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Antithrombotic therapy in atrial fibrillation and coronary artery disease – Does less mean more?

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In the treatment of patients with chronic coronary syndrome, the use of antiplatelets in the form of aspirin is a Class I indication in the prevention of future thrombotic events (1). Similarly, oral anticoagulation (OAC) has a Class I indication for patients with atrial fibrillation (AF) and a CHA_2DS_2-VASc score of ≥2 in males and ≥3 in females in the form of a non-vitamin K antagonist oral anticoagulant (NOAC) for stroke prevention (2). However, the optimal choice of chronic long term antithrombotic therapy in patients with AF in the presence of coronary artery disease (CAD) has been subject to much debate. Striking the right balance between thrombotic and bleeding risk with different mono or combination therapy with OAC and antiplatelet(s) remains a difficult task requiring the understanding of the dynamic nature of and continual assessment of non-modifiable and modifiable bleeding and thrombotic risk factors (3).

In this issue, the AFIRE investigators report a post-hoc secondary analysis of the AFIRE trial (4). The AFIRE (Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease) multicentre, open-label, randomised clinical trial which was terminated early due to the increased mortality in the combination group, compared rivaroxaban monotherapy to combination therapy (rivaroxaban plus a single antiplatelet agent) in patients with AF and stable CAD. The investigators found that rivaroxaban monotherapy was non-inferior to combination therapy for the primary efficacy endpoint, a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularisation or death from any cause (4.14% vs. 5.75%, hazard ratio [HR] 0.72, 95% confidence interval [CI], 0.55 – 0.95; P<0.001 for noninferiority) and superior for the primary safety endpoint of major bleeding (HR 0.59; 95% CI 0.39 – 0.89; P=0.01 for superiority).

Rather than the conventional time-to-first event analysis, the authors of this posthoc analysis utilised the total number of events as the primary endpoint over the study period which was a median follow up of 24.1 months(4). The results supported the findings of the initial analysis – rivaroxaban monotherapy demonstrated *lower total event rates* when compared to combination therapy (HR 0.62; 95% CI 0.48 – 0.80., P<0.001). When looking further into the different types of events, the authors found that first bleeding events are more clinically impactful than first thrombotic events in terms of mortality risk and these occurred more frequently, regardless of the nature of the first event.

This study highlights several aspects of the treatment of patients with AF and CAD. First, the mean age of patients included in the study was 74 years old, reflective of the ageing population that we are currently seeing in our clinics. The benefit of antiplatelet therapy (in the form of aspirin) in the elderly population declines both for primary and secondary prevention of cardiovascular disease (5). The results of Naito et al (4) also highlight that a shift in focus towards the mitigation of bleeding risk would provide more pronounced clinical benefit within our ageing population, with a 'less is more' approach with regards to the choice of antithrombotics. However, this may not be applicable to patients who are at particularly high thrombotic risk i.e. previous stent thrombosis, severe diffuse CAD or extensive complex coronary stenting (6).

Second, the complexity of managing a multimorbid patient requires further thoughts into providing a more individualised approach, consistent with current approaches to AF management which promotes a holistic and integrated care approach(7) that has been associated with improved clinical outcomes(8). The dynamic nature of both bleeding and thrombotic risks in patients require a continual evaluation of risk (combination of clinical

and biomarkers) and subsequent alterations to their therapy to achieve the optimal outcome (3). Although the use of clinical risk scores such as PRECISE-DAPT and ARC-HBR could aid clinicians in identifying high risk patients, most of these scores were developed and validated in the acute post thrombotic event period. Further, the lack of validation of these scores within the stable CAD population, with under-representation of older adults, may limit the discriminatory value in these patients (9).

Third, the study was conducted in Japan and it is increasingly recognised that bleeding risk, both with OAC and with antiplatelet agents, is increased in East Asians, compared to Western, predominantly Caucasian patients (10). The findings may, therefore, not be generalisable to other populations.

Lastly, the analysis of total event rates, separated into first and subsequent events, in both arms provides a more comprehensive view of the overall benefit and risk of the two approaches. The fact that bleeding events impact more on subsequent mortality perhaps emphasises the dilemma faced by clinicians after a bleeding event on how to optimally manage the subsequent antithrombotic regimen, which was not addressed by this study.

In conclusion, the use of OAC monotherapy in patients with AF and stable CAD appears to be effective and safe when compared to combination therapy with OAC and antiplatelets but will require an individualised approach (11). Validation of currently available risk scores is required in this group of AF patients as it may aid the decision-making process.

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