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Coronary Artery Disease (D Feldman and V Voudris, Section Editors)

Antithrombotic Strategies in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

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Abstract

Purpose of review The choice of appropriate antithrombotic therapy in patients with atrial fibrillation (AF) undergoing percutaneous coronary interventions (PCI) should be approached prudently. Careful consideration is necessary, balancing the ischemic and bleeding risk. Traditionally, triple antithrombotic therapy comprising of aspirin, a P2Y12 inhibitor, and an oral anticoagulant is associated with high bleeding rates.
Recent findings Recent trials have evaluated the safety and effectiveness of dual antithrombotic therapy in AF patients undergoing PCI. These studies have shown a significant reduction in bleeding with no increase in ischemic events. Clopidogrel is the preferred P2Y12 agent in the dual antithrombotic regimens. The novel oral anticoagulants (NOAC) rivaroxaban and dabigatran have been evaluated as part of dual antithrombotic therapy and are preferred options for oral anticoagulation in AF patients undergoing PCI. Studies are in progress to evaluate the role of alternate NOACs in this clinical scenario.
Summary This review explores the contemporary management of antithrombotic therapy in AF patients undergoing PCI.

Introduction

Atrial fibrillation (AF) is a global epidemic with an estimated prevalence of 12.1 million patients within the USA by 2030 [1]. A substantial proportion of AF patients (18–46%) will have concomitant CAD and a majority (62%) of these patients will require coronary revascularization, mostly by percutaneous coronary intervention (PCI) [2]. Clinical guidelines recommend the use of oral anticoagulation therapy for stroke reduction in AF patients as driven by individually predicted thromboembolic risk [3, 4]. Patients undergoing PCI require potent antiplatelet strategies, in particular dual antiplatelet therapy (DAPT), to prevent stent thrombosis [5, 6••]. The duration of DAPT is variable and depends on the clinical presentation, type of stent used, and ongoing ischemic risk [6••, 7]. However, traditional triple antithrombotic therapy (TAT) in AF patients undergoing PCI—combining anticoagulation with DAPT—has been associated with high bleeding rates [8, 9]. To mitigate the bleeding risk, some strategies have eliminated the use of anticoagulation in AF patients post PCI with a consequential increased risk of thromboembolism [10]. Recent studies have shown that dual antithrombotic therapy (DAT), combining oral anticoagulation (OAC) only with a P2Y12 inhibitor, can be an effective strategy to balance the risk of bleeding and major cardiovascular adverse events (MACE) [11•, 12••, 13••, 14•, 15••]. In this review, we will explore contemporary antithrombotic strategies in patients with AF who undergo PCI.

Triple therapy

Given the risk of stent thrombosis along with the risk of systemic thromboembolism in AF patients post PCI, there is a clinical need for combining OAC with antiplatelet therapy. However, clinical trials have shown a high risk of bleeding with the combination of OAC and DAPT. The rate of clinically significant bleeding with TAT in clinical trials has ranged as high as 26–44% [11•, 12••, 13••, 15••]. In a Danish registry, the incidence of clinically significant bleeding with TAT was around 14% [16]. The net efficacy of TAT in reducing MACE including death, myocardial infarction, stroke or systemic embolism, and need for urgent revascularization was similar to DAT with a single antiplatelet agent and OAC [11•, 13••, 14•, 15••].

Most observational data and clinical trials are based predominantly on clopidogrel containing TAT regimens. Limited data are available on prasugrel [17, 18] and ticagrelor [19•] use in TAT regimens, which show a significant increase in bleeding complication rates compared to clopidogrel containing TAT regimens. Notably, the use of novel oral anticoagulants (NOAC) preferentially over vitamin K antagonists (VKA) for patients with AF undergoing PCI has become more prevalent over the years [20].

Dual antithrombotic therapy

Several solutions have been proposed to reduce the high rates of bleeding associated with traditional TAT. One strategy has been to eliminate aspirin from TAT. The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial was the first randomized controlled trial comparing traditional TAT (aspirin, clopidogrel, and warfarin) with DAT (clopidogrel and warfarin). This was an open-labeled

trial randomizing 573 patients with a follow-up of 12 months [13••]. Warfarin was dosed to a goal INR between 2.0 and 3.0. All patients received a loading dose of clopidogrel (300 mg or 600 mg) followed by a maintenance dose of 75 mg daily. Patients in the TAT arm received a loading dose of aspirin (320 mg) followed by a maintenance dose of 80–100 mg daily. The total bleeding rate was significantly reduced in the DAT arm compared to TAT arm (19.4% vs. 44.4%, $p = < 0.0001$). This difference was mainly driven by a reduction in minor bleeding. There was statistically significant reduction in TIMI and GUSTO bleeding rates along with the reduction in bleeding requiring blood transfusion. The study was not adequately powered for the efficacy endpoint of MACE, though there was a reduction in MACE in the DAT arm compared to the TAT arm.

A decrease in the duration of TAT has also been studied as a strategy for reducing bleeding risk. The ISAR-TRIPLE (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) trial was an open-labeled randomized controlled trial that compared short-term TAT of 6 weeks with aspirin, clopidogrel, and warfarin with longer term TAT of 6 months [11•]. After 6 weeks in the short-duration arm, clopidogrel was discontinued and therapy with aspirin plus warfarin was continued for 6 months. A total of 607 patients were enrolled in this trial. The study was limited by only 9 months follow-up but showed no difference in MACE or bleeding endpoints between the short-duration or long-duration TAT arms. Notably, this trial suggested that even short-term TAT can lead to a high rate of bleeding (11.5%), as most bleeding events occurred in the first 6 weeks.

The use of NOACs at reduced doses or in DAT regimens has also been recently studied as another approach to mitigate bleeding risk in AF patients after PCI. The PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) trial was an open-labeled randomized controlled trial that enrolled 2124 patients into one of the three groups: rivaroxaban 15 mg daily (10 mg if creatinine clearance was between 30 and 50 ml/min) + P2Y12 inhibitor for 12 months (group 1), rivaroxaban 2.5 mg + aspirin + P2Y12 inhibitor for 1, 6, or 12 months (group 2) and warfarin + aspirin + P2Y12 inhibitor for 1, 6, or 12 months (group 3) [15••]. Most patients (94%) received clopidogrel, while the remainder received prasugrel or ticagrelor. The rates of clinically significant bleeding were much lower in the rivaroxaban arms compared to TAT arm with warfarin (16.8% group 1, 18.0% group 2, and 26.7% group 3). The efficacy end point of MACE was similar between the groups. Compared to TAT with warfarin, the number needed to treat to prevent one clinically significant bleed was 11 patients in the high-dose rivaroxaban DAT arm and 10 patients in the low-dose rivaroxaban TAT arm [21]. It is important to note that both rivaroxaban doses in this study are not the current clinically approved doses in the USA for prevention of thromboembolism in non-valvular AF.

More recently, the RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous

Coronary Intervention) trial was an open-labeled randomized controlled trial that enrolled 2725 patients into one of the three groups: DAT with dabigatran 150 mg twice daily along with clopidogrel or ticagrelor, DAT with dabigatran 110 mg twice daily along with clopidogrel or ticagrelor, and TAT with warfarin with aspirin and clopidogrel or ticagrelor [12••]. In elderly patients > 80 years in the USA and > 70 years in Japan, dabigatran dosing was limited to the 110 mg twice daily. In this trial, 88% of the patients received clopidogrel, while the remainder received ticagrelor. The mean follow-up period was 14 months. The incidence of TIMI major bleeding or clinically significant non-major bleeding was 15.4% in the dabigatran 110 mg DAT arm compared with 26.9% in the warfarin TAT arm, 20.2% in the dabigatran 150 mg DAT arm versus 25.7% in the warfarin TAT arm. The dabigatran 110 mg DAT arm was superior to warfarin TAT for reduction in major bleeding, while the dabigatran 150 mg DAT arm proved non-inferior to warfarin TAT. The number needed to treat to prevent one clinically significant bleeding episode compared to warfarin TAT was 9 patients for dabigatran 110 mg DAT and 18 for dabigatran 150 mg DAT. It is important to note that in the warfarin TAT arm, the duration of aspirin was only 1 to 3 months. The efficacy end point of MACE was similar between the groups. However, the number of myocardial infarctions and stent thromboses were numerically higher in the dabigatran 110 mg DAT arm. Notably, this difference was not statistically significant, though the study was underpowered for this end point. Dabigatran 110 mg dose is currently unavailable in the USA.

Meta-analyses and bivariate analyses of these clinical trials have shown a 47% reduction in major and minor bleeding with no statistically significant change in MACE when DAT is compared with TAT [14•, 22•, 23••].

Clinical trials are currently underway for apixaban DAT and edoxaban DAT in AF patients undergoing PCI [24•, 25•]. Table 1 summarizes the important clinical trials on antithrombotic therapy in AF patients undergoing PCI.

Current guidelines

Various guidelines have addressed the management of AF patients undergoing PCI. While the most recent US guidelines were published before the results of the PIONEER AF-PCI and the RE-DUAL PCI clinical trials were available, the European and Canadian guidelines were recently updated to include these data [4, 6••, 7, 26••, 27, 28]. A recent North American clinical consensus document by Angiolillo DJ et al. is also available [29••]. All guidelines recommend assessing the ischemic and bleeding risk for the patient and tailoring management according to individual risks. Minimizing the duration of TAT is also recommended. When warfarin is used, the dosage should be titrated for a goal INR in the lower portion of the target therapeutic range. Clopidogrel is the preferred P2Y12 inhibitor in AF patients who undergo PCI and receive OAC. Beyond 12 months post PCI, it is reasonable to continue OAC without any antiplatelet therapy. Routine use of proton pump inhibitors is strongly recommended in patients who are on TAT or DAT to minimize risk of GI bleeding. While the US guidelines last updated in 2014 recommended considering bare metal stent (BMS) use in AF patients undergoing PCI [4, 28], more contemporary data on second-generation drug-eluting stents (DES) show a reduction in MACE with DES compared to BMS [30, 31•]. The European guidelines now

Table 1. Comparison of Clinical Trials on Antithrombotic Therapy in Atrial Fibrillation Patients Undergoing Percutaneous Coronary Interventions#

Trial	Trial	Bleeding end point	Efficacy end point	Select baseline characteristics	Results by treatment arm			
WOEST[13]	573 patients VKA+C vs. VKA+A+C	Any bleeding	Death, MI, stroke, target-vessel revascularization, stent thrombosis	ACS 27.5% Ticagrelor 0% Prasugrel 0% DES 67.1%	**VKA+C arm** Bleeding 19.4% Efficacy 11.1%	**VKA+A+C** Bleeding 44.4% Efficacy 17.6%		Bleeding HR 0.36 (0.26–0.50, p < 0.0001) Efficacy HR 0.60 (0.38–0.94, p = 0.025)
ISAR-TRIPLE[11]	614 patients VKA+A+6 mon C vs. VKA+A+6 wk C	TIMI major or minor bleeding	Cardiac death, MI stent thrombosis or ischemic stroke	ACS 32.1% Ticagrelor 0% Prasugrel 0% DES 98.9%	**VKA+A+6wk C** Bleeding 11.5% Efficacy 4.0%	**VKA+A+6 mon C** Bleeding 9.9% Efficacy 4.3%		Bleeding 1.18 (0.73–1.93, p = 0.49) Efficacy HR 0.93 (0.43–2.05, p = 0.87)
PIONEER AF-PCI[15]	2124 patients VKA+A+P2Y12 inhibitor vs. rivaroxaban 2.5mg twice daily+A+P2Y12 inhibitor vs. rivaroxaban 15mg (or 10mg) daily+P2Y12 inhibitor	TIMI major or minor bleeding or requiring medical attention	Cardiac death, MI, or stroke	ACS 51.6% Ticagrelor 4.3% Prasugrel 1.3% DES 68.1%	**VKA+A+P2Y12 inhibitor** Bleeding 26.7% Efficacy 6.0%	**Rivaroxaban 2.5mg twice daily+A+P2Y12 inhibitor** Bleeding 18.0% Efficacy 5.6%	**Rivaroxaban 15mg daily+P2Y12 inhibitor** Bleeding 16.8% Efficacy 6.5%	Bleeding R2.5 vs. VKA 0.59 (0.47–0.76, p < 0.001) R15 vs. VKA 0.63 (0.50–0.80, p < 0.001) Efficacy R2.5 vs. VKA 1.08 (0.69–1.68, p = 0.75) R15 vs. VKA 0.93 (0.59–1.48, p = 0.76)
RE-DUAL PCI[12]	2725 patients VKA+A+P2Y12 inhibitor vs. dabigatran 110mg twice daily+P2Y12 inhibitor vs. dabigatran 150mg twice daily+P2Y12 inhibitor (No Prasugrel)	ISTH major or clinically relevant bleeding	Death, MI, stroke, systemic thromboembolism, or unplanned revascularization	ACS 50.5% Ticagrelor 12% DES 82.6%	**VKA+A+P2Y12 inhibitor** Bleeding 26.9% Efficacy 13.4%	**Dabigatran 110mg twice daily+P2Y12 inhibitor** Bleeding 15.4% Efficacy 15.2%	**Dabigatran 150mg twice daily+P2Y12 inhibitor** Bleeding 20.2% Efficacy 11.8%	Bleeding D110 vs. VKA 0.52 (0.42–0.63, p < 0.001) D150 vs. VKA 0.72 (0.58–0.88, p = 0.002) Efficacy D110 vs. VKA 1.13 (0.90–1.43, p = 0.30) D150 vs. VKA 0.89 (0.67–1.19, p = 0.44)
AUGUSTUS[25*]	4600 patients 4 groups VKA±A+P2Y12 inhibitor vs. apixaban 5mg (or 2.5mg) twice daily ±A+P2Y12 inhibitors	ISTH major or clinically relevant bleeding	Death or hospitalization, composite of death, MI, stroke, stent thrombosis, or urgent revascularization	N/A	N/A	N/A	N/A	N/A

Table 1. (Continued)

Trial	Trial	Bleeding end point	Efficacy end point	Select baseline characteristics	Results by treatment arm			
ENTRUST-AF PCI[24*]	1500 patients VKA+A+P2Y12 inhibitor vs. edoxaban 60mg (or 30mg) daily +P2Y12 inhibitor	ISTH major or clinically relevant bleeding	Cardiac death, MI, stroke, systemic thromboembolism, stent thrombosis	N/A	N/A	N/A	N/A	N/A

Key:
A Aspirin, *ACS* Acute Coronary Syndrome, *C* Clopidogrel, *D110* Dabigatran 110mg twice daily arm, *D150* Dabigatran 150mg twice daily arm, *DES* Drug Eluting Stent, *HR* Hazard Ratio, *ISTH* International Society of Thrombosis and Haemostasis, *MI* Myocardial Infarction, *mon* month, *N/A* Not Applicable, *R2.5* Rivaroxaban 2.5mg twice daily arm, *R15* Rivaroxaban 15mg daily arm, *TIMI* Thrombolysis In Myocardial Infarction, *VKA* Vitamin K Antagonists, *wk* week
[#]some clinical trials also included patients who were on anticoagulants for reason other than atrial fibrillation
[*]Currently in progress

recommend routine use of second-generation DES in all AF patients undergoing PCI [6••, 27]. Several ongoing trials of DES are currently examining shortening the timing of P2Y12 inhibition to 1–3 months in patients at high bleeding risk.

Clinical approach

For AF patients at risk for thromboembolism who undergo PCI, we recommend assessing ischemic risk and bleeding risk early to plan an appropriate antithrombotic strategy. Table 2 highlights various factors associated with high ischemic and bleeding risk.

Assessment of ischemic risk can be aided by the use of scoring systems such as the DAPT score, which have been validated in small cohorts of AF patients undergoing PCI [32]. A DAPT score of > 1 has been associated with higher ischemic risk. High bleeding risk can be assessed with the HAS-BLED and ATRIA risk scores, but these have not been well validated in AF patients undergoing PCI. Small studies have shown only a modest predictive capacity of the HAS-BLED score for identifying patients at risk of bleeding and overall mortality [33, 34]. There remains a need for developing better risk stratification schemes for identifying patients with higher bleeding risk with DAT and TAT.

In patients with high ischemic risk along with low bleeding risk, we recommend tailoring TAT for a duration of 1 to 6 months depending on the perceived ischemic risk, followed by DAT, preferably including rivaroxaban or dabigatran combined with clopidogrel until 12 months after PCI. We recommend clopidogrel as the P2Y12 agent of choice in TAT or DAT regimens until adequate data on the safety of ticagrelor are available. For patients with high ischemic and high bleeding risk, we recommend TAT for duration of 1 month followed by DAT including rivaroxaban or dabigatran combined with clopidogrel until 12 months post PCI. For patients with high bleeding risk and low ischemic risk, we recommend avoiding TAT

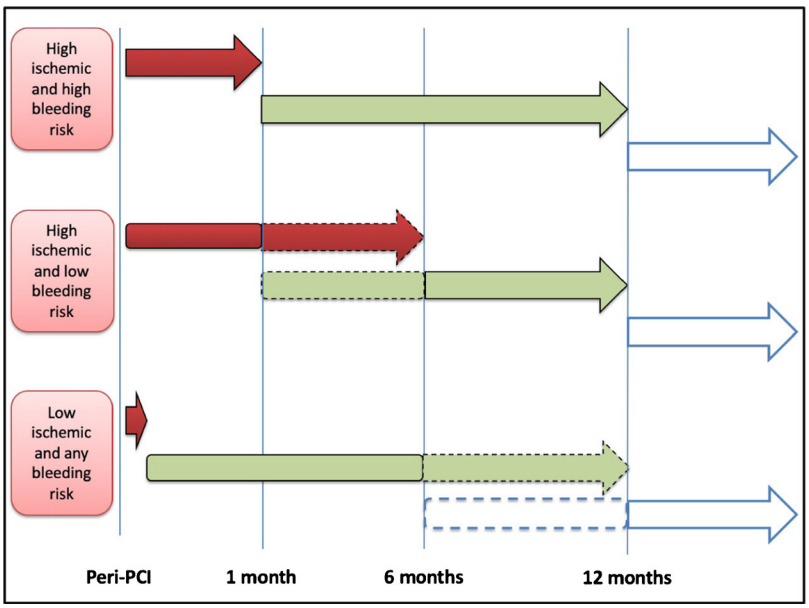
Table 2. Risk Factors for Ischemia and Bleeding

Risk factors for ischemia	Risk factors for bleeding
ACS on presentation	Age >65 years
Prior MI	CKD
Prior stent thrombosis	Prior major bleeding
Multivessel CAD	Labile INR
Multivessel PCI (>2)	Liver disease
Stent <3mm in diameter or >60mm in length	Other medications predisposing to bleeding (e.g., NSAIDS, Steroids)
Complex PCI (Bifurcation or CTO or vein grafts)	Alcohol abuse
Smoker	Malignancy
Diabetes	Frequent falls
CKD	Anemia

Key:
ACS Acute Coronary Syndrome, *CAD* Coronary Artery Disease, *CKD* Chronic Kidney Disease, *CTO* Chronic Total Occlusion, *INR* International Normalized Ratio, *MI* Myocardial Infarction, *NSAIDS* Non-Steroidal Anti-Inflammatory Drugs, *PCI* Percutaneous Coronary Intervention

completely and recommend using DAT with rivaroxaban or dabigatran combined with clopidogrel for 6 to 12 months post PCI. This would also be the default regimen for most AF patients who undergo PCI who do not have a high ischemic risk irrespective of their bleeding risk. After 6 to 12 months of DAT, we recommend stopping antiplatelet therapy and continuing OAC indefinitely. Figure 1 highlights the practical approach of antithrombotic therapy post PCI in AF patients.

We recommend using OAC in all AF patients at risk for thromboembolism undergoing PCI including those with high bleeding risk, as studies have shown mortality and MACE reduction with OAC even in high bleeding risk patients [35]. Regarding NOAC therapy, data are available with reduced dose rivaroxaban (15 mg daily in most patients and 10 mg daily in patients with CrCL of 30–50 ml/min) and dabigatran 150 mg BID. We recommend avoiding dabigatran 110 mg BID dosing as there was a non-statistically significant trend towards increased MACE in these patients [12••]. While it might not be unreasonable to continue using other NOACs such as apixaban and edoxaban in patients who were already taking these medications prior to PCI, we would caution against introducing them de novo post PCI, as the appropriate dose regimen in this scenario has not been studied. The AUGUSTUS and ENTRUST-AF PCI trials will shed more light on the



Key:
- Triple Antithrombotic therapy
- Dual Antithrombotic therapy
- Oral Anticoagulant only

Dotted lines represent an optional period up to the indicated duration where the therapy can be considered depending on the magnitude of the ischemic and bleeding risk.

PCI – Percutaneous Coronary Intervention

Fig. 1. Management of antithrombotic therapy in AF patients undergoing PCI.

use of these drugs in the near future. For patients who have a contraindication to NOAC use, it is reasonable to use warfarin, preferably as part of a DAT regimen.

Conclusion

AF patients who undergo PCI represent a unique clinical challenge. Balancing ischemic risk with bleeding risk is pivotal in selecting the optimal therapeutic strategy. With recent data on the risks of TAT and safety of DAT, most patients who do not have a high ischemic risk would likely benefit from DAT. Future areas of interest for research might include clinical trials studying more potent antiplatelet agents such as ticagrelor as part of TAT and DAT regimens, and also improved risk stratification for assessment of bleeding and ischemic risks in this population.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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