1. Abstract

Acronym/Title	Pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany (EU PAS Register No. ENCePP/SDPP/11145)
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Keywords	Germany, rivaroxaban, vitamin K antagonists, phenprocoumon, safety, effectiveness, atrial fibrillation, venous thromboembolism, acute coronary syndrome
Rationale and background	Rivaroxaban (RVX) is an oral, direct factor Xa inhibitor with multiple indications, including but not limited to: prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery (TKR/THR); treatment and prevention of recurrent deep vein thrombosis and pulmonary embolism (VTE-T); stroke prevention in atrial fibrillation (SPAF); and prevention of atherothrombotic events following an acute coronary syndrome (ACS). As anticoagulant use is associated with bleeding risk, monitoring of the safety profile and patterns of rivaroxaban use in routine care is required. This study forms part of the overall rivaroxaban post-authorization safety monitoring activities in four European countries.
Research question and objectives	To assess patterns of drug utilization and to quantify outcomes related to safety and effectiveness in first-time users of rivaroxaban compared with first-time users of phenprocoumon (PPC), which is the standard of care in Germany for the two main indications.
Study design	This study used a cohort design to assess patterns of rivaroxaban utilization and patient characteristics, and to estimate unadjusted incidence rates of safety and effectiveness outcomes during the first episode of treatment. Bleeding outcomes occurring during complete follow-up were also analyzed using a nested case-control design.

Setting	German Pharmacoepidemiological Research Database (GePaRD) which consists of claims data from four German statutory health insurance providers covering over 25 million individuals throughout Germany.
Subjects and study size, including dropouts	All patients with incident exposure to RVX or SOC during the enrollment period. After application of the inclusion and exclusion criteria, the following first-time users of RVX/SOC were identified: SPAF 127,743/88,655, VTE-T without a recent history of caner 25,914/20,502, VTE-T with a recent history of cancer 5198/-, TKR/THR 30,079/-, ACS 546/-.
Variables and data sources	Baseline covariates included medical history, comorbidity and co-medication. Additionally, for patients with nonvalvular atrial fibrillation, the risks of stroke and bleeding were estimated using the CHA_2DS_2VASc score and the HAS-BLED score, respectively. Potential indications were assessed by diagnoses and procedures. For the indications prevention of stroke in patients with atrial fibrillation (SPAF), treatment and secondary prevention of deep vein thrombosis or pulmonary embolism (VTE-T) and prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS), unadjusted incidence rates were estimated for all primary and secondary outcomes. Additionally, a nested case-control was performed to estimate confounder-adjusted odds ratios (ORs) of the four bleeding events (intracranial hemorrhage, gastrointestinal bleeding, urogenital bleeding, and other bleeding) in current users of RVX and PPC compared to past nonusers in the past year.
Results	For SPAF and VTE-T, unadjusted incidence rates of gastrointestinal and urogenital bleeding observed in first-time RVX users were higher than those observed in first-time PPC users. Unadjusted incidence rates of IC bleeding were similar in both cohorts and unadjusted incidence rates of other bleedings were lower in first-time RVX users. In the nested case-control analysis, current use of rivaroxaban was associated with a higher risk of intracranial, gastrointestinal, urogenital, and other bleeding relative to nonuse, both in the SPAF and VTE indication.
Discussion	As rivaroxaban and SOC are likely to be prescribed to groups of patients with different characteristics that cannot be fully adjusted for in the analyses, no comparative statistical analyses were conducted. Furthermore, informal comparisons of unadjusted incidence rates of bleeding outcomes between the rivaroxaban and SOC cohorts should be interpreted with caution because a greater proportion of the time at risk in the

	rivaroxaban cohort accumulated in the early high-risk period than in the SOC cohort and risk of bleedings is higher. The safety and effectiveness profile of rivaroxaban for SPAF and VTE-T in this real-world population is consistent with its expected profile, based on knowledge from randomized controlled trials and other studies. Limited conclusions can be made regarding the efficacy and safety of rivaroxaban for ACS, owing to very low uptake for this indication over the time period studied. No new safety concerns have been identified.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen, Germany