Article:
Sammut, M.A. and Storey, R.F. orcid.org/0000-0002-6677-6229 (2024) Antithrombotic therapy in patients with atrial fibrillation after percutaneous coronary intervention. Expert Review of Cardiovascular Therapy, 22 (9). pp. 471-482. ISSN 1477-9072

https://doi.org/10.1080/14779072.2024.2388265

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Expert Review of Cardiovascular Therapy

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ierk20

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To cite this article: Mark Anthony Sammut & Robert F Storey (2024) Antithrombotic therapy in patients with atrial fibrillation after percutaneous coronary intervention, Expert Review of Cardiovascular Therapy, 22:9, 471-482, DOI: 10.1080/14779072.2024.2388265

To link to this article: https://doi.org/10.1080/14779072.2024.2388265

Published online: 20 Oct 2024.

EXPERT REVIEW OF CARDIOVASCULAR THERAPY
2024, VOL. 22, NO. 9, 471–482
https://doi.org/10.1080/14779072.2024.2388265

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REVIEW

Antithrombotic therapy in patients with atrial fibrillation after percutaneous coronary intervention

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ABSTRACT

Introduction: Patients who undergo percutaneous coronary intervention (PCI) with stenting usually require a period of dual antiplatelet therapy (DAPT) but, when an indication for long-term oral anticoagulation (OAC) such as atrial fibrillation (AF) coexists, triple antithrombotic therapy (TAT) with DAPT and OAC causes concern for excessive bleeding. Achieving the right balance between bleeding and adequate protection from ischemic events remains an issue of debate and subject to ongoing investigation of various antithrombotic regimens and durations.

Areas covered: This review describes the landmark clinical trials comparing TAT to a period of dual antithrombotic therapy (DAT) and subsequent meta-analyses. It also describes the international recommendations that have been derived from this evidence and identifies outstanding issues that could be addressed in upcoming or future trials.

Expert opinion: The current recommended default strategy of a short period of TAT with clopidogrel followed by the withdrawal of aspirin faces a challenge from the prospect of more consistent $P2Y_{12}$ inhibition provided by ticagrelor and prasugrel. Ticagrelor monotherapy has already been trialed in patients after PCI without an indication for OAC. DAT with ticagrelor or prasugrel immediately post-procedure could emerge as a comparably safe and more efficacious regimen than one involving clopidogrel in the right setting.

ARTICLE HISTORY
Received 4 July 2024
Accepted 31 July 2024

KEYWORDS
Anticoagulation; antiplatelet therapy; antithrombotic therapy; atrial fibrillation; bleeding; clopidogrel; percutaneous coronary intervention; ticagrelor

1. Introduction

Coronary artery disease (CAD) and atrial fibrillation (AF) are both leading causes of morbidity and mortality worldwide [1]. Despite significant progress in management, their prevalence is rising due to aging populations and improved diagnostic capabilities [2,3]. Common comorbidities such as hypertension, diabetes mellitus, and obesity contribute to the pathophysiology of both conditions and therefore they are increasingly likely to coexist [4,5]. Approximately 17 to 46% of patients with AF have or will develop CAD, while 5 to 12% of patients undergoing percutaneous coronary intervention (PCI) have a history of AF [6,7].

Both conditions carry an increased risk of thrombosis but their mechanisms are notably different. CAD predisposes to thrombus formation under high shear conditions whereby disrupted atherosclerotic plaque exposes a thrombogenic surface, predominantly leading to platelet activation and aggregation that supports the production of fibrin through platelet procoagulant activity [8]. Treatment of CAD in an acute or chronic setting with drug-eluting stents during PCI may in itself promote activated platelet-led thrombosis [9]. Stent thrombosis is a rare complication of PCI (0.5–3%) but mortality can be as high as 45% [10]. The risk of stent thrombosis is curbed by the administration of antiplatelet agents while stent endothelialization takes place. Discontinuation of antiplatelet therapy, stent malapposition, underexpansion or undersizing, increased stent length and complex disease are all predictors of early stent thrombosis [10,11]. On the other hand, left atrial thrombus formation in AF occurs under low shear conditions in combination with elevated levels of procoagulants and has a higher percentage composition of fibrin than arterial thrombus [12–15].

These different mechanisms reflect the separate antithrombotic strategies for each condition. Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is recommended after PCI for acute or chronic coronary syndromes to prevent stent thrombosis and other ischemic events, while oral anticoagulation (OAC) is recommended for stroke prophylaxis in patients with AF and elevated risk [16,17]. A number of trials demonstrated superiority of DAPT (aspirin and ticlopidine) over anticoagulation and aspirin in preventing thrombotic and bleeding events after PCI [18–21]. Conversely, OAC was superior to DAPT (aspirin and clopidogrel) for prevention of ischemic events in patients with AF in the ACTIVE-W trial [22]. The perception of inadequate 'cross-cover' thus usually results in both DAPT and OAC being prescribed to patients with AF undergoing stenting. This combination, termed triple antithrombotic therapy (TAT), has raised concern due to an increased risk of bleeding [23,24]. Underlying this increased

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Article highlights

- The default antithrombotic management of patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) is derived from recent landmark trials and consists of triple antithrombotic therapy (TAT) with aspirin, clopidogrel and oral anticoagulation for up to a week followed by dual antithrombotic therapy (DAT) without aspirin for up to a year.
- Bleeding is reduced with DAT compared with TAT but differences in ischemic risk are less clear even among meta-analyses due to trial heterogeneity and predominant use of clopidogrel, which is known to provide inconsistent $P2Y_{12}$ inhibition.
- Aspirin-free strategies involving potent, consistent $P2Y_{12}$ inhibition with ticagrelor have already been trialed in the non-AF setting after PCI and DAT strategies with ticagrelor or prasugrel instead of clopidogrel appear promising in patients with AF.

bleeding risk is the fact that thrombin plays an important role in platelet activation, in addition to driving fibrin formation, and thus OAC has indirect or direct effects on platelet activation (Figure 1).

Since these trials that instigated the use of TAT, several advancements have been made in key aspects of PCI. First, continual improvements in stent technology and stent implantation techniques have reduced the minimum required duration of DAPT [26,27]. Second, the newer $P2Y_{12}$ inhibitors prasugrel and ticagrelor have demonstrated superior efficacy over clopidogrel for the management of acute coronary syndrome (ACS) in the TRITON-TIMI 38 and PLATO trials, respectively [28,29]. Third, direct-acting oral anticoagulants (DOACs) have demonstrated superiority over warfarin for reducing rates of stroke, other systemic embolism, mortality and intracranial hemorrhage (ICH) in patients with AF and have largely replaced it in most settings, excluding in the presence of mechanical heart valves or moderate/severe mitral stenosis [30]. The safety and efficacy of conventional TAT required challenging by alternative regimens. This review explores the evidence that has helped to inform our latest guidance on antithrombotic therapy after PCI in patients with AF and discusses future directions.

2. Randomized controlled trials

With the primary aim of reducing bleeding, different combinations and/or varying durations of antiplatelets and OACs have been compared with TAT consisting of aspirin, a $P2Y_{12}$ inhibitor and a vitamin K antagonist (VKA) in notable randomized controlled trials (RCTs) (Table 1, Figures 2 and 3).

2.1. Trials before the advent of direct-acting oral anticoagulants

The first of these was WOEST (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing), which recruited 573 patients on long-term OAC (all on a VKA) who underwent PCI [31]. AF was the clinical indication for OAC in 69% of patients. Patients were randomized in a 1:1 ratio to receive open-label clopidogrel alone or clopidogrel and aspirin after PCI, in addition to OAC. This was the first large RCT to compare dual antithrombotic therapy (DAT) with TAT. The primary endpoint was occurrence of any bleeding event at 1 year from PCI and classified according to various criteria: Thrombolysis in Myocardial Infarction (TIMI), Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) and Bleeding Academic Research Consortium (BARC). Secondary endpoints included death, myocardial infarction (MI), stroke, revascularization of the target vessel and stent thrombosis according to the Academic Research Consortium (ARC) criteria. Overall bleeding was lower on DAT compared with TAT (19.4 vs 44.4%; hazard ratio (HR) 0.36, 95% confidence interval (CI) 0.26–0.50; $p < 0.001$). However, rates of ICH were similar. There were also significantly less thrombotic events

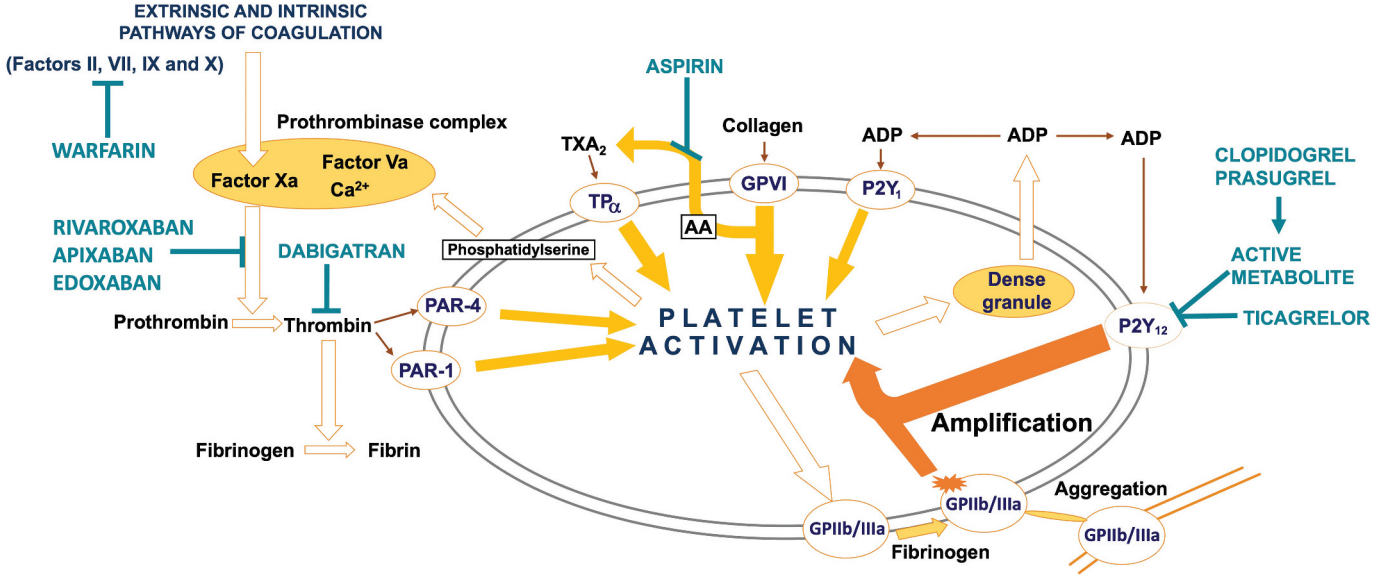

Figure 1. **Schematic of main thrombotic processes involved in platelet activation and antithrombotic drug targets** of particular note, thrombin acts as a potent platelet activator via PAR-1 and – 4. AA = arachidonic acid; ADP = adenosine diphosphate; Ca2+ = calcium; GP = glycoprotein; PAR = protease-activated receptor; TPα = thromboxane receptor α; T×A2= thromboxane A2. Modified with permission from reference [25].

Table 1. Summary of major RCTs involving patients with AF undergoing PCI on various regimens of DAT and TAT.

Trial name (year of publication	Participants	DAT regimen	TAT regimen	OAC of choice	$P2Y_{12}$ inhibitor of choice	Duration of therapy	Primary endpoint (bleeding)
WOEST (2013)	573	VKA + $P2Y_{12}$ inhibitor	VKA + $P2Y_{12}$ inhibitor + aspirin	Warfarin	100% clopidogrel	12 months	TIMI, GUSTO, BARC criteria bleeding (any)
PIONEER AF-PCI (2016)	2124	DOAC (low dose) + $P2Y_{12}$ inhibitor	VKA + $P2Y_{12}$ inhibitor + aspirin	Rivaroxaban or warfarin	94% clopidogrel, 6% ticagrelor or prasugrel	1, 6 or 12 months	TIMI major or minor criteria or bleeding requiring medical attention
RE-DUAL PCI (2017)	2725	DOAC (higher and lower dose) + $P2Y_{12}$ inhibitor	VKA + $P2Y_{12}$ inhibitor + aspirin	Dabigatran or warfarin	88% clopidogrel, 12% ticagrelor	12 months (aspirin discontinued after 1 or 3 months)	ISTH major or CRNM bleeding
AUGUSTUS (2019)	4614	DOAC or VKA + $P2Y_{12}$ inhibitor	DOAC or VKA + $P2Y_{12}$ inhibitor + aspirin	Apixaban or warfarin	93% clopidogrel, 7% ticagrelor or prasugrel	6 months	ISTH major or CRNM bleeding
ENTRUST-AF PCI (2019)	1506	DOAC + $P2Y_{12}$ inhibitor	VKA + $P2Y_{12}$ inhibitor + aspirin	Edoxaban or warfarin	92% clopidogrel, 8% ticagrelor or prasugrel	12 months (aspirin discontinued after 1-12 months)	ISTH major or CRNM bleeding

BARC = Bleeding Academic Research Consortium; CRNM = clinically-relevant non-major; DAT = dual antithrombotic therapy; DOAC = direct-acting oral anticoagulant; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; ISTH = International Society on Thrombosis and Hemostasis; OAC = oral anticoagulant; TAT = triple antithrombotic therapy; TIMI = Thrombolysis in Myocardial Infarction; VKA = vitamin K antagonist; ISAR-TRIPLE and the regimen of very-low-dose rivaroxaban, $P2Y_{12}$ inhibitor and aspirin in PIONEER AF-PCI were not considered for comparison.

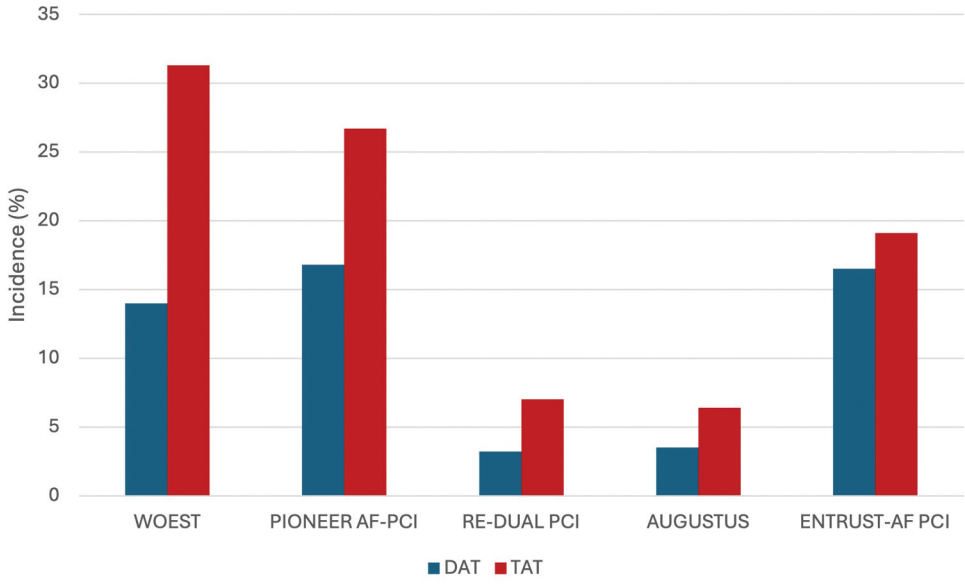

Figure 2. **Incidence of TIMI major and minor bleeding between dual antithrombotic therapy (DAT) and triple antithrombotic therapy (TAT) groups in major studies**. The group of patients receiving very-low-dose rivaroxaban in PIONEER AF-PCI was not included for comparison.

in the DAT group (composite secondary outcome 11.1 vs 17.6%; HR 0.60, 95% CI 0.38–0.94; $p = 0.025$).

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 investigated TAT duration through earlier cessation of the $P2Y_{12}$ inhibitor [32]. 614 patients on long-term OAC (AF in 84%) undergoing PCI were randomized to receive TAT with aspirin, clopidogrel and a VKA for 6 months or 6 weeks before discontinuing clopidogrel. At 9 months, there was no difference in the primary endpoint of death, MI, definite stent thrombosis, stroke or TIMI major bleeding between the shorter and longer TAT regimens (9.8 vs 8.8%; HR 1.14, 95% CI 0.68–1.91; $p = 0.63$). There was also no difference in TIMI bleeding alone. Landmark analysis between 6 weeks and 9 months demonstrated a reduction in BARC bleeding on DAT compared with TAT (20.5 vs 27.9%; HR 0.68, 95% CI 0.47–0.98; $p = 0.04$).

2.2. *Trials after the introduction of direct-acting oral anticoagulants*

PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Explorlng 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) was the first

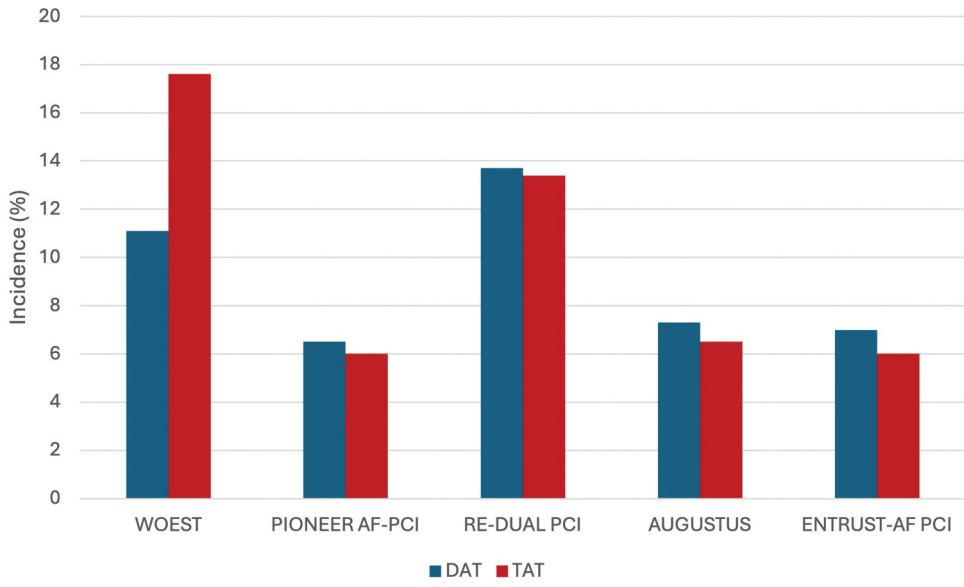

Figure 3. Incidence of the main efficacy endpoint (generally comprising of death, myocardial infarction, stroke, systemic thromboembolism and stent thrombosis) between dual antithrombotic therapy (DAT) and triple antithrombotic therapy (TAT) groups in major studies the group of patients receiving very-low-dose rivaroxaban in.

RCT to include patients on DOACs based on their emerging superiority over VKAs at the time [33]. 2124 patients with AF were randomized to one of three regimens within 72 hours of PCI: low-dose rivaroxaban and a $P2Y_{12}$ inhibitor for 12 months; very-low-dose rivaroxaban, a $P2Y_{12}$ inhibitor and aspirin for 1, 6 or 12 months; or warfarin, a $P2Y_{12}$ inhibitor and aspirin for 1, 6 or 12 months. The doses of rivaroxaban used in this trial are currently not approved for stroke prophylaxis in AF [34]. The primary endpoint was a composite of major or minor bleeding according to TIMI criteria or bleeding requiring medical attention. Secondary efficacy endpoints included the occurrence of a major adverse cardiovascular event (MACE) and stent thrombosis. Excluding the group on very-low-dose rivaroxaban, clinically significant bleeding occurred in 16.8% on DAT compared with 26.7% on TAT (HR 0.59; 95% CI 0.47–0.76; $p < 0.001$). Duration of TAT was ≥6 months in most patients. There were similar rates of MACE and stent thrombosis.

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) compared two doses of dabigatran (110 and 150 mg twice daily) and a $P2Y_{12}$ inhibitor with triple therapy consisting of warfarin, a $P2Y_{12}$ inhibitor and aspirin [35]. 2725 patients with AF were randomized to one of the three regimens within 120 hours of PCI and followed up for at least 6 months (mean 14). In patients receiving triple therapy, aspirin was discontinued after 1 month if treated with bare-metal stents or after 3 months if treated with drug-eluting stents. The primary endpoint was the first major or clinically-relevant non-major (CRNM) bleeding event according to the International Society on Thrombosis and Hemostasis (ISTH) criteria. Secondary efficacy endpoints included definite stent thrombosis and a composite of thromboembolic events, death or unplanned revascularization. Bleeding was lower in both DAT regimens compared with TAT (both HRs < 0.75, both $p < 0.01$). There were similar rates of thromboembolic events and stent thrombosis.

With its factorial design, AUGUSTUS (An Open-Label, 2 × 2Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban Versus Vitamin K Antagonist and Aspirin Versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) independently investigated two aspects of antithrombotic therapy: optimal OAC and the effect of aspirin [36]. 4614 patients with AF and recent ACS or PCI received a $P2Y_{12}$ inhibitor and were randomized to apixaban or VKA and to aspirin or placebo. AUGUSTUS also included patients with ACS who did not undergo PCI but were medically managed (23.9%). The primary outcome was major or CRNM bleeding according to ISTH criteria. Secondary efficacy endpoints included composites of death or hospitalization and death or ischemic events (stroke, MI, stent thrombosis or urgent revascularization). Less bleeding occurred with apixaban compared with VKA (10.5 vs 14.7%; HR 0.69, 95% CI 0.58–0.81; $p < 0.001$). More bleeding occurred with aspirin (TAT) compared with placebo (DAT) (16.1 vs. 9.0%; HR 1.89, 95% CI 1.59–2.24; $p < 0.001$). The combination of a VKA, $P2Y_{12}$ inhibitor and aspirin resulted in the highest number of bleeding events (18.7%) while DAT with apixaban and no aspirin resulted in the lowest (7.3%). There was a non-significantly higher incidence of ischemic cardiovascular events in patients not taking aspirin.

Completing the quartet of currently-approved DOACs, ENTRUST-AF PCI (EdoxabaN Treatment VersUS Vitamin K Antagonist in PaTients with Atrial Fibrillation undergoing Percutaneous Coronary Intervention) investigated the use of

edoxaban in antithrombotic regimens for this patient population [37]. 1506 patients were randomly assigned to a regimen of edoxaban and a $P2Y_{12}$ inhibitor (DAT) or VKA, a $P2Y_{12}$ inhibitor and aspirin (TAT) for 12 months. Aspirin was given for a variable duration at the investigator's discretion but for a minimum of 1 month. Randomization occurred between 4 hours and 5 days after PCI. The primary outcome was major or CRNM bleeding according to ISTH criteria. Secondary efficacy outcomes included stroke, MI, stent thrombosis and death. DAT was non-inferior but not superior to TAT with regards to bleeding events (17 vs 20%; HR 0.83, 95% CI 0.65–1.05). There was an unexpected, significantly lower number of bleeding events in the TAT group compared with DAT in the first 14 days since randomization, which may have been attributed to a high proportion of patients with subtherapeutic INR during this time. Similar rates of ischemic cardiovascular events were reported in both groups.

With the exception of ISAR-TRIPLE, all RCTs compared a regimen of DAT and TAT shortly after PCI but there were some important differences. First, WOEST and AUGUSTUS were the only two trials to compare strategies with the same OAC while the other three, as well as AUGUSTUS, compared a VKA with a DOAC. This means that the direct effect of eliminating aspirin from triple therapy can only be fully appreciated in WOEST and AUGUSTUS. Second, the bleeding criteria used to define the primary endpoint were different. Third, the secondary composite efficacy endpoints varied although they broadly included the same cardiovascular outcomes. With regards to stent thrombosis, RE-DUAL PCI only reported patients with definite stent thrombosis, WOEST, AUGUSTUS and ENTRUST-AF PCI reported patients with definite or probable stent thrombosis and PIONEER AF-PCI did not specify the category. All the studies were underpowered to detect a difference in efficacy outcomes owing to the much lower prevalence of ischemic events, compared with bleeding events, in current practice. Due to an average delay of a few days between PCI and the time of randomization, it is likely that most patients in these trials received a short period of TAT. Combined formal analysis was needed to better appreciate any disparity.

3. Meta-analyses

Lopes et al. conducted a network meta-analysis in 2019 to compare safety and efficacy outcomes of the antithrombotic strategies in the WOEST, PIONEER AF-PCI, RE-DUAL PCI and AUGUSTUS trials [38]. This was updated in 2020 to include ENTRUST-AF PCI and a total of 11,542 patients [39]. The primary safety outcome was TIMI major bleeding and the primary efficacy outcome was MACE as defined by each trial. The previous version reported a degree of heterogeneity among the studies, possibly resulting from the different OACs used, duration of therapy, duration of follow-up and other factors. The meta-analysis demonstrated that DAT, comprising a DOAC and a $P2Y_{12}$ inhibitor, conferred the lowest bleeding risk of all investigated regimens compared with TAT comprising of VKA and DAPT as a reference (odds ratio (OR) 0.52, 95% credible interval 0.35–0.79). No significant differences were reported in the MACE composite or in the individual thrombosis-related outcomes but the authors acknowledged the higher number of patients experiencing stent thrombosis when aspirin was not part of the regimen.

Another meta-analysis by Gargiulo et al. ($n = 10234$) excluded WOEST and the 709 patients on very-low-dose rivaroxaban in PIONEER AF-PCI, reporting similar findings to Lopes et al. related to bleeding risk [40]. However, it also demonstrated a borderline higher risk of MI and stent thrombosis on DAT compared with TAT (3.6 vs 3.0%; risk ratio (RR) 1.22, 95% CI 0.99–1.52; $p = 0.07$ and 1.0 vs 0.6%; RR 1.59, 95% CI 1.01–2.50; p=0.04 respectively). The concern about higher thrombotic risk on DAT was also highlighted in a meta-analysis by Galli et al., which had similar exclusions [41]. Subgroup analysis of patients who underwent PCI after ACS showed a significantly higher rate of MI with DAT compared to TAT (OR 1.43, 95% CI 1.02–2.0). DAT was also associated with an increased risk of stent thrombosis compared with TAT (OR 1.6, 95% CI 1.02–2.52) [41].

The subsequent meta-analysis by Capodanno et al. adds another twist to the tale. It used a different statistical approach to report no significant differences in MACE between DAT and TAT with VKA (HR 1.07, 95% CI 0.94–1.22) [42]. Trial sequential analysis suggested that future studies were unlikely to demonstrate any significant difference between the two investigated regimens regarding MACE (while conclusively demonstrating the superiority of DAT regarding bleeding risk). The contrasting results of these meta-analyses can potentially be explained by a degree of heterogeneity of patient cohorts and definition of outcomes such as stent thrombosis [43].

4. Temporal changes in ischemic and bleeding risk

Prothrombotic effects of the inflammatory response to ACS and/or PCI diminish and stent endothelialization improve over several weeks to months after PCI. These two factors contribute to a gradual reduction in ischemic risk after ACS and/or PCI, so maintaining appropriate balance with bleeding risk in regard to antithrombotic therapy must also take into account their relationship over time [44]. Analysis of 19,826 patients with ACS undergoing PCI from the RENAMI (REgistry of New Antiplatelets in patients with Myocardial Infarction) and BleeMACS (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome) registries demonstrated that the average daily ischemic risk (ADIR) was higher than the average daily bleeding risk (ADBR) in the first 2 weeks (ADIR-ADBR = 0.01%; $p = 0.01$) [45]. This was mostly observed in males, patients with incomplete revascularization, patients with ST-elevation MI and patients taking clopidogrel over other $P2Y_{12}$ inhibitors. Ischemic risk remained higher than bleeding risk until three months after ACS but bleeding risk was higher from months 4 to 12 (end of study) although both trends were nonsignificant. In this study, only 4.2% of patients were taking oral anticoagulation and no subgroup analysis was performed to account for this. The prevalence of AF in this cohort is also unclear.

Most studies have looked at ischemic and bleeding risk within the first 12 months after ACS and/or PCI. There is less clarity on antithrombotic treatment and ischemic/bleeding risk

beyond 1 year, but two RCTs have investigated this in patients with chronic coronary syndromes (CCS) [46,47]. OAC-ALONE (Optimizing Antithrombotic Care in Patients with Atrial Fibrillation and Coronary Stent) randomized patients with AF, stable CAD and >1 year since PCI to receive OAC monotherapy (VKA or DOAC) or DAT (OAC and aspirin or clopidogrel) [46]. The trial experienced slow recruitment and was prematurely terminated. It consequently did not reach sufficient power to demonstrate non-inferiority of OAC monotherapy to DAT for its primary endpoint, a composite of all-cause death, MI, stroke or systemic embolism at 1 year. The AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial included patients with AF who underwent PCI or coronary artery bypass grafting >1 year prior or had significant CAD (≥50% stenosis) confirmed on angiography but being treated medically [47]. 2236 patients were randomized to receive rivaroxaban monotherapy or DAT (rivaroxaban and aspirin or a $P2Y_{12}$ inhibitor). This trial was also terminated prematurely (median treatment duration of 23 months) on the grounds of increased mortality in the DAT group. For the primary efficacy endpoint, a composite of stroke, systemic embolism, MI, unstable angina requiring revascularization, or death from any cause, rivaroxaban monotherapy was non-inferior to DAT (4.14 vs 5.75% per patient-year; HR 0.72, 95% CI 0.55–0.95; $p < 0.001$ for non-inferiority). ISTH major bleeding was lower with rivaroxaban monotherapy compared with DAT (1.6 vs 2.8% per patient-year; HR 0.59, 95% CI 0.39–0.89; $p = 0.01$). Post hoc analysis demonstrated superior efficacy and safety in patients with a history of prior revascularization ($n = 1697$) [48]. One important consideration is that both trials were performed in an East Asian population which may have different ischemic and bleeding risk profiles to other populations [49]. The doses of rivaroxaban and prasugrel used in AFIRE were lower than those licensed in Europe and North America for their respective indications, limiting more widespread validity.

5. Current guidelines

The RCTs have had a major impact on recent European Society of Cardiology (ESC) and North American recommendations, especially with regards to duration of therapies. Barring some slight variation among guidelines for different conditions, the latest default recommended strategy for patients with AF after PCI is TAT for up to 1 week or until hospital discharge, followed by 12 months of DAT (single antiplatelet therapy and OAC), then lifelong OAC [16,17,50,51]. A DOAC is preferred over a VKA unless another indication is present, e.g. mechanical heart valve. For patients at high bleeding risk, a shorter duration of DAT and earlier switching to OAC alone is suggested. The ESC defines high bleeding risk as meeting ≥ 1 major or 2 minor criteria of the Academic Research Consortium for High Bleeding Risk (ARC-HBR) (Table 2) or a PRECISE-DAPT score ≥ 25 (score constituents: age, previous bleeding, white blood cell count, hemoglobin level and creatinine clearance) [16,52,53]. For patients at high ischemic risk, a longer duration of TAT (up to 1 month) can be considered. Based on trial and registry evidence, factors associated with higher risk of thrombosis include multivessel disease in patients with diabetes, length and number of stents, treatment of a chronic total occlusion, a history of stent thrombosis on adequate antiplatelet therapy and chronic kidney disease [16,51].

The guidelines recommend a $P2Y_{12}$ inhibitor over aspirin during DAT, with clopidogrel being the agent of choice because of its high representation in the trials (>90%). The number of patients receiving the more potent $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) was small in the RCTs but the latest ESC guidelines on CCS issued a weak (Class IIb) recommendation for their combination with OAC in DAT when there is moderate or high risk of stent thrombosis [51]. This recommendation is suggested as an alternative to TAT with aspirin, clopidogrel and OAC. The latest ESC guidelines on ACS simply cite limited trial evidence and have in fact removed a similar Class IIb recommendation for DAT with ticagrelor or prasugrel present in the previous version [16,54]. The combination of ticagrelor or prasugrel with aspirin and OAC is not recommended due to higher bleeding risk as reported in small retrospective studies and RCT subgroup analysis [55–57].

6. Future directions

The latest guidelines are comprehensive and based on recent important RCTs but gaps in the evidence continue to fuel debate.

Table 2. Academic research consortium for high bleeding risk criteria for high bleeding risk.

Major criteria	Minor criteria
Anticipated use of long-term OAC	Age ≥75 years
Severe chronic kidney disease	Moderate chronic kidney disease
Hemoglobin <11 g/dL	Hemoglobin 11-12.9 g/dL for men or 11-11.9 g/dL for women
Spontaneous bleeding requiring hospitalization and/or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalization and/or transfusion within the past 12 months not meeting the major criterion
Moderate or severe baseline thrombocytopenia	Chronic use of non-steroidal anti-inflammatory drugs or steroids
Chronic bleeding diathesis	Any ischemic stroke at any time not meeting the major criterion
Liver cirrhosis with portal hypertension	
Active malignancy within the past 12 months (excluding non-melanoma skin cancer)	
Previous spontaneous ICH	
Previous traumatic ICH within the past 12 months	
Presence of a cerebral arteriovenous malformation	
Moderate or severe ischemic stroke within the past 6 months	
Recent major surgery or major trauma within 30 days prior to PCI	
Non-deferrable major surgery on DAPT	

DAPT = dual antiplatelet therapy; ICH = intracranial hemorrhage; OAC = oral anticoagulant; PCI = percutaneous coronary intervention.

6.1. What is the role of aspirin in triple antithrombotic therapy?

The relevance of aspirin in a DAPT regimen after PCI outside the context of AF is already being challenged in favor of earlier single antiplatelet therapy with a sufficient regimen of a potent $P2Y_{12}$ inhibitor [26,58–61]. GLOBAL LEADERS (A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation) was a large trial ($n = 15968$) that compared 1 month of DAPT (aspirin and ticagrelor), followed by 23 months of ticagrelor monotherapy, with 12 months of DAPT (aspirin and ticagrelor or clopidogrel) followed by 12 months of aspirin monotherapy after PCI for ACS or CCS [62]. There was no significant difference in the primary composite outcome of death or new Q-wave MI at 24 months and similar rates of bleeding. Non-inferiority was demonstrated in the GLOBAL LEADERS Adjudication Sub-StudY (GLASSY) analysis involving central adjudication of investigator-reported outcomes [63]. The TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial demonstrated that, after 3 months of event-free DAPT with aspirin and ticagrelor in high-risk patients undergoing PCI, bleeding was reduced over a further 12 months on ticagrelor monotherapy compared with aspirin and ticagrelor, while the composite endpoint of death, non-fatal MI and non-fatal stroke was similar [64]. Meta-analyses including these two RCTs and others highlight the safety of early aspirin discontinuation (after 1–3 months) and comparable efficacy to prolonged DAPT [65,66]. These outcomes may be supportive of even earlier aspirin discontinuation in the presence of OAC for AF but additional considerations come into play.

The default duration of TAT is up to 1 week or hospital discharge, based on most patients likely having received it for some time before randomization in the discussed trials (mean 6.6 days in AUGUSTUS). Landmark analysis of RE-DUAL PCI, which had a much shorter mean time to randomization of 1.6 days, suggested that the observed benefits of DAT over TAT could be achieved even if aspirin is stopped earlier, i.e. immediately post-PCI [67]. However, landmark analysis of ENTRUST-AF PCI reported a reduced composite endpoint of ischemic and bleeding outcomes in the first 14 days with TAT, which may argue in its favor over DAT for this length of time after PCI [68]. A landmark analysis of AUGUSTUS showed that, from randomization to day 30, there were roughly as many excess bleeding events on aspirin (TAT) as there were excess ischemic events on placebo (DAT). With 80% of definite or probable stent thrombosis events in the trial occurring within the first 30 days from PCI, this trade-off would seem to favor TAT [44,69]. Therefore, the question about how long to give aspirin for, if at all, remains in equipoise.

6.2. Is there a role for tailoring antithrombotic regimens?

The factors that could best identify patients more likely to benefit from DAT or TAT in this particular population need clearer definition. Various subgroup analyses have been performed on the individual RCTs. High PRECISE-DAPT and HAS-BLED scores were predictive of increased bleeding [68,70]. Interestingly, increasing CHA_2DS_2-VASc score was associated with both higher bleeding and higher incidence of stent thrombosis in ENTRUST-AF PCI, the latter regardless of treatment regimen [68]. Separate analysis of each trial showed no difference in ischemic outcomes between DAT and TAT regardless of the setting in which patients underwent PCI (ACS or CCS), in contrast to the meta-analysis by Galli et al. [41,57,71–73]. Similarly, procedural complexity did not appear to have a significant impact on ischemic outcomes in either DAT or TAT groups, although these results should be interpreted with caution due to low numbers [73,74].

6.3. What is the role of ticagrelor and prasugrel in dual antithrombotic therapy regimens?

The guidelines recommend clopidogrel as the default $P2Y_{12}$ inhibitor to use in combination with OAC but both ticagrelor and prasugrel are known to achieve more potent and consistent platelet inhibition [75–78]. The concern shared by some meta-analyses about the increased risk of thrombotic events on DAT compared with TAT may be offset by the use of ticagrelor or prasugrel instead of clopidogrel. Trials reflecting more contemporary $P2Y_{12}$ inhibitor use are needed but powering one to detect significant differences in events with low incidence such as stent thrombosis would likely require very large numbers of patients. Nevertheless, the safety of DAT with ticagrelor or prasugrel should be explored more thoroughly in such studies at the least. Preliminary observational data suggest acceptable rates of bleeding with DAT combined with ticagrelor or prasugrel as well as no ischemic penalty when aspirin is stopped immediately after PCI in selected patients, supporting the rationale for RCTs incorporating such regimens [79].

7. Upcoming trials

Over the next few years, we expect to see results from a number of ongoing RCTs that aim to address the aforementioned lingering questions on antithrombotic therapy in patients with AF after PCI through a variety of combinations (Table 3). Most trials are now including DAT with more potent $P2Y_{12}$ inhibitors as a direct comparator arm and focusing on patients with ACS.

The APPROACH-ACS-AF trial (NCT02789917) has recruited patients with AF undergoing PCI for ACS and randomized them to receive DAT with clopidogrel and apixaban or TAT with aspirin, clopidogrel and VKA. The EPIDAURUS trial (NCT04981041) is currently randomizing patients after PCI to receive DAT with ticagrelor/prasugrel and a DOAC for the first month before deescalating the $P2Y_{12}$ inhibitor to clopidogrel or standard DAT with clopidogrel and a DOAC straight away. Meanwhile, the ADONIS-PCI trial (NCT04695106) is randomizing to DAT with ticagrelor (90 mg twice daily for the first month, then 60 mg twice daily) and dabigatran for 12 months or TAT with aspirin, clopidogrel and dabigatran for a variable length of time depending on ACS type, ischemic and bleeding

Table 3. Upcoming randomized controlled trials on antithrombotic therapy in patients with non-valvular atrial fibrillation undergoing percutaneous coronary intervention.

Trial name	Estimated number of participants	PCI indication	Experimental group	Standard or control group	Primary outcome	Estimated completion
ADONIS-PCI (NCT04695106)	2230	ACS only	DAT (ticagrelor + dabigatran) for 12 months N.B. Ticagrelor 90 mg BID for 1 month, then 60 mg BID	TAT (aspirin + clopidogrel + dabigatran) – duration dependent on bleeding and ischemic risk, then DAT (clopidogrel + dabigatran) up to 12 months	ISTH major or CRNM bleeding at 24 months	2026
APPROACH-ACS-AF (NCT02789917)	403	ACS only	DAT (clopidogrel + apixaban) for 6 months	TAT (aspirin + clopidogrel + phrenprocoumon) for 6 months N.B. Aspirin for 1 month only if HAS-BLED score ≥ 3	BARC type ≥ 2 bleeding at 6 months	Completed, awaiting results
EPIDAURUS (NCT04981041)	2334	ACS only	DAT (prasugrel/ticagrelor + DOAC) for 1 month, then standard DAT (clopidogrel + DOAC)	DAT (clopidogrel + DOAC)	Safety: BARC type ≥ 2 bleeding at 6 weeks Efficacy: composite of mortality, MI, definite or probable ST, ischemic stroke and systemic thromboembolism at 6 weeks	2025
MATRIX-2 (NCT05955365)	3010	ACS and CCS (receiving Supraflex Cruz stent)	$P2Y_{12}$ monotherapy for 1 month, then DOAC monotherapy for 11 months	TAT (aspirin + $P2Y_{12}$ inhibitor + DOAC) up to 1 month, then DAT ($P2Y_{12}$ inhibitor + DOAC) up to 12 months	Safety: ISTH major or CRNM bleeding at 12 months Efficacy: composite of mortality, MI, stroke and systemic thromboembolism at 12 months	2026
OPTIMA-4 (NCT03234114)	1472	ACS only	DAT (ticagrelor + DOAC) for 12 months	DAT (clopidogrel + DOAC) for 12 months	Safety: ISTH major or CRNM bleeding at 12 months Efficacy: composite of CV death, MI, ischemic stroke, systemic thromboembolism and unplanned revascularization at 12 months	2024
WOEST-3 (NCT04436978)	2000	ACS and CCS	DAPT (aspirin + $P2Y_{12}$ inhibitor) for 1 month, then DAT ($P2Y_{12}$ inhibitor + edoxaban)	TAT (aspirin + $P2Y_{12}$ inhibitor + edoxaban) up to 1 month, then DAT ($P2Y_{12}$ inhibitor + edoxaban)	Safety: ISTH major or CRNM bleeding at 6 weeks Efficacy: composite of mortality, MI, ST, stroke and systemic thromboembolism at 6 weeks	2027

ACS = acute coronary syndrome; BARC = Bleeding Academic Research Consortium; BID = bis in die (twice daily); CCS = chronic coronary syndrome; CRNM = clinically-relevant non-major; CV = cardiovascular; DAT = dual antithrombotic therapy; DAPT = dual antiplatelet therapy; DOAC = direct-acting oral anticoagulant; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol; ISTH = International Society on Thrombosis and Hemostasis; MI = myocardial infarction; ST = stent thrombosis; TAT = triple antithrombotic therapy.

risk followed by DAT. OPTIMA-4, a sub-study of the larger OPTIMA-3,4 trial (NCT03234114) is directly comparing DAT with dabigatran and ticagrelor/prasugrel or clopidogrel after PCI for 12 months.

Some less conventional approaches that omit OAC just after PCI are also being investigated. The WOEST-3 trial (NCT04436978) is enrolling patients to receive TAT or DAPT for the first month after PCI followed by DAT without aspirin thereafter. The primary safety and efficacy endpoints will look at events up to 6 weeks after randomization. The MATRIX-2 trial (NCT05955365) appears to be going a step further by exploring antithrombotic monotherapy in patients with AF receiving a Supraflex Cruz sirolimus-eluting biodegradable polymer stent: Standard TAT (aspirin up to 1 month) will be compared with a regimen consisting of $P2Y_{12}$ monotherapy for the first month followed by DOAC monotherapy for 11 months.

8. Conclusion

At present, when deciding on the optimal antithrombotic regimen for patients with AF after PCI, the balance between early ischemic and bleeding complications mainly hinges on the duration of post-procedure aspirin. A default strategy of TAT for 1 week or less followed by DAT with clopidogrel aims to minimize the bleeding risk but concerns about stent thrombosis and other ischemic events, albeit rare, persist. The now-widespread use of superior $P2Y_{12}$ inhibitors looks set to challenge the current status quo with greater inclusion in ongoing RCTs that may result in stronger recommendations for the cessation of aspirin and replacement of clopidogrel by ticagrelor or prasugrel immediately after PCI.

9. Expert opinion

Most of the current evidence concerning cessation of aspirin and use of DAT in AF patients following PCI revolves around the use of clopidogrel in combination with a DOAC. However, the higher risk of stent thrombosis in patients with poor pharmacodynamic response to clopidogrel is well established and so this dual antithrombotic strategy is suboptimal since, even with knowledge of *CYP2C19* genotype, the pharmacodynamic response to clopidogrel cannot be confidently predicted for an individual patient. Consequently, using

clopidogrel in DAT may be inadequate for prevention of stent thrombosis if a patient has a poor pharmacodynamic response, whereas using clopidogrel in TAT, even for a short period, may incur unacceptable bleeding risk if the patient has a good pharmacodynamic response. On the other hand, there are limited data on the safety of DAT with ticagrelor or prasugrel in combination with a DOAC, although preliminary observational data are encouraging and results from a small cohort of ticagrelor-treated patients in the AUGUSTUS study did not raise major safety concerns [79,80]. This makes further studies of DAT with ticagrelor or prasugrel a promising avenue for further research.

Indeed, studies of ticagrelor monotherapy early after PCI provide further encouragement that aspirin may not be necessary in many patients when a predictably high level of platelet $P2Y_{12}$ inhibition is achieved. In addition to the strength of available evidence for ticagrelor monotherapy, a major advantage of using ticagrelor is that it is not a pro-drug and achieves the most consistently high level of platelet inhibition during maintenance therapy out of all the available oral $P2Y_{12}$ inhibitors. Predictability of response avoids the need for pharmacodynamic testing in order to individualize therapy (a concept that applies equally to aspirin maintenance therapy, which achieves very predictable platelet inhibition, albeit limited to COX-1-dependent pathways). Avoidance of aspirin immediately after PCI was associated with a signal of increased thrombotic risk when a low-dose regimen of prasugrel was used as monotherapy but this was somewhat predictable given the expected interindividual variability of response to this prasugrel regimen that makes it poorly suited to a monotherapy strategy, in distinction to the much more consistent level of platelet inhibition associated with a standard regimen of ticagrelor [26]. However, there is very limited experience with immediate cessation of aspirin after PCI in patients treated with ticagrelor, other than in those also receiving a DOAC, which targets a second pathway of platelet activation via thrombin (Figure 1).

In terms of the appropriate DOAC to use alongside antiplatelet therapy, the pharmacokinetic profiles of the available oral Xa inhibitors point to a preferred option of using a twice-daily rather than once-daily regimen in order to avoid excessive peaks and troughs of anti-Xa levels that might contribute to bleeding and suboptimal inhibition of thrombin generation, respectively. It makes pharmacological sense to ensure more sustained anti-Xa effect over a 24-hour period in order to maintain indirect inhibition of thrombin-induced platelet activation that could contribute to stent thrombosis risk. Indeed, using a once-daily DOAC regimen combined with clopidogrel in a DAT regimen seems a risky strategy since a poor responder to clopidogrel would have very little antithrombotic effect at 24 hours after the last dose of DOAC, particularly in those with good renal function.

Finally, every patient has their individual risks of stent thrombosis, other thrombotic events and bleeding, requiring careful balancing of these risks and consideration of the most appropriate antithrombotic regimen and its duration after PCI. Patients undergoing PCI following type-1 MI may have higher risk of further atherothrombotic events related to residual atherothrombotic risk that requires more prolonged dual antithrombotic therapy compared to those undergoing PCI for CCS. The greater mean age of patients with AF not only is associated with higher bleeding risk but also increases the likelihood of coronary calcification, which in turn increases the risk of stent thrombosis, and this may require consideration of non-stent PCI techniques, such as drug-eluting balloon angioplasty, in order to limit the intensity and duration of combination antithrombotic regimens.

Acknowledgments

The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Funding

MA Sammut and RF Storey are supported by the National Institute for Health and Care Research (NIHR) Sheffield Biomedical Research Centre [NIHR203321].

Declaration of interest

RF Storey has received research grants and personal fees from AstraZeneca and Cytosorbents, and personal fees from Alfasigma, Chiesi, Daiichi Sankyo, Idorsia, Novartis, Novo Nordisk, Pfizer, PhaseBio, and Tabuk. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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