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Review

Triple therapy: A review of antithrombotic treatment for patients with atrial fibrillation undergoing percutaneous coronary intervention

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ABSTRACT

In patients with atrial fibrillation (AF), concomitant coronary artery disease is often present, and vice versa. Optimal antithrombotic treatment for patients with AF undergoing percutaneous coronary intervention (PCI) is one of the major concerns in the field of cardiology. Triple therapy, a combination of oral anticoagulant (OAC) plus dual antiplatelet therapy with aspirin and $P2Y_{12}$ inhibitor, has been used for patients with AF undergoing PCI in recent decades to reduce ischemic events under guideline recommendations. However, triple therapy is well-known to induce severe bleeding events. Recently, the results of several clinical trials have been published, and the latest guidelines recommend that most patients should undergo dual therapy (i.e. OAC plus $P2Y_{12}$ inhibitor) from the beginning of PCI, or triple therapy only peri-PCI period and immediately shift to dual therapy after hospital discharge. Although these recommendations are useful and appear to be reasonable, no studies have validated this. In addition, there are a number of unresolved issues regarding the antithrombotic treatment for patients with AF undergoing PCI such as risk prediction models and the best combination of OAC with antiplatelet agents, and prospective trials are ongoing. This review article will summarize current evidence and focus on the optimal regimen of antithrombotic treatment for patients with AF undergoing PCI.

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Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia and induces ischemic stroke and other cardiovascular events, with an increasing prevalence with age [1]. In patients with AF, concomitant coronary artery disease (CAD) is often present, and vice versa. Approximately 30% of patients with AF are found to have CAD, of whom up to 15% will require percutaneous coronary intervention (PCI) during their lifetime [2]. Of course, patients with CAD undergoing PCI are also high-risk for subsequent cardiovascular events, thus antithrombotic treatment is needed. On the other hand, 5–8% of patients undergoing PCI have concomitant AF and an additional indication for oral anticoagulation (OAC) [3,4]. Antithrombotic treatment, consisting of anticoagulant and antiplatelet agents, is evident to improve clinical outcomes in patients with AF or CAD, however, has become increasingly complex in subjects with both AF and CAD, especially in those who undergo PCI. Which agents and how long should the physicians prescribe? Recently,

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several randomized controlled trials (RCT) have been reported, and the guidelines of antithrombotic treatment for these patients have dramatically changed. This review article will summarize current evidence and focus on the optimal regimen of antithrombotic treatment for patients with AF undergoing PCI.

Clinical trials and guideline recommendations

Since the STARS (STent Anticoagulation Restenosis Study) and others demonstrated that dual antiplatelet therapy (DAPT) with aspirin plus $P2Y_{12}$ inhibitor is associated with reduced risk of death and subsequent myocardial infarction (MI) including stent thrombosis, DAPT has been the cornerstone of antithrombotic management for CAD patients undergoing PCI [5,6]. In contrast, among patients with AF, OAC using vitamin K antagonist (VKA) (e.g. warfarin) is superior to DAPT in reducing the risk of cardiovascular events [1], although OAC is not necessarily indicated for all AF patients (e.g. low-risk, young subjects). Therefore, triple therapy, a combination of OAC plus DAPT with aspirin and $P2Y_{12}$ inhibitor, has been recognized as being 'theoretically' necessary and 'empirically' recommended for patients with AF undergoing PCI by guidelines against this background. However, there was no evidence form RCTs which test the efficacy of the combination therapy. On the other hand, triple therapy has been well-known to induce severe bleeding events [7].

Here, we describe the history of guideline recommendations of antithrombotic treatment for patients with AF undergoing PCI (Fig. 1). For the first time, the 2010 European Society of Cardiology (ESC) consensus document recommended triple therapy, including VKA, aspirin, and clopidogrel in patients with AF undergoing PCI for as short a period as possible [8], which was based on expert opinions and not on RCTs. Thereafter, the 2014 North American guidelines for AF suggested considering dual antithrombotic treatment consisting of OAC plus clopidogrel but without aspirin as an alternative to triple therapy with Class IIb, Level of Evidence: B recommendation [9], according to the WOEST (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) trial [10]. The WOEST trial was an open-label RCT in 573 patients receiving warfarin and undergoing PCI (69% of indication for OAC was AF), and the first study to successfully demonstrate that omitting aspirin from the traditional triple therapy regimen (i.e. warfarin plus DAPT with aspirin and clopidogrel) was associated with a significant reduction in Thrombolysis In Myocardial Infarction (TIMI) bleeding events at one year (19.4% vs. 44.4%, $p < 0.0001$). Surprisingly, although the study was not powered to find differences in the thrombotic events, the secondary endpoint defined as a composite of death, MI, stroke, systemic embolism, target vessel revascularization, and stent thrombosis was also better in the patients receiving dual therapy (i.e. warfarin plus clopidogrel) compared to the triple therapy (11.1% vs. 17.6%, $p = 0.025$) [10]. There has been some criticism of the study because the difference in the primary endpoint was mainly driven by TIMI minor bleeding, and the event rate was quite high due to the long duration of triple therapy (i.e. 12 months). However, the WOEST trial had a great impact on the antithrombotic regimen in patients with AF undergoing PCI, and have changed the guidelines with following RCTs, including ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation), 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), and RE-DUAL PCI trial (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) [3,11,12]. Of note, in the 2014 North American updated guidelines, VKA rather than direct oral anticoagulant (DOAC) was recommended as the first-choice therapy in AF patients with acute coronary syndrome (ACS) [9]. Subsequently, the 2015 ESC guidelines for non-ST segment elevation myocardial infarction (NSTEMI) indicated that prasugrel or ticagrelor as a part of triple therapy should be avoided due to the absence of safety and efficacy data (Class III, Level of Evidence: C) [13]. It is conceivable that prasugrel and ticagrelor are more potent, whereas clopidogrel may be the safest $P2Y_{12}$ inhibitors as a part of triple therapy because of the lowest bleeding risk among the 3 drugs [14]. Importantly, if VKA is used as a part of triple therapy, the guidelines recommended a target international normalized ratio (INR) of 2.0–2.5 (with the exception of patients with mechanical prosthetic valves in the mitral position). On the other hand, if DOAC is used, the lowest tested dose for stroke prevention should be applied [13].

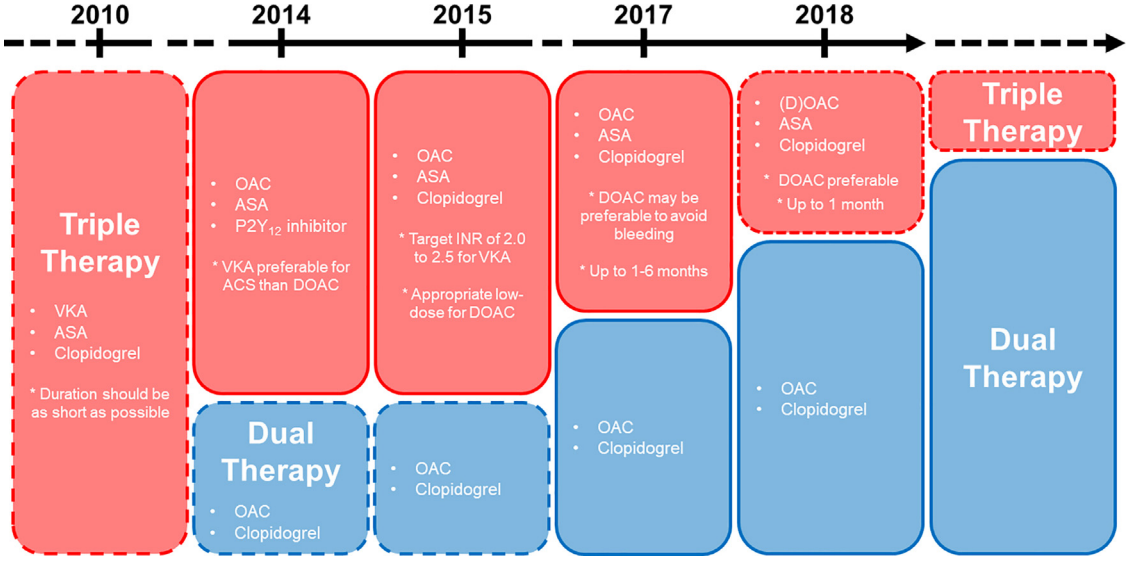

Fig. 1. History of guideline recommendations for triple therapy vs. dual therapy in patients with AF undergoing PCI. ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, aspirin; DOAC, direct oral anticoagulant; INR, international normalized ratio; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist.

In summer 2017, ESC focused update was published on DAPT in CAD [15]. The new guideline recommended triple therapy for 1 month or up to 6 months after PCI, depending on patient characteristics (i.e. ischemic and bleeding risks) [15], according to the ISAR-TRIPLE trial [11]. Several scoring systems were provided to determine ischemic and bleeding risks such as CHA_2DS_2-VASc [Cardiac failure, Hypertension, Age ≥75 years, Diabetes, Stroke–Vascular disease, Age 65–74 years, Sex category], HAS-BLED [Hypertension, Abnormal renal and liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs and alcohol], and ABC [Age, Biomarkers (GDF-15, cTnT-hs, and hemoglobin), and Clinical history (previous bleeding)] scores, and others (Fig. 2). However, there is considerable overlap among risk factors associated with ischemic and bleeding outcomes, and none of the risk predicting models has been prospectively tested in the prospective RCTs, especially in triple therapy settings. Thus, it remains unclear that these scoring systems could discriminate patient ischemic and bleeding risks and improve outcomes in patients with AF undergoing PCI [15]. The 2017 ESC focused update also reinforced recommendation to omit aspirin as a part of triple therapy (i.e. clopidogrel plus OAC) especially in patients in whom the bleeding risk outweighs the ischemic risk (Class IIa, Level of Evidence: A), based on the WOEST and PIONEER AF-PCI trial [3,10]. Note that only low- and very-low-dose rivaroxaban were tested in the PIONEER AF-PCI trial, which were not applied for stroke prevention, and thus these doses of rivaroxaban were not recommended in clinical practice to date, although the guideline indicated the low dose as an alternative to regular dose of rivaroxaban (Class IIb, Level of Evidence: B) [3,15]. The RE-DUAL PCI trial, published following the updated guideline and testing regular doses of dabigatran (i.e. 110 or 150 mg bid), showed similar results to the PIONEER AF-PCI trial, in which dual therapy with dabigatran plus $P2Y_{12}$ inhibitors was superior to triple therapy consisting of warfarin, aspirin, and $P2Y_{12}$ inhibitors in terms of major bleeding in patients with AF undergoing PCI [12]. The new guideline mentioned the consideration to use DOAC instead of VKA to avoid bleeding complications, whereas if VKA is used, a time in the therapeutic range >65–70% is recommended. In addition, routine use of proton pump inhibitors is suggested to prevent gastrointestinal bleeding during DAPT or triple therapy [15].

The most recently, updated recommendations from Europe and North America regarding antithrombotic treatment for patients with AF undergoing PCI were both published in July 2018 [16,17]. The latest European recommendation was basically similar to the 2017 update. In the North American perspectives published as a white paper, most patients were proposed to undergo triple therapy only during the peri-PCI period, and immediately shift to dual therapy (i.e. OAC plus $P2Y_{12}$ inhibitor) after hospital discharge, except for those at high ischemic and low bleeding risks. The term "peri-PCI" (i.e. during hospitalization for PCI) as a novel triple therapy duration is noteworthy. In addition, recommended triple therapy duration has been revised up to 1 month.

In summary, current guidelines recommendations of triple therapy for patients with AF undergoing PCI are as follows: (1) the duration of triple therapy should be as short as possible (i.e. for only peri-PCI period or up to 1 month) based on patient ischemic and bleeding risks, (2) dual therapy with clopidogrel plus OAC is an alternative to triple therapy in patients in whom the bleeding risk outweighs the ischemic risk, (3) DOAC with the lowest tested dose for stroke prevention may have to be used instead of VKA to avoid bleeding complications, and (4) a lower target INR of 2.0–2.5 with sufficient time in the therapeutic range is needed if VKA is used.

Which agents and how long?

Triple therapy comprised two antiplatelet agents and one OAC, and antiplatelet therapy should be aspirin plus clopidogrel. Although prasugrel and ticagrelor are the candidates as a part of triple therapy, these two novel drugs appear to be more potent by platelet function testing and clinical trials [14,18]. One observational study regarding triple therapy showed that patients who received prasugrel instead of clopidogrel had a significant 3-fold increased risk of TIMI major or minor bleeding without differences in ischemic endpoints during 6 months of follow-up despite small sample size [4]. Patients with triple therapy are exposed to high bleeding risk, thus, using novel $P2Y_{12}$ inhibitors (i.e. prasugrel and ticagrelor) as a part of triple therapy is not recommended.

On the other hand, there is still room for consideration of OAC. Recently, DOAC use has been rapidly and dramatically increased for patients with AF [19]. However, the impact of DOAC in the setting

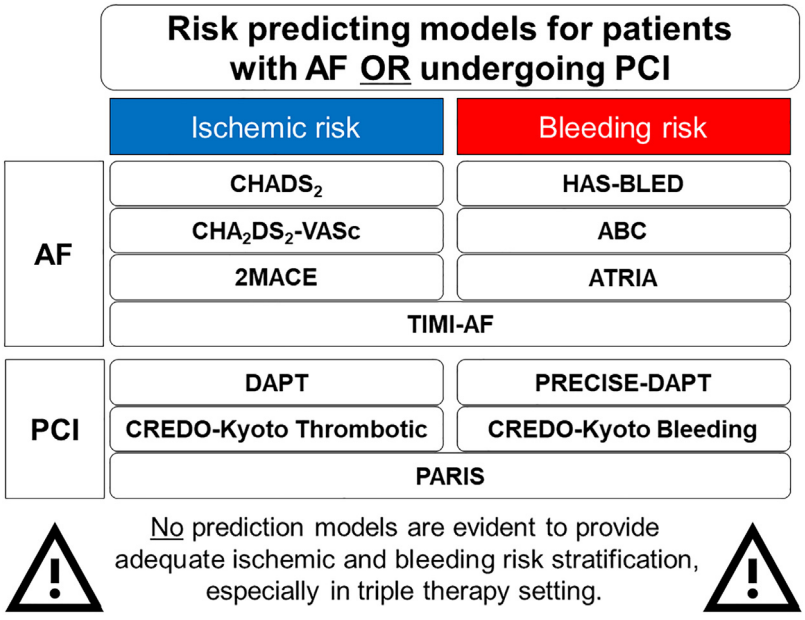

Fig. 2. Risk prediction models for patients with AF or undergoing PCI. AF, atrial fibrillation; PCI, percutaneous coronary intervention.

of triple therapy is unclear. Although the RE-DUAL PCI and PIONEER AF-PCI trial demonstrated that dual therapy with DOAC plus $P2Y_{12}$ inhibitors was superior to triple therapy including VKA in terms of bleeding endpoint, these two RCTs were underpowered to assess efficacy outcomes and were not a head-to-head comparison between DOAC and VKA [3,12]. In addition, a target INR was ranging 2.0–3.0 in the triple therapy arm including VKA in these RCTs, whereas the current guidelines recommend a lower target INR of 2.0–2.5 [15], supported by only a few small observational studies [20]. DOAC seems to have a favorable risk-benefit profile with significant reductions in intracranial hemorrhage by the pivotal phase III clinical trials [21], however, further study is warranted to determine the superiority of DOAC over VKA in the triple therapy settings.

If DOAC is used, the appropriate dosing is also required. Recent studies reported that 10–30% of AF patients received DOAC at inappropriately low dose, and these patients tended to have higher incidence of adverse events [19,22]. The physicians should prescribe the lowest tested dose DOACs according to the manufacturer labeling recommendations as a part of triple therapy [15]. If the patients do not meet the dose reduction criteria of rivaroxaban, apixaban, and edoxaban, dabigatran 110 mg bid can be a reasonable choice for triple therapy because of the following reasons: (a) dabigatran 110 mg bid has been tested and proved in AF patients who do not fulfill the dose reduction criteria in the pivotal phase III clinical trial, (b) among large AF pivotal trials investigating DOACs, only RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial included patients with DAPT and showed that the risk of major bleeding was higher in patients with DAPT than those with no or single antiplatelet therapy but the absolute risks were lowest on dabigatran 110 mg bid compared to dabigatran 150 mg bid and warfarin in patients with DAPT [23], and (c) as of now, only RE-DUAL PCI trial has tested regular doses of DOAC in the triple therapy settings and dabigatran 110 mg bid contributed to the lower incidence of bleeding [12]. In the RE-DUAL PCI trial, however, the dual therapy with dabigatran 110 mg bid and $P2Y_{12}$ inhibitor had numerically higher incidence of thromboembolic events compared to the corresponding triple therapy with warfarin [12]. Interestingly, dosing of antiplatelet agents is also a possible therapeutic challenge. Several platelet function testing and clinical studies have reported that efficacy and safety of aspirin and $P2Y_{12}$ inhibitors depend on patients' age or body weight [24,25]. However, the significance of tailoring dose of antiplatelet therapy have not been proven, especially in the settings of triple therapy.

The duration of triple therapy is recommended to be as short as possible. The ISAR-TRIPLE trial, in which 614 patients were randomized to 6-week versus 6-month triple therapy regimen after drug-eluting stent (DES) implantation, was a negative study to indicate that shortening the duration of DAPT neither affected bleeding nor ischemic events [11]. However, a landmark analysis after six weeks showed 40% reduction of clinically relevant bleeding events, favoring the 6-week regimen with marginal significance ($p = 0.07$). Given the very low rate of stent thrombosis on contemporary DES and established PCI procedures [26], several clinical trials are ongoing to test one month duration of DAPT in patients undergoing PCI with DES (NCT02619760, NCT03344653). DAPT with aspirin plus $P2Y_{12}$ inhibitor is superior to aspirin plus warfarin in terms of thromboembolic events within one month after PCI [5], whereas OAC, especially warfarin, can be alternative to the antiplatelet agent in the chronic phase [27]. Therefore, the appropriate triple therapy duration appears to be up to one month, although patient ischemic and bleeding risks should be taken into account. As most recently suggested in expert opinions, discontinuation of single antiplatelet agent from triple therapy immediately after peri-PCI period can also be a reasonable strategy [17], although there is no prospective study. After the triple therapy period, antithrombotic regimen with one antiplatelet agent and one OAC is recommended. In the case with low ischemic and high bleeding risk, only one OAC after one month from PCI might be possible.

One of the most important learning points from the ISAR-TRIPLE trial and other observational studies is that there are many clinically relevant bleeding events during the early period after PCI [7,11]. In the ISAR-TRIPLE trial, approximately half of the clinically relevant bleeding events occurred within the first six weeks after PCI in the six-month triple therapy group [11]. Many severe bleeding events immediately after PCI cannot be avoided if the duration of triple therapy can be as short as possible (i.e. one month). Hence, dual therapy with clopidogrel plus OAC alternative to the triple therapy has come under the spotlight. Although the above-mentioned RCTs showed the safety of dual therapy with $P2Y_{12}$ inhibitor plus OAC [3,10,12], each study was underpowered to determine the efficacy of dual therapy. In addition, there is a substantial body of observational data suggestive of the better safety and efficacy of triple therapy [28]. Recently, a meta-analysis including four RCTs reported that dual therapy with single antiplatelet agent plus OAC showed a reduction in TIMI bleeding by 47% with equivalent rate of major adverse cardiac events compared to triple therapy [29]. On the other hand, another recent meta-analysis including observational studies demonstrated similar safety and reduced risk of MI with triple therapy [28]. These results seem to oppose each other, however the findings from observational studies may indicate that patients who are able to tolerate triple therapy have better prognosis with a potent antithrombotic regimen. Although triple therapy has been recognized 'theoretically' necessary and 'empirically' recommended so far, the efficacy is not evident, and safety is a concern. Therefore, triple therapy may be no longer needed for most patients with AF undergoing PCI. It is conceivable that only patients in whom the ischemic risk outweighs the bleeding risk are going to be candidates for triple therapy.

In summary, contemporary antithrombotic regimens for patients with AF undergoing PCI based on the latest evidence are as follows: (1) aspirin and clopidogrel plus DOAC or VKA are components of triple therapy, (2) the duration of triple therapy should be only during the peri-PCI period or up to 1 month in most patients, and (3) dual therapy with $P2Y_{12}$ inhibitor plus OAC is an alternative to triple therapy.

To avoid thromboembolic events and bleeding complications

Triple therapy definitely tends to induce severe bleeding events [7], however, patients with AF undergoing PCI are also likely to develop future thromboembolic events [30]. How can we minimize the risks of both bleeding and thromboembolic events? The most important point is antithrombotic regimens as mentioned above. In addition, routine use of proton pump inhibitors and radial access for PCI can reduce bleeding complications [15]. Although there is one latest guideline from Canada which still recommends to determine antithrombotic treatment duration based on coronary stent type (i.e. 1-month DAPT for bare metal stent vs. at least 3-month DAPT for DES) [31], it should be decided irrespective of stent type and contemporary DES should be used [15]. In terms of thromboembolic risk, patients with ACS are well known to have higher incidence of subsequent thromboembolic events and benefit from potent antithrombotic treatment [6,15]. Furthermore, PCI complexity is a possible key factor of the antithrombotic regimen. A prior study indicated that PCI complexity defined by 2-stent procedure, total stent length, chronic total occlusion, and others was significantly associated with thromboembolic events, while, intriguingly, the benefit of long-term DAPT was greater in

patients with more complex PCI [32]. Thus, triple therapy itself and with longer duration (e.g. up to 3-6 months) in patients with ACS and/or complex PCI procedures might be beneficial. Since no predicting models have provided adequate bleeding and thromboembolic risk stratification to date (Fig. 2), clinicians should carefully assess patient ischemic and bleeding risks.

What's the next?

Optimal antithrombotic treatment for patients with AF undergoing PCI is one of the major concerns in the field of cardiology. Thus, there are a number of ongoing large clinical trials (Table 1). The AUGUSTUS trial is an ambitious study, which tests the hypothesis that aspirin could be omitted in the triple therapy, and tries a head-to-head comparison between DOAC and VKA by 2×2 factorial design (NCT02415400). The ENTRUST-AF-PCI is also a large RCT (NCT02866175), which aims to confirm the safety of dual therapy with DOAC plus $P2Y_{12}$ inhibitor compared to VKA triple therapy. This study is similar to the preceding trials (i.e. PIONEER AF-PCI and RE-DUAL PCI). The COACH-AF-PCI trial is another RCT comparing DOAC with VKA as a part of triple therapy (NCT03536611). This study is conducted in China, thus the results will be useful especially in Asian populations. Although these three trials are large scale, the primary outcomes are all bleeding events, and no single study may address the efficacy endpoint. The AUGUSTUS and COACH-AF-PCI trials are expected to prove the recent guidelines recommendation based on the expert opinions which indicates the superiority of DOAC over VKA [17]. However, because target INR in the VKA arms in both studies are ranging from 2.0 to 3.0, a guideline recommended lower target INR is not tested in these trials. The other Chinese RCT (NCT03234114) and the RT-AF trial (NCT02334254) have been validating the lower target INR of VKA (i.e. 2.0–2.5 and 1.8–2.5) as a part of triple therapy. Current guidelines recommend single OAC (i.e. omitting antiplatelet agents) after 6–12 months from PCI, although prospective and robust data are lacking. The AFIRE trial (NCT02642419) will address the usefulness of OAC monotherapy. The WOEST 2 registry (NCT0263520) is a prospective and international registry on concomitant use of OAC and $P2Y_{12}$ inhibitors in patients with AF or heart valve prosthesis undergoing PCI. This study will provide insight into the efficacy and safety of all possible combinations of OACs and antiplatelet therapies in the real-world settings. These ongoing trials and subsequent analyses will address the important issues of patients with AF undergoing PCI, such as the superiority of dual therapy (i.e. OAC plus $P2Y_{12}$ inhibitor) over triple therapy, DOAC vs. VKA in this population, usefulness of lower target INR, the candidate for triple therapy, and others (Table 2).

Table 1
Ongoing clinical trials.

	AUGUSTUS	ENTRUST-AF-PCI	COACH-AF-PCI	WOEST 2 Registry
Clinical trial number	NCT02415400	NCT02866175	NCT03536611	NCT02635230
Design	Open-label, 2×2 factorial RCT	Open label RCT	Open label RCT	Prospective cohort study
Estimated enrollment	4138	1500	1120	2200
Follow-up	6 months	12 months	24 months	24 months
Study start date	June 2015	February 2017	July 2018	June 2014
Estimated completion	December 2018	March 2019	June 2020	December 2019
Arms	1. Apixaban + $P2Y_{12}$ inhibitor + ASA 2. Apixaban + $P2Y_{12}$ inhibitor + Placebo 3. VKA + $P2Y_{12}$ inhibitor + ASA 4. VKA + $P2Y_{12}$ inhibitor + Placebo	1. Edoxaban + $P2Y_{12}$ inhibitor 2. VKA + $P2Y_{12}$ inhibitor + 1–12-month ASA	1. Dabigatran 110 mg bid + clopidogrel + 1-month ASA VKA + clopidogrel + 1-month ASA	All combinations of chronic OAC and a $P2Y_{12}$ inhibitor with or without ASA
Primary endpoint	Time to major bleeding	Major bleeding	Time to major bleeding	1. Cardiovascular death and thromboembolic events Bleeding events

ASA, aspirin; OAC, oral anticoagulant; RCT, randomized controlled trial; VKA, vitamin K antagonist.

Table 2
Unresolved issues regarding antithrombotic treatment for patients with AF undergoing PCI.

Unresolved issues	Comments
Who are the best candidates for triple therapy?	Triple therapy may be beneficial for patients with high ischemic and low bleeding risk (e.g. ACS and complex PCI).
When triple therapy is used, how long should it be prescribed?	Maybe between “peri-PCI” period and 1 month. However, no data exist, especially about “peri-PCI” period.
How can we stratify the ischemic and bleeding risks?	Novel risk prediction models and prospective validation studies to show improved outcomes are needed.
Are DOACs superior to VKA?	Ongoing studies can answer.
Is a lower target INR (e.g. 1.8–2.5) useful?	Ongoing studies can answer.
Does one dose fit for all?	Dose titration of OAC and antiplatelet agent is a potential therapeutic target. Further investigation is warranted.
What is the best antiplatelet agent after triple therapy or as a part of dual therapy?	Clopidogrel should be prescribed as a $P2Y_{12}$ inhibitor for triple therapy. However, the best antiplatelet agent as a companion to OAC is unknown.
Is single OAC enough in the chronic phase?	Ongoing studies can answer. If possible, the next question is “from when we can omit antiplatelet agents?”.
How can we minimize thromboembolic and bleeding events?	In addition to optimization of antithrombotic regimen, comprehensive secondary prevention is needed.

ACS, acute coronary syndrome; AF, atrial fibrillation; DOAC, direct oral anticoagulant; INR, international normalized ratio; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist.

Conclusions

Triple therapy has been used for patients with AF undergoing PCI in recent decades. However, triple therapy should be avoided or limited up to 1-month duration in most patients. The future investigations will provide the established strategy including the optimal antithrombotic regimen and risk stratification.

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Conflicts of interest

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