2020;141:781–783.

49. Whitlock RP, Belley-Cote EP, Paparella D, et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. *N Engl J Med*. 2021;384:2081–2091.

50. Brilakis ES, Rao SV, Banerjee S, et al. Percutaneous coronary intervention in native arteries versus bypass grafts in prior coronary artery bypass grafting patients: a report from the National Cardiovascular Data Registry. *JACC Cardiovasc Interv*. 2011;4:844–850.

51. Rathod KS, Beirne AM, Bogle R, et al. Prior coronary artery bypass graft surgery and outcome after percutaneous coronary intervention: an observational study from the Pan-London Percutaneous Coronary Intervention Registry. *J Am Heart Assoc*. 2020;9:e014409.

52. Beerkens FJ, Singh R, Cao D, et al. Impact of target vessel choice on outcomes following percutaneous coronary intervention in patients with a prior coronary artery bypass graft. *Catheter Cardiovasc Interv*. 2021;98:E785–E795.

53. Galli M, Niccoli G, De Maria G, et al. Coronary microvascular obstruction and dysfunction in patients with acute myocardial infarction. *Nat Rev Cardiol*. 2024;21(5):283–298.

54. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315:1735–1749.

55. Sachdeva A, Bavisetty S, Beckham G, et al. Discontinuation of long-term clopidogrel therapy is associated with death and myocardial infarction after saphenous vein graft percutaneous coronary intervention. *J Am Coll Cardiol*. 2012;60:2357–2363.

56. Sardella G, Beerkens FJ, Dangas G, et al. Ticagrelor with and without aspirin in patients with a prior coronary artery bypass graft undergoing percutaneous coronary intervention: the TWILIGHT-CABG study. *EuroIntervention*. 2022;18:e897–e909.

57. Galli M, Franchi F, Rollini F, et al. Dual pathway inhibition in patients with atherosclerotic disease: pharmacodynamic considerations and clinical implications. *Expert Rev Clin Pharmacol*. 2023;16:27–38.

58. Lamy A, Eikelboom J, Sheth T, et al. Rivaroxaban, aspirin, or both to prevent early coronary bypass graft occlusion: the COMPASS-CABG study. *J Am Coll Cardiol*. 2019;73:121–130.

59. Hoogwerf BJ, Waness A, Cressman M, et al. Effects of aggressive cholesterol lowering and low-dose anticoagulation on clinical and angiographic outcomes in patients with diabetes: the Post Coronary Artery Bypass Graft Trial. *Diabetes*. 1999;48:1289–1294.

60. Avvedimento M, Nuche J, Farjat-Pasos JI, Rodés-Cabau J. Bleeding events after transcatheter aortic valve replacement: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2023;81:684–702.

61. Piccolo R, Pilgrim T, Franzone A, et al. Frequency, timing, and impact of access-site and non-access-site bleeding on mortality among patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2017;10:1436–1446.

62. van Nieuwkerk AC, Aarts HM, Hemelrijk KI, et al. Bleeding in patients undergoing transfemoral transcatheter aortic valve replacement: incidence, trends, clinical outcomes, and predictors. *JACC Cardiovasc Interv*. 2023;16:2951–2962.

63. Généreux P, Head SJ, Van Mieghem NM, et al. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. *J Am Coll Cardiol*. 2012;59:2317–2326.

64. Généreux P, Cohen DJ, Mack M, et al. Incidence, predictors, and prognostic impact of late bleeding complications after transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2014;64:2605–2615.

65. Bendayan M, Messas N, Perrault LP, et al. Frailty and bleeding in older adults undergoing TAVR or SAVR: insights from the FRAILTY-AVR study. *JACC Cardiovasc Interv*. 2020;13:1058–1068.

66. Vlastra W, Chandrasekhar J, García Del Blanco B, et al. Sex differences in transfemoral transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2019;74:2758–2767.

67. Gupta T, Goel K, Kolte D, et al. Association of chronic kidney disease with in-hospital outcomes of transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2017;10:2050–2060.

68. Dribin TE, Schnadower D, Spergel JM, et al. Severity grading system for acute allergic reactions: a multidisciplinary Delphi study. *J Allergy Clin Immunol*. 2021;148:173–181.

69. Galli M, Angiolillo DJ. The evaluation and management of coagulopathies in the intensive therapy units. *Eur Heart J Acute Cardiovasc Care*. 2023;12(6):399–407.

70. 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.

71. Spangenberg T, Budde U, Schewel D, et al. Treatment of acquired von Willebrand syndrome in aortic stenosis with transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2015;8:692–700.

72. Garot P, Neylon A, Morice MC, et al. Bleeding risk differences after TAVR according to the ARC-HBR criteria: insights from SCOPE 2. *EuroIntervention*. 2022;18:503–513.

73. Navarese EP, Zhang Z, Kubica J, et al. Development and validation of a practical model to identify patients at risk of bleeding after TAVR. *JACC Cardiovasc Interv*. 2021;14:1196–1206.

74. Garot P, Morice MC, Angiolillo DJ, et al. Defining high bleeding risk in patients undergoing transcatheter aortic valve implantation: a VARC-HBR consensus document. *EuroIntervention*. 2024;20:536–550.

75. Ng ACT, Holmes DR, Mack MJ, et al. Leaflet immobility and thrombosis in transcatheter aortic valve replacement. *Eur Heart J*. 2020;41:3184–3197.

76. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–2198.

77. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a

self-expanding prosthesis. *N Engl J Med*. 2014;370:1790–1798.

78. Rodés-Cabau J, Masson JB, Welsh RC, et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve: the ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) randomized clinical trial. *JACC Cardiovasc Interv*. 2017;10:1357–1365.

79. Brouwer J, Nijenhuis VJ, Delewi R, et al. Aspirin with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med*. 2020;383:1447–1457.

80. Brouwer J, Nijenhuis VJ, Rodés-Cabau J, et al. Aspirin alone versus dual antiplatelet therapy after transcatheter aortic valve implantation: a systematic review and patient-level meta-analysis. *J Heart Assoc*. 2021;10:e019604.

81. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:450–500.

82. Ten Berg J, Sibbing D, Rocca B, et al. Management of antithrombotic therapy in patients undergoing transcatheter aortic valve implantation: a consensus document of the ESC Working Group on Thrombosis and the European Association of Percutaneous Cardiovascular Interventions (EAPCI), in collaboration with the ESC Council on Valvular Heart Disease. *Eur Heart J*. 2021;42:2265–2269.

83. Kobari Y, Inohara T, Saito T, et al. Aspirin versus clopidogrel as single antithrombotic therapy after transcatheter aortic valve replacement: insight from the OCEAN-TAVI registry. *Circ Cardiovasc Interv*. 2021;14:e010097.

84. Gragnano F, Mehran R, Branca M, et al. P2Y(12) inhibitor monotherapy or dual antiplatelet therapy after complex percutaneous coronary interventions. *J Am Coll Cardiol*. 2023;81:537–552.

85. Gragnano F, Cao D, Pirondini L, et al. P2Y(12) inhibitor or aspirin monotherapy for secondary prevention of coronary events. *J Am Coll Cardiol*. 2023;82:89–105.

86. Jimenez Diaz VA, Tello-Montoliu A, Moreno R, et al. Assessment of platelet REACtivity after transcatheter aortic valve replacement: the REACTAVI trial. *JACC Cardiovasc Interv*. 2019;12:22–32.

87. Vavuranakis MA, Kalantzis C, Voudris V, et al. Comparison of ticagrelor versus clopidogrel on cerebrovascular microembolic events and platelet inhibition during transcatheter aortic valve implantation. *Am J Cardiol*. 2021;154:78–85.

88. Dangas GD, Tijssen JGP, Wöhrle J, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med*. 2020;382:120–129.

89. Collet JP, Van Belle E, Thiele H, et al. Apixaban vs. standard of care after transcatheter aortic valve implantation: the ATLANTIS trial. *Eur Heart J*. 2022;43:2783–2797.

90. Park DW, Ahn JM, Kang DY, et al. Edoxaban versus dual antiplatelet therapy for leaflet thrombosis and cerebral thromboembolism after TAVR: the ADAPT-TAVR randomized clinical trial. *Circulation*. 2022;146:466–479.

91. Nijenhuis VJ, Brouwer J, Delewi R, et al. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med*. 2020;382:1696–1707.

92. Abdul-Jawad Altisent O, Durand E, Muñoz-García AJ, et al. Warfarin and antiplatelet therapy versus warfarin alone for treating patients with atrial fibrillation undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2016;9:1706–1717.

93. Didier R, Lhermusier T, Auffret V, et al. TAVR patients requiring anticoagulation: direct oral anticoagulant or vitamin K antagonist? *JACC Cardiovasc Interv*. 2021;14:1704–1713.

94. Van Mieghem NM, Unverdorben M, Hengstenberg C, et al. Edoxaban versus vitamin K antagonist for atrial fibrillation after TAVR. *N Engl J Med*. 2021;385:2150–2160.

95. Kapadia SR, Krishnaswamy A, Whisenant B, et al. Concomitant left atrial appendage occlusion and transcatheter aortic valve replacement among patients with atrial fibrillation. *Circulation*. 2024;149:734–743.

96. Ahmad Y, Makkar R, Sondergaard L. Hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RELM) of aortic bioprostheses: an imaging finding or a complication? *Prog Cardiovasc Dis*. 2022;72:78–83.

97. De Backer O, Dangas GD, Jilaihawi H, et al. Reduced leaflet motion after transcatheter aortic-valve replacement. *N Engl J Med*. 2020;382:130–139.

98. Jang MH, Ahn JM, Kang DY, et al. Impact of leaflet thrombosis on valve haemodynamic status after transcatheter aortic valve replacement. *Heart*. 2023;110:140–147.

99. Hein M, Schoechlin S, Schulz U, et al. Long--term follow-up of hypoattenuated leaflet thickening after transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2022;15:1113–1122.

100. Abdel-Wahab M, Simonato M, Latib A, et al. Clinical valve thrombosis after transcatheter aortic valve-in-valve implantation. *Circ Cardiovasc Interv*. 2018;11:e006730.

101. Landmesser U, Schmidt B, Nielsen-Kudsk JE, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. *EuroIntervention*. 2017;13:867–876.

102. Saw J, Holmes DR, Cavalcante JL, et al. SCAI/HRS expert consensus statement on transcatheter left atrial appendage closure. *Heart Rhythm*. 2023;20:e1–e16.

103. Price MJ, Reddy VY, Valderrábano M, et al. Bleeding outcomes after left atrial appendage closure compared with long-term warfarin: a pooled, patient-level analysis of the WATCHMAN randomized trial experience. *JACC Cardiovasc Interv*. 2015;8:1925–1932.

104. Kar S, Doshi SK, Sadhu A, et al. Primary outcome evaluation of a next-generation left atrial appendage closure device: results from the PINNACLE FLX trial. *Circulation*. 2021;143:1754–1762.

105. Lakkireddy D, Thaler D, Ellis CR, et al. Amplatzer Amulet left atrial appendage occluder versus watchman device for stroke prophylaxis (Amulet IDE): a randomized, controlled trial. *Circulation*. 2021;144:1543–1552.

106. Price MJ, Slotwiner D, Du C, et al. Clinical outcomes at 1 year following transcatheter left atrial appendage occlusion in the United States. *JACC Cardiovasc Interv*. 2022;15:741–750.

107. Aminian A, De Backer O, Nielsen-Kudsk JE, et al. Incidence and clinical impact of major bleeding following left atrial appendage occlusion: insights from the Amplatzer Amulet Observational Post-Market Study. *EuroIntervention*. 2021;17:774–782.

108. Sulaiman S, Roy K, Wang H, et al. Left atrial appendage occlusion in the elderly: insights from PROTECT-AF, PREVAIL, and continuous access registries. *JACC Clin Electrophysiol*. 2023;9:669–676.

109. Simard T, Jung RG, Lehenbauer K, et al. Predictors of device-related thrombus following percutaneous left atrial appendage occlusion. *J Am Coll Cardiol*. 2021;78:297–313.

110. Leonardi S, Gragnano F, Carrara G, et al. Prognostic implications of declining hemoglobin content in patients hospitalized with acute coronary syndromes. *J Am Coll Cardiol*. 2021;77:375–388.

111. Mesnier J, Cepas-Guillén P, Freixa X, et al. Antithrombotic management after left atrial appendage closure: current evidence and future perspectives. *Circ Cardiovasc Interv*. 2023;16:e012812.

112. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009;374:534–542.

113. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*. 2014;64:1–12.

114. Holmes DR Jr, Reddy VY, Gordon NT, et al. Long-term safety and efficacy in continued access left atrial appendage closure registries. *J Am Coll Cardiol*. 2019;74:2878–2889.

115. Della Rocca DG, Magnocavallo M, Di Biase L, et al. Half-dose direct oral anticoagulation versus standard antithrombotic therapy after left atrial appendage occlusion. *JACC Cardiovasc Interv*. 2021;14:2353–2364.

116. Duthoit G, Silvain J, Marijon E, et al. Reduced rivaroxaban dose versus dual antiplatelet therapy after left atrial appendage closure: ADRIFT a randomized pilot study. *Circ Cardiovasc Interv*. 2020;13:e008481.

117. Holmes DR Jr, Korsholm K, Rodés-Cabau J, Saw J, Berti S, Alkhouli MA. Left atrial appendage

occlusion. *EuroIntervention*. 2023;18:e1038–e1065.

118. Saw J, Holmes DR, Cavalcante JL, et al. SCAI/HRS expert consensus statement on transcatheter left atrial appendage closure. *JACC Cardiovasc Interv*. 2023;16(11):1384–1400.

119. Freeman JV, Higgins AY, Wang Y, et al. Antithrombotic therapy after left atrial appendage occlusion in patients with atrial fibrillation. *J Am Coll Cardiol*. 2022;79:1785–1798.

120. Aradi D, Rideg O, Vorobcsuk A, et al. Justification of 150 mg clopidogrel in patients with high on-clopidogrel platelet reactivity. *Eur J Clin Invest*. 2012;42:384–392.

121. Bergmann MW, Betts TR, Sievert H, et al. Safety and efficacy of early anticoagulation drug regimens after WATCHMAN left atrial appendage closure: three-month data from the EWOLUTION prospective, multicentre, monitored international WATCHMAN LAA closure registry. *EuroIntervention*. 2017;13:877–884.

122. Søndergaard L, Wong YH, Reddy VY, et al. Propensity-matched comparison of oral anticoagulation versus antiplatelet therapy after left atrial appendage closure with WATCHMAN. *JACC Cardiovasc Interv*. 2019;12:1055–1063.

123. Hildick-Smith D, Landmesser U, Camm AJ, et al. Left atrial appendage occlusion with the Amplatzer™ Amulet™ device: full results of the prospective global observational study. *Eur Heart J*. 2020;41:2894–2901.

124. Boersma LV, Ince H, Kische S, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm*. 2017;14:1302–1308.

125. Landmesser U, Tondo C, Camm J, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: one-year follow-up from the prospective global Amulet observational registry. *EuroIntervention*. 2018;14:e590–e597.

126. Patti G, Sticchi A, Verolino G, et al. Safety and efficacy of single versus dual antiplatelet therapy after left atrial appendage occlusion. *Am J Cardiol*. 2020;134:83–90.

127. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373–498.

128. Sorajja P, Whisenant B, Hamid N, et al. Transcatheter repair for patients with tricuspid regurgitation. *N Engl J Med*. 2023;388:1833–1842.

129. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364:1395–1406.

130. Guimarães HP, Lopes RD, de Barros ESPGM, et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. *N Engl J Med*. 2020;383:2117–2126.

131. Ussia GP, Scarabelli M, Mulè M, et al. Dual antiplatelet therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation. *Am J Cardiol*. 2011;108(12):1772–1776.

KEY WORDS anticoagulants therapy, antiplatelet therapy, antithrombotic therapy, cardiac interventions, high bleeding risk

Go to http://www.acc.org/jacc-journals-cme to take the CME/MOC/ECME quiz for this article.