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Clinical Study Synopsis

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Title	**S**afety and **E**ffectiveness of **R**iva**r**oxaban and **A**pixaban compared to warfarin in non-valvular atrial fibrillation patients in the routine clinical practice in the UK SiERRA UK
Report version and date **Author**	v1.0 22 SEP 2021 [redacted] Spanish Centre for Pharmacoepidemiologic Research (CEIFE)
Keywords	Ischaemic stroke; intracranial bleeding; direct oral anticoagulant; warfarin; cohort; nested case–control
Rationale and background	Direct oral anticoagulants (DOACs) are increasingly being used in the prevention of stroke among patients with nonvalvular atrial fibrillation (NVAF). Recent reports suggest that a significant proportion of individuals who are eligible for standard use of these drugs might be receiving reduced doses instead, especially for apixaban. This could undermine the effectiveness of these drugs. We aimed to evaluate this by exploring the risk of ischaemic and haemorrhagic events under the different conditions of use of rivaroxaban or apixaban (reduced/standard dose and appropriate/inappropriate dosing) compared with warfarin.
Research question and objectives	In this population-based study among patients with nonvalvular atrial fibrillation (NVAF) who initiated apixaban, rivaroxaban or warfarin as treatment for stroke prevention, we compared the risk of safety and effectiveness outcomes associated with appropriate/inappropriate use of apixaban/rivaroxaban vs. use of warfarin. **Primary Objectives** • To compare the safety of rivaroxaban (20 mg and 15 mg; once daily) and apixaban (5 mg and 2.5 mg; twice daily) vs. warfarin in patients appropriately/ inappropriately receiving standard/reduced doses of apixaban/rivaroxaban in accordance with the label for stroke prevention in atrial fibrillation (AF). Outcomes were: • Intracranial bleeding (ICB; intracerebral hemorrhage [ICH], subarachnoid hemorrhage [SAH], subdural and epidural hematoma) • Haemorrhagic stroke (HS [ICH and SAH) • To compare the effectiveness of rivaroxaban (20 mg and 15 mg once daily) and apixaban (5 mg and 2.5mg twice daily) vs. warfarin in patients appropriately/inappropriately receiving standard/reduced dose in accordance with the label for stroke prevention in AF. • Ischaemic stroke and systemic embolism (IS/SE) • Myocardial infarction (MI)

	Secondary Objectives • To evaluate the primary objective outcomes in sub-groups of patients with renal impairment and diabetes. • To evaluate all-cause mortality in patients appropriately or inappropriately receiving standard or reduced dose apixaban/rivaroxaban compared to patients receiving warfarin. • Drug utilisation patterns and characteristics of patients receiving standard or reduced dose apixaban/rivaroxaban, and or patients receiving warfarin in accordance and not in accordance with the label • Drug utilisation patterns and characteristics of patients receiving standard or reduced dose apixaban/rivaroxaban, and or patients receiving warfarin following the first ICB or IS/SE during the study period.
Study Design	A population-based retrospective cohort study with nested case-control analysis. Patients with NVAF who were new users of either apixaban, rivaroxaban or warfarin between 01 January 2012 and 30 June 2018 were followed up to 31 December 2018 to identify major safety and effectiveness outcomes. Associations between study exposure and the risk of safety and effectiveness outcomes, and of all-cause mortality, were subsequently analysed in three independent nested-case control analyses.
Setting	United Kingdom primary care – IQVIA Research Data UK (IMRD-UK) primary care database
Subjects and Study Size, including dropouts	A total of 45,164 patients with NVAF were identified: 14,701 started on apixaban, 14,288 started on rivaroxaban and 16,175 started on warfarin
Variables and Data sources	**Exposure:** apixaban/rivaroxaban/warfarin exposure was assessed at the index date. Current use was defined as drug supply that lasted until/over the index date or ended in the 30 days before index date) without current use of any other OAC. **Outcomes:** Primary outcomes were ICB, HS, IS/SE and MI. Secondary outcomes were the primary outcomes within chronic kidney disease (CKD) and diabetes subgroups, allcause-mortality, and OAC use after study outcomes.
Results	For ICB, ORs (95% CIs) for apixaban vs. warfarin were 0.67 (0.44–1.00), for appropriate dose and 0.45 (0.21–0.95) for inappropriate dose; for rivaroxaban vs. warfarin, estimates were 0.81 (0.55–1.20) for appropriate dose, and 1.14 (0.56– 2.31) for inappropriate dose. For HS, ORs (95% CIs) for apixaban vs. warfarin were 0.89 (0.53–1.50), for appropriate dose and 0.55 (0.19–1.59) for inappropriate

	dose; for rivaroxaban vs. warfarin, estimates were 0.98 (0.59–1.63) for appropriate dose, and 2.39 (1.00– 5.72) for inappropriate dose. For IS/SE, ORs (95% CIs) for apixaban vs. warfarin were 1.19 (0.92–1.52) for appropriate dose and 1.01 (0.67–1.51) for inappropriate dose; for rivaroxaban vs. warfarin, estimates were 1.07 (0.83–1.37) for appropriate dose and 1.21 (0.78– 1.88) for inappropriate dose. For MI, ORs (95% CIs) for apixaban vs. warfarin were 1.29 (0.96–1.73), for appropriate dose and 1.73 (1.12–2.67) for inappropriate dose; for rivaroxaban vs. warfarin, estimates were 1.21 (0.89–1.64) for appropriate dose, and 1.68 (1.04– 2.70) for inappropriate dose. Overall risks of IS/SE, ICB, haemorrhagic stroke, MI and allcause-mortality were not significantly different in patients prescribed appropriately/inappropriately dosed apixaban/rivaroxaban and those prescribed of warfarin in either the CKD or diabetes subgroups. Risk of MI was higher in patients with CKD receiving an appropriate dose of rivaroxaban compared with warfarin (OR 1.79, 95% CI: 1.02– 3.16); this effect was not seen for inappropriately dosed rivaroxaban although the numbers of patients in this stratum was small. The proportion of individuals prescribed OAC therapy after their event was 40.6% among the warfarin cohort, 44.8% among the rivaroxaban cohort, and 56.9% among the apixaban cohort. Most patients experiencing an IS/SE were prescribed OAC therapy after their event; 85.3% of the warfarin cohort, 84.5% of the rivaroxaban cohort and 89.2% of the apixaban cohort.
Discussion	In this large population-based study among patients with NVAF, we found no significant difference in the risk of IS/SE between patients prescribed appropriately/inappropriately dosed apixaban or appropriately/inappropriately dosed rivaroxaban and those prescribed warfarin. Risk of ICB was significantly reduced in patients prescribed appropriately/inappropriately dosed apixaban compared with those prescribed warfarin, and was not significantly different between those prescribed appropriately/inappropriately dosed rivaroxaban and those prescribed warfarin. No differences in IS/SE or ICB risk were seen between patients prescribed appropriately/inappropriately dosed apixaban/rivaroxaban and those prescribed warfarin, among those with impaired renal function or diabetes. Residual confounding cannot be excluded as at least a partial explanation for this study's results, as exemplified from our findings for all-cause mortality and MI, where we were unable to demonstrate the reduction in risk seen among patients prescribed apixaban/rivaroxaban in the well-designed pivotal phase III trials.

	In conclusion, apixaban/rivaroxaban dosing in NVAF was not associated with a significant difference in IS/SE risk or increase in ICB risk when compared with warfarin. These findings may reflect clinical scenarios that cannot be readily controlled for in the analyses (i.e. residual/unmeasured confounding), as well as differential exposure misclassification and selection bias.
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