Risk of Major Bleeding with Dabigatran versus Active Controls: a Systematic Review and Meta-analysis of Randomised Clinical Trials

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The direct thrombin inhibitor dabigatran is approved for atrial fibrillation (AF) and for prophylaxis of venous thromboembolism (VTE) as a therapeutic alternative to warfarin and enoxaparin, respectively. The standard dabigatran dose is 300 mg/day for AF and 220 mg/day for VTE. As for other anticoagulants, major bleeding represents a safety issue of this drug. Several meta-analyses have evaluated risk of major bleeding related to dabigatran exposure, but not for both approved indications and according to dose. The aim of this study is to evaluate major bleeding risk of dabigatran in AF and VTE, stratifying by dose. A systematic review and meta-analysis was conducted applying keywords related to *Dabigatran* and *Randomised Controlled Trials* (RCTs) in Medline, SCOPUS, and Cochrane database. Actively controlled RCTs with at least 100 patients treated with dabigatran, administered at doses approved in clinical practice for AF and VTE, and with Oxford-Jadad score ≥3, were included in this meta-analysis. Data were extracted independently by two investigators and verified by a third one. The risk ratio (RR) with 95% confidence intervals (CI) of major bleeding of dabigatran was estimated for each indication, and stratified by dose. The pooled RRs were computed using fixed-effect models and, in case of significant heterogeneity between studies, using random-effect models. Statistical heterogeneity among studies was evaluated using Q statistic, while publication bias was evaluated with funnel plot and Egger's regression test. Eight trials (34,078 patients) were included in the quantitative analysis. In AF there was a reduced risk of major bleeding for any dabigatran dose compared to warfarin (RR 0.88, 95% CI 0.78 to 0.98) (Figure 1); in this indication and compared to warfarin a reduced risk was found for dabigatran 220 mg/day (RR 0.81, 95% CI 0.71 to 0.94), while no difference was found for standard 300 mg/day dose (RR 0.94, 95% CI 0.82 to 1.07). In VTE prophylaxis there was no difference in risk for dabigatran compared to enoxaparin 40 mg/day, both for any dabigatran dose (RR 1.07, 95% CI 0.72 to 1.58), and standard 220 mg/day dose (RR 1.31, 95% CI 0.85 to 2.02) (Figure 2). No evidence of heterogeneity or publication bias was found. In conclusion, in AF and prophylaxis of VTE the risk of major bleeding at standard doses of dabigatran was not different to that of active comparators.