Observational Study Results Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Overall data disclosed, may differ from published or presented data and are a reflection of the limited information provided here. The results from a single study need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

1. Abstract

Acronym/Title	REATTAIN
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IMPACT study number	20030
Keywords	Atrial fibrillation, oral anticoagulants, safety, effectiveness, ischemic stroke, intracranial hemorrhage, real-world evidence
Rationale and background	Oral anticoagulant treatment is essential for the prevention of ischemic stroke or systemic embolism in patients with atrial fibrillation. Evidence from routine clinical practice on the outcomes of reduced doses of non-vitamin K antagonist oral anticoagulants (NOACs) is scarce. This study aimed to assess the effectiveness and safety of these regimens compared to vitamin K antagonists (VKA) for stroke prevention in patients with non-valvular atrial fibrillation.
Research question and objectives	The overall aim of the study is to evaluate the comparative safety and effectiveness of reduced doses of NOACs vs. VKA for stroke prevention in patients with NVAF. **Primary Objective** • To describe the risk of ischemic stroke (IS)/systemic embolism (SE), and intracranial hemorrhage (ICH) in patients with NVAF initiating treatment with reduced doses of individual NOACs (rivaroxaban, apixaban, dabigatran) compared to VKA (warfarin) **Further objectives** Additional objectives are: • To describe the treatment persistence in patients with NVAF initiating treatment with reduced doses of individual NOACs compared to VKA. • To describe the risk of acute kidney injury (AKI) and kidney failure in patients with NVAF initiating

	treatment of reduced doses of individual NOACs compared to VKA. • To describe the risk of severe IS and fatal bleeding in patients with NVAF initiating treatment with reduced doses of an individual NOACs compared to VKA.
Study design	Observational cohort study
Setting	The study was based on data from national registers in four Nordic countries (Denmark, Finland, Norway and Sweden). The study period ran from 1 January 2010 until 31 December 2018. The study was conducted with separate country cohorts, reporting country specific outcomes.
Subjects and study size, including dropouts	Study participants originates from national registers from Denmark, Finland, Norway, and Sweden. The registers have a national coverage and hence, the study population is drawn from the full population within each respective country.
Variables and data sources	Index drug, exposure time and days of supply were used to estimate the individual drug exposure. Outcomes definition included IS/SE, ICH, fatal bleeding, AKI, kidney failure and persistence. Covariates included demographic characteristics, clinical characteristics, comorbidities and comedications. The data was obtained from national administrative registers in Sweden, Denmark, Finland, and Norway, these included the national patient registers, the prescriptions registers and the cause of death registers in each country. Other relevant registries included the national quality of care register on stroke in Sweden.
Results	The study, one of the largest observational investigations to date, involved nearly 135,000 oral anticoagulant-naïve patients, approximately 27,000 of whom received NOACs. The incidence of ischemic stroke and systemic embolism was similar or lower than that of comparable patients who used standard warfarin therapy (rivaroxaban: hazard ratio (HR) 0.93 (95% confidence interval (CI) 0.62-1.40), dabigatran: HR 0.88 (95% CI 0.68-1.14), and apixaban: HR 0.79 (95% CI 0.67-0.94) in meta-analysis across countries.

	The incidences within warfarin groups ranged from 2.16-3.71 per 100 person-years for the four separate countries comparable to those receiving a NOAC. The incidence of intracranial hemorrhage was generally low, with event rates ranging from 0.16 to 1.85 per 100 person-years. In comparison with warfarin patients the meta-analyses across countries yielded HR's; rivaroxaban: HR 1.41 (95% CI 0.78-2.57), dabigatran: 0.35 (95%CI 0.19-0.64), and apixaban: 0.72 (95% CI 0.51-1.04).
Discussion	In this comprehensive nationwide study across Nordic countries, researchers examined AF patients initiated on reduced doses of NOACs, including dabigatran, rivaroxaban, and apixaban. The incidences of ischemic stroke and systemic embolism in patients on reduced NOAC doses were comparable to or even lower than those in patients commencing standard warfarin therapy. The incidence of intracranial hemorrhage events among NOAC-treated patients remained generally low, with rates ranging from 0.16 to 1.85 per 100 person-years. This variability may potentially result from inclusion or non-inclusion of hemorrhagic transformation strokes in the endpoint composite in some of the institutions. HRs for intracranial hemorrhage were generally numerically higher for rivaroxaban compared to the weighted warfarin group, with a pooled HR of 1.41 (95% CI 0.78-2.57). This was primarily influenced by a higher HR observed in Finland among rivaroxaban patients. Finland had a relatively low percentage of new users of reduced dose NOACs, only 7.2%, compared to the other Nordic countries. This resulted in an extremely small sample size and less precise estimates in Finland compared to the other countries, thus the Finish results are more prone to random variability. Conversely, rates among dabigatran and apixaban-treated patients were lower than among comparable warfarin patients, resulting in a pooled HR of 0.35 (95% CI 0.19-0.64) and 0.72 (95% CI 0.51-1.04), respectively. Further differences emerged among Nordic countries, with Finland standing out for offering better protection against ischemic stroke and systemic embolism at the expense of a higher risk of intracranial hemorrhage, particularly with rivaroxaban. Notably, Finland exhibited a relatively low percentage of new users of reduced dose NOACs, suggesting a cautious approach to their use for AF patients.

	The study's findings were consistent with prior research, affirming that reduced dose NOACs in routine clinical use were associated with comparable or lower rates of ischemic stroke and systemic embolism compared to warfarin. The detailed analysis, utilizing comprehensive national registries, highlighted the importance of considering regional variations, timing of NOAC introduction, and differing treatment preferences in understanding outcomes. This research, conducted in a setting with universal healthcare accessibility, similar clinical practices, and high-quality warfarin therapy, contributes insights into the comparative effectiveness and safety of anticoagulants in routine clinical practice, emphasizing the significance of real-world evidence in guiding treatment decisions for AF patients.
Marketing Authorization Holder(s)	Bayer AG