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Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention

A North American Perspective: 2021 Update

ABSTRACT: A growing number of patients undergoing percutaneous coronary intervention (PCI) with stent implantation also have atrial fibrillation. This poses challenges for their optimal antithrombotic management because patients with atrial fibrillation undergoing PCI require oral anticoagulation for the prevention of cardiac thromboembolism and dual antiplatelet therapy for the prevention of coronary thrombotic complications. The combination of oral anticoagulation and dual antiplatelet therapy substantially increases the risk of bleeding. Over the last decade, a series of North American Consensus Statements on the Management of Antithrombotic Therapy in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention have been reported. Since the last update in 2018, several pivotal clinical trials in the field have been published. This document provides a focused updated of the 2018 recommendations. The group recommends that in patients with atrial fibrillation undergoing PCI, a non–vitamin K antagonist oral anticoagulant is the oral anticoagulation of choice. Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor should be given to all patients during the peri-PCI period (during inpatient stay, until time of discharge, up to 1 week after PCI, at the discretion of the treating physician), after which the default strategy is to stop aspirin and continue treatment with a $P2Y_{12}$ inhibitor, preferably clopidogrel, in combination with a non–vitamin K antagonist oral anticoagulant (ie, double therapy). In patients at increased thrombotic risk who have an acceptable risk of bleeding, it is reasonable to continue aspirin (ie, triple therapy) for up to 1 month. Double therapy should be given for 6 to 12 months with the actual duration depending on the ischemic and bleeding risk profile of the patient, after which patients should discontinue antiplatelet therapy and receive oral anticoagulation alone.

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Atrial fibrillation (AF) is a highly prevalent arrhythmia that increases with age.[1] Up to 40% of patients with AF also have coronary artery disease (CAD), many of whom require revascularization.[2] Percutaneous coronary intervention (PCI) with stent implantation is the most common revascularization strategy for patients with CAD, and up to 10% of these patients have AF.[2–4] The concomitant presence of these conditions represents a challenge in clinical practice, particularly with regard to their optimal antithrombotic treatment regimen.[2–4] Most patients with AF require chronic oral anticoagulation (OAC) for the prevention of cardiac thromboembolism, whereas patients undergoing PCI require dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor for the prevention of coronary thrombotic complications.[5–7] The combination of OAC with DAPT, known as triple antithrombotic therapy (or simply triple therapy), substantially increases the risk of bleeding.[4] Bleeding after PCI is associated with increased morbidity and mortality.[8–10] These observations underscore the need to define antithrombotic strategies associated with a lower risk of bleeding while maintaining efficacy among patients with AF treated with PCI.

Since 2011, a series of North American Consensus Statements on the Management of Antithrombotic Therapy in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention representing a consensus opinion of physicians from the United States and Canada have provided recommendations (2011, 2016, and 2018) on the antithrombotic treatment of patients with AF undergoing PCI.[11–14] The group has taken a pragmatic approach in making treatment recommendations for this high-risk patient population. After the most recent North American Consensus Statement on the Management of Antithrombotic Therapy in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention, reported in 2018, results of pivotal clinical trials in the field have been published, prompting the need to update the document.

ANTITHROMBOTIC THERAPY IN PATIENTS WITH AF UNDERGOING PCI: RECENT UPDATES

New data since the 2018 recommendations include results of 2 additional randomized clinical trials (RCTs) conducted in patients with AF undergoing PCI as well as a number of secondary analyses, as described in the following. This new information has expanded our knowledge on the safety and efficacy of the 4 commercially available non–vitamin K antagonist oral anticoagulants (NOACs) that have been tested in dedicated RCTs, including rivaroxaban (PIONEER AF-PCI [A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention]), dabigatran (REDUAL-PCI [Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Atrial Fibrillation That Undergo a PCI With Stenting]), apixaban (AUGUSTUS [An Open-Label, 2×2 Factorial, Randomized, Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention]), and edoxaban (ENTRUST-AF-PCI [Edoxaban Treatment vs Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention]).[15–18] Results of these trials are described in detail elsewhere and summarized in Table 1.[4,15–20]

In brief, the cumulative evidence from these studies, as also summarized in meta-analyses, supports the concept that a NOAC should be the OAC of choice.[21–25] Moreover, data from RCTs suggest that the combination of a NOAC and a single antiplatelet agent (SAPT), preferably a $P2Y_{12}$ inhibitor (clopidogrel has been the most studied), a strategy known as double antithrombotic therapy (or simply double therapy), should be used in preference to triple therapy.[15–18] The use of aspirin in patients assigned to double therapy (ie, NOAC plus a $P2Y_{12}$ inhibitor) was limited to the peri-PCI period. Double therapy was associated with a large reduction in bleeding compared with triple therapy where aspirin is continued (ie, OAC, in particular a VKA, plus DAPT).[15–26] Although none of the individual RCTs was powered to assess major adverse ischemic events, there was no significant increase in thrombotic complications associated with double therapy.[15–18] Advancements in stent designs leading to improved safety (ie, reduced stent thrombosis) and less dependence on the duration and intensity of DAPT have been instrumental toward improved outcomes.[27] However, insights from several trials as well as pooled data suggest the potential for an increase in thrombotic complications with double therapy, mostly confined to the first month after PCI.[25–29] These observations have generated debate on the optimal timing of aspirin withdrawal in patients with AF undergoing PCI.

UPDATED FOCUSED CONSENSUS RECOMMENDATIONS

In our recommendations, we assume that patients with AF undergoing PCI have an indication for OAC in line with practice guidelines.[5,6] It is important to underscore that DAPT is inferior to OAC for prophylaxis of thromboembolic events in patients with AF and accordingly should not be used as a mainstay

Table 1. Comparisons of Double Antithrombotic Therapy Versus Triple Antithrombotic Therapy in Trials of Non–Vitamin K Oral Antagonists in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

Characteristics	PIONEER AF-PCI	REDUAL-PCI	AUGUSTUS	ENTRUST-AF-PCI
Year	2016	2017	2019	2019
Blinding	Open-label	Open-label	Open-label (NOAC vs VKA); placebo-controlled (SAPT vs DAPT)	Open-label
Patients, n	2124	2725	4614	1506
Intervention*	Rivaroxaban plus $P2Y_{12}$ inhibitor for 12 months	Dabigatran plus $P2Y_{12}$ inhibitor for 12 months	Apixaban or VKA plus $P2Y_{12}$ inhibitor for 6 months	Edoxaban plus $P2Y_{12}$ inhibitor for 12 months
Control	Warfarin plus DAPT for 1, 6, or 12 months	Warfarin plus DAPT for 1 (BMS) or 3 (DES) months	Apixaban or VKA plus DAPT for 6 months	VKA plus DAPT for 1 to 12 months
Primary outcome	Clinically relevant bleeding at 12 months	Major or CRNM bleeding through follow-up (mean 14 months)	Major or CRNM bleeding at 6 months	Major or CRNM bleeding at 12 months
Treatment effect for intervention vs control	HR, 0.59 (95% CI, 0.47–0.76); *P*<0.001 for superiority	HR, 0.72 (95% CI, 0.58–0.88); *P*<0.001 for noninferiority, *P*=0.002 for superiority (dabigatran 150 mg bid); HR, 0.52 (95% CI, 0.42–0.63); *P*<0.001 for noninferiority, *P*<0.001 for superiority (dabigatran 110 mg bid)	HR, 0.53 (95% CI, 0.45–0.63); *P*<0.001 for superiority	HR, 0.83 (95% CI, 0.65–1.05); *P*=0.001 for noninferiority, *P*=0.1154 for superiority

Doses of non–vitamin K antagonist oral anticoagulants were 15 mg once daily for rivaroxaban, 150 mg BID or 110 mg BID for dabigatran, 5 mg BID for apixaban (with dose reduction as per the instructions for use), and 60 mg once daily for edoxaban (with dose reduction as per the instructions for use). AUGUSTUS indicates An Open-Label, 2×2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention; BMS; bare metal stent; CRNM, clinically relevant nonmajor; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; ENTRUST-AF-PCI, Edoxaban Treatment vs Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; HR, hazard ratio; NOAC, non–vitamin K antagonist oral anticoagulant; PIONEER AF-PCI, A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; REDUAL-PCI, Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Atrial Fibrillation That Undergo a PCI With Stenting; SAPT, single antiplatelet therapy; and VKA, vitamin K antagonist.

*Interventions are shown for dual antiplatelet therapy groups only.

therapy.[30] The use of left atrial appendage closure devices represents an alternative to OAC for patients with high bleeding risk (HBR), with approval in the United States for patients deemed unsuitable for or unable to take long-term OAC.[31] Indications for the use of left atrial appendage closure devices are beyond the scope of this document and are described elsewhere.[31] Although patients undergoing PCI may have other medical conditions that require treatment with OAC (eg, mechanical valves), the recommendations provided in this document are specific to patients with AF. Moreover, patients enrolled in the RCTs that inform our recommendations were primarily treated with stents, and only a subset from one trial were medically managed patients with acute coronary syndrome (ACS), who also have an indication for DAPT.[32] However, because outcomes were consistent irrespective of management (PCI versus medical therapy), we found it is reasonable to apply our recommendations to medically managed patients with ACS.

In the sections that follow, we provide consensus recommendations for management of patients with AF undergoing PCI, including key procedural (before, during, and after) approaches and antithrombotic management. A summary of these procedural considerations is provided in Figure 1. We refer to other documents for more extensive background description on the topic.[4,20,33] A summary of key changes since the 2018 update is provided in Table 2.

Procedural Considerations

Preprocedural

Clinicians should carefully evaluate the risk of bleeding and thrombotic complications in all patients undergoing PCI, particularly those with AF. Selection of patients for PCI should take into consideration the absolute need for antiplatelet therapy postprocedure, which markedly increases the risk of bleeding when added to OAC. Discussing appropriateness criteria for PCI is beyond the scope of this article and is described elsewhere but should be taken into strong consideration.[34] The consensus of this group is that, whenever possible (ie, elective/nonemergent procedures), a brief period of washout from the effects of an OAC is preferable when undergoing an invasive procedure. The rationale for a washout is to reduce the risk of potential bleeding complications among patients who may require femoral vascular access or resulting from excess anticoagulation during the interventional procedure. Timing of discontinuation of OAC should take into account the timing of the procedure to minimize the duration of treatment interruption. The rapid offset of action of the NOACs has simplified this approach: interruption of therapy for 24 hours (or 48 hours for patients on dabigatran with impaired renal function) is sufficient in most cases.[35] For patients on a VKA, this consensus group recommends an international normalized ratio (INR) ≤2.0 when using a radial approach and ≤1.5 when using a femoral approach. After discontinuation of OAC,

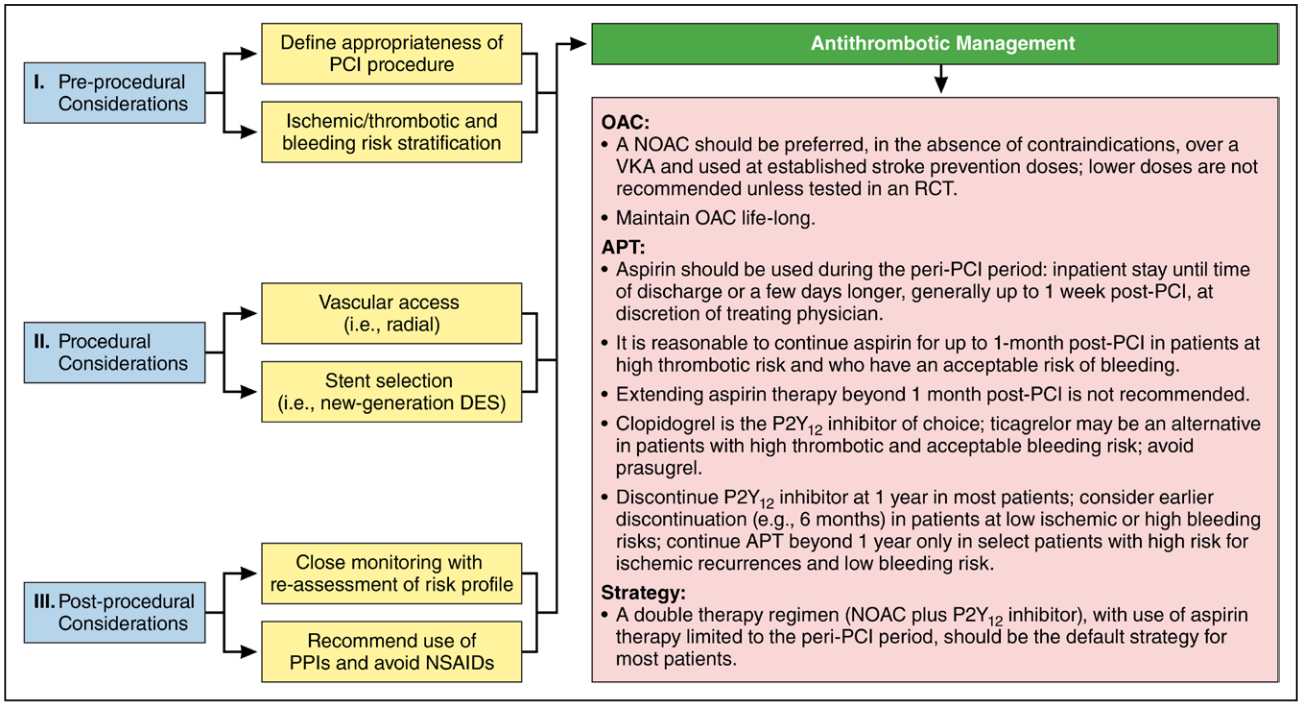

Figure 1. Pragmatic algorithm for the management of patients with atrial fibrillation requiring oral anticoagulation (OAC) undergoing percutaneous coronary intervention (PCI).
APT indicates antiplatelet therapy; DES, drug-eluting stent; NOAC, non–vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; RCT, randomized, controlled trial; and VKA, vitamin K antagonist.

patients presenting with an ACS with planned invasive management should receive parenteral anticoagulation according to usual practice, which is not required for patients with stable CAD. The performance of invasive procedures without withholding OAC should generally be reserved for urgent or emergency procedures.

Intraprocedural

The radial approach is the preferred choice for vascular access to minimize bleeding.[36] Several intraprocedural parenteral antithrombotic agents are available, although none has been directly compared in patients with AF undergoing PCI. Unfractionated heparin is the most commonly used intraprocedural anticoagulant and remains the agent of choice in this setting, with dosing titrated to target recommended activated clotting times. Bivalirudin has been shown to be associated with a reduction in bleeding complications and may be of value in patients with ACS undergoing PCI via a femoral approach who are at increased bleeding risk.[37–39] Bivalirudin is the agent of choice for patients with heparin-induced thrombocytopenia and should also be considered in circumstances of heparin shortage. The North American uptake of enoxaparin for PCI has been limited, but it is important to emphasize that switching from unfractionated heparin to enoxaparin (and vice versa) may increase the risk of bleeding.[40] Parenteral antiplatelet agents (ie, glycoprotein IIb/IIIa inhibitors and cangrelor) should be reserved for selected patients at high risk for thrombotic complications or for bailout situations.[41] Cangrelor may be a more desirable agent if prompt and potent platelet inhibition is needed given its pharmacodynamic profile with rapid offset of action as well as data that suggest that it is possibly associated with a lower risk of bleeding compared with a glycoprotein IIb/IIIa inhibitor.[41–43] New-generation metallic drug-eluting stents have a more favorable safety and efficacy profile over earlier-generation drug-eluting stents and bare metal stents, and some of these novel stent platforms have been specifically tested in patients requiring OAC.[27,44,45] Accordingly, commercially available new-generation metallic drug-eluting stents should be the devices of choice. Patients should resume OAC after PCI before or at hospital discharge once hemostasis is fully obtained, there is no evidence of ongoing periprocedural bleeding complications, and no further in-hospital interventions are anticipated. The rapid onset of action of a NOAC eliminates the need for a parenteral anticoagulant agent after PCI. In patients resuming treatment with a VKA, our consensus-based suggestion is for clinicians to consider continuing treatment with a parenteral agent until an INR is at least 1.8 among patients at high stroke risk, although there are no data to support the efficacy of this approach.

Postprocedural

Patients should ideally be re-evaluated within 1 to 2 weeks of PCI by their cardiologist or interventional cardiologist to assess adherence and determine whether any adjustments in antithrombotic treatment regimens

Table 2. Key Changes Between 2018 and 2020 North American Consensus on Antithrombotic Management of Patients With Atrial Fibrillation (AF) Undergoing Percutaneous Coronary Intervention (PCI)

	2018 Consensus	2021 Consensus update
Definition of high bleeding risk	According to ACC/AHA DAPT guidelines	According to ARC-HBR criteria
Definition of high thrombotic risk	According to ACC/AHA DAPT guidelines	ACS, previous stent thrombosis while on antiplatelet treatment, and complex PCI (3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, surgical bypass graft or chronic total occlusion as target lesions, atherectomy device use, or left main PCI)
Definition of high ischemic risk	According to ACC/AHA DAPT guidelines	Previous myocardial infarction, multivessel CAD, polyvascular disease, diabetes mellitus, chronic kidney disease, heart failure
Definition of peri-PCI period (ie, timing of mandatory aspirin)	Up to hospital discharge	During inpatient stay, until time of discharge (generally occurring 1 to 2 days after PCI), up to 1 week after PCI, at the discretion of the treating physician
Recommendations for medically managed ACS	NA	Consistent with recommendations for patients undergoing PCI

ACC indicates American College of Cardiology; ACS, acute coronary syndrome; AF, atrial fibrillation; AHA, American Heart Association; ARC-HBR, Academic Research Consortium for High Bleeding Risk; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; NA, not applicable; and PCI, percutaneous coronary intervention.

are needed. Key issues include defining timing of stopping of aspirin (if not yet discontinued), evaluating INR control, particularly in patients newly started on a VKA, and monitoring of renal function in patients treated with a NOAC. Patients should be counseled not to stop therapy due to nuisance bleeding or bruising, but rather to contact their physician. Additional strategies to reduce the risk of bleeding should be considered, including optimization of blood pressure control, use of proton pump inhibitors, and avoidance of nonsteroidal anti-inflammatory drugs.[46,47]

Definition of Bleeding and Thrombotic Risk

Defining the risk of developing a bleeding or thrombotic complication in a patient undergoing PCI is of essential importance in defining the intensity and duration of antithrombotic therapy. Although intensive and prolonged antithrombotic treatment regimens reduce the risk of thrombotic complications, this occurs at the expense of increased bleeding.[9,20] The ever-growing evidence on the adverse prognosis, including increased mortality, associated with bleeding after PCI has prompted investigations aimed at reducing bleeding while preserving efficacy, such as shortening DAPT duration, de-escalating $P2Y_{12}$ potency, and using aspirin-free approaches.[9,20,27,48,49] Defining the optimal antithrombotic regimen in the PCI setting is further complicated by the fact that risk factors for bleeding and thrombotic complications frequently overlap.[50] This may partly explain why these risk scores are only modestly predictive.[50] As recommended in practice guidelines, bleeding risk scores (eg, HAS-BLED) can be used to identify potentially modifiable risk factors for bleeding (eg, uncontrolled hypertension, suboptimal INR control on VKA therapy, and concomitant use of excess alcohol or nonsteroidal anti-inflammatory drugs) and not to define whether a patient should be treated with OAC, because patients with high scores derive similar or greater ischemic benefit from treatment compared with patients with lower scores.[5,6] Although other risk scores (eg, PRECISE-DAPT) have been able to identify patients with AF undergoing PCI who are at increased bleeding risk, these have not been prospectively validated in this setting.[51,52] Accordingly, this group consensus cannot recommend the use of a specific risk score to make decisions on treatment. Instead, the use of qualitative or semiquantitative approaches, together with clinical judgment, are recommended to assist practitioners with defining the bleeding and thrombotic risk of an individual patient.

Data suggest that when both ischemic and bleeding risk factors are present, the risk factors for bleeding are more impactful on clinical outcomes.[53] Applying this concept to patients with AF undergoing PCI is challenging given that the OAC treatment itself is a major criterion for HBR according to the Academic Research Consortium definitions.[10] Nevertheless, this group consensus finds the Academic Research Consortium HBR definition useful to inform clinicians of criteria beyond OAC treatment that further affect the risk of bleeding. This is in line with recent findings not only validating the Academic Research Consortium HBR definitions but also showing a progressive increase in bleeding risk with incremental risk criteria.[54,55] Accordingly, a patient with HBR is identified as having 1 major (other than use of OAC) or 2 minor criteria according to Academic Research Consortium definitions (Table 3).[10]

Most thrombotic complications reported in the available RCTs occurred early (ie, within the first month after PCI).[15–19] However, analysis of RCTs has not identified independent predictors of thrombotic complications and available data suggest that the benefit of double

Table 3. Definition of High Bleeding Risk According to Academic Research Consortium Criteria

Major	Minor
Anticipated use of long-term oral anticoagulation*	Age ≥75 years
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30 to 59 mL/min)
Hemoglobin <11 g/dL	Hemoglobin 11 to 12.9 g/dL for men and 11 to 11.9 g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion
Moderate or severe baseline thrombocytopenia† (platelet count <100×10^9/L)	Long-term use of oral NSAIDs or steroids
Chronic bleeding diathesis	Any ischemic stroke at any time not meeting the major criterion
Liver cirrhosis with portal hypertension	—
Active malignancy‡ (excluding non-melanoma skin cancer) within the past 12 months	
Previous spontaneous ICH (at any time)	—
Previous traumatic ICH within the past 12 months	—
Presence of a bAVM	—
Moderate or severe ischemic stroke§ within the past 6 months	—
Nondeferrable major surgery on DAPT	—
Recent major surgery or major trauma within 30 days before PCI	—

Adapted from Urban et al[10] with permission. bAVM indicates brain arteriovenous malformation; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; and PCI, percutaneous coronary intervention.

*Excludes vascular protection doses.

†Baseline thrombocytopenia is defined as thrombocytopenia before PCI.

‡Active malignancy is defined as diagnosis within 12 months or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).

§National Institutes of Health Stroke Scale score ≥5.

therapy over triple therapy is consistent irrespective of thrombotic risk.[28,29,56–59] Nevertheless, there are a number of well-established factors associated with the risk of thrombotic complications after PCI. Patients presenting with an ACS have an increased risk of thrombotic complications, which is highest within the first month after PCI and then diminishes over time.[56,60] Patients with a previous stent thrombosis while on antiplatelet therapy are also at increased risk of a thrombotic recurrence.[61] Procedural characteristics (ie, PCI complexity) are also closely associated with the early risk of thrombotic complications after PCI.[57,62,63] Accordingly, this consensus opinion recognizes that acute clinical presentations, previous stent thrombosis while on antiplatelet therapy, and complex PCI can be considered as factors that can help define the risk of thrombotic events more likely to occur early after PCI (Table 4). Patients with certain risk factors (eg, previous myocardial infarction, multivessel CAD, polyvascular disease, diabetes mellitus, chronic kidney disease, heart failure) are more likely to undergo complex PCI and remain at increased ischemic risk.[64] These factors are associated with long-term ischemic recurrences and can be considered when making assessments on long-term antithrombotic management (Table 4).

Oral Antithrombotic Therapy

The large number of antithrombotic agents that are now available allows for multiple combinations of OAC and antiplatelet regimens.[4] Selection of the antithrombotic regimen should involve a shared decision-making process taking into account physician experience, patient preferences, access, and cost.

Oral Anticoagulation

Choice of Agent and Duration of Therapy

In line with our previous recommendations, now reinforced with recent clinical trial data, this consensus group recommends that, in the absence of contraindications, a NOAC should be preferred over a VKA in patients with AF undergoing PCI. This recommendation stems from the consistent reduction in bleeding complications with a NOAC, including intracranial hemorrhage, without an apparent trade-off in efficacy.[21–24] In line with general guidelines on the use of OAC in patients with AF, the lack of head-to-head comparisons between NOACs does not allow us to recommend one agent over another.[5,6] The selection of a specific agent and dose should take into consideration aspects of the trial design in which a given NOAC was tested that best

Table 4. Definition of High Thrombotic and Ischemic Risk

High thrombotic risk (early events)	High ischemic risk (long-term events)
Acute coronary syndrome	Previous myocardial infarction
Previous stent thrombosis while on antiplatelet treatment	Multivessel coronary artery disease
PCI complexity	Polyvascular disease
3 vessels treated	Diabetes mellitus
≥3 stents implanted	Chronic kidney disease
≥3 lesions treated	Heart failure
Bifurcation with 2 stents implanted	
Total stent length >60 mm	
Surgical bypass graft PCI	
Chronic total occlusion PCI	
Atherectomy device use	
Left main PCI	

PCI indicates percutaneous coronary intervention.

matches the profile of the patient being treated.[15–18] The specific trial results can also provide information on the magnitude of benefit when choosing one agent compared with VKA.[15–18] PIONEER AF-PCI (A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) was the only trial that excluded patients with a previous cerebrovascular event.[15] ENTRUST-AF-PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) was the only trial that did not show superiority in bleeding reduction of a NOAC-based double therapy regimen compared with a VKA, although noninferiority was met.[18] AUGUSTUS (An Open-Label, 2×2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban Versus Vitamin K Antagonist and Aspirin Versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention), the largest trial, was the only trial to test aspirin in a placebo-controlled fashion and the only trial that showed lower bleeding with the NOAC (apixaban) versus VKA in a direct comparison using a factorial design.[17] Patient access to individual NOACs based on availability and cost may also be a driving factor in the decision-making process. Availability of a NOAC in a generic formulation may facilitate broader access. Patients may also have a preference for NOACs that are administered once daily (ie, rivaroxaban, edoxaban) versus twice daily (ie, dabigatran, apixaban). We suggest avoiding switching between NOACs in patients who have already been adherent without complications on a specific agent at a dose that has been approved for stroke prevention in AF. On the other hand, in the absence of contraindications and if drug access is not a limiting factor, patients on a VKA before PCI should consider switching to a NOAC in light of the better safety profile.[65] A VKA remains the only indicated OAC for patients with moderate to severe mitral stenosis, a mechanical prosthetic heart valve, left ventricular thrombus, or other hematologic reasons (eg, antiphospholipid syndrome).[5,6] Although there are emerging data on the safety of a NOAC in patients with severe renal dysfunction, these patients were excluded from trials of patients with AF undergoing PCI.[15–18] Unless contraindicated, the duration of OAC treatment in patients with AF should be lifelong.[5,6]

Dosing Regimen

In real-world practice, NOAC dosing regimens lower than those proven to be effective for stroke prevention are commonly used because of bleeding concerns, particularly because bleeding risk is enhanced with concomitant antiplatelet therapy.[66,67] However, dosing regimens lower than those proven to be efficacious in RCTs of AF should be avoided, unless specifically tested. The dosing regimen should also take into consideration adjustments according to renal function or other instructions for use. The NOAC dosing regimens tested in the randomized trials of patients with AF undergoing PCI are summarized in Table 1.[15–19] With the exception of PIONEER AF-PCI, in all RCTs of patients with AF undergoing PCI the dosing regimens of NOACs tested were those previously established in efficacy trials for stroke prevention (Table I in the Data Supplement).[4–6,15–19] For patients with AF who are treated with a VKA and concomitant antiplatelet therapy, the INR should be targeted to the lower end of the therapeutic range (eg, 2.0 to 2.5).[68]

In PIONEER AF-PCI, 2 dosing regimens of rivaroxaban (both lower than previously established for stroke prevention in AF trials) were tested: 15 mg once daily (10 mg once daily if creatinine clearance was 30 to 50 mL/min) with a $P2Y_{12}$ inhibitor and 2.5 mg twice daily with DAPT. These doses are not approved in North America for stroke prevention and were chosen based on safety investigations evaluating their use in combination with different antiplatelet regimens.[15,69] This consensus suggests that rivaroxaban 15 mg could be used in patients receiving double therapy (ie, in combination with SAPT) as tested in PIONEER AF-PCI.[15] Other dosing regimens, particularly triple therapy with rivaroxaban 20 mg plus DAPT, known to be associated with unacceptably high rates of bleeding should be avoided.[70]

In REDUAL-PCI (Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Atrial Fibrillation That Undergo a PCI With Stenting), 2 dosing regimens of dabigatran were used: 150 mg twice daily with SAPT and 110 mg twice daily with a $P2Y_{12}$ inhibitor.[16] Elderly patients (≥80 years of age; ≥70 years of age in Japan) randomized outside the United States were treated with dabigatran 110 mg twice daily. Although the 150 mg and 110 mg doses are both approved for stroke prevention in patients with AF by most countries' drug-regulating authorities, the 110 mg regimen is not approved by the US Food and Drug Administration. In light of the numeric increase, albeit not statistically significant, of ischemic events among patients treated with dabigatran 110 mg, it is reasonable to prefer a 150 mg dosing regimen in patients considered to be at higher thrombotic risk, while a 110 mg regimen may be preferred in patients with HBR.[16]

In AUGUSTUS, the largest of the available RCTs, apixaban was administered at a regimen of 5 mg twice daily (2.5 mg twice daily if ≥2 of the following dose reduction criteria were met: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL) with a $P2Y_{12}$ inhibitor or DAPT.[17] This regimen is in line with that approved for stroke prevention in patients with AF by most drug-regulating authorities, including the US Food and Drug Administration. Of note, AUGUSTUS was the only trial that by nature of its 2×2 factorial design directly

compared a NOAC (ie, apixaban) versus VKA in patients treated with a dual versus triple (aspirin versus placebo) therapy regimen and the only trial to test aspirin in a placebo-controlled fashion.

In the ENTRUST-AF-PCI trial, edoxaban was administered at a dose of 60 mg once daily (30 mg once daily for patients with creatinine clearance 15 to 50 mL/min, body weight ≤60 kg, or concurrent use of specific potent P-glycoprotein inhibitors [cyclosporine, dronedarone, erythromycin, or ketoconazole]) with a $P2Y_{12}$ inhibitor.[18] This regimen is consistent with that approved for stroke prevention in patients with AF by most drug-regulating authorities, although the US Food and Drug Administration has restricted the approval of edoxaban to patients with a creatinine clearance <95 mL/min (because higher clearance rates were associated with greater stroke risk as compared with patients receiving VKA).

Antiplatelet Therapy

Choice of Agent

DAPT with aspirin and a $P2Y_{12}$ inhibitor is the cornerstone of treatment for the prevention of thrombotic complications in patients undergoing PCI.[4] All patients undergoing PCI, even those with AF requiring OAC, should be treated with aspirin in the peri-PCI period. After a 325 mg loading dose administration (in aspirin-naive patients), the maintenance dose of aspirin should be 75 to 100 mg/d.[4] Clopidogrel is the $P2Y_{12}$ inhibitor of choice because this was used in most (≈88%) patients (at the discretion of the treating physician) enrolled in trials of patients with AF undergoing PCI concomitantly treated with an OAC (Table 1).[15–19] Accordingly, clopidogrel should be administered as a 600 mg loading dose followed by a 75 mg daily maintenance dose. The more potent $P2Y_{12}$ receptor antagonists, prasugrel and ticagrelor, are both approved for use in patients with ACS, with recent approval of ticagrelor in patients with CAD with high ischemic risk as well, with lower rates of cardiovascular events, including stent thrombosis, and higher rates of bleeding than clopidogrel.[71–73] Data on the combination of prasugrel with a NOAC are limited. In one small observational study, triple therapy using a VKA, aspirin, and prasugrel was associated with a 4-fold higher rate of bleeding.[74] The use of prasugrel in the 4 pivotal RCTs was also low (1.3% in PIONEER AF-PCI, 1.1% in AUGUSTUS, 0.5% in ENTRUST-AF-PCI, and excluded in REDUAL-PCI). Accordingly, prasugrel should be avoided in patients concomitantly treated with an OAC. The faster offset of action of ticagrelor (3 to 5 days) compared with prasugrel (7 to 10 days) makes it preferable if more potent $P2Y_{12}$ inhibition is required.[60] Although data with ticagrelor are also limited, its use in the 4 pivotal RCTs was higher than prasugrel (4.3% in PIONEER AF-PCI, 12.0% in REDUAL-PCI, 6.2% in AUGUSTUS, and 7.0% in ENTRUST-AF-PCI). Although the safety and efficacy findings were consistent with the overall trial results, bleeding rates were higher with more potent $P2Y_{12}$ inhibitors.[15–19,56,75] Therefore, it cannot be excluded that larger patient cohorts treated with potent $P2Y_{12}$ inhibitors could have significantly affected the safety outcomes. Moreover, the selection of $P2Y_{12}$ inhibitor type was not randomized and was at the discretion of the treating physician. In light of these considerations, the use of a more potent $P2Y_{12}$ inhibitor (ie, ticagrelor) should be reserved only for patients at highest thrombotic risk (eg, patients with ACS undergoing complex PCI) and acceptable bleeding risk. Ticagrelor should be administered as a 180 mg loading dose and 90 mg twice daily maintenance dose. Although a lower maintenance dose regimen (ie, 60 mg twice daily) is available for clinical use and has been shown to provide more potent and consistent antiplatelet effects than clopidogrel after PCI, this has yet to be tested together with OAC.[76,77] When ticagrelor is combined with OAC, aspirin use should generally be discontinued after the peri-PCI period.

Although studies have shown that a considerable number of patients may have impaired clopidogrel response and may be at increased risk of thrombotic complications, to date there are no outcome studies that have evaluated the use of alternate $P2Y_{12}$ inhibitors in patients with AF undergoing PCI based on results of pharmacodynamic or genetic determinants.[78] The usefulness of platelet function or genetic testing to guide the selection of $P2Y_{12}$-inhibiting therapy goes beyond the scope of this article and is discussed elsewhere.[78]

Strategy (Double Versus Triple Antithrombotic Therapy)

The available evidence demonstrates a reduction in bleeding complications with the use of double compared with triple therapy.[4,15–26,79] Although none of the RCTs were powered to assess major adverse ischemic events or stent thrombosis, there was no significant increase in ischemic events associated with double therapy in the individual trials.[15–18] However, results of some of the available meta-analyses suggest the potential for an increase in thrombotic complications with double therapy.[25,26] In all trials, the use of aspirin was mandatory in the peri-PCI period, indicating that all patients were exposed to triple therapy.[15–18] However, the time from PCI to randomization varied among trials. It is assumed that patients were likely to have been treated with aspirin until randomization. This time frame ranged from 0 to 14 days after PCI across trials. In particular, in 3 of the 4 RCTs (PIONEER AF-PCI, REDUAL-PCI, and ENTRUST-AF-PCI), aspirin was used on average for 1 to 2 days after PCI, and in the other RCT (AUGUSTUS), for 6 days.[15–18] Details on the duration of aspirin before randomization is provided in Table 5.[15–18] Accordingly, we refer to the time frame during which aspirin therapy

Table 5. Timing of Randomization After Percutaneous Coronary Intervention (PCI) in the Pivotal Randomized Trials of Patients With Atrial Fibrillation Undergoing PCI

Timing of randomization	PIONEER AF-PCI	REDUAL-PCI	AUGUSTUS	ENTRUST-AF-PCI
Timing of randomization from PCI procedure	Within 3 days	Within 5 days	Within 14 days	Within 5 days
Median time (interquartile range) to randomization, d	1 (1 to 2)	1 (1 to 2)	6 (3 to 10)	1.9 (0.9 to 3.2)
Mean time (SD) to randomization, d	1.62 (7.98)	1.6 (1.2)	6.6 (4.19)	2.2 (1.4)

AUGUSTUS indicates An Open-Label, 2×2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention; ENTRUST-AF-PCI, Edoxaban Treatment vs Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; PIONEER AF-PCI, A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; and REDUAL-PCI, Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Atrial Fibrillation That Undergo a PCI With Stenting.

was maintained in the pivotal trials (Table 5) to define the peri-PCI period in our consensus recommendations. In line with these considerations, this group recommends as the default strategy the use of aspirin during the peri-PCI period, defined as during inpatient stay, until time of discharge (generally occurring 1 to 2 days after PCI), and up to 1 week after PCI, at the discretion of the treating physician, before lessening to double therapy (Figure 2).[15–18] In all trials, the efficacy outcomes were consistent across all predefined subgroups, including those at increased thrombotic risk.[15–18,28,29,56–59] It is important to consider that, given the irreversible binding of aspirin to the cyclooxygenase-1 enzyme, residual platelet inhibitory effects induced by aspirin persist for the lifespan of the affected platelet (7 to 10 days).[4]

In patients treated with OAC undergoing PCI, bleeding complications occur early and accrue over time.[4,20] Therefore, in patients with additional risk factors for bleeding (Table 3), the duration of aspirin therapy should not go beyond the peri-PCI period as described above, irrespective of their thrombotic risk. However, the first month after PCI coincides with the highest risk period for the occurrence of thrombotic complications.[25–29] Therefore, given that there is potential for an increase in thrombotic complications with double therapy during the first month in patients at high thrombotic risk (Table 4), in the absence of adjunctive major criteria for bleeding (Table 3), it is reasonable to continue aspirin for up to 1 month after PCI. The AUGUSTUS trial showed that the use of aspirin immediately and for up to 30 days results in an equal tradeoff between an increase in severe bleeding and a reduction in severe ischemic events.[29] After 30 days, aspirin continues to increase bleeding without significantly reducing ischemic events. Landmark analysis assessments from other trials to define the trade-off between ischemic and bleeding events are ongoing. Nevertheless, these data are derived from post hoc assessments and there have not been randomized studies to date that have specifically assessed the clinical impact of aspirin therapy for 1 month after PCI. Extending aspirin therapy beyond 1 month after PCI is not recommended (Figure 2).

Duration of Antiplatelet Therapy

In line with previous recommendations, the default duration of the dual antithrombotic regimen and hence the timing of discontinuation of SAPT for most patients is 1 year (Figure 2).[4] This is based on the lack of evidence that continuing antiplatelet therapy provides any additional ischemic benefit but increases bleeding.[80–82] This evidence now expands to patients treated with a NOAC, as recently shown in the AFIRE trial (Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease), which was stopped early because of increased mortality in patients concomitantly treated with single antiplatelet therapy compared with rivaroxaban monotherapy, which was noninferior on efficacy outcomes and associated with reduced bleeding.[82] It may be argued that patients at enhanced risk for ischemic recurrences (eg, previous stent thrombosis) may have been excluded from this trial and hence the net benefit associated with maintaining long-term SAPT may vary according to the thrombotic and bleeding risk profiles of the individual patient. Our group consensus is that continuation of SAPT (in addition to OAC) beyond 1 year should be considered only in patients at high risk for ischemic recurrences and without adjunctive criteria for bleeding risk, although even then the risk may outweigh the benefit. When used, 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. On the other hand, in patients at low ischemic risk as well as 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 was used, in line with PIONEER AF-PCI, it is important to resume the established stroke prevention dose (20 mg once daily; 15 mg once daily in patients with creatinine clearance 15 to 50 mL/min) after suspension of antiplatelet therapy.

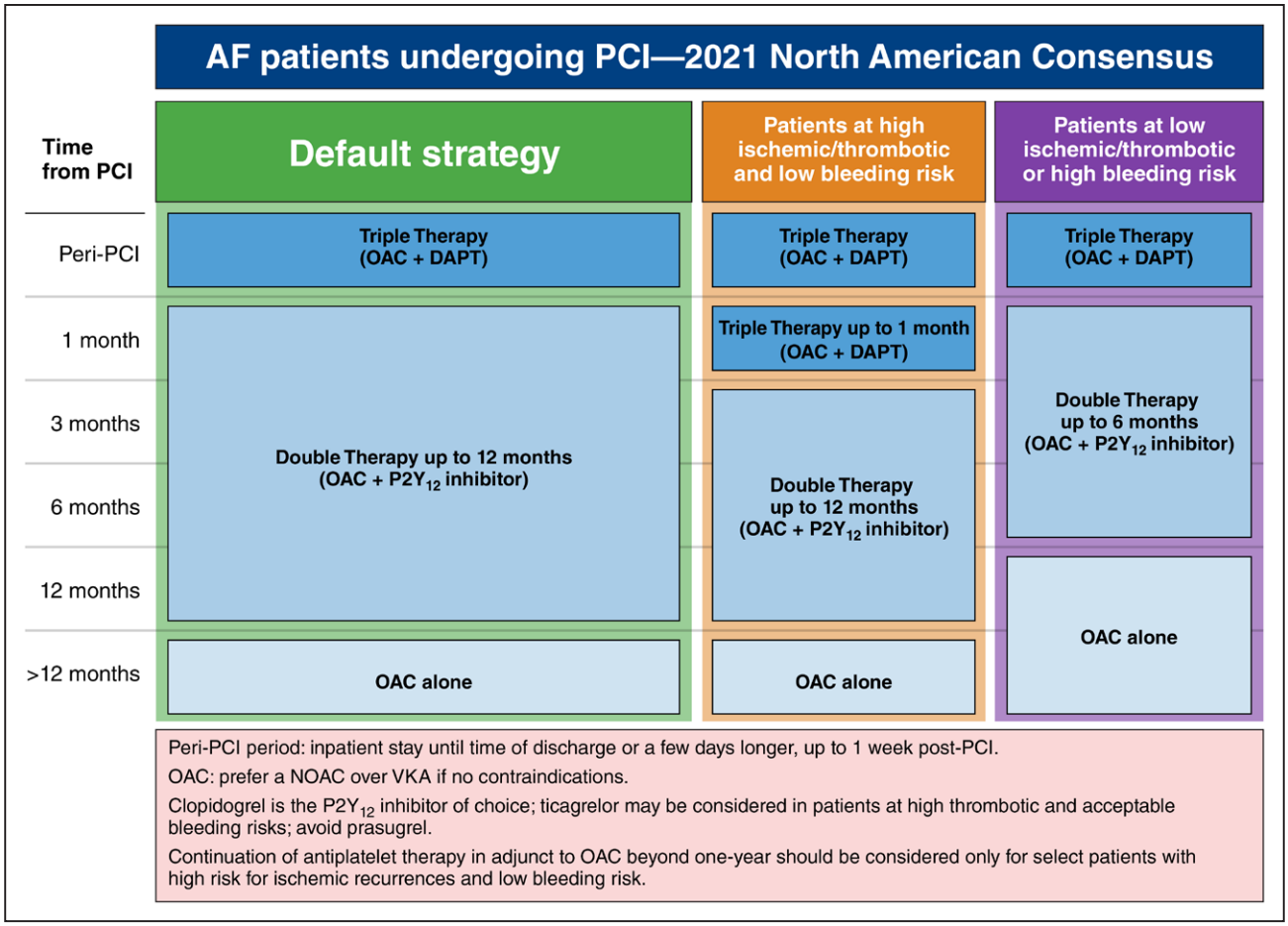

Figure 2. Management of antiplatelet therapy in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) treated with an oral anticoagulant: 2018 North American Consensus Update.
A double-therapy regimen, consisting of oral anticoagulant therapy (OAC) plus a $P2Y_{12}$ inhibitor, should be considered for most patients immediately after the peri-PCI period (Default Strategy). Aspirin should be used during the peri-PCI period, defined as inpatient stay until time of discharge, generally 1 to 2 days after PCI, and in some patients continued for 1 week after PCI. A non–vitamin K antagonist oral anticoagulant (NOAC) should be preferred over a vitamin K antagonist (VKA) unless contraindicated. Clopidogrel is the $P2Y_{12}$ inhibitor of choice; ticagrelor may be an alternative in patients with high thrombotic and acceptable bleeding risk; prasugrel should be avoided. It is reasonable to continue aspirin for up to 1 month after PCI (ie, triple therapy) in patients at high thrombotic risk and who have an acceptable risk of bleeding. Extending aspirin therapy beyond 1 month after PCI is not recommended. $P2Y_{12}$-inhibiting therapy should be discontinued at 1 year in most patients; earlier discontinuation (eg, 6 months) can be considered in patients at low ischemic or high bleeding risk; continuation of antiplatelet therapy beyond 1 year should be considered only in select patients with high risk for ischemic recurrences and low bleeding risk. DAPT indicates dual antiplatelet therapy.

NORTH AMERICAN CONSENSUS ON THE MANAGEMENT OF ANTITHROMBOTIC THERAPY IN PATIENTS WITH AF UNDERGOING PCI: SUMMARY OF THE 2021 FOCUSED UPDATE

This consensus group recommends that for patients with AF requiring the use of OAC and who are treated with stents, DAPT with aspirin and a $P2Y_{12}$ inhibitor should be given to all patients during the peri-PCI period, after which the default strategy is to stop aspirin and continue treatment with a $P2Y_{12}$ inhibitor in combination with a NOAC (ie, double therapy). We recommend as the default strategy the use of aspirin during inpatient stay until time of discharge (generally occurring 1 to 2 days after PCI) up to 1 week after PCI at the discretion of the treating physician before lessening to double therapy. In patients with additional risk factors for bleeding, the duration of aspirin therapy should not go beyond the peri-PCI period. However, given the observation that there is a potential for an increase in thrombotic complications with double therapy during the first month, in patients deemed to be at high thrombotic risk and who have an acceptable risk of bleeding, it is reasonable to continue aspirin for up to 1 month after PCI. Nevertheless, extending aspirin therapy beyond 1 month after PCI is not recommended. Clopidogrel remains the $P2Y_{12}$ inhibitor of choice, but ticagrelor may be considered in selected patients, particularly those at high thrombotic risk and acceptable bleeding risk. In the absence of contraindications, a NOAC should be preferred over a VKA. The dosing regimen of a NOAC should be that recommended for thromboembolic protection in patients with AF; the use of lower doses is not recommended,

unless specifically studied in randomized trials (ie, rivaroxaban 15 mg). Where 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 profile of the patient. Discontinuation of $P2Y_{12}$-inhibiting therapy at 1 year should be considered for most patients who should maintain treatment on stroke prevention doses of OAC. However, in patients at low thrombotic risk as well as those at high risk for bleeding, it is reasonable to discontinue $P2Y_{12}$-inhibiting therapy at 6 months after PCI. Continuation of antiplatelet therapy in adjunct to OAC beyond 1 year should be reserved only for select patients with high risk for ischemic recurrences and low bleeding risk.

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Supplemental Materials

Data Supplement Table I

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