Management of Antithrombotic Therapy in Atrial Fibrillation Patients Undergoing PCI

JACC State-of-the-Art Review

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ABSTRACT

Most patients with atrial fibrillation (AF) and risk factors for stroke require oral anticoagulation (OAC) to decrease the risk of stroke or systemic embolism. This is now best achieved with direct oral anticoagulants that decrease the risk of intracranial bleeding compared with vitamin K antagonists. Of note, approximately 5% to 10% of patients undergoing percutaneous coronary intervention have AF, which complicates antithrombotic therapy in daily practice, because the guidelines recommend that these patients also receive dual antiplatelet therapy (DAPT) to reduce the risk of ischemic complications. However, combining OAC with DAPT, a strategy also known as triple antithrombotic therapy, is known to increase the risk of bleeding compared with the use of OAC or DAPT alone. Studies of direct oral anticoagulants are now emerging that show the favorable safety profile of double antithrombotic therapy with OAC and a P2Y12 inhibitor in comparison with triple antithrombotic therapy including the use of vitamin K antagonists. The scope of this review is to provide an update on this topic as well as to discuss future directions in the management of antithrombotic therapy after percutaneous coronary intervention in AF patients requiring chronic OAC. (J Am Coll Cardiol 2019;74:83–99) © 2019 by the American College of Cardiology Foundation.
Atrial fibrillation (AF) is a highly prevalent condition with increasing age. A 2018 statistical update from the American Heart Association (AHA) reports estimates of AF prevalence in 2010 ranging from 2.7 to 6.1 million in the United States and 8.8 million (95% confidence interval [CI]: 6.5 to 12.3 million) in Europe (1). These estimates are projected to rise to 12.1 million in 2030 in the United States and 17.9 million (95% CI: 13.6 to 23.7 million) in 2060 in Europe (1). AF increases the risk of thromboembolic complications, including stroke and extracranial systemic embolic events, which call for therapeutic prophylaxis with oral anticoagulation (OAC) (2). It is estimated that about 20% to 40% of patients with AF also present with coronary artery disease (CAD), a sizeable proportion of whom requires revascularization using percutaneous coronary intervention (PCI) and stent implantation (3). Such patients need dual antiplatelet therapy (DAPT) to prevent the risk of stent thrombosis and additional thrombotic ischemic events (4). Overall, about 5% to 10% of patients referred to coronary angiography with or without PCI present with AF or other indications for chronic OAC (3).

HIGHLIGHTS

- AF patients require OAC to prevent the risk of thromboembolic events, whereas antiplatelet therapy is required to prevent stent thrombosis in the setting of PCI.
- Several randomized trials have demonstrated that a regimen of DAT with DOACs provides better safety compared with a regimen of TAT with VKA.
- The current paradigm is that TAT (the association of OAC with DAPT) should be as short as possible or even avoided based on the individual’s ischemic and bleeding risk profile.
- The results of the AUGUSTUS trial will likely impact and provide more consistency among guideline recommendations.

The optimal antithrombotic treatment regimen for patients with AF undergoing PCI is a clinical conundrum. The combination of OAC and DAPT, a regimen also known as triple antithrombotic therapy (TAT), is...
theoretically required to decrease both the risk of thromboembolism due to AF and the risk of thrombotic events due to coronary stents in patients with underlying CAD. However, TAT markedly increases the risk of major and fatal bleeding (5). Randomized controlled trials are now available that compare TAT with alternative antithrombotic therapy regimens, such as double antithrombotic therapy (DAT), which combines OAC with single antiplatelet therapy (SAPT) (6-10).

In keeping with the rapid evolution of the field of antithrombotic therapy for AF and PCI, guidelines, focused updates and consensus documents are frequently issued to incorporate the new evidence in the field and inform clinical practice. The American and European guidelines for AF, DAPT, and myocardial revascularization represent a general framework for the management of patients with AF and those undergoing PCI, respectively. The intersection between the 2 scenarios (e.g., patients with AF-PCI) is covered in the United States by the 2019 focused update of the 2014 AF guideline from the American College of Cardiology (ACC), AHA, and Heart Rhythm Society (HRS) (11), and in Europe by the 2018 guidelines on myocardial revascularization from the European Society of Cardiology (ESC) (12), which confirm the recommendations included in the ESC focused update on DAPT published in 2017 (13). These documents provide practical recommendations that are endorsed by international scientific societies. With more focus on the specific subject of AF-PCI, pragmatic approaches to the treatment of AF-PCI patients were also provided in 2018 by an earlier practical guide from the European Heart Rhythm Association (14) and 2 later consensus documents that represent the perspectives of North American and European experts in antithrombotic pharmacotherapy (15,16).

DEFINING THE CONTEXT

ANTITHROMBOTIC THERAPY FOR PATIENTS WITH NONVALVULAR AF. When it comes to stroke prevention for AF, OAC outperforms SAPT (aspirin) or DAPT (aspirin plus clopidogrel). The ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) W trial, comparing OAC with DAPT, was stopped early because of a clear evidence of superiority: OAC with a vitamin K antagonist (VKA) resulted in 31% fewer vascular events at 1 year (p = 0.0003) (17). In AF patients who are deemed unsuitable for OAC with VKA, despite demonstration from the ACTIVE A trial that DAPT reduced the risk of major vascular events compared with aspirin monotherapy (18), the direct oral anticoagulant (DOAC) apixaban was found to reduce the risk of stroke or systemic embolism without increasing the risk of major bleeding when compared with aspirin (19). As such, there is a limited (if any) role for antiplatelet therapy alone in AF for stroke prevention, where
thrombi develop mainly in the left atrial appendage, a region of low shear stress where the platelet component is less prevalent and an advantage of OAC is expected (20).

The 2019 ACC/AHA/HRS guidelines for AF recommend that the selection of antithrombotic therapy for AF is based on the risk of thromboembolism assessed with the CHA2DS2-VASc (Congestive Heart failure, hypertension, Age ≥75 years [doubled], Diabetes, Stroke [doubled], Vascular disease, Age 65 to 74 years, and Sex [female]) score (11). In patients with AF and a CHA2DS2-VASc score ≥2 in men or ≥3 in women, OAC is recommended with warfarin (Class of Recommendation [COR] I, Level of Evidence [LOE]: A) or a DOAC, including dabigatran, rivaroxaban, apixaban, or edoxaban (COR I, LOE B) (11). Notably, a DOAC is now preferred to warfarin in all DOAC-eligible candidates, unless they present with moderate-to-severe mitral stenosis or a mechanical heart valve (COR I, LOE A) (11). Male AF patients with a CHA2DS2-VASc score of 1 and female AF patients with a CHA2DS2-VASc score of 2 may receive OAC (COR IIb, LOE C). Conversely, in male patients with a CHA2DS2-VASc score of 0 and female patients with a CHA2DS2-VASc score of 1 it is reasonable to omit OAC (COR IIa, LOE B), which is not the case for AF patients with CAD undergoing PCI who are assigned by default a score of at least 1 (men) or 2 (women) (11). The 2016 ESC guidelines for AF also recommend risk stratification by the CHA2DS2-VASc score and identify different cut-offs for OAC based on sex, with slightly different grades of recommendation for the time being (21). In particular, similarly to the 2019 AHA/ACC/HRS guideline, OAC is recommended for all male AF patients with a CHA2DS2-VASc score of ≥2 and for all female AF patients with a CHA2DS2-VASc score of ≥3 (COR I, LOE A), but the recommendation for male AF patients with a CHA2DS2-VASc score of 1 and female AF patients with a CHA2DS2-VASc score of 2 is IIa, LOE B (rather than IIb, LOE C) after considering individual characteristics and patient preferences. In addition, OAC is not recommended, rather than simply discouraged, in male patients with a CHA2DS2-VASc score of 0 and female patients with a CHA2DS2-VASc score of 1 (COR III, LOE B). Also in the European guidelines, in the absence of contraindications (e.g., mechanical valves, moderate-to-severe mitral stenosis), a DOAC is recommended as a first choice in preference to a VKA in all eligible candidates (COR I, LOE A). According to both the AHA/ACC/HRS and ESC guidelines, left atrial appendage occlusion may be considered in AF patients with contraindications for long-term OAC (COR IIb, LOE B) (11,21).

ANTITHROMBOTIC THERAPY FOR PATIENTS UNDERGOING PCI. When it comes to thrombosis prevention for patients undergoing PCI, the benefit of DAPT over OAC is unequivocal (4,22–25). DAPT is the present standard of care (COR I) after PCI both in the elective setting, with aspirin and clopidogrel, and in the course of an acute coronary syndrome (ACS), with aspirin and, preferably, ticagrelor or prasugrel (4). Default DAPT durations in these settings are 6 and 12 months, respectively, but these durations are flexible depending on the individual risk of ischemia and bleeding (4). Multiple investigations in PCI patients are ongoing to define whether in the era of new-generation drug-eluting stents (DES) and more potent P2Y12 inhibitors than clopidogrel (e.g., ticagrelor, prasugrel), SAPT is equally, if not more, protective as DAPT (26). The GLOBAL-LEADERS (A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation) trial, a first large study addressing this question, recently failed to meet its primary objective to demonstrate a reduction in ischemic events with ticagrelor monotherapy, although there were no safety concerns compared with standard DAPT followed by aspirin monotherapy (27). Subsequently, 2 currently unpublished trials (STOPDAPT-2 [ShorT and OP timal Duration of Dual AntiPlatelet Therapy-2 Study] and SMART-CHOICE [Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy After DES]) were presented at the 2019 scientific sessions of the ACC conference indicating that short-term DAPT followed by P2Y12-inhibitor monotherapy may provide a safety benefit compared with standard DAPT among selected PCI patients receiving current-generation DES. Other studies of aspirin-free antithrombotic strategies after PCI are ongoing, including the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) study, which has recently completed its enrollment (28).

BLEEDING WITH COMBINATION OF OAC AND ANTIPLATELET THERAPY. Patients with AF on TAT experience high rates of major bleeding (e.g., bleeding requiring hospitalization or fatal bleeding) compared with patients on DAT or SAPT (5). In an updated nationwide Danish cohort study of 272,315 patients with AF patients aged 50 years or older, compared with VKA monotherapy over a total follow-up period of 1,373,131 patient-years, adjusted hazard ratios of major bleeding were 1.13 (95% CI: 1.06 to 1.19) for DAPT, 1.82 (95% CI: 1.76 to 1.89) for DAT with a VKA and SAPT, 1.28 (95% CI: 1.13 to 1.44) for DAT with a DOAC and SAPT, 3.73 (95% CI: 3.23 to 4.31) for TAT with VKA, and 2.28 (95% CI: 1.67 to 3.12) for TAT with
DOAC (5). The highest absolute rates of major bleeding were observed in patients treated with VKA-TAT who were older than 90 years (annualized rate 22.8%), had a CHA2DS2-VASc score > 6 (17.1%), or presented with a history or major bleeding (17.5%) (5). Due to confounding by indication and because TAT with a VKA or DOAC was only prescribed in 1% and 0.3% of patients, respectively, this study was unable to look at the efficacy and net benefit of combining 3 antithrombotic agents in AF patients. It is noteworthy that, in the setting of high-risk ACS without AF, full-dose TAT provided no benefit but increased severe bleeding in the APPRAISE 2 (Apixaban for Prevention of Acute Ischemic Events 2) trial (29). The high bleeding rates of the Danish registry emphasize that treatment with TAT, if deemed necessary, should be as short as possible and likely best avoided altogether.

**DOUBLE VERSUS TRIPLE THERAPY IN AF-PCI PATIENTS**

**TRIALS OF VKAs.** A summary of the study design and key results of the WOEST (What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing) and ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation) trials is provided in Figure 1. In WOEST and ISAR-TRIPLE, simplification of the reference TAT strategy was attempted by aspirin withdrawal or shortening DAPT duration, respectively (6,7). In WOEST, the rationale for withdrawing aspirin was due to the observation that the risk of bleeding is highest in the first month after PCI, likely as the consequence of the procedure itself and of stacking multiple oral and parenteral antithrombotic medications (30). WOEST randomized in an open-label fashion 573 patients on OAC, of whom 69% presented with AF and 28% presented with an ACS. The trial found a 64% relative decrease in bleeding episodes with DAT, driven by a reduced rate of minor bleeding episodes (hazard ratio: 0.36; 95% CI: 0.26 to 0.50; p < 0.0001). Although it was not powered for ischemic events, the trial also showed a decrease in thrombotic events in the DAT group. Notably, in the control group, TAT was prolonged up to 1 year in the two-thirds of patients who received DES. In light of the results of the WOEST trial, the 1-year duration of TAT has been questioned, and the standard duration of TAT, when used, has become shorter. Thus, the
Participants in PIONEER AF were randomly assigned to receive, in a 1:1:1 ratio, low-dose rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 months (group 1); very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months (group 2); or standard therapy with a dose-adjusted vitamin K antagonist (once-daily) plus DAPT for 1, 6, or 12 months (group 3). Participants in RE-DUAL PCI were randomly assigned to receive, in a 1:1:1 ratio, triple antithrombotic therapy with warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and aspirin (for 1 to 3 months) (triple-therapy group); or double antithrombotic therapy with dabigatran (110 or 150 mg twice daily) plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and no aspirin (110- and 150-mg double-therapy groups). Outside of the United States, elderly patients ($\geq$80 years of age; $\geq$70 years of age in Japan) were randomly assigned to the 110-mg double-therapy group or the triple-therapy group. AUGUSTUS = An 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; CRNM = clinically relevant non-major; CV = cardiovascular; DOACs = direct oral anticoagulants; MI = myocardial infarction; NVAF = nonvalvular atrial fibrillation; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban vs. Vitamin K Antagonist and Aspirin in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; SE = systemic embolism; UR = urgent revascularization.
WOEST trial, despite the small sample size and open-label design, provided some randomized evidence that the early discontinuation of aspirin reduces bleeding in comparison to TAT, without any apparent increase in ischemic events, leading to the subsequent initiation of multiple trials of aspirin-free strategies in PCI even outside of the AF context (26).

ISAR-TRIPLE randomized 614 patients with any indication to OAC (83% for AF or atrial flutter) treated with PCI and DES (one-third with an ACS) to either 6 weeks or 6 months of DAPT (7). The primary endpoint, comprising a combination of ischemic and bleeding events, did not differ at 9 months between the 2 groups, and in a landmark analysis of events between 6 weeks and 6 months, the risk of bleeding was higher in the group where clopidogrel was used longer (for 6 months), supporting the safety benefit of DAT versus TAT. Importantly, like WOEST, ISAR-TRIPLE was relatively small and underpowered to detect significant differences in ischemic endpoints (31).

**TRIALS OF DOACs.** Figure 2 is a summary of the study design and key results of 3 trials: PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Dosing Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with atrial Fibrillation who Undergo Percutaneous Coronary Intervention), RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) and AUGUSTUS (An Open-label, 2 x 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) (8,9).

PIONEER AF-PCI compared 3 treatment strategies after PCI in 2,124 patients with AF: a WOEST-like strategy of low-dose rivaroxaban (15 mg once daily [od]) plus a single P2Y₁₂ inhibitor (group 1); a TAT regimen of very low-dose rivaroxaban (2.5 mg twice daily [bid]) plus DAPT, followed by rivaroxaban 15 mg od at the time of P2Y₁₂ inhibitor discontinuation (group 2); and control TAT with a VKA plus DAPT (group 3) (8). It is important to note that the dosing regimens of rivaroxaban used in the trial do not represent the approved doses for stroke prevention in AF, although they were selectively chosen based on prior dose-finding investigations (32). At variance with WOEST, patients were stratified by the intended duration of DAPT (1, 6, or 12 months), with only 22% finally found to be on TAT at 1 year in the control group. Compared with control subjects, the primary endpoint of clinically significant bleeding at 12 months was reduced by both rivaroxaban-based strategies (hazard ratio for group 1 vs. group 3: 0.59; 95% CI: 0.47 to 0.76; p < 0.001; hazard ratio for group 2 vs. group 3: 0.63; 95% CI: 0.50 to 0.80; p < 0.001), driven by lower rates of bleeding requiring medical attention and not by TIMI (Thrombolysis In Myocardial Infarction) major or minor bleeding. The rivaroxaban-based regimen resulted in a reduced risk of total bleeding events and recurrent hospitalization for adverse events (33,34). Conversely, there were no differences in major adverse cardiovascular events, but the power was low for ischemic endpoints (8).

RE-DUAL PCI randomized 2,725 PCI patients with AF (one-half of them in the setting of an ACS) to 2 regimens of DAT that included dabigatran 150 or 110 mg bid and mostly clopidogrel (ticagrelor in 12%) versus a regimen of TAT with warfarin (9). In the TAT group, aspirin was discontinued after 1 month in patients who received a bare-metal stent (17%) and after 3 months in patients who received a DES (83%). At a mean of 14 months, the risk of major or clinically relevant nonmajor bleeding in the 110 mg dabigatran DAT group was noninferior to the risk observed in the control group, and superiority was also established (hazard ratio: 0.52; 95% CI: 0.42 to 0.63; p for noninferiority <0.0001, p for superiority = 0.0001). The 150-mg dabigatran DAT group also met both the noninferiority and superiority objectives compared with the TAT group (hazard ratio: 0.72; 95% CI: 0.58 to 0.88; p for noninferiority <0.0001, p for superiority = 0.002). These results were consistent irrespective of clinical presentation (e.g., stable CAD or ACS) and irrespective of whether clopidogrel or ticagrelor was used in the treatment and control arms (35). The risk of thromboembolic events was noninferior in the 2 DAT groups combined as compared with the TAT group, although a numerical (nonsignificant) absolute risk increase was noted with the lower 110-mg dabigatran dose (11%) ad compared with the higher 150-mg dabigatran dose (7.9%) (9). It is important to note that the 110-mg dabigatran dose is not approved for stroke prevention in the United States. Finally, due to the design of both PIONEER-AF PCI and RE-DUAL PCI, they could not distinguish whether the reduction in bleeding was attributed to the use of a DOAC versus VKA, to the avoidance of aspirin, or both.

In AUGUSTUS, 4,614 patients with ACS and or PCI within 14 days were randomized in a 2 x 2 factorial design to apixaban 5 mg bid versus VKAs (open label) and to aspirin versus placebo (blinded) for 6 months
All patients received a P2Y<sub>12</sub> inhibitor (mostly clopidogrel). About one-quarter of patients had ACS and no PCI. At 6 months, the primary outcome of major or clinically relevant nonmajor bleeding was significantly reduced by apixaban compared with VKAs (hazard ratio: 0.69; 95% CI: 0.58 to 0.81; p < 0.001) and increased by aspirin compared with placebo (hazard ratio: 1.89; 95% CI: 1.59 to 2.24; p < 0.001). Patients in the apixaban group had a lower risk of death or hospitalization than those in the VKA group (hazard ratio: 0.83; 95% CI: 0.74 to 0.93; p = 0.002), whereas no significant differences on this endpoint were noted between patients in the aspirin and placebo groups. By means of its factorial design and at variance with PIONEER-AF PCI and RE-DUAL PCI, AUGUSTUS helps to disentangle the individual contribution of DOACs and aspirin withdrawal on the risk of bleeding, demonstrating that both aspects are beneficial. The benefit of using a DOAC versus VKA in the setting of AF and ACS with or without PCI corroborates the recommendation from current guidelines for AF (11,21). Importantly, compared with prior studies of DOACs, AUGUSTUS also included medically managed ACS patients who did not receive stents, who are known to be at high ischemic risk. Therefore, this data expands on current knowledge in the field. The issue of early aspirin withdrawal in AUGUSTUS should be interpreted in view of some aspects related to the study design and results of the trial. First, patients were enrolled at a median of 6 days from ACS and/or PCI, which suggests that most patients in the trial had at least short-term aspirin use before randomization. Second, the follow-up time was shorter than in PIONEER-AF PCI and RE-DUAL PCI (6 months vs. 12 months). Third, nonsignificant 0.5% and 0.4% absolute increases in myocardial infarction and stent thrombosis, respectively, were noted in patients on placebo compared with those on aspirin. Indeed, a better understanding of patient profiles and timing of these events with relationship to aspirin discontinuation will be informative for clinical practice.

**DOUBLE VERSUS TRIPLE ANTITHROMBOTIC THERAPY IN META-ANALYSES OF BLEEDING AND ISCHEMIC EVENTS.** The safety and efficacy of DAT versus TAT in AF patients undergoing PCI has been the objective of several pooled analyses of WOEST, ISAR-TRIPLE, PIONEER AF-PCI, and RE-DUAL PCI. In the meta-analysis from Golwala et al. (36), encompassing a total of 5,317 patients, compared with the TAT group, TIMI major or minor bleeding was reduced by 47% in the DAT arm (hazard ratio: 0.53, 95% credible interval: 0.36 to 0.85; I<sup>2</sup> = 42.9%). There was no difference in trial-defined major adverse cardiac events (hazard ratio 0.85; 95% credible interval: 0.48 to 1.29, I<sup>2</sup> = 58.4%), or in the individual outcomes of all-cause mortality, cardiac death, myocardial infarction, stent thrombosis, or stroke between the DAT and TAT groups (36). Although the credible interval for the efficacy outcomes remains large in this meta-analysis, these findings suggest that DAT represents a safer option than TAT in PCI patients with AF. It should be noted that AUGUSTUS, the largest study of a DOAC in patients with indication for antiplatelet therapy due to PCI and/or ACS, was not incorporated in this meta-analysis that encompasses approximately the same number of the total patients randomized in the trial.

**PRACTICAL MANAGEMENT OF AF PATIENTS UNDERGOING PCI**

Multiple guidelines and consensus documents have been published over the past decade to inform clinicians on the optimal antithrombotic strategy for AF patients undergoing PCI. Initially, most recommendations were based on expert consensus in the absence of an evidence basis from randomized controlled trials. While the evidence consolidates, some recommendations are strengthened, others abandoned. As noted in the previous text, for the purpose of the following discussion, we refer to the 2019 ACC/AHA/HRS guidelines for AF and the 2018 ESC guidelines for myocardial revascularization when citing recommendations, and to the latest iteration of the consensus documents issued in 2018 by experts on antithrombotic therapy at the 2 sides of the Atlantic for practical issues (11,12,15,16). A summary of practical recommendations from the 2 North American and European consensus documents is provided in Table 1 to highlight current areas of consensus and discrepancy. Key aspects are discussed in the following text, integrated by authors’ consensus on aspects that eventually emerged after the publication of the AUGUSTUS trial.

**PROCEDURAL CONSIDERATIONS.** PCI has become a safer procedure over the years with better patient selection using heart team decisions, avoidance of unnecessary procedures through intracoronary physiology measurements, increasing use of radial arteries for vascular access, and improvement of available DES technologies (12,15). As part of a general periprocedural bleeding avoidance strategy, procedures should be carried out with radial access (4,12,15,16). Indeed, urgent or emergent procedures can be performed without withholding OAC. In general, patients on a DOAC undergoing elective or nonemergent procedures should withhold therapy for 24 h (or 48 h for patients with impaired renal function.
on dabigatran) (15). If the patient is on VKA, the North American recommendation suggests a wash-out period with target INR based on the type of vascular access (≥2 and ≤1.5 for radial and femoral access, respectively), whereas the European document suggests that a strategy of uninterrupted VKA should be preferred over a strategy of interrupted VKA with heparin bridging (15,16,37). Both documents agree that patients with stable CAD can forgo bridging with parenteral anticoagulation, while—according to the North American document only—bridging should be considered for ACS patients as an integral part of their care. Additional unfractionated heparin should be administered as per usual practice to support PCI, at standard dose (70 to 100 U/Kg) in case of DOACs and reduced dose (30 to 50 U/Kg) in case of ongoing VKA. Bivalirudin may also be considered, particularly in patients at high bleeding risk, in those presenting...
with ACS, and if a femoral approach is being used (15). More potent therapies, such as cangrelor or glycoprotein IIb/IIIa inhibitors, are generally only recommended for selected cases at high, life-threatening risk for ischemic complications or for bail-out situations, although cangrelor may be preferred of the 2 approaches due to a shorter half-life (38–41). Pre-treatment with clopidogrel is indicated when PCI is likely or decided (4,12). Importantly, aspirin should be prescribed periprocedurally in all cases to decrease the risk of early stent-related thrombotic complications (4,12).

**RISK STRATIFICATION FOR THROMBOSIS AND BLEEDING.** After the indications for OAC and antiplatelet therapy are established, the North American and European consensus documents suggest that decisions should be guided by balancing the individual risk of atherothrombosis with the risk of major bleeding (15,16). This is an aspect of paramount practical importance, because such risk stratification will shift the pendulum toward, for example, TAT or DAT, or the selection of different P2Y12 inhibitors. The North American document emphasizes that physicians should rely on qualitative factors to characterize the individual risk of ischemia and bleeding, whereas the approach of the European consensus document is more quantitative and relies on risk scores for both ischemia and bleeding. Indeed, to characterize the atherothrombotic risk, the European consensus document suggests using the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score for elective PCI and the GRACE (Global Registry of Acute Coronary Event) score (with a cutoff of 140) for PCI in the context of an ACS (16). In addition, concerns about thrombotic risk apply to anatomic and clinical presentations, such as stenting of the left main, proximal left anterior descending, proximal bifurcation, recurrent myocardial infarctions, and stent thrombosis (16). Also according to the European document, bleeding risk can be estimated using the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol) score (e.g., ≥3) with the aim of screening candidates who require more regular review and earlier follow-up, and to identify and correct modifiable bleeding risk factors. In RE-DUAL PCI, the benefit of DAT with dabigatran in reducing bleeding events compared with TAT with VKA was irrespective of the baseline risk of bleeding defined by the HAS-BLED score (42). It should be recognized that the predictive performance of bleeding risk scores is generally modest, and that patients on OAC represent a high bleeding risk category per se where further discrimination is problematic (43,44). In a study of AF patients comparing different risk stratification tools for bleeding, the HEMORR(2)HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding [doubled], Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke), ATRIA (Anti-coagulation and Risk Factors in Atrial Fibrillation), and HAS-BLED scores showed only weak performance in predicting any clinically relevant bleeding, although the HAS-BLED score performed better than the HEMORR(2)HAGES and ATRIA scores (c-indexes: 0.60 vs. 0.55 and 0.50 for HAS-BLED vs. HEMORR(2) AGES and ATRIA, respectively) (45). Similar findings were reported for different bleeding risk tools in DOAC-treated patients (46). A recent independent systematic review concluded that the HAS-BLED score provides the best prediction for bleeding risk (44). Adding biomarker information significantly but still suboptimally improves the discrimination performance of bleeding risk assessment over HAS-BLED (c-indexes 0.69 to 0.71 vs. 0.62 for HAS-BLED in external validation cohorts) (47,48), and showed no advantage in real-world clinical practice (49). In the absence of accurate predictive tools for bleeding, defining which AF-PCI patients have more or less to benefit from different antithrombotic strategies remains a case-by-case decision. A list of suggested criteria of high risk for ischemia/thrombosis and bleeding from the European focused update on DAPT is provided in **Table 2** (13).

**CHOICE AND DURATION OF ANTITHROMBOTIC STRATEGIES AFTER PCI.** In selecting the optimal antithrombotic regimen for an AF patient who

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**TABLE 2 Criteria of High-Risk Features Tipping the Balance Toward More or Less Intense Antithrombotic Therapy for AF Patients Undergoing PCI**

<table>
<thead>
<tr>
<th>Criteria of High Stent-Driven Thrombotic Risk</th>
<th>Criteria of High Bleeding Risk That Make the Combination of OAC and Antiplatelet Therapy Unfavorable</th>
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</thead>
<tbody>
<tr>
<td>Prior stent thrombosis on adequate antiplatelet therapy</td>
<td>Short life expectancy</td>
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<tr>
<td>Stenting of the last remaining patent coronary artery</td>
<td>Ongoing malignancy with high bleeding potential</td>
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<td>Diffuse multivessel disease especially in diabetic patients</td>
<td>Poor expected adherence</td>
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<td>Chronic kidney disease (e.g., creatinine clearance &lt;60 mL/min)</td>
<td>Poor mental status</td>
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<td>At least 3 stents implanted</td>
<td>End stage renal failure</td>
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<tr>
<td>Bifurcation with 2 stents implanted</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Total stent length &gt;60 mm</td>
<td>Prior major bleeding/prior hemorrhagic stroke</td>
</tr>
<tr>
<td>Treatment of a chronic total occlusion</td>
<td>Chronic alcohol abuse</td>
</tr>
<tr>
<td>Abbreviations as in Table 1.</td>
<td>Anemia</td>
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received PCI, physicians have to consider some fundamental questions. As far as the type of OAC drug is concerned (first question), both the North American and European consensus documents agree with current ACC/AHA/HRS and ESC guidelines (11,12) that, in the absence of contraindications, DOACs should be preferred to VKAs due to the lower risk of bleeding previously demonstrated to be a class effect (50). A bivariate analysis using a measure of risk difference in the net clinical outcome based on data from PIONEER-AF PCI and RE-DUAL PCI demonstrated that both the rivaroxaban- and dabigatran-based regimens are favorable compared with VKA plus DAPT (51). Indeed, the alternative of maintaining VKA is practically more problematic, because the intensity of the INR needs modulation (e.g., values between 2.0 and 2.5) during the TAT term (52). In the AUGUSTUS trial, the median percentage of time when the INR was below 2 was 23% (10). Also, in the same study, the safety
benefit of being on a DOAC compared with VKA was demonstrated on top of considerations on aspirin versus no aspirin use (10). Thus, in patients already on a VKA, switching to a DOAC is a reasonable option to reduce the risk of bleeding. However, a VKA remains the only indicated treatment in patients with moderate to severe mitral stenosis and mechanical prosthetic heart valves, and is generally a more accepted approach in patients with end-stage renal disease—although, in the latter, more recent data show that DOACs may be superior to warfarin (53).

The second question deals with the duration of TAT (Central Illustration). This spans from very short (e.g., until after successful PCI) to extended (e.g., 6 months) depending on various clinical scenarios. Notably, both the 2019 ACC/AHA/HRS guidelines for AF and the 2018 ESC guidelines for myocardial revascularization, published before the AUGUSTUS trial, recommend DAT as an alternative to TAT to reduce bleeding with COR Ila, but in the European guidelines this indication is currently restricted to patients at baseline high bleeding risk (11,12). Based on the North American expert consensus document, the default approach is DAT, and thus to keep aspirin only in the periprocedural period and during hospital stay. The rationale for DAT as a default strategy is based on results of the 3 trials available at the time of publication that showed a more favorable safety profile compared with TAT (6,8,9). It is important to note that all trials testing the safety of dropping aspirin early (i.e., prior to hospital discharge) are based on the observation that most bleeding events occur within the first month, as noted in the previous text, due to periprocedural issues and use of multiple antithrombotic medications. The high rate of bleeding early after PCI was also confirmed in the more recent studies, particularly during the time frame that patients were still on aspirin (6-10). However, the North American document does indicate that TAT for up to 1 month can be considered in patients who have high thrombotic risk and low bleeding risk. In contrast, the European consensus document follows this approach only for patients in whom the bleeding risk exceeds the thrombotic risk, whereas all other patients should receive 1 month of TAT as a default approach, or longer-term (3 to 6 months) TAT if the thrombotic risk exceeds the bleeding risk (COR IIa in the European guidelines for myocardial revascularization [12]). These differences between consensus documents possibly reflect the different weights that the 2 panels of experts have given to the findings of the PIONEER-AF PCI and REDUAL PCI trials, with the North Americans relying more on such clinical trial data to support their recommendations compared with their European counterparts. The results of the AUGUSTUS trial, in the context of previous evidence from the other trials, will likely affect future recommendations and perhaps provide more consistency between North American and European experts who mostly diverge on duration of TAT. Further analyses from the AUGUSTUS trial, which showed consistent benefit of DAT irrespective of baseline risk (e.g., with no significant interaction observed for multiple subgroups) will also better inform practitioners as well as help develop guideline recommendations (10). It should be noted that these recommendations refer essentially to AF patients on DOACs. Indeed, the effect of aspirin withdrawal in VKA patients who are not eligible for DOACs is limited to the small WOEST trial.

The third question deals with the specific antiplatelet drug to be discontinued in the transition from TAT to DAT. The consensus of the North American and European documents is that a P2Y12 inhibitor should be used without aspirin. This recommendation is based on the well-established notion that, post-PCI, the use of a P2Y12 inhibitor is pivotal for the prevention of thrombotic complications (22-25). This is suggested despite the notion that a proportion of patients exhibit substantial variability in the platelet response to clopidogrel (54). However, this pharmacodynamic characteristic was not shown to translate into an increase in adverse outcomes with clopidogrel in a large direct comparison with aspirin, where clopidogrel was actually shown to be superior in reducing ischemic events and also had a more favorable safety profile (i.e., less hospitalization for gastrointestinal bleeding) (55,56). It is, however, important to note that aspirin was used at a 325-mg daily regimen in this trial. Indeed, the key role that the P2Y12 receptor-mediated signaling has on modulating thrombotic processes in stented patients supports keeping an agent blocking this pathway (57). It is also important to note that there is synergism on modulating thrombus formation when a P2Y12 inhibitor is coupled with an OAC (58).

The fourth question deals with the dosing regimen of a DOAC for combination therapy in TAT or DAT regimens. In TAT regimens, both documents recommend using approved doses proven to be effective in regulatory trials of AF, with dose reductions as per the respective package labels (i.e., due to reduced renal elimination in patients with chronic kidney disease). In the case of dabigatran, the North American document suggests to use a higher 150-mg bid dose for patients who are at higher thrombotic risk, which is consistent with the 2019 ACC/AHA/HRS
guidelines for AF, where dabigatran 150 mg has COR IIa, LOE B; the European consensus documents, consistent with the 2018 ESC guidelines on myocardial revascularization, suggest using the 110-mg bid dose during TAT (COR IIa, LOE C) and the 150-mg bid dose during DAT (COR IIb, LOE B), due to concerns of higher thrombotic risk with the lower dose. If rivaroxaban is used, the 15-mg od dose (e.g., rather than the 20-mg od dose tested in the regulatory trial of AF) is considered a reasonable option by the 2018 ESC guidelines for myocardial revascularization according to the design of PIONEER-AF PCI (COR IIa, LOE B in the 2019 ACC/AHA/HRS guidelines for AF; COR IIb, LOE B in the 2018 ESC guidelines for myocardial revascularization) (12). After discontinuation of the P2Y12 inhibitor, OAC should be continued at full stroke prevention doses. Therefore, if a reduced dose regimen of rivaroxaban (e.g., 15 mg od; 10 mg od in patients with renal dysfunction) was being used, it is important to resume the full recommended dose (20 mg od; 15 mg od in patients with renal dysfunction) after suspension of antiplatelet therapy (15,16).

The fifth question deals with the choice of P2Y12 inhibitor. In this category, clopidogrel should be regarded as the agent of choice. Prasugrel and ticagrelor are approved for patients with ACS, and there is limited data for their use in combination with OAC (4). Data of prasugrel for TAT with VKA are disappointing due to an unacceptable high rate of bleeding (59), and the 2018 ESC guidelines on myocardial revascularization formally contraindicate the use of both prasugrel and ticagrelor in combination with OAC (COR III, LOE C), whereas the 2019 ACC/AHA/HRS guidelines for AF recommend clopidogrel in TAT combinations with COR IIa, LOE B. Indeed, in PIONEER-AF PCI, the use of prasugrel and ticagrelor was allowed, but the proportion of patients who actually received them was very small (2% to 4%) (8). In RE-DUAL PCI, ticagrelor was used in 12% of patients, which provides some insights to the treatment effects, although without statistical power. In particular, although no statistical interaction was noted between the treatment effect of the 2 tested doses of dabigatran and the use of clopidogrel or
ticagrelor for DAT, the absolute rates of bleeding were higher when ticagrelor was used in TAT combinations as compared with DAT (9,35). In light of these findings, in patients who are at low risk for bleeding (particularly younger patients) and at high risk for thrombotic events (e.g., ACS, diabetes, complex PCI), the use of ticagrelor combined with a DOAC represents a potential option (15). In AUGUSTUS, the use of prasugrel or ticagrelor was also low (10). Although there are no randomized clinical trial data supporting escalation of P2Y₁₂-inhibiting therapy among patients with inadequate response to clopidogrel, and routine platelet function or genetic testing to define response to clopidogrel is not recommended, the use of ticagrelor may be considered in patients in whom poor response to clopidogrel is known or after a side effect to the drug (60).

Finally, a sixth question deals with the optimal management at 12 months from PCI, when the patient is typically on DAT unless the P2Y₁₂ inhibitor has been discontinued earlier as suggested in both the North American and European consensus documents for patients at very high risk of bleeding. Ideally, the patients should continue on OAC alone, based on registry and other observational data showing that in patients with stable CAD (e.g., >1 year, with no acute events), the addition of antiplatelet therapy to OAC increases bleeding without adding ischemic protection compared with OAC alone (61,62). This consideration is valid unless concerns of thrombotic risk prevail, suggesting the need for continued DAT on a case-by-case basis (Table 1). According to the North American document, the choice of SAPT to use after 1 year (aspirin or clopidogrel) is at the discretion of the treating physician, although it appears to be reasonable to maintain the same antiplatelet drug that the patient was already taking. After discontinuation of SAPT, DOACs should be continued at full stroke-prevention doses as described in the previous text. Because renal function is a dynamic process, it is prudent to reassess renal function before changing the dose or after discontinuation of SAPT. The OAC-ALONE (Optimizing Antithrombotic Care in Patients With Atrial Fibrillation and Coronary stEnt) study, a trial initially designed to enroll 2,000 patients in 12 months but prematurely terminated after enrolling 696 patients in 38 months, did not establish non-inferiority of OAC alone to combined OAC and SAPT in patients with AF and stable CAD beyond 1 year after PCI (63). However, because patient enrollment was prematurely terminated, this study should be considered inconclusive. On the same subject, the AFIRE (Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease Study) study (N = 2,200) is ongoing in Japan to evaluate the efficacy and safety of monotherapy with the DOAC rivaroxaban versus DOAC plus SAPT in stable CAD patients 1 year or more after PCI (NCT02642419), while the French AQUATIC (Assessment of Quitting versus Using Aspirin Therapy In patients treated with oral anticoagulation for atrial fibrillation and with stabilized Coronary artery disease) (currently unregistered on clinicaltrials.gov) trial will investigate, in high-risk stabilized PCI patients requiring OAC for AF, the superiority of DAT with aspirin and full-dose OAC for 24 to 48 months versus placebo and full-dose OAC alone on a composite endpoint including cardiovascular mortality, myocardial infarction, stroke, coronary revascularization, systemic embolism, and acute limb ischemia.

**OTHER BLEEDING AVOIDANCE STRATEGIES.** Both the North American and European consensus documents recommend using proton pump inhibitors in all situations where OAC is combined with antiplatelet therapy (64,65). In addition, concurrent therapy with nonsteroidal anti-inflammatory drugs, possibly potentiating the effect of antithrombotic therapy, should be avoided.

**ONGOING STUDIES OF ANTITHROMBOTIC THERAPY IN AF PATIENTS UNDERGOING PCI**

The ENTRUST-AF PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) will soon complete the landscape of DOAC trials in AF patients who need antiplatelet agents (Figure 3) (66). Edoxaban 60 mg od will be tested against TAT with VKA in about 1,500 patients on a primary endpoint of International Society on Thrombosis and Haemostasis-defined major or clinically relevant nonmajor bleeding. Another trial with a safety focus on bleeding named APPROACH-ACS-AF (APIxaban vs. Phenprocoumon in Patients With ACS and AF) (NCT02789917), comparing DAT with apixaban versus TAT with VKA, is also underway. Two more randomized trials are ongoing in China. The COACH-AF PCI trial (Dabigatran Versus Warfarin With NVAF Who Undergo PCI) (NCT03536611) is an open-label, randomized trial designed to compare the safety and efficacy of 1-month TAT followed by DAT with dabigatran versus 1-month TAT followed by DAT with warfarin in Chinese patients with AF undergoing PCI. This study will address a question remained unanswered by the RE-DUAL PCI trial: whether the superior benefit of the investigational strategies is ascribable to the use of dabigatran versus a VKA or DAT versus TAT. The primary
endpoint will be time to the first occurrence of Bleeding Academic Research Consortium-defined (grade 2 to 5) clinically relevant bleeding. Another multicenter trial (NCT03234114) will enroll 800 ACS patients undergoing PCI to receive 12-month DAT with dabigatran 100 mg bid plus ticagrelor or clopidogrel versus TAT with warfarin randomized for 1 or 6 months, followed by DAT with warfarin and clopidogrel for up to 12 months. The primary composite endpoint will be the composite of all-cause death, nonfatal myocardial infarction, unplanned revascularization, ischemic stroke, or major bleeding. The Japanese SAFE-A (SAFety and Effectiveness trial of Apixaban use in association with dual antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention) study will compare 1-month vs. 6-month DAPT in combination with apixaban in patients with AF who undergo DES implantation (67). Finally, the ongoing MASTER DAPT (Management of High Bleeding Risk Patients Post Bioreosorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen) trial, randomizing approximately 4,300 high-bleeding-risk patients undergoing DES implantation to an abbreviated versus a standard duration of antiplatelet therapy, will include a substantial proportion of patients with concomitant indication to OAC (68).

CONCLUSIONS

When performed in the setting of AF, where OAC is used to prevent the risk of thromboembolic events, PCI requires the use of antiplatelet therapy to prevent the risk of stent thrombosis. The current paradigm is that the association of OAC with DAPT (typically clopidogrel and aspirin), a strategy known as TAT, should be as short as possible or even avoided (69). However, there are different perspectives on the 2 sides of the Atlantic on when and in which patients SAPT should be started. A North American perspective suggests that TAT should be used in-hospital but soon deescalated to DAT with OAC and clopidogrel for 6 to 12 months depending on the bleeding risk, followed by OAC alone in most cases. The European perspective suggests that TAT should be stopped at discharge, 1 month, or 3 to 6 months depending on considerations surrounding the balance between the individual thrombotic and bleeding profile. Indeed, the results of the AUGUSTUS and ENTRUST-AF PCI trials will likely affect future recommendations and perhaps foster more synergism between North American and European experts who mostly diverge on duration of TAT. A number of bleeding-avoidance strategies are also suggested to decrease the risk of bleeding with both TAT and DAT. Three trials of dabigatran, rivaroxaban, and apixaban have provided randomized evidence that a regimen of DAT with DOACs provides better safety compared with a regimen of TAT with VKA. Further evidence is expected soon for edoxaban. Although the DAT strategy has clearly demonstrated a reduction in bleeding complications without any apparent trade-off in efficacy, none of the trials were powered for ischemic events. Given the unlikelyhood of further large-scale trials powered for efficacy, patient-level meta-analyses of the available evidence would indeed be informative to this extent.

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