NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: BEYOND Pooled –Part of the BEYOND study program (BEnefit of NOACs studY of nOn-valvular AF patieNts in NorDic countries)

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Rationale and background: Non-vitamin K oral anticoagulants (NOACs) are an alternative treatment option for patients with non-valvular AF (NVAF), since they allow for a more convenient anticoagulation regimen than VKAs, with comparable efficacy and safety. Many previous observational studies examined the safety and effectiveness of NOACs in routine clinical practice and generally found apixaban, dabigatran and rivaroxaban to have positive benefit to risk balance when comparing each NOAC with warfarin. Among the limitations affecting previous studies are the relatively short follow-up, and insufficient precision, especially in subgroup analysis. Scandinavian countries are an optimal setting for such studies given the universal access to health care, similar clinical practice, uniform recording practices, comparable patterns of hospitalization and referral to specialist care, and high quality of warfarin therapy.

Research question and objectives: The overall aim of this study was to evaluate effectiveness and safety of each NOAC compared with warfarin in treatment-naïve adult initiators of anticoagulants with NVAF in routine clinical practice in Denmark, Norway and Sweden. The primary objective is to compare, among patients treated with each of the NOACs (apixaban, dabigatran, rivaroxaban) vs warfarin; risks of the 1) composite endpoint of any stroke or systemic embolism (SE) at an acute hospitalisation with an overnight stay and 2) any bleeding at an acute hospitalisation with an overnight stay. Secondary objectives include pairwise comparison of each NOAC vs. warfarin with respect to risks of ischaemic stroke, haemorrhagic stroke, intracranial bleeding, gastrointestinal bleeding, SE, acute myocardial infarction, and all-cause mortality. The exploratory objectives include descriptive analysis of health care resource utilization in the four treatment cohorts.

Study design: Cohort study. To compare risks among initiators of each NOAC vs warfarin, Cox's proportional-hazards regression was used. Crude and adjusted (via PS-score matching) hazard ratios (HRs) and 95% CIs for all endpoints were estimated for initiators of each NOAC vs. propensity-score matched initiators of warfarin.

Setting: This study was set in the three Scandinavian countries, each of which has tax-funded universal health care; routine recording of prescription dispensings, hospital diagnoses, migrations and deaths; and individual-level data linkage, thus enabling nearly

complete follow-up of the entire populations and virtually no selection bias or attrition in observational epidemiologic studies.

Subjects and study size, including dropouts: The study population were treatment-naïve adult patients with AF in Denmark, Norway, and Sweden, with a dispensing of apixaban, rivaroxaban or dabigatran ('the NOACs') or warfarin between 01 January 2013 and 31 December 2016, and followed-up until 31 December 2016. After exclusion criteria were applied, 71,585 patients entered the apixaban cohort; 31,209 patients entered the dabigatran cohort; 37,580 patients entered the rivaroxaban cohort and 79,171 patients entered the warfarin cohort.

Variables and data sources: This study was based on routinely collected data from population-based health and administrative registries and databases in Denmark, Norway, and Sweden. Data in all registries and databases accumulate prospectively. The primary study endpoints were serious events requiring hospitalisation and are therefore expected to be well captured in the available data sources.

Results: Patients in the apixaban cohort tended to be older and to have greater comorbidity burden than patients in the other cohorts.

In patients treated with apixaban vs. warfarin the adjusted hazard ratios (HRs [95% confidence intervals, CIs]) were 0.96 (0.87 – 1.06) for any stroke or SE and 0.73 (0.67 – 0.78) for any bleeding. Compared with warfarin, patients treated with apixaban had similar rates of ischaemic stroke and acute MI, and had lower rates of haemorrhagic stroke, any type of bleeding, or systemic embolism. Treatment with apixaban was associated with a slightly higher all-cause mortality than treatment with warfarin.

In patients treated with dabigatran vs. warfarin the adjusted HR (95% CI) were 0.89 (0.80 – 1.00) for any stroke or SE and 0.89 (0.82 – 0.97) for any bleeding. Compared to warfarin, patients treated with dabigatran had similar rates of ischaemic stroke, systemic embolism, acute MI, or death of any cause, had lower rates of haemorrhagic stroke, and intracranial bleeding, but had a substantially higher rate of GI bleeding.

In patients treated with rivaroxaban vs. warfarin the adjusted HR (95% CI) were 1.03 (0.92 – 1.14) for any stroke or SE and 1.15 (1.07 – 1.25) for any bleeding. Compared to warfarin, patients treated with rivaroxaban had similar rates of ischaemic stroke, or acute MI, but substantially higher rate of any type of bleeding except intracranial bleeding. Rates of GI bleeding were substantially higher in initiators of rivaroxaban than in initiators of warfarin.

There were cohort-specific variations observed in treatment switching and discontinuation.

Healthcare resource utilization and cost were described within each country in the first and second year after initiation of the oral coagulant.

Discussion: Compared with warfarin, apixaban and dabigatran were associated with lower rates of bleeding whereas rivaroxaban was associated with a higher rate. The three NOACs had comparable rates of stroke and systemic embolism compared with warfarin.

Marketing Authorization Holder(s): Bristol-Myers Squibb/Pfizer European Economic Interest Group (EEIG)

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