Antithrombotic Therapy in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention
A North American Perspective—2016 Update

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Abstract—The optimal antithrombotic treatment regimen for patients with atrial fibrillation undergoing percutaneous coronary intervention with stent implantation is an emerging clinical problem. Currently, there is limited evidenced-based data on the optimal antithrombotic treatment regimen, including antiplatelet and anticoagulant therapies, for these high-risk patients with practice guidelines, thus, providing limited recommendations. Over the past years, expert consensus documents have provided guidance to clinicians on how to manage patients with atrial fibrillation undergoing percutaneous coronary intervention. Given the recent advancements in the field, the current document provides an updated opinion of selected North American experts from the United States and Canada on the treatment of patients with atrial fibrillation undergoing percutaneous coronary intervention. In particular, this document provides the current views on (1) embolic/stroke risk, (2) ischemic/thrombotic cardiac risk, and (3) bleeding risk, which are pivotal for discerning the choice of antithrombotic therapy. In addition, we describe the recent advances in pharmacology, stent designs, and clinical trials relevant to the field. Ultimately, we provide expert consensus-derived recommendations, using a pragmatic approach, on the management of patients with atrial fibrillation undergoing percutaneous coronary intervention.


Key Words: anticoagulant ■ antiplatelet therapy ■ atrial fibrillation ■ hemorrhage ■ stent ■ thrombosis

Atrial fibrillation (AF) is the most common cardiac arrhythmia occurring in 1% to 2% of the general population, with a prevalence that increases with age. Among AF patients at moderate-to-high risk for cardioembolic events, the use of chronic oral anticoagulant therapy (OAC) is the mainstay of stroke prevention. Similarly, the prevalence of coronary artery disease (CAD) increases with age and coexists in 20% to 30% of patients with AF. Approximately 5% to 7% of patients undergoing percutaneous coronary intervention (PCI) for the treatment of CAD, who are routinely considered for dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor, also have AF or other indications for chronic OAC. These estimates are expected to increase as the global burden of AF increases, driven in large part to the aging population in industrialized countries. Taken together, these observations raise an important clinical problem regarding the optimal antithrombotic management of patients undergoing PCI who also have AF.

Currently, there are limited evidenced-based data on the optimal antithrombotic treatment regimen of PCI patients who also require OAC because of AF. In turn, practice guidelines provide little guidance on the management of these high-risk patients. In light of this, in 2010, the European Society of Cardiology Working Group on Thrombosis published a consensus document on the antithrombotic management of these patients. This was followed in 2011 by a consensus document elaborated by North American experts. In the past several years, there have been several advances in the field, which have recently led to an updated consensus document by the European Society of Cardiology Working Group on
Thrombosis. Accordingly, the current document provides an updated opinion of selected North American experts from the United States and Canada on the treatment of patients with AF undergoing PCI. Given that much of the background information has been extensively described in the European Society of Cardiology consensus documents, prior studies will only be briefly reviewed here. In line with our prior consensus document and because of the extremely limited data for patients who may have other indications for OAC (eg, prosthetic heart valves, pulmonary embolism, transcatheter aortic valve replacement, medically managed acute coronary syndromes [ACS]), only antithrombotic treatment of AF undergoing PCI will be addressed.

Antithrombotic Therapy for Patients With AF Undergoing PCI: Definitions and Considerations

Among patients undergoing PCI, DAPT is superior to OAC for the reduction of early thrombotic complications and represents the mainstay of treatment for the acute and long-term reduction of atherothrombotic events, including stent thrombosis. Although DAPT with aspirin and clopidogrel is more protective than aspirin alone for prevention of cardioembolic events in patients with AF, this combination is inferior to OAC, with comparable bleeding rates, and thus, OAC is the treatment of choice if clinically indicated and feasible. Therefore, clinicians commonly treat PCI patients who also have AF with the combination of DAPT and OAC, known as triple therapy, with the goal of reducing the risk of both atherothrombotic and cardioembolic events. However, triple therapy exposes patients to an increased risk of bleeding complications relative to dual or monotherapy. Importantly, bleeding is associated with increased morbidity and mortality particularly when it occurs early after PCI. Therefore, defining antithrombotic treatment regimens associated with a more favorable safety profile (ie, reduced bleeding complications), while preserving efficacy (ie, prevention of atherothrombotic and cardioembolic events), is of key importance.

Most safety and efficacy data for triple therapy derive primarily from observational studies using aspirin, clopidogrel, and a vitamin K antagonist (VKA), such as warfarin. Although clopidogrel has been the most used P2Y<sub>12</sub> receptor inhibitor, the newer oral P2Y<sub>12</sub> receptor inhibitors, prasugrel and ticagrelor, provide a greater reduction in atherothrombotic events, albeit of the expense of more bleeding, when compared with clopidogrel. Moreover, 4 non-VKA OACs (NOACs; dabigatran, rivaroxaban, apixaban, and edoxaban) have been approved for clinical use, and they are associated with comparable, or in some cases better efficacy, and reduced intracranial bleeding risk compared with VKA. The multitude of currently available oral antplatelet and anticoagulant therapies adds to the difficulty in determining the optimal combination of these agents for individual patients (Figure 1). Fortunately, there have been advancements that have been shown to lessen the risk of cardioembolic events and bleeding complications in patients with AF. Among patients undergoing PCI, studies have shown that the use of the radial approach, bivalirudin, and possibly vascular closure devices reduce the risk of bleeding. In addition, new-generation drug-eluting stents (DES) have been shown to be less vulnerable to thrombotic complications compared with earlier DES and possibly bare metal stents (BMS), including in patients at high risk for stent thrombosis, such as those with diabetes mellitus or ST-segment–elevation myocardial infarction (MI). Overall, this changing landscape has impacted the way physicians choose an antithrombotic treatment regimen for patients with AF who require or who have undergone PCI. In the below sections, we describe the current views of (1) embolic/stroke risk, (2) ischemic/thrombotic cardiac

![Figure 1](https://via.placeholder.com/150)

**Figure 1.** Sites of action of oral anticoagulants (OAC) and dual antiplatelet therapy (DAPT). OAC include vitamin K antagonists (VKA) and 4 non-VKA (NOACs; dabigatran, rivaroxaban, apixaban, and edoxaban). Idarucizumab and Andexanet-alfa are reversal agents of NOACs targeting factor II and X, respectively. DAPT include aspirin, a cyclooxygenase-1 (COX-1) inhibitor, and P2Y<sub>12</sub> receptor inhibitors (clopidogrel, prasugrel, and ticagrelor). ADP indicates adenosine diphosphate; GPVI, glycoprotein receptor VI; and PAR-1, protease-activated receptor-1.
risk, and (3) bleeding risk, which are pivotal for discerning the choice of antithrombotic therapy.

**Embolic/Stroke Risk**

**Pathogenesis, Rationale for Treatment, and Risk Stratification**

AF is associated with mechanical dysfunction of atrial tissue. Loss of contractile function in the left atrium and left atrial appendage (LAA) can lead to local stasis and thrombus formation, which may then embolize into the systemic circulation. Low Doppler inflow velocities, spontaneous echocardiographic contrast, and the presence of thrombus in the LAA have been linked with high stroke risk in AF patients.58 These observations support the hypothesis that the LAA is the nidus for thromboembolism in AF in the majority of patients. However, factors other than atrial dysfunction may contribute to thromboembolic events.59 AF is also associated with a prothrombotic status,60 particularly among patients with risk factors. OACs, and to a lesser degree DAPT with aspirin and clopidogrel, decrease stroke and systemic embolism, presumably primarily by reducing the risk of clot formation within the left atrium and LAA.61 However, the mechanistic connections between many factors predictive of thromboembolic risk and the left atrium and LAA remain to be elucidated.62

Because OAC therapy increases bleeding and other potential drug-related adverse effects, an individualized assessment of thromboembolic risk is a critical part of therapeutic decision-making for the AF patient. The frequency of AF episodes should not be a major factor that influences treatment decisions because paroxysmal, persistent, or permanent AF each increases stroke risk, although paroxysmal AF to a lesser extent.53,64 Even subclinical AF of >6-minute duration has been associated with an increased risk of ischemic stroke or systemic embolism,65 although whether short episodes of subclinical AF should be treated with OAC remains to be determined. Stroke risk is influenced by a variety of factors. The CHADS2 and CHA2DS2VASc score are well-validated risk scores based on an individual’s age and comorbidities that can estimate a yearly risk of thromboembolic events and identify patients who may derive net clinical benefit from OAC66,67 (Table 1). Compared with the CHADS2 score, the CHA2DS2VASc score provides greater weighting for elderly age and incorporates sex and the presence of peripheral vascular disease. This enables the CHA2DS2VASc score to better identify patients who are particularly at low risk for thromboembolism and who do not warrant OAC (ie, those with CHA2DS2VASc score =0).68 Therefore, the CHA2DS2VASc score is the more commonly recommended tool. However, not all factors in the CHA2DS2VASc score carry an equal risk for thromboembolic events.69 Moreover, several other factors not included in these schema have been linked with stroke risk, such as atrial fibrosis detected by magnetic resonance imaging69 and LAA morphology,70,71 and require further evaluation to define their value in thromboembolic risk stratification.

<table>
<thead>
<tr>
<th>CHA2DS2VASc Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke, transient ischemic attack, or thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74 y</td>
<td>1</td>
</tr>
<tr>
<td>Sex category=female</td>
<td>1</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; and PAD, peripheral arterial disease.

There are many guidelines on the use of antithrombotic therapy in patients with AF, most of which have now uniformly embraced the CHA2DS2VASc scoring system.60,72,73 AF patients undergoing PCI have a CHA2DS2VASc score of at least 1 since they have established vascular disease. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society Guideline for the Management of Patients With Atrial Fibrillation recommends the calculation of the CHA2DS2VASc score to assess stroke risk (Class I; Level of Evidence B) and the use of OACs in patients with CHA2DS2VASc score ≥2 (Class I; Level of Evidence A).60 In patients with CHA2DS2VASc score =0, one should not treat with OAC or with aspirin (Class Ila; Level of Evidence B), whereas in patients at intermediate thromboembolic risk (CHA2DS2VASc score =1), no therapy, aspirin, or OAC therapy may be considered (Class Ila; Level of Evidence B).60 The Canadian Cardiovascular Society (CCS) Guidelines for the Management of Atrial Fibrillation also recommend stratification of stroke risk based on the CHADS2 schema, complemented by the inclusion of some, but not all, of the CHA2DS2VASc criteria because they do not consider female sex or vascular disease alone to be sufficient reasons to prescribe OAC therapy.73 Thus, the CCS Guidelines recommend that (1) OAC therapy be prescribed for most patients aged ≥65 years or CHADS2 score ≥1 (Strong Recommendation; Moderate-Quality Evidence); (2) aspirin (81 mg/daily) be prescribed for patients with none of the risks outlined in the CCS algorithm (age <65 years and no CHADS2, risk factors) who have arterial disease (coronary, aortic, or peripheral; Conditional Recommendation; Moderate-Quality Evidence); and (3) no antithrombotic therapy for patients with none of the risks outlined in the CCS algorithm (age <65 years and no CHADS2 risk factors) and free of arterial vascular disease (coronary, aortic, or peripheral; Conditional Recommendation; Low-Quality Evidence).73

**Treatment Options**

In patients with AF, warfarin reduces the risk of thromboembolism by roughly two thirds compared with patients on no therapy.5,6 Because of genetics, diet, and drug–drug interactions, the pharmacokinetics and pharmacodynamics of warfarin vary considerably.74 Warfarin has a narrow therapeutic window, and patients with intensity of anticoagulation below the therapeutic range are at risk for thromboembolic events,75 whereas those above are at increased risk for bleeding, including intracranial hemorrhage.76 Regular laboratory monitoring and dose adjustment are, therefore, required. However, even in patients enrolled in clinical trials, the average time within the therapeutic...
range (TTR) for warfarin-treated patients is between 55% and 65%. Importantly, a TTR <65% is associated with worse outcomes. The optimal performance for TTR on a population level is ≥70%, as has been achieved in Scandinavian countries.

Unlike warfarin, the NOACs have a predictable pharmacodynamic profile and do not require routine coagulation monitoring (Table 2). Randomized clinical trials have demonstrated that these agents are either noninferior or superior to warfarin for the prevention of stroke and systemic embolism in patients with AF. The stroke reduction with NOACs is driven by reductions in hemorrhagic stroke: ischemic stroke rates are similar or, in the case of dabigatran 150 mg twice daily, modestly reduced. Compared with warfarin, the NOACs have similar or lower rates of major hemorrhage, with the exception of gastrointestinal bleeding, which is greater with all the NOACs except apixaban and the lower dose of dabigatran, where it is similar. Moreover, in a meta-analysis of all 4 NOACs studied in the pivotal phase 3 clinical trials for stroke prevention or systemic embolic events in patients with AF, the NOACs had a favorable risk-benefit profile, with significant reductions in stroke, intracranial hemorrhage, and mortality and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding; the relative efficacy and safety of NOACs was consistent across a wide range of patients.

The role of antiplatelet therapy in stroke reduction is of particular importance in the AF patient who requires PCI. The efficacy of aspirin monotherapy in reducing the risk of AF-related strokes has been inconsistent among trials and, accordingly, largely debated or even abandoned in some guideline recommendations. In AF patients for whom VKA therapy was unsuitable, compared with aspirin, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage. In the ACTIVE-A trial (Atrial fibrillation Clopidogrel Trial With Irbesartan for prevention of Vascular Events), the addition of clopidogrel to aspirin provided a 28% relative risk reduction and 0.9% absolute risk reduction in stroke compared with aspirin alone in a cohort of patients deemed unsuitable for a VKA, at the cost of a 57% relative and 0.7% absolute increase in major bleeds. In the ACTIVE-W trial, warfarin was superior to the combination of aspirin and clopidogrel for the prevention of stroke, systemic embolism, MI, or vascular death (relative risk reduction in stroke, 42%; absolute risk reduction, 0.9%), with similar rates of major bleeding. Therefore, although DAPT with aspirin and clopidogrel is more protective than with aspirin alone for prevention of cardioembolic events in patients with AF, this combination is inferior to warfarin, with similar rates of

### Table 2. Summary of Randomized Trials of Non–Vitamin K Antagonist Oral Anticoagulants Compared With Warfarin Therapy in Patients With Nonvalvular Atrial Fibrillation

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct thrombin inhibitor</td>
<td>RE-LY</td>
<td>RE-LY</td>
<td>ROCKET-AF</td>
<td>ARISTOTLE</td>
</tr>
<tr>
<td>Direct thrombin inhibitor</td>
<td>1.11 (0.89–1.40)</td>
<td>0.94 (0.75–1.17)</td>
<td>0.92 (0.74–1.13)</td>
<td>1.00 (0.83–1.19)</td>
</tr>
<tr>
<td>Antifactor Xa inhibitor</td>
<td>0.91 (0.80–1.03)</td>
<td>0.85 (0.70–1.02)</td>
<td>0.89 (0.80–0.998)</td>
<td>0.92 (0.83–1.01)</td>
</tr>
<tr>
<td>Antifactor Xa Inhibitor</td>
<td>0.83 (0.69–0.93)</td>
<td>1.04 (0.90–1.20)</td>
<td>0.69 (0.60–0.80)</td>
<td>0.80 (0.71–0.91)</td>
</tr>
<tr>
<td>CHADS² (mean)</td>
<td>2.1</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td>TTR, % (median)</td>
<td>67%</td>
<td>67%</td>
<td>58%</td>
<td>66%</td>
</tr>
<tr>
<td>Approved dose</td>
<td>150 mg twice daily*</td>
<td>110 mg twice daily*</td>
<td>20 mg once daily (15 mg once daily in selected patients†)</td>
<td>5 mg twice daily (2.5 mg twice daily in selected patients†)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.76 (0.60–0.98)</td>
<td>1.11 (0.89–1.40)</td>
<td>0.94 (0.75–1.17)</td>
<td>0.92 (0.74–1.13)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.26 (0.14–0.49)</td>
<td>0.31 (0.17–0.56)</td>
<td>0.59 (0.37–0.93)</td>
<td>0.31 (0.35–0.75)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.88 (0.77–1.00)</td>
<td>0.91 (0.80–1.03)</td>
<td>0.85 (0.70–1.02)</td>
<td>0.89 (0.80–0.998)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>0.93 (0.81–1.07)</td>
<td>0.80 (0.69–0.93)</td>
<td>1.04 (0.90–1.20)</td>
<td>0.69 (0.60–0.80)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1.50 (1.19–1.89)</td>
<td>1.10 (0.86–1.41)</td>
<td>1.39 (1.19–1.61)</td>
<td>0.89 (0.70–1.15)</td>
</tr>
</tbody>
</table>

ARISTOTLE indicates Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; CrCl, creatinine clearance; ENGAGE AF, Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation; ESRD, end stage renal disease; RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Exetilate; ROCKET AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation; and TTR, time in therapeutic range.

*The United States Food and Drug Administration approved dabigatran at a dose of 75 mg BID for selected patients, but this dose was not tested in the RE-LY trial. The 110 mg BID dose is not approved in the United States for stroke prevention in atrial fibrillation.

†US labeling—Dabigatran: 150 mg twice daily, dose reduction to 75 mg twice daily in patients with creatinine clearance 15–30 mL/min or in patients with creatinine clearance 30–50 mL/min and taking dronedarone or ketoconazole; Rivaroxaban: 20 mg once daily, dose reduction to 15 mg once daily in patients with creatinine clearance 15–50 mL/min; Apixaban: 5 mg twice daily unless patient has any 2 of the following: age ≥80 y, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, then reduce dose to 2.5 mg twice daily. If ESRO requiring hemodialysis, 5 mg twice daily, reduce to 2.5 mg twice daily if age ≥80 y or body weight ≤60 kg; Edoxaban: creatinine clearance 51–90 mL/min, 60 mg once daily; creatinine clearance 15–50 mL/min, 30 mg once daily. Canadian labeling—Dabigatran: 150 mg twice daily, dose reduction to 110 mg twice daily in patients at increased risk of bleeding, including patients ≥75 y with ≥1 risk factor for bleeding; Rivaroxaban: 20 mg once daily, dose reduction to 15 mg once daily in patients with creatinine clearance 30–50 mL/min; Apixaban: 5 mg twice daily, if serum creatinine ≥133 μM/L and either age ≥80 y or body weight ≤60 kg, 2.5 mg twice daily; eCrCl 15–24 mL/min, no dosage adjustments provided in manufacturer’s labeling.

‡The United States Food and Drug Administration restricted the approval of edoxaban to patients with a creatinine clearance <95 mL/min but the results provided in the table apply to the entire ENGAGE trial population in which the approved dose was tested.
bleeding, and thus, OAC is the treatment of choice if clinically indicated and feasible.60 LAA closure has emerged as a treatment option for stroke prevention in nonvalvular AF. The safety and efficacy of Watchman LAA closure compared with warfarin has been evaluated in 2 randomized trials, PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation)83 and PREVAIL (Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device In Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy).84 In the PROTECT-AF trial, LAA closure was superior to warfarin for the primary efficacy end point of stroke, systemic embolism, and cardiovascular/unexplained death at a mean follow-up of 3.8 years (2621 patient-years).82 In the smaller PREVAIL trial, LAA closure met the prespecified criterion for safety, but did not achieve noninferiority to warfarin for the primary efficacy end point; the rate of ischemic stroke in the warfarin arm was substantially lower than expected based on CHA2DS2-VASc scores.84 A patient-level meta-analysis of these 2 trials showed that LAA closure was associated with a comparable rate of the composite primary efficacy outcome and significantly lower hemorrhagic stroke and cardiovascular death.64 A strategy of LAA closure significantly reduced bleeding beyond the immediate periprocedural period, particularly once adjunctive postprocedural pharmacotherapy (warfarin followed by DAPT) was discontinued. This bleeding benefit was consistent across baseline bleeding risk strata.65 The safety and efficacy of LAA closure has not been compared with the NOACs. The Watchman device is indicated to reduce the risk of thromboembolism from the LAA in patients with AF who (1) are at increased risk for stroke or systemic embolism based on CHADS2 or CHA2DS2-VASc and are recommended for anticoagulation; (2) are deemed by their physicians to be suitable for warfarin; and (3) have an appropriate rationale to seek a nonpharmacological alternative to warfarin, taking into account the safety and effectiveness of the device compared with warfarin.86 The American Heart Association/American Stroke Association 2014 Guidelines for the Primary Prevention of Stroke states that LAA closure may be considered for high-risk patients with AF who are deemed unsuitable for prolonged anticoagulation if performed at a center with low rates of periprocedural complications and the patient can tolerate the risk of at least 45 days of postprocedural anticoagulation (aspirin and VKA; Class IIb; Level of Evidence B).87 The CCS Guidelines currently suggest that LAA closure devices not be used, except in research protocols or in systematically documented use protocols in patients at high risk of stroke (CHADS2 score ≥ 2) for whom antithrombotic therapy is precluded (Conditional Recommendation; Low-Quality Evidence).83 The use of LAA closure in patients with AF undergoing PCI has not been studied.

Ischemic/Thrombotic Risk

Pathogenesis, Rationale for Treatment, and Risk Stratification

Patients with AF and atherothrombosis are at high risk not only for thromboembolic risk but also for ischemic cardiac events.88 The most powerful predictor of a future cardiac ischemic event is a prior ischemic event, in particular, within the past year.89 Patients who have had a prior MI or ACS are at much greater risk than those with stable CAD. This principle carries over to those who receive stents and has important implications regarding intensity and duration of oral antiplatelet therapy.90 The platelet plays a vital role in response to plaque rupture in ACS, initiating clot formation and obstructing coronary blood flow, leading to myocardial damage.91,92 Similarly, in response to vessel injury with PCI and stenting, platelet-rich thrombus formation may occur. In addition to ACS, other factors, such as patient age, presence of certain risk factors (ie, diabetes mellitus, renal failure, cigarette smoking), congestive heart failure or low ejection fraction, and burden of atherosclerotic disease (eg, number of implanted stents, lesion complexity, nonrevascularized segments, coexistence of peripheral vascular or cerebrovascular disease), are important determinants of ischemic risk. Hence, antiplatelet agents play an important role in the acute and chronic management of such patients and in the secondary prevention of cardiac ischemic events.91,92

Treatment Options

Treatment options for oral antiplatelet agents in ACS and PCI include aspirin and P2Y12 inhibitors. In general, aspirin is used as the first-line agent, and a P2Y12 inhibitor is added. Clopidogrel had been the standard for many years, but in patients with ACS, prasugrel (if the patient is planned for PCI) and ticagrelor are now generally preferred for the first year after the event (Class IIa).41,44,93–95

In parallel with the advances in antiplatelet therapy, stents have become safer, with new-generation DES having a lower rate of stent thrombosis than the first-generation DES, and even potentially lower rates than with BMS across CAD manifestations, including in patients with diabetes mellitus and those presenting with ST-segment–elevation MI undergoing primary PCI.52–57 Although bioresorbable scaffolds represent an emerging treatment option, to date, there is no evidence that they provide any greater safety than new-generation DES. On the contrary, in more complex settings, current bioresorbable scaffold are associated with higher stent thrombosis rates, particularly within the first 30 days and through at least the first year of follow-up.96,97 These increased events seem to be largely attributed to the increased strut thickness, which is ≥2-fold those of second-generation DES, and a higher rate of scaffold malapposition.96,97

DAPT Duration

Numerous trials have shown that the risk of stent thrombosis is greatest in the first month after either BMS or DES, and premature discontinuation of DAPT during this time period is associated with a significant increase in ischemic events, particularly among those with ST-segment–elevation MI.98–100 Several recent, small-to-modest-sized stent trials with relatively lower-risk patients found no benefit to longer durations of DAPT.101–104 The much larger DAPT trial found that 30 months of DAPT was superior to 12 months of DAPT in reducing MI and stent thrombosis after DES implantation, though there was increased bleeding with the longer DAPT
duration. A similar finding was seen with BMS, albeit in a smaller cohort, not powered to determine benefit. A subsequent analysis of the DAPT trial showed a greater benefit of longer DAPT among patients with an ACS versus those without ACS, but with a similar increase in bleeding with longer DAPT in either group. Although a nominally higher mortality risk was observed, there was no difference in fatal bleeding. An analysis from the Food and Drug Administration analysis of multiple trials of DAPT versus aspirin did not show any increase in mortality and meta-analysis of studies and subset analyses of patients with prior MI have shown a reduction in cardiovascular death. The PEGASUS (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared With Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) trial found that DAPT with ticagrelor beyond 12 months reduced the rate of the primary outcome of cardiovascular death, MI, and stroke. Moreover, ticagrelor reduced recurrent MI in patients with a prior MI, consistent with subgroup findings seen with clopidogrel. However, prolonging ticagrelor beyond 12 months also caused an increased risk of bleeding.

Stent thrombosis rates with second-generation DES for stable CAD are now low enough that the decision regarding duration of DAPT is based on anticipated risks of a future MI (unrelated to the stent) versus bleeding. Importantly, in patients who present with an ACS, ischemic events accrue over time and are equally attributable to recurrence at the site of culprit lesions and to nonculprit lesions, which represents the rationale for intensified and prolonged secondary prevention therapies, including antiplatelet drugs. Thus, the key to proper patient selection for prolonged DAPT may have more to do with the underlying ischemic risk (eg, prior MI, presence of cardiovascular risk factors, lesion complexity, or extensive vascular disease) than with having received a stent per se, especially if that stent is a second-generation DES. Risk scores have been developed to define patients at risk for thrombotic and bleeding complications and, thus, help identify patients who may have net benefit or harm with prolonged DAPT. However, data regarding duration of therapy and score or decision tools developed from these data either exclude or contain a minority of patients with concomitant OAC, where uncertainty remains regarding ischemic risk, and bleeding risk is further increased. A predictive tool developed in patients on triple therapy might be helpful in stratifying ischemic versus bleeding risk and selecting an intensity and duration of antithrombotic therapy for this patient population.

The most recent 2016 American College of Cardiology/American Heart Association guideline update on DAPT duration indicate that in patients with ACS, P2Y₁₂ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months irrespective of the stent type (Class I; Level of Evidence B); in patients with stable ischemic heart disease, P2Y₁₂ inhibitor therapy with clopidogrel should be given for at least 1 and 6 months after BMS (Class I; Level of Evidence A) and DES (Class I; Level of Evidence B) implantation, respectively. DAPT prolonged beyond 1 year after-stenting received a Class IIb; Level of Evidence A recommendation. The 2012 CCS Antiplatelet Guidelines provide similar recommendations, including P2Y₁₂ inhibitor therapy with aspirin for 12 months post ACS and PCI, with shorter DAPT duration in the non-ACS setting, particularly with newer-generation DES. However, both guidelines also provide an opportunity to prolong or shorten DAPT duration, albeit with a lower class of recommendation, according to the ischemic and bleeding risk profile of the individual patient. For patients with AF in association with ACS and PCI, the 2016 CCS Atrial Fibrillation Guidelines recommend ticagrelor in addition to aspirin for 12 months (Strong Recommendation; High-Quality Evidence) for patients <65 years with no CHADS₂ risk factors (or prasugrel if the coronary anatomy is known and there is no history of previous TIA or stroke or clopidogrel in patients not eligible for ticagrelor or prasugrel). For these lower stroke-risk patients, who are particularly at high risk of major bleeding, the P2Y₁₂ inhibitor therapy could be discontinued earlier than 12 months (ie, aspirin alone; Conditional Recommendation; Low-Quality Evidence). For those at higher risk of stent thrombosis and whose risk of major bleeding is acceptable, DAPT for longer than 12 months could be considered (Conditional Recommendation; Low-Quality Evidence). In contrast, for those whose stroke risk warrants OAC (age ≥65 years or CHADS₂ score ≥1), triple therapy with aspirin, clopidogrel (rather than prasugrel or ticagrelor), and OAC (preferably a NOAC), is recommended for 3 to 6 months (duration depending on the perceived risks of coronary thrombosis and major bleeding). After 3 to 6 months, the combination of clopidogrel and OAC is suggested until 12 months post ACS/PCI, followed by OAC alone (Conditional Recommendation; Low-Quality Evidence).

**Bleeding Risk**

**Generalities: Pathogenesis and Risk Stratification**

Observational studies suggest that patients treated with the combination of an OAC and DAPT have major bleeding rates of 5% to 15% at 1 year depending on the population, the antithrombotic drugs, and definition of major bleeding. Bleeding was historically considered to be a reversible event without independent prognostic importance unless the bleeding was life-threatening. Now it is known from multiple observational studies and randomized controlled trials that both minor and major bleeding events are independently predictive of major adverse cardiovascular outcomes, including stroke, MI, and cardiovascular death. Among patients with ACS, undergoing PCI, cerebrovascular disease, peripheral artery disease, or venous thromboembolism, major bleeding is associated with a 2- to 8-fold increase in the risk of death and nonfatal cardiovascular events.

The risk of bleeding varies by agent and is also related to the intensity of antithrombotic therapy. In patients treated with a single antiplatelet drug, aspirin and clopidogrel are associated with similar rates of any bleeding, although clopidogrel is associated with a lower rate of hospitalization for gastrointestinal bleeding. The more potent P2Y₁₂ receptor antagonists prasugrel and ticagrelor are associated with a higher rate of bleeding than clopidogrel. The NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) have lower rates of life-threatening bleeding than warfarin.
the number of antithrombotic drugs also increases the risk of bleeding. Thus, DAPT is associated with a higher frequency of bleeding than treatment with a single antiplatelet drug, and the combination of an OAC and an antiplatelet drug is linked with a higher occurrence of bleeding than either treatment alone. The risk of bleeding on warfarin is greatest during the first 3 months after initiation and thereafter seems to accrue at a stable rate; the risk of bleeding with aspirin and clopidogrel is also higher during the early months after initiation. Patients who do not bleed during the 9 to 12 months of aspirin plus clopidogrel therapy may have a lower risk of bleeding when treatment is continued long term.

Clinical risk scores may help to identify patients at high risk of bleeding, but their predictive ability is limited (C statistics 0.55–0.70). Thus, patients with AF who are at high risk of stroke are also at high risk of bleeding. HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [≥ 65 years], drugs/alcohol concomitantly) has been recommended as a bleeding risk score for patients with AF, with scores ≥3 considered high risk. Although the HAS-BLED score has been found to significantly predict bleeding, its discriminating value is overall limited and similar to CHA2DS2-VASc score for prediction of bleeding. In a study of patients with AF and CHA2DS2-VASc score ≥1 undergoing PCI (n=590), 71% had a HAS-BLED score ≥3. In these patients, OAC was found to independently reduce the risk of death at 12 months, whereas the use of DES (with subsequent need for prolonged DAPT) independently predicted the risk of major bleeding. Similar observations have been made among octogenarian AF patients undergoing PCI who had a mean HAS-BLED score of 3.05. Overall, these findings suggest that the use of OAC on top of DAPT improves prognosis, despite the increased risk of bleeding, even in patients with HAS-BLED score ≥3. This is also in line with registry data showing that patients with AF undergoing PCI have a CHA2DS2-VASc score ≥2 in 70% of cases, so that OAC treatment should not be withdrawn even when combined anticoagulant and antiplatelet treatment is warranted. Indeed, there are many other bleeding scores. The discriminatory value of these scores after PCI is uncertain.

Bleeding Prevention Strategies
The prognostic implications associated with bleeding underpin the need to define strategies to prevent and manage hemorrhagic events. In addition to procedural related and other adjunctive approaches as discussed later, a key principle to prevention of bleeding is to minimize the intensity and duration of antithrombotic effect, yet to allow it to maintain therapeutic efficacy for prevention of atherothrombotic and thromboembolic events over the necessary interval. To this extent, targeting an INR in the lower therapeutic range in patients receiving a VKA in combination with DAPT seems logical. Although this strategy has not been proven to be helpful in a randomized trial, registry data showed that among patients undergoing coronary stenting on triple therapy, targeting lower therapeutic INR values was associated with significantly lower risk of bleeding complications. However, maintaining a high TTR, which is critical for efficacy of VKA, remains a well-known challenge in real-world practice (Table 2). The pharmacological limitations of VKA underscore the need for agents with more reliable pharmacokinetic and pharmacodynamic profiles, such as the NOACs. Unfortunately, there are limited studies assessing the effects of NOACs in combination with DAPT. A pharmacodynamic study conducted in patients on DAPT with aspirin and clopidogrel showed that adjunctive therapy with dabigatran 150 mg twice daily interfered with parameters related to thrombin activity and delayed fibrin clot formation, but was not related with modulation of profiles of platelet reactivity. DAPT use at baseline was an exclusion criteria in all of the pivotal randomized NOAC trials, with the exception of the RE-LY trial (Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etxilate). The RE-LY trial results showed that estimates of the efficacy and safety of dabigatran 110 mg twice daily and 150 mg twice daily compared with warfarin are consistent in the presence or absence of concomitant single-agent or dual-agent antiplatelet therapy.

Most evidence support that low-dose aspirin (<100 mg) is associated with a better safety profile (ie, less gastrointestinal bleeding) compared with high-dose aspirin (>300 mg) without a trade-off in efficacy. Thus, for PCI patients requiring OAC, low-dose (<100 mg) aspirin is recommended. The role for aspirin in addition to a P2Y12 receptor inhibitor in patients undergoing PCI who are also treated with an OAC has recently been questioned. Evidence from the WOEST trial (What is the Optimal Antiplatelet and Anticoagulant Therapy In Patients With Oral Anticoagulation and Coronary Stenting), described in more details below, suggests that omission of aspirin from the antithrombotic treatment regimen in patients undergoing elective or urgent PCI with BMS or DES might be able to reduce bleeding without compromising efficacy. These results are consistent with a large (n=12,165) nationwide study of unselected patients with AF in Denmark, with indication for multiple antithrombotic drugs after ACS/PCI, showing that the combination of OAC and clopidogrel was equal or better for both benefit and safety outcomes compared with triple therapy. This strategy of dropping aspirin is being further tested as part of several ongoing trials in different clinical settings, including among patients with AF undergoing PCI testing the NOACs as described below.

Ultimately, the intensity and duration of P2Y12 antiplatelet therapy is a key determinant of bleeding complications. Prasugrel and ticagrelor are associated with a higher risk of bleeding complications compared with clopidogrel, making clopidogrel the treatment of choice in PCI patients also requiring OAC. The duration of DAPT has been subject of controversy over the past years, particularly with the introduction of second-generation DES characterized by better safety profiles (ie, reduced stent thrombosis) compared with first-generation DES and even BMS. The most recent 2016 American College of Cardiology/American Heart Association guideline update on DAPT duration reflects such evidence as described above. Importantly, guidelines also provide an opportunity to shorten DAPT duration in patients at higher bleeding risk.
With regards to patients on treatment with OAC, guidelines indicate that discontinuation of P2Y<sub>12</sub> inhibitor therapy may be reasonable after 3 months for stable ischemic heart disease or after 6 months for ACS (Class IIb; Level of Evidence C). However, details on the optimal antithrombotic treatment regimen of patients with AF undergoing PCI are not elaborated in the guidelines.

**Advances in the Field of Management of Antithrombotic Therapy in PCI Patients With AF**

**Randomized Clinical Trials: WOEST and ISAR-TRIPLE**

To date, only 2 randomized clinical trials have been completed. The WOEST study compared OAC (warfarin) with single antiplatelet therapy (SAPT; clopidogrel) versus OAC and DAPT (aspirin and clopidogrel) among patients undergoing stent implantation. A total of 573 patients were randomized (27.5% ACS; 65% DES; 69% AF; 74% femoral approach) and followed for 1 year. All patients received aspirin during hospitalization. The warfarin–clopidogrel arm was associated with less total bleeding (TIMI [Thrombolysis in Myocardial Infarction] major plus minor) without statistically significant differences in major bleeds. The rates of ischemic events (including MI, stent thrombosis, stroke, or target vessel revascularization) did not differ significantly, although was numerically smaller in the warfarin plus clopidogrel only arm. Although there was a reduction in mortality, this needs to be interpreted with caution, given that the study was underpowered for this end point. Although this represents the only available data from a randomized trial, several limitations should be taken into consideration, including the small number of events, open-label design, low proton pump inhibitor (PPI) use, majority of femoral access, high (70%) prevalence of stable CAD, the relatively simple lesions intervened upon, the 1-year triple therapy duration when DES was implanted, the target INR of 2.0 to 3.0 without knowledge of the actual level achieved and TTR, and the limited power to detect potential differences in stent thrombosis. Although dual therapy with clopidogrel and warfarin could be considered in patients with higher risk of bleeding and low risk of ischemic events, the limitations of the WOEST trial restrict the applicability of these results particularly among populations at higher ischemic/thrombotic risk, such as patients with ACS or highly complex coronary anatomy.

ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug-Eluting Stent Implantation) is the other randomized clinical trial available, which addresses the question about triple therapy duration in patients undergoing DES implantation. In this trial, 614 patients (two third with stable CAD) were randomized to 6 weeks or to 6 months of clopidogrel (in addition to aspirin and warfarin) to assess net clinical outcome at 9 months (the composite of definite stent thrombosis, MI, death, stroke, or TIMI major bleeding). The primary net outcome was similar in the 2 arms (9.8% versus 8.8%; 95% confidence interval 0.68–1.91; P=0.63) for the 6-week versus the 6-month triple therapy, respectively. No significant differences were observed between the 2 durations for individual ischemic or bleeding end points, and therefore, the hypothesis that a shorter duration of clopidogrel would be beneficial was not met. On landmark analysis from 6 weeks to 6 months (ie, placebo versus clopidogrel), total bleeding and Bleeding Academic Research Consortium (BARC) ≥2 bleeding tended to be higher in the group receiving longer-duration clopidogrel. Although this represents the only randomized trial of duration of triple therapy in PCI, the small sample size and the limited number of ACS patients should be taken into consideration.

**Current Trends in Clinical Management of PCI Patients With AF**

The management of PCI patients with AF requires balancing the bleeding risks with the ischemic/thromboembolic risks in a given patient. Therefore, defining the antithrombotic treatment regimen with the safest profile without a tradeoff in efficacy represents the greatest unmet need for this complex clinical setting. In general, the consensus is to continue OAC therapy and to modify antiplatelet intensity or duration. The heterogeneity of this patient population, in terms of risk of atherothrombotic recurrences, thromboembolic events, and bleeding complications, lend difficulty in defining uniform treatment algorithms for these patients. This is further convoluted by the large number of potential treatment options, both antiplatelet and anticoagulants available, and the limited evidence for their combined use. This is particularly true for the NOACs, which have several advantages over VKA (Table 2). Moreover, the availability of more potent P2Y<sub>12</sub> inhibitors, prasugrel and ticagrelor, raises questions regarding how these agents will fit into the clinical setting of the AF patient treated with an invasive strategy for ACS. Although clopidogrel remains the treatment of choice for PCI patients requiring OAC because of the reduced risk of bleeding complications, concerns remain with regards to its efficacy. A large number of studies have shown that a considerable number of patients, particularly in high-risk settings, such as ACS, elderly, diabetics, chronic kidney disease, are more likely to have suboptimal response to clopidogrel, exposing these patients to an increased risk of thrombotic complications. Drug–drug interactions with cytochrome P450 CYP3A4–interfering PPIs (eg, omeprazole) and VKAs have been associated with impaired clopidogrel response, though the impact on clinical events remains unproven. Importantly, many of these predictors of impaired clopidogrel response are common in patients with AF. These observations have raised interest in investigating the newer P2Y<sub>12</sub> receptor inhibitors for PCI patients with AF, for which there is limited data, though an increased risk of bleeding. In a study of patients needing triple therapy, substitution of prasugrel for clopidogrel (mostly because of identified poor clopidogrel response) was accompanied by a 3-fold increased risk of bleeding. These observations have prompted studies to assess discontinuation of aspirin therapy as a strategy to minimize bleeding complications. Preliminary investigations have suggested reduction in bleeding complications, without a tradeoff in efficacy, linked with discontinuation of aspirin therapy in PCI patients treated with a VKA and clopidogrel. However, this approach needs to be validated in larger studies and include NOACs and new P2Y<sub>12</sub> receptor inhibitors. Moreover, the role of platelet function and genetic testing in patients treated with an OAC and antiplatelet therapy after PCI remains poorly explored and warrants investigation.
Expert Consensus Recommendations

Unfortunately, there remain large knowledge gaps regarding the optimal management of AF patients undergoing PCI, which impacts clinical decisions and guideline recommendations. Thus, until more data from large, randomized clinical trials are available, recommendations are expert consensus-based. It is well accepted that limiting the intensity and duration of antithrombotic therapy for PCI patients with AF is essential to reduce bleeding complications. Recommendation on the antithrombotic treatment regimen to be used in AF patients undergoing coronary stenting should be made based on the clinical setting and patient characteristics for risk of ischemic or thromboembolic events, as well as a dynamic assessment of the risk of bleeding. Moreover, a series of other aspects are key toward the management of these patients, which go beyond the choice of antithrombotic treatment regimen and are explained in more details below (Figure 2).

Preprocedural Considerations

Appropriateness Criteria for PCI

The inherent complexity connected with defining the optimal antithrombotic treatment regimen for PCI patients requiring OAC underscores the importance of appropriate patient selection for coronary stenting. The appropriate use criteria for coronary revascularization were developed to critically evaluate and improve patient selection for PCI. Discussing appropriateness criteria for revascularization by PCI goes beyond the scope of the present study and is extensively discussed elsewhere. In brief, the use of coronary revascularization for patients with ACS and in those with significant symptoms or ischemia are viewed as appropriate; in contrast, revascularization of asymptomatic patients or patients with low-risk findings on noninvasive testing and minimal medical therapy are viewed as rarely indicated. For patients in whom the benefits of revascularization are considered uncertain, defining the bleeding risk of an individual patient may be a determinant of whether to proceed with PCI or even consider surgical revascularization, depending on coronary anatomy. In patients in whom coronary stenting is performed, risk stratification is key toward defining their antithrombotic treatment regimen.

Risk Stratification

Management of patients who require OAC in addition to antiplatelet therapy requires careful decision-making focused on individual characteristics. The heterogeneity of this patient population, in terms of risk of atherothrombotic recurrences, thromboembolic events, and bleeding complications, contributes to challenges of defining a one-size-fits-all treatment algorithm for these patients. Risk scores may assist in identifying subsets at risk of ischemic, thromboembolic, and bleeding events. These can help the clinician decide on the intensity and duration of a specific antithrombotic treatment regimen. Unfortunately, the risk for ischemic, thromboembolic, and bleeding events frequently coexists in the same patient because these complications share common risk factors. In such cases, the risk and benefit of each drug choice should be carefully weighed, also taking into account the preference of the patient. Indeed, the risk profile of an individual patient also can be dynamic, with an intrinsic propensity to thrombotic and bleeding complications that may vary over time, and should always be considered when defining the intensity and duration of antithrombotic therapy.

Details of risk stratification have been described earlier. In brief, the CHA2DS2-VASc score allows for a more precise assessment of stroke risk factors than the CHADS2 score and, thus, should be preferred for defining whether a patient should be prescribed OAC. The risk of ischemic recurrences is largely dependent on the clinical presentation of the patient, with those who have had a prior MI at much greater risk than those with stable CAD. Other factors such as patient age, presence of certain risk factors, and burden of atherosclerotic disease are also important determinants of ischemic risk. In patients deemed to be at higher ischemic risk, the use of more potent...
antithrombotic treatment regimens for a more prolonged period of time may be favored. Given (1) the limited discriminating value of bleeding risk score and (2) that even among patients with high bleeding risk scores OAC should still be used (because the benefits outweigh the risks), this group does not recommend routine use of any specific bleeding score to guide therapy. Patients with prior bleeding and with anemia are at higher risk for bleeding and not at higher risk for stroke, so these factors may be more relevant for the decision of whether to treat with less aggressive antithrombotic therapy. Bleeding risk scores, such as HAS-BLED, should be considered mainly to identify modifiable risk factors related to bleeding, such as uncontrolled hypertension, suboptimal INR control on VKA therapy, and concomitant use of excess alcohol or nonsteroidal anti-inflammatory drugs.

Procedural Considerations

Vascular Access

Several, large randomized trials among patients undergoing PCI have consistently demonstrated a reduced risk of bleeding complications using the radial compared with femoral approach. In a meta-analysis of over 19,000 patients, compared with femoral access, radial access was associated with lower mortality, major adverse cardiovascular events, and major bleeding in patients with ACS undergoing invasive management.49 The radial approach should be the preferred choice for vascular access for patients at high risk of bleeding complications, including those to be managed with combination of antiplatelet and anticoagulant therapy. Moreover, radial access may be safer in patients on OAC, which cannot be withdrawn before the procedure, or if the INR remains in the therapeutic range at the time of the procedure.

Management of Oral Anticoagulant for Patients Already on Therapy

There has been much controversy on whether patients already on OAC should have therapy interrupted before undergoing invasive coronary evaluation with the intent to perform PCI. Concerns include the bleeding risk related with intensified antithrombotic therapy during an invasive procedure and uncertainty because of the adjunctive anticoagulant drug regimen used during PCI. It is common practice to allow for a wash-out of the anticoagulant effect before performing an invasive procedure. However, there are some observational data suggesting that uninterrupted OAC does not increase perioperative complications during coronary stenting.152,153 The reduced risk of bleeding complications with a radial approach may allow the clinician to shorten the duration of OAC or simply continue VKA therapy. In the PCI subgroup of a small randomized trial, patients on uninterrupted warfarin therapy were found to experience a lower rate of access-site complications, with radial access compared with femoral access (0% versus 37.5%; P=0.034).154 Whether continuation of OAC is a safe option in the peri-PCI period remains unproven without adequately powered randomized clinical trial evidence. Moreover, the absolute thromboembolic risk related with a temporary discontinuation of OAC is likely minimal in most nonvalvular AF patients. The shorter biological half-lives of the NOACs have reduced the duration

<table>
<thead>
<tr>
<th>NOAC and Renal Function,*</th>
<th>NOAC Half-Life, h (range)</th>
<th>Timing of Last Dose of NOAC Before Procedure</th>
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</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50 mL/min</td>
<td>15 (12–34)</td>
<td>Day (−2); skip 2 doses</td>
</tr>
<tr>
<td>&gt;30 to ≤50 mL/min</td>
<td>18 (13–23)</td>
<td>Day (−3); skip 4 doses</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30 mL/min</td>
<td>9 (5–13)</td>
<td>Day (−2); skip 1 dose</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30 mL/min</td>
<td>12 (10–15)</td>
<td>Day (−2); skip 2 doses</td>
</tr>
<tr>
<td>Edoxaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30 mL/min</td>
<td>10 (9–14)</td>
<td>Day (−2); skip 1 dose</td>
</tr>
</tbody>
</table>

Day 0=day of the invasive procedure. CrCl indicates creatinine clearance; eGFR, estimated glomerular filtration rate; and NOAC, non-vitamin K antagonist oral anticoagulant.

*The suggested timings do not consider use of NOACs in patients with severe renal insufficiency with creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) <30 mL/min. The last dose of these drugs should not be taken any later than the above recommended times. Bridging (eg, with low-molecular-weight heparin) is not recommended or necessary for these agents unless a longer period of interruption occurs.

of needed drug discontinuation compared with VKA, with wash-out of anticoagulant effects obtained within 24 to 48 hours in most cases, varying according to the particular agent and patient renal function (Table 3).155 Questions have also emerged regarding the need of bridging OAC patients with a parenteral agent while oral therapy is withheld for an upcoming invasive coronary evaluation. In an assessment of patients with AF who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of thromboembolism and decreased the occurrence of major bleeding.156

This expert-based consensus recommends that invasive procedures without withholding OAC should be reserved for urgent or emergency procedures and should be preferentially performed using a radial approach. Whenever possible (ie, elective/nonemergent procedures), a brief period of wash-out from the anticoagulant effect of OAC is preferable. In particular, for patients on a VKA, this expert consensus recommends an INR to be preferably ≤2.0 when using a radial approach. In patients treated with the femoral approach, an INR ≤1.5 should be targeted. Patients on an NOAC should withhold therapy for 24 hours (or 48 hours for patients with impaired renal function with dabigatran), irrespective of vascular access site. Although patients with stable CAD can forgo bridging with parenteral anticoagulation, this should be considered for patients presenting with an ACS. Timing of discontinuation of OAC should be judiciously estimated according to timing of the scheduled procedure to avoid a lack of antithrombotic protection for a prolonged time frame. In nearly all cases, OAC should be resumed immediately post PCI.
Choice of Intraprocedural Anticoagulation
Numerous intraprocedural parental antithrombotic agents are currently available and are associated with different bleeding potentials. Although these agents have not been specifically tested in patients on OAC, there is consensus that the routine use of intraprocedural agents known to be related with an increase in the risk of bleeding should be avoided. The use of parenteral antiplatelet agents (ie, glycoprotein IIb/IIIa inhibitors; cangrelor) should be reserved for select cases at high risk for thrombotic complications or for bailout situations. Irrespective of practice patterns, bivalirudin has consistently demonstrated a reduced risk of bleeding compared with heparin with or without glycoprotein IIb/IIIa inhibitors, particularly in those presenting with an ACS. Moreover, a recent meta-analysis has confirmed the reduced bleeding risk, albeit at the expense of increased risk of stent thrombosis, associated with bivalirudin compared with unfractionated heparin monotherapy. The broad uptake of the radial approach has led to question the residual benefit of bivalirudin as a bleeding-avoidance strategy. The MATRIX trial (Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) showed that in ACS patients undergoing invasive management, radial access, as compared with femoral access, reduced net adverse clinical events, through a reduction in major bleeding and all-cause mortality. Although the rates of major adverse cardiovascular events and net adverse clinical events were not significantly lower with bivalirudin than with unfractionated heparin, major bleeding complications were significantly reduced, with consistent treatment effects irrespective of approach (radial versus femoral), although the absolute risk reduction was substantially lower among patients with radial access, in large part because of the overall reduced frequency of bleeding among these patients. Given the current controversies over the net benefits of bivalirudin over other antithrombotic treatment regimens as well as differences in practice patterns among interventionalists, this expert consensus does not recommend a specific parenteral antithrombin agent over another. However, bivalirudin seems to be a reasonable treatment option in patients at higher risk of bleeding, particularly in those presenting with ACS and if a femoral approach is being used. Nevertheless, there are no studies exploring whether such benefit is consistent among patients who are on OAC.

For ACS patients treated with enoxaparin at the time of clinical presentation, continuing enoxaparin is a reasonable option. For patients treated with upstream subcutaneous enoxaparin in the context of an non–ST-segment–elevation-ACS, an additional dose of 0.3 mg/kg IV should be administered at the time of PCI to those who have received <2 therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose 8 to 12 hours before PCI. Enoxaparin may be administered intravenously (0.5–0.75 mg/kg IV bolus) at the time of PCI for patients who have not received previous antithrombin therapy. In fact, in elective PCI patients, mostly composed of stable CAD patients, a single intravenous bolus of 0.5 mg/kg of enoxaparin reduced bleeding rates and a dose of 0.75 mg/kg yields rates similar to those for unfractionated heparin, with more predictable anticoagulation levels. However, there are no studies exploring enoxaparin among patients who are on OAC. It is important to note that switching from unfractionated heparin to enoxaparin (and vice versa) may increase the risk of bleeding and is discouraged.

Stent Selection
For years, BMS have been considered the stent of choice for OAC-requiring patients because of the known shorter durations of DAPT after BMS. However, the favorable safety profile of new-generation DES, with stent thrombosis rates lower than first-generation DES and possibly even BMS, including shorter duration of DAPT, has prompted reconsideration of prior recommendations. Recent studies conducted among patients at high risk for bleeding, including the use of OAC, have shown superior safety and efficacy using certain DES platforms (which are currently not Food and Drug Administration–approved) compared with BMS using short DAPT duration. It is important to note that AF patients requiring PCI are frequently affected by comorbidities that are often associated with more complex coronary anatomy (eg, multivessel disease, long lesions, bifurcations, small vessels). The superiority of second-generation DES over BMS for reduction of restenosis and revascularization procedures is also key for these patients. Stent failure because of restenosis would likely require additional interventions, frequently with multiple layers of stents, which could further contribute to the thrombotic risk of these patients. Thus, the use of a stent with a superior safety and efficacy profile, currently represented by commercially available new-generation DES, should be the device of choice. However, BMS still represent a treatment alternative for noncomplex PCI (ie, short lesions with large reference vessel diameters) and potentially considered for patients who are at high risk of bleeding complications who may not tolerate >4 weeks of DAPT, such as patients with a recent major bleeding event (eg, gastrointestinal bleeding) and those with poor or unpredictable medication compliance. Although bioresorbable scaffold may have the potential for reducing late thrombotic events in patients undergoing PCI, they are associated with higher scaffold thrombosis rates, particularly in more complex settings, more notably within the first 30 days and out to at least a year of follow-up. Thus, although the technology seems promising, further investigations are warranted before bioresorbable scaffold becoming recommended for PCI patients, with AF requiring OAC. Other advancements in stent technology that may allow shorter DAPT duration include DES with abluminal bioabsorbable polymers, polymer-free DES, and BMS with thomboresistant coatings, which are subject of ongoing investigations (NCT02605447 and NCT02594501).

Oral Antithrombotic Therapy: Choice and Duration of Therapy
Defining the optimal antithrombotic treatment regimen for AF patients treated with stents is challenging because of the paucity of data, particularly from randomized clinical trials, to support specific recommendations. In this section, we report the outcome of our expert consensus regarding the choice, combination, and duration of antithrombotic treatment regimens for this population.
OAC

Factors affecting decisions on whether to use OAC (eg, bleeding risk, compliance, risk for falls) should apply especially for those patients treated with stents requiring antiplatelet therapy. For AF patients in whom OAC is recommended, the duration of treatment should be lifelong, unless otherwise contraindicated. In patients undergoing coronary stenting who require OAC, the choice of agent (VKA versus NOAC) frequently represents a dilemma both for patients who have not been previously treated with an OAC, as well as for those who are already on treatment with a given OAC. For the latter, it may be reasonable to continue with the same agent post stenting, particularly if the patient has been compliant and has not experienced complications. Such an approach would avoid switching among antithrombotic therapies, which may potentially increase the risk of bleeding, add a higher-risk period of initiation if warfarin is used, or result in unknown adverse reactions or intolerance to the new agent, complicating post-PCI management. However, there are limited evidence-based data to support a particular choice of OAC. As described earlier, the currently available observational and randomized trial data for combination of OAC and antiplatelet therapy are derived from patients treated with a VKA.

Nevertheless, given the favorable safety profile of the NOACs and their ever increasing use in everyday clinical practice without manifest safety concerns thus far, this expert consensus believes that these agents may also be considered as a first-line therapy. In addition, an NOAC may be preferred over a VKA in patients who are unable to have their INR routinely monitored or are unable to maintain an INR in the therapeutic range. There are no head-to-head data to support the preferential use of one NOAC over another at this time.

Although there are some data to support the lower therapeutically ranged INR (ie, 2.0–2.5) in VKA-treated patients requiring antiplatelet therapy after PCI, there are no data regarding the appropriate intensity of anticoagulant effect that is required of an NOAC in this clinical setting. To minimize bleeding complications, some have advocated the use of lower dosing regimens of an NOAC when used in combination with antiplatelet therapy. The rationale for such a strategy derives from clinical trial experience in ACS patients, which showed a dose-dependent effect of NOACs on major bleeding complications, including greater rates of intracranial hemorrhage and fatal bleeding when added to DAPT (mainly aspirin and clopidogrel). However, it is unknown whether reduced dosing regimens preserve their thromboembolic protective effects in patients outside of specific cohorts (eg, renal dysfunction, elderly, low weight). Although the use of the lowest effective dose of NOAC to prevent stroke is appropriate (ie, dabigatran 110 mg BID rather than 150 mg BID), the opinions of the expert consensus members differed with regard to the optimal dosing regimen for an NOAC in the setting of DAPT post PCI.

In summary, this expert consensus recommends that in AF patients treated with stents (requiring antiplatelet therapy), the choice of OAC (VKA or NOAC) be at the discretion of the treating physician, with patients informed of the risk–benefit profiles of each agent based on available data. Continuing with the same OAC after PCI may be reasonable, particularly if the patient has been compliant and has not experienced complications. If a VKA is chosen, patients should maintain an INR in the 2.0 to 3.0 range and ideally between 2.0 and 2.5. An NOAC should be preferred over a VKA in patients unable to have their INR routinely monitored or are unable to maintain INR in the therapeutic range. Although the use of full dose (approved) of NOACs can be recommended as an option for thromboembolic protection, a recommendation on use of doses lower than the full anticoagulant dose of a specific NOAC cannot be provided until further data become available.

Antiplatelet Therapy

DAPT with aspirin and a P2Y12 receptor inhibitor represents the standard-of-care treatment regimen for patients undergoing stent implantation. Aspirin exerts a dose-dependent effect on the rate of bleeding complications. Accordingly, the maintenance dose of aspirin in patients treated with OAC after PCI should be 75 to 100 mg/d. There are currently 3 P2Y12 receptor inhibitors used (clopidogrel, prasugrel, and ticagrelor). The lower risk of bleeding complications with clopidogrel makes this agent the oral P2Y12 receptor inhibitor of choice in stented patients with AF treated with OAC. After loading dose (600 mg) administration, clopidogrel should be used at a maintenance dose of 75 mg/d. Because DAPT duration is linked with risk of bleeding complications, limiting the duration of DAPT therapy and considering treatment with a SAPT has been subject of investigation. This expert consensus recommends that the duration of DAPT in AF patients treated with stents also on OAC should not extend to a full 12 months and to consider SAPT starting within the first 6 months (0–6 months post stenting depending on the ischemic/thrombotic and bleeding risk profile) for ≤12 months. This group consensus recommends that dropping aspirin rather than a P2Y12 receptor inhibitor should be considered (favoring the use of clopidogrel and avoiding prasugrel or ticagrelor). The rationale for the preference of prolonged clopidogrel over aspirin is based on the following: (1) pivotal role of P2Y12-mediated signaling in thrombotic and inflammatory processes; (2) established clinical efficacy of P2Y12 inhibitors to reduce stent thrombosis, including among patients requiring OAC; (3) although bleeding risk with the combination of OAC plus clopidogrel is higher than with OAC plus aspirin (and nonsignificantly lower than triple therapy), the combination of OAC plus clopidogrel is comparable to triple therapy in respect to the prevention of ischemic stroke, with a trend toward benefit of MI/coronary death; moreover, the risk of all-cause mortality is similar between OAC plus clopidogrel and triple therapy but markedly increased for OAC plus aspirin; (4) superior anti-ischemic efficacy of clopidogrel monotherapy versus aspirin monotherapy, with better gastrointestinal tolerability (discomfort and hemorrhage) when aspirin 325 mg is used. Nevertheless, dropping clopidogrel may also be a reasonable option, particularly, if patients are known to be poor clopidogrel responders (or have high on-clopidogrel platelet reactivity) or are at risk for this condition because of cytochrome P450 2C19 loss-of-function allele carrier status. However, in the absence of data demonstrating a benefit of use of platelet function or genetic testing to tailor antiplatelet treatment regimens in PCI settings,
in line with practice guidelines, this expert consensus recommends against the routine use of these tests. Moreover, switching to a more potent P2Y₁₂ receptor inhibitor (prasugrel or ticagrelor) is strongly discouraged because of the increased risk of bleeding complications.

The optimal duration of DAPT after stenting is a subject of controversy and is even more so among patients on a background of OAC. In fact, although risk stratifying patients for ischemic, thromboembolic, and bleeding events can assist in decision-making, the lack of outcome data stratified according to the presence of these factors do not allow for evidence-based recommendations. In line with these observations, the consensus of this expert opinion group was to consider a qualitative rather than quantitative approach to define the duration of antiplatelet therapy. In particular, this expert consensus deems that providing a definitive treatment duration of DAPT (eg, 0, 1, 3, and 6 months), stratifying patients according to specific ischemic/thrombotic (eg, ACS versus non-ACS) and bleeding risk (eg, HAS-BLED score ≥3) criteria, while seemingly logical, would not at this time be evidence-based. Moreover, specific schema for ischemic/thrombotic and bleeding risk stratification are subject to limitations and are not universally accepted. Therefore, strict adherence to an algorithm based on scoring systems to define DAPT duration would make their implementation subject to controversy. In light of the absence of evidence-based data to define DAPT duration in AF patients requiring OAC undergoing PCI, this expert consensus agreed that DAPT duration should be constructed on qualitative assessments of ischemic/thrombotic and bleeding risks, based on physician judgment and according to stent type. This would, therefore, allow for more flexibility in physician decision-making on DAPT duration, thus, more reflective of real-world practice. In particular, the definition of ischemic/thrombotic risk may embrace factors other than ACS presentation, including clinical, angiographic, and procedural features, which should all be accounted for in decision-making. Similar considerations apply for defining bleeding risk. Factors that have been associated with increased ischemic/thrombotic and bleeding risks are listed in Table 4. Individual patients may have factors for both increased ischemic/thrombotic and bleeding risk, and some factors are related with both increased ischemic and bleeding risk, making the assessment of the benefit/risk ratio of prolonged DAPT difficult in many patients. However, this qualitative approach allows for clinical judgment on behalf of the treating physician who can take into consideration these factors and have some flexibility in decision-making on DAPT duration. Such an approach is also in line with most recent guideline updates on DAPT duration.

Overall, although discontinuation of one antiplatelet agent should be considered 1 to 3 months after PCI, this may occur sooner (including immediately after PCI) or later (but not beyond 6 months) according to the ischemic/thrombotic and bleeding risk profiles of the patient (Figure 3). DAPT duration in patients with balanced ischemic/thrombotic/bleeding risk, low ischemic/thrombotic–high bleeding risk, and high ischemic/thrombotic–low bleeding risk are summarized in Figure 4A–4C, respectively. More specifically, this consensus supports the following duration of antiplatelet therapy in stented patients with AF who are concomitantly treated with OAC:

- Patients at low ischemic/thrombotic risk treated with a BMS should be treated with DAPT for 0 to 1 month. Stopping aspirin immediately after PCI may be considered for patients at very high bleeding risk, whereas patients at lower bleeding risk should be treated with 1 month of DAPT followed by SAPT.
- Patients at low ischemic/thrombotic risk treated with a DES should be treated with DAPT for 0 to 3 months. Shorter DAPT duration, including stopping aspirin immediately after PCI, may be considered for patients with very high bleeding risk, while clinicians should consider treating patients at lower bleeding risk with ≤3 months of DAPT followed by SAPT.
- Patients at high ischemic/thrombotic risk treated with a BMS should be treated with DAPT for 1 to 3 months. Shorter DAPT duration, including stopping aspirin at 1 month after PCI, should be considered for patients with higher bleeding risk, while clinicians should consider treating patients at lower bleeding risk with ≤3 months of DAPT followed by SAPT.
Patients at high ischemic/thrombotic risk treated with a DES should be treated with DAPT for 1 to 6 months. Shorter DAPT duration, including stopping aspirin at 1 month after PCI, should be considered for patients with higher bleeding risk, while in patients at lower bleeding risk, ≤6 months of DAPT followed by SAPT should be considered.

The duration of SAPT in addition to OAC (which should be maintained lifelong unless contraindicated) should take into consideration the ischemic/thrombotic and bleeding risk profiles of the individual patient. Large registry data have shown that continuing antiplatelet therapy beyond 1 year in patients treated with OAC is associated with an increase in bleeding complications without offering further ischemic protection. These observations may be attributed to the reduced risk of ischemic events beyond 1 year, particularly in patients at low thrombotic risk, thereby limiting the ability to demonstrate a treatment effect. Moreover, the potential benefit of antiplatelet therapy after 1 year may be offset by the increase in bleeding complications early after PCI and initiation of OAC therapy, patients should be monitored more closely during the first few months post procedure. Moreover, for patients treated with VKA, the variability in INR levels particularly during the early phases of treatment underscore the need for close monitoring, and with NOACs, renal function should be monitored in case the dose needs adjustment. Patients should be counseled not to stop therapy because of nuisance bleeding or bruising, but rather to call their physician. Ultimately, reassessment of patient risk profile over time may be warranted and require treatment modification.

Postprocedural Considerations
Close monitoring of PCI patients with AF treated with OACs is required, given their increased risk of ischemic, thromboembolic, and bleeding complications. Ideally, the care of these patients should be guided by the cardiologist/interventional cardiologist rather than by the primary care physician who may be less abreast of the complexity of the PCI procedure and the available antithrombotic treatment options for these patients. Given the higher risk of both ischemic and bleeding complications early after PCI and initiation of OAC therapy, patients should be monitored more closely during the first few months post procedure. Moreover, for patients treated with VKA, the variability in INR levels particularly during the early phases of treatment underscore the need for close monitoring, and with NOACs, renal function should be monitored in case the dose needs adjustment. Patients should be counseled not to stop therapy because of nuisance bleeding or bruising, but rather to call their physician. Ultimately, reassessment of patient risk profile over time may be warranted and require treatment modification.
In addition to recommended standard-of-care therapies for secondary prevention of ischemic events, strategies to reduce the risk of bleeding complications should be considered. PPI use should be considered to reduce the risk of gastrointestinal bleeding, particularly in patients on OAC.190,191 Although concerns have emerged regarding drug–drug interactions between PPIs and clopidogrel based on pharmacokinetic and pharmacodynamic studies, prompting a box warning of drug-regulating authorities on this drug combination, clinical studies have not consistently shown an increase in thrombotic complications.144,145,147 The interaction between PPIs and clopidogrel is not class-specific; it applies to only those drugs (ie, omeprazole and esomeprazole) interfering with the cytochrome P450 2C19 activity.144,145 Therefore, in line with PCI (ie, omeprazole and esomeprazole) interfering with the cytochrome P450 2C19 activity.144,145 Therefore, in line with PCI (ie, omeprazole and esomeprazole) interfering with the cytochrome P450 2C19 activity.144,145 Therefore, in line with PCI (ie, omeprazole and esomeprazole) interfering with the cytochrome P450 2C19 activity.144,145 Therefore, in line with PCI (ie, omeprazole and esomeprazole) interfering with the cytochrome P450 2C19 activity.

Managing Bleeding Complications

The most effective way to reduce the burden of bleeding is prevention (Figure 5). Even with optimal preventive strategies, patients receiving combined anticoagulant and antiplatelet therapy remain at high risk. The goals of bleeding management are to control the bleeding, diagnose, and treat the underlying cause of bleeding and minimize the duration of interruption of antithrombotic therapy to reduce the risk of thromboembolic complications during antithrombotic treatment interruption.188–190

Minor bleeding (eg, self-limiting epistaxis, bruising, self-limited hematuria, hemorrhoidal bleeding) can be managed in most cases without interruption of treatment.191 However, even minor bleeding is predictive of risk of subsequent major adverse cardiovascular events (cardiovascular death, MI, stroke), in part, because recurrent episodes lead to treatment discontinuation, and it is, therefore, important to make every attempt to diagnose the underlying cause and implement effective strategies to prevent recurrent episodes.

Major bleeding management requires interruption of some or all antithrombotic therapies; attempts to control bleeding with local measures (eg, pressure, injection) or via endoscopy (eg, injection, cautery), arteriography (eg, embolization, coiling) or surgery; supportive measures to replace blood loss (eg, crystalloids, red blood cell transfusion); general measures to promote hemostasis (eg, antifibrinolytic drugs, prothrombin complex concentrates); and for life-threatening bleeding reversal of the hemostatic defect (eg, platelet infusions, specific antidote such as idarucizumab for dabigatran, and potentially andexanet-alfa for Xa inhibitors).190–193

Aspirin and the P2Y12 receptor antagonists, clopidogrel and prasugrel, bind irreversibly to their platelet target, exerting their effects for the life span of the platelet; ticagrelor binds reversibly to the P2Y12 receptor on platelets, and its speed of offset is faster than that of clopidogrel and prasugrel.93,194–196 The efficacy of platelet transfusions to restore normal platelet aggregation may vary according to antithrombotic agent.197–199 Platelet transfusion can rapidly reverse the antiplatelet effect of aspirin because 10% to 20% of platelets not inhibited by aspirin are sufficient to sustain normal thromboxane-dependent aggregation.198 In contrast, restoration of normal platelet aggregation in patients treated with any of the P2Y12 receptor antagonists requires infusion of large numbers of platelets and may not be as effective in ticagrelor-treated patients because of its mechanism of action.199

The anticoagulant effect of warfarin can be reversed by replacing deficient functional clotting factors using a 4-factor prothrombin complex concentrate (eg, octaplex and beriplex) or the combination of a 3-factor concentrate with the addition of a small dose of recombinant factor VII because the 3 factor concentrates contain little factor VII.200 The effect of prothrombin complex concentrates is transient because the half-life of factor VII is only ≈6 hours. Therefore, patients requiring sustained reversal of VKA therapy should also receive a dose of vitamin K to promote hepatic synthesis of factor VII. Fresh plasma should generally not be used for reversal of warfarin because it is relatively ineffective and associated with a high risk of adverse events.201,202

Idarucizumab is a humanized monoclonal antibody fragment that was recently approved by the Food and Drug Administration as a specific reversal agent for dabigatran (Figure 1).203 It is an intravenous agent that binds to dabigatran with high affinity, and the dabigatran-idarucizumab complex is subsequently cleared via the kidney. The REVERSE-AD study (Reversal Effects of Idarucizumab on Active Dabigatran) demonstrated that >90% of dabigatran-treated patients presenting with life-threatening bleeding or requiring urgent surgery who received a 5 g dose of idarucizumab had rapid (within minutes), complete, and sustained (12 hours or more) reversal of anticoagulant effect.193 The half-life of idarucizumab is ≈8 hours in patients with normal renal function, enabling resumption of dabigatran within 24 hours if clinically indicated.
Table 5. Ongoing Trials of NOACs in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th>NOAC</th>
<th>PIONEER AF-PCI</th>
<th>REDUAL-PCI</th>
<th>AUGUSTUS</th>
<th>ENTRUST AF-PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Dabigatran</td>
<td>Apixaban</td>
<td>Edoxaban</td>
<td></td>
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<tr>
<td>Clinicaltrials.gov identifier</td>
<td>NCT01830543</td>
<td>NCT02164864</td>
<td>NCT02415400</td>
<td>NCT02866175</td>
</tr>
<tr>
<td>Trial status</td>
<td>Enrollment completed</td>
<td>Enrolling</td>
<td>Enrolling</td>
<td>Planning</td>
</tr>
<tr>
<td>Study type</td>
<td>Open-label, randomized</td>
<td>Open-label, randomized</td>
<td>Open-label (apixaban vs warfarin) and blinded (aspirin vs placebo), randomized</td>
<td>Open-label, randomized</td>
</tr>
<tr>
<td>Patients</td>
<td>2169 patients with AF who undergo a PCI with stenting</td>
<td>2500 patients with AF undergoing PCI with stenting (elective or post ACS)</td>
<td>4600 patients with AF undergoing PCI with stenting or an ACS</td>
<td>1500 patients with AF after successful PCI with stenting (elective or post ACS)</td>
</tr>
<tr>
<td>Investigational arm(s)</td>
<td>Rivaroxaban 2.5 mg BID plus aspirin ≤100 mg OD plus clopidogrel 75 mg OD or prasugrel 10 mg OD or ticagrelor 90 mg BID followed by rivaroxaban 15 mg (or 10 mg for subjects with moderate renal impairment) OD plus aspirin ≤100 mg</td>
<td>Dabigatran etexilate 110 mg clopidogrel 75 mg OD or ticagrelor 90 mg BID</td>
<td>2×2 factorial: Apixaban (5 or 2.5 mg twice daily)*</td>
<td>Edoxaban-based regimen: Edoxaban 60 mg OD (dose reduced to 30 mg OD in selected subjects†)</td>
</tr>
<tr>
<td>Investigational arm(s)</td>
<td>Rivaroxaban 15 mg (or 10 mg for subjects with moderate renal impairment) OD plus clopidogrel 75 mg OD or prasugrel 10 mg OD or ticagrelor 90 mg BID</td>
<td>Dabigatran etexilate 150 mg plus clopidogrel 75 mg OD or ticagrelor 90 mg BID</td>
<td>Aspirin vs placebo</td>
<td>Concomitant use of another antiplatelet agent (ie, aspirin) is not allowed</td>
</tr>
<tr>
<td>Control arm</td>
<td>Warfarin plus clopidogrel 75 mg OD or prasugrel 10 mg OD or ticagrelor 90 mg BID plus aspirin ≤100 mg</td>
<td>Warfarin plus clopidogrel 75 mg OD or ticagrelor 90 mg BID plus aspirin ≤100 mg</td>
<td>2×2 factorial: warfarin</td>
<td>VKA-based regimen: The VKA of choice with OD dosing for target international normalized ratio (INR) between 2.0 and 3.0, inclusive.</td>
</tr>
<tr>
<td>Control arm</td>
<td></td>
<td></td>
<td></td>
<td>Clopidogrel 75 mg OD or prasugrel (5 mg or 10 mg OD) or ticagrelor (90 mg BID)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>12 mo</td>
<td>30 mo</td>
<td>6 mo</td>
<td>12 mo</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Clinically significant bleeding (TIMI major bleeding, minor bleeding, and bleeding requiring medical attention)</td>
<td>ISTH major bleeding event</td>
<td>Time to first occurrence of ISTH major or CRNM</td>
<td>Time to first occurrence of ISTH major or CRNM bleeding</td>
</tr>
</tbody>
</table>

(Continued)
Atrial Fibrillation and Coronary Stenting

### Table 5. Continued

<table>
<thead>
<tr>
<th>Key secondary end points</th>
<th>PIONEER AF-PCI</th>
<th>REDUAL-PCI</th>
<th>AUGUSTUS</th>
<th>ENTRUST AF-PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of each component of the TIMI clinically significant bleeding composite (TIMI major bleeding, minor bleeding, and bleeding requiring medical attention); composite of adverse cardiovascular events (cardiovascular death, MI, and stroke); cardiovascular death, MI, stroke, and stent thrombosis</td>
<td>Death or first thrombotic event (all-cause death, myocardial infarction, stroke/systemic embolism)</td>
<td>Superiority on major-CRNM bleeding; composite end points of death and ischemic events (stroke, myocardial infarction, stent thrombosis, urgent revascularization) for apixaban vs warfarin; first rehospitalization for any cause for apixaban vs warfarin and for aspirin vs placebo; composite end points of death and ischemic events (stroke, myocardial infarction, stent thrombosis, urgent revascularization) for apixaban vs warfarin and for aspirin vs placebo</td>
<td>Main efficacy end point, defined as the composite of CV death, stroke, SEE, spontaneous MI, and definite stent thrombosis; net clinical benefit, defined as the composite of CV death, stroke, SEE, spontaneous MI, definite stent thrombosis, and ISTH-defined major bleeding; main thromboembolic event, defined as composite of cardiac or thromboembolic death, ischemic stroke, SEE, spontaneous MI, and definite stent thrombosis; ISTH-defined major bleeding</td>
<td></td>
</tr>
<tr>
<td>Comment</td>
<td>Open-label, randomized, multicenter clinical study assessing the safety of 2 rivaroxaban treatment strategies and a warfarin treatment strategy. The randomization will be stratified by the intended duration of DAPT (1, 6, or 12 mo).</td>
<td>Open-label, randomized, multicenter clinical study assessing the safety of 2 dabigatran treatment strategies and a warfarin treatment strategy.</td>
<td>Open-label (apixaban vs warfarin) and blinded (aspirin vs placebo), randomized, multicenter clinical study assessing the safety of apixaban compared with warfarin and aspirin compared with placebo. P2Y12 inhibitor for all patients &gt;6 mo; aspirin for all on the day of ACS or PCI; aspirin versus placebo after randomization</td>
<td>Open-label, randomized, multicenter, Phase 3b clinical study with PROBE design assessing the safety of an edoxaban-based antithrombotic regimen against a VKA-based antithrombotic regimen. The randomization will be stratified by clinical presentation, requirement for dose adjustment of edoxaban, and geographical region.</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndromes; AF, atrial fibrillation; AUGUSTUS, Apixaban Versus Vitamin K Antagonist in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention; CRNM, clinically relevant nonmajor; CV, cardiovascular; DAPT, dual antiplatelet therapy; ENTRUST AF-PCI, Evaluation of the Safety and Efficacy of an Edoxaban-Based Compared to a Vitamin K Antagonist-Based Antithrombotic Regimen in Subjects With Atrial Fibrillation Following Successful Percutaneous Coronary Intervention With Stent Placement; ISTH, International Society of Thrombosis and Hemostasis; MI, myocardial infarction; PCI, percutaneous coronary intervention; PIONEER AF-PCI, Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antibiotic in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; REDUAL-PCI, Evaluation of Dual Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Atrial Fibrillation Who Undergo a PCI With Stenting; SEE, systemic embolic events; TIMI, Thrombolysis in Myocardial Infarction; and VKA, vitamin K antagonist.

*Apixaban 2.5 mg BID (instead of 5 mg BID) for patients with at least 2 of the following: age >80 y, weight <60 kg, and serum creatinine >1.5 mg/dL (133 μmol/L).
†Edoxaban dose reduced to 30 mg once daily in patients with CrCL ≤60 kg, or concomitant therapy with certain P-gp inhibitors.

Andexanet-alfa is a modified coagulation factor X molecule that lacks procoagulant or anticoagulant effects (Figure 1). It works by competing with native factor Xa for binding to anticoagulants that target factor Xa. Volunteer studies have shown that andexanet-alfa given as a bolus followed by an infusion can rapidly and completely reverse the anticoagulant effect of rivaroxaban, apixaban, and edoxaban and the anti-Xa effects of low-molecular-weight heparin (eg, enoxaparin). The ANNEXA-4 study (Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding) examined the use of andexanet-alfa to reverse anticoagulation in patients treated with an anti-Xa agent who present with bleeding. This study showed that an initial bolus and subsequent 2-hour infusion of andexanet substantially reduced median anti-factor Xa activity by 89% from baseline among patients receiving rivaroxaban and by 93% among patients receiving apixaban. These levels remained similar during the 2-hour infusion. Four hours after the end of the infusion, there was a relative decrease from baseline of 39% in the measure of anti-factor Xa activity among patients receiving rivaroxaban and of 30% among those receiving apixaban. Twelve hours after the andexanet infusion, effective hemostasis occurred in 79%; thrombotic events occurred in 18% during the 30-day follow-up.

Ciraparantag is a small molecule reversal agent that has been reported to reverse the anticoagulant effects of a large number of anticoagulants, including heparin, low-molecular-weight heparin, and NOACs. It has undergone only limited evaluation, and clinical studies are ongoing.

In the absence of a specific reversal agent, attempts to negate the anticoagulant effect of the NOACs may involve the use of an unactivated or activated prothrombin complex concentrate or recombinant factor VIIa. Dabigatran can be removed by hemodialysis because it is only partially protein bound; as much as 60% of the drug can be removed during a 4- to 6-hour session.

The decision to reverse the effect of an antiplatelet or antithrombotic drug in a patient with major bleeding and the choice of agent to reverse needs to be individualized, taking into account the balance between thrombosis risk and potential complications of bleeding. If the event occurs early (ie, within 1 month) when the ischemic risk is the greatest, a higher threshold should be considered than if it occurs later (ie, >3 months later). The interruption and the duration of interruption should be tailored to the severity of the bleeding and the likelihood of controlling the bleeding. Where possible, it may be preferable to first target reversal of anticoagulation in cases of bleeding because anticoagulation alone likely offers minimal protection against stent thrombosis, whereas DAPT offers moderate protection against cardioembolic stroke in addition to protecting against stent thrombosis.
Ongoing Trials

The gap of knowledge in our understanding of the optimal antithrombotic treatment regimen for PCI patients with AF, along with the availability of numerous antplatelet and anti-coagulant treatment options, have prompted the design of a series of new trials. These include trials specifically testing the NOACs, used at various dosing regimens, in combination with antplatelet therapy in AF patients undergoing PCI with stent implantation. PIONEER AF-PCI trial (A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) has recently completed enrollment.200 Other studies include the REDUAL-PCI (Evaluation of Dual Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Atrial Fibrillation That Undergo a PCI With Stenting); AUGUSTUS study (the Apixaban Versus Vitamin K Antagonist in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention); and ENTRUST AF-PCI (Evaluation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention With Stent Placement). Details on the trial designs of these pivotal studies are summarized in Table 5. In addition to these trials, a series of other smaller studies are currently being performed. These include the APPROACH-ACS-AF study (Apixaban Versus Phenprocoum in Patients With ACS and AF; NCT02789917) testing dual therapy with apixaban plus clopidogrel versus triple therapy with a VKA plus aspirin and clopidogrel; OAC-ALONE study (the Optimizing Antithrombotic Care in Patients With Atrial Fibrillation and Coronary Stent; NCT01962545) testing OAC alone versus OAC plus SAPT (in which the OAC may be a VKA or any NOAC); MUSICA-2 study (Anticoagulation in Stent Intervention; NCT01141153) comparing 6 months of triple therapy versus DAPT without warfarin; and the MANJUSRI trial (Safety of Ticagrelor Plus Warfarin Versus Clopidogrel+Aspirin+Warfarin in Patients With Persistent or Permanent Atrial Fibrillation and Undergoing PCI; S; NCT02206815) comparing triple therapy with aspirin, clopidogrel, and warfarin versus warfarin and ticagrelor.

There are a number of ongoing or planned studies of LAA occlusion devices for prevention of stroke in the setting of nonvalvular AF. Most of these involve the Watchman device, although those from European centers have access to several additional devices. The study designs include randomized clinical trials, registries and postmarketing surveillance, and feasibility evaluations; however, none of these specifically focus on patients with AF undergoing PCI who are exposed to triple therapy (ie, aspirin, P2Y12 inhibitor, and OAC).

Disclosures

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