



# Ticagrelor or prasugrel vs. clopidogrel in combination with anticoagulation for treatment of acute coronary syndrome in patients with atrial fibrillation

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**Abstract:** For patients with atrial fibrillation (AF) and acute coronary syndrome (ACS), it is often challenging to find the optimal balance between the risk for ischemic and hemorrhagic complication when using both antiplatelet therapy and oral anticoagulation (OAC) with vitamin K antagonist (VKA) or direct oral anticoagulants (DOACs). Current guidelines recommended: (I) double therapy with a P2Y<sub>12</sub> inhibitor and dose adjusted VKA is reasonable post-stenting; (II) double therapy with clopidogrel and low-dose rivaroxaban (15 mg daily) may be reasonable post-stenting; (III) double therapy with a P2Y<sub>12</sub> inhibitor and dabigatran 150 mg twice daily is reasonable post-stenting. In the AUGUSTUS trial, most patients were given clopidogrel as part a DAPT regimen, however prasugrel and ticagrelor use allowed albeit in a small percentage of the trial population, underestimating its effect. Ticagrelor and prasugrel are known to have a stronger antiplatelet effect compared to clopidogrel, however randomized studies have not been adequately powered to date allowing comparisons between ticagrelor, prasugrel and clopidogrel together in the setting of anticoagulation for the treatment of patients with ACS and AF. Careful consideration should be given to this scenario to avoid falling into the concept of sacrificing efficacy for safety.

**Keywords:** Acute coronary syndrome (ACS); atrial fibrillation (AF); antiplatelets

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## Introduction

In the United States, there are more than 5 million patients with atrial fibrillation (AF) (1). Nearly 20% to 30% of patients with AF have or will develop coronary artery disease (CAD), leading to more than 100,000 patients annually with AF undergoing percutaneous coronary intervention (PCI) with coronary stenting (2-4). At the same time, nearly 5% of patients undergoing PCI already have AF and require long-term oral anticoagulation (OAC) therapy (5).

Regarding patients with AF and CAD, it's often challenging to find the optimal balance between the risk for ischemic and hemorrhagic complications in patients requiring both antiplatelet therapy and OAC with a vitamin K antagonist (VKA) or direct oral anticoagulants (DOACs) (6,7).

The use of dual antiplatelet therapy (DAPT) in combination with an anticoagulant has been referred to as "triple oral antithrombotic therapy". The WOEST trial introduced the concept that removing aspirin (ASA)

from a triple antithrombotic regimen of ASA, clopidogrel and VKA (e.g., warfarin) may reduce major bleeding without increasing thrombotic risk in patients undergoing PCI and concomitant AF (8). Since, many studies have demonstrated similar findings, the most recent being the AUGUSTUS trial using DOACs (apixaban) (9). Some studies have allowed ticagrelor or prasugrel as an alternative to clopidogrel. We aim to compare the available data with ticagrelor or prasugrel versus clopidogrel in combination with anticoagulation for treatment of patients undergoing PCI with AF.

## Discussion

### *Current guidelines for treatment of patients with ACS/AF using dual antiplatelet agents and anticoagulation*

American and European guidelines recommend the use of anticoagulation for patients with acute coronary syndrome (ACS) and AF at increased risk of systemic thromboembolism (based on CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score), unless the bleeding risk exceeds the expected benefit (10). Current American guidelines, most recently updated in January 2019, Current guidelines recommended the followings:

- (I) The use of DAPT with aspirin plus a platelet P2Y<sub>12</sub> inhibitor in addition to warfarin or a non-vitamin K oral anticoagulant (“triple therapy”) in patients with AF treated for ACS with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or greater.
- (II) If triple therapy is prescribed for patients with AF who are at increased risk of stroke and who have undergone PCI with stenting for ACS, a transition to double therapy at 4–6 weeks may be considered.
- (III) If triple therapy is prescribed post-stent placement, clopidogrel is preferred over prasugrel.
- (IV) Double therapy with a P2Y<sub>12</sub> inhibitor and dose adjusted VKA is reasonable post-stenting.
- (V) Double therapy with clopidogrel and low-dose rivaroxaban (15 mg daily) may be reasonable post-stenting.
- (VI) Double therapy with a P2Y<sub>12</sub> inhibitor and dabigatran 150 mg twice daily is reasonable post-stenting (11). Based on class IIa recommendation, if triple therapy is prescribed, it is reasonable to choose clopidogrel over prasugrel due to significantly higher risk of bleeding (11,12). Double therapy interventions, combining a P2Y<sub>12</sub> inhibitor (clopidogrel or ticagrelor) with an oral

anticoagulant (low-dose rivaroxaban, dabigatran or dose-adjusted VKAs) are proposed as alternatives to triple regimen to further reduce the risk of bleeding (8,13,14). Current guidelines suggest an early transition to double therapy may be considered at 4 to 6 weeks during the period of greatest risk of stent thrombosis, if triple therapy was initiated, especially in patients with ST-segment elevation myocardial infarction (MI) (15,16). To date, there are several randomized control trials addressing the topic of anticoagulation after PCI in patients with AF, including the WOEST (8), PIONEER AF-PCI (17) and RE-DUAL PCI (18). A meta-analysis combining these three suggests that the likelihood of an excess of thromboembolic events during dual therapy versus triple therapy is low (19). However, these trials focus on bleeding as the primary endpoint and are underpowered to address ischemic/thromboembolic events including stroke, re-infarction and stent thrombosis (20). The recently released AUGUSTUS trial, and the ongoing ENTRUST-AF-PCI trial (21), will certainly add further information to our current guidelines.

### *Ticagrelor in PLATO and AUGUSTUS trials*

Based on the PLATO trial results, it was obvious that ticagrelor was superior to clopidogrel in an ACS population (22). Ticagrelor resulted in a 16% relative risk reduction in death from vascular causes, MI or stroke by compared to clopidogrel. Moreover, there was 21% significant relative risk reduction in cardiovascular death with ticagrelor versus clopidogrel (22). A benefit of ticagrelor over clopidogrel is not only shown in ACS patients but also for stable CAD patients (23). According to Orme *et al.* ticagrelor 60 and 90 mg bid regimens had superior platelet inhibition compared to clopidogrel in stable CAD patients (23).

In the AUGUSTUS trial, among patients with AF treated with long term anticoagulation (apixaban or VKA) undergoing PCI with or without ACS who would require a P2Y<sub>12</sub> inhibitor for at least 6 months (9). Apixaban treatment resulted in a statistically significant reduction in major or clinically relevant non-major bleeding and a lower rate of rehospitalization and death compared to VKA therapy (9). The P2Y<sub>12</sub> inhibitors included in the trial were clopidogrel, ticagrelor, or prasugrel. However, ticagrelor was only used in 6.2% of cases despite an ACS population

of 61.2%. Within this group of patients, there was no significant increase in bleeding risk with either apixaban or VKA use. Ticagrelor had a low percentage use in the trial despite previous trial showing superiority of ticagrelor over clopidogrel in ACS population (22).

### ***Prasugrel use in PIONEER-AF, AUGUSTUS and other trials***

The PIONEER-AF trial, the subgroup analysis of the prasugrel-treated patients was limited to 2% of P2Y12 inhibitors prescribed. This small sample size limited its usefulness in subgroup analysis and unable to observe any benefit in terms of bleeding risk, major advanced cardiac events (MACE), time to first stroke, and time to first ischemic stroke (17). Even less use of prasugrel was utilized in the AUGUSTUS trial (9), with only 1.2% of all patients on treatment and again without any clear conclusions regarding risk or benefit. Despite the lack of data in these trials concerning prasugrel and its risk of bleeding, there are a few single center studies that compared the different P2Y12 inhibitors as part of triple therapy (11,24).

First, Verlinden *et al.* compared prasugrel/ticagrelor against clopidogrel as part of triple therapy with the primary outcome of incidence of any bleeding during 12-month period after index hospitalization, with secondary outcomes of MACE within 12 months (24). In the 42 patients treated with ticagrelor or prasugrel, 28% experienced a bleeding event, compared to 12.7% of patients treated with clopidogrel (OR 3.3; 95% CI, 1.38–8.34;  $P=0.017$ ). There was no significant difference between the groups for the outcomes of MACE, MI, ischemic stroke, or cardiac death.

Second, Sarafoff *et al.* looked at 377 patients who underwent successful stenting and platelet function testing and were discharged with a 6-month regimen of triple anticoagulation therapy (11). Among these patients 21 were treated with prasugrel of which 18 were due to high platelet reactivity despite clopidogrel treatment. Even though the study was not powered to assess clinical endpoints, including thrombolysis in MI (TIMI) major and minor bleeding at 6 months. Combined major and minor bleeding was seen in 28.6% of patients given prasugrel, compared to 6.7% of those given clopidogrel (HR 4.6; 95% CI, 1.9–11.4;  $P<0.001$ ). There was no significant difference in MACE. However, in both of these studies warfarin was the oral anticoagulant used in the study in conjunction with ASA. While these data are from single centers, and have small sample sizes, they underline the need for more careful

consideration of prasugrel as a component of triple therapy.

### ***Oral anticoagulant in PIONEER-AF and AUGUSTUS trials***

The PIONEER-AF trial sought to understand if there was a difference in the risk of bleeding for patients with nonvalvular AF undergoing PCI with stent placement. Low dose rivaroxaban with single or DAPT reduced the risk of TIMI, major and minor bleeding when compared to warfarin with DAPT at 1 year.

The AUGUSTUS trial sought to understand whether OAC with apixaban is superior to warfarin with regard to thrombotic events and bleeding, and whether the addition of ASA to OAC with P2Y12 inhibitor therapy is superior to placebo. The study found that apixaban is associated with a 4.2% absolute reduction in major bleeding compared to warfarin, and ASA use in addition to OAC and P2Y12 inhibitor therapy was associated with a 7.1% absolute increase in major bleeding. There was no difference in thrombotic events or for secondary outcomes.

In summary, in the group of patients where antiplatelet and anticoagulation therapy is needed, the preference between ticagrelor, prasugrel and clopidogrel was difficult to decide upon, and this is due to many factors. First, most of the leading studies focus on bleeding as primary outcome and not thrombotic outcomes, which is the desired outcome when choosing more potent P2Y12 inhibitors (19,20). Consequently, it is difficult to compare different antiplatelets agents' effect on thrombotic outcome when used together with anticoagulation.

Second, in case of ticagrelor for example, previous studies done comparing clopidogrel to ticagrelor, already proved that ticagrelor is more efficient and superior to clopidogrel for prevention of thrombotic events (22), therefore, there is a considerable chance that ticagrelor will be more efficient than clopidogrel in combination with anticoagulation in preventing thrombotic events. Therefore, we should explore more in that regard and not to fall in the pit of sacrificing efficacy for safety.

Third, Verlinden trial (24) and Sarafoff *et al.* (11) were underpowered to assess clinical endpoints, including TIMI major and minor bleeding at 6 months, therefore, well powered studies are needed. Moreover, in both of these studies, only warfarin was used. Caldeira *et al.* (25) showed that DOACs were at least as effective as VKAs in preventing stroke in AF patients and were associated with less bleeding, particularly less ICH, which is intriguing as DOACs may offset the increased bleed risk of potent antiplatelet therapy.

Additionally, both Verlinden *et al.* and Sarafoff *et al.* included ASA and did not evaluate dual antithrombotic therapy.

Fourth, the AUGUSTUS trial, which is the most recent randomized trial for the use of antiplatelet and anticoagulant together, was not powered sufficiently to compare outcomes between different antiplatelet agents. More randomized trials need to be conducted for further clarification of the choice of antiplatelet in combination with anticoagulation in this challenging group of patients diagnosed with ACS and AF.

## Conclusions

Clopidogrel is the current default P2Y<sub>12</sub> inhibitor used in ACS/AF patients recommended by guidelines. Ticagrelor and prasugrel are known to have a stronger antiplatelet effect yet are not used because of the increased risk whether real or perceived which have not been confirmed with large randomized studies in this patient population. In AUGUSTUS, only 9 patients needed to be treated to prevent a major or clinically-relevant non-major bleeding event and only 18 patients needed to be treated to prevent a death or hospitalization when comparing apixaban plus a P2Y<sub>12</sub> inhibitor to triple therapy with VKA, P2Y<sub>12</sub> inhibitor plus aspirin. With the robust safety benefit of DOACs, perhaps the most intriguing combination may be with the ticagrelor or prasugrel to minimize the increased bleeding risk in combination. However, well-designed studies are justified to better inform choice of P2Y<sub>12</sub> inhibitor used until this strategy can be widely implemented

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## Footnote

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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