Patients with atrial fibrillation and diabetes: does apixaban remain the drug of choice?

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This editorial refers to ‘Clinical outcomes of patients with diabetes and atrial fibrillation treated with apixaban: results from the ARISTOTLE trial’ by J.A. Ezekowitz et al., on page 86

Oral anticoagulation (OAC) is recommended for patients with atrial fibrillation (AF) who are at risk of stroke.¹ The CHA₂DS₂-VASc score, which encompassed a group of common co-morbidities for cardiovascular disease, has been validated to risk stratify patients with AF for OAC treatment.¹ – ³ Nevertheless, reports have shown that the conventional OAC—vitamin K antagonist (VKA) has been overtly underused in real-life situations due to perceived inconvenience associated with frequent monitoring of international normalized ratio, and fear of life-threatening haemorrhage especially during periods of over-anticoagulation.⁴ – ⁶ Recently, non-VKA oral anticoagulants (NOACs) have become an appealing alternative treatment for patients with AF. Overall, they have much more predictable pharmacokinetics and pharmacodynamics, and considerably lower potentials for food and drug interactions when compared with VKA.⁷ Clinical trials have shown that NOACs are at least as efficacious as VKA for the prevention of stroke in patients with AF and at least one risk factor for thromboembolism. More importantly, they are also associated with fewer life-threatening haemorrhage and intracranial haemorrhage.⁸ – ¹⁰ In the ARISTOTLE trial, the use of apixaban was associated with lower rates of stroke or systemic embolism, all-cause mortality, International Society on Thrombosis and Haemostasis (ISTH) major bleeding and intracranial bleeding, and a net clinical benefit of reducing stroke, systemic embolism, major bleeding, or all-cause mortality when compared with adjusted-dose VKA.¹⁰ Nevertheless, recent post hoc analysis of the trial has shown that risk factors for thromboembolism including older age, prior stroke, or transient ischaemic attack in diabetes are independently associated with increased risk of major haemorrhage.¹¹ These do not only underscore the challenge of shared risk factors of stroke and haemorrhage during management of patients with AF, but also raise a question on the impact of individual risk factors on the net clinical benefit of NOAC over warfarin. Indeed, there are very limited data on the risk and benefit of OAC in the subgroup of AF patients with diabetes.

In this issue, Ezekowitz et al. performed a subgroup analysis of the ARISTOTLE trial, and has confirmed that treatment with apixaban is associated with lower rates of stroke or systemic embolism, all-cause mortality, and cardiovascular mortality when compared with adjusted-dose VKA in AF patients with diabetes. Nevertheless, the benefit of reducing major ISTH bleeding with apixaban compared with VKA was not shown in this group of AF patients with diabetes. Furthermore, the benefits of apixaban over VKA in diabetic patients were significantly lower than non-diabetic patients; these differences remained significant even after adjustment for known factors associated with ISTH major bleeding and variables that differed between patients with and without diabetes.

There are some interesting observations regarding the locations of the bleeding events and types of bleeding definition among those patients with or without diabetes. Indeed, a substantial reduction in intracranial haemorrhage was observed in both patients with and without diabetes, and the treatment effect was not altered by the presence of diabetes. This is an important finding because intracranial haemorrhage, which is associated with major morbidity and mortality, is the major barrier for both prescription and acceptance OAC therapy for AF.⁵,¹² Moreover, this reassuring result encourages the use of apixaban in patients with both AF and diabetes. Furthermore, in contrast to ISTH major bleeding, reductions in Thrombolysis in Myocardial Infarction (TIMI) major bleeding and Global Use of Strategies to Open Occluded Arteries (GUSTO) severe bleeding with the use of apixaban when compared with warfarin remained significant in patients with diabetes. A previous study has emphasized the discrepancies in identifying major bleeding using different definitions.¹³ The pitfalls of both TIMI and GUSTO bleeding criteria have been discussed in the Consensus Report From the Bleeding Academic Research Consortium.¹⁴ The ISTH major bleeding, as defined by all
acute and subacute clinically overt bleeding accompanied by either (i) a decrease in haemoglobin level of ≥ 2 g/dL, (ii) transfusion of ≥ 2 U of packed red blood cells, or (iii) fatal bleeding or bleeding from intracranial, intrapacral, pericardiac intra-articular, intramuscular with compartment syndrome, or retroperitoneal spaces, shows a broader coverage of clinically significant bleeding, and has been employed a safety endpoint measure in recent clinical trials. Nevertheless, its prognostic value over TIMI and GUSTO bleeding criteria has not been addressed. As a result, the implication of this isolated increase in ISTH major bleeding remains unknown, and the lack of significance may only be due to inadequate sample size in this subgroup analysis.

In conclusion, this subgroup analysis of the ARISTOTLE trial has confirmed the efficacy of apixaban in reducing stroke or systemic embolism, all-cause mortality, and intracranial haemorrhage when compared with warfarin in patients with and without diabetes. While the reduction of other major bleeding with apixaban in the diabetic patients seems to be less when compared with non-diabetic patients, apixaban should still remain a preferred option for thromboembolism prevention in patients with AF and diabetes.

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References