Clinical Study Synopsis

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1. Abstract

Acronym/Title	Pattern of use of direct oral anticoagulants in non-valvular atrial fibrillation patients in UK general practices THIN-CPRD Study
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Authors	PPD, PPD Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain
Keywords	Non-vitamin K antagonist oral anticoagulants (NOACs), atrial fibrillation, drug utilization; dosing; discontinuation
Rationale and background	There are limited data on prescription and usage patterns of NOACs in the UK among patients with NVAF. This information is, however, needed to evaluate continuation with therapy and compliance with the drug labelling information.
Research question and objectives	This population-based descriptive study characterized first-time users of apixaban, dabigatran and rivaroxaban in NVAF patients and patterns of use in routine UK primary care. Primary objectives • To describe baseline characteristics of patients with NVAF who are prescribed apixaban, dabigatran or rivaroxaban) for the first time for stroke prevention, and to compare these with the corresponding characteristics of patients in clinical trials. • To assess the pattern of use (daily dose, dose posology, treatment duration, naïve status) of rivaroxaban, dabigatran and apixaban for stroke prevention in NVAF patients in the UK. • To assess the proportion of patients with NVAF and renal impairment who are prescribed rivaroxaban, dabigatran, or apixaban at the index date, and to assess the daily dose, dose posology and duration of NOAC treatment. Secondary objective • To determine time-trends in the characteristics of

	first-time use of rivaroxaban, dabigatran and apixaban in patients with NVAF.
Study design	Population-based cohort study.
Setting	UK primary care, 01 January 2011 to 31 December 2016.
Subjects and study size, including dropouts	The study population included 30,467 individuals with NVAF aged ≥18 years with a first recorded prescription (index date) for apixaban, dabigatran or rivaroxaban.
Variables and data sources	Patient characteristics at the index date: demographics, lifestyle variables, healthcare use, comorbidities (including renal function calculated from estimated glomerular filtration rates values), co-medications and oral anticoagulant (OAC) naïve status. NOAC prescriptions: dose, dose posology, duration of use of index NOAC, appropriateness of dosing, discontinuation, switching and reinitiation, predictors of discontinuation and inappropriate dosing. **Data sources:** The Health Improvement Network and Clinical Practice Research Datalink databases of primary care electronic health records**.**
Results	A total of 30,467 patients with NVAF starting OAC therapy on a NOAC: 15,252 (50.1%) patients started NOAC therapy on rivaroxaban, 10,834 (35.6%) on apixaban and 4381 (14.4%) on dabigatran. The majority of patients prescribed a reduced dose were aged 70 years or older (apixaban 93.6%, dabigatran 88.4%, rivaroxaban 91.4%), and were moderately or severely frail (apixaban, 70.2%, dabigatran 61.7%, rivaroxaban 74.0%) The mean age of patients was 74–75 years, which is just slightly higher than that seen among the three pivotal NOAC AF clinical trials. The gender ratio in our study population was more balanced (50–60% were male) than that in the NOAC AF trials where ≥60% were male. OAC naïve status was: apixaban 53% (vs. 43% in ARISTOTLE), dabigatran 42% (vs. 50% in RE-LY), rivaroxaban 47% (vs. 38% in ROCKET-AF). Hypertension was the most commonly recorded comorbidity (approx. two-thirds of patients in each NOAC cohort), which is less than that seen among participants in ARISTOTLE (87%), RE-LY (79%) and ROCKET-AF (90%). Heart failure was notably less prevalent (approximately 17% in each cohort)

	than patients in the clinical trials (36% in ARISTOTLE, 32% in RE-LY and 63% in ROCKET-AF). Approximately a third of patients in each cohort were obese, while a little under a third each had IHD and hyperlipidaemia. Most patients had normal renal function (apixaban 67.3%, dabigatran 74.4%, rivaroxaban 70.1%), a medium risk of bleeding (HAS-BLED score of 1–3) and a high mean CHA2DS2-VASc score (comorbidity index) of between 3.5 and 3.7. Approximately two-thirds of patients in each NOAC cohort (approx. two-thirds) had a $CHADS_2$ score of between 0 and 2, in line with scores seen among ARISTOTLE and RE-LY trial participants, but indicating a lower comorbidity profile than participants in ROCKET-AF. As expected from patients' comorbidity profile, the most frequently prescribed comedications were antihypertensives, statins, proton pump inhibitors, antiplatelets and diuretics. The majority of patients were prescribed an appropriate dose according to the EU labels: apixaban 74.9 %, dabigatran 74.4%, rivaroxaban 84.2%. There was a trend towards dose reduction with increasing renal impairment. Among patients with severe renal impairment, the majority received a reduced dose NOAC: apixaban 91.1%, dabigatran 80.0%, rivaroxaban 83.0%. Potential underdosing occurred in 21.6% of patients starting NOAC therapy on apixaban compared with 8.7% starting on dabigatran and 9.1% starting on rivaroxaban. potential overdosing was more frequent for dabigatran (16.9%) than for rivaroxaban (6.6%) or apixaban (3.5%). In the discontinuation analysis (N=11,481), one-year discontinuation rates were: apixaban 26.1%, dabigatran 40.0%, rivaroxaban 29.6%. One-year re-initiation rates were: apixaban 18.1%, dabigatran 21.7%, rivaroxaban 17.3%; (≥93% of re-initiations were with the index NOAC). Switching rates were: apixaban 2.8%, dabigatran 8.8%, rivaroxaban 4.9%; discontinuation with no reinitiation was: apixaban 5.2%, dabigatran 9.6%, rivaroxaban 7.4%. Compared with patients starting on apixaban, ORs (% CIs) for discontinuation due to switching were 4.28 (95% CI: 3.24–5.65) for dabigatran and 1.89 (95% CI: 1.49–2.39) for rivaroxaban. Severely reduced renal function was a predictor of any discontinuation, OR 1.77 (95% CI: 1.28–2.44). Only 7% of NVAF patients in our study permanently discontinued OAC therapy (i.e. discontinued their index NOAC and did not reinitiate and type of OAC).

Discussion	Our findings highlight the importance of monitoring the prescribing of NOACs in the post-marketing period. Further research is warranted into reasons for inappropriate prescribing of reduced and standard dose NOACs in UK primary care, the impact this has on risks of clinical outcomes, including stroke, systemic embolism and major bleeding in this setting, and ways to improve levels of correct dosing to ensure patients receive maximum benefit from treatment. Efforts are needed to increase NOAC continuation rates in order to increase the number of NVAF patients benefitting from NOAC-mediated stroke protection, and well-designed large cohort studies are warranted to quantify the impact of interrupting NOAC therapy on thromboembolism risk. Our findings also underscore the importance of considering differences in characteristics when comparing outcomes between real-world populations prescribed NOACs for SPAF and NOAC-AF clinical trials.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen
Names and affiliations of principal investigators	**Principal Investigator**: PPD Co-investigator: PPD Spanish Centre for Pharmacoepidemiologic Research (CEIFE) Almirante, 28, 2 28004 Madrid, Spain Phone: PPD Email: PPD