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Comparative effectiveness and safety of apixaban, dabigatran, and rivaroxaban in patients with non-valvular atrial fibrillation☆

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ABSTRACT

Background: The comparative effectiveness and safety of individual direct oral anticoagulants (DOACs) in clinical practice is largely unknown. The study objectives were to compare effectiveness and safety of DOACs in patients with non-valvular atrial fibrillation (NVAF).
Methods: Based on nationwide registers we established a population-based historical cohort study of 12,638 new users of standard dose DOACs (apixaban 5 mg twice daily, dabigatran 150 mg twice daily and rivaroxaban 20 mg once daily) with NVAF in Denmark, July 2013 to March 2016. Patients were matched on propensity scores in a 1:1 ratio comparing apixaban vs. dabigatran (for a total of 6470 patients), apixaban vs. rivaroxaban (7352 patients), and rivaroxaban vs. dabigatran (5440 patients). Hazard ratios (HRs) for stroke or systemic embolism (effectiveness outcome) and major bleeding (safety outcome) were estimated.
Results: In propensity-matched comparisons of the risk of stroke or systemic embolism, the HRs were 1.27 (95% confidence interval [CI], 0.82–1.96) for apixaban vs. dabigatran, 1.25 (95% CI, 0.87–1.79) for apixaban vs. rivaroxaban, and 1.17 (95% CI, 0.69–1.96) for rivaroxaban vs. dabigatran. For the risk of major bleeding, the HRs were 0.94 (95% CI, 0.62–1.41) for apixaban vs. dabigatran, 0.88 (95% CI, 0.64–1.22) for apixaban vs. rivaroxaban, and 1.35 (95% CI, 0.91–2.00) for rivaroxaban vs. dabigatran.
Conclusions: Among patients with NVAF in routine clinical practice, there were no statistically significant differences in risk of stroke or systemic embolism or major bleeding in propensity-matched comparisons between apixaban, dabigatran, and rivaroxaban used in standard doses. While analyses indicate that more than moderate differences can be excluded, smaller differences cannot be ruled out.

1. Introduction

Atrial fibrillation is the most common arrhythmia in developed countries and is associated with an up to five-fold increased risk of stroke and with increased mortality [1–4]. Anticoagulants are critical for prevention of stroke, and since the introduction of direct oral anticoagulant (DOAC) drugs their use has become widespread in clinical practice [5–7].

Anticoagulant treatment for stroke prevention should be weighed against the primary concern of an increased risk of bleeding. In clinical trials, the efficacy of DOACs (apixaban, dabigatran, rivaroxaban, and edoxaban) has been shown to be at least non-inferior to warfarin, but with superior safety profiles, mainly due to lower rates of intracranial bleeding [8–17]. To date, however, no head-to-head trials comparing individual DOACs have been published. In network meta-analyses of randomized controlled trials (RCTs), similar rates of stroke and systemic embolism were found for apixaban, dabigatran, and rivaroxaban. Further, there were significantly lower risks of clinically relevant bleeding for apixaban compared to both dabigatran and rivaroxaban and for dabigatran compared to rivaroxaban [17–20]. However, potential heterogeneity in the included study populations and trial methodology might have influenced the validity of these indirect comparisons [8,17].

In the absence of RCTs comparing individual DOACs, observational studies utilizing data from clinical practice can provide means to assess the comparative effectiveness and safety of individual DOACs [20–22]. Given lack of randomization, observational studies are inherently

Abbreviations: DOAC, direct oral anticoagulant; NVAF, non-valvular atrial fibrillation; ATC, Anatomic Therapeutic Classification system; ICD-10, International Classification of Diseases version 10; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack; PPV, positive predictive value.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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susceptible to confounding and other types of bias [23]. Careful attention and study designs that appropriately prioritize internal validity are therefore necessary. In a nationwide cohort study, we investigated the association between use of apixaban, dabigatran, and rivaroxaban and risk of stroke or systemic embolism and major bleeding among patients with non-valvular atrial fibrillation (NVAF).

2. Methods

2.1. Study design

We conducted a historical register-based cohort study from July 1, 2013 to March 31, 2016. The source population consisted of new users of apixaban, dabigatran, and rivaroxaban, aged 45 years of age or older, with a recent diagnosis of NVAF. The start of the study period was selected to avoid the inclusion of very early users of each of the included DOACs (dabigatran was introduced in Denmark August 2011; rivaroxaban February 2012; and apixaban, December 2012 [24]), who may have been selected individuals [25]. This study was designed with the purpose of maximizing internal validity allowing simpler interpretation and a more robust comparison of cohorts. Firstly, the study was restricted to new users of anticoagulants, with no previous use of any DOACs or warfarin within one year prior to study entry. The new user design reduced the potential influence from previous treatments with the study drugs or factors associated herewith which could otherwise bias the results [26]. Secondly, the study only included patients with a recent diagnosis of NVAF within 90 days prior to start of DOAC treatment to reduce confounding by indication as well as to ensure more similar time points in course of disease (details and International Classification of Diseases [ICD] codes for inclusion in Supplemental Table 1). Thirdly, the study was restricted to patients receiving standard dose treatment of DOAC (apixaban 5 mg twice daily, dabigatran 150 mg twice daily, and rivaroxaban 20 mg once daily) with the intention to reduce the potential for unmeasured confounding. Reduced dose of DOAC are generally prescribed to elderly patients and patients with more advanced comorbidity, such as renal disease, and is likely to be associated with poorer health and frailty; factors that are difficult to capture using register data. Fourth, to further reduce the potential for confounding by indication and unmeasured confounding, we excluded participants who: i) had major musculoskeletal surgery within the last 30 days, ii) had chronic kidney disease (stage 4, 5 or receiving dialysis), iii) had heart valve disorder, prosthesis, or surgical heart valve procedure, or iv) had venous thromboembolism within the last six months (see Supplemental Table 1 for further details). Fifth, propensity score matching was used to take into account a broad range of baseline characteristics that may potentially influence the risk of the outcome.

The study included three sets of analyses in separate propensity score-matched cohorts. We estimated the risk of stroke or systemic embolism and major bleeding associated with use of apixaban compared with dabigatran in the first cohort, apixaban vs. rivaroxaban in the second cohort and rivaroxaban vs. dabigatran in the third cohort. The date of the first filled prescription for a DOAC was defined as the study index date. The primary effectiveness outcome was defined as a hospital admission with a primary or secondary diagnosis of stroke or systemic embolism. The primary safety outcome "major bleeding" was defined as a hospital admission with a diagnosis of intracranial bleeding, gastrointestinal bleeding (bleeding ulcer, hematemesis or melena) or other serious bleeding (anemia caused by bleeding, bleeding of unknown origin, bleeding of the respiratory or urinary tract, peritoneal, retinal or orbital bleeding). Outcome definitions are provided in Supplemental Table 2.

2.2. Data sources

Individual-level data were linked between different registers using the unique personal identification number assigned to all inhabitants in Denmark. We established the cohort on the basis of records of diagnoses of NVAF obtained from the National Patient Register [27] and information on filled prescriptions of anticoagulants obtained from the Register of Medicinal Product Statistics [27,28]. Information on outcomes was obtained from the National Patient Register. Supplemental Table 1 list all study drugs with ATC (Anatomic Therapeutic Classification system)-codes. Data on potential confounders was obtained from the National Patient Register (medical history), the Danish Civil Registration System (demographic variables) [29] and the Register of Medicinal Product Statistics (drug utilization). Definitions for all covariates are provided in Supplemental Table 3. A detailed description of the various registers is provided in the supplementary material.

2.3. Exposure definition

Episodes of apixaban, dabigatran, and rivaroxaban treatment were defined to last as long as new overlapping prescriptions were filled. The duration of each filled prescription was defined by the number of tablets in the package and the recommended treatment regimen with standard dose for each drug (i.e. for apixaban, dabigatran, and rivaroxaban, respectively, two, two, and one tablets a day). To avoid gaps in continuous treatment episodes, we allowed a 30-day gap between the last day of the previous prescription and the date of the new prescription.

2.4. Confounder control

The propensity score was estimated using a logistic regression model, including as predictors all variables in Table 1. Users of individual DOACs were matched 1:1 on the propensity score to create three pair-wise matched cohorts: apixaban vs. dabigatran, apixaban vs. rivaroxaban, and rivaroxaban vs. dabigatran [30]. Matching was performed using the nearest neighbor algorithm (caliper width 0.2 of the standard deviation of the logit score).

2.5. Statistical analyses

Follow-up started on the index date and ended on the first instance of an outcome event, death, disappearance, emigration, one year after index date, end of treatment, switch to another DOAC or warfarin, or end of study period (March 31, 2016). All analyses were conducted using Cox proportional hazards regression, estimating hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazard assumption was assessed using a Wald test for the interaction between time since index date and treatment. *P* values were based on Wald tests. All statistical tests were two-sided; CIs that did not overlap 1.0 were considered to indicate statistical significance. Analyses were performed with the use of SAS software 9.4. Subgroup analyses were conducted according to sex, age (≥65 years vs. <65 years), history of stroke or transient ischemic attack (TIA), and history of bleeding. In secondary analyses, we analyzed all-cause mortality along with subtypes of primary effectiveness and safety outcomes as well as fatal primary outcome events.

The study was approved by the Danish Data Protection Agency. Ethics approval is not required for register-based research in Denmark.

3. Results

3.1. Cohort selection

During the study period, we identified a total of 13,957 new users of DOACs with NVAF, of whom 12,638 were eligible for inclusion (4920 apixaban, 3913 dabigatran, and 3805 rivaroxaban [Fig. 1]). Supplemental Table 4 displays the unmatched baseline characteristics for each individual DOAC. After propensity score estimation and matching in a 1:1 ratio, the cohorts used in the analyses of apixaban vs. dabigatran included a total of 6470 participants; apixaban vs. rivaroxaban a total of 7352 participants and rivaroxaban vs. dabigatran included a total of 5440 participants. In each of the matched cohorts, baseline characteristics were well balanced between the groups (Table 1) with standard deviations below 10% and nicely weighted (see Supplemental Table 6).

3.2. Primary outcomes

Fig. 2 reports HRs for the primary effectiveness outcome of stroke or systemic embolism and primary safety outcomes of any major bleeding for the three propensity score-matched analyses during one-year follow-up along with incidence curves. The proportional hazard assumption was fulfilled for all primary effectiveness and safety analyses.

3.2.1. Apixaban vs. dabigatran

Mean follow-up was 210 days for apixaban and 241 days for dabigatran. For use of apixaban, stroke or systemic embolism occurred with an event rate of 2.36 per 100 person compared with 1.78 per 100 person years for use of dabigatran (HR, 1.27; 95% CI, 0.82–1.96). Major bleeding occurred with an event rate of 2.25 per 100 person years for use of apixaban compared with 2.34 per 100 person years for use of dabigatran (HR, 0.94; 95% CI, 0.62–1.41). During use of apixaban, death from any cause occurred with an event rate of 3.19 per 100 person years compared with 2.79 per 100 person years for use of dabigatran (HR, 1.12; 95% CI, 0.79–1.61).

3.2.2. Apixaban vs. rivaroxaban

Mean follow-up was 212 days for apixaban and 201 days for rivaroxaban. Stroke or systemic embolism occurred with an event rate of 3.19 per 100 person years for use of apixaban compared with 2.57 per 100 person years for use of rivaroxaban (HR, 1.25; 95% CI, 0.87–1.79). Major bleeding occurred with an event rate of 3.37 per 100 person years for use of apixaban vs. 3.87 per 100 person years

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