Risk of intracranial haemorrhage in patients with atrial fibrillation treated with novel oral anticoagulants: testing the equivalence margins between dabigatran, rivaroxaban and apixaban

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To the Editor—In evaluating novel oral anticoagulants (NOACs) in atrial fibrillation, the efforts of many researchers worldwide have permitted the advantages of these new drugs over warfarin, in terms of effectiveness and safety, to be reliably determined by direct head-to-head comparisons [1]. As regards safety, incidence rates of intracranial haemorrhage (ICH) among patients treated with NOACs or warfarin in different populations have been explored by several studies, and a significant reduction of ICH has been found with NOACs [1, 2]. On the other hand, the issue of whether the presently approved NOACs (dabigatran, rivaroxaban, and apixaban) differ in their respective risk of ICH has been investigated to a lesser extent. The most comprehensive study in this field is the meta-analysis by Chatterjee and co-workers [2], in which five trials comparing a NOAC with warfarin were included, as well as one trial comparing apixaban with aspirin; each of the NOACs significantly reduced the risk of ICH compared with warfarin or aspirin, while no significant difference was found between specific NOACs by indirect comparison [2]. On the other hand, many publications try to state equivalence, or even superiority, in the risk of ICH between the approved NOACs, but these statements are not supported by specific data.

An increasing amount of research [3] has recently been aimed at differentiating between “no proof of difference” (i.e. failed demonstration of superiority) and “proof of no difference” (demonstration of non-inferiority/equivalence or futility, where futility is essentially represented by equivalence with no treatment). Clearly, proof of no difference is a much more informative result than no proof of difference; however, the former requires that an equivalence (or non-inferiority margin) is incorporated in the analysis.

To study the differences between individual NOACs in ICH incidence, we re-analyzed the results by Chatterjee and co-workers [2], and in particular, we carried out a formal equivalence testing based on confidence intervals (CIs). Our results were expressed as risk differences (RDs), the values of which were incorporated in the standard equivalence graph [4–6]. In handling these equivalence tests, we did not declare any predefined margin of equivalence, but we carried out a post-hoc analysis in which we determined which equivalence margins were compatible with the conclusion of equivalence (see our Supplementary document for methodological details).

Figure 1 summarises, in Panel A, the results of our network meta-analysis; Panel B shows our equivalence testing. In light of these findings, no statement of superiority of a single NOAC over the others is justified based on indirect comparisons in different populations; this conclusion (no proof of difference) is in keeping with HTA reports from Canada [7] and Norway [8].

More interestingly, our results indicate that the equivalence between the four treatments can be considered demonstrated only if the margin is extended up to an unreasonable RD of \( \pm 10.2 \% \). Therefore, stating that these agents are equivalent in their risk of ICH is not currently justified, because this
approach based on network meta-analysis seems to be the
only feasible method for the ranking of NOACs. Finally, one
issue that has not been adequately studied in this field is to
compare the incidence of ICH among warfarin-treated patients
with good or poor standard of care; these analyses, which
would require access to individual patient information, could
be of particular value because the pivotal trials were all global
and they all reported regional differences in ICH incidence,
particularly between Western European vs. Asian and Eastern
European countries.

Conflict of interest None declared.

References