Science For A Better Life

Clinical Study Synopsis

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Title	Real-world comparative effectiveness of stroke prevention in patients with atrial fillibration treated with Rivaroxaban vs vitamin K antagonists (RELOAD).
Keywords	Claims data, Rivaroxaban, atrial fibrillation, safety, effectiveness
Rationale and background	Non-valvular atrial fibrillation (NVAF), the most common cardiac arrhythmia worldwide, affects approximately 1-2% of the general population and is a major risk factor for ischemic stroke. Xarelto® (Rivaroxaban) is a Factor Xa inhibitor which is marketed for stroke prevention in patients with NVAF. This study was conducted to obtain a better understanding on the comparative effectiveness of Rivaroxaban versus Phenprocoumon for stroke prevention in patients with NVAF in a routine care setting.
Research question and objectives	The aim of this study was to assess the real world comparative effectiveness of Rivaroxaban prescribed in non-valvular atrial fibrillation (NVAF) routine care patients in Germany. The primary objective of this study was to assess the risk of ischemic stroke (effectiveness) and intracranial hemorrhage (ICH, safety) in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon. The secondary objectives of this study were: - to assess the cerebral benefit defined as the combined endpoints of ischemic stroke and ICH in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon. - to assess combined effectiveness defined as the endpoints of ischemic stroke, systemic embolism (SE) and transient ischemic attack (TIA) in patients treated with Rivaroxaban compared to patients treated with Phenprocoumon. The components of this combined endpoint were also analyzed separately.
Setting	The study included data from the inpatient and outpatient setting as well as information on drug prescriptions from a sample of German sick funds. Two study cohorts were observed: • NVAF patients who were initiated on Rivaroxaban for stroke prevention • NVAF patients who were initiated on Phenprocoumon for stroke prevention.
Subjects and Study Size, including dropouts	A preliminary feasibility assessment using the HRI database identified a total of approximately 39,600 treatment naïve users of Phenprocoumon and 22,800 treatment naïve users of Rivaroxaban between January 1, 2011 and September 30, 2015 being eligible for the planned cohort study.
Variables and Data sources	The study was conducted using data from the HRI research database. This database includes information about the utilization of

	services on a case-by-case individual level. To support claims, indications (ICD-10-GM codes) and procedure codes are provided together with costs. The size of the dataset has been reduced to a sample of approximately 4 million patients per year, representative of the German population in terms of age and gender (as of 31.12.2013). Demographic characteristics, co-morbidities, relevant co-medications, bleeding and stroke risk scores as well as the clinical outcome parameters were analyzed. The primary outcome parameters were ischemic stroke and ICH; Secondary outcome parameters were the combined endpoints cerebral benefit (ischemic stroke or ICH) as well as combined effectiveness (ischemic stroke, SE or TIA). Single events included in all combined endpoints were analyzed as part of the secondary objective. Components of ICH (subarachnoid hemorrhage, intracerebral hemorrhage, other and unspecified non-traumatic intracranial hemorrhage) were assessed separately as well.
Results	Patient characteristics were analyzed descriptively and showed that Rivaroxaban patients were slightly younger and healthier than Phenprocoumon patients. The mean of CHA2DS2-VASc Score and modified HAS-BLED score was slightly higher in the Phenprocoumon group. The mean follow-up time for the primary effectiveness endpoint in the main analyses (derived by the empirical defined daily dose) was 367 days for Rivaroxaban patients and 408 days for Phenprocoumon patients. The mean follow-up time for the primary effectiveness endpoint in the sensitivity analyses (1 tablet per day (3mg) for Phenprocoumon) was 367 days for Rivaroxaban patients and 241 days for Phenprocoumon patients. The unadjusted incidence rate for the primary effectiveness endpoint ischemic stroke was 1.76 per 100 person years and for primary safety endpoint intracranial hemorrhage 0.49 per 100 person years in the Rivaroxaban group. The unadjusted incidence rate for the primary effectiveness endpoint ischemic stroke was 1.62 per 100 person years and for primary safety endpoint intracranial hemorrhage 0.51 per 100 person years in the Phenprocoumon group. Results of primary endpoints in the main analysis (empirical defined daily dose) based on a multivariate regression showed lower risks for Rivaroxaban for both, ischemic stroke and intracranial hemorrhage. However, results were statistically not significant. Results of primary endpoints in the sensitivity analysis (1 tablet per day (3mg)) based on a multivariate regression showed a significant

	risk reduction for ischemic stroke of 23% for patients receiving Rivaroxaban. Results for the primary safety endpoint were consistent with the main analysis. These results were consistent across different models, i.e. propensity score matching and IPTW. A sensitivity analysis was conducted, where only patients diagnosed with renal impairment were included. 1954 Rivaroxaban patients were compared with 3871 Phenprocoumon patients. The mean follow-up time for the primary effectiveness endpoint in this analysis using the empirical defined daily dose was 346 days for Rivaroxaban patients and 367 days for Phenprocoumon patients. The mean follow-up time for the primary effectiveness endpoint in this analysis using the 1 tablet per day (3mg) definition for Phenprocoumon was 367 days for Rivaroxaban patients and 203 days for Phenprocoumon patients. The unadjusted incidence rate for the primary effectiveness endpoint ischemic stroke was 2.60 per 100 person years and for primary safety endpoint intracranial hemorrhage 0.53 per 100 person years in the Rivaroxaban group. The unadjusted incidence rate for the primary effectiveness endpoint ischemic stroke was 2.98 per 100 person years and for primary safety endpoint intracranial hemorrhage 0.71 per 100 person years in the Phenprocoumon group. Results of primary endpoints in this analysis was consistent across different models. Results showed a strong trend towards lower risks for Rivaroxaban for both, ischemic stroke and intracranial hemorrhage, although results were statistically not significant. Further sensitivity analyses were conducted for 20mg Rivaroxaban initiators (sensitivity analysis 1), patients without any events from the combined endpoints (sensitivity analysis 2) and including cancer patients (sensitivity analysis 3). Results in these sensitivity analyses were consistent with overall findings. Other analyses: As a further exploratory analysis a more recent data cut of the underlying data source was used to additionally look into a renal subgroup population. With the inclusion of additional data, collected up to December 2016, a total of 4164 patients with renal impairment were prescribed rivaroxaban and 7002 were prescribed phenprocoumon. Patients with renal impairment prescribed rivaroxaban or phenprocoumon were of similar age (76.9 years and 77.2 years, respectively), had similar CHA2DS2-VASc (4.4 and 4.5,

	espectively) and CHADS2 (2.9 in both groups) scores, and received similar baseline medication
Discussion	In the main analysis of this study, the use of Rivaroxaban was not associated with significant differences regarding safety and effectiveness compared to Phenprocoumon when applying an algorithm for an empirical defined daily dose for Phenprocoumon exposure time calculation. When applying the literature based defined daily dose for Phenprocoumon the exposure time differed substantially. Results showed a significant reduction in risk for ischemic stroke for patients receiving Rivaroxaban. As a conclusion, results showed differences depending on how exposure time in Phenprocoumon patients was measured, however results within renal impaired patients showed a consistent trend across all different models towards better effectiveness and safety of Rivaroxaban vs. Phenprocoumon. Further analyses with more recent data cuts are necessary to confirm these findings. Sensitivity analyses for a renal impaired subgroup showed a strong trend towards a protective effect of Rivaroxaban vs. phenprocoumon. As of the small sample size, there was not enough power to show significance. Although patient numbers in this subgroup were low, the results presented here suggest that rivaroxaban is more effective and safer than phenprocoumon in patients with NVAF and renal impairment. The results of this subgroup analysis were generally consistent with the trends observed in the main analysis, showing evidence for the improved effectiveness and safety profile of rivaroxaban versus phenprocoumon in this patient population.
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