Managing the Antithrombotic Therapy After Percutaneous Coronary Intervention in Patients on Oral Anticoagulation

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Abstract

In patients on chronic oral anticoagulation (OAC) who are undergoing a percutaneous coronary intervention (PCI), dual antiplatelet therapy (aspirin and a P2Y₁₂ inhibitor) is required. However, combining dual antiplatelet therapy with OAC increases the risk of bleeding. Newer and stronger P2Y₁₂ inhibitors also add more complexity to the regimen, as these antiplatelet agents are currently recommended as standard treatment in patients with acute coronary syndromes (ACS). It remains unclear whether these ACS patients on chronic OAC undergoing PCI should be treated with these new P2Y₁₂ inhibitors as part of the antiplatelet therapy. Another issue to address is that new non-vitamin K oral anticoagulants have emerged as possible alternatives for stroke prevention in patients with AF. Thus, the anticoagulated patient undergoing PCI faces a treatment dilemma. Based on a real-life case, we will discuss the optimal anticoagulant and antiplatelet treatment with a review of the literature.

Keywords

Oral anticoagulation, non-vitamin K oral anticoagulants, percutaneous coronary intervention

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Dual antiplatelet therapy (DAPT) is indicated in patients who need to undergo percutaneous coronary intervention (PCI) procedures.¹ Compared with oral anticoagulation (OAC) and aspirin, DAPT has been shown to reduce the risk of thrombotic events and the rate of bleeding events.² Chronic OAC is required in up to 10 % of the patients undergoing PCI, and is usually indicated for AF and mechanical heart valves.³ However, when combining OAC with DAPT, which is also known as triple therapy (TT), the risk of bleeding increases two- to threefold.^{4–7} In contrast, the thromboembolism risk increases when OAC is not prescribed in the antithrombotic regimen, while the risk of stent thrombosis, leading to MI, increases when DAPT is not prescribed as part of the TT.^{8–11} To further complicate this antithrombotic regimen, newer and stronger P2Y₁₂ inhibitors such as prasugrel and ticagrelor are currently recommended as standard treatment in patients with acute coronary syndromes (ACS). It remains unclear whether prasugrel or ticagrelor should be included as part of antiplatelet therapy in these patients with ACS who are on chronic OAC and need to undergo PCI. Another issue to address is that several non-vitamin K oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixiban and edoxaban have been shown to be at least equal or superior to vitamin K antagonists (VKAs) in reducing the risk of stroke in patients with AF.^{12–15} Hence, the anticoagulated patient undergoing PCI faces a treatment dilemma. At present, evidence from randomised controlled trials (RCTs) regarding the optimal antithrombotic regimen is minimal. This article will describe a case report and discuss the optimal anticoagulant and antiplatelet treatment with an overview of the literature.

Case report

An 81-year-old man was admitted to the St Antonius Hospital, Nieuwegein, The Netherlands, with typical chest pain during the night. He experienced no pain at hospitalisation despite his ECG showing ST-segment depression. He had a medical history of hypertension, diabetes mellitus and paroxysmal non-valvular AF. He was diagnosed with non-ST segment elevation MI (NSTEMI), as his ECG showed ST depression and his troponin-T test result was positive. He had been treated with an angiotensin-converting enzyme inhibitor, oral antidiabetics and an NOAC for 2 years. Prior to this treatment, he had been treated with VKA; however, his international normalised ratio (INR) levels remained unstable, which led to the switch to NOAC.

A loading dose of aspirin 300 mg, then 80 mg/day, and a loading dose of clopidogrel 600 mg, then 75 mg/day were started and a coronary angiography was planned. Neither prasugrel nor ticagrelor were given due to their association with increased risk of bleeding in combination with an OAC. The lower-dose NOAC tested for AF was administered. Angiography was performed via the radial approach and low-dose unfractionated heparin (60 IE/kg) was added to prevent catheter thrombosis. A second-generation drug-eluting stent (DES) was implanted when it became clear that this diabetic patient suffered from a long lesion in the left anterior descending artery. No glycoprotein IIb/IIIa inhibitor was added to the antithrombotic regimen, as the risk of bleeding was deemed high. On the second day after PCI, the patient was discharged with the combination of low-dose aspirin, clopidogrel, lower-dose NOAC and a proton pump inhibitor (PPI). Unfortunately, he was readmitted to the hospital 5 weeks later presenting with shock

due to a major bleeding in the gastrointestinal tract. At this time, all antithrombotic agents were temporarily discontinued; red blood cell and platelet transfusions, prothrombin complex concentrate and intravenous PPI were given. A gastric visible vessel was sclerosed, and after 2 days the patient returned to a stable condition. Due to a high risk of stent thrombosis and an acceptable risk of rebleeding, clopidogrel and the lower-dose NOAC were restarted. Aspirin was omitted from the regimen and clopidogrel was discontinued 3 months later.

How to Manage the Anticoagulation During Percutaneous Coronary Intervention?

The current European Society of Cardiology (ESC) guidelines on patients with AF presenting with ACS and/or undergoing PCI or valve interventions recommend uninterrupted OAC with no addition of heparin in the elective setting in those patients at moderate to high risk of thromboembolism (CHA₂DS₂-VASC score of ≥ 2) if the INR is >2.5 .¹⁶ As the patient in this case report had unstable INR levels, VKA was replaced with NOAC. Whether it is safe for patients treated with NOAC to undergo PCI without additional periprocedural heparin or bridging is unknown, except for dabigatran. A small randomised Phase IIa study found that in patients treated with dabigatran alone during elective PCI, the rate of thrombotic events was increased in comparison with patients treated with unfractionated heparin (UFH).¹⁷ In patients on NOAC undergoing PCI, addition of low-dose heparin (60 IU/kg) is recommended to prevent catheter thrombosis.^{18,19}

At present, the X-PLORER (Exploring the Efficacy and Safety of Rivaroxaban to Support Elective Percutaneous Coronary Intervention) study is investigating whether rivaroxaban can prevent thrombosis and other adverse ischaemic events in comparison with UFH during elective PCI.²⁰ This study will hopefully shed some more light on heparin use during PCI in NOAC-treated patients. The Stenting and Oral Anticoagulant (STENTICO) registry found a significant difference in bleeding risk between the radial and the femoral approach (3.8 % versus 10.3 %; $P=0.01$) in patients on OAC undergoing PCI, which resulted in the general consideration that in order to reduce periprocedural bleeding risk, the radial access should be adopted, especially in the OAC-treated patient.²¹ Another consideration in the prevention of bleeding during PCI, is to avoid glycoprotein IIb/IIIa inhibitors in patients on NOAC, unless they are required for the management of complications that emerge during PCI such as thrombus formation during the procedure or no-reflow.²² Stent thrombosis was a frequent consequence after implantation of early generation DES in patients undergoing PCI.²³ The risk of developing stent thrombosis with new-generation DES is comparable to that with bare-metal stents (BMS).^{24–26} Thus, current guidelines recommend that when considering implanting a stent during PCI, second-generation DES and BMS are preferred over first-generation DES.¹⁶

Which Antiplatelet Agents Should be Given in Patients with Acute Coronary Syndrome and AF?

Elective or NSTEMI patients on (N)OAC undergoing PCI with coronary stenting require TT including an antithrombotic regimen that consists of a loading dose of aspirin 150–300 mg followed by 75–100 mg/day and a loading dose of clopidogrel 300–600 mg followed by a daily intake of 75 mg.

Although there are no reports of RCTs comparing NOAC and VKA in patients with AF undergoing PCI, the ESC position paper states that in patients who require TT, NOACs could be used instead of

VKA.¹⁶ Data supporting the current guidelines are mostly based on the post-hoc analysis from the Randomised Evaluation of Long-term Anticoagulation Therapy (RELY) trial.²⁷ A total of 6,952 patients with AF in the RELY study were, at some point during the study, on antiplatelet therapy when comparing the different dabigatran doses (110 mg or 150 mg twice daily [BID]) and VKA. Of this subgroup, there were 812 patients who were simultaneously on aspirin, clopidogrel and VKA or dabigatran, and it was observed that the relative risk of bleeding was similar whether dabigatran or VKA was given in conjunction with DAPT. In addition, 110 mg dabigatran was associated with the lowest rates of absolute bleeding, regardless of the patient's use of only VKA, VKA and a single antiplatelet agent or VKA with DAPT.²⁷ When considering adding NOAC to DAPT, it is advised to use the lower tested dose for stroke prevention in AF patients (dabigatran 110 mg BID, rivaroxaban 15 mg once daily or apixaban 2.5 mg BID).¹⁶

The new P2Y₁₂ inhibitors ticagrelor and prasugrel, which are recommended as the drugs of choice in patients presenting with ACS, are both more potent than clopidogrel. There has been only one small observational study comparing prasugrel ($n=21$) with clopidogrel ($n=356$) in patients undergoing a DES implantation, who received DAPT and had an indication for OAC.²⁸ The patients receiving prasugrel had an increased risk of bleeding (HR 4.6; 95 % CI [1.9–11.4]; $P<0.001$), compared with clopidogrel. Another study investigating a P2Y₁₂ inhibitor was a Swedish registry, in which ACS patients on ticagrelor and VKA ($n=107$) were compared with patients treated with aspirin, clopidogrel and VKA ($n=159$).²⁹ The rates of thrombotic events (recurrent ACS, stroke/transient ischaemic attack and embolism) and major bleeding events were similar in both treated groups (4.7 % versus 3.2 % and 7.5 % versus 7.0 %, respectively). Nonetheless, the regular use of both P2Y₁₂ inhibitors should not be recommended until further research concerning the safety and efficacy of combining prasugrel or ticagrelor with OAC has been completed.

What Should be Done After the Percutaneous Coronary Intervention?

The use of PPIs is recommended to prevent gastrointestinal bleeding in all patients receiving OAC in combination with antiplatelet agents, as this type of bleeding is common among patients undergoing PCI.³⁰ Following the PCI procedure, another consideration is whether to omit aspirin in patients who require TT. The What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) study is the only published RCT that has investigated dual therapy (VKA and clopidogrel) in comparison with TT (VKA, aspirin, clopidogrel).³¹ This study consisted of 573 patients on chronic OAC undergoing PCI with stent implantation between 2008 and 2011. The primary endpoint was the occurrence of any bleeding event, and secondary endpoints were major adverse cardiac/cerebrovascular events. Dual therapy reduced the rates of any bleeding complication in comparison with TT (HR 0.36; 95 % CI: 0.26–0.50; $P<0.001$), while not increasing the rates of stent thrombosis (HR 0.44; 95 % CI [0.14–1.44]; $P=0.165$) or thrombotic endpoints (HR 0.69; 95 % CI [0.29–1.60]; $P=0.382$).

The finding that dual therapy appears to be as effective and safe as TT was supported by two other studies. A Danish registry of patients with AF reported that the risk of thrombosis and bleeding was not increased in patients treated with OAC and clopidogrel ($n=548$) compared with patients treated with OAC, clopidogrel and aspirin ($n=1896$).³² Another registry study ($n=975$) observed that

VKA, clopidogrel and aspirin (TT), clopidogrel and aspirin (DAPT) and VKA and clopidogrel (dual therapy) were comparable in terms of safety and efficacy³³.

Overall, these studies demonstrated that omitting aspirin from the TT did not lead to an increased risk of thromboembolic events and these data may imply that dual therapy (OAC and clopidogrel) may be an alternative to TT. However, it should be taken into account that these studies were not powered to detect differences in the occurrence of thrombotic events. Omission of clopidogrel from the antithrombotic regimen is not recommended in light of findings from a study by van Werkum et al., who showed that discontinuing clopidogrel within 30 days after PCI was the strongest predictor of stent thrombosis (HR 6.5; 95 % CI [8.0–167.8]).³⁴ In contrast, the risk of developing late stent thrombosis may be reduced, as there have been several RCTs that have shown that patients who received 3 months of DAPT after PCI with second-generation DES implantation

had similar rates of stent thrombosis compared with patients who received 12 months DAPT.^{35,36} For the reasons mentioned above, it seems unsafe to cease clopidogrel within the first 3 months after PCI, but one may consider to stop clopidogrel after 3 months of PCI in patients at high risk of bleeding.¹¹

Conclusions

The optimal antithrombotic therapy remains unknown for patients on chronic OAC following PCI with coronary stenting. (N)OAC and DAPT are currently recommended by the ESC guidelines, but are associated with increased risk of bleeding. Some studies have shown evidence that clopidogrel plus OAC may be an alternative for TT. In addition, NOACs may be as effective as VKA as part of TT or dual therapy. Currently, P2Y12 inhibitors (ticagrelor and prasugrel) are not recommended as part of TT in AF patients after PCI. Further research in RCTs are required to clarify the optimal antithrombotic regimen for patients on long-term (N)OAC following PCI. ■

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