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# Dual Antiplatelet Therapy and Anticoagulation in Patients Post Percutaneous Coronary Intervention

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## Abstract

In patients who have had percutaneous coronary intervention for acute coronary syndromes or stable angina dual antiplatelet therapy is required. If there is a history of atrial fibrillation, thrombosis or presence of a mechanical heart valve then long term anticoagulation may be necessary. However, the use of antiplatelets with anticoagulation increases the risk of bleeding. The need for anticoagulation in such patients needs to be carefully assessed by taking into account the risk of bleeding with anticoagulation and the risk of thromboembolic events without anticoagulation. If triple therapy is required then the shortest duration of treatment should be prescribed.

**Keywords:** Percutaneous coronary intervention; Antiplatelets; Anticoagulation; Atrial fibrillation

## Introduction

Concomitant anticoagulation with Dual Antiplatelet Therapy (DAPT) may be required in 6-8% of patients who require Percutaneous Coronary Intervention (PCI) due to other co-existing conditions [1]. The presence of Atrial Fibrillation (AF), mechanical heart valves and thrombotic events may necessitate the need for anticoagulation. In such cases the need for anticoagulation with antiplatelet therapy needs to be assessed due to the excess bleeding rates associated with triple therapy i.e aspirin, clopidogrel and anticoagulant. The risk of bleeding, thromboembolism and ischemic events needs careful consideration before deciding on management strategy. Furthermore the required duration of anticoagulation with DAPT is unclear but the shortest possible duration is ideal to reduce the risk of bleeding. With the development of newer anticoagulants such as the non vitamin K antagonist oral anticoagulant (NOACS), this poses a further management conundrum. Due to lack of clinical data surrounding the management of such patients much of the guidelines are based on consensus expert opinion.

Current guidelines from the American Heart Association (AHA), American College of Cardiology (ACC) and the European Society of Cardiology (ESC) recommend 12 months of DAPT for patients with NSTEMI irrespective of treatment strategy. This would entail aspirin with a combination of a P2Y12 receptor antagonist such as clopidogrel/prasugrel/ticagrelor. Use of these agents causes a reduction in death, MI, stroke [1,2]. Treatment becomes challenging if there is also an indication for anticoagulation.

The first studies on patients requiring DAPT and anticoagulation were performed in 2004 but the results were based on retrospective data with limited sample size. Triple therapy with aspirin, clopidogrel and anticoagulation is the most effective way of preventing stent thrombosis and thromboembolism in patients who have had PCI and require long term anticoagulation. When triple therapy is used proton pump inhibitors, antacids or H-2 receptor blockers should be prescribed to reduce the risk of gastrointestinal bleeding [3].

## Risk Scoring in Patients who have AF

Anticoagulation can be in the form of vitamin K antagonists such as warfarin or the NOACS. The NOACS include dabigatran a direct thrombin inhibitor, rivaroxaban, edoxaban and apixaban which are direct factor Xa inhibitors. The NOACS are approved in patients with non valvular AF as well as prevention and treatment of deep vein thrombosis and pulmonary embolus. AF is the commonest cardiac arrhythmia and is associated with ischaemic stroke and systemic thromboembolism which is reduced with anticoagulation treatment [3]. In patients with paroxysmal, persistent or permanent AF the CHA2DS2VASc score needs to be calculated to determine the stroke risk. A score of 1 is given for each of the categories; cardiac failure, hypertension, age  $\geq 75$  (2 points), diabetes, stroke (2 points), peripheral vascular disease, age 65-74 and sex (female sex scores 1). The higher the score the greater the stroke risk. It is recommended that in patients with a CHA2DS2VASc score of  $>1$  then anticoagulation should be considered providing that the bleeding risk is low. Bleeding risk is calculated by the HAS-BLED score. Each component is given a score of 1 and include the following; hypertension, abnormal renal function, abnormal liver function, stroke,

bleeding history or predisposition, labile INR, >65 years, Drugs and alcohol use [4]. A HAS-BLED score of 0-2 suggests low to intermediate risk of bleeding and a HAS-BLED score of >3 suggests a high risk for bleeding [1].

## Bleeding with Antiplatelets and Anticoagulation

The use of antiplatelets and anticoagulation in patients increases the risk of bleeding. Registries have given insight with regards to the rates of bleeding events with specific antiplatelets and anticoagulation. In a registry of 40,812 patients post MI bleeding with aspirin was 2.6%, 4.6% for clopidogrel, 4.3% with DAPT, 5.1% with aspirin and anticoagulant, 12.3% for clopidogrel and anticoagulant and 12% for triple therapy (aspirin, clopidogrel and anticoagulant) after a mean follow up of 16 months. In a meta-analysis of trials involving the use of triple therapy the risk of major bleeding at 1 month was 2.2% but this increased to 4-12% at 1 year suggesting that the longer the duration of triple therapy the higher the risk of bleeding [2]. In a further registry of 82,854 patients surviving their first hospitalisation with AF, the risk of bleeding with a single, dual or triple therapy was assessed. During a mean follow up of 3.3 years the highest bleeding event rates were for dual therapy with clopidogrel and warfarin (13.9% per year) and for triple therapy with aspirin, clopidogrel and warfarin (15.7% per year). Bleeding risk was therefore three times higher with dual or triple therapy for AF when compared to warfarin alone [5]. Warfarin has consistently been shown to be superior to DAPT in reducing embolic events in patients with AF.

## Anticoagulation with DAPT

Several trials have assessed the treatment strategies in patients who are on long term oral anticoagulation and have had PCI. In the 'What is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation trial' (WOEST) 573 patients who were taking anticoagulation and had PCI were randomised to receive clopidogrel and anticoagulant (dual therapy) versus aspirin, clopidogrel and anticoagulant (triple therapy). Treatment duration varied depending on if a bare metal stent (BMS) or drug eluting stent (DES) was used. Bleeding was significantly higher in patients receiving triple therapy versus dual therapy (44.4% versus 19.4% respectively  $p < 0.0001$ ). Blood transfusion was required in 3.9% of patients receiving dual therapy and 9.5% in the triple therapy group ( $p < 0.011$ ). All cause mortality was significantly lower in patients on dual therapy; 2.5% and 6.4% in the triple therapy group. The combined secondary end points of death, myocardial infarction (MI), stroke, target vessel revascularisation and stent thrombosis was significantly lower with dual therapy, 11.1% and 17.6% in the triple therapy group ( $p < 0.025$ ). Therefore at 1 year follow up, the combination of clopidogrel with an anticoagulant resulted in lower bleeding complications without increased risk of ischaemic events or stent thrombosis when compared to triple therapy. However it is important to note the sample size was

too small to allow for any robust conclusions, but given the positive findings with clopidogrel and an anticoagulant this may be considered as an alternative to triple therapy particularly in patients with a high bleeding risk [6]. A further study of 12,165 patients largely supported the findings of the WOEST trial. The risk of thrombosis and bleeding was assessed in patients with a history of AF requiring long term anticoagulation and antiplatelet therapy post PCI. The bleeding and ischaemic events were analysed for patients prescribed different combinations of antiplatelet therapy with anticoagulation. Bleeding rates were lower in patients prescribed clopidogrel and warfarin when compared to patients prescribed triple therapy (aspirin, clopidogrel and warfarin). Bleeding was significantly lower when warfarin and aspirin were combined or if the combination of aspirin and clopidogrel was used. There was no increase in recurrent coronary events with the use of clopidogrel and warfarin, warfarin and aspirin or aspirin and clopidogrel when compared to triple therapy. Ischaemic stroke rates were highest for the use of aspirin and clopidogrel combined. All cause mortality was highest in patients prescribed warfarin and aspirin combined or aspirin and clopidogrel combined. Therefore in patients who require long term anticoagulation for AF and antiplatelet therapy post PCI the use of warfarin and clopidogrel combined was equal or better to triple therapy with regards to bleeding rates, recurrent coronary events and ischaemic stroke events [7].

## Duration of Antiplatelet and Anticoagulation Therapy

The duration of antiplatelet therapy with anticoagulation is unclear due to the lack of clinical trials. Early discontinuation of DAPT is the greatest risk for stent thrombosis. There is a 5-36 fold increase in stent thrombosis if DAPT is stopped within the first month of PCI and 2.5-5 fold increase in stent thrombosis if DAPT is stopped between 1-6 months [2]. In general all patients who have had PCI with stents, DAPT is required for longer than a month to reduce the risk of stent thrombosis.

If triple therapy is required this should be prescribed for a duration of 1 to 6 months post PCI depending on the type of stent deployed, bleeding risk, and thromboembolic risk [1,2]. In the ISAR TRIPLE study 614 patients who had PCI with a DES and already established on long term oral anticoagulation were randomised to receive triple therapy (aspirin, oral anticoagulant and clopidogrel) for 6 weeks or 6 months. The aim was to assess the primary end point of death, MI, stent thrombosis, stroke and major bleeding. The composite primary end point was similar between the two groups and was seen in 9.8% of patients prescribed 6 weeks of triple therapy and 8.8% prescribed 6 months of triple therapy [8].

The ESC, AHA, and ACC guidelines recommend 12 months of DAPT in patients who have had an MI, however multiple trials have demonstrated that shorter duration of DAPT may suffice in patients who have had an MI or elective PCI. In the OPTIMIZE trial 3 months of DAPT was compared to 12 months

of therapy in patients who had PCI with zotarolimus-eluting stents. This trial demonstrated that 3 months of DAPT was non inferior to 12 months with regards to major adverse cardiovascular events and without increasing risk of stent thrombosis [9]. The excellent trial demonstrated that 6 months of DAPT was non inferior to 12 months in patients who had PCI with a xience or promus stent. The incidence of stent thrombosis was slightly higher in the 6 month group this was not significant [10]. In a further study of patients who had PCI with a DES or BMS, 24 months of DAPT with aspirin and clopidogrel was not more effective than 6 months of DAPT. Bleeding was higher in patients who were prescribed 24 months of DAPT [11]. Stent thrombosis rates were similar in patients who had PCI with a zotarolimus eluting stent and prescribed 3 or 6 months of DAPT [12]. Based on these trials patients who require DAPT for PCI as well as long term anticoagulation the duration of DAPT may be shortened to allow for anticoagulation.

## Stent Type and Duration of Treatment

The development of newer stents have allowed for shorter duration of DAPT especially in patients who are at higher risk of bleeding or may require early discontinuation of DAPT to enable surgery [2]. The polymer free biolimus A9 coated stent has provided favourable results with shorter duration of DAPT. Outcomes such as cardiac death, MI and stent thrombosis were assessed with the biolimus A9 coated stent and compared to a BMS after 1 month of DAPT was prescribed. The primary end point occurred in 9.4% of patients who had PCI with the biolimus A9 coated stent and 12.9% in the BMS group ( $p < 0.001$ ). Target vessel revascularisation was required in 5.1% of patients who had PCI with a biolimus A9 coated stent versus 9.8% with a BMS. The biolimus A9 coated stent provides an alternative option in patients who require long term anticoagulation so that DAPT can be prematurely discontinued without increasing adverse events [13].

## NOAC Data

Patients on DAPT who require a vitamin K antagonist for AF require regular assessment of their Internationalised normalised ratio (INR) to ensure that this is maintained between 2-2.5 [14]. The target INR should be adjusted depending on the indication for treatment and it is advised that the INR should be at the lower range of normal to prevent excess bleeding if prescribed with DAPT.

The development of newer potent antiplatelets as well as the NOACS have posed a management challenge due to the scarce data regarding the use of these drugs in combination. Much of the guidelines available is therefore based on consensus expert opinion. The available evidence suggests that the NOACS have a better safety profile than vitamin K antagonists with regards to bleeding.

In patients who require coronary intervention and have been taking a NOAC then this should be stopped the evening before the intended procedure. Radial access is recommended to avoid vascular access related complications. Post PCI, if a

NOAC is required for the treatment of non valvular AF then the lowest tested dose for stroke prevention should be used. For instance dabigatran 110 mg BD should be prescribed instead of 150 mg BD, 2.5 mg BD apixaban instead of 5 mg BD and 20 mg rivaroxaban. If a P2Y12 receptor inhibitor is required then the one with the lowest bleeding risk should be prescribed such as clopidogrel 75 mg OD instead of prasugrel and ticagrelor as these are associated with higher bleeding events [1].

If triple therapy is required the type of stent to be used should be considered as BMS often require shorter duration of antiplatelet therapy.

There are ongoing trials to examine bleeding rates with the combination of NOACS and antiplatelets in patients with non valvular AF having undergone PCI. One trial will randomise patients to receive rivaroxaban 15 mg OD plus clopidogrel 75 mg, rivaroxaban 2.5 mg BD with DAPT, or vitamin K antagonist with DAPT at varying treatment durations [15]. This will provide insight with regards to the safety profile of NOACS with antiplatelets and the length of time treatment is required. In the REDUAL PCI trial the two doses of dabigatran (110 mg BD and 150 mg BD) combined with clopidogrel/ticagrelor will be compared with warfarin plus DAPT in patients who have non valvular AF undergoing PCI [16].

## Management of patients with medically managed non ST elevation myocardial infarction (NSTEMI)+AF

Dual therapy is advised for a minimum of 12 months. Combinations can include aspirin and oral anticoagulation, OR clopidogrel and oral anticoagulation. After 12 months lifelong oral anticoagulation monotherapy is advised.

## Management of patients with NSTEMI, AF and PCI

In patients with a low to intermediate HAS BLED score (score of 0-2) triple therapy is advised for 6 months following PCI. Dual therapy is advised thereafter with oral anticoagulation and clopidogrel OR anticoagulation and aspirin for the remaining 6 months. After 12 months lifelong oral anticoagulation monotherapy therapy is advised.

## Management of patients with NSTEMI, AF and PCI

In patients with a high HAS BLED score (score of >3) triple therapy is advised for 1 month. For the remaining 11 months dual therapy is advised with oral anticoagulation and aspirin OR oral anticoagulation and clopidogrel. Lifelong oral anticoagulation monotherapy is advised thereafter.

Treatment must be individualised since each scenario is unique. For example in patients who have recurrent ischaemia or high risk coronary stenting the above guidance may not be applicable.

## Conclusion

The management of patients who are on long term anticoagulation and require dual antiplatelet therapy following percutaneous coronary intervention is often challenging due to the limited available evidence to guide management. The risk of bleeding and thromboembolism needs to be assessed before deciding on management. When a non vitamin K oral anticoagulant is prescribed with antiplatelets the lowest approved dose for stroke prevention should be prescribed. The use of anticoagulation with prasugrel or ticagrelor should be avoided due to the bleeding risk associated. If triple therapy is used a short term strategy should be aimed for. Further studies are required to identify the optimal drug to be used and duration.

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