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CRITICAL PERSPECTIVE

Antithrombotic therapy in patients with non-valvular atrial fibrillation undergoing percutaneous coronary intervention: should we change our practice after the PIONEER AF-PCI and RE-DUAL PCI trials?

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Abstract

The number of patients with atrial fibrillation undergoing percutaneous coronary intervention (PCI) is increasing. Since these patients have a CHA_2DS_2-VASc score of 1 or higher, they should be treated with oral anticoagulation to prevent stroke. However, combination therapy with oral anticoagulation for prevention of embolic stroke and dual platelet inhibition for prevention of coronary thrombosis significantly increases bleeding complications. The optimal combination, intensity and duration of antithrombotic combination therapy is still not known. In the rather small randomized WOEST trial, the combination of a vitamin K antagonist (VKA) and clopidogrel decreased bleeding compared to the conventional triple therapy with VKA, clopidogrel and aspirin. In the PIONEER AF-PCI trial, two rivaroxaban-based treatment regimens significantly reduced bleeding complications compared to conventional triple therapy without increasing embolic or ischemic complications following PCI. Dual therapy with rivaroxaban and clopidogrel appeared to provide an optimal risk–benefit ratio. In the RE-DUAL PCI trial, dual therapy with dabigatran also reduced bleeding complications compared to conventional triple therapy. With respect to the composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization dabigatran-based dual therapy was non-inferior to VKA-based triple therapy. The upcoming trials AUGUSTUS with apixaban and ENTRUST-PCI with edoxaban will further examine the use of NOACs in this setting. While recent guidelines recommend NOAC-based dual therapy in only a subset of patients (those who are at increased risk of bleeding), the available data now suggest that this should be the preferred choice for the majority of patients. Adding aspirin to this primary choice for up to 4 weeks in patients at especially high ischemic risk would likely prevent atherothrombotic events, but this needs further investigation. Taken together, it is time to adjust our practice and move to dual therapy consisting of a NOAC plus clopidogrel in most patients.

Keywords Oral anticoagulation · Percutaneous coronary intervention · Atrial fibrillation · Bleedings

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Introduction

The optimal antithrombotic management strategy for patients with non-valvular atrial fibrillation (AF) presenting with an acute coronary syndrome or undergoing percutaneous coronary intervention (PCI) for stable coronary artery disease continues to represent a clinical challenge. As with the use of any antithrombotic drug, clinicians need to balance the risks of ischemic stroke and thromboembolism, recurrent cardiac ischemia and/or stent thrombosis, and bleeding and hemorrhagic stroke. This document provides an update of the evidence after publication of the PIONEER AF-PCI and RE-DUAL PCI studies and presents statements on a best practice antithrombotic therapy guideline for the management of antithrombotic therapy in AF patients requiring PCI [1, 2].

Background

Randomized trials comparing placebo with antithrombotic therapies and different antithrombotic therapies have provided evidence that oral anticoagulation (OAC) is the most effective therapy to protect patients with AF from embolic stroke and systemic embolism. Therefore, current guidelines recommend considering OAC in patients with a CHA_2DS_2-VASc score of ≥ 1 class I recommendation with a CHA_2DS_2-VASc score ≥ 2 (male) or ≥ 3 (female patients) and class IIa recommendation with a score of 1 (male) and 2 (female patients) [3]. In the early days of stent implantation, dual antiplatelet therapy (DAPT) with aspirin and ticlopidine or clopidogrel was superior to aspirin and intense anticoagulation with high dose unfractionated heparin followed by oral anticoagulation with vitamin K antagonists (VKA) [4]. Since then DAPT has been recommended after stent implantation to protect the patient from stent thrombosis [5–7]. In consequence, conventional triple antithrombotic therapy with OAC, aspirin and clopidogrel has been considered as standard of care by expert consensus for a long time, even without direct evidence from randomized trials and despite the knowledge of its limitation of an increased bleeding risk [3, 5, 8–19].

This paradigm has been challenged by the randomized WOEST study, in which the combination of a VKA and clopidogrel reduced bleeding complications compared to the conventional triple therapy, without increasing thrombotic or embolic events [20] (Fig. 1a). However, this trial

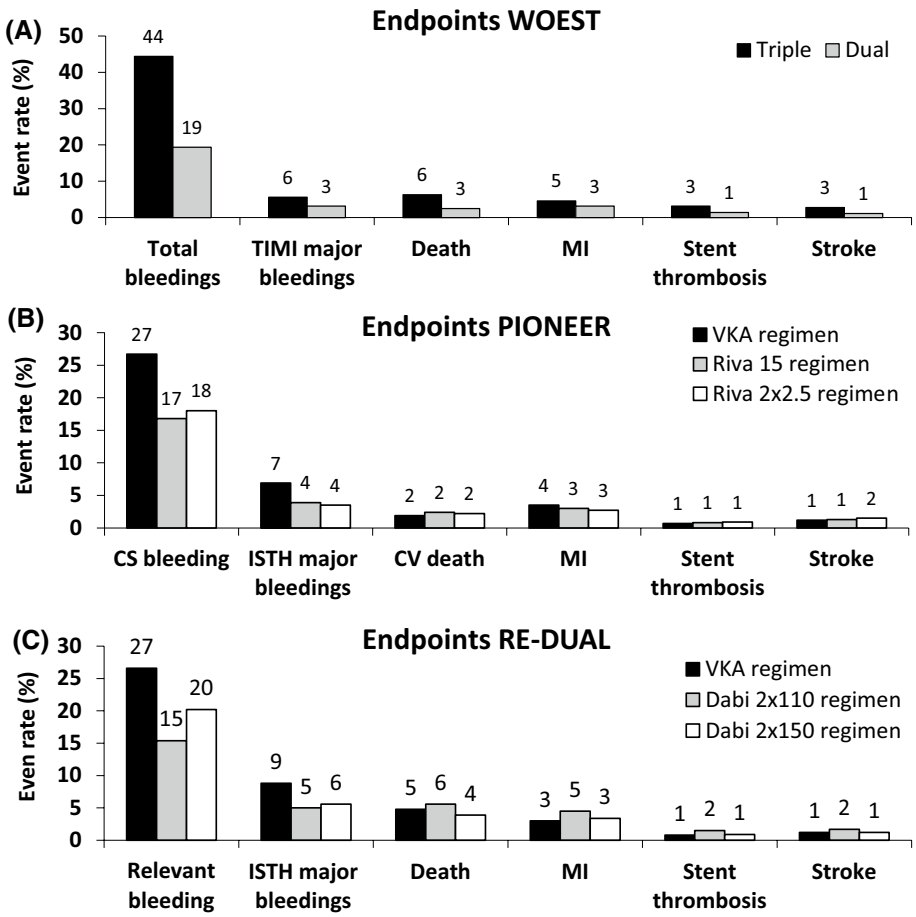

Fig. 1 **a** Results of the randomized WOEST trial comparing triple therapy with a vitamin K antagonist plus clopidogrel plus aspirin versus dual therapy with a vitamin K antagonist and clopidogrel in patients undergoing PCI with stent implantation and an indication for oral anticoagulation [20]. *MI* myocardial infarction. **b** Cumulative incidence rates of the primary safety endpoint of clinically significant bleeding and secondary efficacy endpoints in the PIONEER AF-PCI trial [1, 25]. *CS* clinically significant, *CV* cardiovascular. **c** Cumulative incidence rates of the denoted endpoints in the RE-DUAL PCI trial [2]

was not powered for efficacy (with approximately 280 patients in each arm) and many interventionalists continued to use triple therapy, because of the fear of stent thrombosis. In the ISAR-TRIPLE study, a shortened course of triple therapy over 6 weeks was non-inferior compared to a 6-month therapy [21]. In a recent position statement of the ESC, triple therapy was still considered mandatory in most patients, with the option to shorten the duration in patients at increased risk for bleeding [22]. This scheme was also recommended in the current ESC revascularization and NSTE-ACS guidelines [6, 23]. More recently, the ESC issued guidelines for dual antiplatelet therapy (DAPT) following PCI that also contain recommendations for patients with an indication for oral anticoagulation undergoing PCI [24]. The DAPT guidelines recommend dual therapy with a NOAC for patients at high risk for bleeding based on the data from the PIONEER AF-PCI trial as described below.

PIONEER AF-PCI trial

The PIONEER AF-PCI trial was the first large-scale trial to compare the conventional, VKA-based combination therapy with a NOAC-based therapy in patients with AF undergoing PCI [1]. In this trial, 2,124 participants with AF undergoing PCI with stenting were randomly assigned to receive, in a 1:1:1 ratio, low-dose rivaroxaban (15 mg once daily with further reduction to 10 mg in patients with creatinine clearance of 30–50 ml/min) plus a $P2Y_{12}$ inhibitor for 12 months ("Riva 15 regimen"), very low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months ("Rivaroxaban 2 x 2.5 mg regimen"), or standard therapy with a dose-adjusted VKA plus DAPT for 1, 6, or 12 months ("VKA regimen"). Duration of DAPT and type of $P2Y_{12}$ inhibitor were specified by the investigator before randomization. Triple therapy was maintained for 12 months in about 50% of the patients and the indication for PCI was acute coronary syndrome (ACS) in about 50% of the patients. The primary safety outcome was clinically significant bleeding [a composite of major bleeding or minor bleeding according to thrombolysis in myocardial infarction (TIMI) criteria or bleeding requiring medical attention]. While there was a significantly lower incidence of bleedings with both rivaroxaban regimens compared to VKA plus DAPT, ischemic complications, death or stroke rates were similar (but the trial was not powered for establishing non-inferiority of efficacy endpoints). Hospitalization rates were significantly lower in the rivaroxaban groups than in the VKA group in a post hoc analysis [25]. The results of the primary endpoint and secondary bleeding and ischemic endpoints are summarized in Fig. 1b.

RE-DUAL PCI trial

The RE-DUAL PCI trial was the second large-scale trial in this setting [2]. In this trial, 2725 participants with AF undergoing PCI were randomly assigned to receive conventional triple therapy with a VKA or one of the two doses of dabigatran approved for stroke prevention in AF (2× 110 mg or 2× 150 mg) in combination with a $P2Y_{12}$ inhibitor (predominantly clopidogrel). Triple therapy was maintained for 1 month in patients who received a bare-metal stent and for 3 months after implantation of a drug-eluting stent. Indication for PCI was ACS in about 50% of the patients. The primary safety outcome was major or clinically relevant non-major bleeding according to the International Society of Thrombosis and Haemostasis (ISTH) criteria. The risk for bleeding was significantly reduced with the dabigatran 2× 110 mg regimen as compared to triple therapy and non-inferior with the dabigatran 2× 150 mg regimen (Fig. 1c). RE-DUAL PCI also demonstrated non-inferiority of dual therapy with dabigatran (both doses combined) to triple therapy with warfarin in a composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization.

Clinical implications

The results of the WOEST, PIONEER and RE-DUAL trials challenge the role of triple therapy with VKA as standard of care in patients with atrial fibrillation undergoing PCI. While in the periprocedural phase aspirin in combination with a $P2Y_{12}$ inhibitor should be given to all patients, in contrast to earlier assumptions, longer term dual antiplatelet therapy does not seem mandatory after PCI in patients treated with OAC. From a pathophysiological view, this seems plausible, because thrombin is the most potent stimulus for platelet activation and aggregation and direct factor Xa inhibition with rivaroxaban has been associated with a significant reduction in stent thrombosis in the ATLAS ACS2-TIMI 51 trial [26]. In addition, improved stent designs and better implantation techniques have reduced the rate of stent thrombosis, which is now $< 1\%$ in most trials. However, in certain situations, longer DAPT might still be desirable. It is therefore tempting to speculate about implications for subgroups of patients, such as those with STEMI or those undergoing complex PCI (e.g., bifurcation or left main PCI or PCI with multiple stents), who are considered at highest risk for stent thrombosis and recurrent ACS.

Importantly, PIONEER AF-PCI was not powered for assessing ischemic endpoints, especially not in subgroups

(only a total of 257 patients had STEMI and data about complex PCI were not reported). Reassuringly, the rate of stent thrombosis was low in all rivaroxaban groups (< 1%, without significant differences). The rate of MACE for patients with STEMI was numerically higher in the 2× 2.5 mg rivaroxaban group, but this did not reach statistical significance (5.1% with the Riva 15 regimen, 10.8% with the Rivaroxaban 2 x 2.5 mg regimen, and 9.5% with the VKA regimen, n.s.). However, the relative risk reduction in the primary (bleeding) endpoint was especially large in the STEMI subgroup (14.6% with the Riva 15 regimen, 19.2% with the Rivaroxaban 2 x 2.5 mg regimen, and 35.9% with the VKA regimen, $p < 0.05$). Taken together, it is unclear whether patients with STEMI or complex PCI would benefit from DAPT in combination with 2× 2.5 mg rivaroxaban or if a single $P2Y_{12}$ inhibitor in combination with 15 mg rivaroxaban would be a "one fits all" solution. Extrapolating from the available data and the guideline-derived assumption that DAPT is beneficial, it seems reasonable to consider adding aspirin for up to 4 weeks to the 15 mg rivaroxaban regimen in patients at especially high risk for atherothrombotic events, although this has not been tested in PIONEER AF-PCI [16]. Figure 2 provides a scheme favoring the "one fits all" solution, allowing this consideration.

With the dabigatran 2× 110 mg regimen, the risk for myocardial infarction was numerically higher than with 2× 150 mg in the RE-DUAL PCI trial. For high-risk patients undergoing PCI, most clinicians may therefore prefer the 2× 150 mg dabigatran regimen if dabigatran is chosen over rivaroxaban.

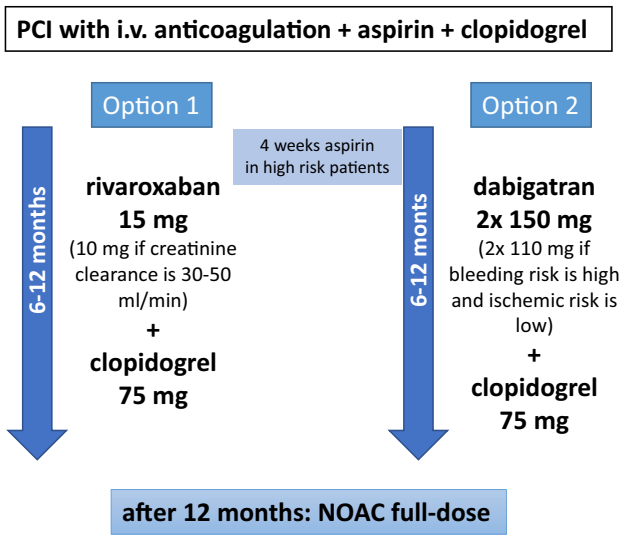

Fig. 2 Scheme of two options for antithrombotic combination therapy for patients with non-valvular AF undergoing PCI according to the results from the PIONEER AF-PCI and RE-DUAL PCI trials

It is also not entirely clear, which $P2Y_{12}$ inhibitor should be preferred [27]. Only 3–5% of study participants had been assigned to ticagrelor and < 2% to prasugrel in PIONEER AF-PCI and 12% to ticagrelor in RE-DUAL PCI by their treating physician, while most patients received clopidogrel in both trials. According to subgroup analyses from PIONEER AF-PCI as well as from the GEMINI-ACS-1 trial (with 56% treated with ticagrelor) [28], clopidogrel may be the ideal combination partner for rivaroxaban.

Whether protection from stroke is as effective with lower doses of a NOAC when combined with clopidogrel, as the full dose tested in the AF trials is a matter of debate. PIONEER AF-PCI tested a 25% lower dose than the recommended dose for stroke prevention in lone AF of 20 mg. Although the study was not powered to test efficacy, there was no important signal suggesting that stroke risk was elevated, especially with the 15 mg rivaroxaban regimen (1.3 versus 1.2% with triple therapy, HR 1.07, 95% CI 0.39–2.96). In RE-DUAL PCI, only AF-approved doses were tested. Numerically, the stroke risk with the dabigatran 2× 110 mg regimen appeared slightly higher than with VKA-based triple therapy, but this was not significant and possibly due to chance (HR 1.3, 95% CI 0.63–2.67). The extended efficacy endpoint defined in RE-DUAL PCI allowed testing for non-inferiority for both dabigatran arms compared to triple therapy, which was achieved. Taken together, the efficacy data in both trials suggest that there was no sign for increased stroke rates in patients assigned to dual therapy.

Outlook

Two additional large randomized trials are still ongoing (AUGUSTUS and ENTRUST-PCI) examining different combination therapies in patients with non-valvular AF undergoing PCI. After the publication of these trials, at least a year from now, the role of all four NOACs and also the dosing (full or reduced) in the setting after PCI will be clearer, and broader recommendations for the optimal antithrombotic combination therapy might be possible. However, at present, patients should be treated according to the available evidence and the conclusions presented in this report.

Summary

The results of the PIONEER AF-PCI and the RE-DUAL PCI trials suggest that antithrombotic combination therapy with a reduced dose of rivaroxaban of 15 mg or a regular dose of dabigatran in combination with clopidogrel seems to provide a better risk–benefit ratio than conventional triple

therapy. Based on these considerations, triple therapy with VKA after PCI should no longer be standard of care.

Compliance with ethical standards

Conflict of interest Duerschmied D: Speaker honoraria from Bayer, Daiichi-Sankyo, Pfizer, Brachmann J: none, Darius H: Speaker's honoraria and consulting fees from Bayer, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Boehringer Ingelheim, Frey N: none, Katus HA: none, Rottbauer W: none, Schäfer A: Speaker honoraria from Daiichi, Bristol-Myers Squibb/Pfizer; Consulting fees from Bayer, Boehringer Ingelheim, Thiele H: none, Bode C: Research grants from Bayer, GlaxoSmithKline, Merck; Speaker's honoraria from Bayer, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Boehringer Ingelheim; Consulting fees from Bayer, Zeymer U: Speaker's honoraria and consulting fees from Bayer, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Boehringer Ingelheim.

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