Clinical Study Synopsis

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1. Abstract

Acronym/Title	Final study report comprising the pharmacoepidemiological study program of rivaroxaban use and potential adverse outcomes in routine clinical practice in the UK, Germany, the Netherlands and Sweden
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Authors	UK: PPD Spain Germany: PPD Germany Netherlands: PPD Netherlands Sweden: PPD Sweden
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Keywords	UK, Germany, Sweden, Netherlands, rivaroxaban, vitamin K antagonists, safety, effectiveness, atrial fibrillation, venous thromboembolism, acute coronary syndrome
Rationale and background	Rivaroxaban 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 program 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 standard of care anticoagulants (hereafter referred to as SOC).

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	All patients with incident exposure to rivaroxaban or SOC during the enrollment period.
Subjects and study size, including dropouts	After application of the inclusion and exclusion criteria, the following first-time users of rivaroxaban/SOC were identified in each study. Sweden: rivaroxaban, 58,974; SOC, 121,908 UK: rivaroxaban, 24,953; SOC, 25,346 Germany: rivaroxaban, 265,584; SOC, 172,727 Netherlands (overall): rivaroxaban, 23,670; SOC, 85,112 Netherlands (subcohort with available general practitioner data): rivaroxaban, 5641; SOC, 18,918
Variables and data sources	Detailed descriptive variables were captured relating to demographics, healthcare resource utilization, lifestyle characteristics, mediations, medical history and renal function. The data sources used for these studies included the IQVIA Medical Research Data-UK (IMRD-UK) database in the UK, the German Pharmacoepidemiological Research Database (GePaRD), the PHARMO Database Network in the Netherlands and the Swedish Health Registers.
Results	For SPAF, the majority of patients were prescribed 20 mg once daily, while the remainder were prescribed 15 mg. Almost all patients who received rivaroxaban for TKR/THR were prescribed 10 mg once daily. For VTE-T, patients were predominantly prescribed either 15 mg or 20 mg, with 15 mg being more common than 20 mg in Sweden, the Netherlands and Germany. In the ACS cohort, which was very limited in size across all studies, few patients were prescribed the 2.5 mg tablet. For SPAF, unadjusted incidence rates of intracranial and other bleeding were lower for rivaroxaban users than SOC users, whereas unadjusted incidence rates of gastrointestinal bleeding and urogenital bleeding were higher, although there were some minor deviations from this trend in the individual countries. For VTE-T, unadjusted incidence rates of intracranial and other bleeding were lower for rivaroxaban users than SOC users in Sweden and Germany, but unadjusted incidence rates of urogenital bleeding were higher. Unadjusted incidence rates of gastrointestinal bleeding

	were higher among rivaroxaban users than SOC users in all countries. There were few bleeding events among rivaroxaban users for the ACS indication. In the nested case-control analysis, current use of rivaroxaban for SPAF was associated with a similar risk of intracranial bleeding and urogenital bleeding as nonuse in the UK, the Netherlands and Sweden. Current use of rivaroxaban was associated with a higher risk of gastrointestinal bleeding relative to nonuse in all countries except Sweden. Current use of rivaroxaban was associated with a higher risk of other bleeding relative to nonuse in Germany and the UK, but not in the Netherlands or Sweden. For VTE-T, current use of rivaroxaban conferred a similar risk of intracranial bleeding as nonuse in Sweden or the UK, but a higher risk in Germany. Current use of rivaroxaban was associated with a higher risk of gastrointestinal bleeding relative to nonuse in all countries except the Netherlands. Current use of rivaroxaban was associated with a higher risk of urogenital and other bleeding relative to nonuse in Germany and Sweden, but not in the UK or the Netherlands.
Discussion	Based on the characteristics of first prescription/dispensation, dose posology (UK, Netherlands) and tablet strengths (Germany, Sweden) were broadly in line with the dose recommendations for each indication except for ACS. 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 for the SOC cohorts in the UK, Sweden and Germany. The safety and effectiveness profile of rivaroxaban for SPAF and VTE-T in these real-world populations 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.
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