Risk of bleeding with non-vitamin K oral antagonists and phenprocoumon in routine care patients with non-valvular atrial fibrillation


Introduction

- Oral anticoagulation therapy (OAC) substantially reduces the risk of stroke in patients with non-valvular atrial fibrillation (NVAF) (1).
- The most important side effect of OAC is bleeding.

Since 2011 non-vitamin K oral anticoagulants (NOACs) are available for stroke prevention in patients with NVAF.

NOACs are easier to use than vitamin-K antagonists (VKA) and have demonstrated equivalent or even superior efficacy and safety in comparison to VKA in large randomized controlled trials (RCTs) (2).

The efficacy and safety achieved in RCTs may not necessarily translate into routine practice.

Phenprocoumon is the predominantly used VKA in Germany.

This study was conducted under the acronym CARROS (Comparative risk of major bleeding with new oral anticoagulants (NOACs) and phenprocoumon in patients with atrial fibrillation).

Objectives

- To compare the risk of major bleeding, gastrointestinal bleeding and any bleeding in daily practice among German NVAF patients newly anticoagulated with apixaban, dabigatran, rivaroxaban or phenprocoumon, respectively.

Methods

Study Population:

This non-interventional, retrospective study was based on an anonymized research data base from the Health Risk Institute (HRI) (3,4) which contains data of about 4 million statutory health insured subjects in Germany, approximately 5% of the total population.

The HRI (periods by Spectrum) conducts independent statistical analyses on anonymized claims data for patient-level risk predictions, outcome research, and patient safety.

- All patients ≥18 years with one year of baseline period were included if they were newly prescribed OAC from January 1, 2013 to December 31, 2014 and had a documented NVAF (based on ICD-10 DM 458.1,1468.1,2494.9) diagnosis in the same or the preceding quarter of the treatment initiation.
- Patient selection is presented in Figure 1.

Obervation start date: Date of first prescription for oral anticoagulants from Jan 1, 2013 to Dec 31, 2014.

Study endpoints:

- Bleeding on anticoagulant was defined as bleeding documented at hospital discharge any time during the period from the starting date of the last supply of treatment prescription to 30 days from the last supply of treatment prescription.
- Major bleeding consists of emergency admission to hospital and pre-specified ICD-10 GM hospital discharge diagnosis.

- Gastro-intestinal (GI) bleeding: Bleeding at any time during exposure time with localization in the GI-tract and documented as hospital discharge diagnosis.

- Any bleeding: Pre-specified or secondary ICD-10 GM hospital discharge diagnoses at any time.

- Bleeding events that occurred on treatment, defined as the time after the first prescription till the end of the study period, discontinuation of treatment, death, end of continuous enrollment, or switching to another OAC were included (whatever occurred first).

Analytical Statistics

- Unadjusted rates of bleeding events were described as number of bleeding events per 100 person-years.
- The study population included 71,335 patients with NVAF from 3 different regions of Germany (Munich, Munich, Rueil-Malmaison, France).

Sensitivity Analysis

- Analyses with the highest approved doses (2x5mg for apixaban, 2x150 mg for dabigatran, and 1x20 mg for rivaroxaban) were performed.

Results

- Among 35,013 eligible patients, 3,833 (10.8%) were initiated on apixaban, 3,138 (8.96%) on dabigatran, 12,063 (34.45%) on rivaroxaban, and 16,179 (46.21%) on phenprocoumon.
- The mean follow-up for patients initiated on apixaban was 207.78 days, dabigatran was 264.45 days, rivaroxaban was 262.78 days, and phenprocoumon was 284.93 days.
- Patients initiated on apixaban or phenprocoumon were older compared to those initiated on dabigatran or rivaroxaban, had on average a higher CHA2DS2-VASc score, and more comorbidities (Table 1).
- Patients initiated on apixaban had greater use of ASA, NSAIDs, antiplatelet drugs and proton-pump-inhibitors compared to patients initiated on phenprocoumon, dabigatran, or rivaroxaban (Table 1).

- After adjusting for baseline characteristics, apixaban was associated with lower risks for major bleeding, gastrointestinal bleeding and any bleeding compared with phenprocoumon (Figure 2).

- Rivaroxaban was associated with higher risk of GI bleeding and any bleeding, whereas there was no significant difference in the risk of major bleeding between rivaroxaban and phenprocoumon users (Figure 2).

- Table 2: Adjusted hazard ratios with 95% confidence intervals (CI) for each pairwise comparison (apixaban, dabigatran, and rivaroxaban each vs phenprocoumon).

Conclusions

- This is the first evaluation related to bleeding events comparing different NOACs and phenprocoumon in daily clinical practice in Germany.
- Our results indicate that treatment with apixaban is associated with a significantly reduced risk for bleeding events compared to phenprocoumon. Bleeding risk with dabigatran was comparable to phenprocoumon but rivaroxaban seems to be higher.
- Sensitivity analyses (e.g. subgroup of highest approved doses of NOACs) were consistent with the primary findings in demonstrating the better safety profile of apixaban vs. phenprocoumon in this real world setting.

Disclosure

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References