Title: Rigorous Bivariate Synthesis of Benefit-Risk Profiles for Direct Oral Anticoagulants in Atrial Fibrillation

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Abstract

Selection of anticoagulant therapy relies on a balance between ischemic stroke prevention (the benefit) and (the risk) of major bleeding.[1] This analysis highlights a bivariate random effect meta-analysis of the four key Phase III trials. Making a comparison of Direct Oral Anticoagulant (DOACs) versus warfarin drawing on the four key Phase III trials:RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48. This is done by incorporating modern small sample adjustments and conformal prediction intervals, in order to provide a strengthened framework for evidence based decision making under uncertainty.

Synthesis

Traditionally, meta-analytical methods evaluate efficacy and safety outcomes independently. Yet in anticoagulant therapy, these outcomes are inherently linked. The greater the anticoagulant potency typically correlates with reduced stroke incidence, however there is an increased risk of bleeding. To account for this, we applied a bivariate random effects model that accounts for the correlation between the outcomes [2]. This enables an estimation of joint prediction distribution, yielding a more realistic characterisation of net clinical benefit for future patients.

A major challenge is that the evidence base has a limited number of studies ($k=4$). Standard Wald type confidence intervals and DerSimonian-Laird estimators often provide an underestimate in the error rates within sparse data settings, leading to misleading precision and over confidence in pooled estimate. To address this, we utilised the Restricted Maximum Likelihood (REML) estimator with corrected information matrices for estimating between study variance (τ^2) [3]. Furthermore, we implemented the). We also implemented the Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustment, this in turn replaces normal distribution with a t-distribution, which provides an improvement in the confidence interval coverage, when a few studies are available [1].

Lastly, to further enhance external validity and individual prediction, we applied split conformal prediction. This is an assumption lean method that guarantees a finite sample coverage coverage [4]. Although the small sample size limits attainable predictive coverage to around 80%, ($k/[k+1]$), this technique provides a reliable, distribution-free quantification of uncertainty that does not lean on normality assumptions. Hence, this strategy confirms and supports the favourable benefit versus risk profile of DOACs, while also emphasising the importance of rigorous statistical approaches in small sample meta-analysis.

References

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https://github.com/mahmood726-cyber/Bivariatehtml-