Treatment Persistence in Atrial Fibrillation: The Next Major Hurdle

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In the October issue of *Thrombosis and Haemostasis*, Geng et al reported treatment satisfaction with dabigatran versus warfarin among patients with atrial fibrillation (AF) in China.[1] This time-intensive, patient-centred study with high completion rate of standardized telephone interviews provides high-quality data and key insights from the patients' perspectives. At 6 months, 33.5% of patients had discontinued dabigatran compared with 19.2% for warfarin. The authors report no difference in the global Anti-Clot Treatment Scale (ACTS) Burdens score or the global ACTS Benefits score. The favourable effects of dabigatran regarding decreased concern for dietary or drug interactions and medication-related hassles were offset by the economic burden of dabigatran which is not covered by medical insurance in China. As noted by the authors, the cost of dabigatran is 70 times the cost of warfarin. Factors associated with treatment persistence included older age, longer duration of anticoagulation therapy, global ACTS Benefits score and warfarin therapy.

Other important findings of this study include the overall low proportion of patients in the registry receiving anticoagulant therapy, 27%, for stroke prevention. In addition, of the 4,511 patients in the registry receiving an oral anticoagulant, only 18.5% ($n = 834$) were ultimately enrolled in the study. Prior to propensity score matching, warfarin-treated patients were older, had higher CHA_2DS_2-VASc scores, lower education level and longer duration of anticoagulation use. The investigators did not assess changes in patient satisfaction over time. One would anticipate different attitudes among patients newly starting an anticoagulant opposed to longer term users whose mere persistence is a marker of drug tolerability and patient acceptance. The reasons for medication discontinuation are also of note with 47.6% (dabigatran-treated patients) and 42.9% (warfarin-treated patients) stopping treatment for non-bleeding adverse events, and 13.1 and 11.4%, respectively, for minor bleeding.

Although initiation of anticoagulation among patients with AF remains a major global challenge, treatment persistence is an increasingly recognized major clinical hurdle. Reported rates of treatment persistence vary widely, including within country, depending on the population studied and methodology used to ascertain treatment exposure. Definitions of gaps in treatment that constitute permanent discontinuation vary across studies. In addition, observational studies restricted to new users of anticoagulant treatment provide different insights and conclusions than those studies composed of switchers, restarts or patients already established on treatment. In a retrospective study conducted in Ontario, Canada, investigators used administrative data to assess treatment discontinuation defined as a gap in dabigatran or rivaroxaban prescriptions of 14 days or greater.[2] The cohort was comprised of 15,857 dabigatran-treated patients and 10,119 rivaroxaban users. At 6 months, 36.4% of patients had discontinued dabigatran and 31.9% of patients had stopped rivaroxaban. In the United Kingdom, using the primary care Clinical Practice Research Datalink, patients newly starting anticoagulant therapy for incident AF were identified (12,307 vitamin K antagonist [VKA] and 914 non-VKA oral anticoagulant [NOAC]).[3] Treatment persistence at 12 months for VKA was 63.6% and 79.2% for NOACs.[3] In the Dresden AF Registry, 124 of 341 patients treated with dabigatran discontinued treatment during follow-up (25.8 per 100 patient-years).[4] Similar to Geng et al, the main reasons for treatment discontinuation were non-bleeding side effects. Higher rates of treatment persistence were reported from a prospective study of 1,305 patients with AF in Italy. At 12 months, 15.4% of patients stopped NOAC treatment with most of the discontinuations occurring in the first 6 months.[5] In the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation, 1-year persistence rates for dabigatran were lower than warfarin (adjusted persistence rates: 66% [95% confidence interval [CI], 60–72] vs. 82% [95% CI, 80–84]).[6] This is in contrast to a retrospective cohort analysis of a large U.S. commercial insurance database ($n = 64,661$) of patients with AF that found 47.5% of NOAC-treated patients had a proportion of

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days covered of ≥80%, compared with 40.2% in warfarin-treated patients.[7]

The risk of stroke with treatment discontinuation has been shown in multiple studies including several randomized trials, the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial.[8,9] This risk of stroke has also been shown in clinical practice, and its association with time off treatment (1–3 months: hazard ratio [HR], 1.96, 3–6 months: HR, 2.64, ≥6 months: HR, 3.66; all $p< 0.001$).[7] Given the high morbidity and mortality associated with AF-related stroke, physician and patient thresholds to discontinue treatment and physician and patient reluctance to resume an anticoagulant warrant further study.[10] Geng et al found that nearly half of all discontinuations were for non-bleeding reasons. Access and out-of-pocket patient costs are major determinants of drug adherence and persistence.[11,12] However, having paroxysmal versus permanent AF has also been associated with treatment discontinuation.[13] Certainly the mixed messages that patients receive regarding drug safety from the media warrant clarification by the medical community.

As recently demonstrated by the GARFIELD registry, progress has been made in extending appropriate treatment to patients with AF at high risk of stroke.[14] Targeted educational interventions as employed in the IMPACT AF trial are proven strategies to improve global use of anticoagulants for stroke prevention in AF.[15] Parallel with these efforts is increasing focus on the challenge of long-term medication persistence.[16,17] Perhaps stated best by Raparelli et al, 'A multi-level approach, including patients' preferences, factors determining physicians'prescribing habits and healthcare system infrastructure and support, is warranted to improve initiation and adherence of anticoagulants'.[18]

Conflict of Interest
Research: Janssen. Advisory Board: Bayer, Boehringer Ingelheim, Bristol Myers Squibb/Pfizer, Janssen, Medtronic and Portola. Symposium: Boehringer Ingelheim and Bristol Myers Squibb/Pfizer.

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