Is concomitant aspirin helping novel oral anticoagulants? Focus on apixaban

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INTRODUCTION
Apixaban is the third novel oral anticoagulant approved by the Food and Drug Administration for the reduction in the risk of stroke in patients with atrial fibrillation. Apixaban showed a significant reduction in mortality as well as a reduction in strokes compared with warfarin in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.1 However, it is unclear how much of this benefit was derived from the negative benefit to risk ratio (RR) when combining aspirin with warfarin compared with warfarin alone. Approximately one-third of patients receiving combination warfarin-acetylsalicylic acid (ASA) therapy in ARISTOTLE at baseline (31.3% on apixaban, 30.5% on warfarin), with approximately 20–25% of patients receiving aspirin with long-term anticoagulation,2 despite the fact that only 14% of patients randomised to warfarin had a definitive indication for concomitant aspirin therapy (ie, patients having a previous myocardial infarction (MI)). Most patients receiving aspirin had arterial vascular disease, but the majority did not have a recent MI, which is a more appropriate indication for concomitant warfarin-ASA therapy (ie, a history of MI <6 months, depending on the stent used). The high percentage of warfarin-ASA use in ARISTOTLE, despite no clear indication for many of these individuals, introduces a significant confounder. Did aspirin increase the harm in patients on warfarin over and above what would be seen in patients receiving apixaban?

ARISTOTLE
A total of 20–25% of patients were on combination warfarin-ASA in the ARISTOTLE trial, despite the fact that only 14% and 16% of patients had a history or occurrence of MI before and throughout the trial duration, respectively.1 2 It is a conundrum as to why there was such a high rate of concomitant warfarin-ASA allowed, when a favourable benefit to risk ratio for combination warfarin-ASA therapy has only been shown for patients with mechanical heart valves, the very patients excluded from this trial.1 3 4

Combined warfarin-ASA therapy confers a 1–2% absolute risk increase in major bleeds per year compared with warfarin alone, with each major bleed conferring a 9–10% death rate per year.3–5 Therefore, for every 1000 patients treated with combination warfarin-ASA in ARISTOTLE, 20 additional major bleeds and 2 additional deaths per year would occur compared with the group on warfarin alone. It has been previously shown that aspirin in addition to another new oral anticoagulant (dabigatran 150 mg twice daily) does not significantly increase major bleeds. Indeed, aspirin did not significantly increase major bleeds, clinically relevant plus major bleeds, or total bleeds, compared with dabigatran 150 mg twice daily without aspirin in the Dabigatran With or Without Concomitant Aspirin Compared With Warfarin Alone in Patients With Nonvalvular Atrial Fibrillation (PETRO) study.6 This is despite the fact that dabigatran increased gastrointestinal bleeding compared with warfarin in the RE-LY trial. Thus, aspirin may not increase bleeding with concomitant use of apixaban (as it did not with dabigatran); it is generally recognised that apixaban may be the safest novel oral anticoagulant compared to dabigatran and rivaroxaban. If indeed aspirin does not increase the risk of a major bleed with apixaban, then this could potentially affect the interpretation of the ARISTOTLE trial.7

Further evidence supporting the hypothesis that concomitant aspirin use with warfarin may be partially driving apixaban’s ‘benefit’ is the fact that the primary efficacy outcome, stroke and systemic embolism were significantly improved with apixaban versus warfarin in those who were taking aspirin at randomisation (70 events (1.5% per year) vs 94 events (1.9% per year), OR=0.72, 95% CI 0.53 to 0.99, p=0.0474), whereas there was no...
significant benefit with apixaban versus warfarin in patients who were not taking aspirin at randomisation (142 events (1.2% per year) vs 171 events (1.5% per year), OR=0.84, 95% CI 0.67 to 1.05, p=0.1226).\(^{1}\) Additionally, these data indicate that for warfarin patients treated with aspirin at baseline, stroke or systemic embolism was worse (1.9% per year) compared with warfarin patients not treated with aspirin at baseline (1.5% per year; RR 1.23; 95% CI 0.96 to 1.57, p=0.11, albeit not significantly different), whereas stroke/systemic embolism for apixaban patients treated with aspirin at baseline (1.3%) was very similar to apixaban patients not taking aspirin at baseline (1.2%; RR 1.10; 95% CI 0.83 to 1.46, p=0.51). While these data should be interpreted with caution, as patients receiving vs those who are not receiving aspirin are no longer randomised (ie, patients not receiving aspirin may be at a lower risk and differ in other important ways (hidden confounding) that could be contributing to the difference), it does introduce the possibility that concomitant aspirin use affected patients on warfarin differently (and perhaps more detrimentally) than those on apixaban. Generally, when one medication is superior to another there is a trend for benefit throughout all regions. However, the largest geographic region (Europe, n=7343) showed no significant benefit with apixaban versus warfarin for reducing stroke and systemic embolism. In summary, the high use of concomitant aspirin with warfarin in ARISTOTLE may have driven some of apixaban’S ‘benefit’ over warfarin (ie, increased harm, especially haemorrhagic stroke).

**REFERENCES**

Correction

DiNicolantonio JJ, Tomek A, Meier P, et al. Is concomitant aspirin helping novel oral anticoagulants? Focus on apixaban. Open Heart 2014;1:e000134. Competing interest section was published with an incomplete sentence. The correct sentence should be ‘GB-Z has consulted, lectured and served on the advisory board for Astra Zeneca, Bayer, Bristol Myers Squibb, Pfizer and Sanofi Aventis’.

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