Science For A Better Life

Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial 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.

Title	An observational post-authorization safety Specialist Cohort Event Monitoring study (SCEM) to monitor the safety and utilization of rivaroxaban (Xarelto®) for the prevention of stroke in patients with AF, treatment of DVT and PE, and the prevention of recurrent DVT and PE in the secondary care hospital setting in England and Wales (The ROSE study)
Keywords	Rivaroxaban – Post-marketing – Safety – SCEM – ROSE
Rationale and background	Rivaroxaban (XARELTO®) is a highly selective direct factor Xa inhibitor which inhibits thrombin formation and the development of thrombi. This post-marketing Specialist Cohort Event Monitoring (SCEM) safety study of rivaroxaban was carried out by the Drug Safety Research Unit (DSRU) as part of the Risk Management Plan (RMP) for rivaroxaban
Research question and objectives	The primary objective was to quantify the cumulative incidence of haemorrhage (within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites) occurring during the study period in patients treated with rivaroxaban. In addition to the primary objective there were several secondary and exploratory objectives aimed at exploring differences in the prevalence of non-clinical reasons for prescribing and prognostic and clinical risk factors for the risks of interest between rivaroxaban and an alternative anticoagulant therapy (contextual) cohort, as well as describing changes in the health profile of patients over the course of the study and the risk of non-major bleeding events.
Study Design	An observational, population-based cohort design of 2 cohorts (rivaroxaban and a contextual cohort (warfarin) with data collection at start of treatment (index date) and 12 weeks post-index date. The contextual and rivaroxaban cohorts had different exclusion criteria and therefore no formal comparative analyses were planned or conducted between the cohorts.
Setting	Secondary care hospital setting in England and Wales.
Subjects and Study Size, including dropouts	4846 patients provided consent to participate in the study. Baseline and 12 week questionnaires were provided for 4625 (95.4%) patients; of these four (0.1%) were ineligible leaving 4621 patients evaluable patients, of which 55.0% (n=2542) were prescribed rivaroxaban and 44.7% (n=2067) were prescribed warfarin.
Variables and Data sources	Patient data were derived from medical charts at index date and 12 weeks post-index date via questionnaires. Information on specialist characteristics was derived from self-reported information, supplemented from publically available professional body registration data.
Results	**Site/HCP engagement** 1196 specialists recruited patients to the study, with no obvious

differences in the geographic distribution or distribution of socioeconomic status overall between participating and non-participating trusts. For three indicators of adoption of new medicines, the proportions were higher for participating compared to non-participating trusts.

Patient characteristics at baseline

Demographics

Demographic variables were broadly similar between the rivaroxaban and warfarin cohorts.

Although numbers were small, approximately twice as many rivaroxaban patients had a history of previous substance abuse (1.5% vs 0.8% respectively) although the history of previous alcohol misuse was similar between groups (5.1% vs 5.8% respectively).

The primary clinical condition for which anticoagulant therapy was used was similar in both cohorts. AF and DVT/PE indications accounted for the primary indication for 98.3% of patients. Consequently the other subgroups have limited data although information on these groups is presented in the report.

Prior and concurrent medical conditions

Similar baseline history for important risk factors such as haemorrhage and cardiovascular disease was seen in each treatment cohort for the AF indication, although for the DVT/PE indication the baseline history of haemorrhage was higher in the warfarin treatment group.

Stroke and bleeding risk prediction score for all indications

Most of the HAS-BLED indicators were similarly distributed between the two treatment groups for each indication, except that more rivaroxaban patients in the AF group had a history of stroke (30.9% rivaroxaban vs. 20.9% warfarin).

The individual criteria included within the CHA2DS2-VASc score also had broadly similar distributions within the treatment groups although there appeared to be more patients within the rivaroxaban AF group with a prior history of stroke, TIA or thromboembolism.

Outcomes

Rivaroxaban group: The overall unadjusted cumulative incidence of major bleeding within gastrointestinal, urogenital and intracranial sites was 0.5% (n=13), 0.3% (n=7), and 0.1% (n=3) respectively.

Contextual Warfarin group: The overall unadjusted cumulative incidence of major bleeding within gastrointestinal, urogenital and intracranial sites was 0.2% (n=3), 0.1% (n=2) and 0.1% (n=2) respectively.

For all indications, the unadjusted cumulative risk for clinically relevant non-major bleeds, major bleeds (all) and a composite was also higher in the rivaroxaban group in relation to the contextual warfarin group 4.8% (n=121), 1.3% (n=33), 6.1% (n=154) vs. 3.2% (n=67), 0.7% (n=14), 3.9%

	(n=81). **Deaths** 41 (1.6%) patients in the rivaroxaban cohort and 35 (1.7%) patients in the warfarin cohort died within the 12-week observation period. A further patient in the warfarin treatment group (Mixed indication) died but the date of death was unknown. Causes of death between the rivaroxaban and warfarin cohorts were similar for patients with AF but differed between the treatment groups for patients with DVT/PE. Within the DVT/PE group there were three fatal cases of acute renal failure on rivaroxaban and one fatal case of acute renal failure on warfarin.
Discussion	This study shows that rivaroxaban is largely being prescribed in accordance with prescribing recommendations and also national clinical guidelines. The estimates of risk of major bleeding at any specific site in the AF and DVT/PE rivaroxaban user populations are currently consistent with those estimated from clinical trial data and are low (<1%). An increase in the unadjusted risk of major bleeding was observed for rivaroxaban in relation to the warfarin contextual cohort; a possible explanation is the baseline differences between both cohorts. No adjusted analyses were carried out in the scope of this study. *Conclusion* This study was not designed as a comparative study. The risk of gastrointestinal, urogenital or intracranial bleedings were low and in line with previous knowledge based on RCTs as well as observational studies. Rivaroxaban was in most cases used according to the label and national guidelines. This study is part of a broader literature in the safety of rivaroxaban and any conclusions on safety should be put into context with results from other post marketing studies for the product.
Marketing Authorisation Holder(s)	Bayer AG, 51368, Leverkusen, Germany
Names and affiliations of principal investigators	SAW Shakir MB ChB LRCP&S FRCP FFPM FISPE MRCGP, Director DSRU, Bursledon Hall, Southampton SO31 1AA, UK