Non-vitamin K antagonist oral anticoagulants (NOACs) in the cardiac catheterisation laboratory: Friends or Foes?

Nay Min Htun1,2; Karlheinz Peter1,2,3
1Atherothrombosis and Vascular Biology Lab, Baker IDI Heart and Diabetes Institute, Melbourne, Australia; 2Department of Medicine, Monash University, Melbourne, Australia; 3Heart Centre, The Alfred Hospital, Melbourne, Australia

Managing periprocedural anticoagulation during percutaneous coronary interventions (PCI) of patients on long term oral anticoagulation presents a significant practical problem for the clinicians as 5% to 8% of patients undergoing PCI have an indication for oral anticoagulation therapy (1–3). On the other hand, up to 20–30% of patients on oral anticoagulation for atrial fibrillation (AF) have coexisting coronary artery disease (4). Indeed, it is a very delicate task to get the balance right between the risk of periprocedural bleeding (systemic as well as vascular access site) and thrombotic complications during PCI. This clinical dilemma, present since the days of vitamin-K antagonists (VKAs), becomes even more challenging in the light of the emergence of the "Non-vitamin K antagonist Oral AntiCoagulants" (5) such as rivaroxaban, apixaban, dabigatran and edoxaban.

Recent European registry data showed that in patients with AF while the majority of oral anticoagulants used are still VKAs (78%), NOACs represent 6.1% (6) which is likely to increase as the clinicians’ experience and knowledge of NOACs grow. Currently the lack of specific antidotes for NOACs makes the situation even more complicated for performing invasive procedures, although much effort is currently invested to find specific antidotes which will be highly welcome by clinicians, particularly interventional cardiologists (7).

Consensus guidelines from the learned societies such as European Society of Cardiology (ESC) and American Heart Association (AHA), are constantly being updated to reflect this growing clinical problem with new bodies of evidence whenever available. Current European guidelines endorsed by The European Association of Percutaneous Cardiovascular Interventions (EAPCI) suggest the radial access to be the preferred approach with no additional anticoagulation for elective PCI cases provided INR is above 2 on VKAs whereas NOACs are currently advised to discontinue 48 hours (h) before PCI with periprocedural parenteral anticoagulation as per standard practice (3, 8, 9). In addition, the recent joint European consensus document recommends that whenever oral anticoagulation is used, this can be as well-controlled adjusted dose VKA (with time in therapeutic range (TTR) >70%) (10) or one of the NOACs (9). This is because high TTRs in VKA users are associated with best efficacy (i.e. lower thromboembolism) and safety (i.e. lower bleeding risks) (11).

In the current issue of Thrombosis and Haemostasis, the X-PLORER trial by Vranckx et al. is a much welcome addition to the current literature addressing the important issue of periprocedural anticoagulation in patients undergoing PCI, who are on NOACs – specifically, the oral Factor Xa inhibitor, rivaroxaban (12). The investigators found that the activation of the coagulation system during PCI was effectively suppressed by either 10 or 20 mg of rivaroxaban with or without heparin, based on markers of thrombin generation such as prothrombin fragments 1+2 and thrombin-antithrombin complex.

Although the numbers of patients in this study were quite small and the study was not designed to have enough power to compare the clinical outcomes, it is nevertheless reassuring to see no significant bleeding complications in all patient groups. If this finding can be reproduced in a larger clinical study with enough statistical power, it could potentially warrant updating the guidelines yet again, perhaps making the recommendation of "the 48-h wait after the last dose of rivaroxaban before elective PCI" obsolete. This would be quite desirable especially as we know that the interruption of anticoagulants may expose patients to increased risk of thromboembolic events at least in the case of VKAs (3, 13) and periprocedural bridging by anticoagulation with heparin may increase the overall risk of bleeding without a significant reduction in thromboembolism (14, 15).

Unfortunately, no information regarding the types of vascular access used for PCI is available for the X-PLORER study (12). As the radial approach is becoming increasingly more popular due to improved patient satisfaction and less access site complications including bleeding (16–19), it would be interesting to see whether the study findings of a favourable low bleeding incidence would be equally applicable to both radial and femoral approaches. The advantage of the radial access over the femoral access in terms of bleeding complications was mainly obtained so far in the setting of acute coronary syndromes (ACS)(17–19). Baker et al. found radial access to be associated with fewer bleeding and vascular complications than the femoral approach in patients on warfarin, who underwent PCI (20), but evidence is still quite sparse for patients on NOACs.

What else was interesting and perhaps hypothesis generating? The incidence of peri-procedural myocardial infarction (MI) seemed to be quite different among
the different groups in the X-PLORER cohorts: 31.3% in the heparin group, 13.8% in the heparin plus rivaroxaban 10mg group, 9.4% in the rivaroxaban 20mg group and 0% in the rivaroxaban 10 mg group, respectively (12). This trend of less peri-procedural MI in the rivaroxaban groups is fascinating, even though the study is under-powered for clinical outcomes. In fact, ATLAS ACS2-TIMI 51 investigators found that in patients with recent ACS, rivaroxaban 2.5mg or 5mg twice a day lead to the reduction of the study primary end points (the composite of cardiovascular death, MI or stroke) (21). This protective effect of rivaroxaban in patients with coronary artery disease might potentially explain the incidence of less MIs in the rivaroxaban groups in the X-PLORER study (12).

The patients in the X-PLORER study were required to be on dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for at least five days before PCI. Hence some caution should perhaps be exercised before the study findings can be applied to the patients who present for elective angiograms without full DAPT on-board, which is not uncommon in day to day clinical practice.

Another important point, which the X-PLORER investigators rightly pointed out, is that only elective PCI cases were included in their study and hence it might not be fully applicable to emergency PCI or ACS scenarios. The state of the play is going to be more complex in these acute cases with higher thrombotic burden as well as higher risk of bleeding. But the findings of the X-PLORER study are still thought-provoking and similar studies should follow for acute cases. Current European guidelines suggest primary PCs to be performed via the radial approach with additional parental anticoagulation regardless of the timing of the last dose of oral anticoagulants (3).

Several randomised control studies as well as many meta-analyses have shown that bivalirudin during PCI seemed to have less risk of bleeding with similar mortality rates compared to heparin at the expense of increased stent thrombosis (22–26). HEAT-PPCI was the only study which showed heparin during primary PCI was superior to bivalirudin with less major adverse ischaemic events and no increase in bleeding complications (27), leading to much heated debates since the study was published in 2014. Currently, both European and American guidelines recommend either bivalirudin or heparin as alternative agents during PCI in stable as well as acute cases (3, 28). Now would be the prime time to investigate how “continuing rivaroxaban during PCI” would compare to bivalirudin in patients on long-term NOACs, based on the reassuring findings from the X-PLORER study with heparin.

In this exciting era of defining the spectrum of clinical applications of NOACs, more studies looking into the safety and the different aspects of interaction of NOACs with pre-existing well-established antiplatelets and anticoagulants during PCI are definitely warranted. The X-PLORER study is a good example of pharmacodynamic, clinically relevant studies that are needed to advance our understanding of anti-thrombotic efficacy and to initiate clinical outcome-driven large scale clinical trials. The importance of such studies has been demonstrated in a similar pharmacodynamic study indicating that not all NOACs may provide sufficient anticoagulant effects during PCI (29). Such studies will ultimately have to guide the clinicians in providing the best possible evidence-based care to the patients in the cardiac catheterisation laboratory and beyond. Convincing pharmacodynamic studies such as X-PLORER, clinical endpoint-driven large scale clinical trials, the increasing use of the radial access for PCI and the foreseeable availability of NOAC antidotes have the potential to make NOACs rather than a friend than a foe of interventional cardiologists.

Conflicts of interest
None declared.

References


