Antithrombotic Therapy in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

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KEYWORDS

• Triple antithrombotic therapy • Dual antithrombotic therapy • Atrial fibrillation
• Percutaneous coronary intervention

KEY POINTS

- The antithrombotic strategy in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) should be chosen after a thorough assessment of an individual patient's bleeding and ischemic risks.
- Dual antithrombotic therapy with a direct oral anticoagulant should be the default antithrombotic strategy in most patients with AF undergoing PCI.
- Monotherapy with an oral anticoagulant after 6 months or 1-year post-PCI should be favored over a dual antithrombotic strategy, combining an oral anticoagulant with an antiplatelet agent, especially in patients whose bleeding risk outweighs the ischemic risk.

INTRODUCTION

It is estimated that 20% to 40% of patients with atrial fibrillation (AF) have coronary artery disease (CAD) and approximately 10% of patients who undergo percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation have AF.[1] AF is associated with increased risk of thromboembolic events, thus warranting prophylaxis with long-term oral anticoagulation (OAC).[1] In contrast, dual antiplatelet therapy (DAPT) with a combination of aspirin and an oral $P2Y_{12}$-receptor inhibitor is necessary to prevent coronary thrombotic events after PCI with DES.[2] Historically, triple antithrombotic therapy (TAT), combining OAC and DAPT, has been the default antithrombotic strategy for these patients. TAT is associated, however, with a high risk for bleeding complications, which are associated with morbidity and mortality.[3] Therefore, balancing the risk of cardiogenic embolism, coronary events, and major bleeding in this patient population poses a clinical dilemma. Evidence from randomized controlled trials (RCT)[4–9] has prompted the rapid evolution of recommendations surrounding optimal antithrombotic strategies for patients with AF after PCI.[10–16] The purpose of this review is to provide an update on the evidence, recommendations, and future directions in the field of antithrombotic therapy for patients with AF who undergo PCI.

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ANTITHROMBOTIC STRATEGIES IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION WITHOUT AN INDICATION FOR ORAL ANTICOAGULATION

The evidence informing antithrombotic strategies in patients undergoing PCI with stent implantation who do not have an indication for OAC favors DAPT over OAC with respect to both ischemic and bleeding events.[17–20] American and European guidelines both provide a class I recommendation for DAPT after PCI with stent implantation with the type of $P2Y_{12}$ inhibitor dependent on the clinical scenario.[14,21]

With respect to DAPT duration, prolonged DAPT reduces the risks of stent thrombosis and myocardial infarction (MI) but increases the risk of bleeding. Both the American and European guidelines strongly recommend a shorter course (eg, 6 months) of DAPT in patients with stable CAD undergoing PCI with implantation of a DES (American College of Cardiology [ACC]/American Heart Association [AHA]: class of recommendation [COR] I, level of evidence [LOE] B; European Society of Cardiology [ESC]: COR I, LOE A).[14,21] For patients with acute coronary syndrome (ACS) undergoing PCI with DES, the guidelines recommend a minimum of 12 months of DAPT (ACC/AHA: COR I, LOE B; ESC: COR I, LOE A) unless the patient is at high bleeding risk (HBR), when shorter therapy (eg, 6 months) should be considered (ACC/AHA: COR IIb, LOE C; ESC: COR IIa, LOE B).[14,21] After this period, in patients who have tolerated DAPT without adverse events and who are not at HBR, DAPT might be extended beyond 12 months (ACC/AHA COR: IIb, LOE A).

More recently, multiple randomized controlled trials (RCTs) compared the efficacy and safety of single antiplatelet therapy (SAPT) using a $P2Y_{12}$-receptor inhibitor monotherapy, instead of aspirin, versus DAPT after PCI with newer-generation DES.[22–25] None of these trials included patients with AF or another indication for chronic OAC. The Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) study tested the hypothesis that after a 3-month course of DAPT using aspirin and ticagrelor, ticagrelor monotherapy would be superior to DAPT with respect to clinically significant bleeding without ischemic harm in a cohort of HBR and ischemic risk patients after PCI.[22] In this randomized, double-blind trial, the investigators found a significantly lower rate of Bleeding Academic Research Consortium (BARC) 2 to 5 bleeding (primary endpoint) in the experimental arm (hazard ratio [HR] 0.56; 95% CI, 0.45–0.68; $P<.001$) without an increased risk of death, nonfatal MI or nonfatal stroke.[22]

ANTITHROMBOTIC THERAPIES IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION WITH AN INDICATION FOR ORAL ANTICOAGULATION

Vitamin K Antagonist Trials

The What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) trial was the first of a series of studies comparing double antithrombotic therapy (DAT) using a vitamin K antagonist (VKA) plus a $P2Y_{12}$-receptor inhibitor to TAT, using a VKA, a $P2Y_{12}$-receptor inhibitor, and aspirin in patients with an indication for chronic OAC following PCI.[6] WOEST was an open-label RCT that included 573 patients (69% of whom had AF) randomized to DAT (VKA plus clopidogrel) versus TAT (VKA plus clopidogrel plus aspirin) after PCI in order to test the hypothesis that SAPT with clopidogrel would reduce the risk of bleeding without increasing the risk of thrombotic events compared with DAPT. WOEST demonstrated that the early discontinuation of aspirin reduced the relative risk of any bleeding event by 64%, which was driven largely by Thrombolysis in Myocardial Infarction (TIMI) minor and Global Strategies for Opening Occluded Coronary Arteries (GUSTO) moderate bleeding.[6] Although underpowered, the DAT group did not show any increase in the risk of ischemic events and all-cause death was significantly lower in the DAT group.[6]

The Intracoronary Stenting and Antithrombotic Regimen–Testing of a 6-Week versus a 6-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting (ISAR-TRIPLE) trial tested whether 6 weeks of DAPT was superior to 6 months of DAPT in patients with an indication for chronic OAC after PCI.[7] The study randomized 614 patients (83% AF or atrial flutter) and found no difference in its primary composite endpoint of death, MI, definite stent thrombosis, stroke, or TIMI major bleeding at 9 months between the 2 groups. Furthermore, the abbreviated strategy showed a lower risk of BARC types 2 to 5 bleeding in a post hoc landmark analysis of events between 6 weeks and 6 months.[7]

Direct Oral Anticoagulant Trials

Multiple trials have evaluated the safety and efficacy of a direct oral anticoagulant (DOAC)-based antithrombotic strategy after PCI in patients with AF requiring chronic OAC. These trials had varying

designs and randomization schemes and were powered to demonstrate superiority for reduction in bleeding with a DOAC-based strategy versus a VKA-based strategy. Individually, they were underpowered to detect significant differences in major adverse cardiac events between antithrombotic strategies.

The Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) study included 2124 patients who were stratified prior to randomization by DAPT duration (1 month, 6 months, or 12 months) and $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, or prasugrel) and then were randomized into 2 groups: (group 1) low-dose rivaroxaban (15 mg daily) plus SAPT with a $P2Y_{12}$ inhibitor; (group 2) very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT; and (group 3, control) VKA plus DAPT.[5] Only 22% of patients received TAT for 1 year. The rivaroxaban-based strategies led to a reduction in the primary safety endpoint of clinically significant bleeding driven by reduction in rates of bleeding requiring medical attention as opposed to TIMI major or minor bleeding without significant differences in rates of major adverse cardiovascular (CV) events between the 3 groups.[5]

In the Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting (RE-DUAL PCI) trial, 2725 patients were randomized post-PCI to DAT consisting of dabigatran, 110 mg or 150 mg twice daily, plus a $P2Y_{12}$ inhibitor (86.6% clopidogrel, 12.4% ticagrelor) or TAT consisting of warfarin plus DAPT (90.3% clopidogrel, 7.8% ticagrelor).[8] Aspirin was discontinued 1 month after bare-metal stent implantation or 3 months after DES implantation in the TAT group. Although powered for noninferiority analysis, both DAT regimens proved superior to the TAT regimen with respect to the primary endpoint of major or clinically relevant nonmajor bleeding at 14 months irrespective of clinical presentation or $P2Y_{12}$ inhibitor selection.[8]

Although both PIONEER AF-PCI and RE-DUAL PCI support a DAT over a TAT strategy, neither was designed to delineate whether the reduction in bleeding was due to aspirin withdrawal, the doses of DOACs, or both. This was addressed in the an open-label, 2 × 2 factorial, randomized controlled trial to evaluate the safety of apixaban versus VKA and aspirin versus placebo in patients with AF and acute coronary syndrome and/or percutaneous coronary intervention (AUGUSTUS) trial.[4] AUGUSTUS randomized 4614 AF patients within 14 days after having an ACS or PCI in a 2 × 2 factorial design to apixaban, 5 mg twice daily, or VKA (open-label) and to aspirin or matching placebo (double-blind) for 6 months.[4] A $P2Y_{12}$ inhibitor was prescribed for all patients: 92.6% clopidogrel, 6.2% ticagrelor, or 1.1% prasugrel. The primary endpoint of major or clinically relevant nonmajor bleeding was lower in those receiving apixaban compared with a VKA (HR 0.69; 95% CI, 0.58–0.81; $P<.001$ for both noninferiority and superiority) and higher in those receiving aspirin compared with placebo (HR 1.89; 95% CI, 1.59–2.24; $P<.001$).[4] Additionally, the apixaban group had a lower incidence of death or hospitalization compared with the VKA group (HR 0.83; 95% CI, 0.74–0.93) without a significant difference in rates of ischemic events.[4] Although aspirin increased the risk of bleeding compared with placebo, there was no significant difference in the incidence of coronary ischemic events (eg, MI, CV death, stent thrombosis, and urgent revascularization).[4] The results from AUGUSTUS support a DAT strategy with DOACs over VKAs and early aspirin withdrawal, but the optimal duration of aspirin therapy remains uncertain and may vary based on a patient's thrombotic risk.

The recent Edoxaban Treatment versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (ENTRUST-AF PCI) trial randomized 1506 AF patients after successful PCI (52% ACS) to a DAT strategy with edoxaban (60 mg daily) and a $P2Y_{12}$ inhibitor (92% clopidogrel) or a TAT strategy with a VKA.[9] DAT was noninferior to TAT with regards to the primary composite endpoint of major or clinically relevant nonmajor bleeding at 12 months. There was no significant difference in rates of ischemic events between groups. It is important to acknowledge the results from the landmark analysis at 14 days, when a higher risk of bleeding was observed with edoxaban and a high proportion of patients in the VKA group had an international normalized ratio less than 2 (69% in the first week and 42% in the second week). Beyond 14 days, edoxaban consistently was associated with less bleeding (HR 0.68; 95% CI, 0.53–0.88; $P_{interaction}<0.0001$).

A meta-analysis of these 4 DOAC-based trials comparing DAT versus TAT in 10,234 AF-PCI/ACS patients[26] found DAT associated with a reduction in major or clinically relevant nonmajor bleeding compared with TAT (risk ratio [RR] 0.66; 95% CI, 0.56 to 0.78) at the cost of an increase in stent thrombosis (RR 1.59; 95% CI, 1.01–2.50).[26] There were no significant differences in rates of MI, CV death, or all-cause death. There were 1715 major or clinically relevant nonmajor bleeding events (523 major bleeding events)

versus 85 stent thrombosis events across the more than 10,000 patients with no between-group differences in CV death or major adverse clinical events.[26] Given that bleeding complications are numerically significantly more frequent than stent thrombosis and associated with substantial morbidity and mortality, these findings support the safety of a DAT strategy using a DOAC over a TAT strategy, whereas patients at very high risk of stent thrombosis may benefit from a brief course of TAT.

Summaries of the study designs and trial results of the VKA and DOAC trials are provided in Figs. 1 and 2, respectively.

ANTITHROMBOTIC MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION AFTER PERCUTANEOUS CORONARY INTERVENTION: GUIDELINE AND CONSENSUS RECOMMENDATIONS

Guideline and Consensus Recommended Strategies

Emerging RCT data largely have replaced expert consensus as the basis for international guidelines and consensus recommendations.[10–13] The precepts underlying these recommendations as follows:

1. Assess individual patient thrombotic and bleeding risks.
2. Minimize TAT duration to mitigate bleeding.
3. DOAC preferred over a VKA unless contraindicated.
4. Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
5. Beyond 1 year, OAC monotherapy preferred over DAT.

International guidelines and consensus documents, at present, do not incorporate results from AUGUSTUS or ENTRUST-AF PCI. Summaries of the American and European consensus document recommendations are provided in Figs. 3 and 4, respectively.

Assessment of Thrombotic and Bleeding Risks

Once the need for OAC has been established, risk stratification according to the individual risk of coronary thrombosis and major bleeding becomes critical, because this determines subsequent decisions surrounding TAT duration and antiplatelet selection. The most recent North American

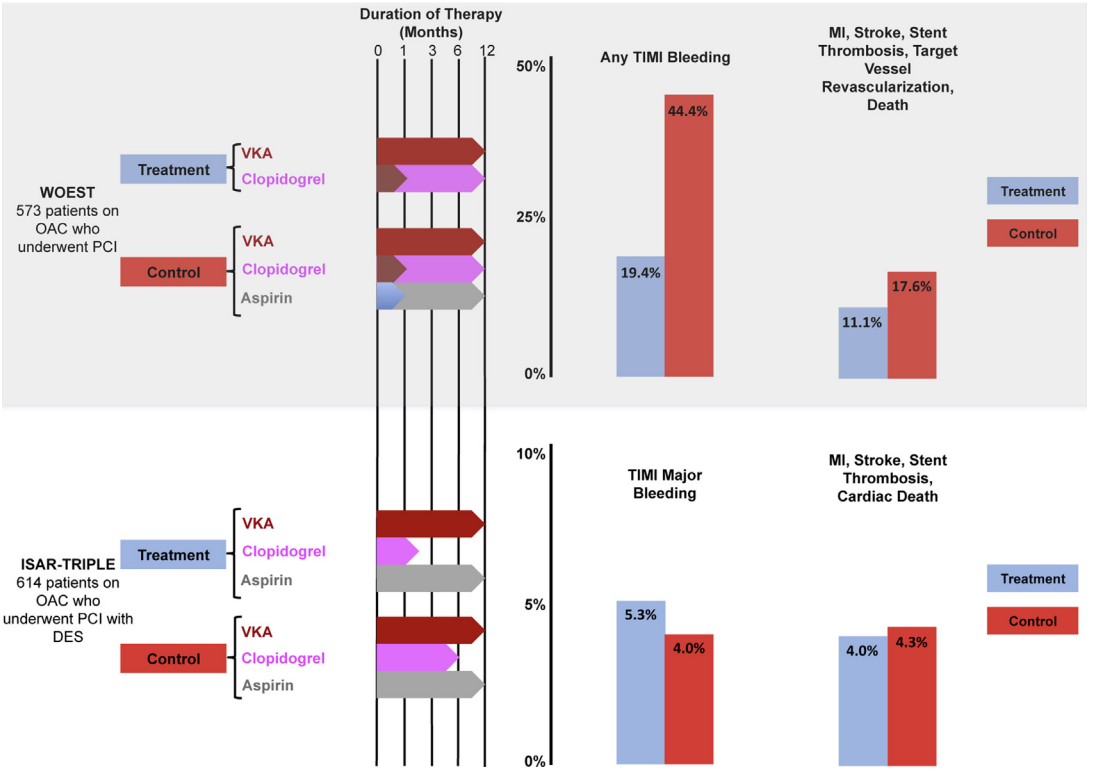

Fig. 1. Study design and outcomes of WOEST and ISAR-TRIPLE: patients with atrial fibrillation on VKAs undergoing PCI.

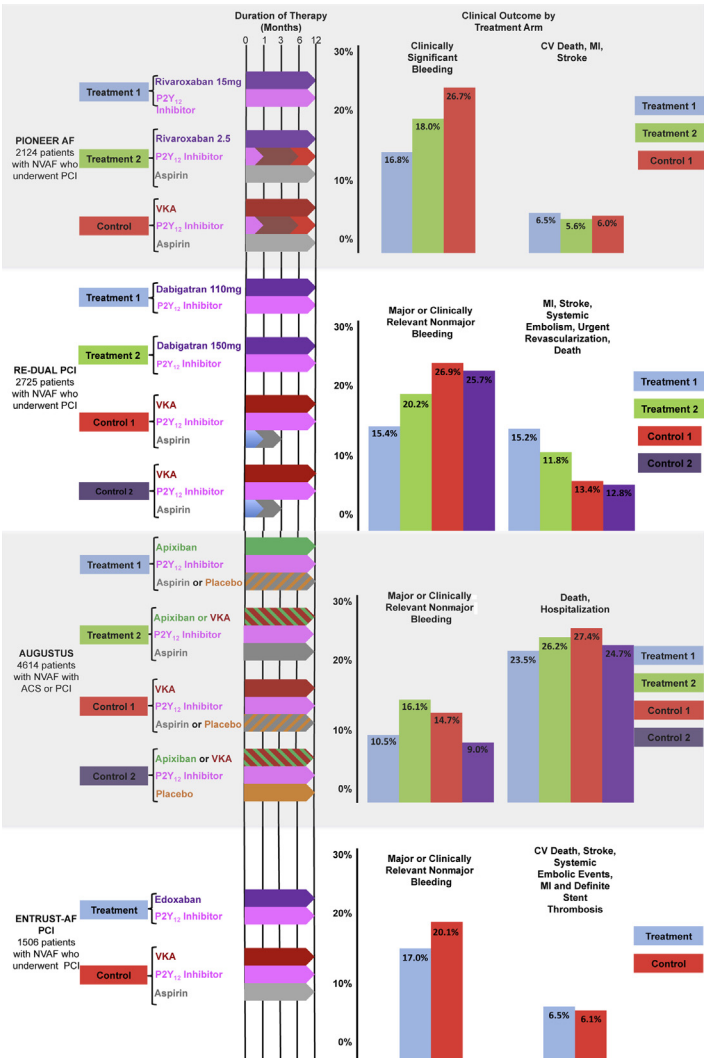

Fig. 2. Study design and outcomes of PIONEER AF, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI: patients with atrial fibrillation DOACs undergoing PCI. NVAF, nonvalvular atrial fibrillation.

consensus document highlights multiple patient and complex procedural characteristics that may predispose to increased ischemic and thrombotic risks, including ACS presentation, age, prior MI, extent of CAD, diabetes mellitus, chronic kidney disease, older-generation stents, smaller stent diameter, longer stent length, and bifurcation stents, among others.[12] In a similar, qualitative fashion, the North American document cites a history of prior bleeding, OAC therapy, female sex, age, diabetes mellitus, chronic kidney disease, and anemia, among others, as bleeding risk factors.[12] The European counterpart emphasizes the use of risk scores to quantify ischemic and bleeding risk in addition to patient and procedural characteristics.[10] For ischemic risk assessment, the European document recommends the Synergy Between Percutaneous Coronary Intervention With Taxus (SYNTAX) score in elective cases and the Global Registry of Acute Coronary Events (GRACE) score (>140) in patients with ACS, while accounting for other risk factors, including left main PCI, proximal left anterior descending artery, proximal bifurcation, recurrent MI, and a history of stent thrombosis.[10] For bleeding risk assessment, the European document recommends the Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly (HAS-BLED) score.[10] A consensus document from the Academic Research Consortium (ARC) proposed 20 clinical criteria (14 major and 6 minor) to define patients at HBR undergoing PCI (ARC-HBR definition).[27] Although long-term OAC use is a major criterion, this definition may inform the estimation of

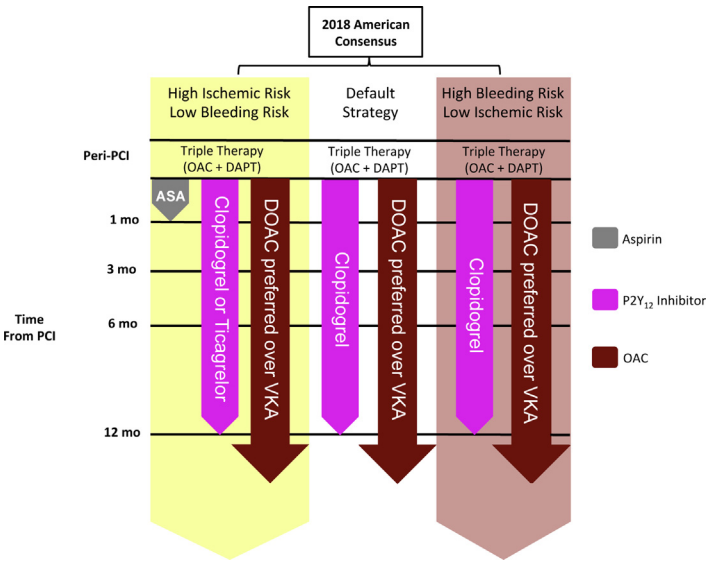

Fig. 3. American consensus recommendations on the management of antithrombotic therapy in patients with atrial fibrillation undergoing PCI. ASA, aspirin.

bleeding risk. The ARC-HBR definition has not been validated in an independent patient data set.[27]

Triple Antithrombotic Therapy Duration

The recommended duration of TAT differs slightly between the 2019 ACC/AHA/Heart Rhythm Society (HRS) guidelines for AF and the 2018 ESC guidelines for myocardial revascularization.[11,13] Both provide a COR IIa recommendation for DAT as an alternative to TAT to reduce bleeding, but the European document limits this to patients at HBR.[11,13] The European guidelines otherwise recommend a default 1-month TAT strategy that can be extended for 3 months to 6 months depending on a patient's thrombotic risk (COR IIa). The American guidelines, conversely, recommend a default DAT strategy, limiting aspirin to the periprocedural, in-hospital period.[11] Moreover, the American guidelines recommend 4 weeks to 6 weeks of TAT in patients at greatest risk of stent thrombosis, such as those with STEMI (COR IIb).[11]

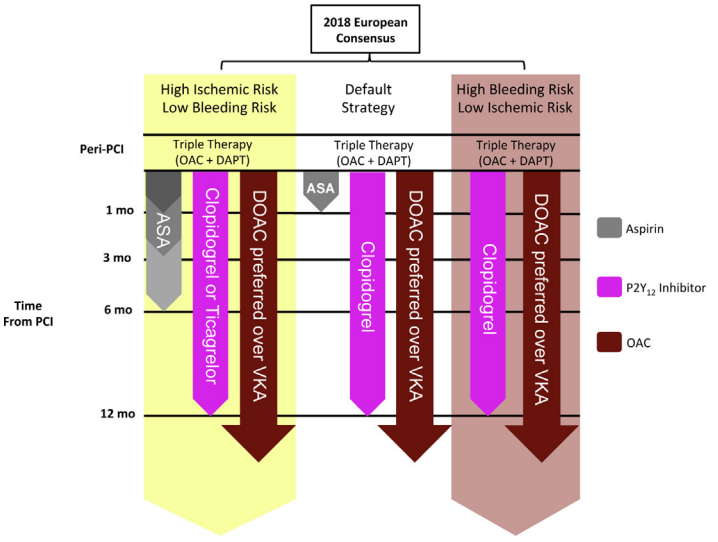

Fig. 4. European consensus recommendations on the management of antithrombotic therapy in patients with atrial fibrillation undergoing PCI. ASA, aspirin.

Oral Anticoagulation Selection and Dosage

Unless contraindicated, DOACs are favored over VKAs given their relative safety and ease of use.[10–13] Regarding dosing, the North American consensus document recommends DOACs as dosed in the AF-PCI trials. Because the 110-mg twice daily dose of dabigatran is not approved in the United States for stroke prevention, the 2018 AHA/ACC/HRS guidelines for AF recommend 150 mg twice daily (COR IIa, LOE B),[11] whereas the 2018 ESC guidelines on myocardial revascularization offer a COR IIa, LOE C recommendation for the 110-mg twice daily dose during TAT and a COR IIb, LOE B recommendation for the 150-mg twice daily dose during DAT.[13] The American and European guidelines also differ slightly in recommendations for rivaroxaban, 15 mg daily, with the 2019 ACC/AHA/HRS guidelines for AF providing a COR IIa, LOE B recommendation and the 2018 ESC guidelines for myocardial revascularization providing a COR IIb, LOE B recommendation.[11,13] When a decision is made to discontinue the $P2Y_{12}$ inhibitor (typically at 1 year), the North American and European consensus documents recommend increasing the OAC to its labeled dose.[10,12] Lastly, specific dosage recommendations for apixaban and edoxaban are not provided by either the guidelines or consensus documents, which were written prior to publication of the results from AUGUSTUS and ENTRUST-AF PCI. In both trials, the full recommended doses of DOACs were used, and it is likely that future guidelines and consensus documents will incorporate these options.[4,9]

Antiplatelet Regimen

The default $P2Y_{12}$ inhibitor per American and European guidelines and consensus documents should be clopidogrel.[10–13] The 2019 ACC/AHA/HRS guidelines for AF provide a COR IIa, LOE B recommendation for clopidogrel irrespective of TAT versus DAT strategy whereas the 2018 ESC guidelines for myocardial revascularization provide a COR IIa, LOE A recommendation for clopidogrel in DAT strategies and COR IIa, LOE B recommendation for clopidogrel during TAT treatment.[11,13] The 2018 ESC guidelines for myocardial revascularization caution against the use of more potent $P2Y_{12}$ inhibitors (ie, prasugrel or ticagrelor) in combination with OAC.[13] The North American consensus document also recommends against prasugrel, given the results from a small study that demonstrated a 4-fold increase in bleeding with prasugrel-based TAT[28] but recommends ticagrelor as a suitable option for patients at high thrombotic and low bleeding risk who otherwise are not on triple therapy.[12]

Once the transition from TAT to DAT occurs, aspirin should be dropped in favor of continuing $P2Y_{12}$ inhibitor therapy.[10,12] A significant proportion of patients who undergo PCI might be hyporesponsive to clopidogrel.[29] High platelet reactivity on clopidogrel reflects inadequate platelet inhibition and has been associated with an increased risk of stent thrombosis.[29] Randomized trials comparing platelet function-guided antiplatelet therapy failed to show benefit,[30–32] but further research is needed to evaluate the use of platelet function testing to guide antiplatelet therapies in patients treated concurrently with OAC.

Long-Term Oral Anticoagulation

Upon completion of DAT therapy, patients should continue OAC monotherapy at the dose recommended for stroke prevention, accounting for renal function.[10,12] Because there appears to be little advantage to continuing SAPT plus OAC beyond 1 year,[33–35] these recommendations are aimed at reducing bleeding in patients with AF and stable CAD. Support for this recommendation comes from the Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease (AFIRE) trial.[36] The investigators randomized 2236 patients with stable CAD to rivaroxaban, 15 mg daily, or a DAT with rivaroxaban plus SAPT (70% aspirin vs. 27% P2Y12 inhibitor). When the trial was terminated because of increased mortality in the DAT group, rivaroxaban monotherapy was noninferior to DAT for the primary efficacy endpoint of all-cause mortality, MI, stroke, unstable angina requiring revascularization, or systemic embolism ($P<.001$) and superior to DAT for the primary safety endpoint of major bleeding.[36] Still, those at high thrombotic risk may benefit from a prolonged course of DAT. The ongoing French Assessment of Quitting versus Using Aspirin Therapy In Patients Treated With Oral Anticoagulation for Atrial Fibrillation and With Stabilized Coronary artery disease (AQUATIC) trial aims to study the superiority of DAT with aspirin plus OAC for 24 months to 48 months versus placebo plus OAC in high-risk, stable CAD-AF patients and will provide more data on this issue.

Additional Strategies and Future Directions

Other practices to incorporate in the routine care of AF-PCI patients include radial over femoral access, use of bivalirudin in HBR patients, use of newer-generation DES, use of proton pump inhibitors post-PCI for patients on DAPT or DAT/TAT,

Table 1
Ongoing trials evaluating antithrombotic strategies in patients with atrial fibrillation undergoing percutaneous coronary intervention

Trials	ClinicalTrials.gov Identifier	Target Population	Experimental Arm(s)	Control Arm	Endpoint(s)	Timeline	Anticipated Completion Date
APPROACH-ACS-AF (N = 400)	NCT02789917	ACS + NVAF or atrial flutter + successful PCI	Apixaban and clopidogrel for 6 mo	VKA, clopidogrel, and aspirin for 6 mo if HAS-BLED <3 VKA, clopidogrel, and aspirin for 1 mo followed by VKA and clopidogrel for 5 mo if HAS-BLED $\geq$3	Primary: major bleeding Secondary: combined death, MI, ST, STE	6 mo	TBD
COACH-AF-PCI (N = 1120)	NCT03536611	NVAF + successful PCI with DES	Dabigatran, aspirin, and clopidogrel for 1 mo followed by dabigatran and clopidogrel for 5 mo	Warfarin, aspirin and clopidogrel for 1 mo followed by Warfarin and Cclopidogrel for 5 mo	Primary: clinically relevant bleeding Secondary: death MI, STE, ischemia-induced revascularization	24 mo	June 2020
OPTIMAL-1/2 (N = 1550)	NCT03234114	ACS + NVAF + successful PCI with DES	OPTIMAL-1: warfarin, clopidogrel, and aspirin for 1 mo, then quit aspirin until 12 mo after PCI OPTIMAL-2: dabigatran with ticagrelor for 12 mo	OPTIMAL-1: warfarin, clopidogrel, and aspirin for 6 mo, then quit aspirin until 12 mo after PCI OPTIMAL-2: dabigatran with clopidogrel for 12 mo	OPTIMAL-1: combined death, MI, STE, unplanned revascularization OPTIMAL-2: major or clinically relevant bleeding	12 mo	December 2021
SAFE-A (N = 600)	N/A	NVAF + PCI with DES	Aspirin and apixaban for 12 mo with $P2Y_{12}$ inhibitor for 1 mo	Aspirin and apixaban for 12 mo with $P2Y_{12}$ inhibitor for 6 mo	Primary: all bleeding complications Secondary: combined death, MI, STE	12 mo	TBD

MASTER-DAPT (N = 430	NCT03023020	HBR who underwent PCI	DAPT for 1 mo, then SAPT for 11 more months	DAPT for 6 mo, then aspirin for 6 more months	Combined death, MI, stroke, bleeding Major or clinically relevant bleeding	12 mo	March 2021

Abbreviations: APPROACH-ACS-AF, APixaban Versus PhenpRocoumon: Oral AntiCoagulation Plus Antiplatelet therapy in Patients With Acute Coronary Syndrome and Atrial Fibrillation; COACH-AF-PCI, Comparing Dabigatran Etexilate Versus Warfarin in Chinese Patients With Nonvalvular Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention With Stenting (DES); MASTER-DAPT, Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen; NVAF, nonvalvular atrial fibrillation; OPTIMAL-1/2, Optimal Antithrombotic Therapy for Acute Coronary Syndrome Patients Concomitant Atrial Fibrillation Undergoing New Generation Drug Eluting Stent Implantation; SAFE-A, SAFety and Effectiveness trial of Apixaban use in association with dual antiplatelet therapy in patients with AF undergoing percutaneous coronary intervention; STE, systemic thrombolic event; TBD, to be determined.

and avoidance of nonsteroidal anti-inflammatory drugs.[10,12] Finally, ongoing trials evaluating novel approaches to antithrombotic strategies using contemporary DES platforms will provide more data to inform clinical decision making (**Table 1**).

SUMMARY

PCI in the setting of AF necessitates concomitant antiplatelet and anticoagulant agents to prevent ischemic events. The totality of data supports use of a DOAC-based DAT strategy, combining OAC with a $P2Y_{12}$-receptor inhibitor for most patients requiring chronic OAC who undergo PCI. A TAT strategy should be considered in selected cases, when the thrombotic risk exceeds bleeding risk. In this setting, the optimal duration of aspirin, in combination with an OAC and a $P2Y_{12}$-receptor inhibitor, remains unclear and could vary from weeks to months. Finally, in patients who have completed an initial 6-month or 1-year course of DAT, withdrawal of the $P2Y_{12}$-receptor inhibitor and ongoing treatment with an OAC alone are recommended to reduce the risk of bleeding.

DISCLOSURE

Dr J.L. Halperin has received consulting fees from Boehringer Ingelheim, Bayer Healthcare, Ortho-McNeil-Janssen Pharmaceuticals, and Medtronic. Dr G. Giustino received consultation fees (Advisory Board) for Bristol-Myers Squibb/Pfizer. The other coauthors have no conflicts of interest to disclose.

REFERENCES

1. Baber U, Mastoris I, Mehran R. Balancing ischaemia and bleeding risks with novel oral anticoagulants. Nat Rev Cardiol 2015;12(2):66.
2. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358(9281):527–33.
3. van Rein N, Heide-Jorgensen U, Lijfering WM, et al. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy. Circulation 2019;139(6):775–86.
4. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019;380(16):1509–24.
5. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016;375(25):2423–34.
6. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013;381(9872):1107–15.
7. Fiedler KA, Maeng M, Mehilli J, et al. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPLE trial. J Am Coll Cardiol 2015;65(16):1619–29.
8. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377(16):1513–24.
9. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet 2019;394(10206):1335–43.
10. Lip GYH, Collet JP, Haude M, et al. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Europace 2019;21(2):192–3.
11. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a Report of the American College of Cardiology/American Heart association Task Force on clinical practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019;74(1):104–32.
12. Angiolillo DJ, Goodman SG, Bhatt DL, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention. Circulation 2018;138(5):527–36.
13. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40(2):87–165.
14. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European

Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39(3):213–60.
15. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39(16):1330–93.
16. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41(3): 407–77.
17. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med 1998;339(23):1665–71.
18. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334(17):1084–9.
19. Bertrand ME, Legrand V, Boland J, et al. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (fantastic) study. Circulation 1998;98(16):1597–603.
20. Urban P, Macaya C, Rupprecht HJ, et al. Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the multicenter aspirin and ticlopidine trial after intracoronary stenting (MATTIS). Circulation 1998;98(20):2126–32.
21. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a Report of the American College of Cardiology/American Heart association Task Force on clinical practice guidelines. J Am Coll Cardiol 2016;68(10):1082–115.
22. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med 2019;381(21):2032–42.
23. Hahn JY, Song YB, Oh JH, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. JAMA 2019;321(24): 2428–37.
24. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. JAMA 2019;321(24):2414–27.
25. Vranckx P, Valgimigli M, Juni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392(10151):940–9.
26. Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. Eur Heart J 2019;40(46):3757–67.
27. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. Circulation 2019;140(3): 240–61.
28. Sarafoff N, Martischnig A, Wealer J, et al. Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. J Am Coll Cardiol 2013;61(20):2060–6.
29. Stone GW, Witzenbichler B, Weisz G, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. Lancet 2013;382(9892):614–23.
30. Collet JP, Cuisset T, Range G, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 2012;367(22):2100–9.
31. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA 2011; 305(11):1097–105.
32. Cayla G, Cuisset T, Silvain J, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet 2016;388(10055):2015–22.
33. Lamberts M, Gislason GH, Lip GY, et al. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: a nationwide cohort study. Circulation 2014;129(15): 1577–85.
34. Hamon M, Lemesle G, Tricot O, et al. Incidence, source, determinants, and prognostic impact of major bleeding in outpatients with stable coronary artery disease. J Am Coll Cardiol 2014;64(14):1430–6.
35. Alexander JH, Lopes RD, Thomas L, et al. Apixaban vs. warfarin with concomitant aspirin in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J 2014;35(4):224–32.
36. Yasuda S, Kaikita K, Akao M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. N Engl J Med 2019;381(12):1103–13.