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Is it time to follow the guidelines and go OAC alone one year after PCI in patients with AF?

Jonathan Hinton

Background:

Take Home Messages
• There is uncertainty about the optimal antiplatelet/antithrombotic regime for patients one year post PCI with AF, resulting in a discrepancy between guidelines and clinical practice • The OAC-ALONE study does not give us clear answers to this question • It is likely that the optimal strategy will be based on an assessment of the thrombotic and haemorrhagic risk for each individual patient

Antiplatelet therapy is essential for the prevention of stent thrombosis following percutaneous coronary intervention (PCI) (1, 2). However, antiplatelet therapy offers little protection against embolic stroke in patients with atrial fibrillation (AF), particularly when compared with oral anticoagulation (OAC) (3-5). This issue is particularly important because AF is frequently seen in combination with ischaemic heart disease (6). Given that the prevalence of both AF and ischaemic heart disease (IHD) is closely associated with age, this issue is likely to be encountered more frequently going forward. The optimal strategy during the first year post PCI has been evaluated using both warfarin and direct oral anti-coagulants (DOACs). Three trials have demonstrated that the use of an OAC plus dual antiplatelet therapy is associated with a higher risk of haemorrhage without any difference in thrombotic events when compared with the use of an OAC plus single antiplatelet therapy (7-9). The evidence after one year however is less clear.

The European Society of Cardiology (ESC) recommends that antiplatelet therapy be discontinued one year following PCI and that patients be maintained

on OAC alone, unless the patient is considered to be at very high risk of future coronary events. The American Heart Association also recommend dropping antiplatelet therapy at one year post PCI and continuing with an OAC alone, but only in patients considered to have a low thrombotic risk and a high bleeding risk (10). These recommendations are based on retrospective registries demonstrating that the addition of an antiplatelet to OAC one year after PCI is associated with excess bleeding without clear ischaemic benefit (2, 10-13). It is however important to note that these studies are not randomised and hence are open to confounding (6). Furthermore there is reluctance amongst clinicians to stop antiplatelet therapy at this stage due to concerns about the lack of robust evidence and the consequences of stent thrombosis. Thus the results of the Optimising Antithrombotic Care in Patients with Atrial Fibrillation and coronary stent (OAC-ALONE) study were eagerly awaited (14).

The trial:

OAC-ALONE study was a prospective, multi-centre, randomised, open label, non-inferiority study conducted across 111 centres in Japan (14). Patients with AF and stable IHD who had had a PCI more than one year previously were randomised in a 1:1 fashion to either OAC alone or OAC with single antiplatelet (aspirin or clopidogrel). The OAC could be either warfarin or one of the direct oral anticoagulants (DOAC). In Japan the INR target is age adjusted, with patients under 70 years aiming for an INR 2.0-3.0 and those above 70 years aiming for an INR between 1.6-2.6. The study planned to recruit 2000 patients in order to have 90% power to detect non-inferiority at a level of 1-sided error of 0.025.

The study struggled to recruit patients, possibly as a result of clinician reluctance to drop antiplatelet therapy. In order to ameliorate this issue, the study follow up was lengthened and the non-inferiority margin was amended to a hazard ratio of 1.5. The study ended up enrolling 690 patients across a three year period from

2013-2016. The study population, as expected, were elderly (mean age 75 years) and co-morbid (30% had diabetes, 42% had heart failure) with a mean CHADSVASc of 4.6 +/-1.4. The median interval from PCI to enrolment was 4.5 years and a drug eluting stent (DES) was used in 71% (a third of these were first generation DES). Warfarin was the most frequently used OAC (75%). The warfarin therapy was well managed; INR measurements were within the therapeutic range around 75% of the time.

After a median follow up of 2.5 years (IQR 1.8 – 3.4) the primary endpoint (a composite of all cause death, myocardial infarction, stroke or systemic embolism), occurred in 15.7% in the OAC alone group and 13.6% in the OAC and single antiplatelet group and as such failed to meet the threshold for non-inferiority (HR 1.16 (95% CI 0.79-1.72, p=0.20 for non-inferiority). However with regards to the major secondary endpoint (a composite of the primary endpoint or major bleeding (according to the ISTH classification) the study did demonstrate non-inferiority of OAC alone (19.5% in the OAC alone group and 19.4% in the OAC and single antiplatelet group (HR 0.99, 95% CI 0.71-1.31, p=0.016 for non-inferiority)). Patients in the OAC alone group were numerically more likely to suffer from a myocardial infarction (2.3% vs 1.2%) and stent thrombosis (0.58% vs 0%), whilst stroke and systemic embolism occurred more frequently in the OAC plus antiplatelet group (5.5% vs 3.8%). Importantly however none of these differences were statistically significant.

Discussion:

This study attempted to address an important and as yet unresolved clinical issue, but as a result of the slow recruitment and the subsequent under powered nature of the study, it does not provide a clear mandate for practice. This cohort of patients is frequently encountered in clinical practice and as such this study should have been easy to recruit to, particularly as it was run over three years in over one hundred centres. The lack of uptake could be explained by reluctance

amongst clinicians to stop antiplatelet therapy in this patient group. Whilst the baseline characteristics of the patients in the study demonstrate an elderly, multi-morbid cohort that we would expect, it is possible that clinicians were selective when referring patients into the study and only referred patients that they would be happy to stop antiplatelet therapy in.

The study protocol was adjusted due to slow recruitment, resulting in a non-inferiority margin of 1.5 on the hazard ratio scale. This margin is large and as such raises concern that clinically relevant differences could be missed. Interestingly the cross over between study groups was high (12.2% in the OAC alone group and 9.0% in the OAC plus antiplatelet group). Despite most of this crossover being considered clinically appropriate this observation was not expected and could have affected the observed outcome. (6, 14) The open label nature of the study also has the potential to bias the observed results and future studies should consider blinding both patients and clinicians.

There are some potentially important differences between patients in this study and current practice. Firstly warfarin was the OAC used in the majority of patients. Given the improved safety profile of the DOACs it is likely that the haemorrhagic risk would be lower when single antiplatelet therapy was added to a DOAC rather than warfarin (15-18). Furthermore the results of the COMPASS trial suggest that DOACs have a role in the prevention of IHD progression and as such could conceivably provide improved protection in patients post PCI (19). Interestingly only three quarters of the stents in this study were DES and a third of these were first generation DES devices, which given that these devices have a higher stent thrombosis rate limits the applicability of this study to current practice.

The OAC-ALONE study demonstrates that the rate of stent thrombosis is low (0.28%). This is supported by other large studies demonstrating a stent

thrombosis risk of <1% at 2 years (1). Importantly the risk of fatal haemorrhage in OAC-ALONE was higher than the risk of stent thrombosis (11 patients, compared with 2 patients). Whilst the incidence of cardiovascular death was higher than the risk of fatal haemorrhage, it is important to consider that some of these deaths will be arrhythmic or a result of heart failure due to a previous ischaemic insult, which we would not expect antiplatelet therapy to have an effect upon. Given the higher risk of fatal bleeding compared to that of stent thrombosis, a careful assessment of each individual patient's risk is mandated to assess whether the potential benefits of the ongoing addition of a single anti-platelet agent outweigh the bleeding risk.

Further studies are now required to evaluate this important group of patients and the role of maintaining anti-platelet therapy after one year. Furthermore the use of DOACS with their improved safety profile and potential impact on coronary thrombosis needs to be further assessed.

Conclusions

Whilst the conclusions that we can draw from this study are limited by its lack of power, it does highlight an important area of clinical uncertainty where guideline recommended practice and clinical practice are often disparate. The group of patients with AF and IHD with PCI are often elderly and co-morbid and therefore it is crucial that we are able to balance the ongoing ischaemic risk with the risk of haemorrhage. Both the guidelines and the data thus far highlight the need for an individualised assessment of the ongoing risk of haemorrhage and stent thrombosis when considering the optimal treatment strategy. Further research is needed to clarify this important issue.

Disclosures

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