Post-authorisation Safety Study (PASS) Report - Study Information

Title	Xarelto (rivaroxaban) risk-minimisation plan evaluation: patient and physician knowledge of key safety messages (wave 3)
Report version and date	v 1.0 09 JUN 2020
Study type / Study phase	☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS3911
Active substance	INN: Rivaroxaban; ATC code: B01AF01
Medicinal product	Xarelto (rivaroxaban)
Product reference	EU/1/08/472/001-024, EU/1/08/472/036-040, EU/1/08/472/042-045, EU/1/08/472/048-049
Procedure number	EMEA/H/C/000944/X/00017
Study initiator and funder	Bayer AG
Research question and objectives	The primary objective of this cross-sectional epidemiologic study was to measure physician and patient awareness and understanding of the key safety messages, respectively, in the prescriber guide and patient alert card concerning two indications: (1) prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) and (2) treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults. Specifically, the following objectives were addressed: • Investigate whether physicians and their patients have received the educational materials. • Assess knowledge and understanding among physicians regarding key safety information contained in the prescriber guide and assess how physicians use the materials in their daily practice. • Assess knowledge and understanding of patients regarding the key safety information contained in the patient alert card and determine if the patients use and carry the patient alert card with them. Evaluations were planned for administration at approximately 18 months (wave 1), 3 years (wave 2), and 7 years (wave 3) after drug launch. The wave 1 assessment was conducted among both patients and physicians. The wave 2 and 3 studies involved only a physician assessment. The current report presents data from the wave 3 assessment.
Country(-ies) of study	France, Germany, Spain, and the United Kingdom

Authors	PPD PPD PPD PPD PPD

Marketing authorisation holder

Marketing authorisation holder(s)	Bayer AG 51368 Leverkusen Germany
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1. Abstract

Acronym/Title	Xarelto (rivaroxaban) risk-minimisation plan evaluation: patient and physician knowledge of key safety messages (wave 3)
Report version and date	v 1.0, 09 JUN 2020
Authors	PPD PPD PPD PPD PPD PPD
Keywords	Xarelto (rivaroxaban); post-authorisation safety study; evaluation of risk-minimisation measures; physician survey
Rationale and background	At the request of the European Medicines Agency (EMA), a prescriber guide and patient alert card were developed and distributed to increase awareness and understanding about the potential bleeding risk associated with rivaroxaban. The current study was designed to evaluate physician and patient awareness and understanding of the key safety messages in these educational materials at 18 months (wave 1), 3 years (wave 2), and 7 years (wave 3) post–drug launch. The wave 1 assessment was conducted among both patients and physicians. Based on the results of wave 1 and in agreement with the EMA, the wave 2 and wave 3 assessments included physicians only. This report summarises results from the wave 3 assessment to evaluate physicians' knowledge of the key messages in the prescriber guide and includes a brief comparison with the wave 1 and wave 2 physician assessments.
Research question and objectives	The primary objectives were to measure whether physicians and patients received and used the prescriber guide and patient alert card, respectively, and to evaluate their awareness and understanding of the key safety messages concerning two indications: (1) prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (NVAF) and (2) treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

Study design	The study was an observational, cross-sectional study among physicians and patients with recent rivaroxaban experience. Eligible physicians and patients were invited to complete a brief questionnaire regarding their knowledge of key safety information in the rivaroxaban educational materials.
Setting	France, Germany, Spain, and the United Kingdom
Subjects and study size, including dropouts	Physicians were eligible to participate if they had prescribed rivaroxaban in the past 6 months for one of the indications of interest. A total of 26,964 physicians were invited to participate in wave 3; 1,750 responded. Of those who responded, 145 physicians opted not to continue, 152 were not eligible, 148 did not provide informed consent, and 8 started the questionnaire but did not answer enough questions to meet the definition for a completed survey. The remaining 1,297 physicians, between 310 to 351 per country, completed the questionnaire for an evaluable response rate of 4.8%.
Variables and data sources	Data were obtained through questionnaire responses.
Results	In general, physicians' knowledge of the key safety information in the Xarelto educational materials was high. Physicians' knowledge was particularly high for questions related to the risk of bleeding (94% responding correctly), populations that are at increased risk of serious side effects (67%-95%), and contraindications (79%-95%). Physician knowledge was also high for questions related to invasive procedures (88%) and medically important bleeding (76%-82%). Fewer physicians (75%) were aware that rivaroxaban 15 mg or 20 mg should be taken with food for stroke prevention in patients with NVAF and DVT treatment and secondary prevention. Knowledge was lower for the two situations that require international normalised ratio monitoring (63% and 75%, respectively), the two steps required for converting from vitamin K antagonist (VKA) to rivaroxaban (56% and 72%, respectively), the two steps required for converting from rivaroxaban to VKA (63% and 36%, respectively), and the two requirements for converting from parenteral anticoagulants to rivaroxaban (53% and 61%, respectively). Physicians' knowledge of dosing recommendations varied by question. The proportion of correct responses was 77% for the standard recommended dose of rivaroxaban for stroke prevention in patients with NVAF, 63% for the recommended dose of rivaroxaban in patients with renal impairment, and 63%

	for the recommended dose of rivaroxaban for DVT treatment and secondary prevention. More than half of physicians reported that they received the prescriber guide for rivaroxaban (57%), and of those physicians, 80% felt the guide was very helpful or extremely helpful. Most physicians (86%) reported that they would discuss information on the patient alert card with patients when first prescribing rivaroxaban.
Discussion	Physicians' knowledge was highest for the most important risks in the educational materials and lower for more complex aspects of safe use for which we would assume that physicians would consult the prescriber guide and/or label rather than relying on memory. The results of the 3 waves of the physician survey were remarkably similar, and physician knowledge improved slightly over time on several knowledge questions, suggesting that the knowledge patterns were maintained during the entire study period.
Marketing authorisation holder(s)	Bayer AG
Names and affiliations of principal investigators	PPD PPD PPD RTI Health Solutions, Research Triangle Park, NC

2. List of abbreviations

ASA	acetylsalicylic acid
ATC	Anatomical Therapeutic Chemical Classification System
CI	confidence interval
DVT	deep vein thrombosis
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS Register	European Union Electronic Register of Post-Authorisation Studies
GP	general practitioner
INR	international normalised ratio
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
LMWH	low molecular weight heparin
NVAF	non-valvular atrial fibrillation
OQA	Office of Quality Assurance
PAS	post-authorisation study
PASS	post-authorisation safety study
PE	pulmonary embolism
PPD	PPD
SOP	standard operating procedure
SPAF	stroke prevention in atrial fibrillation
UK	United Kingdom
VKA	vitamin K antagonist

3. Investigators

Investigators	Country	Institutional Affiliation
PPD	United States	PPD PPD
PPD	United States	PPD PPD
PPD	United States	PPD PPD

4. Other responsible parties

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5. Milestones

Table 1: Milestones

Milestone	Actual date
EMA endorsement of protocol version 1.0	09 DEC 2011
Registration in the EU PAS Register	06 DEC 2013
Wave 1 IRB approval	30 JUL 2013
Wave 1 lead ethics committee approvals	05 NOV 2013 to 27 AUG 2014
Wave 1 data collection for physician assessment	15 SEP 2014 to 20 NOV 2014
Wave 1 data collection for patient assessment	11 NOV 2014 to 30 APR 2015
Wave 1 summary report	16 OCT 2015
EMA endorsement of protocol version 4.0	21 JUL 2016
Wave 2 approval of exemption from IRB review	23 NOV 2016
Wave 2 ethics committee approval (applicable to Spain only)	16 MAR 2017
Wave 2 data collection for physician assessment	30 MAR 2017 to 12 JUN 2017
Wave 2 summary report	24 MAY 2018
Wave 3 approval of exemption from IRB review	10 JAN 2020
Wave 3 data collection for physician assessment	13 JAN 2020 to 21 FEB 2020
Wave 3 database lock	03 MAR 2020
Final report of study results	09 JUN 2020
Study progress reports	Every 12 months throughout the study, included in the Periodic Safety Update Reports

EMA = European Medicines Agency; EU = European Union; IRB = institutional review board; PAS = post-authorisation study.

6. Rationale and background

Rivaroxaban is approved in the European Union (EU) for the following:

- Prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke or transient ischaemic attack.
  - This indication is referenced as *stroke prevention in atrial fibrillation (SPAF)*[a] throughout the report.
- Treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult patients.
  - This indication is referenced as *DVT treatment and secondary prevention* throughout the report.
- Rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome with elevated cardiac biomarkers.
- Co-administered with ASA for the prevention of atherothrombotic events in adult patients with coronary artery disease or symptomatic peripheral artery disease at high risk of ischaemic events (i.e., coronary artery disease or symptomatic peripheral artery disease) (1).

As part of a safety risk-management plan for rivaroxaban, a physician-educational packet was developed that includes the prescriber guide and patient alert card, with the aim to increase awareness and understanding among physicians and patients about the potential bleeding risk during treatment with rivaroxaban. The patient alert card was initially provided to patients by their treating physicians. It is now included in the product packaging so patients receive the card every time they fill a prescription for rivaroxaban.

PPD collaborated with Bayer to develop and implement this study to evaluate physician and patient awareness and understanding of the key safety messages, respectively, in the prescriber guide and patient alert card concerning two indications: SPAF and DVT treatment and secondary prevention. Evaluations of patient and physician use of these materials were planned for administration at 18 months (wave 1), 3 years (wave 2), and 7 years (wave 3) after drug launch.

The wave 1 assessment was conducted among patients and physicians. Based on the results of wave 1 and in agreement with the European Medicines Agency (EMA) (EMEA/H/C/000944/MEA/023.3), the wave 2 and wave 3 assessments included only physician assessments and no patient assessment. This report summarises results from the wave 3 assessment to evaluate physicians' knowledge of the key messages in the prescriber guide and includes a brief comparison of results across the three waves.

[a] More completely, prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation.

The five countries initially planned to be included in the study were the France, Germany, Italy, Spain, and the United Kingdom (UK). Because of drug approval delays in Italy, the wave 1 assessment was conducted only in four countries (France, Germany, Spain, and the UK). Italy was intended to be included in wave 2; however, it was again excluded based on the requirement to obtain ethics committee approval for each of the 300 physicians in Italy in accordance with the country regulation, a process not considered feasible within the timeline agreed upon in the EU risk-management plan. This requirement was confirmed by the Italian Medicines Agency (Agenzia Italiana del Farmaco [AIFA]) and is based on the "Linee guida per la classificazione e conduzione degli studi osservazionali sui farmaci" (published in the Gazzetta Ufficiale 76, dated 31-Mar-2008). Italy was not included in wave 3 for the same reasons as noted above.

7. Research question and objectives

The primary objective of this cross-sectional epidemiologic study was to measure physician and patient awareness and understanding of the key safety messages, respectively, in the prescriber guide and patient alert card. Specifically, the following objectives were to be addressed:

- To investigate whether physicians and their patients have received the educational materials.
- To assess knowledge and understanding among physicians regarding key safety information contained in the prescriber guide and to assess how physicians use the materials in their daily practice.
- To assess knowledge and understanding of patients regarding the key safety information contained in the patient alert card and to determine if the patients use and carry the patient alert card with them.

The wave 2 and wave 3 assessments included only physicians and no patients.

As part of good research practices, the protocol, and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) checklist were registered in the EU Post-Authorisation Study (PAS) Register (2) before the start of wave 1 data collection. The study was designed and implemented in line with the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices* (3); the EMA *Guidelines on Good Pharmacovigilance Practices, Module VIII – Post-authorization Safety Studies* (4); and the ENCePP *Guide on Methodological Standards in Pharmacoepidemiology* (5). The contract between PPD and Bayer includes independent publication rights.

The study received exemption from review by the PPD PPD for wave 3 data collection on 10 JAN 2020.

8. Amendments and updates

None.

[a] PPD is a unit of the non-profit research organisation PPD

9. Research methods

9.1 Study design

The study was an observational, cross-sectional study of knowledge, understanding, and self-reported behaviour among a sample of physicians with recent rivaroxaban experience in a total of four European countries. A cross-sectional survey approach was selected for this study because the main information on knowledge and understanding of the educational material could be obtained only through direct interaction with physicians.

The study was planned in three consecutive waves for assessments at 18 months (wave 1), 3 years (wave 2), and 7 years (wave 3) to allow physicians additional time for gaining experience prescribing rivaroxaban for the indications of interest and to observe temporal changes in their knowledge. Some delays have occurred because of unplanned circumstances (see Table 1 for actual dates); these actual dates have been agreed on with EMA.

Wave 1 of the study included a survey administered to general practitioners as well as physicians covering a variety of specialties (i.e., neurology, cardiology, haematology, and oncology) to evaluate their knowledge of key safety messages outlined in the rivaroxaban educational materials. For wave 2, internal medicine and pulmonology physicians also were included. For wave 3, accident and emergency medicine physicians were included in addition to the other specialties included in the previous waves, with a goal to cover all specialties that may be prescribing rivaroxaban across all of the waves.

Physicians were recruited from an online physician panel.[a] For waves 1 and 2, a stratified random sample of physicians in the panel was selected to recruit such that the distribution of the physician specialties that were invited was proportional to the distribution of specialties seen in country-specific prescribing information supplied by Bayer. For waves 1 and 2, soft recruitment quotas were set for each physician specialty to help ensure that the final distribution of respondents was consistent with the prescribing information and that all specialties were represented. For wave 3, no recruitment quotas were set due to a shorter data collection period.

For wave 3, the survey was open to physicians who participated in the wave 1 and/or 2 assessments (i.e., repeat respondents), as well as physicians who did not participate in the wave 1 and/or 2 assessments (i.e., new respondents). The initial batch of invitations was sent to physicians who did not participate in wave 1 or 2 of the survey to maximise the number of new respondents with a goal of obtaining a minimum of 150 new respondents per country. Subsequent invitations included physicians who had participated in waves 1 and 2.

For wave 3, invitations were extended via e-mail to the selected sample of physicians, inviting them to participate and providing a link to a web-based questionnaire. Interested physicians logged in to the study website by entering a unique identification number and password. The physicians then completed an informed consent and a screening question to confirm that they had prescribed rivaroxaban to at least one patient within the past 6 months. Physicians who

[a] The panel of physicians is maintained by a proprietary organisation. The panel comprises physicians derived from multiple sources (e.g., hospital books, medical directories, physician referrals). Each panel member is recruited by telephone and opts into the panel twice. A stringent sampling procedure for panel member recruitment is in place to target a representative demographic cross section. A rigorous verification process is implemented to confirm potential panelists' practising status. The verification process includes checking physician background data against medical directories. Panel membership is only finalised once live contact and verification is made with the physician at an office location.

completed the consent and were deemed eligible could continue and complete the self-administered questionnaire.

The physician survey was administered as an online questionnaire. Physicians were not able to go back to previous questions, which kept them from changing their answers based on subsequent questions. The web-based format for completion of the consent form and self-administered questionnaire was chosen because of the efficiency and utility of the mode (e.g., question-branching logic and ability to stop respondents from going back to previous questions to change answers). Most physicians have convenient access to complete a web-based questionnaire, so the use of this technology is not believed to have introduced a respondent bias.

9.2 Setting

The wave 3 physician survey was conducted in four European countries (France, Germany, Spain, and the UK). The four countries included were chosen to provide some diversity in physician specialties and practice patterns, and to observe differences in physician knowledge in these settings. In addition, prescribing levels in these countries were such that there were enough eligible physicians with rivaroxaban experience to participate in the study.

Data collection ran from 13 JAN 2020 to 21 FEB 2020.

9.3 Subjects

The wave 3 survey was conducted with physicians who had prescribed rivaroxaban to at least one patient in the past 6 months for one of the following indications:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (SPAF)
- Treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults

9.4 Variables

The wave 3 physician questionnaire contained closed-ended questions (e.g., multiple choice, true/false), with no free-text response fields and included items in the following content areas:

- Prescribing practices
- Knowledge of key safety messages outlined in the prescriber guide
  - Most important risk with taking rivaroxaban
  - Populations at higher risk of bleeding
  - Contraindications
  - Necessity of taking the 15 mg and 20 mg tablets with food
  - Use of coagulation tests and their interpretation
  - Converting from or to rivaroxaban treatment
  - Perioperative management
  - Actions related to medically important bleeding
  - Dosing recommendations

- Sources of information about rivaroxaban and ratings of their helpfulness
- Experience with information contained in the patient alert cards
- Physician and practice characteristics

Annex 2 contains the questionnaire.

9.5 Data sources and measurement

Self-reported data collected from physicians using a standard questionnaire with closed-ended response choices served as the source of information for wave 3.

The questionnaire was developed prior to wave 1 using best practices for instrument development. The questions were tailored to the study aims and the information provided in the prescriber guide for rivaroxaban. Additional questions were included to obtain the information needed to describe the study population and to assess potential differences across subgroups.

To thoroughly evaluate the questionnaire before fielding the study in wave 1, the questionnaire was tested through cognitive interviews with physicians in France, Germany, Italy, Spain, and the UK before data collection. The pretest interviews helped to identify problems with questionnaire items, wording, response choices, etc., and ensured that participants understood the questions. The cognitive testing helped to identify cultural or translational issues with the draft questionnaire so that it could be modified to meet the individual needs of each country while maintaining comparability across the study.

In wave 1, nine interviews were first conducted with physicians in the UK to identify issues and optimise wording in English. After the UK interviews, the questionnaires were revised and translated into German, French, Italian, and Spanish. Four interviews (for a total of 16) were then conducted with physicians in each of the remaining countries to confirm wording and facilitate cultural adaptation to each country. Changes to the questionnaire were made based on the results of the cognitive testing and additional feedback from the sponsor before the start of wave 1 data collection. Subsequently, before wave 2 data collection, minor wording changes were made to the consent language and to a few questions for further clarification. In addition, two questions related to receipt and distribution of the patient alert card were removed because the card is now distributed in the product packaging and not by the physician. The wave 3 questionnaire remained the same as the wave 2 questionnaire, with the exception of updates that were made to the consent language.

9.6 Bias

In any observational study, researchers must address the potential for biases, particularly if there is a possibility that the respondents are not representative of the target population. Likewise, the potential for response error may present additional sources of bias. Efforts were made to both minimise and identify potential sources of bias in this study as described below.

As noted above, the physician questionnaire was cognitively pretested prior to wave 1 data collection in order to identify any problems with the questionnaire items, wording, and response choices, and to ensure consistency across cultures and languages. The questionnaire was modified based on feedback from the cognitive interviews with physicians. This process helped to ensure that the questions measured the appropriate concepts consistently and accurately across all countries, and thus was intended to minimise bias in responses.

The physician survey was administered as an online questionnaire. Physicians were not able to go back to previous questions. This kept them from changing their answers based on subsequent questions. The level of missing data was minimal; most participants who began the survey completed all items of the questionnaire.

Although a comparison of participating physician characteristics with nonparticipating physicians was not possible within the panel recruitment framework, the diversity of physician characteristics and experience with rivaroxaban in the final sample gave some assurance that the target population was well represented. However, despite efforts to ensure a representative sample of physicians, participants may have differed from non-participants on key characteristics measured in the questionnaire (e.g., knowledge, reading the educational materials). The direction and magnitude of such potential bias is not known.

9.7 Study size

The target study size for the wave 3 physician survey was 300 physicians per country, for a total of 1,200. Physicians who completed at least one knowledge question were included in the analysis. With a study size of 300 physician responses for a given question, the maximum width of an exact 95% confidence interval (CI) around the percentage of physicians who responded correctly is 11.6%; with 1,200 responses, the maximum width is 5.7%. Ultimately, the number of physician surveys eligible for the analysis was 351 from France, 316 from Germany, 310 from Spain, and 320 from the UK, for a total of 1,297.

9.8 Data transformation

Derived variables were created for each of the six knowledge questions that asked the respondent to select all that apply and that have more than one correct response option (Questions 7, 10-13, and 15); these variables indicate the number of correct responses selected.

9.9 Statistical methods

All analyses were performed using SAS 9.4 statistical software (SAS Institute, Inc., Cary, North Carolina). No formal hypothesis testing was conducted.

9.9.1 Main summary measures

Data analyses were descriptive in nature and focused primarily on summarising the questionnaire responses. Summary tables consisting of frequencies with percentages were created for all questionnaire responses. Response distribution percentages for a question were based on the total number of respondents who had an opportunity to answer the question. This total excluded those who were asked to skip the question because of an answer given in a previous question (skip pattern). The sum of respondents who were asked to skip the question was listed in a row labelled “Not applicable skip pattern” under the question with no percentage calculated for that row. The counts of respondents who had an opportunity but did not answer were included in the row labelled “No answer” with a calculated percentage.

Exact 95% CIs were generated around the percentage of participants who answered each knowledge question correctly. These CIs were calculated for the overall results and for each country but not for other stratified tables.

9.9.2 Main statistical methods

The analysis population consisted of respondents who were eligible for the study, provided informed consent, and completed at least one knowledge question in full (Questions 5-18).

Questionnaire items were divided into the following categories:

- Physician and practice characteristics
- Physician prescribing practices
- Physician knowledge
- Sources of information about rivaroxaban
- Ratings of those sources
- Experiences with information contained in the patient alert cards

Separate analysis tables were generated to display the response distributions of the questions in each category. Table 2 presents the table numbers and question numbers that correspond to each table. The tables are provided in Annex 3 and include results overall and by country.

Table 2: Listing of main analysis tables

Table number	Table title	Question numbers
Table A-1	Physician and practice characteristics	24-27
Table A-2	Physician prescribing practices	1-4
Table A-3	Knowledge questions	5-18
Table A-4	Sources of information about Xarelto	19
Table A-5	Ratings of sources of information about Xarelto	20
Table A-6	Physicians' experiences with information contained in the patient alert cards	23

In addition, the knowledge questions were stratified to explore the association between each variable and physician knowledge levels. Note that some stratifications produced small sample sizes; thus, caution should be taken when interpreting the stratified data.

Study sizes for a stratification variable can be smaller than the overall study size if some survey respondents skipped the question. The stratification variables and associated study sizes are as follows:

- Whether or not the physician also was included in wave 1 or wave 2 of this study
  - Participated in wave 1 or 2: n = 517
  - Did not participate in wave 1 or 2: n = 780
- Physician specialty (based on response to Question 24)
  - General/internal medicine: n = 659
  - Neurology: n = 111

  - Cardiology: n = 238
  - Haematology: n = 60
  - Oncology: n = 77
  - Other: n = 135
- Whether or not the physician is responsible for initiating Xarelto treatment or converting treatment from or to Xarelto (based on response to Question 4)
  - Is responsible for initiating or converting rivaroxaban treatment: n = 1,160
  - Is responsible for maintenance only: n = 137
- Whether or not the physician received the Xarelto prescriber guide (based on response to Question 19)
  - Received Xarelto prescriber guide: n = 744
  - Did not receive Xarelto prescriber guide: n = 537
- Indications for which the physician prescribed rivaroxaban (based on response to screening Question 1)
  - SPAF only: n = 264
  - DVT only: n = 107
  - SPAF and DVT: n = 926
- Number of patients prescribed Xarelto in past 6 months (based on response to Questions 1 and 2)
  - 1-10 patients: n = 379
  - 11-20 patients: n = 390
  - > 20 patients: n = 528
- Physician specialty limited to general medicine/internal medicine and cardiologist, by wave
  - Wave 1
    - General medicine: n = 552
    - Cardiologist: n = 241
  - Wave 2
    - General medicine/internal medicine: n = 693
    - Cardiologist: n = 182
  - Wave 3
    - General medicine/internal medicine: n = 659
    - Cardiologist: n = 238

Table 3 presents the table numbers and the question numbers that correspond to each table. Annex 4 presents these stratified results tables.

Table 3: Listing of other stratification analysis tables

Table number	Table title	Question numbers
Table A-7	Knowledge questions by repeater status	5-18
Table A-8	Knowledge questions by physician specialty	5-18
Table A-9	Knowledge questions by whether or not physician is responsible for initiating rivaroxaban treatment or converting treatment from or to rivaroxaban	5-18
Table A-10	Knowledge questions by whether or not physicians received the Xarelto prescriber guide	5-18
Table A-11	Knowledge questions by indication(s) for which physicians prescribed Xarelto	11-13
Table A-12	Knowledge questions by number of patients prescribe Xarelto in past 6 months	5-18
Table A-13	Knowledge questions by cardiologist versus general practitioner/internal medicine, by waves 1, 2, and 3	5-18

9.9.3 Missing values

Missing values were treated as missing; no imputation was performed.

9.9.4 Sensitivity analyses

None.

9.9.5 Amendments to the statistical analysis plan

None.

9.10 Quality control

This project was conducted in accordance with internal standard operating procedures (SOPs) of participating institutions. The PPD Office of Quality Assurance (OQA), an independent unit that reports to the Executive Vice President of PPD oversaw quality assurance for this study.

PPD followed our established quality management system to conduct this study including:

- Training of PPD staff
- Ensuring data protection and integrity
- Collecting, analysing, and managing data
- Maintaining records
- Performing vendor qualification, quality control, and quality-review activities

PPD SOPs were used to guide the conduct of the study. These procedures included rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

PPD OQA qualified Kantar Health as an approved vendor (via on-site audit in 2017) before this study was initiated. Kantar Health has been a trusted partner and has been continuously qualified throughout the duration of this study without interruption.

In accordance with relevant PPD SOPs, quality-control activities were performed throughout the project. This included the following activities:

- The initial programmer reviewed all programme log files for errors and warning messages and retained electronic copies of all final log files in the project folder.
- The programmer accounted for the number of observations reported at each executed data step and noted in the programme code when the number of observations increased or decreased. A second programmer independently wrote programme code and confirmed the findings of the initial programmer.
- A quality-control checklist has been maintained for the project, and a hard copy was printed, signed, and retained in the project folder.
- All key study documents, such as the analysis plan, questionnaires, and study reports, underwent quality-control review, senior scientific review, and editorial review.

Versions of SOPs and records of quality-review and quality-control activities used throughout the course of a study are maintained and available with the study records.

10. Results

10.1 Participants

A total of 26,964 physicians were invited to participate in the survey. Of those, 1,750 physicians responded to the invitation. Of the physicians who responded, 145 opted not to continue, 152 were not eligible, 148 did not provide informed consent, and 1,280 completed the survey. An additional 25 physicians started but did not finish the questionnaire; of those, 17 physicians answered at least one knowledge question to meet the definition of a completed survey. Therefore, a total of 1,297 physicians (351 in France, 316 in Germany, 310 in Spain, and 320 in the UK) were included in the analysis. The overall evaluable response rate was 4.8%. Figure 1 presents the disposition of physicians invited to participate.

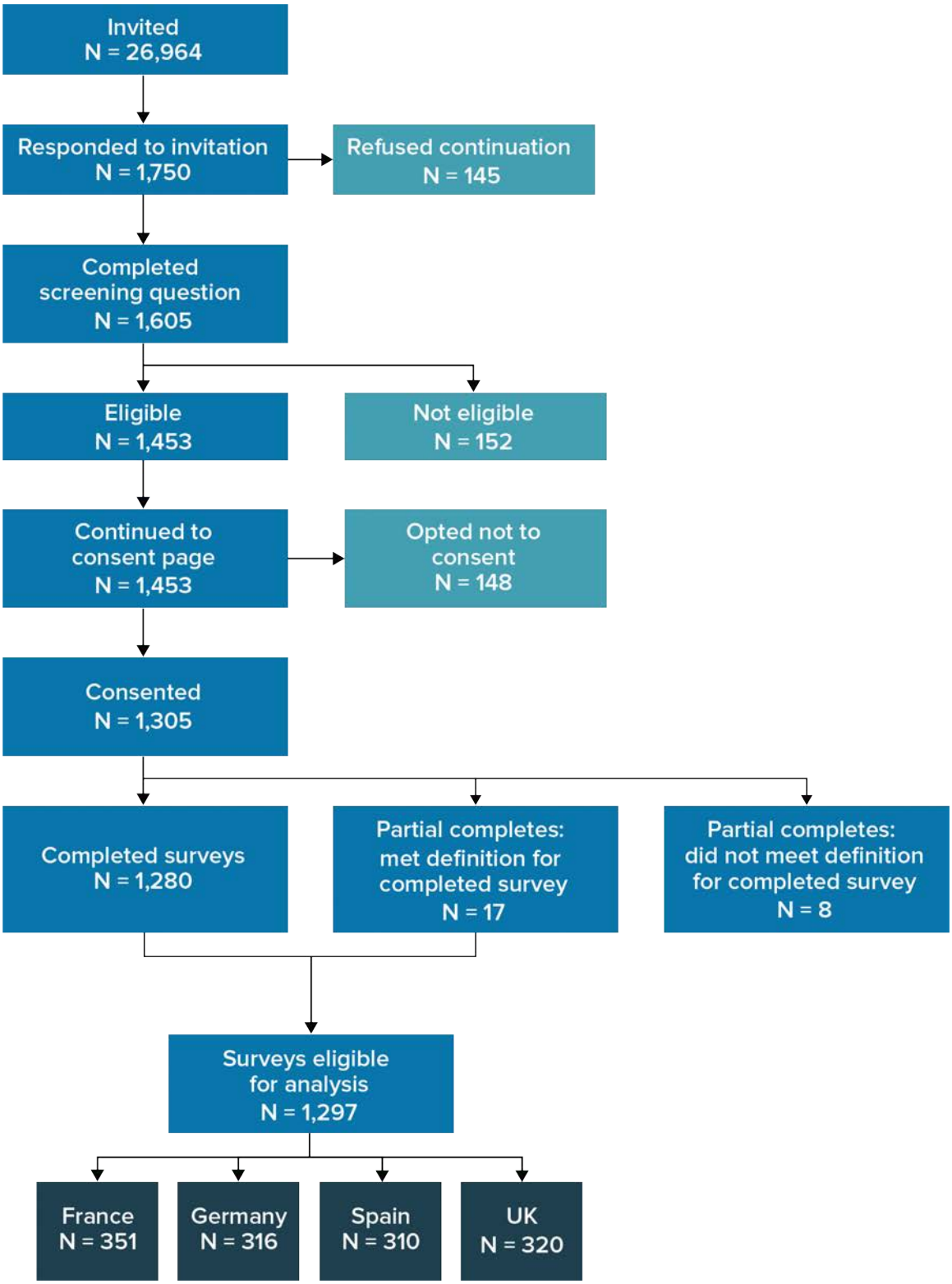

Figure 1: Disposition of physicians

UK = United Kingdom.

Because of the limited number of eligible physicians on the panel, wave 3 included a mix of new participants and physicians who participated in prior waves. The numbers of new participants in wave 3 were as follows: 229 (65% of respondents) in France, 208 (66%) in Germany, 129 (42%) in Spain, and 214 (67%) in the UK.

Table 4 displays a summary of the total surveys included in the wave 3 analysis, stratified by country and by participation (or not) in prior waves.

Table 4: Summary of completed surveys in wave 3 stratified by country and by physicians who previously completed waves 1, 2, and/or both

		Number of physicians who completed wave 3 survey and previous waves			
Country	**Total surveys for analysis**	**New participants**	**Only completed wave 1**	**Only completed wave 2**	**Completed waves 1 and 2**
France	351	229	28	76	18
Germany	316	208	21	28	59
Spain	310	129	66	98	17
UK	320	214	40	65	1
Total	**1,297**	780	155	267	95

UK = United Kingdom.

10.2 Descriptive data

Physicians were identified using the specialty recorded for each physician in the online panel's database. However, physicians were also asked to specify their specialty as part of the questionnaire. The most frequent specialties represented in the survey population were general medicine (36%), cardiology (18%), internal medicine (15%), and neurology (9%) (Table 5).

A total of 55% of physicians described their practice setting as a general practice, and 51% described their practice setting as a hospital-based clinic.[a] Physicians' experience (as measured by years in practice) was categorised into 5-year increments up to 25 years. Most physicians (91%) reported practising medicine for more than 10 years, and 25% reported practising medicine for more than 25 years. Most participants (75%) were male (Table 5).

[a] This was a "select all that apply" question; thus, the sum of responses can be greater than 100%.

Table 5: Physician and practice characteristics

Characteristic	France N = 351 n (%)	Germany N = 316 n (%)	Spain N = 310 n (%)	UK N = 320 n (%)	Overall N = 1,297 n (%)
Physician specialty					
General medicine (including GPs)	97 (28)	82 (26)	95 (31)	188 (59)	462 (36)
Internal medicine	38 (11)	87 (28)	52 (17)	20 (6)	197 (15)
Neurology	31 (9)	39 (12)	30 (10)	11 (3)	111 (9)
Cardiology	77 (22)	61 (19)	59 (19)	41 (13)	238 (18)
Haematology	12 (3)	10 (3)	29 (9)	9 (3)	60 (5)
Accident & emergency medicine	23 (7)	13 (4)	5 (2)	3 (1)	44 (3)
Oncology	22 (6)	8 (3)	22 (7)	25 (8)	77 (6)
Pulmonology	15 (4)	4 (1)	9 (3)	12 (4)	40 (3)
Other	30 (9)	9 (3)	5 (2)	7 (2)	51 (4)
No answer	6 (2)	3 (1)	4 (1)	4 (1)	17 (1)
Years practising medicine					
5 years or less	9 (3)	2 (1)	1 (< 0.5)	6 (2)	18 (1)
6 to 10 years	27 (8)	10 (3)	17 (5)	23 (7)	77 (6)
11 to 15 years	63 (18)	45 (14)	85 (27)	62 (19)	255 (20)
16 to 20 years	79 (23)	97 (31)	65 (21)	89 (28)	330 (25)
21 to 25 years	71 (20)	72 (23)	73 (24)	65 (20)	281 (22)
More than 25 years	96 (27)	87 (28)	65 (21)	71 (22)	319 (25)
No answer	6 (2)	3 (1)	4 (1)	4 (1)	17 (1)
Sex					
Male	276 (79)	260 (82)	204 (66)	232 (73)	972 (75)
Female	69 (20)	53 (17)	102 (33)	84 (26)	308 (24)
No answer	6 (2)	3 (1)	4 (1)	4 (1)	17 (1)

Characteristic	France N = 351 n (%)	Germany N = 316 n (%)	Spain N = 310 n (%)	UK N = 320 n (%)	Overall N = 1,297 n (%)
Practice type[a]					
General practice	140 (40)	199 (63)	189 (61)	191 (60)	719 (55)
Hospital-based clinic	218 (62)	124 (39)	185 (60)	130 (41)	657 (51)
Nursing home	6 (2)	2 (1)	2 (1)	3 (1)	13 (1)
Other	2 (1)	3 (1)	4 (1)	2 (1)	11 (1)
No answer	6 (2)	3 (1)	4 (1)	4 (1)	17 (1)

GP = general practitioner; UK = United Kingdom.
[a] This was a "tick all that apply" question; thus, the sum of responses can be greater than 100.

10.3 Outcome data

Not applicable.

10.4 Main results

In the following sections, we present key results from physicians who completed the questionnaire. The results are organised in the following categories:

- Physician prescribing practices
- Knowledge of key safety information
- Sources of information about rivaroxaban and ratings of those sources
- Physicians' experiences with information contained in the patient alert cards

The knowledge of key safety information Section (10.4.2) describes results for the overall sample and stratified by country. Each knowledge question was additionally stratified by the following:

- Physician specialty
- Physician prescribing responsibility (initiating or converting vs. maintenance only)
- Whether the physician reported receiving the prescriber guide for rivaroxaban
- Prescribing volume in past 6 months
- Whether the physician had participated in a prior wave of the study

In addition, a subset of knowledge questions (Questions 11-13) was stratified by the indication for which the physician prescribes rivaroxaban.

Differences between levels of the stratification variables at least 10% are referenced in the text of this section. We also compared the knowledge results across the three waves of the survey and noted differences in this section.

Graphs are included to highlight the stratification results in which the largest differences were seen or where the stratifications seem of most interest.

An overall summary of the results for each stratification variable also is included in Section 10.5.1, and a summary of changes across waves is included in Section 10.5.2.

Annex 3 includes tables presenting the complete set of knowledge question results overall and by country. Annex 4 includes tables presenting results by other stratification variables. Annex 5 provides a graphical representation showing knowledge results across the three survey waves.

10.4.1 Physician prescribing practices

Most physicians (79%) had written a prescription for rivaroxaban less than 1 month before completing the survey. Almost all physicians (98%) had prescribed rivaroxaban for SPAF in the past 6 months, and most physicians (88%) had prescribed rivaroxaban for DVT treatment and secondary prevention in the past 6 months. In Spain, where rivaroxaban is not approved for reimbursement for DVT, 22% of physicians reported that they had not prescribed rivaroxaban for DVT in the past 6 months. Most physicians (89%) reported that they were responsible for initiating rivaroxaban treatment or converting from or to rivaroxaban, and the majority (70%) reported that they wrote follow-up (maintenance) prescriptions (see Annex 3, Table A-2; Questions 1, 2, 3, and 4).[a]

10.4.2 Knowledge of key safety information

10.4.2.1 Risks of side effects and safe use

Almost all physicians (93%) correctly reported that the most important risk associated with taking rivaroxaban is the risk of bleeding. Results were consistent across the countries, ranging between 92% and 93% correct in each country (Annex 3, Table A-3; Question 5). Overall, knowledge of this risk was 88% or higher among each category of specialist except for oncologists (81%) (Figure 2). Marked differences were not observed in any of the other stratifications (Annex 4, Tables A-9, A-10, and A-12; Question 5).

[a] Question 4 was a “tick all that apply” question; thus, the sum of responses can be greater than 100.

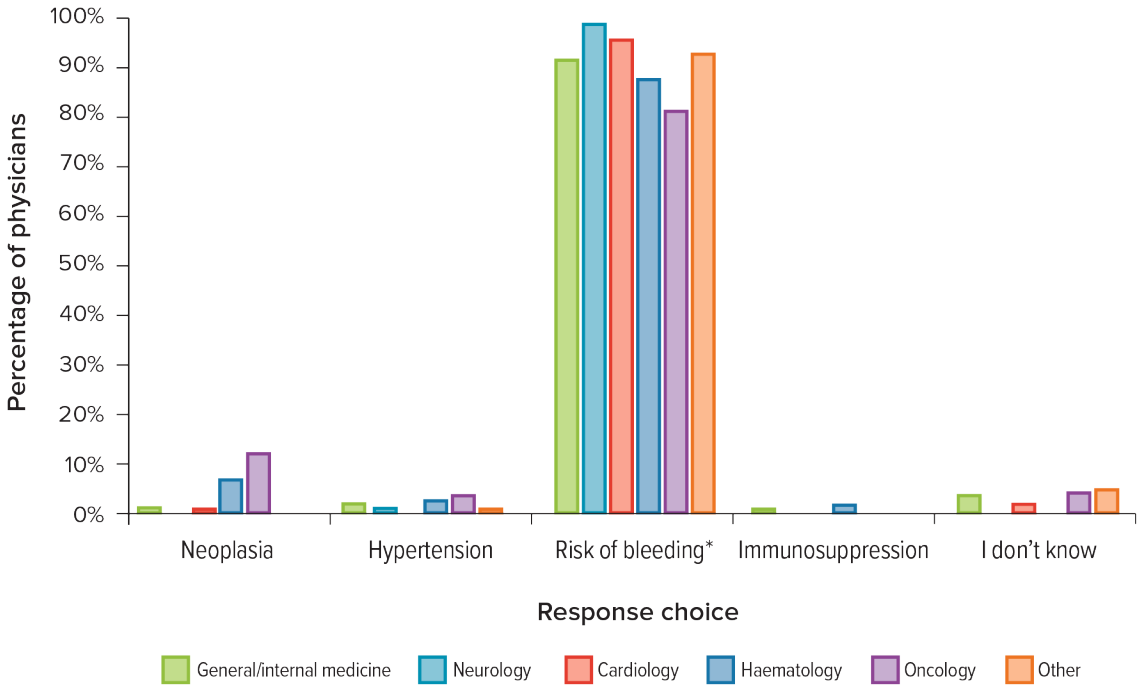

Figure 2: Responses to Question 5: What is the most important risk associated with taking Xarelto? (N = 1,280)

* Correct response is marked with an asterisk.

Physicians' knowledge of patient populations at risk of experiencing serious side effects with rivaroxaban was also high, ranging from 68% to 93% correct for the individual response options, with the lowest percentage (68%) for those who correctly identified chronic constipation as *not* being a risk factor (Figure 3). The item regarding chronic constipation also had the most variation in correct responses across countries, with 73% of the physicians in Germany and France answering correctly versus 64% in Spain and the UK. Correct responses to other side effect items were much more consistent across countries (Annex 3, Table A-3; Question 6).

For most of the side effect questions, the correct response proportions were highest among the cardiologists and neurologists and lowest among the haematologists, oncologists, and the "other" category, with the general/internal medicine in between (Annex 4, Table A-8; Question 6). The proportions of correct responses were higher by > 10% for two of the four questions, for physicians responsible for initiating rivaroxaban treatment or converting treatment to or from rivaroxaban compared with those responsible only for maintenance treatment (Annex 4, Table A-9; Question 6). There was no notable difference in the proportions of correct responses in any of the other stratification variables (Annex 4, Table A-10 and A-12; Question 6).

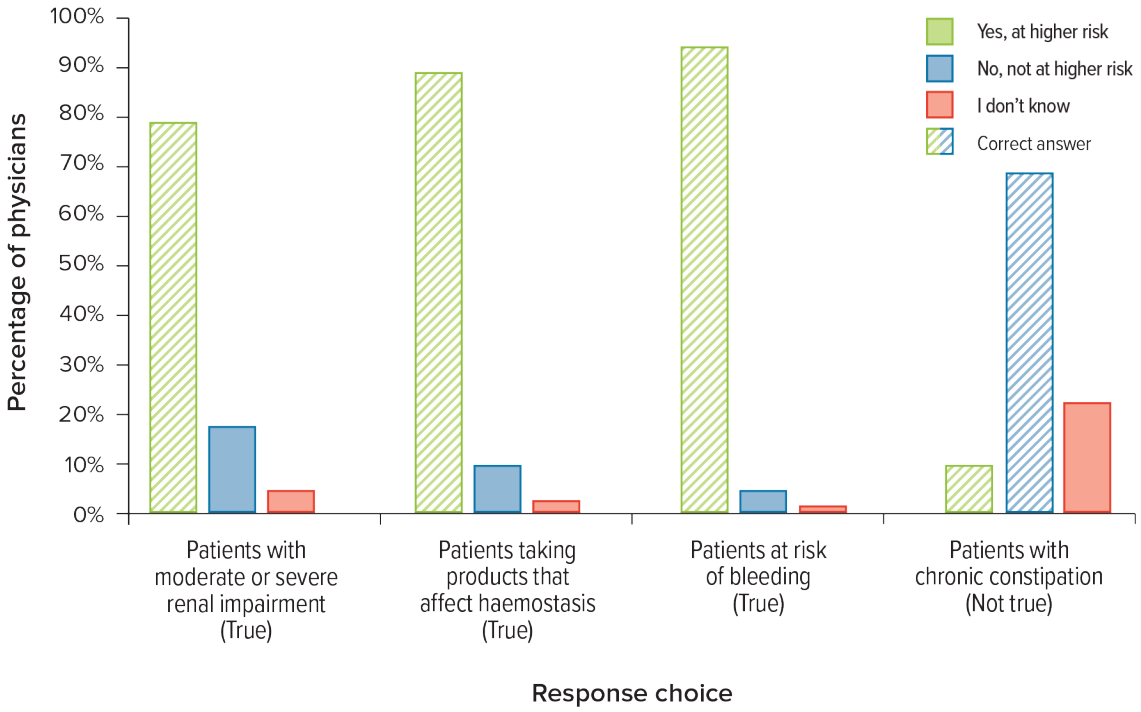

Figure 3: Responses to Question 6: Which of the following populations are at an increased risk of experiencing serious side effect(s) associated with Xarelto?

Note: The N ranged from 1,284 to 1,286 across the 4 statements included in Question 6.

Most physicians (62%) correctly identified all four patient groups for which rivaroxaban is contraindicated; 82% correctly identified at least three of the four, with the correct response proportions being consistently lower in the UK than in the other three countries (Annex 3, Table A-3; Question 7). The proportions of correct responses were similar across specialties, except for oncologists, who had lower correct response proportions than the other physician specialties (Figure 4).

Physicians responsible for initiating and/or converting rivaroxaban treatment had higher proportions of correct responses compared with those responsible for writing maintenance prescriptions only, with 63% selecting all four correct responses compared with 53%, respectively (Annex 4, Table A-9; Question 7). Physicians who reported receiving the prescriber guide for rivaroxaban had higher proportions of correct responses compared with those who did not report receiving the guide, with 69% selecting all four correct responses compared with 54%, respectively (Annex 4, Table A-10; Question 7). There were no differences in the proportions of correct responses to these questions when stratified by number of Xarelto prescriptions in the last 6 months (Annex 4, Table A-12; Question 7).

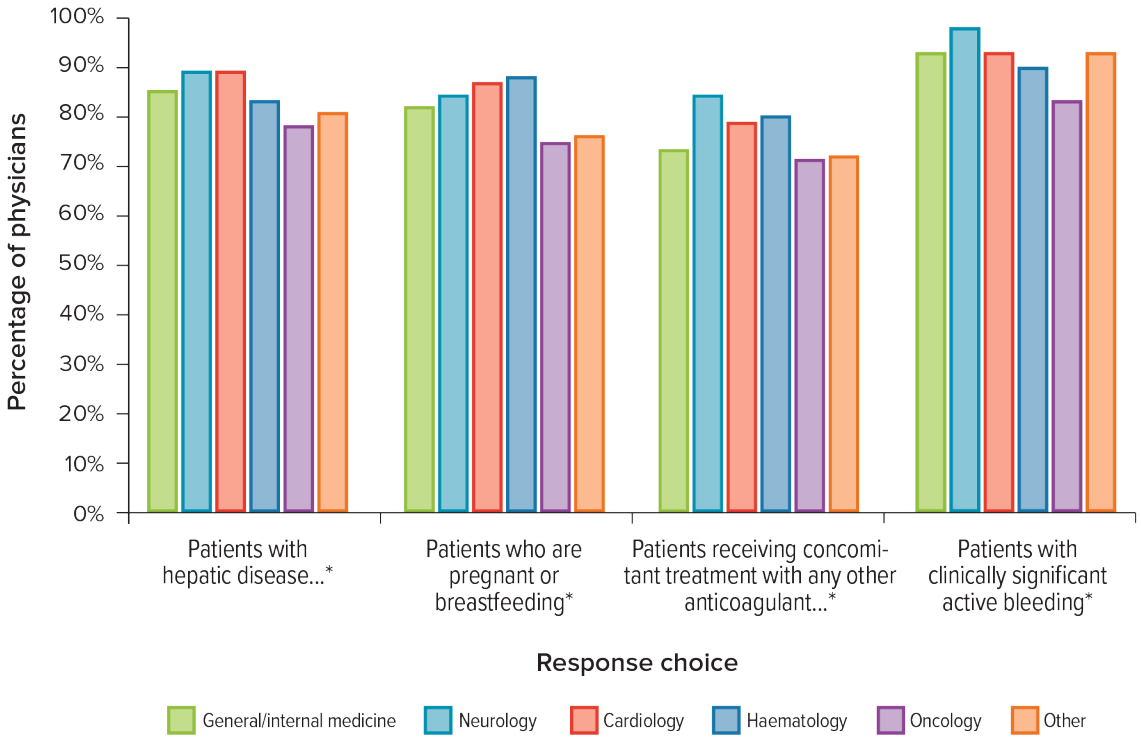

Figure 4: Responses to Question 7: To which patient groups is Xarelto contraindicated? (tick all that apply) (N = 1,279)

* Correct response is marked with an asterisk.

Physicians were asked whether rivaroxaban 15 mg or 20 mg could be taken on an empty stomach or whether it must it be taken with food. Sixty-eight percent correctly answered that rivaroxaban 15 mg or 20 mg should be taken "with food/on a full stomach". Physicians in Germany, France, and Spain had similar proportions of correct responses to this question (73%, 71%, and 70%, respectively), and physicians from the UK had the lowest proportion of correct responses (60%) (Annex 3, Table A-3; Question 8). Across prescriber specialties, specialists in cardiology and haematology had the highest proportions of correct response (84% and 77%, respectively), while specialists in general/internal medicine (65%), oncology (61%), and other (62%) had noticeably lower correct response proportions (Annex 4, Table A-8; Question 8).

There was a particularly large difference in the proportion of correct responses between physicians responsible for initiating and converting rivaroxaban treatment (70% correct) and those responsible for writing maintenance prescriptions only (55% correct) (Annex 4, Table A-9; Question 8). A large difference was also seen between physicians who reported that they had received the prescriber guide for rivaroxaban compared with those who did not report receiving the prescriber guide (75% vs. 60%) (Figure 5).

There were some positive trends indicating an increased knowledge over time across all three waves of the study, with the overall percentage of correct responses increasing from 59% in wave 1 to 62% in wave 2 to 68% in wave 3 (Annex 5).

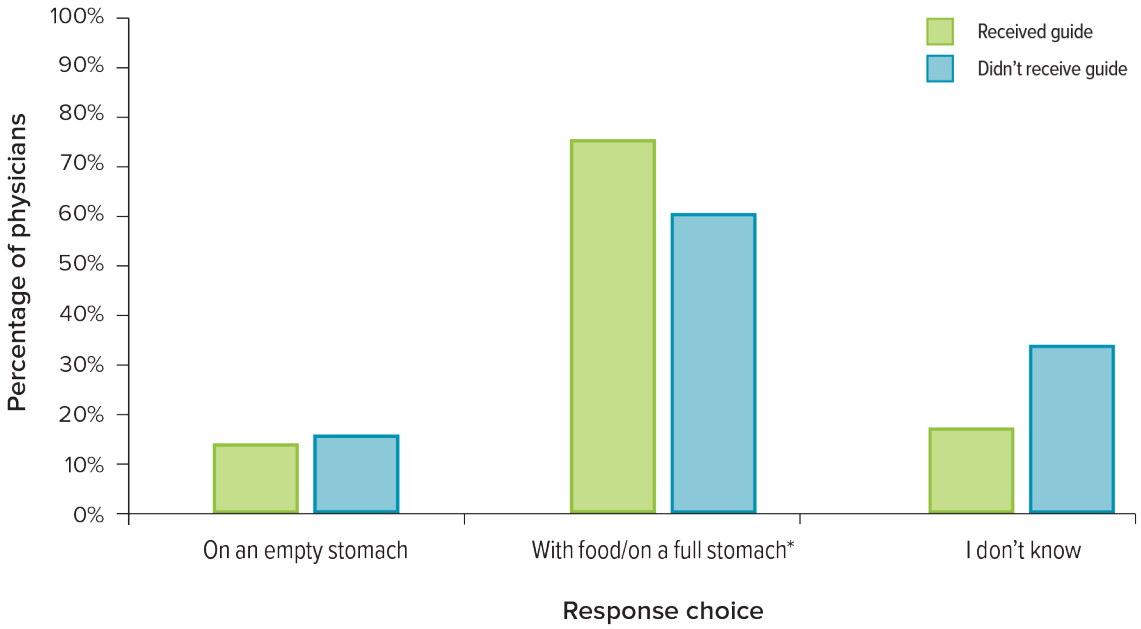

Figure 5: Responses to Question 8: Xarelto (15 or 20 mg) must be taken…? (N = 1,281)

* Correct response is marked with an asterisk.

10.4.2.1.1 Monitoring and converting

Almost all physicians (93%) knew that routine coagulation monitoring is not required for patients taking rivaroxaban, and there was little variability across the subgroups, although the knowledge among haematologists and oncologists (87% answered this question correctly) was slightly lower than among other specialist categories (range of correct responses, 93%-97%) (Annex 3, Table A-3; Question 9 and Annex 4, Tables A-8, A-9, A-10, and A-12; Question 9).

Knowledge was lower when physicians were asked about what *situations* require international normalised ratio (INR) monitoring: 62% correctly indicated there was a need when converting from vitamin K antagonist (VKA) to rivaroxaban, and 75% correctly indicated there was a need when converting from rivaroxaban to VKA. There was some difference in correct response proportions by country, with the proportion of correct responses to the first situation ranging from a low of 53% in France to a high of 73% in Germany and to the second situation ranging from a low of 66% in Spain to a high of 85% in France (Annex 3, Table A-3; Question 10). There was also considerable variability based on physician specialty (Figure 6). Oncologists performed poorer than most of the other categories of specialties for both situations, while interestingly the "other" category performed the worst of any physician specialty on the first situation (45% correct) and by far the best of any on the second situation (86% correct) (Annex 3, Table A-8; Question 10).).

Physicians responsible for initiating rivaroxaban treatment had somewhat higher proportions of correct responses than those responsible for maintenance only (Annex 4, Table A-9; Question 10), and physicians who reported receiving the prescriber guide for rivaroxaban had higher proportions of correct responses than those who did not report receiving the prescriber guide (Annex 4, Table A-10; Question 10).

There was a slight positive trend across the three waves of the survey in the proportion indicating INR monitoring was needed when converting from VKA to rivaroxaban, with the percentage increasing from 57% in wave 1 to 58% in wave 2 to 62% in wave 3 (Annex 5).

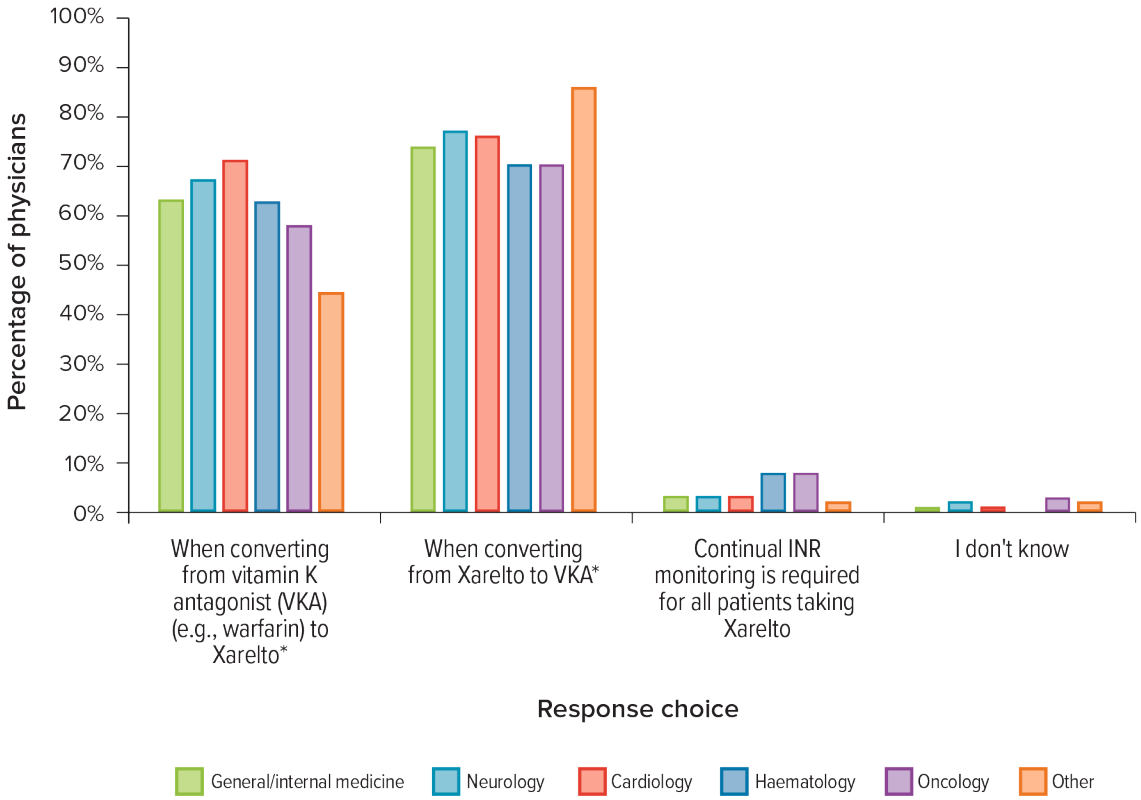

Figure 6: Responses to Question 10: In which of the following situations is INR monitoring needed? (tick all that apply) (N = 1,284)

INR = international normalised ratio; VKA = vitamin K antagonist.
* Correct response is marked with an asterisk.

In two separate "tick all that apply" questions, physicians were asked about procedures for converting patients from VKA to rivaroxaban and from rivaroxaban to VKA. There were two correct responses for each question (Annex 3, Table A-3; Questions 11 and 12). Knowledge was lower when physicians were asked about the steps required for converting from VKA to rivaroxaban:

- 54% of all physicians correctly indicated to stop VKA and initiate rivaroxaban when the INR is ≤ 3 for patients treated for prevention of stroke and systemic embolism.
- 71% of all physicians correctly indicated to stop VKA and initiate rivaroxaban when INR is ≤ 2.5 for patients treated for DVT and secondary prevention.

Knowledge was low when physicians were asked about the steps required for converting from rivaroxaban to VKA:

- 62% correctly indicated to overlap the two drugs until INR is ≥ 2.0.
- 35% correctly indicated to measure INR but make sure it has been longer than 24 hours since the last dose of rivaroxaban.

For both questions, few physicians selected both correct responses (42% and 14%, respectively), but for each of the questions, 83% selected at least one correct response. There was considerable fluctuation across countries, with physicians from Germany generally having the highest proportion of correct responses (Annex 3, Table A-3; Questions 11 and 12). There was not much variability in correct response proportion by specialty. The only marked difference was that fewer physicians in the general/internal medicine and oncologist

specialties correctly indicated that they should overlap the two drugs until INR is ≥ 2.0 (59% and 57%, respectively, compared with 64% to 72% for the other categories) (Annex 4, Table A-8; Questions 11 and 12).

Physicians responsible for initiating or converting rivaroxaban treatment had a higher proportion of correct responses than those responsible for writing maintenance prescriptions only (Figure 7 and Figure 8; Annex 4, Table A-9; Questions 11 and 12) Likewise, physicians who reported receiving the prescriber guide for rivaroxaban had higher proportions of correct responses than those who did not report receiving the prescriber guide (Annex 4, Table A-10; Questions 11 and 12). There were no differences in the proportion of correct responses based on stratification by prescription volume for these questions (Annex 4, Table A-12; Questions 11 and 12).

The proportion of correct responses was slightly higher for physicians who treated both SPAF and DVT compared with physicians who treated for SPAF only or DVT only (Annex 4, Table A-11, Questions 11 and 12).

There was a positive trend across the three waves in the proportion of physicians who selected both of the correct responses to the question about the steps to take when converting patients from VKA to rivaroxaban, with 35% selecting both correct responses in wave 1, 38% in wave 2, and 42% in wave 3 (Annex 4, Table A-13; Question 11).

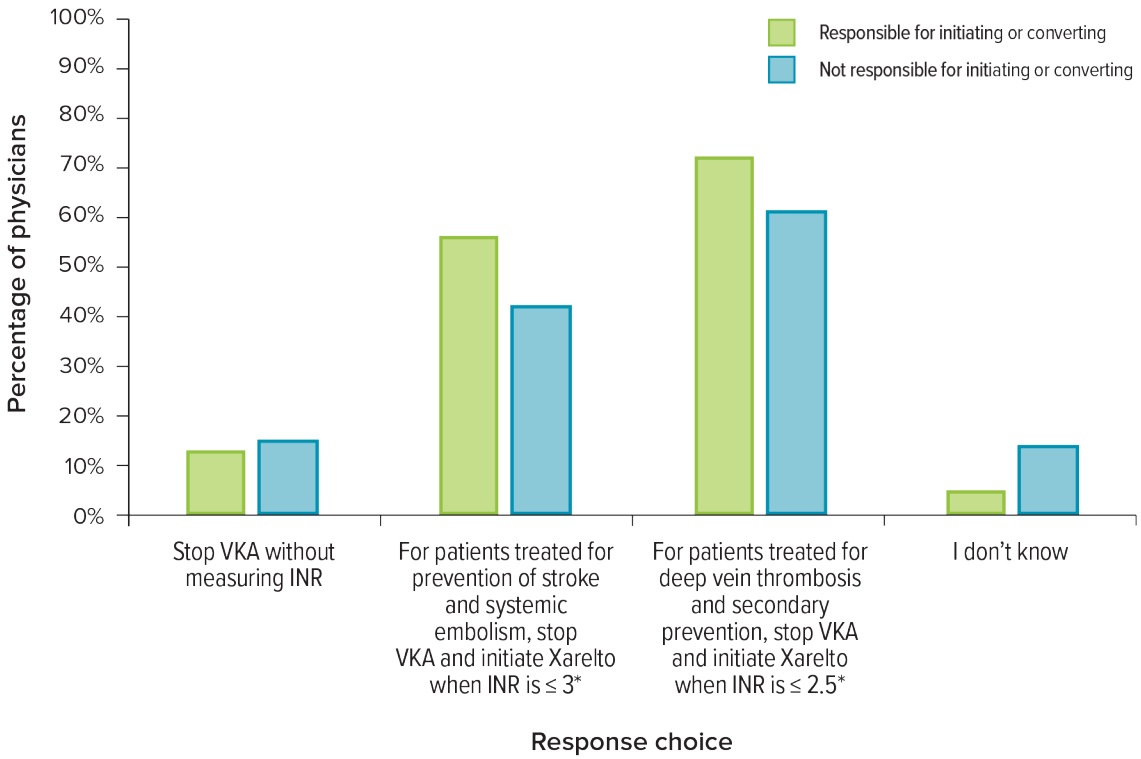

Figure 7: Responses to Question 11: Which of the following steps should be taken when converting patients from VKA (e.g., warfarin) to Xarelto? (tick all that apply) (N = 1,284)

INR = international normalised ratio; VKA = vitamin K antagonist.
* Correct response is marked with an asterisk.

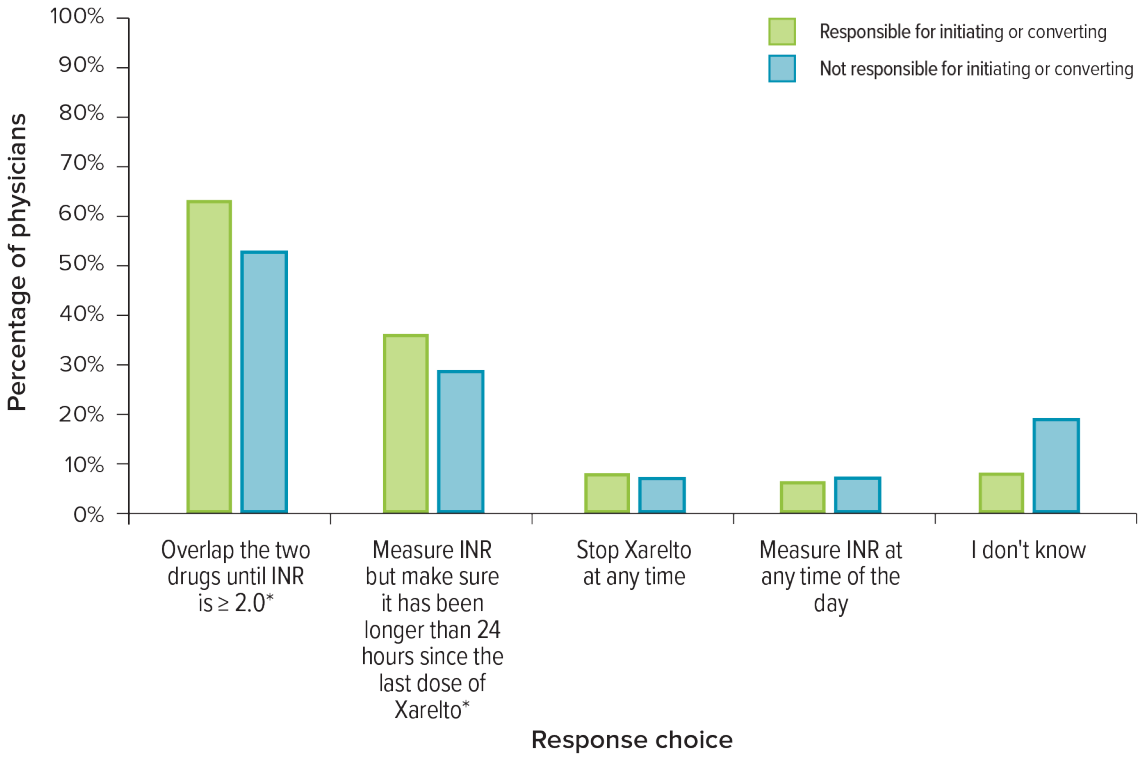

Figure 8: Responses to Question 12: Which of the following steps should be taken when converting patients from Xarelto to VKA (e.g., warfarin)? (tick all that apply) (N = 1,283)

INR = international normalised ratio; VKA = vitamin K antagonist.
* Correct response is marked with an asterisk.

Physicians were also asked about procedures for converting patients from parenteral anticoagulants to rivaroxaban. There were two correct responses for the question:

- For patients with continuously administered parenteral anticoagulants such as intravenous unfractionated heparin, Xarelto should be started at time of drug discontinuation.
- For patients with parenteral drug on a fixed dosing scheme such as low molecular weight heparin (LMWH), Xarelto should be started 0 to 2 hours before the next scheduled drug administration.

The correct responses were selected by 51% and 59% of all physicians, respectively, and 82% selected at least one of the correct responses. Physicians in the UK had much lower proportions of correct responses than physicians from the other countries (Annex 3, Table A-3; Question 13). In general, cardiologists and haematologists had the highest proportions of correct responses compared with other physician specialties, and general/internal medicine practitioners and oncologists had the lowest (Annex 4, Table A-8; Question 13).

Physicians responsible for initiating or converting rivaroxaban treatment had much higher proportions of correct responses (20%-25% higher) than those who did maintenance prescriptions only, and physicians who reported receiving the prescriber guide for rivaroxaban had higher proportions of correct responses (10%-15% higher) than those who did not report receiving the prescriber guide. There was a noticeable difference in the proportion selecting the correct response options based on the number of patients prescribed Xarelto in the past 6 months, with higher prescribing corresponding to higher proportions of correct responses (Annex 4, Tables A-9, A-10 and 12; Question 13).

10.4.2.1.1.1 Monitoring and converting stratified by indication

Questions about converting patients to or from rivaroxaban (Questions 11-13) were asked of all physicians. Given that monitoring and converting activities are indication specific, these questions were stratified by the indication(s) for which physicians reported that they prescribed rivaroxaban (in screening Question 1). The stratification consisted of physicians who prescribe rivaroxaban for the following:

- SPAF only
- DVT and secondary prevention only
- Both SPAF and DVT

In response to Question 11, as expected, physicians who prescribed for SPAF only had a higher proportion of correct responses than physicians who prescribed for DVT only for the response category that was specific to SPAF (54% vs. 38%), and the proportion of correct responses for those who prescribed for both indications was similar to those who only prescribed for SPAF (56%) (Figure 9). Physicians who prescribed for DVT only had a higher proportion of correct responses than physicians who prescribed for SPAF only for the response category specific to DVT (74% vs. 64%), and the proportion of correct responses for those who prescribed for both indications was similar to those who only prescribed for DVT (72%).

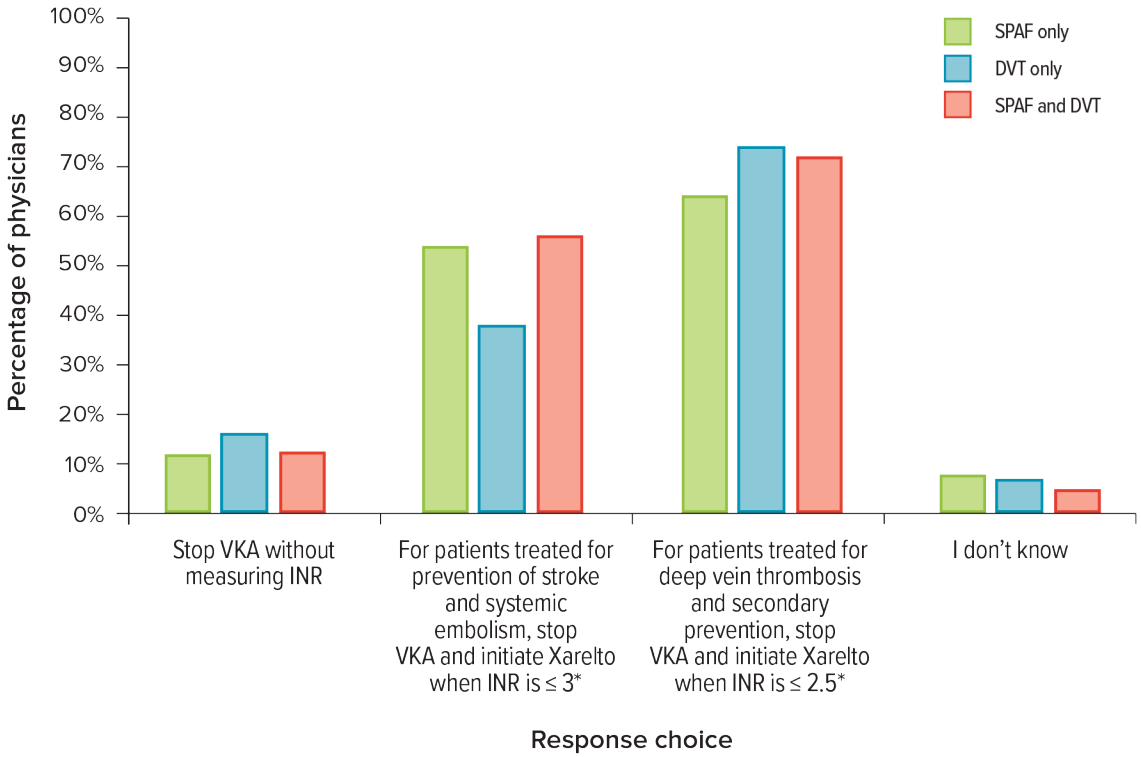

Figure 9: Responses to Question 11: Which of the following steps should be taken when converting patients from VKA (e.g., warfarin) to Xarelto? (tick all that apply) (N = 1,284)

DVT = deep vein thrombosis; INR = international normalised ratio; SPAF = stroke prevention in atrial fibrillation; VKA = vitamin K antagonist.
* Correct response is marked with an asterisk.

In response to Question 12, the correct response proportion was similar across indications for which the physicians prescribed Xarelto for the response category "Overlap the two drugs until INR is ≥ 2.0". However, for the response category "Measure INR but make sure it has been longer than 24 hours since the last dose of Xarelto", those who prescribed for both SPAF and DVT had a higher correct response proportion (38%) than those who prescribed for SPAF only (31%) or DVT only (27%) (Figure 10).

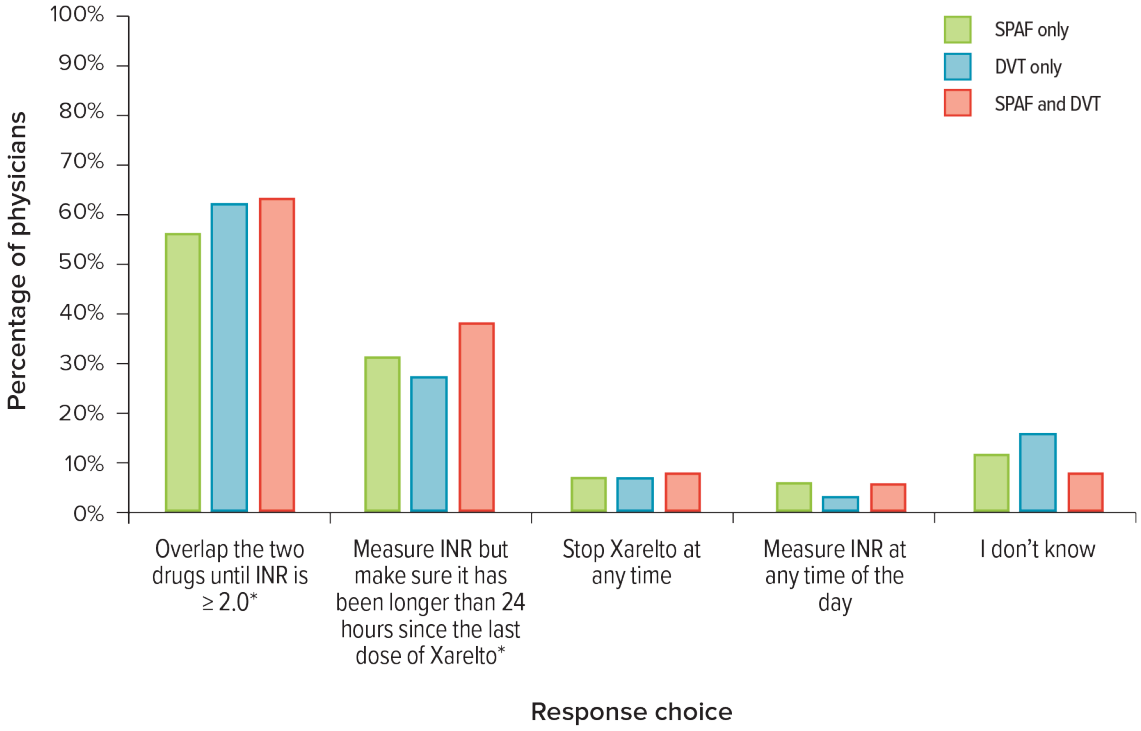

Figure 10: Responses to Question 12: Which of the following steps should be taken when converting patients from Xarelto to VKA (e.g., warfarin)? (tick all that apply) (N = 1,283)

DVT = deep vein thrombosis; INR = international normalised ratio; SPAF = stroke prevention in atrial fibrillation; VKA = vitamin K antagonist.
* Correct response is marked with an asterisk.

The proportion of physicians who selected both of the correct responses for Question 13 (i.e., converting from parenteral anticoagulants to Xarelto) were slightly higher among physicians who treated both SPAF and DVT compared with physicians who treated for SPAF only and DVT only (29% vs. 23% vs. 26%, respectively). This trend was similar for the proportion of physicians who selected at least one of the two correct responses (83% vs. 77% vs. 79%, respectively). (Annex 4, Table A-11; Question 13).

10.4.2.1.2 Invasive procedure and medically important bleeding

Overall, 82% of physicians correctly responded that rivaroxaban treatment should be suspended at least 24 hours prior to an invasive procedure or surgical intervention. The correct response proportions varied considerably across countries, from 91% in Germany to 73% in the UK (Annex 3, Table A-3; Question 14). Neurologists (94%), haematologists (93%), and cardiologists (93%) had the highest correct response proportions among physician specialties, considerably higher than oncology (66%), general/internal medicine (80%), and the combined group of all other specialties (79%) (Figure 11) (Annex 4, Table A-8; Question 14).

Physicians responsible for initiating rivaroxaban treatment or converting treatment to or from rivaroxaban had a much higher correct response proportion (84%) than physicians responsible for writing maintenance prescriptions only (69%). Physicians who reported receiving the prescriber guide for rivaroxaban had a higher proportion of correct responses than those who did not (88% vs. 76%), and physicians who had prescribed to more than 20 patients in the past 6 months had a higher proportion of correct responses than those who had prescribed to 1 to 10 patients (88% vs. 77%) (Annex 4, Tables A-9, A-10 and A-12; Question 14).

There was a slight positive trend across the three waves of the survey in the proportion providing the correct response, with the percentage increasing from 76% in wave 1 to 80% in wave 2 to 82% in wave 3 (Annex 4, Table A-13; Question 12).

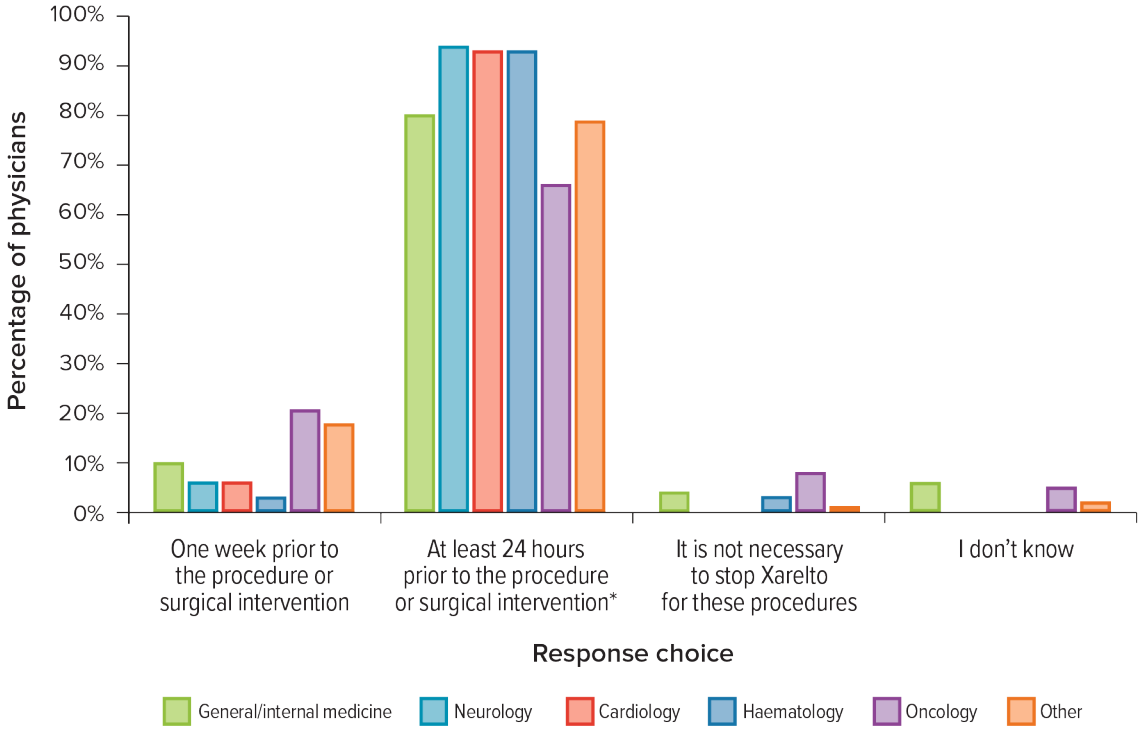

Figure 11: Responses to Question 14: If an invasive procedure or surgical intervention is required, when should treatment with Xarelto (15 to 20 mg) be suspended (if possible, based upon clinical judgement of physician)? (N = 1,279)

* Correct response is marked with an asterisk.

Physicians were asked to select the most appropriate actions if a patient taking rivaroxaban presents with a medically important bleeding complication; there were five correct responses for Question 15. The proportions of correct responses for the five options were similar and ranged from 69% for the option "Administer procoagulant reversal agent (for life-threatening bleeding)" to 77% for the option "Delay the next administration of Xarelto or discontinue Xarelto as appropriate". Forty-seven percent of physicians selected all five correct responses. Physicians in Germany had markedly higher proportions of correct responses compared with the other three countries on this question (Annex 3, Table A-3; Question 15). A smaller proportion of general/internal medicine physicians and oncologists selected the correct responses for this question: 42% and 39% selected all five correct answers respectively, compared with 49% to 60% for the other categories of specialists (Figure 12 and Annex 4, Table A-8; Question 15). General/internal medicine did have the highest proportion who selected one of the five correct response options, "Refer the patient to emergency care", which is probably not surprising as these types of physicians often refer patients to other specialists.

Physicians responsible for initiating or converting rivaroxaban treatment had a higher proportion of correct responses than did physicians who wrote only maintenance prescriptions (49% vs. 31% selected all five correct answers). In addition, physicians who reported receiving the prescriber guide for rivaroxaban had a higher proportion of correct responses than those who did not receive the prescriber guide (54% vs. 39% selected all five correct answers). Physicians who had prescribed to more than 20 patients in the past 6 months had a

slightly higher proportion of correct responses than those who had prescribed to 1 to 10 patients (51% vs. 44%) (Annex 4, Tables A-9, A-10, and A-12; Question 15).

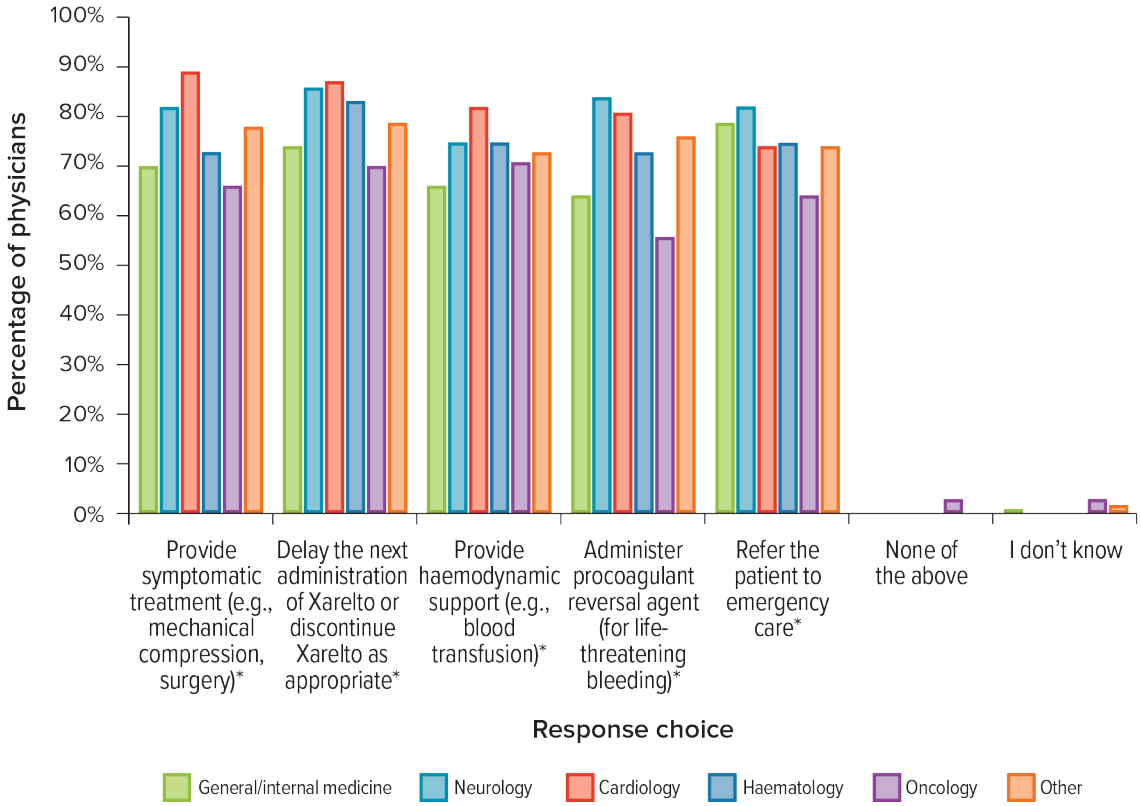

Figure 12: Responses to Question 15: What are the most appropriate actions you should take if a patient taking Xarelto presents with a medically important bleeding complication? (tick all that apply) (N = 1,279)

* Correct response is marked with an asterisk.

10.4.2.1.3 Dosing

10.4.2.1.3.1 Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Questions 16 and 17 were presented to a subset of physicians who reported that they prescribed for SPAF. Of these physicians, 76% correctly reported 20 mg taken once daily was the standard recommended dose of rivaroxaban for this indication, while 61% of physicians were aware that 15 mg taken once daily was the recommended dose of rivaroxaban for SPAF patients with moderate or severe renal impairment. For both questions, physicians in Germany had a higher proportions of correct responses (79% and 67%) than did physicians from the other countries (Annex 3, Table A-3; Questions 16 and 17). Cardiologists had by far the highest correct response proportions for these two questions, with 94% and 81% correct, respectively (Figure 13 and Figure 14) (Annex 3, Table A-8; Questions 16 and 17).

Physicians responsible for initiating or converting rivaroxaban treatment had a higher correct response proportion than did those responsible for maintenance prescriptions only (77% vs. 66% on the first question; 63% vs. 47% on the second question). In addition, physicians who reported receiving the prescriber guide for rivaroxaban had a higher correct response proportion than those who did not report receiving the prescriber guide (83% vs. 69% on the first question; 68% vs. 53% on the second question). Physicians with higher prescribing

volumes tended to have higher correct response proportions than those with lower volumes (Annex 4, Tables A-9, A-10, and A-12; Questions 16 and 17).

There was a slight increase across the three waves in the proportion of physicians providing the correct response to both of these questions. Among those who indicated they prescribed for SPAF, the percentage who correctly reported 20 mg taken once daily was the standard recommended dose increased from 71% to 76% across the three waves; those who prescribed for SPAF and indicated that 15 mg taken once daily was the recommended dose for SPAF patients with moderate or severe renal impairment increased from 56% to 61% across the waves (Annex 4, Question 16-17).

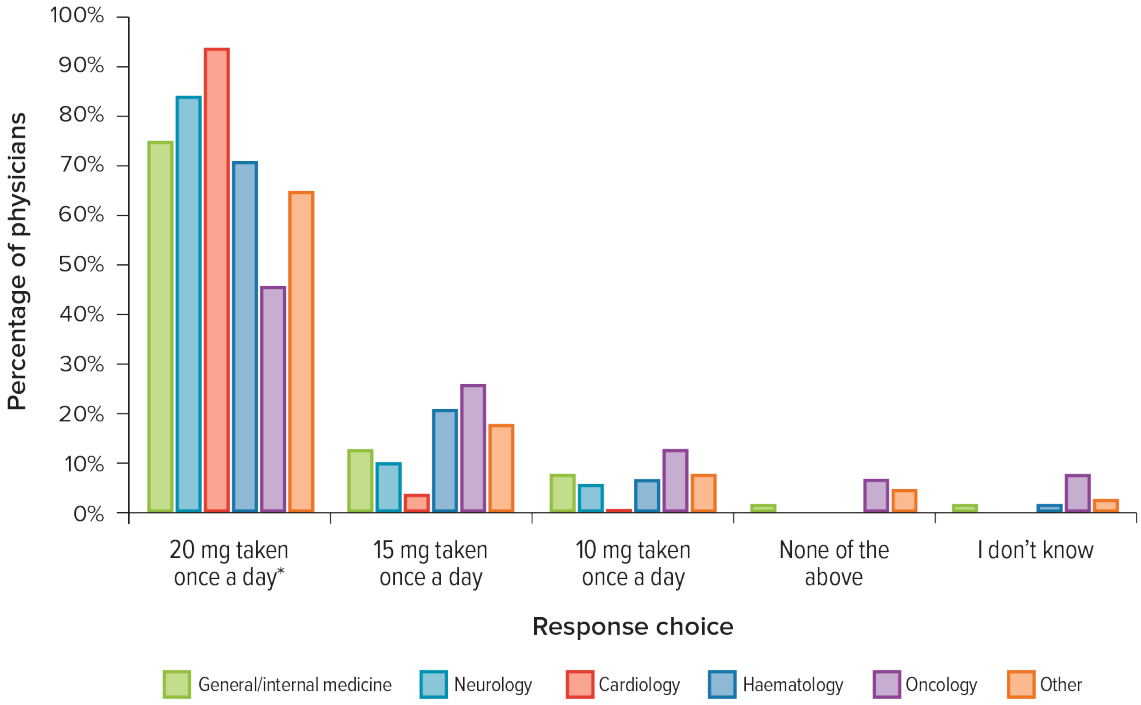

Figure 13: Responses to Question 16: What is the standard recommended dose of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation? (N = 1,249)

* Correct response is marked with an asterisk.

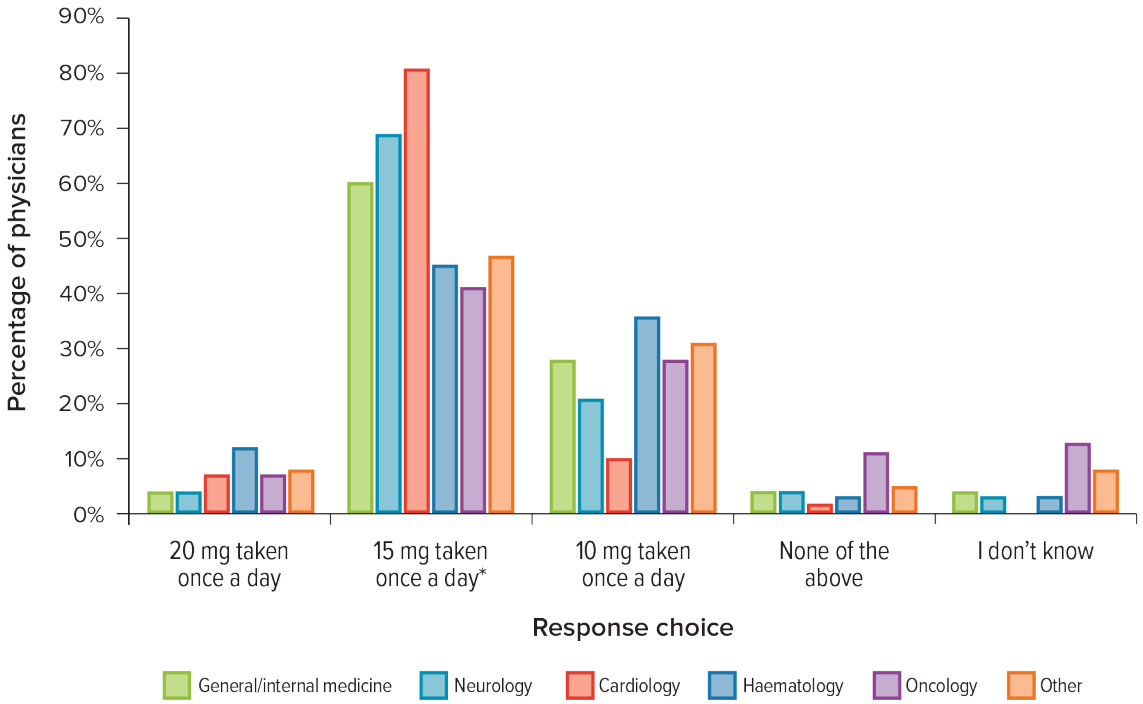

Figure 14: Responses to Question 17: What is the recommended dose for patients with moderate or severe renal impairment (creatinine clearance of 15-49 mL/min) receiving Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation? (N = 1,249)

* Correct response is marked with an asterisk.

10.4.2.1.3.2 Deep vein thrombosis treatment and secondary prevention

Of the physicians who were presented with Question 18, of those who reported that they prescribed rivaroxaban for DVT and secondary prevention, 62% correctly selected the response option for the standard recommended dose for this indication. Physicians from Spain, where rivaroxaban is not reimbursed for the treatment of DVT, were less likely than physicians from the other three countries to select the correct response option (54% vs. 59% to 72% in the other three countries) (Annex 3, Table A-3; Question 18). Again, cardiologists had the highest correct response proportion (72%) among the specialty categories, with the percentage of correct responses ranging among other categories from 55% to 66% (Figure 15) (Annex 4, Table 8; Question 18).

Physicians responsible for initiating rivaroxaban treatment had a slightly higher proportion of correct responses than did those responsible for maintenance prescriptions only (63% vs. 53%). A similar difference was seen between physicians who reported receiving the prescriber guide for rivaroxaban and those who did not (68% vs. 56%). There was no apparent difference when stratified by prescribing volume (Annex 4, Tables A-9, A-10, and Table A-12; Question 18).

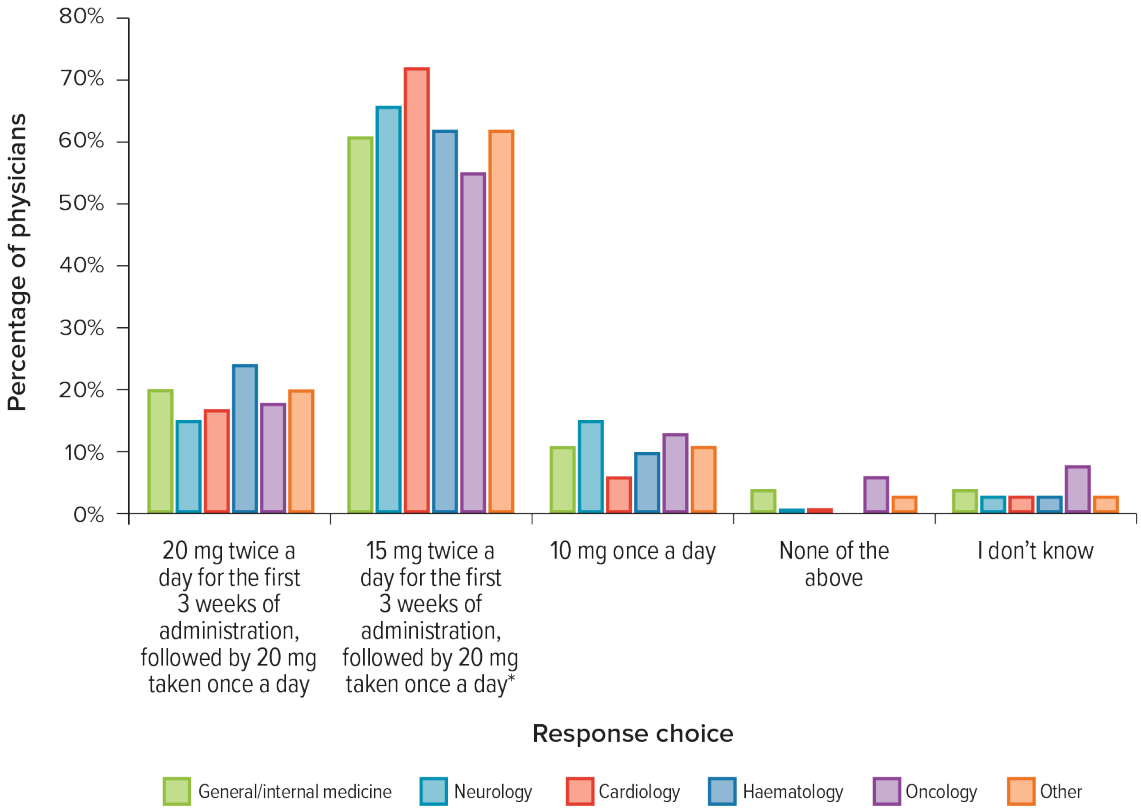

Figure 15: Response to Question 18: What is the standard recommended dose for patients receiving Xarelto for deep vein thrombosis treatment and secondary prevention? (N = 1,131)

* Correct response is marked with an asterisk.

10.4.3 Sources of information about rivaroxaban and their ratings

Overall, as well as within each of the four countries, the three most frequently reported sources of information received about rivaroxaban were the following:

- Summary of product characteristics (58%)
- Prescriber guide (57%)
- Briefing from a company representative (56%)

Physicians in Germany reported the highest rates of receipt of each of these sources of information (86%, 73%, and 65%, respectively), whereas physicians in the UK reported the lowest rates of receipt for each (39%, 31%, and 43%, respectively) (Annex 3, Table A-4; Question 19). Other response options included "Clinical trials published in the medical literature" (selected by 42% of all physicians), "Discussion with a clinical expert" (25%), and "Other" (6%) (Annex 3, Table A-4; Question 19).

Of the physicians who reported receiving the prescriber guide for rivaroxaban, 80% rated it as either very helpful or extremely helpful. Of those who listed "briefing from a company representative", 68% rated that source as very helpful or extremely helpful. Of those who selected "discussion with a clinical expert", 79% rated these discussions very helpful or extremely helpful. Of those who selected "summary of product characteristics", 74% rated the summary as very helpful or extremely helpful; and of those who selected "medical

publications", 78% rated these publications as very helpful or extremely helpful (Annex 3, Table A-5; Question 20).

10.4.4 Experiences with information contained in the patient alert cards

The vast majority (86%) of physicians reported that they discussed the information in the patient alert cards with their patients when first prescribing rivaroxaban. This was consistent across countries ranging from 79% in France to 93% in Germany. Approximately one-third of physicians reported that they discussed the information in the patient alert cards at each of the other 3 times outlined in this question: "when a patient is facing an invasive procedure or surgical intervention" (35%), "when a patient has bleeding complications" (32%), and "when a patient has a Xarelto related adverse event" (30%) (Annex 3, Table A-6; Question 23).

10.5 Other analyses

10.5.1 Stratified knowledge results

This section provides a general summary of the knowledge question results by each of the stratification variables that were explored. As opposed to the previous section where the results of stratification are presented on a question-by-question basis, this section assesses the general impact of each stratification variable across the entire set of knowledge questions.

The survey included 14 knowledge questions that consisted of a total of 28 correct response options, as some questions had a single correct response whereas others had up to five correct response options. To quantify the knowledge across the various categories within each stratification variable, results are reported when there was a difference at least 10% between each specific stratification compared with the highest correct response proportion. For example, for each of the 28 correct response options, we determined the number of times that oncologists selected the correct response at least 10% less often than the highest response proportion among all of the other specialty categories. We repeated this process for each of the other five specialty categories. The results are discussed in the subsequent sections for each of the stratifications. The value of 10% was chosen somewhat arbitrarily, but we felt a difference of that scale might represent a real difference in knowledge as opposed to just random chance resulting from sampling variability.

10.5.1.1 Country

Germany had the highest correct response proportion on most of the questions, with France and Spain usually following fairly closely behind. The UK tended to have the lowest correct response proportion.

10.5.1.2 Physician specialty

In general, cardiologists and neurologists, followed by haematologists, had the highest proportions of correct responses on the knowledge questions. The other categories of specialties, including general/internal medicine, oncology, and the combined category of accident and emergency medicine, pulmonology, and "other" tended to have somewhat lower correct response proportions. (Annex 4, Table A-8).

10.5.1.3 Prescribing responsibility (initiating or converting vs. maintenance only)

Physicians responsible for initiating rivaroxaban treatment or for converting treatment from or to rivaroxaban had a higher proportion of correct responses than those who were only prescribing maintenance treatment for all questions. For 19 of 28 of the correct responses, the difference in knowledge was at least 10%.

10.5.1.4 Reported receiving the Xarelto prescriber guide

Physicians who reported receiving the prescriber guide for rivaroxaban consistently provided more correct responses than those who did not report receiving the guide for all questions. For 14 out of 28 of the correct responses, the difference in knowledge was at least 10%.

10.5.1.5 Prescribing volume

Physicians who reported a higher rivaroxaban prescribing volume in the past 6 months (> 20 patients) had higher correct response proportions compared with physicians who reported a lower prescribing volume (1-10 patients).

10.5.1.6 Repeaters and non-repeaters

There was no difference in the correct response proportions between the physicians in the wave 3 survey who participated in a previous administration (i.e., repeaters) and those who were participating in the survey for the first time. For most of the questions, the difference in correct response proportions between these repeaters and non-repeaters was 0% to 3%, and the largest difference, which only occurred once, was 8%.

10.5.2 Results across waves

Annex 5 provides PowerPoint slides showing a graphical summary of all survey response distributions across the three waves. The sex and years in practice of respondents was consistent across survey administrations. The number of physicians prescribing Xarelto to over 20 patients in the last 6 months for the prevention of stroke and systemic embolism increased over the course of the waves, from 19% to 38%, whereas the number prescribing to over 20 patients for DVT and secondary prevention decreased from 22% to 12%. Wave 3 had a higher proportion of physicians who identified their practice as a hospital-based clinic.

Physicians' knowledge was quite similar across the three waves of the survey, although the respondents in wave 3 had slightly higher correct response rates on many of the questions. For most of the knowledge questions, physicians who identified their specialty as cardiologist had a higher proportion of correct responses on knowledge questions compared with those who identified their specialty as general practitioner or internal medicine. This pattern was consistent for each of the three waves of the survey (Annex 4, Table A-13).

There were some positive trends indicating an increased knowledge over time across all three waves of the study as described below (Annex 5):

- Selected correct response related to taking Xarelto 15 mg or 20 mg with food (wave 1, 59%; wave 2, 62%; wave 3, 68%)
- Selected both correct responses related to situations where INR monitoring is needed (wave 1, 37%; wave 2, 39%; wave 3, 41%)

  - When converting from VKA to Xarelto (wave 1, 57%; wave 2, 58%; wave 3, 62%)
  - When converting from Xarelto to VKA (wave 1, 75%; wave 2, 76%; wave 3, 75%)
- Selected both correct responses for steps to be taken when converting patients from VKA to Xarelto (wave 1, 35%; wave 2, 38%; wave 3, 42%)
  - For prevention of stroke and systemic embolism, stop VKA and initiate rivaroxaban when INR is ≤ 3 (wave 1, 51%; wave 2, 52%; wave 3, 54%)
  - For DVT and secondary prevention, stop VKA and initiate rivaroxaban when INR is ≤ 2.5 (wave 1, 62%; wave 2, 66%; wave 3, 71%)
- Selected both correct answers for identifying what steps should be taken when converting patients from Xarelto to VKA (wave 1, 11%; wave 2, 13%; wave 3, 14%)
  - Overlap the two drugs until INR is ≥ 2.0 (wave 1, 63%; wave 2, 62%; wave 3, 62%)
  - Measure INR but make sure it has been longer than 24 hours since the last dose of Xarelto (wave 1, 30%; wave 2, 36%; wave 3, 35%)
- Selected both correct responses related to converting patients from parenteral anticoagulants to rivaroxaban (wave 1, 25%; wave 2, 24%; wave 3, 28%)
  - For patients with continuously administered parenteral anticoagulants, Xarelto should be started at the time of drug discontinuation (wave 1, 48%; wave 2, 51%; wave 3, 51%)
  - For patients with parenteral drug on a fixed dosing scheme, Xarelto should be started 0 to 2 hours before the next scheduled drug administration (wave 1, 54%; wave 2, 54%; wave 3, 59%)
- Selected correct response related to suspending treatment with Xarelto if an invasive procedure or surgical intervention is required (wave 1, 76%; wave 2, 80%; wave 3, 82%)
- Selected at least four of the five correct responses for the most appropriate actions to be taken if a patient taking Xarelto presents with a medically important bleeding complication (wave 1, 60%; wave 2, 64%; wave 3, 65%)
- Selected correct response for recommended dose of Xarelto for the prevention of stroke and systemic embolism in patients with NVAF (wave 1, 71%; wave 2, 75%; wave 3, 76%)
- Selected correct response for recommended dose in patients with moderate or severe renal impairment receiving Xarelto (wave 1, 56%; wave 2, 58%; wave 3, 61%).

10.6 Adverse events/adverse reactions

This study was not designed to collect information on individual adverse events or adverse drug reactions, which are better collected using other study designs. No adverse events were reported during the wave 3 survey as the survey included only closed-ended questions.

11. Discussion

11.1 Key results

One of the most important factors when dealing with anticoagulation is understanding the risks associated with each product and how to mitigate these risks. In general, physicians' knowledge of the key safety information in the educational materials for rivaroxaban was high.

Physicians' knowledge was particularly high for questions related to the risks of side effects with rivaroxaban treatment and use of rivaroxaban with special populations. Almost all physicians (93%) correctly reported that bleeding is the most important risk associated with rivaroxaban. Physicians' knowledge of patient populations at risk of experiencing serious side effects was high ranging from 68% to 93% correct for individual response options, and physicians' knowledge of contraindications was also high ranging from 74% to 92% correct for individual response options. A lower percentage of physicians (68%) were aware that rivaroxaban should be taken with food.

While almost all physicians (93%) knew that routine coagulation monitoring is not required for patients taking rivaroxaban, knowledge was lower for situations that require INR monitoring, with 41% of physicians selecting the two correct response options. Knowledge was lower regarding procedures for converting from VKA to rivaroxaban, with 42% selecting both correct responses, and for converting from rivaroxaban to VKA, with 14% selecting both correct responses. Knowledge was low for converting from parenteral anticoagulants to rivaroxaban, with 28% selecting both correct response options.

Physician knowledge was high for questions related to invasive procedures and medically important bleeding. Eighty-two percent of physicians correctly reported that rivaroxaban treatment should be suspended at least 24 hours before an invasive procedure or surgical intervention. Physicians' knowledge of the most appropriate actions to take if a patient taking rivaroxaban presents with a medically important bleeding complication ranged from 69% to 77% correct for individual response options.

Physicians' knowledge of dosing recommendations varied by question. Of physicians who prescribed for SPAF, 76% correctly indicated that 20 mg taken once daily was the standard recommended dose for this indication. A lower proportion of physicians (61%) selected the correct recommended dose for SPAF patients with moderate or severe renal impairment. Sixty-two percent of physicians who prescribed for DVT treatment and secondary prevention selected the correct recommended dose for this indication.

Physicians in Germany had the highest correct response proportion on most of the questions, with France and Spain usually following closely behind. Physicians who reported prescribing Xarelto to 21 or more patients in the past 6 months had higher correct response proportions compared with those physicians who reported prescribing to 10 or fewer patients. Physicians who reported specialties in cardiology, neurology, and haematology had higher proportions of correct responses than physicians in other specialty categories for most of the knowledge questions, and oncologists tended to have lower proportions of correct responses. Physicians

responsible for initiating rivaroxaban treatment or converting treatment from or to rivaroxaban had a higher proportion of correct responses than those who were responsible for maintenance treatment only. Physicians who reported receiving the prescriber guide for rivaroxaban also consistently provided more correct responses than those who did not report receiving the guide.

There were no notable differences in correct response proportions between the physicians who participated in the previous waves (wave 1, wave 2, or both) and physicians who were new to the survey.

Physicians' knowledge was remarkably similar across the three waves, with some improvement over time for several knowledge questions. The differences in the proportions of correct responses were less than 5% for almost all the questions in the survey. Annex 5 provides a graphic comparison of results across waves 1, 2, and 3.

More than half of physicians reported that they received the prescriber guide for rivaroxaban (57%), ranging from 31% in the UK to 73% in Germany. The source of information about rivaroxaban reported most frequently by physicians was the summary of product characteristics (58%), followed by the prescriber guide (57%), and a company representative (56%). Of the physicians who reported using the prescriber guide, most (80%) found it helpful or extremely helpful. Most physicians reported that they discussed the information on the patient alert cards with their patients when first prescribing rivaroxaban (86%).

11.2 Limitations

As with all voluntary studies, some limitations are inherent. Many methodologic and operational challenges are well recognised (6). Although the study was designed to ensure the selection of a diverse and generally representative sample of prescribers to participate in this study, there was no exhaustive list of all rivaroxaban prescribers from which to draw a sample; hence, it was impossible to select a random sample of all prescribers. Therefore, although participants were diverse in characteristics, the study participants may not necessarily represent all relevant prescribers. In addition, as is true with most surveys, it was possible that respondents who completed the questionnaire differed from non-respondents in characteristics measured in the questionnaire (e.g., knowledge, reading, and use of the educational materials). The direction and magnitude of such potential respondent bias is not known. A comparison of participants and non-participants was not possible because physicians who did not wish to participate in the survey did not respond to the invitation, and characteristics of the invited physicians were not otherwise available. We could not compare physician and practice characteristics of the physician participants with what is known about the overall prescribing population because that information was not available to us.

11.3 Interpretation

Knowledge and behaviour may be influenced by many factors, including availability and access to information, years of experience, practice setting, country-specific health care systems, literacy and numeracy, cultural differences, beliefs, and motivation.

No *a priori* thresholds of correct responses to the knowledge questions were specified for this study. Sponsors and regulators in the United States and Europe often find reassurance if correct responses for knowledge questions are reported by at least 80% of study participants (4, 6-8). In a review of survey-based studies evaluating the effectiveness of risk-minimisation measures in Europe, a threshold of 80% of correct responses was used to define the success of risk-minimisation measures in 2 of 11 surveys registered in the EU PAS Register (9). In the

other nine surveys, most participants responding correctly was considered a successful result (9).

For this study, the following questions were answered correctly by ≥ 80% of participants:

- The most important risk associated with taking Xarelto (i.e., bleeding) (93%)
- Patients at increased risk for serious side effects
  - Patients taking products that affect haemostasis (88%)
  - Patients at risk of bleeding (93%)
- Patient groups in which Xarelto is contraindicated
  - Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child-Pugh class B and C (84%)
  - Patients who are pregnant or breastfeeding (82%)
  - Patients with clinically significant active bleeding (92%)
- Routine coagulation monitoring required for patients taking Xarelto for the specified indications (93%)
- If an invasive procedure or surgical intervention is required, when treatment with Xarelto should be suspended (82%)

Knowledge varied across categories of information, with higher knowledge associated with the most important information (e.g., greatest risk, populations at increased risk, and contraindications) and lower knowledge associated with procedures, such as treatment switching, which are encountered less frequently by physicians and might require physicians to refer to the summary of product characteristics or other guidance documents. However, awareness of the need to take rivaroxaban 15 mg or 20 mg with food was low but improved across the three waves. The Xarelto patient alert card, which instructs patients to take Xarelto 15 mg or 20 mg with food, is included in the product packaging, ensuring that patients receive the card each time they receive a Xarelto prescription. In addition, pharmacists provide counselling to patients when dispensing prescriptions in each country.

In our study, physicians who reported receiving the prescriber guide for rivaroxaban displayed higher knowledge than those who did not report receiving the guide. These findings suggest that the educational materials are effectively communicating the desired information. The reported receipt of the physician prescriber guide ranged from 31% in the UK to 73% in Germany. Low levels of reported receipt of educational materials may reflect poor recall—if the material had indeed been received—or barriers to the receipt of the material (e.g., inaccurate physician contact information). A recent publication (10) reported the results of a multinational survey of 800 European physicians that assessed the receipt of educational materials. For that study, physician-reported receipt of the educational materials ranged from 16% to 69% across the participating countries.

Variability across countries could reflect the following:

- Different distributions of specialists prescribing initial and maintenance therapy
- Inherent differences in physician behaviour

- Variations in prescribing guidelines (e.g., National Institute for Health and Care Excellence in the UK)
- Variations in practices across country-specific health care systems
- Differences in distribution practices for educational materials
- Different intensity of the educational efforts

The overall response rate for the survey was 4.8%. The response rates for wave 1 and wave 2 were 9.0% and 6.0%, respectively. The response rate for this study is somewhat artificial because responses were not allowed once country quotas for responders were met; thus, the true response rate, although unmeasurable, would be higher.

From experience with comparable physician surveys (in particular PASS studies) conducted by the panel provider (Kantar), response rates are commonly rather low and mostly lie below 10%. Moreover, multiple physician surveys addressing risk-minimisation measures in the United States and Europe have shown response rates below 10% (11-13). However, comparing the physicians' participation in this survey with that of other, similar studies is challenging. In a recent review of 39 survey-based studies evaluating the effectiveness of risk-minimisation measures in the EU, the authors assessed how researchers report physician participation in the surveys. This review revealed high variability in the way this participation is reported, and authors noted the use of different terminologies and indicators to measure participation, which ranged from 1.7% (screened/invited-undelivered) to 98.3% (ineligible + eligible/screened) (14).

Some literature has suggested that it is common for response rates for physician surveys to be below 20% (15) (Dykema et al., 2013). A variety of factors related to survey methodology may account for the low response rates of physicians to survey studies (e.g., method of contact, mode of survey administration, use of incentives) (16, 17). However, physician-related factors that may also be related to low response rates include (a) the lack of time, which, if coupled with the increasing number of requests for participation in survey studies, may discourage participation and (b) lack of interest or low relevance of the survey topic to motivate participation. Other factors identified as contributing to the low response are incorrect or incomplete contact information of listings, physicians being away or retired, and office policies of not participating in any survey (18).

11.4 Generalizability

As noted in Section 10.2, the study achieved great diversity in physician characteristics within the four countries, allowing for stratification of results by those characteristics. We saw heterogeneity of most results by country; it is unknown how well these results would relate to other countries.

12. Other information

None.

13. Conclusion

The study spanning three waves met its objectives to evaluate whether physicians and their patients receive the educational materials for rivaroxaban and to assess physician and patient awareness and understanding of the key safety messages, respectively, in the prescriber guide and patient alert card for rivaroxaban.

More than half of physicians in each of the three waves reported that they received the prescriber guide for rivaroxaban. The relatively high level of knowledge among physicians also suggests that the key safety information is available to treating physicians. Additionally, more than half of patients in wave 1 reported receiving the patient alert card, which at the time was provided to patients by their treating physicians. Since wave 1, the patient alert card has been included in the product packaging, ensuring that patients receive the card each time they receive a Xarelto prescription.

In general, the observed patterns of knowledge among the physicians (as assessed in all 3 waves) are as expected—with greatest knowledge on the most important risks emphasised in the educational material and other product information and lower knowledge on more complex aspects of safe use (e.g., concepts related to dosing, converting to/from rivaroxaban, and patient monitoring) for which we would assume that physicians would consult the label and/or prescriber guide rather than relying on recall. Likewise, the highest levels of patient knowledge (as assessed in wave 1) were on the most important risks (e.g., bleeding) and safe use conditions (e.g., taking rivaroxaban as prescribed, when to consult with their doctor, when to inform other physicians they are taking rivaroxaban).

The results of the three waves of the physician survey were remarkably similar, and physician knowledge improved slightly over time on several knowledge questions, suggesting that the knowledge patterns were maintained during the entire study period. The knowledge retention suggests that the existing channels of educational communication are effective.

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Appendices

Annex 1: List of stand-alone documents

Not applicable.

Annex 2: Physician questionnaire

Annex 3: Results tables, overall and by country

Annex 4: Results tables, by other stratifications

Annex 5: Graphic comparison of wave 1, 2, and 3 results

Annex 6: Signature pages

Signature Page -

Title	Xarelto (rivaroxaban) risk-minimisation plan evaluation: patient and physician knowledge of key safety messages (wave 3)
Report version and date	v 1.0 09 JUN 2020
Study type / Study phase	☒ <PASS> Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS911
Medicinal product	Xarelto (rivaroxaban)
Product Reference	EU/1/08/472/001-024, EU/1/08/472/036-040, EU/1/08/472/042-045, EU/1/08/472/048-049
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

PPD

X

Signer 1

Date, Signature:

12-June-2020, PPD

Signature Page -

Title	Xarelto (rivaroxaban) risk-minimisation plan evaluation: patient and physician knowledge of key safety messages (wave 3)
Report version and date	v 1.0 09 JUN 2020
Study type / study phase	☒ <PASS> Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS911
Medicinal product	Xarelto (rivaroxaban)
Product reference	EU/1/08/472/001-024, EU/1/08/472/036-040, EU/1/08/472/042-045, EU/1/08/472/048-049
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 9 Jun 2020

Signature Page -

Title	Xarelto (rivaroxaban) risk-minimisation plan evaluation: patient and physician knowledge of key safety messages (wave 3)
Report version and date	v 1.0 09 JUN 2020
Study type / study phase	☒ <PASS> Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS911
Medicinal product	Xarelto (rivaroxaban)
Product reference	EU/1/08/472/001-024, EU/1/08/472/036-040, EU/1/08/472/042-045, EU/1/08/472/048-049
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 09 Jun 2020 12:04 PM PPD

Signature Page -

Title	Xarelto (rivaroxaban) risk-minimisation plan evaluation: patient and physician knowledge of key safety messages (wave 3)
Report version and date	v 1.0 09 JUN 2020
Study type / study phase	☒ <PASS> Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS911
Medicinal product	Xarelto (rivaroxaban)
Product reference	EU/1/08/472/001-024, EU/1/08/472/036-040, EU/1/08/472/042-045, EU/1/08/472/048-049
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 09 Jun 2020 10:33 AM PPD

Signature Page -

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09 Jun 2020 1:43 PM

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