

## Review article

# Atrial fibrillation with percutaneous coronary intervention: Navigating the minefield of antithrombotic therapies



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## HIGHLIGHTS

- This review provides insights into contemporary antithrombotic options for patients with atrial fibrillation undergoing percutaneous coronary intervention.
- Nuances between key international guidelines regarding recommendations for these patients are discussed.
- Evidence supports a dual antithrombotic pathway approach as the recommended therapy for the majority of these patients. If triple antithrombotic therapy is chosen, its duration should be kept as short as possible.

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## ABSTRACT

This review aims to provide insights into contemporary therapeutic options for the treatment of patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) and compares current international guidelines. AF is a common cardiac arrhythmia and a major risk factor for stroke. The risk of stroke can be reduced with the use of oral anticoagulant (OAC) therapy. However, for patients with AF, PCI necessitates the use of combined antithrombotic therapies (OAC and antiplatelet therapies) to reduce thrombotic coronary complications. Optimal combinations and durations of OAC and/or antiplatelet therapy remains an area of clinical debate. Nuances exist within the current guidelines regarding duration and combination of antithrombotic therapy for AF patients requiring PCI. However, consensus was found across the following key points: (i) recent evidence supports a preferred role for a dual antithrombotic approach (OAC plus 1 antiplatelet); (ii) limited use of triple antithrombotic therapy is recommended across all guidelines for patients where the ischemic risk outweighs the risk of bleeding, with the duration to be kept as short as possible; and (iii) lifelong management using monotherapy with an OAC from 12 months post PCI is recommended for stable patients across all guidelines.

## 1. Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia with a higher prevalence in older populations and in patients with existing atherosclerotic disease. Approximately 20–30% of ischemic strokes are related to AF, associated with increased risk of heart failure, cardiovascular morbidity, and mortality [1]. Approximately 3 million patients undergo percutaneous coronary intervention (PCI) each year worldwide [2]. In randomized trials, dual antiplatelet therapy (DAPT; a P2Y<sub>12</sub> receptor inhibitor plus aspirin) after PCI reduces the risk of future ischemic or atherothrombotic events, particularly stent-related thrombosis, recurrent myocardial infarction (MI), or cardiovascular

death [2]. Clinical trials involving patients treated with newer-generation stents have shown 3–6 months' duration of DAPT to be as effective as 12 months' therapy after elective PCI [3–8], although in acute coronary syndrome (ACS) patients these results are inconclusive due to a lack of adequately powered trials [9]. In contrast, other studies observed a reduction in the risk of thromboembolic, major adverse cardiovascular and cerebrovascular events with DAPT beyond 1 year with an associated increased risk of bleeding [10,11]. For patients undergoing PCI, approximately 5–10% have concomitant AF or other indications for long-term oral anticoagulant (OAC) therapy [12]. The optimal antithrombotic management of patients undergoing PCI who also have AF has become a clinical conundrum related to the optimal

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duration and combination of therapies to reduce subsequent ischemic and thromboembolic risk without incurring unacceptably increased bleeding risk [12]. Moreover, the lack of consensus within current guidelines regarding duration and selection of combined therapy adds to this challenge [13–15]. This article will discuss the most recent contemporary therapeutic options for atrial fibrillation patients requiring PCI and compare current European, North American, and Canadian guidelines for the antithrombotic management.

## 2. Rationale for oral anticoagulation in patients with atrial fibrillation

For many years, vitamin K antagonists (VKAs; international normalized ratio 2.0 to 3.0) were the only OAC available for the prevention of strokes in patients with AF [16]. If a VKA was not used, aspirin could be prescribed [16]. However, the challenges with clinical application of VKAs are well defined, requiring regular monitoring, dose adjustments and interactions with numerous foods and drugs [1,17]. Clinical trials of non-VKA direct oral anticoagulants (NOACs) have demonstrated noninferiority (and even superiority) for stroke prevention compared with VKAs, consistently with lower rates of intracranial hemorrhage (ICH) and lower mortality [18]. In general, for patients with non-valvular AF (NVAF) and risk factors for stroke, thromboembolic prevention therapy with a NOAC is recommended over VKA therapy [17,19,20].

## 3. Rationale for dual antiplatelet therapy in acute coronary syndrome/percutaneous coronary intervention

The basis for the use of DAPT after stenting compared to OAC came from the ISAR-SAFE trial (Intracoronary Stenting and Antithrombotic Regimen: Safety and efficacy of 6 months dual antiplatelet therapy after drug-eluting stenting), FANTASTIC study (Full ANTicoagulation versus ASpirin and TIClopidine), STARS study (Stent Anticoagulation Restenosis Study) and the MATTIS (multicenter aspirin and ticlopidine trial after intracoronary stenting) trial [21–24]. However, because these trials had been performed in an era of large sheaths, femoral access, and ultra-high doses of heparin in the OAC groups (with older thick stent struts), it is not clear if the results could be replicated with contemporary PCI techniques. The CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study investigated clopidogrel plus aspirin regimens in patients with ACS without ST-segment elevation [25]. The rate of stroke, MI, or death from cardiovascular causes was 9.3% in the clopidogrel plus aspirin group compared with 11.4% in the aspirin only group ( $p < 0.001$ ) [25]. However, the clopidogrel arm had significantly more major bleeding events compared with aspirin alone (3.7% vs 2.7%, respectively;  $p = 0.001$ ) [25]. The PCI-CURE sub-analysis, which included patients from CURE who were undergoing PCI, observed a reduction in ischemic events in patients treated with DAPT for 8 months, compared with aspirin alone [26]. Subsequently, studies such as CURRENT-OASIS 7 (Clopidogrel optimal loading dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for InterventionS), TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis In Myocardial Infarction 38) and PLATO (Study of Platelet Inhibition and Patient Outcomes) have shown that a more potent P2Y<sub>12</sub> receptor agonist regimen reduces recurrent ischemic events at the price of higher bleeding rates at 12 months [27–29].

### 3.1. Prolonged dual antiplatelet therapy

More recently, the DAPT study (Dual AntiPlatelet Therapy study), a double-blind, randomized controlled trial (RCT), aimed to determine the appropriate duration for DAPT (aspirin and a thienopyridine [10]) in patients who had received drug-eluting stent implantation [10]. A total of 9961 patients tolerating DAPT for 12 months were randomly

assigned to receive a thienopyridine or placebo for a further 18 months. The risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events were reduced in patients who received thienopyridine relative to patients who received the placebo (0.4% vs 1.4%; hazard ratio [HR] 0.29, 95% confidence interval [CI] 0.17 to 0.48; and 4.3% vs 5.9%; HR 0.71, 95% CI 0.59 to 0.85, respectively). The incidences of moderate and severe bleeding were elevated in the thienopyridine arm relative to those receiving placebo (2.5% vs 1.6%, respectively;  $p = 0.001$ ) [10]. The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial observed that the addition of either ticagrelor 90 mg twice daily (bid) or ticagrelor 60 mg bid significantly reduced the risk of cardiovascular death, MI or stroke but with more major bleeding (more so with ticagrelor 90 mg bid), compared with placebo in patients with a prior MI with extended duration DAPT (median 33 months) [30]. A meta-analysis demonstrated that, compared with aspirin alone, prolonged DAPT beyond 1 year is beneficial in stabilized high-risk patients with prior MI [31].

### 3.2. Prolonged dual pathway

Although not a dual antiplatelet strategy, the recent COMPASS (Cardiovascular Outcomes for People using Anticoagulation Strategies) trial studied patients with stable coronary artery disease (CAD) and/or peripheral artery disease receiving a very low dose of rivaroxaban (2.5 mg bid) plus aspirin (100 mg once daily [od]), rivaroxaban (5 mg bid), or aspirin alone (100 mg od) [32]. Results showed that rivaroxaban 2.5 mg bid plus aspirin 100 mg daily reduced major adverse cardiovascular and limb events compared with aspirin alone. Although the risk of major bleeding events increased, the rates of fatal and critical organ bleeding did not. Cardiovascular death alone was also reduced with this rivaroxaban and aspirin strategy. However, it is worth noting that patients with an indication for DAPT, oral anticoagulation, or other antithrombotic therapy were excluded from this trial.

## 4. Rationale for and limitations of triple therapy

Given the rationale of DAPT for PCI/ACS and OAC for patients with AF, the default became ‘triple therapy’ with OAC and DAPT for patients with AF undergoing PCI. As such, triple therapy with a VKA plus DAPT after PCI was the standard of care despite an associated increase in bleeding risk and the lack of clinical trials to test efficacy [33,34]. Several RCTs have now evaluated the safety of traditional triple therapy (VKA plus clopidogrel plus aspirin) compared with a dual antithrombotic regimen (OAC plus antiplatelet) in patients undergoing PCI. In the context of these studies, only a small component used ticagrelor or prasugrel and no randomized studies exclusively with these agents has been performed. Results of these studies are summarized below and in Table 1.

The WOEST (What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) trial investigated patients receiving a VKA undergoing PCI (including patients with and without AF), assigned to clopidogrel plus aspirin or clopidogrel alone [35]. At 1-year follow-up, the rate of any bleeding episode was significantly higher for traditional triple therapy (VKA plus clopidogrel plus aspirin) (approaching 50%) compared with dual antithrombotic (VKA plus clopidogrel) [35]. Patients in the triple therapy arm were also more likely to have experienced multiple bleeding events and to have required a blood transfusion ( $P = 0.011$ ), compared with the dual therapy arm [35]. The trial results showed no increase in thrombotic events by withholding of aspirin in the dual antithrombotic arm [35]. For the first time in a randomized fashion, a dual antithrombotic approach with VKA plus clopidogrel was shown to be a viable alternative to traditional triple therapy. However, this trial was underpowered to test efficacy including only a small subset of patients

**Table 1**  
RCT results comparing triple therapies with dual therapies in patients with atrial fibrillation, or other indications requiring an OAC, and undergoing PCI.

RCT	WOEST [34] (N = 563)	ISAR-TRIPLE [35] (N = 614)	PIONEER AF-PCI [36] (N = 2124)	RE-DUAL PCI [39] (N = 2725)	AUGUSTUS [40] (N = 4614)
<b>Patient population</b>	Patients receiving an OAC undergoing PCI	Patients receiving an OAC undergoing PCI	Patients with NVAF undergoing PCI	Patients with NVAF undergoing PCI	Patients with AF who had an acute ACS or had undergone PCI
<b>Follow-up Study arms</b>	Standard triple therapy Comparator arms	Standard triple therapy Comparator arms	Standard triple therapy Comparator arms	Standard triple therapy Comparator arms	Standard triple therapy Comparator arms
<b>Bleeding rates</b>	Standard therapy: 44.4% Comparator: 19.4% HR, 0.36 95% CI, 0.26–0.50; $p < 0.0001$	Standard therapy: 4.0% Comparator (6 weeks TT): 5.3% HR, 1.35 95% CI 0.64–2.84; $p = 0.44$	Standard therapy: 26.7% Rivaroxaban dual therapy: 16.8% HR, 0.59 95% CI, 0.47–0.76; $p < 0.001$ Standard therapy: 26.7% Rivaroxaban triple therapy: 18.0% HR, 0.63 95% CI, 0.50–0.80; $p < 0.001$	Standard therapy: 26.9% 110 mg dabigatran: 15.4% HR, 0.52 95% CI, 0.42–0.63; $p < 0.001$ Standard therapy: 25.7% (corresponding warfarin patients) 150 mg dabigatran: 20.2% HR, 0.72 95% CI, 0.58–0.88; $p < 0.001$	Apixaban: 10.5% VKA: 14.7% HR, 0.69; 95% CI 0.58–0.81; $p < 0.001$ for noninferiority and superiority Aspirin: 16.1% Placebo: 9.0% HR, 1.89; 95% CI 1.59–2.24; $p < 0.001$
<b>Thromboembolic events</b>	TT: 17.6% DT: 11.1% HR, 0.56 95% CI: 0.35–0.91, $p = NR$	TT 6 weeks: 4.0% TT 6 months: 4.3% HR, 0.93 95% CI: 0.43–2.05, $p = 0.87$	TT (warfarin): 6.0% TT (rivaroxaban): 5.6% DT: 6.5%; $p = NS$	TT: 13.4% DT: 13.7% HR, 1.04 95% CI, 0.84–1.29; $p = 0.005$	Apixaban: 6.7% VKA: 7.1% HR, 0.93; 95% CI 0.75–1.16; $p = NS$ Aspirin: 6.5% Placebo: 7.3% HR, 0.89; 95% CI 0.71–1.11; $p = NT$

bid, twice daily; CI, confidence interval; DAPT, dual antiplatelet therapy; DT, dual therapy; HR, hazard ratio; ISAR-TRIPLE, Intracoronary Stenting and Antithrombotic Regimen: Testing of Six-week versus a Six-month Clopidogrel Treatment Regimen in Patients with Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-eluting Stenting study; NR, not reported; NS, not significant; NT, not tested; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant; od, once daily; PCI, percutaneous coronary intervention; PIONEER AF-PCI, Open-label, Randomized, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and A Dose-adjusted Oral VKA Treatment Strategy in Subjects with AF Who Undergo PCI study; RCT, randomized controlled trial; RE-DUAL PCI, (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular AF Undergoing PCI study; TT, triple therapy; WOEST, What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting study.

with acute coronary syndrome at baseline (approximately one third), and included predominantly PCI procedures performed via the femoral access site (over 70% of procedures were performed via the femoral access site) [35].

The ISAR-TRIPLE study (Intracoronary Stenting and Antithrombotic Regimen: Testing of Six-week versus a Six-month Clopidogrel Treatment Regimen in Patients with Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-eluting Stenting) investigated the duration of traditional triple therapy, with OAC (VKA), aspirin and clopidogrel [36]. Shortening traditional triple therapy from 6 months to 6 weeks did not increase the risk of ischemic events and neither reduced the risk of major bleeding [36]. However, a landmark analysis at 6 weeks (because both study arms received traditional triple therapy for up to 6 weeks) did show a reduction in bleeding events, as defined using Bleeding Academic Research Consortium (BARC) criteria, with shortened duration traditional triple therapy [36].

In the PIONEER AF-PCI (oPen-label, randomized, controlled, multicenter study exploring two treatment strategies of Rivaroxaban and a dose-adjusted oral VKA treatment strategy in subjects with AF who undergo PCI) trial, patients exclusively with NVAF undergoing PCI were studied. Patients received a dual antithrombotic approach with rivaroxaban 15 mg od plus a P2Y<sub>12</sub> inhibitor, a very low-dose triple therapy approach with rivaroxaban 2.5 mg bid plus DAPT, or traditional triple therapy (VKA plus DAPT) [37]. The rate of clinically significant bleeding was significantly lower in both rivaroxaban arms compared with the VKA plus DAPT arm ( $p < 0.001$  for both groups) [37]. A composite of all-cause mortality and recurrent hospitalization were also lower in the rivaroxaban arms compared with the VKA plus DAPT arm [38]. Rates of cardiovascular events (MI, stroke, or death from cardiovascular causes) were similar across the 3 treatment groups acknowledging this study was not powered for these endpoints [37]. However, the fact that there was no increase in thrombotic events with the dual antithrombotic approach, and no increase in stroke in the low-dose rivaroxaban triple therapy arm at 1 year was reassuring.

The rationale for choosing rivaroxaban 15 mg od with a P2Y<sub>12</sub> inhibitor was based on the original dose-finding ATLAS TIMI 46 study. The study demonstrated the use of an antiplatelet and rivaroxaban 15 mg od was associated with similar efficacy and a lower risk of bleeding compared with an antiplatelet and rivaroxaban 20 mg [39].

Worthy of note is the value of very low-dose triple therapy in this study, the use of which may be relevant in patients with complex PCI where a duration of DAPT may be required, at the discretion of the treating interventional cardiologist, due to concerns of stent thrombosis.

The RE-DUAL PCI trial (Randomized Evaluation of DUAL antithrombotic therapy with dabigatran versus triple therapy with warfarin in patients with nonvalvular AF undergoing PCI) compared traditional triple therapy (VKA plus P2Y<sub>12</sub> inhibitor and aspirin [for 1–3 months]) with a dual antithrombotic approach (dabigatran 110 mg or 150 mg plus P2Y<sub>12</sub> inhibitor) [40]. Rates of major or clinically relevant non-major bleeding events were also observed to be lower in the dual pathway arms compared with the traditional triple therapy arm (both dual pathway arms demonstrated  $p < 0.001$  for noninferiority;  $p < 0.001$  for superiority in the dabigatran 110 mg group only) [40]. Rates of thromboembolic events, death, or unplanned revascularization were similar for the combined dual antithrombotic arms and the triple therapy group ( $p = 0.005$  for noninferiority) [40]. Although not significant, a trend towards greater risk of myocardial infarction was observed with the dabigatran 110 mg group compared to traditional triple therapy only.

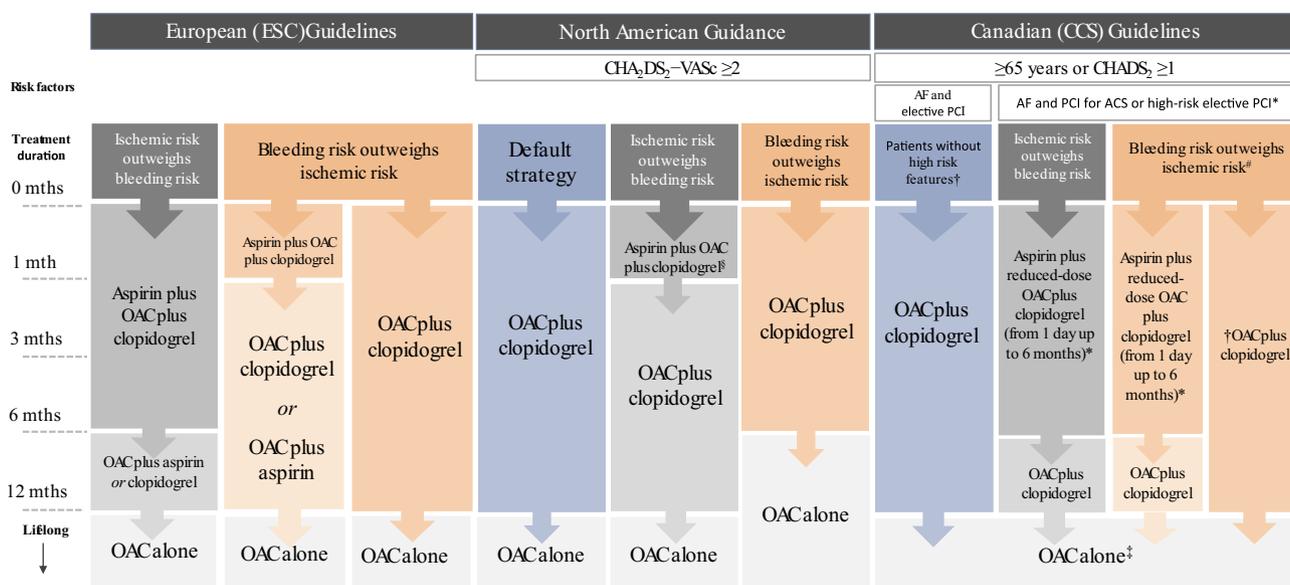
The AUGUSTUS trial, using a 2-by-2 factorial design, randomly assigned patients with nonvalvular AF who had an ACS or PCI who were planning on staying on a P2Y<sub>12</sub> receptor antagonist, to receive apixaban 5 mg twice daily or a VKA (1st randomization – open label) and to receive aspirin or placebo (2nd randomization – double blinded)

for 6 months [41]. In the largest randomized study to date, the primary endpoint of major or clinically relevant nonmajor bleeding was lower in those receiving apixaban at 10.5% compared with 14.7% in those receiving a VKA (HR 0.69, 95% CI 0.58 to 0.81;  $p < 0.001$  for both noninferiority and superiority) and was 16.1% in those receiving aspirin compared with 9.0% in those receiving placebo (HR 1.89, 95% CI 1.59 to 2.24;  $p < 0.001$ ) [41]. The apixaban patients had a lower rate of the secondary composite endpoint of death or hospitalization compared with patients receiving a VKA (23.5% vs 27.4% [HR 0.83, 95% CI 0.74 to 0.93;  $p = 0.002$ ], respectively) with similar rates of the secondary composite endpoint of death or ischemic events (6.7% vs 7.1% [HR 0.93, 95% CI 0.75 to 1.16;  $p = NS$ ], respectively) [41]. Those in the aspirin group had similar risk of death or hospitalization and death or ischemic events compared with placebo (26.2% vs 24.7% [HR 1.08, 95% CI 0.96 to 1.21;  $p = NS$ ], respectively, and 6.5% vs 7.3% [HR 0.89, 95% CI 0.71 to 1.11;  $p = NS$ ], respectively) [41]. Given there were no significant interactions of the 2 randomized strategies on the primary or secondary outcomes, comparisons were made according to intervention combination [41]. Major or clinically relevant nonmajor bleeding was highest in the patients receiving traditional triple therapy with aspirin, P2Y<sub>12</sub> receptor inhibitor and VKA (18.7%), intermediate in those receiving apixaban triple therapy (13.8%) and dual antithrombotic approach with VKA (10.9%) and lowest in those receiving dual antithrombotic approach with apixaban (7.3%) [41]. For the composite endpoint of death or hospitalization, event rates were highest with traditional triple therapy (27.5%) and dual antithrombotic approach with VKA (27.3%) and lower with apixaban triple therapy (24.9%) and apixaban dual therapy (22.0%) [41]. No real difference was seen with the composite endpoint of death or ischemic events with traditional triple therapy (5.7%), apixaban triple therapy (6.2%), apixaban dual antithrombotic therapy (6.2%) and VKA dual antithrombotic therapy (7.3%) [41].

Important to note is the mean time to randomization in this study of  $6.6 \pm 4.2$  days. As such, it is likely many patients on the apixaban dual antithrombotic therapy were still receiving aspirin 1 week (or longer) following the admission to hospital or PCI [41]. Patients are at high risk of ischemic events during this period [2]. Also, coronary atherothrombotic events numerically occurred more commonly when aspirin was omitted (on a background of a P2Y<sub>12</sub> receptor inhibitor and oral anticoagulation) including myocardial infarction (aspirin: 6.3% vs placebo: 7.8%; HR 0.81, 95% CI 0.59 to 1.12), ARC definite or probable stent thrombosis (aspirin: 0.5% vs placebo: 0.9%; HR 0.52, 95% CI 0.25 to 1.08) and urgent revascularization (aspirin: 1.6% vs placebo: 2.0%; HR 0.79, 95% CI 0.51 to 1.21) although none of these events were statistically significant [41]. However, we still feel these concerning trends should be mentioned given the trial was not powered for these clinical endpoints. Finally, AUGUSTUS outcomes were at 6 months leading to ambiguity of therapy following this interval [41].

The dual antithrombotic approach with a NOAC and an anti-platelet appears to provide the optimal balance for protecting patients from a thromboembolic event and stent thrombosis while mitigating bleeding events. From a pathologic perspective, the need to target the coagulation cascade is paramount with oral anticoagulation to reduce systemic embolization from atrial fibrillation as anti-platelet therapy alone is known to be insufficient. However, it has become apparent the use of an oral anticoagulant and a single anti-platelet appears safe in protecting patients from stent thrombosis – recognizing the excellent safety profile of our newer generation drug-eluting stents. This is a paradigm shift for interventional cardiologists (which requires continued investigation) and will undoubtedly change clinical practice in patients with atrial fibrillation requiring PCI.

Overall, the totality of evidence would support a dual antithrombotic pathway approach with a NOAC (rivaroxaban, dabigatran or apixaban) plus clopidogrel which appears to provide the optimal benefit-risk ratio for reducing ischemic events whilst minimizing bleeding



**Fig. 1.** Comparison of the guidelines for patients with AF undergoing PCI [1,13–15,43,45].

\*For patients with high-risk features based on clinical and angiographic features such as diabetes, prior acute coronary syndrome; chronic renal dysfunction (creatinine clearance < 60 mL/min), prior stent thrombosis, current smoker, multi-vessel coronary artery disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, chronic occlusion intervention or bioabsorbable scaffold implantation [15].

†For patients without high-risk features [15].

‡The addition of antiplatelet therapy with aspirin or clopidogrel for long-term treatment (beyond 1 year) is advised in patients with high ischemic and low bleeding risk.

#For patients where the bleeding risk outweighs ischemic risk, OAC plus clopidogrel is preferred from 1 day post PCI, with low-dose OAC (rivaroxaban 2.5 mg twice daily) to be considered if triple therapy is to be extended [15].

§AHA/ACC guidelines state that if triple therapy (OAC, aspirin and P2Y<sub>12</sub> inhibitor) is to be used, based on an assessment of the patients ischemic/thrombotic risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of ≥ 2), a transition to dual therapy may be considered at 4–6 weeks [44].

AF = atrial fibrillation; AHA/ACC = American Heart Association/American College of Cardiology; CCS = Canadian Cardiovascular Society; ESC = European Society of Cardiology; OAC = oral anticoagulant; PCI = percutaneous coronary intervention.

risk. The ongoing ENTRUST-PCI trials investigating edoxaban in patients who require PCI will provide further insights into the use of NOACs in this setting [42].

## 5. Comparison of current guidelines

Existing evidence from RCTs, registry data, and meta-analyses have supported the development of the latest guidelines for patients with AF undergoing PCI. Fig. 1 provides a comparison of the European, North American, and Canadian guidelines for the treatment of patients with AF undergoing PCI.

### 5.1. European guidelines

The 2017 European Society of Cardiology (ESC) guidelines provided a focused update on DAPT with recommendations for triple therapy [14]. For patients with AF undergoing PCI who are at high risk of bleeding, the ESC have put forward 2 recommended treatment courses upon patient discharge, these are namely: (1) the use of dual antithrombotic therapy (OAC plus clopidogrel) for up to 12 months post PCI; or (2) the use of triple therapy (OAC plus clopidogrel plus aspirin) for 1 month followed by dual antithrombotic therapy (OAC plus clopidogrel) up to 12 months, with OAC monotherapy recommended from 12 months post PCI in both instances. In cases where the patient's ischemic risk outweighs the risk of bleeding, the ESC guidelines recommend triple therapy for 1 month to reduce the risk of both atherothrombotic and cardioembolic events, which can be continued for up to 6 months. This is followed by treatment with dual antithrombotic therapy (OAC plus clopidogrel or aspirin) for 6 months up to 1 year post PCI, with OAC monotherapy recommended from 1 year [1,14,43].

### 5.2. North American guidelines

The 2018 North American expert consensus on the management of antithrombotic therapy in patients with AF undergoing PCI recommended the use of a dual antithrombotic therapy regimen (OAC plus a P2Y<sub>12</sub> inhibitor) immediately after hospital discharge for up to 12 months as the default strategy for most patients [13]. This is followed by OAC monotherapy from 12 months post PCI. Clopidogrel is recommended as the P2Y<sub>12</sub> inhibitor of choice, with NOACs preferred for use as an anticoagulant. In patients with high ischemic/thrombotic risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of ≥ 2) and where the risk of bleeding is low, the use of 1 month of triple therapy (OAC plus aspirin plus clopidogrel) is reasonable. This is followed by dual antithrombotic therapy (OAC plus clopidogrel) for up to 12 months, and subsequent OAC monotherapy from 12 months post PCI. Although clopidogrel is recommended as the P2Y<sub>12</sub> inhibitor of choice, the use of ticagrelor can be considered in this patient group where the ischemic risk prevails, and the risk of bleeding is low. In patients where the risk of bleeding outweighs the ischemic/thrombotic risk, dual antithrombotic therapy with OAC and clopidogrel is recommended for up to 6 months, followed by OAC monotherapy from 6 months post PCI. The intensity of anticoagulant and antiplatelet treatments should be tailored according to the bleeding and thrombotic risk profiles of the patient [13].

Since the publication of the consensus document, the 2019 guidelines from the American College of Cardiology/American Heart Association for the management of patients with AF have been published. These guidelines recommend the use of a dual antithrombotic therapy regimen (OAC plus a P2Y<sub>12</sub> inhibitor) to reduce the risk of bleeding as compared with triple therapy in patients with high ischemic/thrombotic risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of ≥ 2) [44]. In terms of OAC and P2Y<sub>12</sub> inhibitor selection, dose-adjusted VKA, low-dose

rivaroxaban (15 mg od) and dabigatran 150 mg bid were all considered reasonable options to be used in combination with clopidogrel [44]. Guidelines also state that if triple therapy (OAC, aspirin and P2Y<sub>12</sub> inhibitor) is to be used, based on an assessment of the patients ischemic/thrombotic risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 2$ ), a transition to dual therapy may be considered at 4–6 weeks [44].

### 5.3. Canadian guidelines

The Canadian Cardiovascular Society (CCS) 2018 antiplatelet guidelines and the 2018 CCS AF guidelines do recommend a strategy for patients with AF who undergo PCI, in which the choice of antithrombotic regimen upon discharge should be based on a balanced assessment of risk of: (1) ischemic stroke; (2) future coronary events (risk of PCI); and (3) clinically significant bleeding associated with the use of antithrombotic agents [15,45]. These CCS guidelines define high-risk PCI (i.e. high ischemic risk) based on clinical and angiographic features such as: diabetes mellitus, prior ACS, chronic renal dysfunction (creatinine clearance < 60 mL/min), prior stent thrombosis, current smoker, multi-vessel disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, chronic total occlusion intervention, or bioabsorbable vascular scaffold implantation. For patients undergoing elective PCI (age  $\geq 65$  years or CHADS<sub>2</sub>  $\geq 1$ ) without the aforementioned high-risk features, dual antithrombotic approach with OAC plus clopidogrel is recommended for 1 month for patients receiving a bare-metal stent, with 3 months up to 12 months treatment duration advised for patients receiving a drug-eluting stent. Otherwise DAPT with aspirin and clopidogrel is recommended following PCI (age < 65 years and CHADS<sub>2</sub> = 0) for the duration of treating the stent. For patients with AF undergoing PCI for ACS or high-risk elective PCI (age  $\geq 65$  years or CHADS<sub>2</sub>  $\geq 1$ ), reduced-dose triple therapy is recommended with aspirin 81 mg daily plus clopidogrel 75 mg daily plus lower intensity OAC from 1 day up to 6 months. The guidelines recognize the benefits of a dual antithrombotic approach (i.e. can be started as early as 1-day post PCI) and advocate a NOAC (rivaroxaban 15 mg od or dabigatran 110 mg bid – recognizing the risk of MI recurrence – or dabigatran 150 mg bid) over a VKA with clopidogrel 75 mg daily. Alternatively, if a triple therapy is selected for a longer duration, the guidelines support very low-dose triple therapy (rivaroxaban 2.5 mg bid with aspirin 81 mg od and clopidogrel 75 mg od) over a VKA regimen. Following the shortened duration of triple therapy, the CCS guidelines advocate for a dual antithrombotic approach (as above) for up to 12 months post PCI, and OAC monotherapy (regular dose) as a long-term strategy beyond 12 months. For patients with lower thromboembolic risk (< 65 years and CHADS<sub>2</sub> = 0) following PCI, DAPT with aspirin and a more potent P2Y<sub>12</sub> inhibitor (as opposed to clopidogrel) is recommended for 1 year given the benefits demonstrated in ACS. Of note, for long-term treatment beyond 1 year, the CCS guidelines endorse regular dose OAC and provide the option of single antiplatelet therapy in patients with high ischemic and low bleeding risk. The CCS guidelines strongly endorse that OAC dosing be based on doses studied in RCTs of patients with AF who undergo PCI. These are summarized in Table 1.

## 6. Treatment of patients with AF undergoing PCI: patient case studies

### 6.1. Patient A

- 65-year-old male, retired teacher
- 87 kg, 1.80 m, used to be a heavy smoker
- History: Diagnosed with NVAf 5 years ago
- Antithrombotic therapy: Rivaroxaban 20 mg od
- Following investigation for chest pain with a positive myocardial perfusion imaging scan, he receives a second-generation drug-eluting stent in his mid-left anterior descending artery

Cardiologist recommends elective PCI following chest pains and CAD diagnosis.

**Treatment options:** The existing evidence and international guidelines suggest a reduced OAC dose and antiplatelet therapy. Reducing the patient's rivaroxaban dose to 15 mg od plus a single antiplatelet (clopidogrel) would be appropriate given he was on rivaroxaban. The rivaroxaban regimen is associated with lower bleeding rates and fewer hospitalizations compared with standard VKA plus DAPT therapy [1,37,38]. Treatment should be maintained for up to 12 months, after which the original dose of rivaroxaban 20 mg od for stroke prevention in patients with AF could be reintroduced (if no contraindications) and the antiplatelet discontinued [1]. Alternatively, apixaban 5 mg twice daily or dabigatran 150 mg twice daily plus a single antiplatelet (clopidogrel) could be considered.

### 6.2. Patient B

- 72-year-old male, main caregiver for his wife at home
- 90 kg, 1.78 m
- History: Stable CAD and has had prior PCI ~2 years ago with normal left ventricular function and valvular function
- Antithrombotic therapy: Aspirin
- He presents with palpitations and a 12-lead electrocardiogram assessment demonstrates AF

**Treatment options:** Patients with stable CAD who develop AF should receive anticoagulation. Because the patient's PCI procedure was over 12 months ago, long-term use of OAC (NOAC monotherapy preferred over VKA) without additional antiplatelet agents is an option. This is considered sufficient and is supported by expert opinion and retrospective analysis in international guidelines for most patients with AF and stable CAD.

### 6.3. Patient C

- 80-year-old female, lives alone, daughter visits regularly
- 75 kg, 1.65 m
- History: Diagnosed with NVAf 8 years ago, borderline renal impairment (creatinine clearance 60 mL/min)
- Antithrombotic therapy: Apixaban 5 mg twice daily
- Has a non-ST-elevation MI with primary PCI

**Treatment options:** To manage the patient's stroke and coronary thrombotic risk, 12 months of apixaban 5 mg twice daily plus clopidogrel would be advisable because of the patient's high bleeding risk [14,46]. Alternatively, rivaroxaban 15 mg daily or dabigatran 110 mg or 150 mg bid plus a single antiplatelet (clopidogrel) could be considered.

## 7. Conclusions

Nuances exist within the current guidelines regarding the duration of combined therapy and when to use dual antithrombotic therapy (OAC plus antiplatelet) versus triple therapy (OAC plus DAPT) in patients with AF undergoing PCI. However, consensus was found across the following key points: (i) recent evidence supports a role for a dual antithrombotic approach including a NOAC plus clopidogrel for up to 12 months after PCI in selected patients; (ii) the limited use of triple therapy is recommended across all guidelines for patients where the ischemic risk outweighs the risk of bleeding, with the duration to be kept as short as possible; and (iii) lifelong management using monotherapy with regular dose OAC from 12 months post PCI is recommended across all guidelines. However, given the accumulating randomized data, it has become apparent that the risk of bleeding with traditional triple therapy including aspirin, a P2Y<sub>12</sub> receptor inhibitor and VKA is just too high and needs to be markedly attenuated. As such,

after assessment of patients' ischemic and bleeding risk, we feel the optimal route forward would be a shift to the dual pathway approach. Finally, clopidogrel is the P2Y<sub>12</sub> inhibitor more extensively investigated in combination with NOACs. Prasugrel was not considered due to a potentially very high risk of bleeding. Ticagrelor was used in these trials in very few patients leading to difficulty in establishing any specific recommendations. So far, the question of whether aspirin or a P2Y<sub>12</sub> inhibitor is the optimal antiplatelet for use in combination therapy has not been studied.

### Conflicts of interest

Dr Welsh reports grants and personal fees from AstraZeneca and Bayer, grants from Eli Lilly, and personal fees from Amgen, Pfizer/Bristol-Myers Squibb, and Boehringer Ingelheim. Dr Morais reports grants or personal fees (over the past 2 years) from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Menarini, Merck Sharp & Dohme, Novartis, and Servier. Dr Zeymer reports grants or personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Ferrer, Eli Lilly, Novartis, Pfizer, and Sanofi. Dr Bainey reports grants or personal fees from AstraZeneca, Bayer, Pfizer/Bristol-Myers Squibb, and Boehringer Ingelheim.

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### Appendix A. Supplementary data

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