# Rivaroxaban for stroke prevention in people with atrial fibrillation and diabetes mellitus

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Atrial fibrillation (AF) is associated with various cardiovascular comorbidities, such as hypertension, heart failure and diabetes mellitus, which increases not only the risk of ischaemic stroke but also of myocardial infarction and mortality. Oral anticoagulation for stroke prevention is the cornerstone of management for people with AF, both with vitamin K antagonists, or with non-vitamin K antagonist oral anticoagulants (NOACs), which show efficacy, safety and convenience compared with vitamin K antagonists [1].

In a recent issue of *Diabetic Medicine*, Coleman *et al.* [2] reported on their 'real-world' retrospective study which used US national MarketScan claims data. Their study included a large sample size of 11 034 people with AF, with a median 1.5 years of follow-up, and compared the performance of rivaroxaban with that of propensity-score matched warfarin (*n*=5517 in each arm). The authors found

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that standard-dose rivaroxaban (20 mg) resulted in a non-significant difference in the efficacy endpoint (stroke or systemic embolism and ischaemic stroke alone), but reduced-dose rivaroxaban (15 mg, used in ~20% of participants) was associated with a 67% lower risk of stroke or systemic embolism (hazard ratio 0.33, 95% CI 0.13--0.79) and an 80.0% lower risk of ischaemic stroke (hazard ratio 0.20, 95% CI 0.07--0.62). Also, both standard and reduced doses of rivaroxaban were associated with similar major bleeding and intracranial haemorrhage compared with warfarin. Based on the results of this study, rivaroxaban was similar to warfarin with regard to effectiveness and safety in people with non-valvular AF and diabetes who were seen in routine clinical practice.

The effectiveness results were generally consistent with the overall results from the phase III randomized ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial, which showed that rivaroxaban was non-inferior to warfarin in reducing ischaemic stroke or systemic embolism in participants [3]. In the ROCKET-AF trial, 40.0% participants had diabetes, and a subgroup analysis showed a twofold increase in the risk of ischaemic stroke amongst people with diabetes compared with those without diabetes; nevertheless, rivaroxaban showed similar results in terms of efficacy and safety in people with AF with and without diabetes [4].

Interestingly, Coleman *et al*. [2] found that rates of ischaemic stroke/systemic embolism in people with diabetes were lower than those seen in the participants with diabetes in the ROCKET-AF trial (0.87 vs 1.74 per 100 patient-years, respectively) [4]. In the international XANTUS (XArelto on preveNtion of sTroke and non-central nervoUS system systemic embolism in people with non-valvular atrial fibrillation) registry, which included 6784 participants treated with rivaroxaban from 311 centres in Europe, Israel and Canada, the overall rate of ischaemic stroke/systemic embolism was 0.8 per 100 patient-years [5]. Lower incidence rates of major bleeding on rivaroxaban were also reported by Coleman *et al*. [2] (2.7 per 100 patient-years) than in people with diabetes in the ROCKET-AF trial (3.79 per 100 patient-years) [4]. Major bleeding rates with rivaroxaban treatment

were also low, at 2.1 events per 100 patient-years in the XANTUS study [5] and 3.0 per 100 patient-years in the Dresden NOAC registry [6].

These inter-study rates should be interpreted with caution, however, given the differences in study designs, settings and patient profiles. Also, outcomes in observational registries are not necessarily independently adjudicated as they are in randomized trials, and the reimbursement for sponsored registries may introduce some channelling biases; that is, negative results are less likely to be published. Indeed, evidence from real-world studies is confounded by methodology issues including patient selection, duration of follow-up and definition of outcomes. Despite reflecting more accurately the clinical characteristics of patients encountered in clinical practice, observational data can only establish an association between the studied variables rather than a cause--effect relationship.

Overall, these data would suggest that in the real-world of people with AF treated with rivaroxaban, the rates of outcomes (both ischaemic and bleeding) are lower than those observed in clinical trials [7]. We also need to see results on cardiovascular outcomes from the cohort studied by Coleman *et al.* [2], as people with diabetes are at elevated risk of myocardial infarction and vascular death. In the subgroup of people with diabetes in the ROCKET-AF trial, for example, the rate of myocardial infarction was 1.35 vs 0.75 ($P$<0.0001) per 100 patient-years in people with vs without diabetes, respectively [4]. Explanations for the difference in stroke outcomes between standard- and reduced-dose rivaroxaban regimens also require further study. Treatment adherence and patient values and preferences should also be addressed, given the importance of these aspects in AF management in the era of NOAC [8,9].

In conclusion, the study by Coleman *et al.* [2] gives us some confidence in prescribing rivaroxaban in people with AF and diabetes. Indeed, evidence from observational studies will continue playing an important role in orientating NOAC prescription in everyday clinical practice.

**Competing interests**

The authors have no competing interests directly related to this paper. G.Y.H.L. has been a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo and a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees were directly received personally.

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