ABSTRACT: The optimal antithrombotic treatment regimen for patients with atrial fibrillation undergoing percutaneous coronary intervention with stent implantation represents a challenge in clinical practice. In 2016, an updated opinion of selected experts from the United States and Canada on the treatment of patients with atrial fibrillation undergoing percutaneous coronary intervention was reported. After the 2016 North American consensus statement on the management of antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention, results of pivotal clinical trials assessing the type of oral anticoagulant agent and the duration of antiplatelet treatment have been published. On the basis of these results, this focused update on the antithrombotic management of patients with atrial fibrillation undergoing percutaneous coronary intervention recommends that a non–vitamin K antagonist oral anticoagulant be preferred over a vitamin K antagonist as the oral anticoagulant of choice. Moreover, a double-therapy regimen (oral anticoagulant plus single antiplatelet therapy with a P2Y12 inhibitor) by the time of hospital discharge should be considered for most patients, whereas extending the use of aspirin beyond hospital discharge (ie, triple therapy) should be considered only for selected patients at high ischemic/thrombotic and low bleeding risks and for a limited period of time. The present document provides a focused updated on the rationale for the new expert consensus–derived recommendations on the antithrombotic management of patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention.

Key Words: anticoagulants ◼ atrial fibrillation ◼ platelet aggregation inhibitors ◼ stents

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The optimal antithrombotic treatment regimen for patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) with stent implantation represents a challenge in clinical practice. Patients with AF undergoing PCI would theoretically require treatment with the combination of oral anticoagulation (OAC) and dual antiplatelet therapy with aspirin and a P2Y$_{12}$ inhibitor, also known as triple antithrombotic therapy, to optimally reduce the risk of cardioembolic and coronary thrombotic complications. However, triple therapy substantially increases the risk of bleeding, underscoring the need to define antithrombotic strategies associated with a lower risk of bleeding while maintaining efficacy in patients with AF undergoing PCI. In 2016, an updated opinion of selected experts from the United States and Canada on the treatment of patients with AF undergoing PCI was reported. This North American perspective provides a pragmatic approach to the treatment of these high-risk patients and does not represent a guideline because it is not endorsed by a cardiovascular society. Since then, results of pivotal clinical trials assessing the type of OAC agent and the duration of antiplatelet treatment have been published, prompting the need to refine some of these recommendations. Given the relevance of this new information, the expert consensus group reconvened to provide an update focused on the management of antithrombotic therapy in patients with AF treated with OAC undergoing PCI.

**ADVANCES IN THE MANAGEMENT OF ANTITHROMBOTIC THERAPY IN PATIENTS WITH AF UNDERGOING PCI**

Our 2016 recommendations indicated that in patients with AF treated with stents (requiring antiplatelet therapy), the choice of OAC (vitamin K antagonist [VKA] or non-VKA oral anticoagulant [NOAC]) be at the discretion of the provider, with patients informed on the risk-benefit profiles of each agent based on available data. However, the results of 2 randomized clinical trials have subsequently become available: PIONEER AF-PCI and RE-DUAL PCI. Both of these tested an NOAC (rivaroxaban or dabigatran) in combination with antiplatelet therapy in patients with AF undergoing PCI. Results of these trials are described in detail elsewhere and summarized in Table 1. In brief, both studies support the concept that an NOAC in combination with single antiplatelet therapy (SAPT) with a P2Y$_{12}$ inhibitor (without aspirin), a strategy known as double antithrombotic therapy, is superior to a strategy of triple therapy consisting of the combination of a VKA and dual antiplatelet therapy in reducing bleeding complications. The more favorable safety profile associated with a double antithrombotic treatment regimen occurred without any apparent tradeoff in efficacy. The outcome of all-cause mortality plus hospitalization also appears to be reduced as a consequence. These trial results add to the results of the 2 previously reported randomized trials in which a VKA was tested in combination with different antiplatelet therapy regimens. In particular, the WOEST trial supports the double antithrombotic treatment regimen strategy by showing that in patients undergoing PCI and taking VKA, the use of clopidogrel without aspirin was associated with a significant reduction in bleeding complications and no increase in the rate of thrombotic events compared with a triple therapy strategy in which aspirin therapy was maintained in combination with VKA and clopidogrel.

A meta-analysis of the 3 trials testing double versus triple therapy was recently reported. Although the duration of triple therapy and the anticoagulants used in each study differed, this meta-analysis demonstrated a halving of the odds of major and minor bleeding with double therapy compared with triple therapy (odds ratio, 0.48; 95% confidence interval, 0.34–0.68; P<0.001) with no apparent increase in major adverse cardiovascular events (eg, death, myocardial infarction, revascularization, thromboembolic events, or stent thrombosis; odds ratio, 0.91; 95% confidence interval, 0.64–1.29; P=0.61). Similar results have been reported in other meta-analyses. Additional trials studying the use of other NOACs (apixaban and edoxaban) are ongoing. Moreover, the AUGUSTUS trial (Apixaban in Patients With Atrial Fibrillation and ACS/PCI - Design, Rationale, and Status) is testing aspirin versus no aspirin in a factorial design, along with apixaban versus warfarin, thus directly testing the benefit and risk of dropping aspirin with both warfarin and NOAC.

**UPDATED FOCUSED EXPERT CONSENSUS RECOMMENDATIONS**

On the basis of the recent advances in the field described above, we provide here an update on our recommendations focused on antithrombotic treatment considerations for patients with AF treated with OAC undergoing PCI. A summary of key updates is provided in Table 2. The definitions of risk (ischemic and bleeding) and recommendations on other aspects of management of these patients, including preprocedural consideration (ie, appropriateness criteria for PCI and risk stratification), procedural considerations (ie, vascular access and intraprocedural anticoagulation), and postprocedural considerations (ie, adjunctive therapies and other bleeding reduction strategies), remain unchanged and are described in detail in our 2016 consensus document (Figure 1). We also refer to other consensus documents for a background description on the topic.
tion drug-eluting stents, the recommendations provided on antithrombotic regimens in this document apply regardless of stent type.25,26 In fact, results of the PIO-
NEER AF-PCI and RE-DUAL PCI trials showed consistent findings supporting the benefit of a double therapy approach regardless of stent type.6,7

Oral Antithrombotic Therapy

Patient preference should be accounted for in this decision-making process of selecting antithrombotic agents. Indeed, costs may have an impact on the choice of therapy. In this section, we report our group consensus on the choice, combination, and duration of antithrombotic treatment regimens for this population.

In line with our 2016 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), only antithrombotic treatment for patients with AF undergoing PCI is addressed.5

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>Indication for PCI</th>
<th>Primary Safety End Point</th>
<th>Secondary Efficacy End Point</th>
<th>End Points</th>
<th>Treatment Arms and Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-DUAL PCI</td>
<td>AF with PCI and stent (DES, 82.6%) CrCl&gt;30 mL/min No major bleed within 1 mo No stroke within 1 mo n=2725</td>
<td>ACS, 50.5%</td>
<td>ISTH major or clinically relevant nonmajor bleeding</td>
<td>Death, MI, stroke, SE, or unplanned revascularization</td>
<td>Safety</td>
<td>Warfarin with ASA* and P2Y12 inhibitor†</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Safety</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Efficacy</td>
</tr>
<tr>
<td>PIONEER AF-PCI</td>
<td>AF with PCI and stent (DES, 66.1%) CrCl &gt;30 mL/min No major bleed within 1 mo No GI bleed within 12 mo No prior stroke or TIA n=2124</td>
<td>ACS, 51.6%</td>
<td>Any clinically significant bleeding</td>
<td>CV death, MI, stroke</td>
<td>Safety</td>
<td>Warfarin with ASA and P2Y12 inhibitor‖</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Safety</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Efficacy</td>
</tr>
</tbody>
</table>

Although dabigatran 110 mg twice daily was tested in the RE-LY trial, this dose is not approved in the United States for stroke prevention in atrial fibrillation. R2.5 and R15 dosing regimens were not tested in the ROCKET-AF trials and are not approved for stroke prevention in AF. ACS indicates acute coronary syndrome; AF, atrial fibrillation; ASA, aspirin 75 to 100 mg daily; CrCl, creatinine clearance; CV, cardiovascular; D, dabigatran; D110, dabigatran 100 mg twice daily; D150, dabigatran 150 mg twice daily; DES, drug-eluting stent; GI, gastrointestinal; ISTH, International Society of Thrombosis and Haemostasis; MI, myocardial infarction; NI: non inferiority; PCI, percutaneous coronary intervention; R15, rivaroxaban 15 mg daily; R2.5, rivaroxaban 2.5 mg twice daily; SE, systemic embolism; TIA, transient ischemic attack; and W, warfarin.

*Aspirin discontinued at 1 month (bare metal stents) or at 3 months (DES).
†Clopigogrel or ticagrelor; ticagrelor was prescribed in 12% of enrolled patients.
‡Patients >80 years of age outside of the United States were randomized to only warfarin or dabigatran 110 mg twice daily.
§The individual comparisons for D110 and D150 with W had slightly different control groups, with event rates of 13.4% and 12.8%, respectively.
‖Clopigogrel, prasugrel, or ticagrelor; clopidogrel was used in 94% of the enrolled population.
¶Rivaroxaban 10 mg daily if CrCl was 30 to 50 mL/min.
ing,6,7 this expert consensus recommends that an NOAC (rather than a VKA) should generally be preferred in most patients and in the absence of contraindications. Although clinical trials have not been powered to assess differences in ischemic and cardioembolic events, the reduction in bleeding complications with an NOAC (including intracerebral hemorrhage) has been consistent without an apparent tradeoff in efficacy.27–31 The lack of head-to-head comparative data between NOACs does not allow recommendation for preferential use of 1 agent over another. Nevertheless, for patients on VKA before PCI, this expert consensus also deems it reasonable to continue with the VKA agent after stenting, provided that the patient has been compliant with a well-controlled international normalized ratio and has not experienced related complications.32 A VKA remains the only indicated treatment for patients with AF with moderate to severe mitral stenosis or who have a mechanical prosthetic heart valve and is generally preferred in patients with severe renal dysfunction at the present time.21,22 Among patients with AF for whom OAC is recommended, the duration of treatment should be lifelong unless otherwise contraindicated.21,22

Dosing Regimen

NOACs should be dosed according to the manner in which they were tested in the trials of patients with AF undergoing PCI (Table 1).6,7 If an NOAC has not been specifically studied in this setting, the doses tested in the pivotal AF trials leading to drug approval should be used (Table 3).27–31 Clinical trial data of combining an NOAC with antiplatelet therapy for patients with AF undergoing PCI are available for rivaroxaban (in which doses...
lower than previously established for stroke prevention were used) and dabigatran (in which the same stroke prevention doses were used).6,7 In particular, in patients with AF undergoing PCI, 2 dosing regimens have been tested with both rivaroxaban (15 mg once daily plus aspirin-naïve patients), the maintenance dose of aspirin in patients with AF who have undergone PCI and are also treated with OAC should be 75 to 100 mg/d.34,35 More potent P2Y12 receptor antagonists (prasugrel, ticagrelor) are associated with a higher rate of bleeding than clopidogrel.36–38 Thus, the lower risk of bleeding complications with clopidogrel makes it the oral P2Y12 receptor inhibitor of choice for most patients with AF undergoing PCI and receiving concomitant OAC treatment. After loading dose (600 mg) administration, clopidogrel should be used at a maintenance dose of 75 mg/d. Although clopidogrel is the P2Y12 receptor inhibitor that has been used most in trials of patients with AF undergoing PCI, there are few data with ticagrelor, particularly in combination with dabigatran, which showed safety and efficacy findings consistent with those of clopidogrel.6,7 However, as expected, the rates of bleeding were numeri-
cally higher among patients who were treated with ticagrelor compared with those treated with clopidogrel, consistent with the data from PLATO and its higher antiplatelet effect. Thus, more data on the use of ticagrelor in combination with OAC are warranted. This expert consensus suggests tailoring the intensity of P2Y<sub>12</sub>-inhibiting therapy according to risk. Therefore, among patients at high ischemic/thrombotic (eg, patients with acute coronary syndromes) and low bleeding risks, ticagrelor may represent a reasonable treatment option. Ticagrelor should be administered as a 180-mg loading dose and 90-mg twice daily maintenance dose; a 60-mg twice daily maintenance dose regimen immediately after PCI has not been studied. This expert consensus recommends that if ticagrelor is chosen as the P2Y<sub>12</sub> agent, concomitant aspirin not be given (ie, avoid triple therapy), as was done in the RE-DUAL PCI trial. Data on the combination of prasugrel with an NOAC are very limited, but 1 small study found a nearly 4-fold increase in bleeding with triple therapy with prasugrel and thus, the use of this agent is not recommended. Furthermore, this expert consensus continues to recommend against the routine use of platelet function or genetic testing to guide the selection of antiplatelet therapy.

### Strategy (Double Versus Triple Therapy) and Duration of Therapy

Randomized clinical trials have shown that a strategy of double antithrombotic therapy, consisting of OAC in combination with a P2Y<sub>12</sub> (without aspirin), started at the time of hospital discharge is associated with significantly lower risk of bleeding complications without an apparent tradeoff in thrombotic events compared with triple therapy. Accordingly, this consensus recommends double therapy for most patients (default strategy; Figure 2). In patients in whom double therapy is considered, aspirin is recommended in the peri-PCI phase. Given the irreversible binding of aspirin to the COX-1 enzyme, residual platelet inhibitory effects persist for the life span of the affected platelet (7–10 days). However, in selected patients considered at high ischemic/thrombotic risk and low bleeding risk, this expert consensus finds it reasonable to continue with aspirin therapy (ie, triple therapy) for a limited period of time after hospital discharge. Although the duration of aspirin treatment is at the discretion of the treating physician, in these selected patients, it is reasonable to extend aspirin therapy up to 1 month after PCI and rarely beyond this time (Figure 2).

The duration of the dual-therapy regimen and thus timing of discontinuation of SAPT should also take into

![Figure 2. Management of antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention (PCI) treated with an oral anticoagulant (OAC): 2018 North American expert consensus update.](http://ahajournals.org)

A double-therapy regimen immediately after hospital discharge should be considered for most patients (default strategy). A non–vitamin K antagonist oral anticoagulant (NOAC) should be preferred over a vitamin K antagonist (VKA) unless contraindicated. Single antiplatelet therapy (SAPT), preferably with a P2Y<sub>12</sub> inhibitor, should be started as soon as possible, including at hospital discharge. It is reasonable to extend low-dose aspirin therapy (ie, triple therapy) up to 1 month after PCI in selected patients at high ischemic/thrombotic and low bleeding risks. Clopidogrel remains the P2Y<sub>12</sub> inhibitor of choice; ticagrelor may be considered in patients at high ischemic/thrombotic and low bleeding risks; avoid prasugrel.

**Table**

<table>
<thead>
<tr>
<th>Time from PCI</th>
<th>Default strategy</th>
<th>Patients at high ischemic/thrombotic and low bleeding risks</th>
<th>Patients at low ischemic/thrombotic or high bleeding risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-PCI</td>
<td>Triple Therapy (OAC + DAPT)</td>
<td>Triple Therapy (OAC + DAPT) up to 12 months (OAC + SAPT)</td>
<td>Triple Therapy (OAC + DAPT) up to 6 months (OAC + SAPT)</td>
</tr>
<tr>
<td>1 month</td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td>Double Therapy up to 6 months (OAC + SAPT)</td>
</tr>
<tr>
<td>3 months</td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td>Double Therapy up to 6 months (OAC + SAPT)</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>OAC</td>
<td>OAC</td>
<td>OAC</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>OAC</td>
<td>OAC</td>
<td>OAC</td>
</tr>
</tbody>
</table>

OAC: prefer a NOAC over VKA if no contraindications
SAPT: prefer a P2Y<sub>12</sub> inhibitor over aspirin
Clopidogrel is the P2Y<sub>12</sub> inhibitor of choice; ticagrelor may be considered in patients at high ischemic/thrombotic and low bleeding risks; avoid prasugrel.

Consider SAPT in addition to OAC after >12 mo. only in select patients at high ischemic/thrombotic and low bleeding risks.

DAPT indicates dual antiplatelet therapy.
consideration the ischemic/thrombotic and bleeding risk profiles of the patients (Figure 2). In line with prior recommendations, discontinuation of SAPT at 1 year should be considered for most patients.5,20,23 However, in patients at low thrombotic risk and those at high risk for bleeding, it is reasonable to discontinue SAPT at 6 months after PCI. After discontinuation of SAPT, OAC should be continued at full stroke-prevention doses. Therefore, if a reduced dose regimen of rivaroxaban (eg, 15 mg once daily, 10 mg once daily in patients with a creatinine clearance of 30–50 mL/min) was being used, it is important to resume the full recommended dose (20 mg once daily, 15 mg once daily in patients with a creatinine clearance of 30–49 mL/min) after suspension of antiplatelet therapy. Continuation with SAPT (in addition to OAC) may be reasonable for patients with high ischemic/thrombotic and low bleeding risks. The choice of SAPT to use after 1 year (aspirin or clopidogrel) is at the discretion of the treating physician, although it appears to be reasonable to maintain the same antiplatelet drug that the patient was already taking rather than switching.42

NORTH AMERICAN EXPERT CONSENSUS ON THE MANAGEMENT OF ANTITHROMBOTIC THERAPY IN PATIENTS WITH AF UNDERGOING PCI: SUMMARY OF THE 2018 FOCUSED UPDATE

In summary, this expert consensus recommends that for patients with AF requiring the use of OAC and who are treated with stents (requiring antiplatelet therapy), a double-therapy regimen (OAC plus P2Y12 inhibitor) immediately after hospital discharge should be considered for most patients. An NOAC should be preferred over a VKA. The dosing regimen of an NOAC should be that recommended for thromboembolic protection in patients with AF, whereas the use of lower doses is not recommended unless specifically studied in randomized trials (ie, rivaroxaban 15 mg). When different therapeutic dosing options (ie, dabigatran 110 and 150 mg) are available, the intensity of anticoagulant treatment should be tailored according to the bleeding and thrombotic risk profiles of the patient. In patients already on a VKA, continuing with the same agent after PCI may be reasonable, particularly if the patient has been compliant, has a well-controlled international normalized ratio, and has not experienced complications, targeting an international normalized ratio in the lower therapeutic range. The intensity and duration of antiplatelet treatment should also be tailored according to the bleeding and thrombotic risk profiles of the patient. The consistency of significantly lower risk of bleeding with double therapy across major trials argues against the use of a triple-therapy regimen. Therefore, a double-therapy approach should represent the default strategy for most patients, and SAPT, preferably with a P2Y12 inhibitor, should be started as soon as possible, including at hospital discharge. However, it is reasonable to extend low-dose aspirin therapy (ie, triple therapy) for a limited period of time (eg, 1 month) after PCI in selected patients at high ischemic/thrombotic and low bleeding risks. Clopidogrel remains the P2Y12 inhibitor of choice, but ticagrelor may be considered in selected patients, particularly those at high ischemic/thrombotic risk and low bleeding risk. Discontinuation of SAPT at 1 year should be considered for most patients who should continue treatment on stroke-prevention doses of OAC. However, in patients at low ischemic/thrombotic risk and those at high risk for bleeding, it is reasonable to discontinue SAPT at 6 months after PCI, whereas continuation with SAPT (in addition to OAC) may be reasonable for select patients with high ischemic/thrombotic and low bleeding risks.

ARTICLE INFORMATION

Correspondence
Dominick J. Angiolillo, MD, PhD, University of Florida College of Medicine–Jacksonville, 655 W 8th St, Jacksonville, FL 32209. E-mail dominick.angiolillo@jax.ufl.edu

Affiliations
Division of Cardiology, University of Florida College of Medicine–Jacksonville (D.J.A.). St. Michael’s Hospital, University of Toronto, and the Canadian Heart Research Centre, Canada (S.G.G.). Canadian Virtual Coordinating Centre for Global Collaborative Cardiovascular Research Centre, University of Alberta, Canada (S.G.G.). Brigham and Women’s Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA (D.L.B., C.P.C., L.M., D.P.F.). Department of Medicine, Population Health Research Institute, Thrombosis & Atherosclerosis Research Institute, Hamilton, Canada (J.W.E.). Division of Cardiovascular Diseases, Scripps Clinic, La Jolla, CA (M.J.P.). Division of Cardiovascular Medicine and Gill Heart Institute, University of Kentucky, Lexington (D.J.M.). Department of Medicine, Montreal Heart Institute, Université de Montréal, Canada (J.-F.T.). Duke Clinical Research Institute, Duke University, Durham, NC (C.B.G.). Mayo Clinic, Rochester, MN (D.R.H.). Division of Cardiology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA (C.M.G.).

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