Letter to the editor: the new CHEST guidelines on antithrombotic therapy for atrial fibrillation should consider recent data on rivaroxaban

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Dear Professor Irwin,

We are writing to you regarding the recently updated CHEST guidelines on antithrombotic therapy for atrial fibrillation (AF).1 These guidelines recommend the use of non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) over VKAs for the prevention of stroke in patients with AF. However, a recommendation specifically to use apixaban, dabigatran (110 mg twice daily) or edoxaban in patients with prior unprovoked bleeding or at high risk of bleeding is also included, based on the fact that all three agents have demonstrated a significantly lower risk of bleeding compared with warfarin. This is listed as a weak recommendation based on ‘very low quality evidence’. Furthermore, the proposed schema for selecting an anticoagulant suggests the use of apixaban, dabigatran or edoxaban, but not rivaroxaban, in Asian patients.1 We believe that these recommendations could benefit from a number of refinements, the rationale and evidence for which we outline below.

It is not possible to compare directly the event rates observed with individual NOACs in the phase III trials comparing NOACs with warfarin for stroke prevention in patients with AF, and no phase III trials have been conducted specifically to compare one NOAC with another. It is, therefore, inappropriate to imply the existence of evidence on the relative safety of the NOACs by recommending specific NOACs over others.2 The guideline recommendations were based primarily on the results of two meta-analyses of the phase III clinical trials comparing apixaban (ARISTOTLE),3 dabigatran (RE-LY),4 edoxaban (ENGAGE AF-TIMI 48)5 or rivaroxaban (ROCKET AF6 and J-ROCKET AF7) with warfarin for stroke prevention in patients with AF.8,9 However, these meta-analyses did not compare the safety outcomes between the individual NOACs or conclude that the safety profiles of apixaban, dabigatran and edoxaban are more favourable than that of rivaroxaban, in either the overall patient population or the subgroup of Asian patients. The meta-analyses only confirmed the efficacy and safety of the NOACs as a class versus warfarin.8,9 Furthermore, the recommendation to use only apixaban, dabigatran or edoxaban in Asian patients does not appear to consider the evidence from the ROCKET AF trial, which clearly demonstrated a reduced risk of intracranial haemorrhage and a trend towards a reduced risk of major bleeding with rivaroxaban versus warfarin in Asian patients.6,9,10 In addition, no differences in primary efficacy or safety outcomes were observed in any of the phase III trials comparing individual NOACs with warfarin in Asian or non-Asian patients with AF.3-6,11

The real-world evidence on rivaroxaban cited in the anticoagulant selection schema1 was a nationwide retrospective cohort study based on data from the Taiwan National Health Insurance Research Database (NHIRD). This study demonstrated that the risk of hospitalization for gastrointestinal bleeding was higher with rivaroxaban compared with dabigatran, but this difference was not maintained in the on-treatment analysis and the authors concluded that either rivaroxaban or dabigatran would be preferable to warfarin in Asian patients in this setting.12 Additionally, two relevant studies providing real-world information on rivaroxaban were not considered in the schema. XANAP was a prospective, observational study that demonstrated low rates of bleeding in Asian patients with AF who received rivaroxaban for stroke prevention, consistent with the results of the ROCKET AF trial as well as other real-world studies such as XANTUS.13,14 A dynamic cohort study, which also used data from the Taiwan NHIRD, demonstrated a lower risk of stroke/systemic embolism, major bleeding, intracranial haemorrhage, gastrointestinal bleeding and all-cause mortality with rivaroxaban compared with warfarin.15

Overall, we believe that it is not possible to recommend the preferential use of individual NOACs in patients at high risk of bleeding and that the evidence supports the use of rivaroxaban in Asian patients. In our view, this should be reflected in the guidelines to encourage evidence-based selection of anticoagulants in patients with AF at risk of stroke, which will ultimately improve patient outcomes.

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