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Challenges and Lessons Learned from a Long-Term Post-Authorisation Safety Study Programme of Rivaroxaban in Europe

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ABSTRACT

Objectives: To describe opportunities and challenges experienced from the four pharmacoepidemiologic database studies included in the programme and propose ways to maximise the value of population-based observational research when addressing regulatory requirements.

Design: Post authorisation safety study (PASS) programme of rivaroxaban carried out as part of the regulatory post-approval commitment to the European Medicines Agency.

Setting: Clinical practice in Germany, the Netherlands, Sweden, and the UK (electronic health records) – undertaken by pharmacoepidemiology research teams using country-specific databases with different coding structures.

Participants: 355,152 patients prescribed rivaroxaban and 338,199 patients prescribed vitamin K antagonists.

Results: Two major challenges that were encountered throughout the lengthy PASS programme related to: i) finalising country-tailoured study designs before the extent of rivaroxaban uptake was known, and ii) new research questions that arose during the programme (e.g. those relating to an evolving prescribing landscape).

Recommendations: We advocate the following strategies to help address these major challenges (should they arise in any future PASS): conducting studies based on a common data model that enable the same analytical tools to be applied when using different databases; maintaining early, clear, continuous communication with the regulator (including discussing the potential benefit of studying drug use as a precursor to planning a safety study); consideration of adaptive designs whenever uncertainty exists and following an initial period of data collection; and setting milestones for the review of study objectives.

INTRODUCTION

Rivaroxaban is a factor Xa inhibitor with several cardiovascular indications.[1] Between 2011 and 2020, Bayer and partners conducted a large rivaroxaban post-authorisation safety study (PASS) programme comprising eight observational studies as part of the regulatory post-approval commitment to the European Medicines Agency (EMA). Hereafter, we describe opportunities and challenges experienced from the four pharmacoepidemiologic database studies included in the programme and propose ways to maximise the value of population-based observational research when addressing regulatory requirements.

A detailed description of the rivaroxaban PASS programme (designed to address the approved cardiovascular indications) has been published previously.[2] Briefly, of the eight observational studies, four were population-based database studies aimed at evaluating rivaroxaban prescribing, safety and effectiveness in routine primary and/or secondary care versus the existing standard of care (vitamin K antagonists [VKAs]) over a 9-year period from approval – learnings from which are the focus of this paper. All four database studies were based on secondary use of patient-level data from electronic healthcare sources well-established for pharmacoepidemiologic research, with rivaroxaban use captured from prescriptions issued by primary care physicians or pharmacy dispensations.[2] The four other studies included in the programme are not discussed hereafter. The database studies were conducted by experienced independent research organisations (all members of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance)[2] in collaboration with Bayer, with data collected from four European countries (Germany, the Netherlands, Sweden, and the UK).

The PASS programme was initially designed to support three cardiovascular indications in adults that were authorised in Europe from 2008: prevention of venous thromboembolism (VTE) in adults undergoing elective hip/knee replacement (THR/TKR) surgery; treatment of VTE and prevention of its recurrence; and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF indication). Three of the four database studies (from the UK, Germany and the Netherlands) were designed with respect to those indications. In 2013, the EMA approved rivaroxaban for concomitant use with acetylsalicylic acid with/without clopidogrel/ticlodipine for the prevention of atherothrombotic events in adults with elevated cardiac biomarkers after an acute coronary syndrome (ACS). This approval included the condition to collect further information in the post-authorisation stage to monitor rivaroxaban use and address safety when used for secondary prevention of ACS in real-world clinical practice. In particular, reassurance was sought regarding whether the distribution of risk factors among patients prescribed rivaroxaban in clinical practice was consistent with the ATLAS ACS2 TIMI 51 trial population.[3] To meet this request, Bayer expanded the programme with the development of the fourth database study (from Sweden). Additionally, the protocols for the three original database studies were modified to also capture rivaroxaban use in patients with ACS, and were upgraded from PASS category 3 (i.e. legally required to investigate safety of the authorised drug as part of the pharmacovigilance plan) to category 1 (imposed as a condition of the marketing authorisation, which is included in the Risk Management Plan [RMP]). The programme was extended in duration with the requirement for annual progress reports and additional interim reports; in total eleven interval or cumulative interim/final reports since 2015 were provided. The four pharmacoepidemiologic database studies, each covering all four indications, included a total of 355,152 patients receiving rivaroxaban and 338,199 patients

receiving VKAs. The programme completed in autumn 2020, with EMA's assessment and opinion adopted in September 2022 and endorsed by the European Commission in December 2022.

Patient and public involvement

No patient involved.

Opportunities demonstrated from the PASS programme

This unique PASS programme exemplifies an approach whereby the prescription of a medication and its safety and effectiveness can be evaluated in a single initiative, covering all indications to be assessed, and by using well-established and validated population-based European databases already familiar to researchers, industry, and regulators. By using a cohort study design in the database studies, we were able to evaluate real-world patterns of rivaroxaban use including episode of use between treatment interruptions, and by performing nested case–control analyses, we were able to evaluate its safety and effectiveness, including by duration and recency of use. Additionally, although the coding structures of the country-specific databases differed, study investigator teams harmonised the design, objectives, exposures, outcomes, and available look-back periods of the four studies through clear communication and transparency. However, while this approach was implemented successfully, we recognise that it was labour intensive and more operationally efficient processes are now available for managing these scenarios. The past decade has seen major developments in harmonising data from country-specific electronic health record (EHR)/claims databases with different coding systems into a common data model (CDM), enabling the same analytical tools to be applied. One such initiative, increasingly being adopted

in pharmacoepidemiological research, is the Observational Health Data Sciences and Informatics (OHDSI) community, which provides access to a global network of administrative claims and EHR data sources standardised to OHDSI's Observational Medical Outcomes Partnership CDM 5.[4] Providing that no detailed information is lost through the application of a CDM, we advocate consideration of such an approach in future multi-country umbrella programmes that encompass several pharmacoepidemiological studies, as in the DARWIN European Union project.[5]

Challenges encountered during the PASS programme

Two major challenges that were encountered throughout the lengthy PASS programme related to: i) finalising country-tailoured study designs before the extent of rivaroxaban uptake was known, and ii) new research questions that arose during the programme. We outline these challenges below and propose ways to manage them for future PASS initiatives (see also the **Box**).

Finalising study designs before product uptake is known

In contrast to randomised controlled trials or epidemiological studies of established medications, the level of future uptake of newly approved medications cannot necessarily be accurately predicted at product launch. Also, the sample size and type of drug exposure can vary between countries due to treatment guidelines and reimbursement practices introduced at different times. Consequently, upfront planning of prospective pharmacoepidemiological safety studies with undefined follow-up duration – potentially of many years – is challenging. Rivaroxaban uptake for the ACS indication was expected to be low in the initial months after EMA approval yet to increase over time. However, uptake remained low throughout follow-up. This limited the

drawing of any robust conclusions (after data analysis) about risk factor distribution between these patients in clinical practice vs. those in the pivotal ATLAS ACS2 TIMI 51 trial population. In hindsight, it would have been operationally more efficient, and in line with pharmacoepidemiological thinking, to have considered a stepwise approach starting with a drug utilisation study to inform the regulator about the feasibility of a safety study for this indication. This could have involved formulating potential scenarios, based on different assumptions of projected sample sizes and timelines, to inform when would sufficient sample size be obtained for a safety study.[6] Such an approach could potentially be harnessed for any drug indication. It could also inform about appropriate timings for final data analysis, which could be earlier for some indications – as transpired with the SPAF indication due to high uptake and availability of a large dataset soon after the study began – thereby enabling earlier regulatory review and dissemination of results. Like a clinical trial scenario, we also advocate systematically including a statement in the study protocols that a) premature study cessation will be considered whenever clinically justified, and b) interim analyses will be conducted where the study objectives will be reviewed (i.e. further objectives added where deemed necessary).

Research questions/challenges that emerged throughout the programme

We received several relevant scientific questions following programme completion that related to safety. Although some of these did not relate to the original study protocol, we were able to provide satisfactory responses following appropriate *post-hoc* analyses based on additional data released. Furthermore, we were also able to adequately respond to requests relating to data gaps specified in the Risk Management Plan (RMP) concerning specific patient subgroups. Another challenge encountered during the programme was that direct oral anticoagulants overtook VKAs

as the standard of care for the indications studied. Consequently, patients treated with VKA during the end of the study period were probably substantially different from those treated in the beginning,[7] making safety comparisons between rivaroxaban and VKAs challenging.

Key lessons learned

We propose three key strategies that could help avoid/effectively manage these challenges in future PASS initiatives to facilitate operationally efficient programmes that generate timely results and enable robust conclusions to be drawn from the analyses. Firstly, we advocate maintaining early, clear, continuous, and open communication with the regulator, as encouraged by the EMA through the seeking of their scientific advice. Secondly, for programmes intended to span several years, we propose setting milestones for study review following an initial period of data collection. This could potentially be linked to the formal interim review period where key discussions between the regulator and MAH are undertaken – preferably during meetings to accompany the assessment reports. Crucially, this would be an opportune time for the MAH and regulator to discuss any additional study questions that arose after PASS initiation, and for feedback on programme direction. A proactive approach involving dialogue about feasibility evaluations, and appropriate changes to statistical analysis plans, could then be undertaken accordingly, in turn helping investigators with resource and operational planning. The third is to, in consultation with the regulator, allow adaptation of study protocols to enable the inclusion of additional, or changes in, study objectives as well as modifications of study designs to reflect evolving prescription behaviours, newly emerging treatments and guidelines changes. This would ensure the outcomes of the PASS are relevant for regulators and clinical practice.

Box. Summary of opportunities recognised and challenges encountered during the rivaroxaban PASS programme, and recommendations to help effectively address these should they arise in future.

Opportunities/challenges experienced	Recommendation
Alignment in identifying study outcomes and other co-variates	• Consider studies based on a CDM if analysis of multiple country-specific datasets is planned. • Consider all data to inform the key safety concerns from the RMP. • Consider potential impact on any section of the label.
Planning studies before product uptake is known	• Maintain early, continuous, open communication with the regulator before programme initiation and during the interim reviews. • Discuss with the regulator the potential benefit of studying drug use as a precursor to planning a safety study. • Propose a stepwise approach with the potential of implementing changes to the study design (e.g. adaptive designs) whenever uncertainty exists – such as the possibility of an evolving prescribing landscape, especially in the early period following product launch. • Set milestones for the review of study objectives and design following an initial period of data collection; documenting any agreed changes (such as those made to respond to an evolving prescription environment from the introduction of competitor drugs and/or potential changes in clinical guidelines to ensure alignment and transparency)

Opportunities/challenges experienced	Recommendation
	• Including a statement in the study protocols that premature study cessation will be considered whenever clinically justified, and b) interim analyses will be conducted where the study objectives will be reviewed (i.e. further objectives added where deemed necessary).
Plan for expectations relating to the RMP	• Clear alignment of objectives in the protocols to address the key safety concerns in the RMP. • Obtain scientific advice and ensure clear dialogue with the regulator before programme initiation to ensure alignment regarding the expectations of the study • Ensure this is discussed at the interim review periods (or other set milestone review periods).
Capturing long-term treatment, and accounting for changes in treatment guidelines and discontinuation	• Consider use of nested case–control analyses to handle all varying episodes of drug use efficiently.[8, 9]
New requests after study initiation - addressing known study limitations (e.g. available data) - emerging interest in patient subgroups - changes in the current standard of care - relevant comparators	• Ensure this is discussed during the interim reviews and/or at set milestone review periods so that: - expectations remain aligned and are realistic - dialogue can be undertaken in terms of protocol amendments (e.g. incorporating new study objectives, such as addressing new patient populations or comparators; meaningful cut-off points for statistical analyses) - investigators can undertake resource and operational planning.

Opportunities/challenges experienced	Recommendation
	• Anticipate potential changes to standard of care during planned programme duration, and allow for flexibility in the comparison groups in study designs, as stated in the study protocol.

CDM, common data model; EMA, European Medicines Agency; PASS, post-authorisation safety study; PRAC, Pharmacovigilance Risk Assessment Committee; RMP, risk management plan

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Author contributions

Gunnar Brobert developed the original manuscript draft. All authors commented on subsequent drafts and approved the final version for journal submission. In addition, medical writing assistance was provided by Susan Bromley, EpiMed Communications Ltd, Abingdon, UK, according to Good Publication Practice, and funded by Bayer AG.

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Competing interests

GB was an employee of Bayer AB, Sweden, at the time the PASS programme was conducted and has received consultancy fees from Bayer AG, Germany, thereafter as an external consultant.

YB, CT, KS-W, MSG, PV, TD, GN, and PA are current employees of Bayer AG, Germany. MH was an employee of Bayer AG, Germany, at the time the PASS programme was conducted. AR and LAGR work for Spanish Centre for Pharmacoepidemiological Research, Spain, which received research funding for the study carried out within the rivaroxaban PASS programme. TS is an employee of Leibniz Institute for Prevention Research and Epidemiology, Germany, which received research funding for the study carried out within the rivaroxaban PASS programme. AV was an employee at BIPS at the time when the study was conducted. RH, ES, and KS-P work for PHARMO Institute for Drug Outcomes Research, Netherlands, which received research funding for the study carried out within the rivaroxaban PASS programme. LF works for Friberg Research AB, Sweden, which received research funding for the study carried out within the rivaroxaban PASS programme.

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Challenges encountered during the PASS programme

Two major challenges that were encountered throughout the lengthy PASS programme related to: i) finalising country-tailoured study designs before the extent of rivaroxaban uptake was known, and ii) new research questions that arose during the programme. We outline these challenges below and propose ways to manage them for future PASS initiatives (see also **Box 1** and **2**).

Finalising study designs before product uptake is known

In contrast to randomised controlled trials or epidemiological studies of established medications, the level of future uptake of newly approved medications cannot necessarily be accurately predicted at product launch. Also, the sample size and type of drug exposure can vary between countries due to treatment guidelines and reimbursement practices introduced at different times. Consequently, upfront planning of prospective pharmacoepidemiological safety studies with

undefined follow-up duration – potentially of many years – is challenging. Rivaroxaban uptake for the ACS indication was expected to be low in the initial months after EMA approval yet to increase over time. However, uptake remained low throughout follow-up. This limited the drawing of any robust conclusions (after data analysis) about risk factor distribution between these patients in clinical practice vs. those in the pivotal ATLAS ACS2 TIMI 51 trial population. In hindsight, it would have been operationally more efficient, and in line with pharmacoepidemiological thinking, to have considered a stepwise approach starting with a drug utilisation study to inform the regulator about the feasibility of a safety study for this indication. This could have involved formulating potential scenarios, based on different assumptions of projected sample sizes and timelines, to inform when would sufficient sample size be obtained for a safety study.[7] Such an approach could potentially be harnessed for any drug indication. It could also inform about appropriate timings for final data analysis, which could be earlier for some indications – as transpired with the SPAF indication due to high uptake and availability of a large dataset soon after the study began – thereby enabling earlier regulatory review and dissemination of results. Like a clinical trial scenario, we also advocate systematically including a statement in the study protocols that a) premature study cessation will be considered whenever clinically justified, and b) interim analyses will be conducted where the study objectives will be reviewed (i.e. further objectives added where deemed necessary).

Research questions/challenges that emerged throughout the programme

We received several relevant scientific questions following programme completion that related to safety. Although some of these did not relate to the original study protocol, we were able to provide satisfactory responses following appropriate *post-hoc* analyses based on additional data

released. Furthermore, we were also able to adequately respond to requests relating to data gaps specified in the Risk Management Plan (RMP) concerning specific patient subgroups. Another challenge encountered during the programme was that direct oral anticoagulants overtook VKAs as the standard of care for the indications studied. Consequently, patients treated with VKA during the end of the study period were probably substantially different from those treated in the beginning,[8] making safety comparisons between rivaroxaban and VKAs challenging.

Key lessons learned

We propose three key strategies that could help avoid/effectively manage these challenges in future PASS initiatives to facilitate operationally efficient programmes that generate timely results and enable robust conclusions to be drawn from the analyses. Firstly, we advocate maintaining early, clear, continuous, and open communication with the regulator, as encouraged by the EMA through the seeking of their scientific advice. Secondly, for programmes intended to span several years, we propose setting milestones for study review following an initial period of data collection. This could potentially be linked to the formal interim review period where key discussions between the regulator and MAH are undertaken – preferably during meetings to accompany the assessment reports. Crucially, this would be an opportune time for the MAH and regulator to discuss any additional study questions that arose after PASS initiation, and for feedback on programme direction. A proactive approach involving dialogue about feasibility evaluations, and appropriate changes to statistical analysis plans, could then be undertaken accordingly, in turn helping investigators with resource and operational planning. The third is to, in consultation with the regulator, allow adaptation of study protocols to enable the inclusion of additional, or changes in, study objectives as well as modifications of study designs to reflect

evolving prescription behaviours, newly emerging treatments and guidelines changes. This would ensure the outcomes of the PASS are relevant for regulators and clinical practice.

BOX 1. Examples/wider context of the two main challenges encountered during the PASS programme.

Challenge encountered	Example / wider context
Finalising country-tailoured study designs before the extent of rivaroxaban uptake was known	Uncertainty in the level of future rivaroxaban uptake in different European countries meant that finalising country-specific designs for each database study was challenging. This was particularly pertinent when evaluating the safety of rivaroxaban in the context of the ACS indication. Here it transpired that rivaroxaban uptake remained low, and in hindsight, it would have been more pragmatic to have undertaken a drug utilisation study as a precursor to a rivaroxaban safety study.
New research questions that arose during the programme	Because the database studies included in the PASS programme were truly observational, they provided an opportunity to learn not only about safety/effectiveness of rivaroxaban but also about physicians' prescribing patterns regarding indications and dosing over a long period. As we had communicated to the EMA that access to the data sources was still possible (post addressing the original research questions), we received several comprehensible and relevant requests that were not included in the original protocol: - rivaroxaban use in certain patients with VTE and cancer with low risk of bleeding (as DOAC use in these patients was introduced, and observational studies had indicated that DOACs could be an alternative treatment option to LMWH). - use of rivaroxaban in patients with prosthetic valves (although rivaroxaban was not recommended for use in these patients, it was a relevant issue and in the regulator's interest to see how well physicians were following guidelines).

Challenge encountered	Example / wider context
	- use of rivaroxaban in patients with severe kidney function (<15 ml/min/1.73m^2), which rarely or never happens in practice, yet is a measure of how physicians comply with treatment guidelines. - use of rivaroxaban in certain subgroups of patients for which there is missing information in the patient risk management plan, which we had overlooked in the original study report. • consideration of VKA no longer being the standard of care as treatment practices changed over the length of the programme (i.e. VKA was the clear standard of care at the beginning of the study period but was significantly less prescribed at the end).

ACS, acute coronary syndrome; DOAC, direct oral anticoagulant; EMA, European Medicines Agency; LMWH, low-molecular-weight heparin; PASS, post-authorisation safety study; VKA, vitamin K antagonist; VTE, venous thromboembolism

Box 2. Summary of opportunities recognised and challenges encountered during the rivaroxaban PASS programme, and recommendations to help effectively address these should they arise in future.

Opportunities/challenges experienced	Recommendation
Alignment in identifying study outcomes and other co-variates	• Consider studies based on a CDM if analysis of multiple country-specific datasets is planned. • Consider all data to inform the key safety concerns from the RMP. • Consider potential impact on any section of the label.
Planning studies before product uptake is known	• Maintain early, continuous, open communication with the regulator before programme initiation and during the interim reviews. • Discuss with the regulator the potential benefit of studying drug use as a precursor to planning a safety study. • Propose a stepwise approach with the potential of implementing changes to the study design (e.g. adaptive designs) whenever uncertainty exists – such as the possibility of an evolving prescribing landscape, especially in the early period following product launch. • Set milestones for the review of study objectives and design following an initial period of data collection; documenting any agreed changes (such as those made to respond to an evolving prescription environment from the introduction of competitor drugs and/or potential changes in clinical guidelines to ensure alignment and transparency)

Opportunities/challenges experienced	Recommendation
	• Including a statement in the study protocols that premature study cessation will be considered whenever clinically justified, and b) interim analyses will be conducted where the study objectives will be reviewed (i.e. further objectives added where deemed necessary).
Plan for expectations relating to the RMP	• Clear alignment of objectives in the protocols to address the key safety concerns in the RMP. • Obtain scientific advice and ensure clear dialogue with the regulator before programme initiation to ensure alignment regarding the expectations of the study • Ensure this is discussed at the interim review periods (or other set milestone review periods).
Capturing long-term treatment, and accounting for changes in treatment guidelines and discontinuation	• Consider use of nested case–control analyses to handle all varying episodes of drug use efficiently.[9, 10]
New requests after study initiation - addressing known study limitations (e.g. available data) - emerging interest in patient subgroups - changes in the current standard of care - relevant comparators	• Ensure this is discussed during the interim reviews and/or at set milestone review periods so that: - expectations remain aligned and are realistic - dialogue can be undertaken in terms of protocol amendments (e.g. incorporating new study objectives, such as addressing new patient populations or comparators; meaningful cut-off points for statistical analyses) - investigators can undertake resource and operational planning.

Opportunities/challenges experienced	Recommendation
	• Anticipate potential changes to standard of care during planned programme duration, and allow for flexibility in the comparison groups in study designs, as stated in the study protocol.

CDM, common data model; EMA, European Medicines Agency; PASS, post-authorisation safety study; PRAC, Pharmacovigilance Risk Assessment Committee; RMP, risk management plan

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Author contributions

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Competing interests

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