PASS Information

Title	Xarelto (Rivaroxaban) Risk Minimisation Plan Evaluation: Patient and Physician Knowledge of Key Safety Messages
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Marketing authorisation holder(s)	Bayer Pharma AG D-13353 Berlin, Germany
Joint PASS	No
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 messages in the prescriber guide and patient alert card. Specifically, the study addressed the following objectives: ▪ Investigate whether physicians and their patients 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
Country(-ies) of study	France, Germany, Spain, and the United Kingdom
Author	PPD PPD

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Bayer Pharma AG D-13353 Berlin, Germany
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Approval Page, PPD

Project Title: Xarelto (Rivaroxaban) Risk Minimisation Plan Evaluation: Patient and Physician Knowledge of Key Safety Messages

Protocol ID Number: 16167

Authors: PPD

Report version: Version 1.0

Date: 16 October 2015

The following people have reviewed the final report and give their approval:

PPD

26 Oct 2015
Date

Approval Page, Bayer Pharma AG

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PPD

Signature

27.10.2015

Date

Bayer Pharma AG

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1 Abstract

Title: Xarelto (Rivaroxaban) Risk Minimisation Plan Evaluation: Patient and Physician Knowledge of Key Safety Messages

16 October 2015

PPD

Keywords: Xarelto (rivaroxaban); post-authorisation safety study; evaluation of risk minimisation measures; physician survey; patient survey

Rationale and background: At the request of the European Medicines Agency (EMA), a prescriber guide and patient alert card (PAC) were developed and distributed to increase awareness and understanding about risks associated with rivaroxaban. The current study was conducted to evaluate the understanding and use of these materials.

Research question and objectives: The primary objectives were to measure whether physicians and patients received and used the prescriber guide and PAC, respectively, and to evaluate their awareness and understanding of the key safety messages.

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 in the rivaroxaban educational materials.

Setting: United Kingdom, Germany, France, and Spain

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 13,221 physicians were invited to participate, of whom 1,452 responded. Of these, 14 did not consent, 149 were ineligible, 65 did not met the definition for a completed survey, and 1,224 physicians completed the questionnaire for a response rate of 9%.

Patients were eligible if they had taken rivaroxaban within the last 3 months for one of the indications of interest. Of the 499 patients approached to participate, 26 were ineligible. Of the 473 eligible, 41 declined and 432 completed the questionnaire. One patient later withdrew consent and 4 patients did not meet the criteria for a completed questionnaire. Therefore, 427 patients were included in the final analysis for a response rate of 90%.

Variables and data sources: Data were obtained through questionnaire responses.

Results: For physicians, the highest percentages of correct responses centred on overall risk of bleeding (> 90%) as well as the risks for populations with contraindications and populations that are at increased risk of serious side effects (70%-91%). A lower percentage of physicians (59%) were aware that rivaroxaban should be taken with food. The lowest percentages of correct responses related to converting to and from vitamin K

antagonist (VKA), monitoring, and dosing. More than half (56%) of physicians reported that they used the Xarelto Prescriber Guide as a source for information.

Among patients, 80% responded correctly that blood thinners can cause bleeding. Knowledge was generally high (> 85% correct) for questions about the indication for treatment, when to consult with their doctor, and when to inform other physicians they are taking rivaroxaban. A lower percentage of patients (60%) correctly reported rivaroxaban should be taken with food. Knowledge about the signs or symptoms of bleeding varied by symptom, with the highest correct response proportion (61%) for unusual bruising and the lowest (18%) for pain. Approximately half of patients (47%) reported having received the PAC. Among those patients, 81% reported having read the card.

Discussion: Physicians' knowledge was highest on the most important risks in the educational materials and lower on 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 recall. Likewise, the highest levels of patient knowledge were on the most important risks and safe-use conditions.

Marketing Authorisation Holder(s): Bayer Pharma AG

Names and affiliations of principal investigators: PPD

2 List of Abbreviations

AF	atrial fibrillation
CI	confidence interval
DVT	deep vein thrombosis
EMA	European Medicines Agency
HCP	health care professional
INR	international normalised ratio
PAC	patient alert card
PE	pulmonary embolism
PPD	
SPAF	stroke prevention in atrial fibrillation
UK	United Kingdom
US	United States
VKA	vitamin K antagonist

3 Investigators

Table 1 provides information for the study principal investigator as well as the country-level investigators. A full list of site-level investigators who participated in the patient assessment is available in a stand-alone document and can be provided upon request.

Table 1. Principal and Country-Level Investigators

Investigators	Country	Institutional Affiliation
Principal		
PPD	United States	PPD
Country-Level		
PPD	United Kingdom	PPD
PPD	France	PPD
PPD	Germany	PPD
PPD	Spain	PPD

4 Other Responsible Parties

PPD an independent non-profit research organisation, is responsible for the design, conduct, analysis, and reporting of the study. Bayer Pharma AG is the marketing authorisation holder of Xarelto (rivaroxaban) and the sponsor of the study. Bayer collaborated with PPD on the study design and is also responsible for fulfilling any obligations for reporting results to regulatory agencies. Kantar Health, a global research operations partner, was responsible for cognitive pretesting of the questionnaires, ethics committee submissions, physician recruitment, monitoring sites for patient recruitment, and data collection.

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PPD

5 Milestones

Milestone	Actual Date
EMA approval of protocol	09 December 2011
Registration in the EU PAS register	06 December 2013
Lead ethics committee approvals	
PPD	PPD 2013
	PPD 2014
	PPD 2013
	PPD 2014
	PPD 2014
	PPD 2014
Data collection for physician assessment	
UK	15 September 2014 to 10 October 2014
Germany	10 November 2014 to 20 November 2014
France	27 October 2014 to 13 November 2014
Spain	27 October 2014 to 07 November 2014
Data collection for patient assessment	
UK	11 November 2014 to 29 April 2015
Germany	24 November 2014 to 30 April 2015
France	25 November 2014 to 30 April 2015
Spain	18 November 2014 to 30 April 2015
Database lock	28 May 2015
Final report of study results	16 October 2015

UK =United Kingdom.

[a] A list of all ethics committees consulted with dates of approval is provided in Annex B.

6 Rationale and Background

In 2011, Xarelto® (rivaroxaban) was approved for use in the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (SPAF) and in the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults (Xarelto Summary of Product Characteristics, EU, 2011).

Atrial fibrillation (AF) is the most common cardiac arrhythmia of clinical significance and is an important independent risk factor for cardiogenic thromboembolic events. Atrial fibrillation is estimated to affect more than 6 million people in Europe and approximately 2.3 million in the United States (US), and the number of people with AF continues to grow in the ageing population (Kannel and Benjamin, 2008). Atrial fibrillation is associated with a four- to five-fold increased risk of ischaemic stroke and accounts for an increasing proportion of strokes with increasing age, from approximately 1.5% of strokes

in individuals aged 50 to 59 years to approximately 23.5% of strokes in individuals aged 80 to 89 years (Wolf et al., 1991).

Acute venous thromboembolism (i.e., DVT or PE) is a common disorder, with an annual incidence of approximately 1 or 2 cases per 1,000 persons in the general population; it is the third most common cause of vascular death, after myocardial infarction and stroke.

As a part of a safety risk management plan revision 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 current study was conducted to address the request by the European Medicines Agency (EMA) to evaluate these elements of the risk management plan.

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 messages in the prescriber guide and patient alert card.

Specifically, the study addressed the following objectives:

- Investigate whether physicians and their patients receive the educational materials for rivaroxaban
- 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 among 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

Although not specifically stated as an objective, the patient assessment also sought to measure patient knowledge immediately after patients read the patient alert card, which was presented to them after they completed the first questionnaire.

8 Amendments and Updates

None.

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 and patients with recent rivaroxaban experience in four European countries (the United Kingdom [UK], Germany,

France, and Spain). Eligible physicians and patients were invited to complete a brief questionnaire regarding their knowledge of key safety messages as outlined in the rivaroxaban educational materials. 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 and patients. Annex C presents the educational materials.

9.1.1 Physician Assessment

The physician assessment was initiated in each country after a period of time sufficient to allow prescribers to have received the prescriber education packets and use the information in their practice. Physicians were recruited using a random sample of physicians from a physician online panel with the aim of obtaining a sample generally representative of physicians who have prescribed rivaroxaban in the selected countries. Invitations were sent 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 questionnaire began with informed consent. After participants consented, they completed the self-administered questionnaire. A screening question was included at the beginning of the questionnaire to confirm that the physician had prescribed rivaroxaban within the past 6 months for at least one of the indications of interest.

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 participants 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.

9.1.2 Patient Assessment

The patient assessment was initiated after the new educational materials had been disseminated. Patients taking rivaroxaban were identified through a diverse sample of medical sites (practices) representing specialties that prescribe rivaroxaban across the target countries. The sites selected for participation in the patient assessment were excluded from the physician assessment described above; however, participating physicians from these sites were asked to complete the physician questionnaire to allow exploratory evaluation of the possible impact of the study on physician knowledge and to evaluate patient responses by level of knowledge of their physician.

Patients were invited to participate only after they had received at least one rivaroxaban prescription such that they had had an opportunity to receive the alert card and their recall of receiving, reading, and carrying the patient alert card could be evaluated. Eligible patients who were present for a scheduled visit were invited to participate by their physicians at that visit, so as not to allow the patient to prepare for the survey beforehand. Those patients who consented completed two paper questionnaires during their visit prior to receiving any specific rivaroxaban counselling. Patients completed the first questionnaire without referring to the patient alert card. Patients were then asked to review the patient alert card and reanswer select questions related to key safety information to gather additional data on patient knowledge after recent exposure to the

card. The paper format for completion of the consent form and questionnaires was chosen both for practical reasons in the administration of a questionnaire during site hours (i.e., ease of use by an older patient population and minimal burden on site) and to assure patients of their privacy in completing the forms.

Each participating site kept a simple log, collecting de-identified information on sex, age range, and indication for which rivaroxaban was prescribed on all patients invited to participate to evaluate any differences between participants and non-participants that should be considered in the analysis. Patients who were approached by the study coordinator and then refused to participate were asked their reason for refusal.

9.2 Setting

This cross-sectional study was conducted in four western European countries (the UK, Germany, France, and Spain). The four countries included were chosen to provide some diversity in physician specialties and practice patterns and patient age and treatment indication, and to observe differences in physician and patient knowledge in these settings. In addition, prescribing levels in these countries were such that there was a sufficient number of eligible physicians and patients with rivaroxaban experience to participate in the study. The study originally included a fifth country, Italy. However, due to delays in rivaroxaban approval in Italy at the time of ethics committee submissions for the study, Italy was removed from the study design.

Data collection for the physician assessment ran from 15 September 2014 to 20 November 2014, and data collection for the patient assessment ran from 11 November 2014 to 30 April 2015.

9.3 Subjects

9.3.1 Physician Assessment

9.3.1.1 Physician Selection and Recruitment

The physician sampling frame was constructed from a physician panel made up of convenience samples of physicians derived from multiple sources (e.g., hospital books, medical directories, yellow pages, peer referrals). A country-specific sampling approach was developed where a stratified random sample of physicians 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. Physicians were then recruited via e-mail to participate in the survey, and quotas were set for each physician specialty to help ensure that the final distribution of respondents was consistent with the prescribing information.

9.3.1.2 Physician Eligibility

Physicians were eligible to participate if they 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 adults with non-valvular atrial fibrillation (SPAF)
- Treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults

9.3.2 Patient Assessment

9.3.2.1 Site Selection and Recruitment

Thirty-five physician sites were selected from a list of 77 sites identified by Bayer that were known to prescribe rivaroxaban. Geographic location and physician specialty were evaluated to ensure a diverse representation of sites that reflected prescribing practices in each country. Sites were contacted to determine interest in the study, to confirm eligibility, and to assess the feasibility of implementing data collection at each site. Physicians who were selected to participate in the patient assessment were excluded from participating in the physician assessment.

To encourage diversity among the patients participating, enrolment was targeted at 10 patients per site. Toward the end of the data collection period, some sites were allowed to enrol additional patients to compensate for sites unable to recruit the targeted sample. However, enrolment was capped at 20 patients per site to prevent any site from providing more than 5% of the overall study population.

9.3.2.2 Site Eligibility

To participate in the study, sites met the following criteria:

- Saw a sufficient number of eligible patients to recruit at least 10 to complete the questionnaire
- Were able to provide a semiprivate space for patient recruitment, the consent process, and completion of the patient-reported questionnaires
- Had a staff member available to coordinate research activities

9.3.2.3 Patient Selection and Recruitment

Participating sites identified and recruited eligible patients to participate in the study while the patient was at the site for a previously scheduled visit. To minimise the possibility of a study intervention effect, sites were trained not to discuss the study with patients in advance of their visit so as not to allow patients to prepare for the survey beforehand. In addition, sites were asked not to deviate from their customary patient counselling practices and were asked to administer the questionnaires to patients prior to any patient counselling. Sites were provided with and used a sampling methodology designed to maximise the probability that each patient treated with rivaroxaban during the data collection period had an equal opportunity to be selected. The sampling approach was customised for the site based each site's estimates of the total number of patients at the site who would be eligible for the study. Sites were instructed to collect de-identified information on sex, age range, and rivaroxaban indication on all patients approached about the study so that characteristics of participants could be compared with non-participants.

9.3.2.4 Patient Eligibility

To be eligible for the study, patients met all of the following criteria:

- Patient has taken rivaroxaban within the last 3 months for SPAF or treatment of DVT and prevention of recurrent DVT and PE following an acute DVT
- Patient was aged 18 years or older
- Patient was able to understand and complete the consent form and patient questionnaires
- Patient could read and understand the native language of the country in which the study was being conducted
- Patient had not participated in a clinical trial for a treatment to prevent blood clots in the past 12 months

9.4 Variables

9.4.1 Physician Questionnaire

The physician questionnaire contained closed-ended questions (e.g., multiple choice, true/false), with no free-text response fields, eliciting responses measuring physician knowledge and understanding of the key information in the Xarelto Prescriber Guide. The physician questionnaire 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
  - Switching 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 patient alert cards
- Physician and practice characteristics

Annex D provides the physician questionnaire.

9.4.2 Patient Questionnaire

The patient questionnaires contained primarily closed-ended questions (e.g., multiple choice, true/false) eliciting responses measuring patient knowledge and understanding of the key information contained in the Xarelto Patient Alert Card. The patient questionnaires included items in the following content areas:

- Patients' experience with Xarelto
- Sources of Xarelto information
  - Knowledge of the key safety messages outlined in the patient alert card
    - Risk of bleeding
    - Signs or symptoms of bleeding
    - When to seek attention from a health care provider
    - Importance of treatment compliance
    - Necessity of taking the 15-mg and 20-mg tablets with food
    - Necessity of informing their health care provider that they are taking rivaroxaban prior to taking other medications and if they need to have surgery or invasive procedures
- Demographics
  - Receipt and use of the patient alert card

Patients completed two questionnaires. The first patient questionnaire covered all of the concepts above except for receipt and use of the patient alert card. Patients completed the first questionnaire without referring to the patient alert card. The second questionnaire included only the knowledge questions and questions related to receipt and use of the patient alert card. Patients completed the second questionnaire after reviewing the card to evaluate patient knowledge after exposure to the card. Annex E provides the patient questionnaires.

9.5 Data Sources and Measurement

The source of information for the study was self-reported data collected from physicians and patients using standard questionnaires with primarily closed-ended response choices.

Questionnaires for physicians and patients were developed using best practices for instrument development. The questions were tailored to the study aims and the information provided in the Xarelto Prescriber Guide and patient alert card. Additional questions were included to obtain information needed to describe the study populations and assess potential differences across subgroups.

To thoroughly evaluate the physician and patient questionnaires before fielding the study, the questionnaires were tested through cognitive interviews with physicians and

patients in the UK, Germany, France, Spain, and Italy[1]. The pretest interviews helped to identify problems with questionnaire items, wording, response choices, etc., and ensured that participants understood the questions. Likewise, the cognitive testing helped to identify cultural or translational issues with the draft questionnaires so that they could be modified to meet the individual needs of each country while maintaining comparability across the study.

Eighteen interviews were first conducted 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. Eight interviews (32 total) then were conducted in each of the remaining countries to confirm wording and facilitate cultural adaptation to each country. Changes to both questionnaires were made based on the results of the cognitive testing and additional feedback from the sponsor prior to the start of data collection.

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 intervention effects and/or 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.

9.6.1 Cognitive Pretesting

The physician and patient questionnaires were cognitively pretested prior to data collection in order to identify any problems with the questionnaire items, wording, and response choices as well as to ensure consistency across cultures and languages. The questionnaires were modified based on feedback from the cognitive interviews with physicians and patients. This process helped to ensure that the questions measured the appropriate concepts consistently and accurately across all countries.

9.6.2 Sample Selection

To minimise sampling bias in the physician assessment, the sampling frame was stratified by speciality in an effort to recruit a sample that was generally representative of the distribution of prescribers in each country. From these strata, physicians were randomly selected and invited to participate. Although a comparison of participating physician characteristics to non-participating physicians was not possible within the panel recruitment framework, the diversity of specialties included in the final sample gave some assurance that the target population was well represented.

For the patient assessment, sites' geographic location and physician specialty were evaluated to ensure a diverse representation of sites that reflected prescribing practices in each country. In addition, participating clinical sites used a patient sampling

[1] The questionnaires were tested in Italy; however, ultimately, the survey was not conducted in Italy due to delays in approval of Xarelto.

methodology to maximise the probability that each patient treated with rivaroxaban would have an equal opportunity to be selected. Information on sex, age range, and indication for which rivaroxaban was prescribed was collected on all patients approached about the study. Each site kept a simple log of information on the number of patients approached about the study, the number of patients confirmed eligible, and the number of patients who refused. Patients who were invited to participate and then refused were asked their reason for refusal. Response rates were high in the patient assessment, and the characteristics of participants and non-participants were similar across demographic characteristics (with the exception of non-participants being slightly older than participants).

However, despite efforts to ensure representative samples for both the physician and patient assessments, participants may have differed from non-participants on key characteristics measured in the survey (e.g., education, knowledge, reading the patient alert card, or educational materials). For patients, the recruiting sites may differ in their treated population and/or education practices from sites not selected to participate in the study. The direction and magnitude of such potential bias is not known.

9.6.3 Data Collection Methods

The physician assessment was administered as an online questionnaire. Physicians were not able to go back to previous questions thus prohibiting them from changing their answers based on subsequent questions.

For the patient assessment, participants were recruited by their treating physician and completed the questionnaires during a normal visit to the site. As such, there was potential for these patients to receive additional education about the key safety messages for rivaroxaban beyond what would typically be provided and thus potentially resulting in an overestimate of knowledge among patients. To minimise the potential for this intervention, sites were trained not to provide any additional education to patients nor discuss specific details of the study with patients before their visit, so that patients could not prepare beforehand. However, it is unknown whether this practice occurred, and, if so, what the impact on the study results would be. Nonetheless, the questionnaires were self-administered without the aid of an alert card for referral, thus relying on patients' recall of the key messages for completion. Furthermore, the patients were readministered questions related to key safety information after being provided an opportunity to review the alert card to see if there were measurable differences in their recollection.

9.7 Study Size

The target sample size for physicians was 300 per country, for a total of 1,200 overall. With a sample size of 300 physician responses for a given question, the maximum width of an exact 95% confidence interval (CI) around the percentage who responded correctly would be 11.6%, and 1,200 responses would give a maximum width of 5.7%.

The target sample size for patients was 100 per country, for a total of 400 overall. With a sample size of 100 patient responses for a given question, the maximum width of an exact 95% CI around the percentage who responded correctly would be 20.3%; with a sample size of 400, the maximum width would be 10%. The patient sample size

calculations reported in the protocol took into account the recruitment strategy of selecting multiple patients from the same site and factored in the potential intraclass correlation; however, the observed intraclass correlation was very low, ranging from 0.003 to 0.09 for the knowledge questions, and the average number of patients per site was not large, 12.2; thus, we treated the patients as independent individuals in the study size calculation above.

The maximum CI widths for each assessment were deemed acceptable to allow reasonable precision to describe physician and patient knowledge of the key safety messages in the Xarelto educational materials.

9.8 Data Transformation

The following summary variables were derived to facilitate evaluation and interpretation of the study results. Most variables used in the analysis did not require any transformation.

9.8.1 Physician Assessment

Derived variables were created for each of the six knowledge questions that asked the respondent to “select all that apply” and that had more than one correct response option (questions 7, 10, 11, 12, 13, and 15). Derived variables indicated the number of correct responses selected. For example, question 15, which had five correct responses, had the following five derived variables:

- Q15_5 Correct: Yes if all five correct responses were selected; No otherwise
- Q15_4+ Correct: Yes if at least four correct responses were selected; No otherwise
- Q15_3+ Correct: Yes if at least three correct responses were selected; No otherwise
- Q15_2+ Correct: Yes if at least two correct responses were selected; No otherwise
- Q15_1+ Correct: Yes if at least one correct response was selected; No otherwise

9.8.2 Patient Assessment

Derived variables were created for the knowledge questions that asked the respondent to “select all that apply” and that had more than one correct response option (question 17 in patient questionnaire 1 and question 9 in patient questionnaire 2). As with the physician knowledge questions, derived variables for the patient knowledge question indicated the number of correct responses selected.

9.9 Statistical Methods

All analyses were performed using SAS 9.3 statistical software (SAS Institute, Inc., Cary, North Carolina).

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 closed-ended questionnaire responses. Both open-ended text responses were reported in a listing.

Descriptive tables summarising questionnaire responses were generated for the physicians and patients by country and overall. No imputation of missing data was performed, and no formal hypothesis testing was conducted.

Response distribution percentages for each question were based on the total number of respondents who had an opportunity to answer the question. Due to the paper-based administration, patients were able to provide responses even when they should have skipped the question. These data were omitted from the summary tables in efforts to enforce the skip pattern logic of the questionnaire. This total excluded those who were asked to skip due to an answer given in a prior question (skip pattern).

Exact 95% CIs were generated around the percentage of participants that 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

9.9.2.1 Analysis of Physician Questionnaire

Main Analysis

The analysis population for the physician assessment results consisted of respondents who were eligible for the study, provided informed consent, and completed at least one of the knowledge questions (Q5-Q18).

Questionnaire items were divided into the following categories for the analysis: (1) physician and practice characteristics, (2) physician prescribing practices, (3) knowledge questions, (4) sources of information about rivaroxaban, (5) ratings of those sources, and (6) experiences with 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 F and include results overall and by country.

Table 2. Listing of Main Analysis Tables for Non-Recruiting Physicians (Overall and by Country)

Table Number	Table Title	Question Number(s)
Table F-1	Physician and Practice Characteristics	24-27
Table F-2	Physician Prescribing Practices	1-4
Table F-3	Knowledge Questions	5-18
Table F-4	Sources of Information About Xarelto	19
Table F-5	Ratings of Sources of Information About Xarelto	20
Table F-6	Physicians' Experiences With Patient Alert Cards	21-23

Stratification of Physician Results

In addition to the overall and by-country results, the knowledge questions have been stratified by the following variables to explore the association between each variable and physician knowledge levels:

- Physician specialty (based on response to question 24)
- Whether or not physician is responsible for initiating Xarelto treatment or converting treatment from or to Xarelto (based on response to question 4)
- Whether or not physician received information from the Xarelto Prescriber Guide (based on response to question 19)
- Indication(s) for which physician prescribed rivaroxaban (based on response to screening question 1)
- Whether or not physician received patient alert cards (based on response to question 21)

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

Table 3. Listing of Stratification Analysis Tables for Non-Recruiting Physicians

Table Number	Table Title	Question Number(s)
Table G-1	Physician Specialty	5-18
Table G-2	Whether or not Physicians Received Information From Xarelto Prescriber Guide	5-18
Table G-3	Indication(s) for Which Physicians Prescribed Xarelto	11-13
Table G-4	Whether or not Physician is Responsible for Initiating Xarelto Treatment or Converting Treatment From or to Xarelto	5-18

Analysis of Recruiting Physicians Participating in the Patient Assessment

The main physician results tables include only those physicians who participated in the physician assessment (also known as *non-recruiting physicians*) and do not include

physicians who participated in the patient recruitment (also known as *recruiting physicians*). Separate analyses were conducted for the physicians who recruited patients into the patient assessment. A comparison of results for recruiting and non-recruiting physicians is included in Section 10.

Table 4 presents the table numbers and question numbers that correspond to each table. The tables are provided in Annex H and include results overall and by country.

Table 4. Listing of Analysis Tables for Recruiting Physicians (Overall and by Country)

Table Number	Table Title	Question Number(s)
Table H-1	Physician and Practice Characteristics	24-27
Table H-2	Physician Prescribing Practices	1-4
Table H-3	Knowledge Questions	5-18
Table H-4	Sources of Information About Xarelto	19
Table H-5	Ratings of Sources of Information About Xarelto	20
Table H-6	Physicians' Experiences With Patient Alert Cards	21-23

9.9.2.2 Analysis of Patient Questionnaires

The analysis population for the patient results consisted of respondents who were eligible for the study, provided informed consent, and completed at least one of the knowledge questions (Q6, Q10-Q17) on the first questionnaire.

Questionnaire items were divided into the following categories for the analysis: (1) patient demographics, (2) experience with rivaroxaban, (3) experience with the patient alert card, and (4) knowledge questions. Separate analysis tables were generated to display the response distributions of the questions in each category.

In addition to the overall and by-country questionnaire results tables, patient response tables have been stratified by patients' previous experience with blood thinners (based on responses to question 7).

Confidence intervals for the knowledge questions, by country and overall, were calculated using exact 95% methods. This method assumed independence between patients, which was determined to be appropriate despite the design of sampling multiple patients per site because there were relatively few patients per site (mean, 12.2) and the observed intraclass correlation among the patients within the sites was very low, ranging from 0.003 to 0.09 for the various knowledge questions.

Table 5 presents the table numbers and question numbers that correspond to each table. The tables are provided in Annex I and include results overall and by country.

Table 5. Listing of Analysis Tables for Patients (Main Analysis and Stratification Variables)

Table Number	Title (Analytical Table)	Question Number(s)
Table I-1	Patient Demographics	Questionnaire 1: 19-21
Table I-2	Patient's Xarelto Background	Questionnaire 1: 3-5, 7, 18
Table I-3	Sources of Xarelto Information	Questionnaire 1: 8, 9
Table I-4	Patient Alert Card Experience	Questionnaire 2: 10-15
Table I-5	Patient Knowledge	Questionnaire 1: 6, 10-17 Questionnaire 2: 1-9
Table I-6	Patient Knowledge Change After Reviewing Patient Alert Card	Questionnaire 1: 6, 10-17 Questionnaire 2: 1-9
Table I-7	Patient Open-Text Responses	Questionnaire 1: 8, 18
Table I-8	Characteristics of Participants and Decliners	Screening questions
Table I-9	Patient Knowledge by Previous Experience With Taking Prescription Anti-Coagulants	Questionnaire 1: 6, 10-17 Questionnaire 2: 1-9

9.9.3 Missing Values

Individuals who had the opportunity to but did not answer a question were included in the count of respondents. These counts (true missing data) and their respective percentages were summarised in the row labeled "No answer" under the question in the results. The count of individuals who were instructed to skip a question (not true missing data) were listed in a row labeled "Not applicable skip pattern" under the question without percentages and were not included in the percentage calculations.

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 the internal standard operating procedures of participating institutions.

All key study documents, such as the analysis plan, data collection forms, and study progress reports, underwent quality-control review, senior scientific review, and editorial review.

During data collection, the logic, range, and edit checks that were programmed in the electronic data capture system allowed for real-time resolution of data errors or data discrepancies.

During the analysis, the principal programmer reviewed all programs, logs, and output for accuracy according to relevant PPD standard operating procedures. All analyses were confirmed through double independent programming.

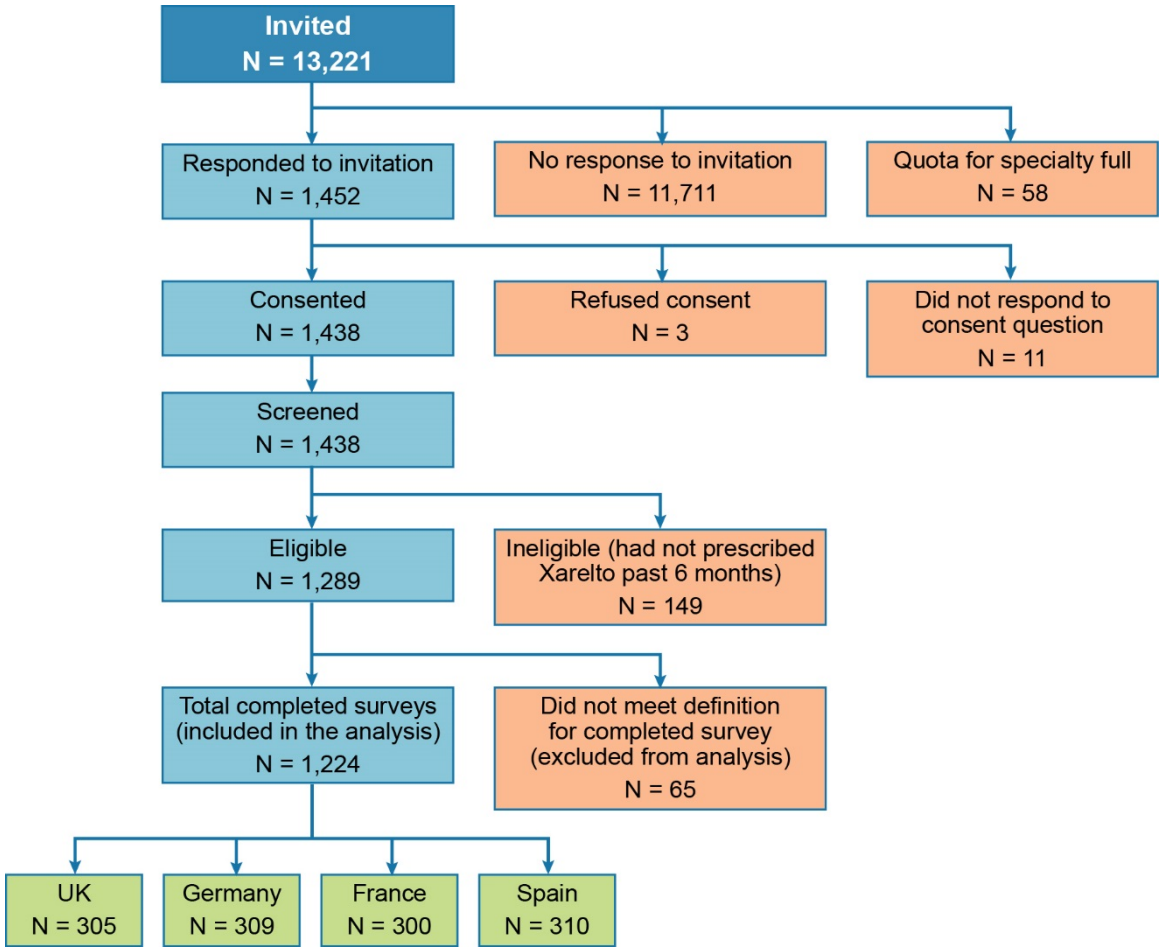
10 Results

10.1 Physician Assessment Results

10.1.1 Participants

A total of 13,221 physicians were invited to participate in the survey. Of those, 1,452 physicians responded to the invitation. Of the physicians who responded, 14 refused consent or did not respond to the consent question, 149 were ineligible, and 65 did not meet the definition for a completed survey. The remaining 1,224 physicians, approximately 300 per country, completed the questionnaire. The overall response rate was 9%. Figure 1 presents the distribution of physicians invited to participate.

Figure 1. Distribution of Physicians



UK = United Kingdom.

10.1.2 Descriptive Data

Physicians were sampled 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 data on specialty provided in this report are based on the latter. Physician specialties represented in the survey included general medicine (45%), cardiology (20%), neurology (9%), haematology (6%), oncology (4%), and accident and emergency medicine (3%). Approximately 13% of physicians reported "other" to this question. A total of 63% of physicians reported that they practiced in a general setting, and 43% of physicians reported that they practiced at a hospital-based clinic.[1] Most (74%) participants were male. Physicians' experience (as measured by years in practice) was categorized into 5-year increments up to 25 years. More than 98% of physicians had been in practice more than 5 years, with durations fairly evenly distributed across the increments beyond 5 years. Approximately 1 in 5 physicians (20%) reported having been in practice more than 25 years.

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

Table 6. Physician and Practice Characteristics

Question	No. of Physicians (%)				
	UK n = 305	Germany n = 309	France n = 300	Spain n = 310	Overall N = 1,224
Physician specialty					
General medicine	85 (28%)	176 (57%)	171 (57%)	120 (39%)	552 (45%)
Neurology	22 (7%)	41 (13%)	0[a]	44 (14%)	107 (9%)
Cardiology	69 (23%)	62 (20%)	54 (18%)	56 (18%)	241 (20%)
Haematology	33 (11%)	7 (2%)	16 (5%)	17 (5%)	73 (6%)
Accident and emergency medicine	9 (3%)	2 (1%)	5 (2%)	23 (7%)	39 (3%)
Oncology	0[a]	4 (1%)	30 (10%)	10 (3%)	44 (4%)
Other[b]	84 (28%)	16 (5%)	24 (8%)	34 (11%)	158 (13%)
No answer	3 (1%)	1 (0%)	0	6 (2%)	10 (1%)
Sex					
Male	236 (77%)	248 (80%)	247 (82%)	180 (58%)	911 (74%)
Female	66 (22%)	60 (19%)	53 (18%)	124 (40%)	303 (25%)
No answer	3 (1%)	1 (0%)	0	6 (2%)	10 (1%)
Years practicing medicine					
5 years or less	3 (1%)	2 (1%)	0	6 (2%)	11 (1%)
6 to 10 years	34 (11%)	14 (5%)	27 (9%)	54 (17%)	129 (11%)
11 to 15 years	73 (24%)	66 (21%)	58 (19%)	80 (26%)	277 (23%)
16 to 20 years	88 (29%)	71 (23%)	55 (18%)	64 (21%)	278 (23%)
21 to 25 years	63 (21%)	91 (29%)	74 (25%)	45 (15%)	273 (22%)
More than 25 years	41 (13%)	64 (21%)	86 (29%)	55 (18%)	246 (20%)
No answer	3 (1%)	1 (0%)	0	6 (2%)	10 (1%)
Practice type[c]					
General practice	139 (46%)	236 (76%)	204 (68%)	189 (61%)	768 (63%)
Hospital-based clinic	161 (53%)	80 (26%)	103 (34%)	177 (57%)	521 (43%)
Nursing home	0	5 (2%)	10 (3%)	10 (3%)	25 (2%)
Other	4 (1%)	2 (1%)	0	6 (2%)	12 (1%)
No answer	3 (1%)	1 (0%)	0	6 (2%)	10 (1%)

UK = United Kingdom.

[a] A review of the prescribing data available at survey launch indicated that, in general, neurologists were not prescribing Xarelto in France, and oncologists were not prescribing in the UK; therefore, neurologists were not sampled in France, and oncologists were not sampled in the UK.

[b] The specialties as reported in the online panel's database for physicians who responded "other" in the questionnaire include accident, general practice, intensive care, and pulmonary disease doctors in the UK; cardiology, internal medicine, nephrology, and pulmonary disease doctors in Germany; pulmonary disease doctors in France; and general practitioner, internal medicine, and pulmonary disease doctors from Spain.

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

As described in Section 9.9.2.1, the physician knowledge questions were stratified by several variables to evaluate whether there were variations in knowledge among subgroups. Table 7 presents each variable and the distribution of responses overall and by country. Discussion of the results for these variables is included in the relevant results sections below.

Table 7. Stratification Variables for Physicians

Category	No. of Physicians (%)				
	UK n = 305	Germany n = 309	France n = 300	Spain n = 310	Overall N = 1,224
Whether or not physician is responsible for initiating Xarelto treatment or converting treatment from or to Xarelto					
Yes	245 (80%)	297 (96%)	239 (80%)	264 (85%)	1045 (85%)
No[a]	60 (20%)	12 (4%)	61 (20%)	46 (15%)	179 (15%)
Whether or not physicians received information from Xarelto Prescriber Guide					
Yes	114 (37%)	171 (55%)	191 (64%)	207 (67%)	683 (56%)
No	188 (62%)	137 (44%)	109 (36%)	97 (31%)	531 (43%)
No answer	3 (1%)	1 (0%)	0	6 (2%)	10 (1%)
Indication(s) for which physicians prescribed Xarelto					
SPAF only	107 (35%)	42 (14%)	65 (22%)	158 (51%)	372 (30%)
DVT only	40 (13%)	6 (2%)	48 (16%)	20 (6%)	114 (9%)
SPAF and DVT	158 (52%)	261 (84%)	187 (62%)	132 (43%)	738 (60%)
Whether or not physicians received Xarelto Patient Alert Cards					
Yes	89 (29%)	246 (80%)	119 (40%)	127 (41%)	581 (47%)
No	213 (70%)	62 (20%)	181 (60%)	176 (57%)	632 (52%)
No answer	3 (1%)	1 (0%)	0	7 (2%)	11 (1%)

DVT = deep vein thrombosis; SPAF = stroke prevention in atrial fibrillation; UK = United Kingdom.

[a] Physicians were responsible for maintenance prescriptions only.

10.1.3 Outcome Data

Not applicable.

10.1.4 Main Results

In the following sections, we present key results from the non-recruiting physicians who completed the physician questionnaire. The results are organised in the following categories, which also correspond to the analysis tables provided in Annexes F and G: (1) physician prescribing practices, (2) knowledge of key safety information, (3) sources of information about rivaroxaban and ratings of those sources, and (4) physicians' experiences with patient alert cards.

First, we describe the results for the overall sample, then results stratified by country, physician specialty, physician prescribing responsibility (initiating and converting vs. maintenance only), whether the physician reported receiving information from the Xarelto Prescriber Guide, and indication for which the physician prescribes rivaroxaban.

Graphs highlight the stratification results in which the largest differences were seen or where the stratifications seem of most interest. In general, physicians who reported specialties in neurology, cardiology, and haematology had a higher proportion of correct responses than physicians in other specialty categories on most of the knowledge questions. Likewise, physicians responsible for initiating rivaroxaban treatment or converting treatment from or to rivaroxaban had a higher proportion of correct responses than those who were not. Physicians who reported receiving information from the Xarelto Prescriber Guide also consistently provided more correct responses than those who did not report receiving information from this source.

Annexes F and G include tables presenting the complete set of knowledge question results for non-recruiting physicians overall and by each of the stratification variables.

10.1.4.1 Physician Prescribing Practices (Annex F, Table F-2 and Annex G, Tables G-1, G-2 and G-4; Questions 1, 2, 3, 4)

Most physicians (75%) had written a prescription for rivaroxaban within the last month. Almost all physicians (96%) had prescribed rivaroxaban for SPAF in the past 6 months, and most physicians (78%) 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, more than one-third of physicians (37%) reported that they had not prescribed rivaroxaban for DVT in the past 6 months.

Most physicians (85%) reported that they were responsible for initiating rivaroxaban treatment or converting from or to rivaroxaban, and more than half (63%) reported that they wrote follow-up (maintenance) prescriptions.[1]

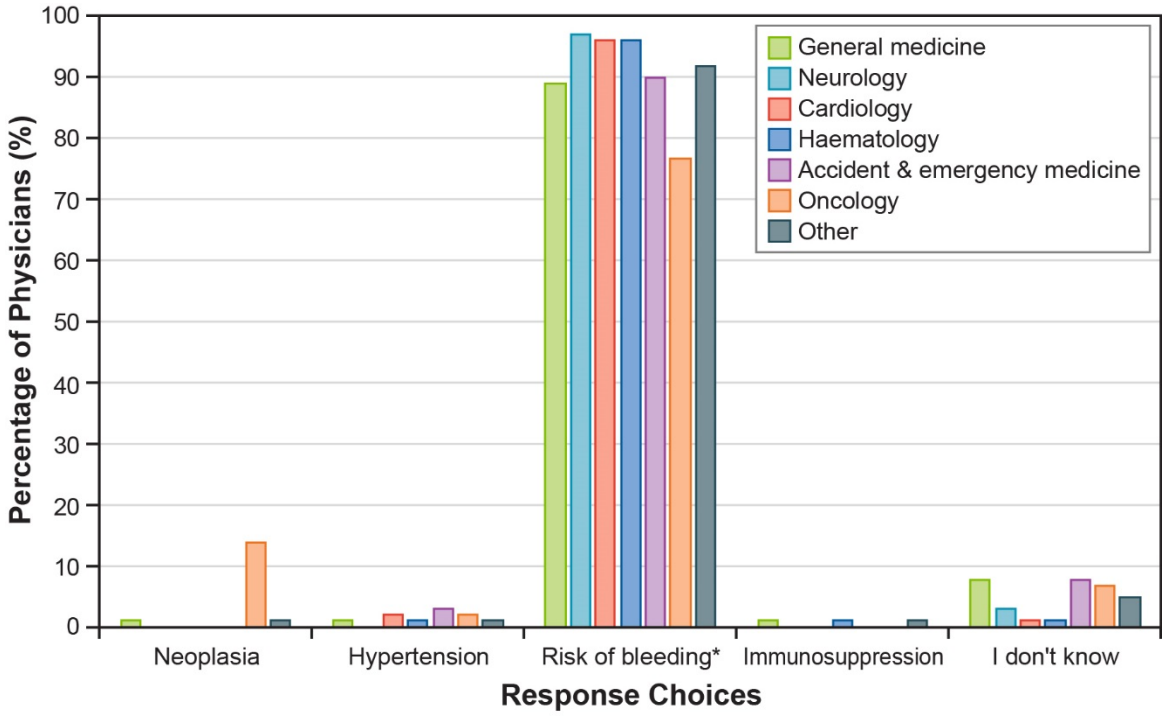
[1] This was a "tick all that apply" question; thus, the sum of responses can be greater than 100.

10.1.4.2 Knowledge of Key Safety Information

Risks of Side Effects and Safe Use (Annex F, Table F-3; Questions 5, 6, 7, 8)

Almost all physicians (92%) correctly reported that the most important risk associated with taking rivaroxaban is the risk of bleeding. Results were consistent across the countries, ranging from 88% correct in France to 94% in Germany. Overall, knowledge of this risk was particularly high among neurologists (97% correct), cardiologists (96%), and haematologists (96%) and poorest among oncologists (77%) (Figure 2). Physicians responsible for initiating rivaroxaban treatment or converting treatment to or from rivaroxaban scored better on this question than those responsible for writing maintenance prescriptions only (93% vs. 82% correct).

Figure 2. Responses to Question 5: What Is the most important risk associated with taking Xarelto?

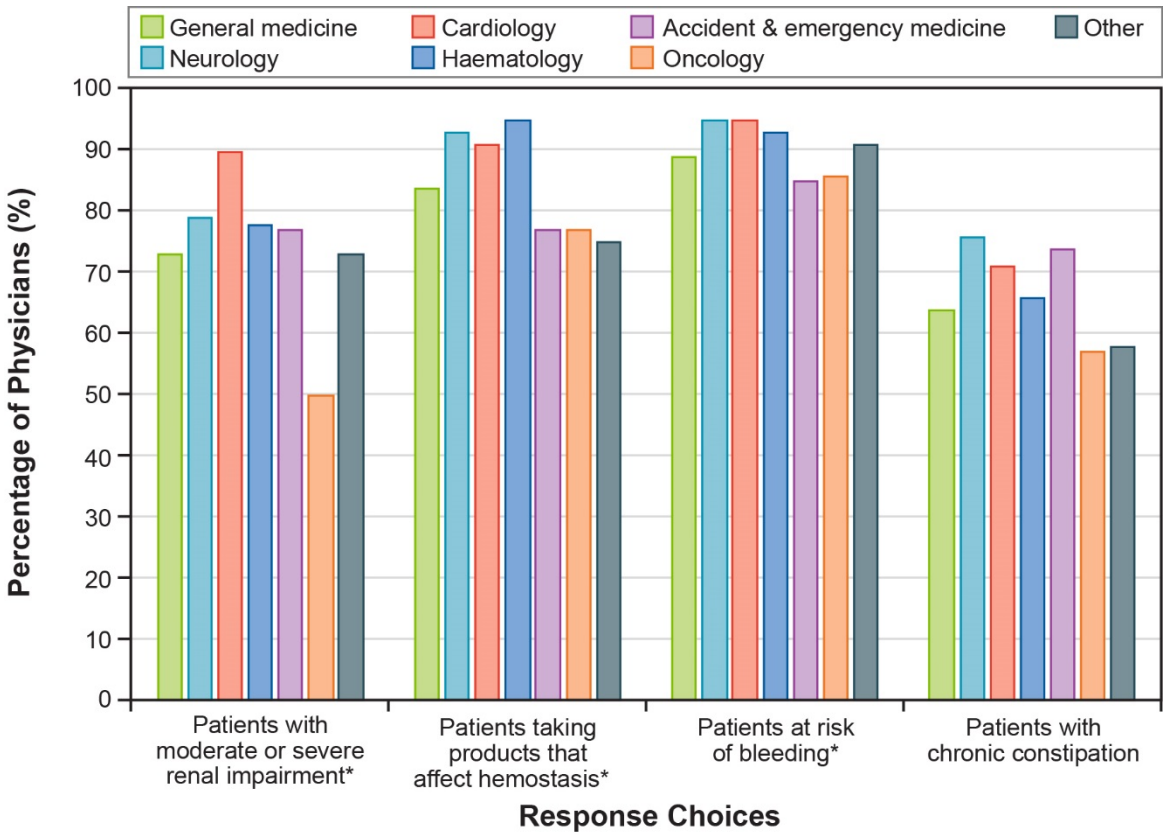


*Correct response is marked with an asterisk.

Physicians' knowledge of patient populations at risk of experiencing serious side effects with rivaroxaban was also fairly high, ranging from approximately 70% to 91% correct for the individual response options; a relatively low percentage (66%) correctly indicated that patients with chronic constipation were not at higher risk. The item regarding chronic constipation also had the most variation in correct responses across countries among the "serious side effect" items, with 76% of the German physicians correctly answering versus 69% of the Spanish, 62% of the French, and 55% of the UK physicians responding correctly. Responses to other questions related to side effects were much more consistent across countries.

For most of the side effect questions, the correct response rate was highest among neurologists, cardiologists, and haematologists compared with the other specialties (Figure 3) and among those physicians responsible for initiating rivaroxaban treatment or converting treatment to or from rivaroxaban compared with those responsible only for maintenance treatment. Also, physicians who reported receiving information from the Xarelto Prescriber Guide generally scored approximately 10% higher on each of these questions than those who did not.

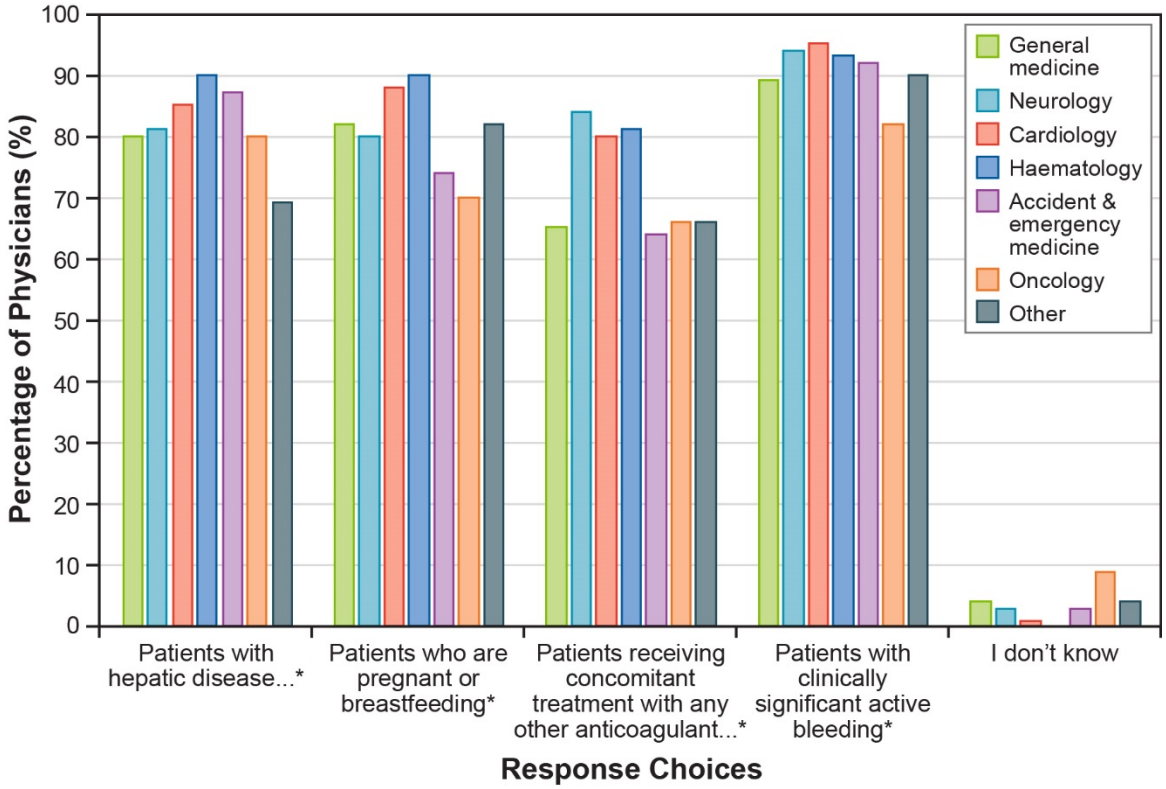
Figure 3. Responses to Question 6: Which of the following populations are at an increased risk of experiencing serious side effect(s) associated with Xarelto?



*Correct response is marked with an asterisk.

Most physicians (57%) were able to identify all four patient groups for which rivaroxaban is contraindicated, and 80% were able to identify at least three of the four, with the correct response proportions being relatively consistent across countries. Figure 4 presents correct responses for each patient group by physician specialty. As with other questions, correct responses were highest among haematologists (73% selected all 4 correct responses), neurologists (70%), and cardiologists (68%). Physicians responsible for initiating rivaroxaban treatment were also more likely to select all four correct responses than those who were not (59% vs. 46%, respectively) as were physicians who reported receiving information from the Xarelto Prescriber Guide compared with those who did not (63% vs. 50%, respectively).

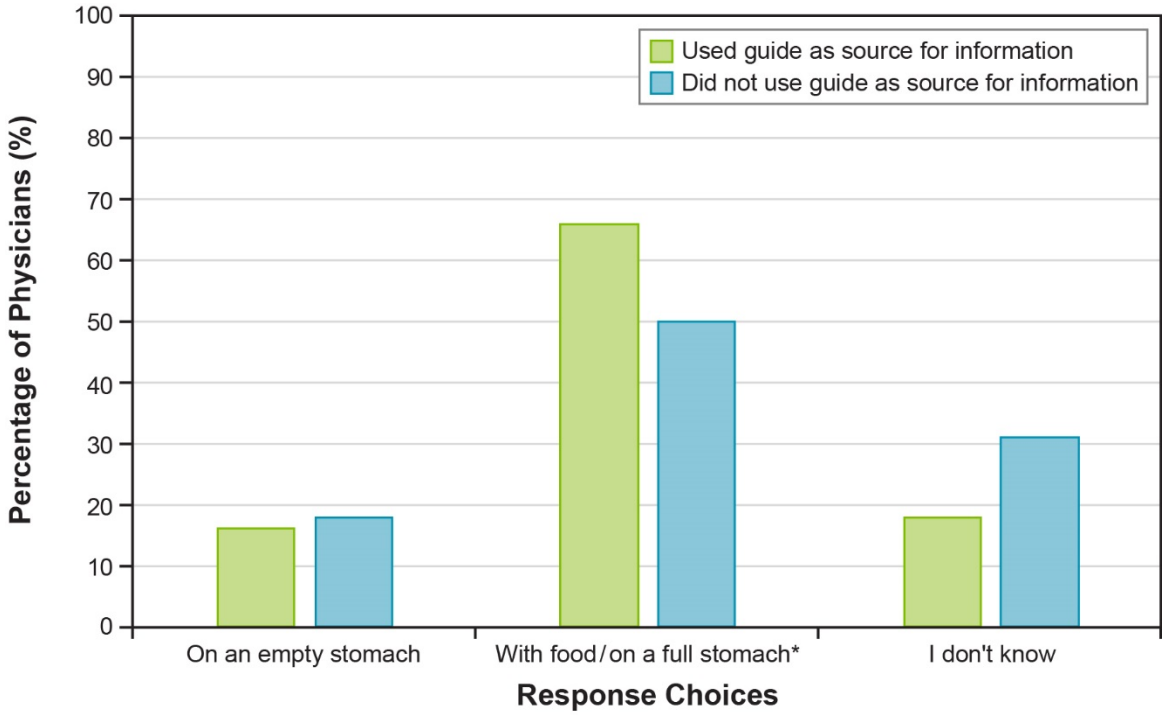
Figure 4. Responses to Question 7: To which patient groups is Xarelto contraindicated? (Tick all that apply.)



*Correct response is marked with an asterisk.

For the question of whether rivaroxaban must be taken with food, 59% correctly answering that rivaroxaban should be taken "with food/on a full stomach." French physicians did best on this question (66% correct) and physicians from the UK did worst (46% correct). There was consistency across prescriber specialty for most of the specialty categories; however, those falling into the categories of general medicine (53% correct) and other (49% correct) did noticeably worse than any of the other categories (64%-71% correct). There was a particularly large difference between physicians responsible for initiating rivaroxaban treatment (61% correct) and those not responsible (43% correct). Comparing physicians who received information from the Xarelto Prescriber Guide versus those who did not showed those receiving information were more likely to respond correctly (66% vs. 50%) (Figure 5).

Figure 5. Responses to Question 8: Xarelto (15 or 20 mg) must be taken….?



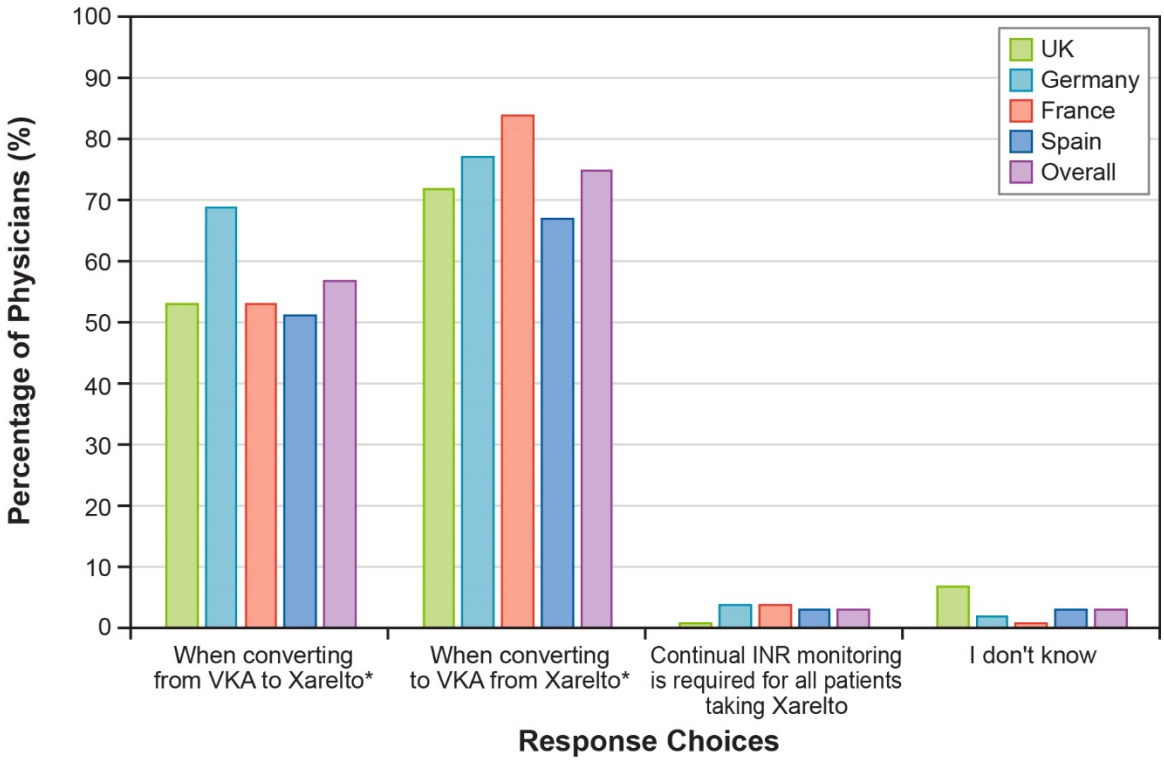
*Correct response is marked with an asterisk.

Monitoring and Converting (Annex F, Table F-3 and Annex G, Tables G-1, G-2, and G-4; Questions 9, 10, 11, 12, 13)

Almost all physicians (95%) knew that routine coagulation monitoring is not required for patients taking rivaroxaban, and there was little variability across the subgroups, with the possible exception of oncologists, 80% of whom got this question correct while all other specialist categories had at least 93% correct response rates.

Knowledge was lower when physicians were asked about what situations cause there to be a need for international normalised ratio (INR) monitoring: 57% 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 proportion by country, but it was not consistent across the two situations that called for monitoring (Figure 6). Similar patterns as with other knowledge questions were seen among the key subgroups, with physicians responsible for initiating rivaroxaban treatment scoring better than those responsible for maintenance only and physicians who reported receiving information from the Xarelto Prescriber Guide scoring better than those who did not. Atypical to what was observed on most knowledge questions, when looking at physician specialty, neurologists, cardiologists, and haematologists did not have noticeably higher correct response rates than the other specialist categories (general medicine, accident & emergency medicine, oncology, other) on the correct answer choice about converting from rivaroxaban to VKA.

Figure 6. Responses to Question 10: In which of the following situations is INR monitoring needed? (Tick all that apply.)

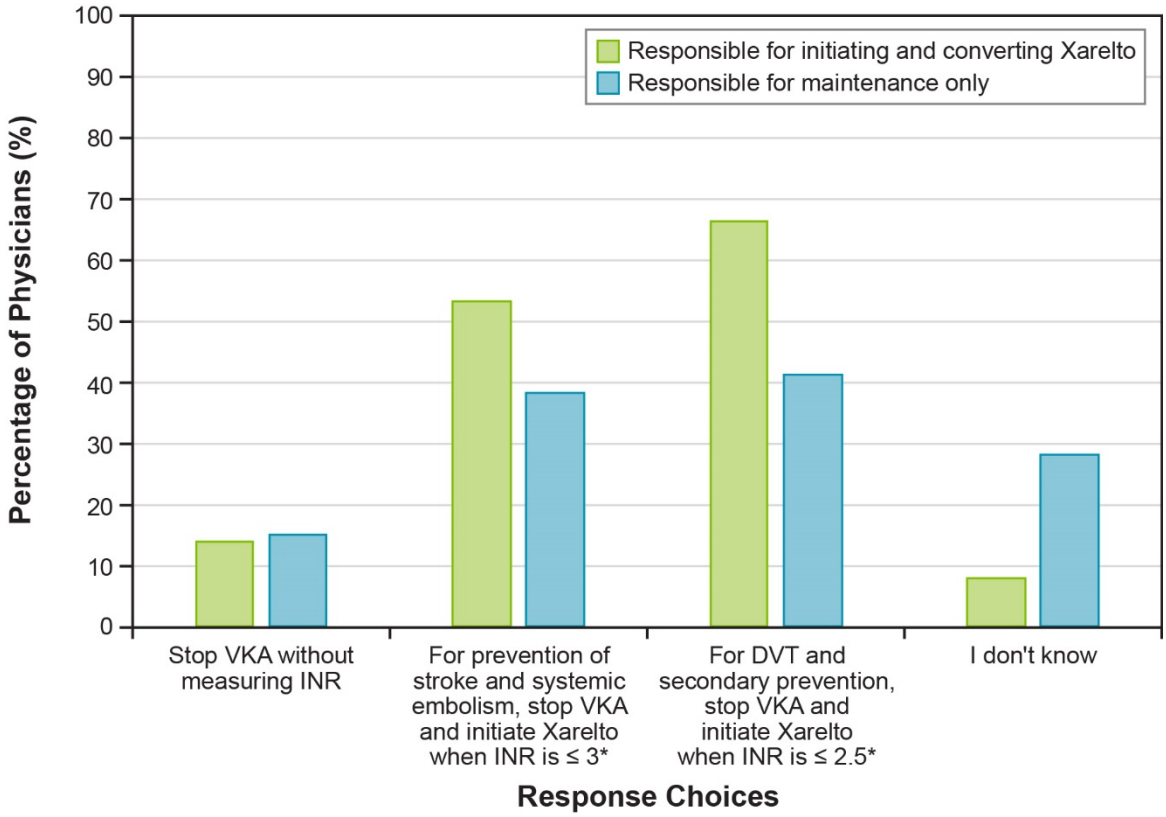


INR = international normalised ratio; VKA = vitamin K antagonist.

*Correct response is marked with an asterisk.

In two separate "tick all that apply" questions (Questions 11 and 12), physicians were asked about procedures for converting patients from VKA to rivaroxaban and from rivaroxaban to VKA. There were two correct responses for each of the questions; for both questions, well under half of the physicians correctly ticked both correct responses, but 78% and 82%, respectively, correctly selected at least one. Similar patterns as with other knowledge questions were seen among the key subgroups evaluated: physicians responsible for initiating rivaroxaban treatment scored better those who were not (Figure 7 and Figure 8) and physicians who reported receiving information from the Xarelto Prescriber Guide scored better than those who did not, and haematologists and oncologists provided slightly higher correct responses than other physician specialties.

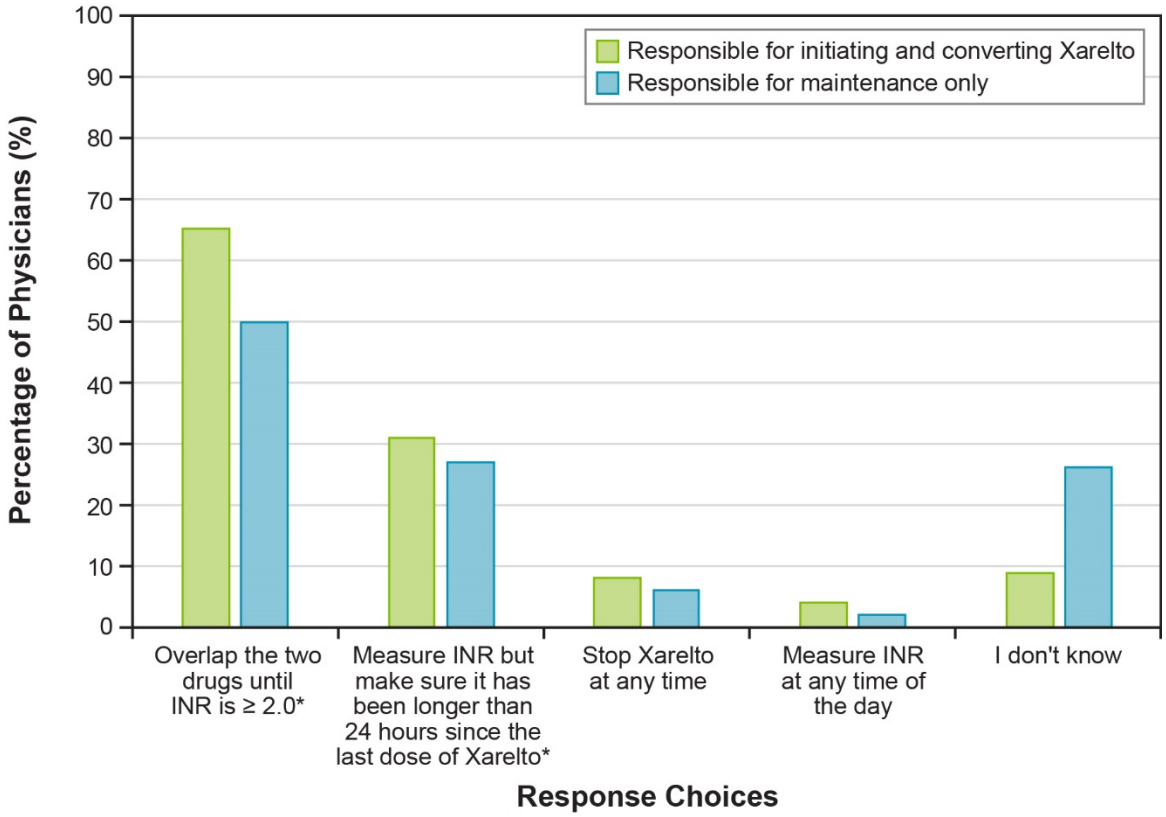
Figure 7. Responses to Question 11: Which of the following steps should be taken when converting patients from VKA (e.g., warfarin) to Xarelto? (Tick all that apply.)



DVT = deep vein thrombosis; 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.)



INR = international normalised ratio; VKA = vitamin K antagonist.

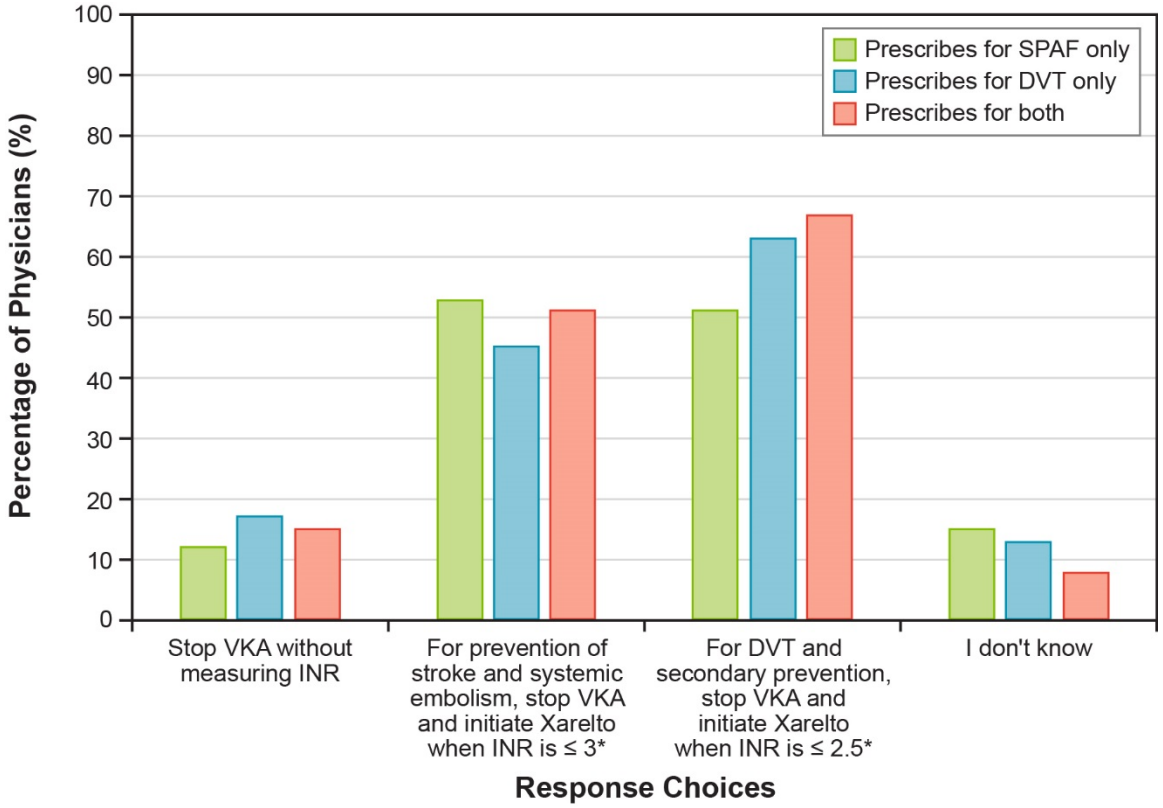
*Correct response is marked with an asterisk.

The questions about converting patients to or from rivaroxaban (Questions 11, 12, and 13) were also 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, physicians who prescribed for SPAF only were more likely than physicians who prescribed for DVT only to correctly select the response category that was specific to SPAF (53% vs. 45%) and correct responses for those who prescribed for both were in between (Figure 9) (51%). Physicians who prescribed for DVT only were more likely than physicians who prescribed for SPAF only to select the response category specific to DVT (63% vs. 51%), and physicians who prescribed for both indications were even more likely to select the correct response (67%).

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.)

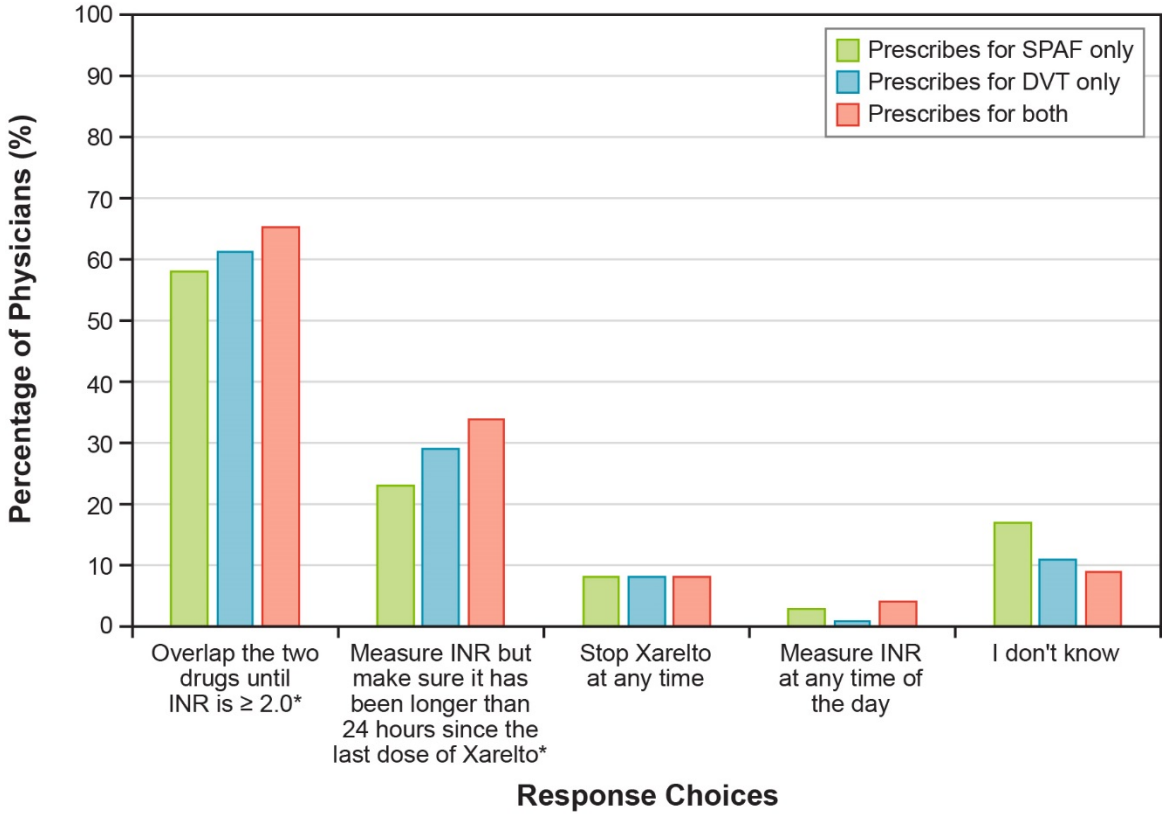


DVT = deep vein thrombosis; INR = international normalised ratio; SPAF = stroke prevention in atrial fibrillation; VKA = vitamin K antagonist.

*Correct response is marked with an asterisk.

In response to Question 12, correct response proportions for physicians who prescribed for DVT only were similar to physicians who prescribed for SPAF only for the response category "Overlap the two drugs until INR is ≥ 2.0" (61% vs. 58%) and slightly higher for "Measure INR but make sure it has been longer than 24 hours since the last dose of Xarelto" (29% vs. 23%); those who prescribed for both SPAF and DVT did better on each response category (65% and 34%, respectively) (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.)



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.

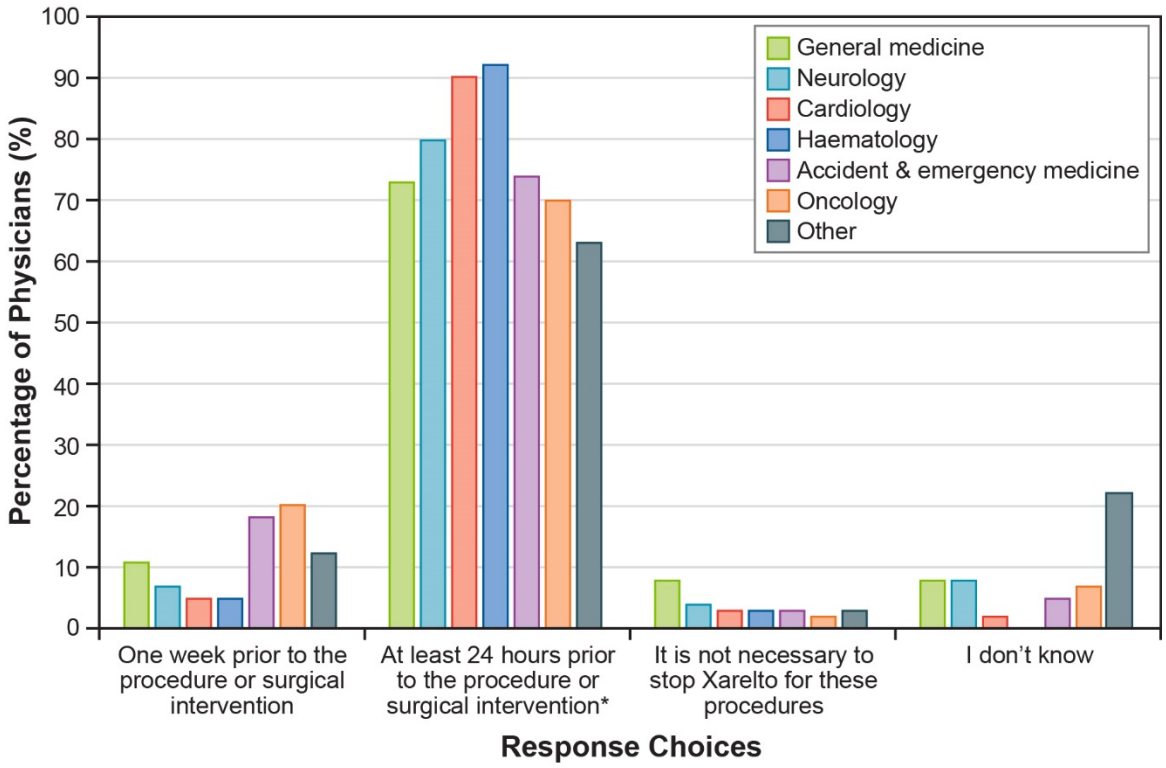
Question 13, also a "tick all that apply" question, asked physicians about procedures for converting patients from parenteral anticoagulants to rivaroxaban. As with the previous questions about converting between rivaroxaban and VKA, there were two correct response items for the question. Overall, the correct responses were selected by 48% and 54% of the physicians, respectively, and 77% selected at least one of the correct responses. Again, the UK physicians had less knowledge than physicians in the other countries for both of the correct response options. Haematologists performed particularly well on this question. The typical patterns were seen with physicians responsible for initiating or converting rivaroxaban treatment having higher scores than those who did maintenance prescriptions only and physicians who reported receiving information from the Xarelto Prescriber Guide scoring better than those who did not. Correct response rates were slightly higher among physicians who treated DVT only than those who treated SPAF only (45% vs. 43% for one response option and 52% vs. 46% for the

other), and physicians who treated both SPAF and DVT did slightly better on both options (50% and 59%, respectively).

Invasive Procedure and Medically Important Bleeding (Annex F, Table F-3 and Annex G, Tables G-1, G-2, and G-4; Questions 14 and 15)

A total of 76% of physicians correctly responded that rivaroxaban treatment should be suspended at least 24 hours prior to an invasive procedure or surgical intervention, with Germany having the highest correct response rate (88%) and France the lowest (68%). Haematologists (92%), cardiologists (90%), and neurologists (80%) had the highest correct response rate among physician specialties (Figure 11). Physicians responsible for initiating rivaroxaban treatment or converting treatment to or from rivaroxaban had a much higher correct response rate (81%) than physicians responsible for maintenance prescriptions only (51%). Physicians who reported receiving information from the Xarelto Prescriber Guide had higher correct responses than those who did not (82% vs. 70%).

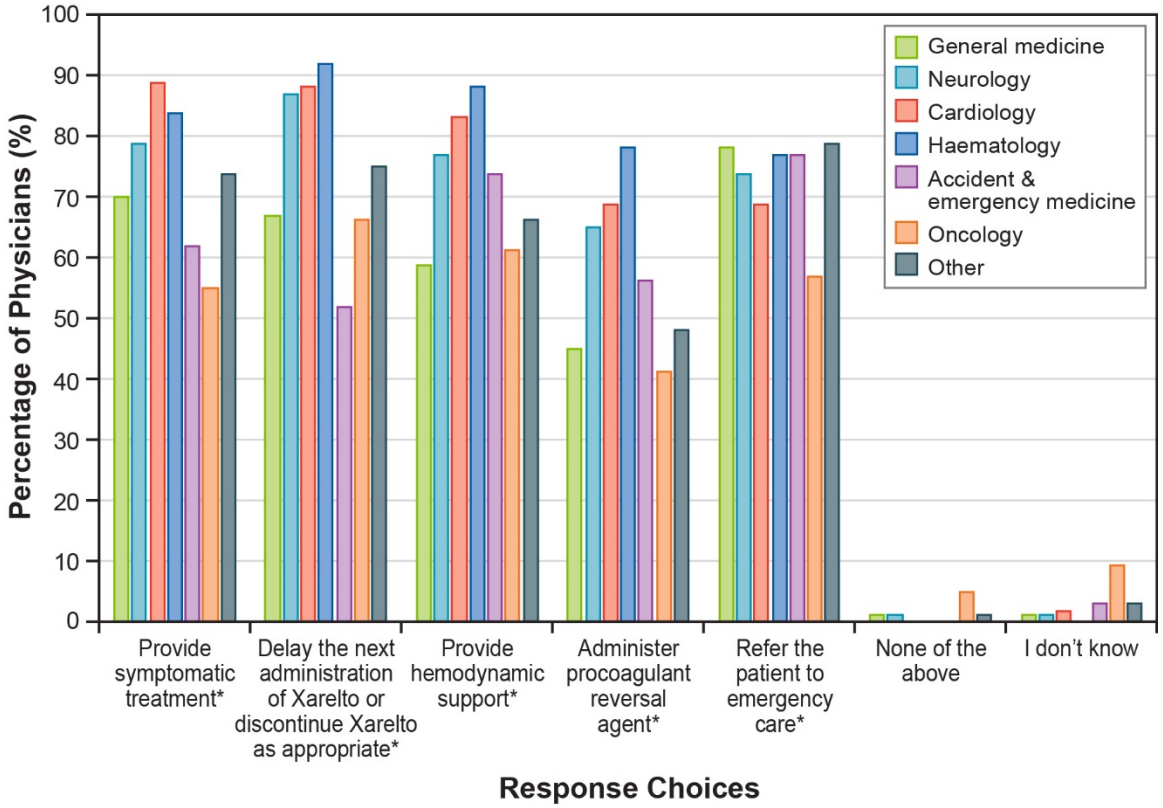
Figure 11. Responses to Question 14: If an invasive procedure or surgical intervention is required, when should treatment with Xarelto (15 to 20 mg) be suspended (if possible, based upon clinical judgement of physician)?



*Correct response is marked with an asterisk.

Question 15 asked physicians to select the most appropriate actions if a patient taking rivaroxaban presents with a medically important bleeding complication; the response options included five correct responses that physicians should have selected. The correct response proportions for the five options ranged from 54% for the option "administer procoagulant reversal agent (for life-threatening bleeding)" to 75% for each of the options "Refer the patient to emergency care" and "Provide symptomatic treatment (e.g., mechanical compression, surgery." Thirty-seven percent selected all five correct responses. For this question, the French physicians tended to do poorest among the countries on most of the response options. Haematologists were particularly likely to select the correct response options (60% selected all 5), followed by cardiologists (51% all 5) and neurologists (50% all 5) (Figure 12). The typical patterns were seen with physicians responsible for initiating or converting rivaroxaban treatment having higher scores than those who did maintenance prescriptions only and physicians who reported receiving information from the Xarelto Prescriber Guide scoring better than those who did not (42% vs. 30% selected all 5 correct).

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.)



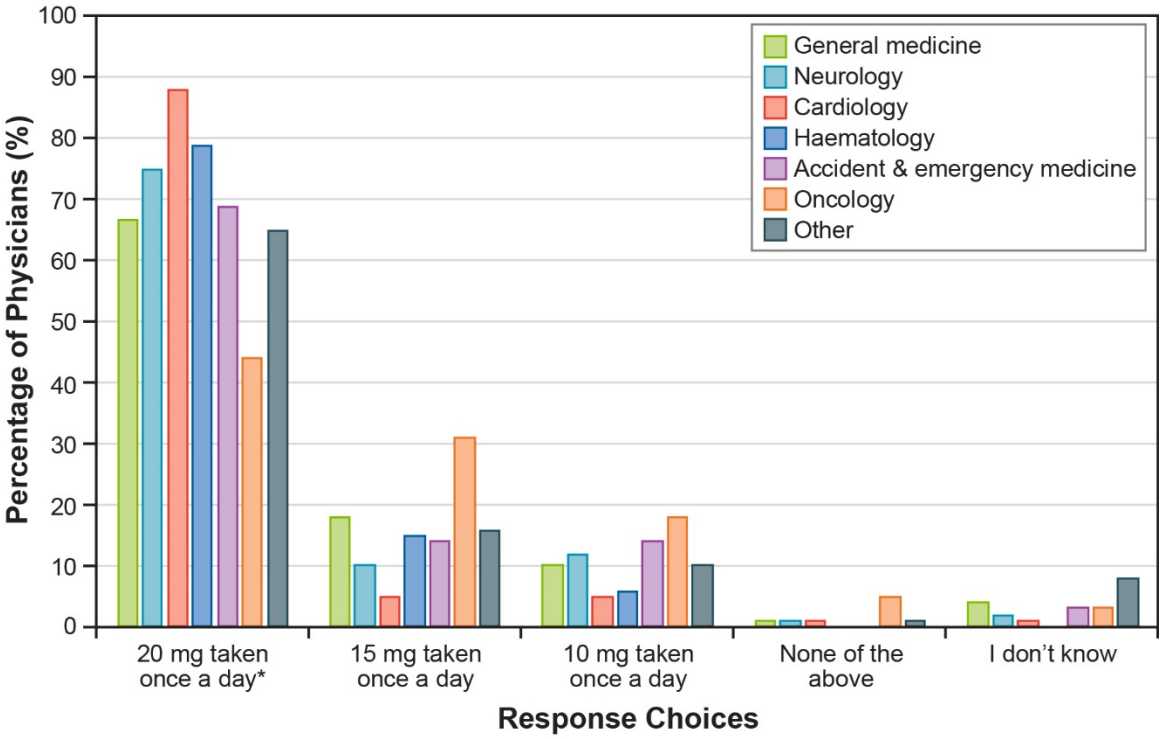
*Correct response is marked with an asterisk.

Dosing (Annex F, Table F-3 and Annex G, Tables G-1, G-2, and G-4; Questions 16, 17, and 18)

Prevention of Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation[1]

Of the physicians who reported that they prescribed for SPAF, 71% correctly reported 20 mg taken once a day was the standard recommended dose of rivaroxaban for this indication, while 56% of physicians were aware that 15 mg taken once a day was the recommended dose of rivaroxaban for this indication for patients with moderate or severe renal impairment. For both of these questions, physicians in Germany had the highest correct responses (79% and 63%) and physicians in France had the lowest (61% and 44%). Neurologists, cardiologists, and haematologists had the highest correct response rates for these two questions, with cardiologists doing the best with 88% and 74% correct, respectively (Figure 13). Physicians responsible for initiating or converting rivaroxaban treatment had a much higher correct response rate than those not responsible for initiating treatment (75% vs. 50% on the first question; 59% vs. 33% on the second question), and physicians who reported receiving information from the Xarelto Prescriber Guide scored better than those who did not (77% vs. 64% on the first question; 62% vs. 49% on the second question).

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?



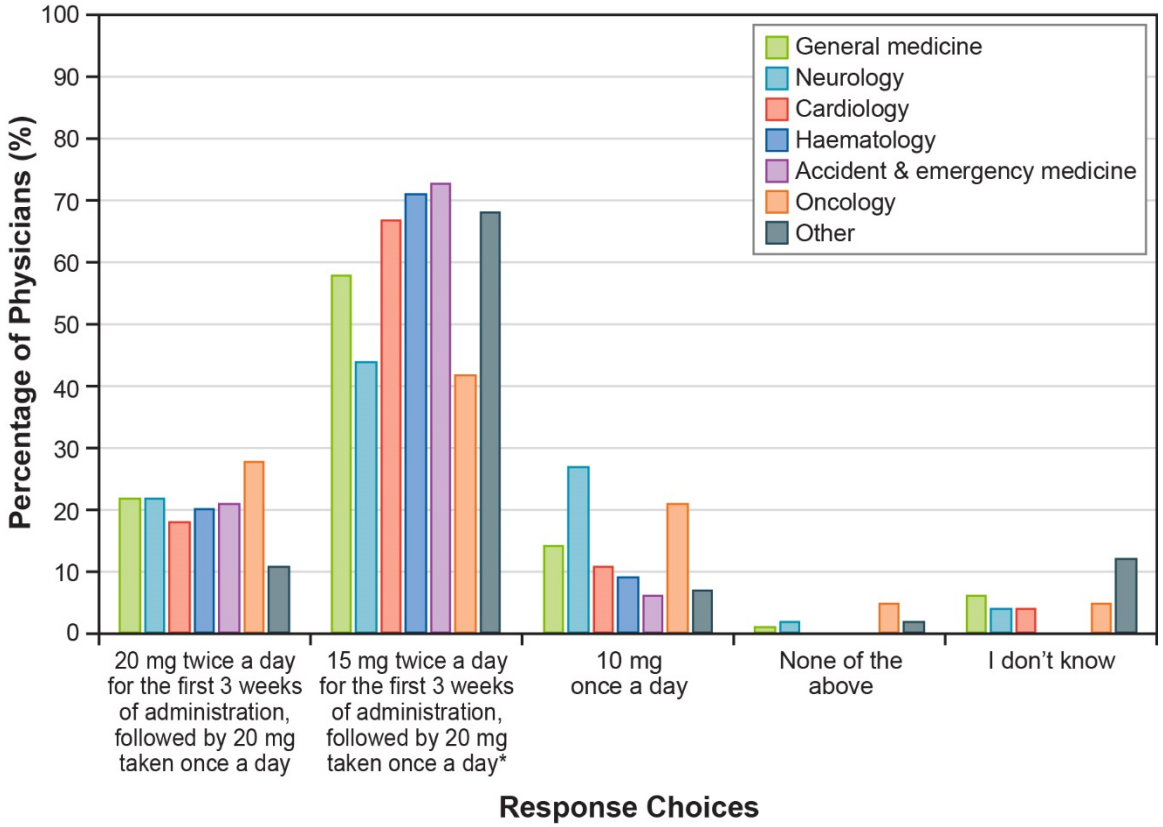
*Correct response is marked with an asterisk.

[1] Only a subset of physicians who reported that they prescribed for SPAF were presented with the questions in this section.

Deep Vein Thrombosis Treatment and Secondary Prevention[1]

Of the physicians who reported that they prescribed rivaroxaban for DVT and secondary prevention, 61% correctly selected the response option for the standard recommended dose for patients receiving rivaroxaban 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 (49% vs. 61%, 63%, and 67% in France, Germany and the UK, respectively). Emergency medicine physicians (73%), haematologists (71%), and cardiologists (67%) scored particularly high on this question, while neurologists (44%) and oncologists (42%) scored the lowest (Figure 14). Physicians responsible for initiating rivaroxaban treatment did better than and those responsible for maintenance prescriptions only (63% vs. 44%), and physicians who reported receiving information from the Xarelto Prescriber Guide scored better than those who did not (66% vs. 54%).

Figure 14. Response to Question 18: What is the standard recommended dose for patients receiving Xarelto for deep vein thrombosis treatment and secondary prevention?



*Correct response is marked with an asterisk.

[1] Only a subset of physicians who reported that they prescribed for DVT were presented with the questions in this section.

10.1.4.3 Sources of Information About Rivaroxaban and Their Ratings (Annex F, Table F-4 and F-5; Questions 19 and 20)

The most frequently reported source of information about rivaroxaban was a company representative (64%); this held true for France (68%) and the UK (55%). Spanish physicians' most frequently reported source was the Xarelto Prescriber Guide (67%) and those from Germany were most likely to cite the Summary of Product Characteristics (76%). Overall, more than half of physicians reported that they used the Xarelto Prescriber Guide (56%) or Summary of Product Characteristics (54%) as a source for information. Physicians in Spain (67%) and France (64%) had the highest rates for using the prescriber guide as a source of information, whereas a lower percentage of physicians (37%) in the UK reported using it. Use of the Xarelto Prescriber Guide was fairly consistent across physician specialties.

Of the physicians who reported using the Xarelto Prescriber Guide, 81% rated it as either a 4 or 5 on a scale from 1 (not at all helpful) to 5 (extremely helpful). Similarly, of those who listed "briefing from a company representative," 74% rated that source a 4 or 5; of those who selected "discussion with a clinical expert," 87% rated these discussions a 4 or 5; of those who selected "Summary of Product Characteristics," 77% rated the Summary a 4 or 5; and of those who selected "medical publications," 83% rated these a 4 or 5.

10.1.4.4 Physicians' Experiences With Patient Alert Cards (Annex F, Table F-6; Questions 21, 22, and 23)

Across all countries, 47% of physicians reported receiving Xarelto Patient Alert Cards to provide to their patients. The estimates varied by country from 29% of physicians in the UK to 80% of physicians in Germany reporting that they received Xarelto Patient Alert Cards. Haematologists, cardiologists, neurologists, and general medicine doctors reported receiving Xarelto Patient Alert Cards more often than accident and emergency medicine physicians and oncologists.

Of the physicians who reported receipt of Xarelto Patient Alert Cards, 79% reported that they provided the card to either most or all of their patients. These reports were highest in Germany (85%) and the UK (84%) and were lowest in France (67%). Nearly all of these physicians (90%) reported that they discussed the information in the card with patients when first prescribing rivaroxaban.

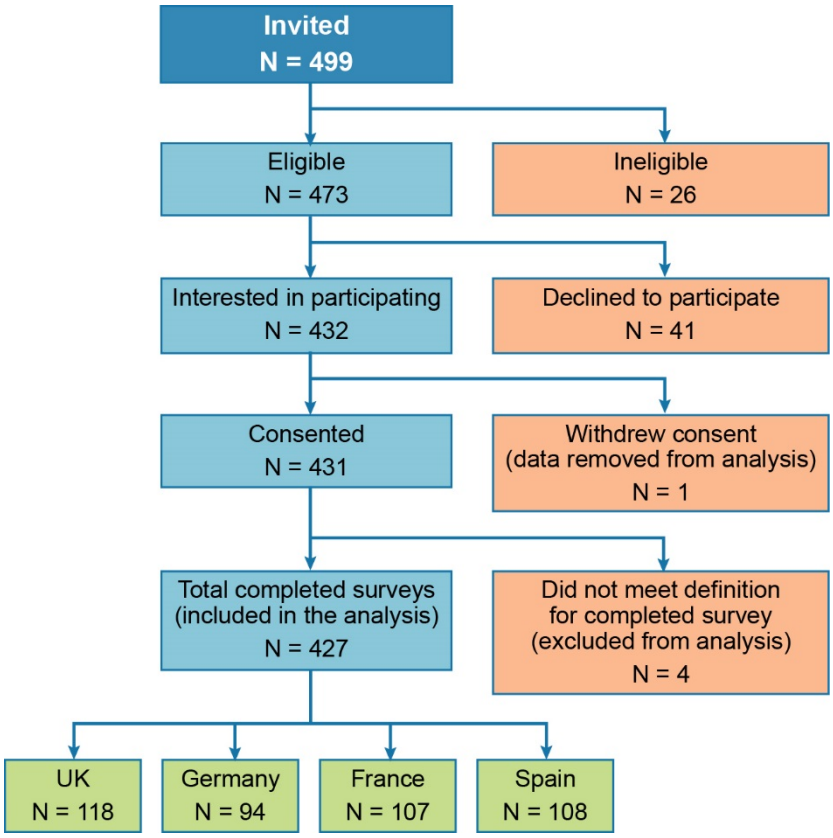
10.2 Patient Assessment Results

10.2.1 Participants

Across the 35 sites, 499 patients were approached about participation in the study; of these, 26 were deemed ineligible based on the screening criteria. Of the 473 patients who were eligible, 41 declined to participate, leaving 432 patients interested in completing the questionnaire. One patient later withdrew consent and 4 patients did not meet the criteria for a completed questionnaire; these patients were not included in the final analysis dataset. Therefore, 427 patients (86% of those invited) were included in the final analysis dataset. Patient counts ranged from 2 to 20 across the 35 sites, with

an average of 12.2 per site. The overall response rate was 90%. Figure 15 provides the distribution of patients invited to participate in the patient assessment.

Figure 15. Distribution of Patients



10.2.2 Descriptive Data

10.2.2.1 Characteristics of Recruiting Physicians

Over half of the physicians (57%) recruited to participate as sites for the patient assessment were cardiologists. The other half consisted of haematologists (23%), neurologists (6%), and general medicine practitioners (3%). Four physicians (11%) selected the other category for physician specialty. Most physicians (77%) reported working in a hospital-based clinic, and 49% reported working in a general practice setting.[1] In addition, 74% of participants were male.

Physicians' experience was measured by years in practice and was categorised into 5-year increments up to 25 years. All physicians had been in practice more than 5 years, with durations fairly evenly distributed across the increments beyond 5 years. Over one-fourth of physicians (29%) reported having been in practice more than 25 years. Table 8 provides additional detail on the characteristics of recruiting physicians.

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

Table 8. Recruiting Physician and Practice Characteristics

Question	No. of Physicians (%)				
	UK n = 7	Germany n = 10	France n = 7	Spain n = 11	Overall n = 35
Physician specialty					
General medicine	1 (14%)	0	0	0	1 (3%)
Neurology	0	2 (20%)	0	0	2 (6%)
Cardiology	1 (14%)	6 (60%)	7 (100%)	6 (55%)	20 (57%)
Haematology	3 (43%)	0	0	5 (45%)	8 (23%)
Accident and emergency medicine	0	0	0	0	0
Oncology	0	0	0	0	0
Other	2 (29%)	2 (20%)	0	0	4 (11%)
No answer	0	0	0	0	0
Years practicing medicine					
5 years or less	0	0	0	0	0
6 to 10 years	1 (14%)	0	0	6 (55%)	7 (20%)
11 to 15 years	2 (29%)	3 (30%)	1 (14%)	1 (9%)	7 (20%)
16 to 20 years	1 (14%)	3 (30%)	3 (43%)	0	7 (20%)
21 to 25 years	0	2 (20%)	2 (29%)	0	4 (11%)
More than 25 years	3 (43%)	2 (20%)	1 (14%)	4 (36%)	10 (29%)
No answer	0	0	0	0	0
Sex					
Male	4 (57%)	9 (90%)	6 (86%)	7 (64%)	26 (74%)
Female	3 (43%)	1 (10%)	1 (14%)	4 (36%)	9 (26%)
No answer	0	0	0	0	0
Practice type[a]					
General practice	3 (43%)	4 (40%)	0	10 (91%)	17 (49%)
Hospital-based clinic	4 (57%)	6 (60%)	7 (100%)	10 (91%)	27 (77%)
Nursing home	0	0	0	0	0
Other	0	0	0	2 (18%)	2 (6%)
No answer	0	0	0	0	0

UK = United Kingdom.

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

10.2.2.2 Patient Demographics (Annex I, Table I-1; Questions 19-21)

Overall, most patients (83%) were aged 46 to 85 years, and 52% were aged 66 to 85 years (Table 9). Patients tended to be slightly younger in France and UK (55% and 47% ≤ 65 years, respectively) and slightly older in Spain and Germany (25% and 29% ≤ 65 years respectively). Patients were fairly evenly split between males (52%) and females (41%), with 7% not reporting their sex. Approximately half of patients (48%) reported having secondary school education or less, and the remainder reported having professional or work-related college qualifications (27%), an undergraduate degree (15%), or postgraduate degree (4%), and 5% did not provide an answer. Annex I (Table I-1) presents the full demographic results for the overall sample.

Table 9. Patient Demographics

	No. of Patients (%)				
Question	**UK n = 118**	**Germany n = 94**	**France n = 107**	**Spain n = 108**	**Overall N = 427**
Age					
18-45 years	19 (16%)	4 (4%)	8 (7%)	3 (3%)	34 (8%)
46-65 years	36 (31%)	23 (24%)	51 (48%)	24 (22%)	134 (31%)
66-85 years	56 (47%)	53 (56%)	41 (38%)	70 (65%)	220 (52%)
86 years or older	5 (4%)	4 (4%)	1 (1%)	8 (7%)	18 (4%)
No answer	2 (2%)	10 (11%)	6 (6%)	3 (3%)	21 (5%)
Sex					
Male	53 (45%)	50 (53%)	60 (56%)	59 (55%)	222 (52%)
Female	62 (53%)	33 (35%)	40 (37%)	40 (37%)	175 (41%)
No answer	3 (3%)	11 (12%)	7 (7%)	9 (8%)	30 (7%)
Education					
Primary school education or less	12 (10%)	7 (7%)	15 (14%)	51 (47%)	85 (20%)
Secondary school education (e.g., GCSE/A level, Scottish Standard Grades/Highers)	46 (39%)	39 (41%)	23 (21%)	13 (12%)	121 (28%)
Professional or work-related college qualifications (e.g., Certificate of Higher Education, Diploma of Higher Education, foundation degree)	34 (29%)	22 (23%)	46 (43%)	15 (14%)	117 (27%)
Undergraduate university degree (e.g. BSc/BA)	17 (14%)	15 (16%)	9 (8%)	24 (22%)	65 (15%)
Postgraduate university degree (e.g. MSc/MA, MPhil, PhD)	6 (5%)	2 (2%)	8 (7%)	2 (2%)	18 (4%)
No answer	3 (3%)	9 (10%)	6 (6%)	3 (3%)	21 (5%)

UK = United Kingdom.

Note: For patients with multiple responses for Question 21, only the highest, indicated education level was used in this analysis.

10.2.3 Outcome Data

Not applicable.

10.2.4 Main Results

In the following sections, we present key results from the patient survey. The results are organised in the following categories, which also correspond to the analysis tables provided in Annex I: (1) disease and medication characteristics, (2) knowledge of key safety information, and (3) sources of information about rivaroxaban and patient alert card use.

Results for the overall sample are described first followed by results stratified by country. For the knowledge questions, difference in patient knowledge levels in the first questionnaire (before reviewing the patient alert card) and in the second questionnaire (after reviewing the patient alert card) also are described. In addition, stratification by whether patients had ever taken prescription blood thinners before they started rivaroxaban (Question 7) was examined, but it was found that the stratified results did not differ for any of the knowledge questions. Graphs highlight the results in which the largest differences were seen or where the results seem of most interest.

Annex I includes tables presenting the complete set of knowledge question results for patients overall and broken out by each of the stratification variables.

10.2.4.1 Disease and Medication Characteristics (Annex I, Table I-2; Questions 3, 4, 5, 7 and 18)

Per the study inclusion criteria, all patients had received a prescription for rivaroxaban in the past 3 months. Most patients (95%) reported that they were currently taking rivaroxaban (Table 10). Approximately half of patients (51%) had been taking rivaroxaban for 6 months or less, while over one-third of patients had been taking rivaroxaban for more than 1 year. A higher proportion (50%) of patients from Spain had been taking rivaroxaban for over 1 year than any other country, and the UK had the lowest proportion (19%). Only 13% of patients reported that rivaroxaban was the only prescription medication that they were currently taking, and most patients (60%) had been taking prescription blood thinners at some point prior to starting rivaroxaban. Approximately half (48%) of patients were taking rivaroxaban for prevention of stroke, 42% were taking it for a blood clot in a vein, and 16% reported they were taking rivaroxaban for another reason.[1]

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

Table 10. Medication Characteristics and Previous Experience With Blood Thinners

Question	No. of Patients (%)				
	UK n = 118	Germany n = 94	France n = 107	Spain n = 108	Overall N = 427
Length of time on rivaroxaban					
Less than 1 month	22 (19%)	17 (18%)	23 (21%)	3 (3%)	65 (15%)
From 1 to 6 months	59 (50%)	27 (29%)	33 (31%)	32 (30%)	151 (35%)
More than 6 months but less than 1 year	13 (11%)	9 (10%)	12 (11%)	18 (17%)	52 (12%)
More than 1 year	23 (19%)	37 (39%)	36 (34%)	54 (50%)	150 (35%)
I don't know	1 (1%)	0	2 (2%)	0	3 (1%)
No answer	0	4 (4%)	1 (1%)	1 (1%)	6 (1%)
Reason for rivaroxaban prescription					
Prevention of stroke	44 (37%)	42 (45%)	52 (49%)	65 (60%)	203 (48%)
A blood clot in a vein	68 (58%)	37 (39%)	46 (43%)	30 (28%)	181 (42%)
I don't know	2 (2%)	1 (1%)	8 (7%)	5 (5%)	16 (4%)
Other	24 (20%)	12 (13%)	15 (14%)	17 (16%)	68 (16%)
No answer	2 (2%)	12 (13%)	6 (6%)	2 (2%)	22 (5%)
Previous experience with blood thinners					
Yes	73 (62%)	48 (51%)	62 (58%)	73 (68%)	256 (60%)
No	40 (34%)	45 (48%)	41 (38%)	32 (30%)	158 (37%)
I don't know	4 (3%)	1 (1%)	4 (4%)	2 (2%)	11 (3%)
No answer	1 (1%)	0	0	1 (1%)	2 (0%)

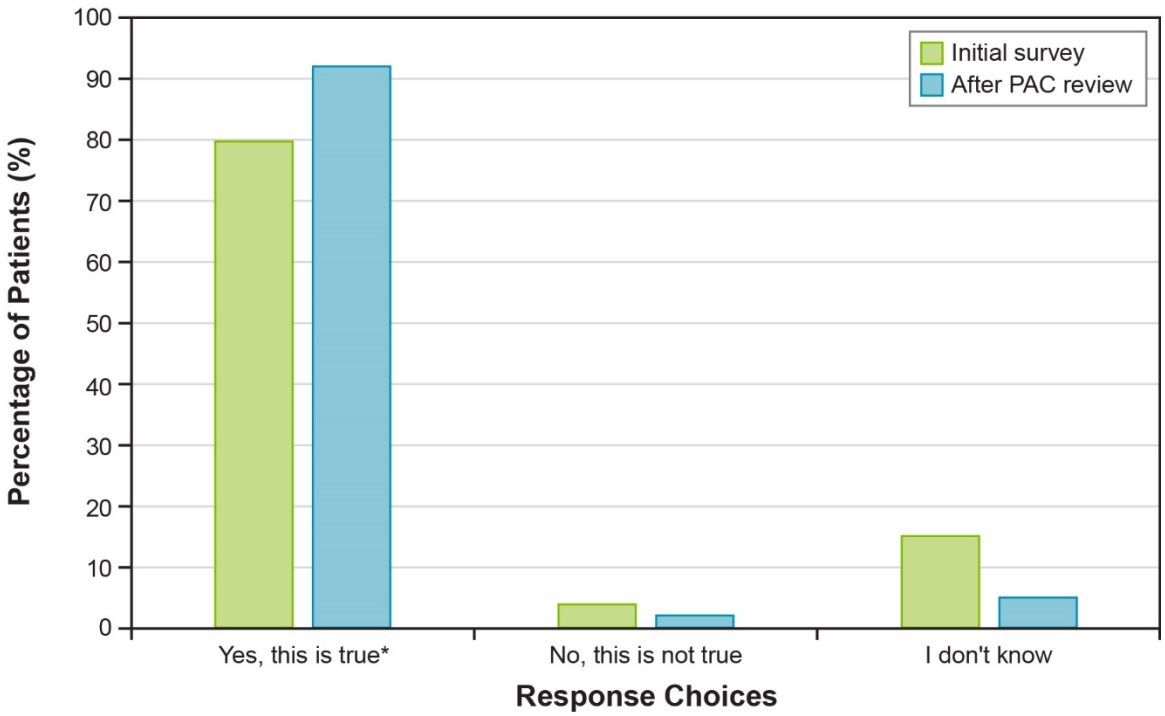
UK = United Kingdom.

10.2.4.2 Knowledge Questions

Risk and Symptoms of Bleeding (Annex I, Tables I-5; Questions 10 and 11)

Most patients (80%) knew that blood thinning medications, such as rivaroxaban, may cause bleeding (Figure 16); this was fairly consistent across countries ranging from 77% in France to 86% in the UK. Overall, correct responses to this question increased by 12 percentage points to 92% after patients reviewed the patient alert card, with improvement being seen consistently across all four countries.

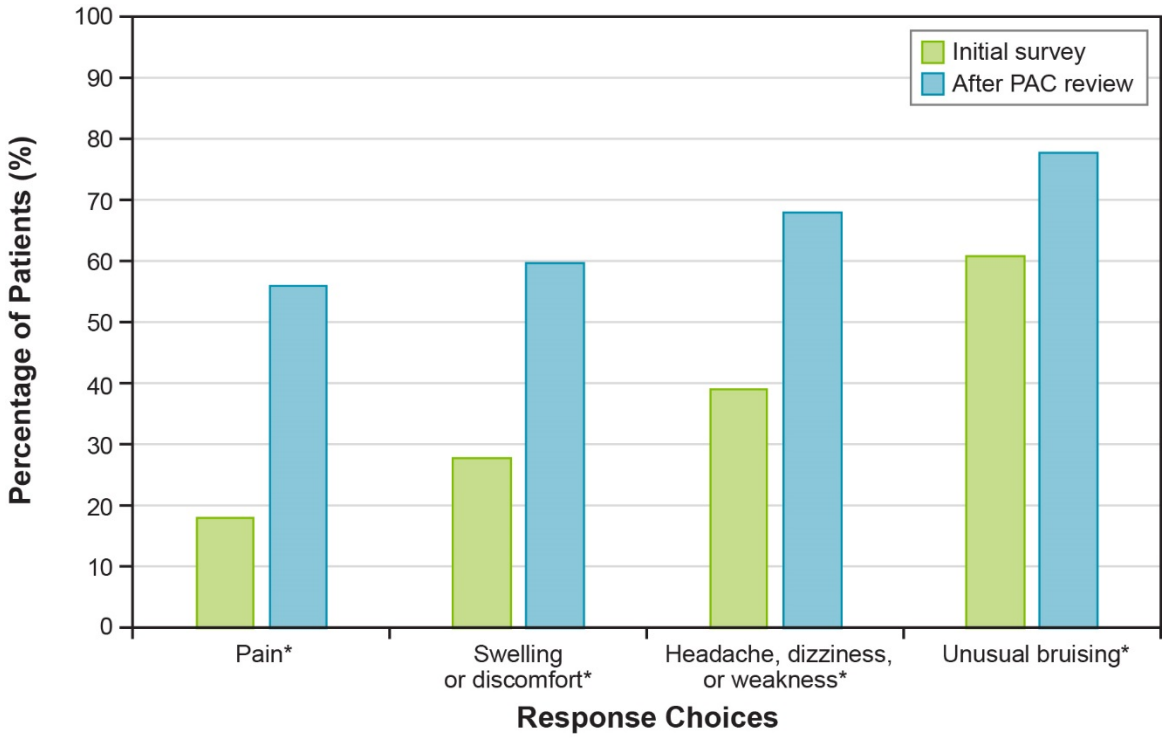
Figure 16. Response to Questionnaire 1, Question 10 and Questionnaire 2, Question 2: Blood thinning medications, such as Xarelto, may cause bleeding



*Correct response is marked with an asterisk.

Patients' knowledge of the possible signs or symptoms of bleeding while taking rivaroxaban varied by sign/symptom (Figure 17). Knowledge was highest for "unusual bruising" (61% reported correctly) and lowest for "pain" (18% reported correctly) with 28% correctly identifying "swelling or discomfort" and 39% "Headache, dizziness, or weakness." Correct responses improved noticeably for each sign/symptom after the patient reviewed the patient alert card. Overall, patients in the UK demonstrated a slightly better knowledge of signs and symptoms than the overall average, and patients in Germany and France showed knowledge rates that were slightly lower than average.

Figure 17. Response to Questionnaire 1, Question 11 and Questionnaire 2, Question 3: Which of the following are possible signs or symptoms of bleeding while taking Xarelto?



*Correct response is marked with an asterisk.

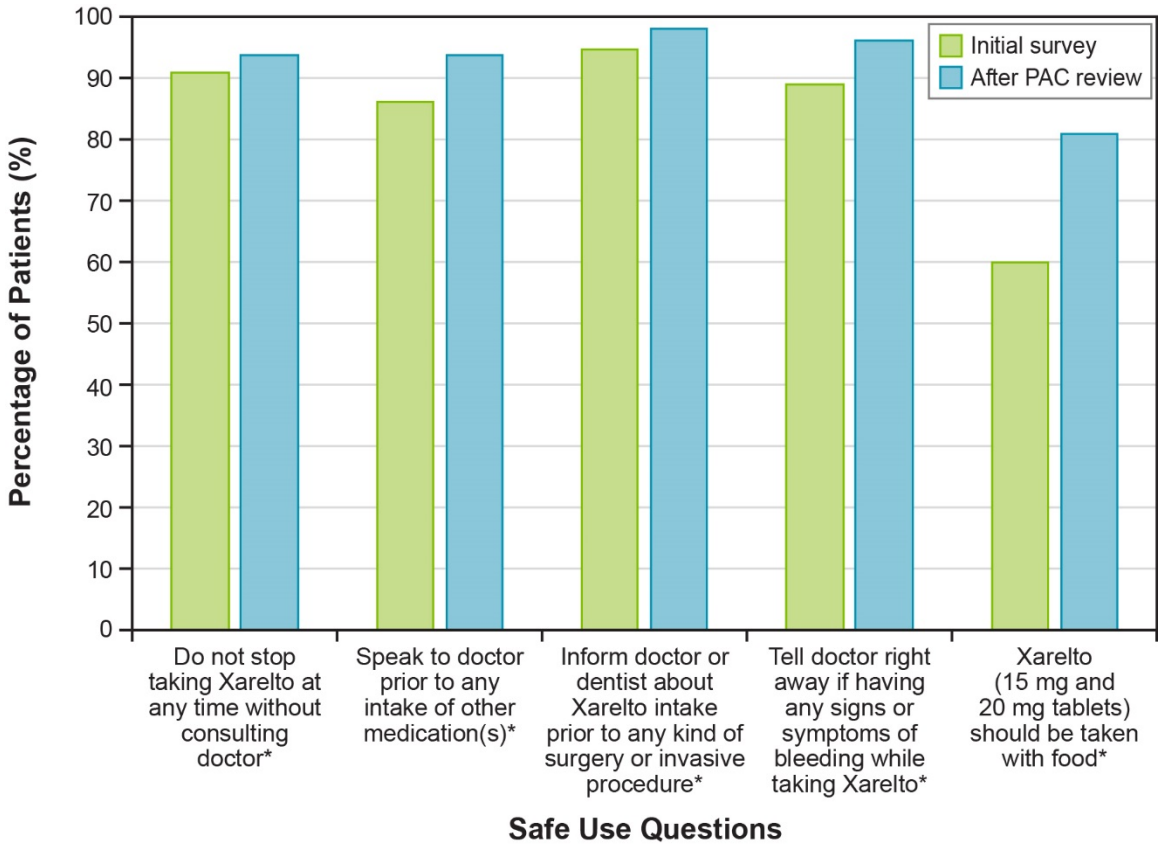
Drug Indication and Safe Use (Annex I, Tables I-5 Questions 6 and 12-17)

Overall, patients' knowledge on questions related to the indication for which rivaroxaban was prescribed (question 6) and safe use of the drug (questions 12-17) was high and consistent across all countries. Almost all patients (96%) correctly responded that rivaroxaban is used to thin the blood to prevent clots.

Most patients (91%) knew that they must not stop taking rivaroxaban at any time without consulting their doctor, and most patients (86%) knew that they need to speak to their doctor prior to any intake of other medications (Figure 18). Likewise, 89% of patients knew that they should tell their doctor if they have any signs or symptoms of bleeding while taking rivaroxaban. Although most (60%) patients correctly reported that rivaroxaban should be taken with food, this improved to 81% after reviewing the patient alert card.

Correct response rates for these items were fairly consistent across countries with the exception of those reporting that rivaroxaban should be taken with food: Germany (47%) was below the other countries (range, 55%-68%). Even after reviewing the patient alert card, Germany, although improving to 70%, still lagged behind the other countries (range, 78%-89%).

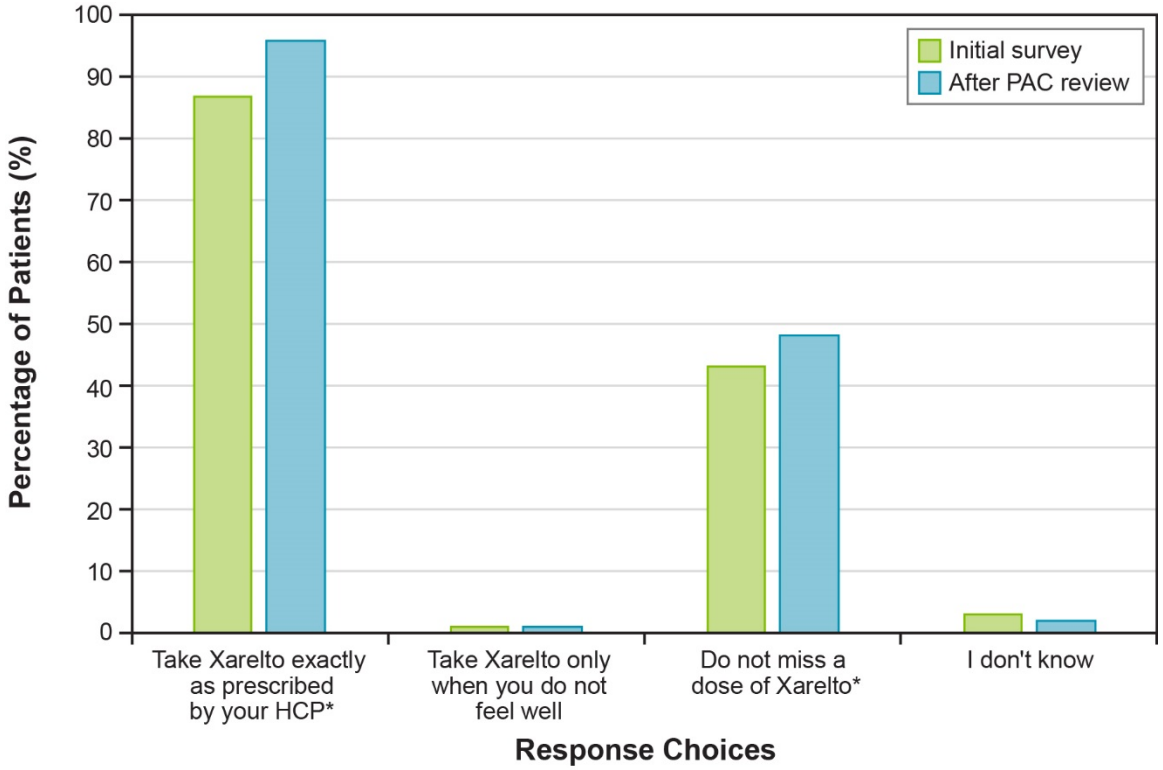
Figure 18. Responses to Questionnaire 1, Question 12-16 and Questionnaire 2, Questions 4-8: Safe-use questions



*Correct response is marked with an asterisk.

When asked how to ensure that rivaroxaban is effective in preventing blood clots, most patients (87%) knew to take rivaroxaban exactly as prescribed, but less than half (43%) knew not to miss a dose of rivaroxaban; 92% selected at least one of these two responses (Figure 19). There was less variability by country in the percentage of correct responses to this question, although Germany had a slightly smaller proportion of patients who selected both correct response choices.

Figure 19. Responses to Questionnaire 1, Question 17 and Questionnaire 2, Question 9: What should you do to ensure Xarelto is effective in preventing blood clots? (Select all that apply.)



HCP = health care professional; PAC = patient alert card.

*Correct response is marked with an asterisk.

10.2.4.3 Sources of Information About Rivaroxaban and Patient Alert Card Use

Source of Information About Rivaroxaban (Annex I, Table I-3; Questions 8 and 9)

The most frequently reported source of information about rivaroxaban was "from a specialist at the hospital" (55%) followed by "from my doctor" (32%); this was consistent across all countries. A relatively small number of patients (ranging from 7% in Spain to 20% in the UK) reported that they received most of their information "from the Xarelto Patient Alert Card and/or patient information leaflet." Approximately half of patients (ranging from 38% in Germany to 59% in the UK) reported that their health care professional had ever talked to them about the possible side effects of rivaroxaban.

Table 11. Sources of Information about Xarelto

	No. of Patients (%)				
Question	**UK n = 118**	**Germany n = 94**	**France n = 107**	**Spain n = 108**	**Overall N = 427**
Source of information about Xarelto					
From my doctor	39 (33%)	33 (35%)	22 (21%)	42 (39%)	136 (32%)
From a specialist at the hospital	56 (47%)	42 (45%)	68 (64%)	68 (63%)	234 (55%)
From my pharmacist	2 (2%)	2 (2%)	4 (4%)	3 (3%)	11 (3%)
From a friend or family member	0	1 (1%)	1 (1%)	3 (3%)	5 (1%)
From my career	0	1 (1%)	0	0	1 (0%)
From articles in newspapers or magazines	0	2 (2%)	1 (1%)	0	3 (1%)
From the Internet	2 (2%)	4 (4%)	3 (3%)	3 (3%)	12 (3%)
From the Xarelto Patient Alert Card and/or patient information leaflet	24 (20%)	12 (13%)	15 (14%)	8 (7%)	59 (14%)
Other	2 (2%)	3 (3%)	12 (11%)	1 (1%)	18 (4%)
No answer	0	1 (1%)	2 (2%)	0	3 (1%)

UK = United Kingdom.

Note: Some patients provided multiple responses for Question 8.

Patient Alert Card Use (Annex I, Table I-4; Questions 10-15 of the follow-up questionnaire)

Approximately half of patients (ranging from a low of 27% in Spain to a high of 64% in the UK) reported that they had received or been given the patient alert card for rivaroxaban prior to their participation in the study. Among those who had received the patient alert card previously, there was considerable variability in the number of patients who had read it; with the lowest reported (59%) from Spain and the highest (96%) from the UK (Table 12).

Table 12. Receipt and Review of Patient Alert Card

	No. of Patients (%)				
Question	UK n = 118	Germany n = 94	France n = 107	Spain n = 108	Overall N = 427
Received the patient alert card	76 (64%)	44 (47%)	53 (50%)	29 (27%)	202 (47%)
Read the patient alert card (among those who received it)	74 (96%)	32 (68%)	48 (86%)	20 (59%)	174 (81%)

UK = United Kingdom.

Of the patients who had not previously read the card, 34% reported that "someone else had explained it to them," and 26% did not answer this question.

In a question that allowed multiple responses, 45% of patients reported that information in the Xarelto Patient Alert Card had been explained to them prior to their participation in the study by a doctor, 10% said by a nurse, and 7% said by a pharmacist or someone at the chemists. Overall, 41% reported that no one had explained the information to them previously, ranging from 29% in the UK to 54% in Spain.

Most patients (85%) kept the patient alert card with them some (14%) or all (71%) of the time. Three-quarters of patients reported that they showed the patient alert card to every doctor or dentist who they visit (ranging from 41% in Spain to 87% in the UK). Twenty percent of patients showed it only to health care professionals who asked for it (ranging from 12% in the UK to 41% in Spain).

10.2.5 Other Analyses

10.2.5.1 Comparison of Recruiting and Non-recruiting Physicians

Two independent groups of physicians were selected to participate in the patient and physician assessments: physicians who recruited patients for the patient assessment (*recruiting physicians*) and physicians who only participated in the physician assessment (*non-recruiting physicians*). Both groups were asked to complete the same physician questionnaire. Analyses were conducted to compare responses between recruiting and non-recruiting physicians to explore the potential that the study created greater awareness of the safety information. Annex H presents the complete set of tables providing the questionnaire responses from the recruiting physician.

Physician and Practice Characteristics

Recruiting and non-recruiting physicians were similar in terms of years practicing medicine and sex. Compared with non-recruiting physicians, recruiting physicians were more likely to describe their specialty as cardiology (57% vs. 20%) or haematology (23% vs. 6%) and were much less likely to describe their specialty as general medicine (3% vs. 45%). Recruiting physicians were more likely to describe their practice type as a hospital-based clinic than general practice (77% vs. 49%), whereas non-recruiting physicians were more likely to describe their practice as general practice than hospital-based clinic (63% vs. 43%).[1]

Physician Prescribing Practices

Compared with non-recruiting physicians, the recruiting physicians, in general, prescribed rivaroxaban to more patients in the past 6 months and more had written a rivaroxaban prescription in the last month (97% vs. 75%).

Knowledge

Across the board, the recruiting physicians scored higher on the knowledge questions, often getting at least 90% correct, whereas the non-recruiting physicians often scored in the 60% to 80% range on the same questions.

Sources of Information About Rivaroxaban

For every potential source listed, the recruiting physicians were much more likely to report receiving information about rivaroxaban (e.g., Prescriber Guide, 94% vs. 56%; clinical trial publications in the literature, 91% vs. 35%; briefing from a company representative, 83% vs. 64%; Summary of Product Characteristics, 80% vs. 54%; discussion with clinical expert, 69% vs. 25%). Among the recruiting and non-recruiting physicians using each source, both types of physicians rated the helpfulness of each of the sources similarly on a scale of 1 to 5 and none of the sources in particular were rated as more helpful than another.

Physician Experience With Patient Alert Card

Most recruiting physicians reported receiving patient alert cards, whereas less than half of non-recruiting physicians did (94% vs. 47%). Of those who reported receiving cards, the frequency of distribution of cards to patients and discussing the card with patients was very similar between both types of physicians.

10.2.5.2 Comparison of Patient Knowledge Stratified by Recruiting Physician Knowledge

We explored whether there was an association between the proportion of correct responses among the recruiting physicians and the proportion of correct responses among the patients recruited at their sites. To do this, we created an overall knowledge score for each recruiting physician by calculating the percentage of correct responses selected out of all correct responses in the questionnaire. Among the 35 recruiting physicians, this knowledge score ranged from 66% to 100%. We then dichotomised this score to create two groups of physicians, “high knowledge” (score ≥ 85%) and “not high

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

knowledge" (score < 85%). We then stratified the patient data by their recruiting physician's knowledge category. Overall, 326 of the 427 patients were recruited at sites with a physician in the high knowledge category. Examining the stratified patient results, we found the distribution of correct responses on the knowledge questions was similar between the two groups of patients, both for the initial questionnaire and the questionnaire after PAC review. Therefore, we did not see any evidence that physician knowledge was associated with the correct responses among their patients.

10.2.5.3 Comparison of Patient Participants to Non-participants

Each site kept a simple log with information on the number of patients approached about the study, the number of patients confirmed eligible, and the number of patients who refused. For every patient approached about the study, the site recorded the patient's age range, sex, and the indication for which rivaroxaban was prescribed.

There were 427 patients who completed the questionnaire and 41 who refused participation. The 41 eligible patients who did not agree to participate provided the following reasons for declining: 13 too busy, 8 not interested, 6 other, 4 not feeling well, 4 no booklet, 3 consent issue, and 3 no reason given. Patients who refused participation generally were slightly older (78% ≥ 66 years) than participants (60% ≥ 66 years). The distributions for both sex and indication were similar across the two groups (Table 13).

Table 13. Comparison of Patient Participants to Nonparticipants

Variable	No. of Patients (%)	
	Completed[a] N = 427	Declined n = 41
Age		
18-25 years	5 (1.2%)	0
26-35 years	12 (2.8%)	1 (2.6%)
36-45 years	19 (4.4%)	1 (2.6%)
46-55 years	59 (13.8%)	2 (5.1%)
56-65 years	77 (18.0%)	3 (7.7%)
66-75 years	118 (27.6%)	13 (33.3%)
76-85 years	119 (27.9%)	12 (30.8%)
86 years or older	18 (4.2%)	7 (17.9%)
Missing	0	2
Sex		
Female	191 (44.7%)	19 (48.7%)
Male	236 (55.3%)	20 (51.3%)
Missing	0	2
Indication for which rivaroxaban was prescribed		
Atrial fibrillation	289 (67.7%)	27 (71.1%)
Deep vein thrombosis and secondary prevention	138 (32.3%)	11 (28.9%)
Missing	0	3

[a] Data are based on screening information collected by the sites at recruitment, which may be different than patient self-reported responses to the questionnaire.

10.3 Adverse Events and Adverse Reactions

This study was not designed to collect information on individual adverse events, serious adverse events, or product complaints. However, reports on potential adverse events were identified during the cognitive pretesting interviews and on completed patient questionnaires (by way of open-ended responses or other handwritten patient notes).

Overall, six adverse events were reported during the study. Three were reported during the cognitive pretest interviews, and three were reported during the course of the main study (Table 14). Those reported during the pretest interviews were related to drugs other than rivaroxaban and are not described in this report. All six events were forwarded to Bayer for evaluation; further follow-up, as appropriate; and reporting.

Table 14. Adverse Events Reported During the Full Study

Patient Number	Country	Date of Report	Event Description	Drug
PPD		15	The patient added text to Question 10 in the first patient questionnaire (example Xarelto, can lead to bleeding). They answered yes and added it was too hard to stop bleeding.	Not available
		-15	The patient added additional text to Question 11—bleeding in the eye. (Note: this is a knowledge question).	Not available
		-15	Patient indicated he was prescribed rivaroxaban for diabetes (in “other”) in Question 18.	Not available

11 Discussion

11.1 Key Results

11.1.1 Physician Assessment

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 Xarelto educational materials was high. The questions with the highest correct responses were on overall risk of bleeding (> 90%) as well as the risks for populations with contraindications and populations that are at increased risk of serious side effects (70%-91%). A lower percentage of physicians (59%) were aware that rivaroxaban should be taken with food. The lowest knowledge was around converting to and from VKA, monitoring, and dosing.

In general, physicians who reported specialties in neurology, cardiology, and haematology had higher proportions of correct responses than physicians in other specialty categories on most of the knowledge questions. Likewise, 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 only for maintenance treatment. Physicians who reported receiving information from the Xarelto Prescriber Guide also consistently provided more correct responses than those who did not report receiving information from this source.

More than half of physicians reported that they used the Xarelto Prescriber Guide (56%). The source of information about rivaroxaban reported most frequently by physicians was a company representative (64%), followed by the Xarelto Prescriber Guide and the Summary of Product Characteristics (54%). Of the physicians who reported using the Prescriber Guide, most (81%) found it helpful or extremely helpful.

Approximately half of physicians (47%) overall reported receiving Xarelto Patient Alert Cards to provide to their patients; the estimates varied greatly by country (from 29% of physicians in the UK to 80% in Germany). Of the physicians who reported receipt of Xarelto Patient Alert Cards, the use of the cards was high. The highest use was in Germany (85%) and the UK (84%), where the most physicians reported that they provided the card to most or all of their patients, and the lowest use of the card was in France (67%). Nearly all of the physicians (90%) reported that they discuss the information in the card with patients when first prescribing rivaroxaban.

11.1.2 Patient Assessment

The most important information communicated in the patient alert card is the risk of bleeding and steps to take to minimize bleeding. Among patients, 80% responded correctly that blood thinners, such as rivaroxaban, can cause bleeding; these results were similar across countries. Knowledge was generally high (> 85% correct) in responses to questions about the indication for treatment, when to consult with their doctor, and when to inform other physicians they are taking rivaroxaban. A lower percentage of patients (60%) correctly reported rivaroxaban should be taken with food. Fewer than half of patients (43%) knew that they should not miss a dose of rivaroxaban in order for rivaroxaban to be effective in preventing blood clots. Knowledge about the signs or symptoms of bleeding varied by symptom, with the highest correct response proportion (61%) for unusual bruising and the lowest (18%) for pain. Knowledge levels were not different by patients' prior experience with blood thinners. Knowledge in all areas improved after patients reviewed the alert card.

Approximately half of patients (ranging from 27% in Spain to 64% in the UK) reported having received the patient alert card. Among patients who reported receiving it, 81% reported having read the card, with 85% keeping the card with them some of the time (14%) or all of the time (71%). Most patients reported they show it to every doctor or dentist they visit (ranging from 41% in Spain to 87% in the UK).

11.2 Strengths

A key strength of the study is diversity of physician and patient participants. The targeted numbers of physician (~300 per country) and patient (~100 per country) respondents were achieved. The distribution of physicians by specialty, practice type, and rivaroxaban prescribing practices represented a broad diversity of physicians. The characteristics of patients by demographics and prior use of blood thinners was diverse, as were the 35 physician practices from which the patients were recruited.

The physician assessment was conducted after physicians had received the educational material and had a chance to use the prescriber guide and the patient alert card in their practice. The patient assessment was conducted after patients had received rivaroxaban and had the opportunity to receive the educational materials for patients. Moreover, the study also collected information immediately after the patient reviewed the patient alert card following completion of the first questionnaire. Therefore, the study evaluated both recall and proximal understanding of the safety and safe use of rivaroxaban. The improvement in patients' knowledge after reviewing the card suggested that the patient alert card was effectively communicating the desired information.

Another strength of the patient assessment was the high response rate (427 patients took the questionnaire among 473 who were invited and eligible [90%]) given that the study was introduced by a trusted physician. A relatively small number of patients refused (9%), withdrew consent (< 1%), or did not complete at least one knowledge question on the questionnaire (< 1%). Individuals who declined were slightly older than participants but were similar in sex and rivaroxaban indication.

Accuracy of responses among physicians and patients was facilitated by the pretesting of the questionnaires through formal cognitive pretesting with physicians and patients in each country. The wording of the questions and response choices should have been easily understood by the respondents.

11.3 Limitations

As with all voluntary studies, some limitations are inherent. Although the study was designed to ensure the selection of a diverse and generally representative sample of prescribers and patients to participate in this study, there was no exhaustive list of all rivaroxaban prescribers and patients from which to draw a sample; hence, it was impossible to select a random sample of all prescribers/patients. Therefore, although participants were diverse in characteristics, the study participants may not necessarily represent all relevant prescribers and patients. 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 the patient participants and non-participants revealed a difference in age but not in other characteristics. A comparison of participants and non-participants in the physician assessment was not possible because physicians who did not wish to participate in the survey did not to 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 to what is known about the overall prescribing population because that information was not available to us.

Another potential limitation of the patient assessment is that the study could influence sites to provide more education to patients than they normally would provide. To minimise this risk, sites were trained to provide only limited information about the study prior to the patients' participation in the study, and patients were asked to complete the questionnaire at the site prior to receiving any additional counselling about treatment. We also compared the patient responses by knowledge level of the recruiting physicians and saw no differences.

11.4 Interpretation

Little information is in the public domain to set thresholds for acceptable levels of knowledge and behaviour related to risk minimisation measures. A recent publication (Knox, 2015) reported on patient understanding of medication guides from a review of 66 assessment reports submitted to the US Food and Drug Administration. Few of the studies (30%) achieved an 80% knowledge level (% correct) for the single most important risk communicated in the medication guide. The mean knowledge level was

63.8%. In this study, 90% of physicians and 80% of patients responded accurately to the question of the most important risk.

Knowledge varied across categories of information, with higher knowledge associated with the most important information (e.g., greatest risk, what actions to take for safe use) and lower knowledge associated with procedures, such as treatment switching, which might require physicians to refer to guidance documents. However, awareness of the importance of not missing a dose and the need to take rivaroxaban with food was surprisingly low for patients already taking the product.

Physicians who reported receiving information from the Xarelto Prescriber Guide displayed higher knowledge than those who did not report receiving information from this source, and patients' knowledge was higher after reviewing the patient alert card. These findings suggest that the educational materials are effectively communicating the desired information.

Knowledge and behaviour reflect many factors, including availability and access to information, literacy and numeracy, beliefs, and motivation. The relatively low level of reported receipt of the physician prescriber guide and the patient alert card may reflect poor recall, if the material had indeed been received, or barriers to the receipt of the material. Variability across countries could reflect (1) the different distributions of specialists prescribing initial and maintenance therapy, (2) inherent differences in physician and patient behaviour, (3) variations in prescribing guidelines/practices across country-specific health care systems, or (4) different intensity of the educational efforts. It was encouraging to see that, among physicians and patients who reported receipt of the material, use of the material was extremely high.

11.5 Generalisability

As noted in Section 11.2, the study achieved great diversity in physician and patient characteristics within the four countries, allowing for stratification of results by those characteristics. We saw heterogeneity of some results by country; it is unknown how well these results would relate to other countries.

12 Other Information

Not applicable.

13 Conclusion

The study met its objectives to evaluate whether physicians and their patients receive the educational materials for rivaroxaban and to assess physician and patient knowledge and understanding of key safety information as well as use of the materials.

In general, the observed patterns of knowledge among the physicians 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 Xarelto, 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 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).

14 References

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Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22:983-8.

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Appendices

Annex A. List of Stand-Alone Documents

Number	Document reference number	Date	Title
1		16 October 2015	Full list of principal investigators

Annex B. List of Ethics Committee Reviews and Approval Dates

Table B-1. Individual Ethics Committee Approvals: Germany

Investigator	Site	Ethics Committee	Approval Date
PPD			14
			14
			-14
			-15
			-14
			-14
			-14
			-14
			-14
			-14

Table B-2. Individual Ethics Committee Approvals: Spain

Investigator	Site	Ethics Committee	Approval Date
PPD			14
			14
			14
			14
			14
			14
			14
			14

Annex C. Physician and Patient Xarelto Educational Materials

297 mm

NOW UPDATED AND INCLUDES A NEW INDICATION

XARELTO® ▼ (RIVAROXABAN) EDUCATIONAL PACK

FOR 15MG AND 20MG DOSING

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors*

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults**

211 mm

* Such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack

** Xarelto is not recommended for haemodynamically unstable PE patients

Xarelto® rivaroxaban

Prescribing Information can be found on pages 10 and 11

Bayer HealthCare

Date of preparation: November 2012
L.GB.10.2012.07818

DO NOT PRINT GUIDES

297 mm

211 mm

Bayer HealthCare have designed this educational pack to support you in the appropriate prescribing of Xarelto. It contains important information specifically relating to 15mg and 20mg dosing of Xarelto, for use in stroke prevention in AF and treatment of DVT and PE.

Within this pack you will find a:

- Prescriber guide
- Summary of product characteristics (SmPC)
- Patient alert card

If you would like to order more copies of the Xarelto educational pack, please visit **www.xarelto-info.co.uk**

Alternatively, please contact Bayer Medical Information at **medical.information@bayer.co.uk** or call **01635 563116.**

DO NOT PRINT GUIDES

NOW UPDATED AND INCLUDES A NEW INDICATION

XARELTO® (RIVAROXABAN) PRESCRIBER GUIDE FOR 15MG AND 20MG DOSING

Xarelto® ▼
rivaroxaban

Prescribing information can be found on pages 10 and 11

This guide is to be used to support the appropriate use of Xarelto in eligible atrial fibrillation (AF) patients and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).

It includes the following information:

- **Indications**
- **Dosing recommendations**
- **Populations potentially at higher risk of bleeding**
- **Perioperative management**
- **Overdose**
- **How to manage bleeding complications**
- **Coagulation testing**

Xarelto patient alert card

You must provide a patient alert card to each patient who is prescribed Xarelto 15mg or 20mg.

Please explain the implications of anticoagulant treatment to patients, in particular highlighting the need for:

- treatment compliance
- taking medication with food
- signs or symptoms of bleeding
- when to seek medical attention.

The patient alert card will inform treating physicians and dentists about the patient's anticoagulation treatment and will contain emergency contact information.

Please instruct patients to carry the patient alert card with them at all times and present it to every health care provider.

INDICATIONS

Prevention of stroke and systemic embolism in adult patients with non-valvular AF with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

Treatment of DVT and PE and prevention of recurrent DVT and PE in adults. (See section 4.4 of the SmPC for haemodynamically unstable PE patients).

DOSING RECOMMENDATIONS

Xarelto 15mg and 20mg must be taken with food to ensure sufficient absorption of the drug. The intake of these doses with food at the same time supports the required absorption of the drug, thus ensuring a high oral bioavailability.

Note: Xarelto is also available at a 10mg dose for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. This dose can be taken with or without food.

Dosing in patients with AF

The recommended dose for prevention of stroke and systemic embolism in patients with non-valvular AF is 20mg once daily.

*In patients with moderate or severe renal impairment the recommended dose is 15mg once daily.

Patients with renal impairment:

In patients with moderate (creatinine clearance 30-49 ml/min) or severe (15-29 ml/min) renal impairment the recommended dose is 15mg once daily. Xarelto is to be used with caution in patients with severe renal impairment as limited clinical data indicates a significantly increased plasma concentration. Use is not recommended in patients with creatinine clearance < 15 ml/min.

Duration of therapy:

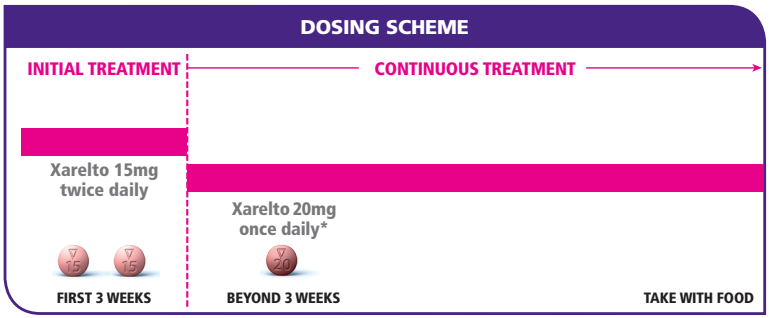
Xarelto should be continued long term provided the benefit of stroke prevention therapy outweighs the potential risk of bleeding. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Missed dose:

If a dose is missed the patient should take Xarelto immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Dosing in treatment of DVT and PE, and prevention of recurrent DVT and PE in adults

Patients are initially treated with 15mg **twice daily** for the first three weeks. This initial treatment is followed by 20mg **once daily** for the continued treatment period.



* Patients with DVT/PE and renal impairment

Patients with renal impairment

Patients with moderate (creatinine clearance 30-49 ml/min) or severe (15-29 ml/min) renal impairment treated for acute DVT, acute PE and prevention of recurrent DVT and PE do not require a dose reduction.

However, during the continuous treatment phase, a reduction of the dose from 20mg once daily to 15mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15mg is based on PK modelling and has not been studied in this clinical setting.

The use of Xarelto is not recommended in patients with creatinine clearance < 15 ml/min.

Duration of therapy:

The duration of therapy should be individualised after assessment of the treatment benefit against the risk for bleeding. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

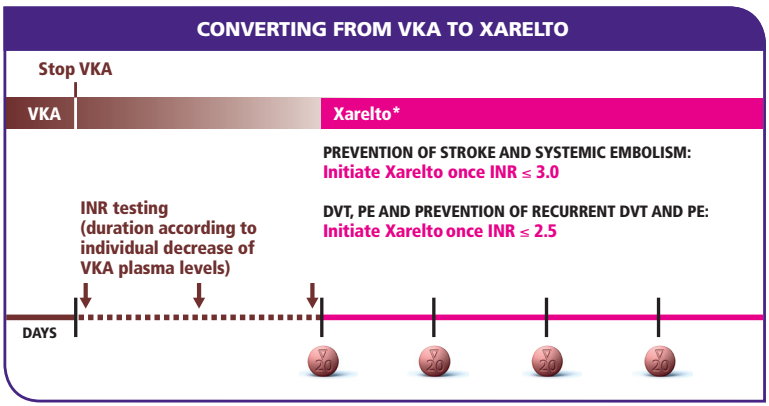
Missed dose:

- **Twice daily treatment period** (15mg bid for the first three weeks): If a dose is missed, the patient should take Xarelto immediately to ensure intake of 30mg Xarelto per day. Continue with the regular 15mg twice daily intake on the following day.
- **Once daily treatment period** (beyond three weeks): If a dose is missed, the patient should take Xarelto immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO XARELTO

For patients treated for **prevention of stroke and systemic embolism,** treatment with VKA should be stopped and Xarelto therapy should be initiated when the international normalised ratio **(INR)** is ≤ **3.0**.

For patients treated for **DVT, PE and prevention of recurrent DVT and PE**, treatment with VKA should be stopped and Xarelto therapy should be initiated when the **INR** is ≤ **2.5**.



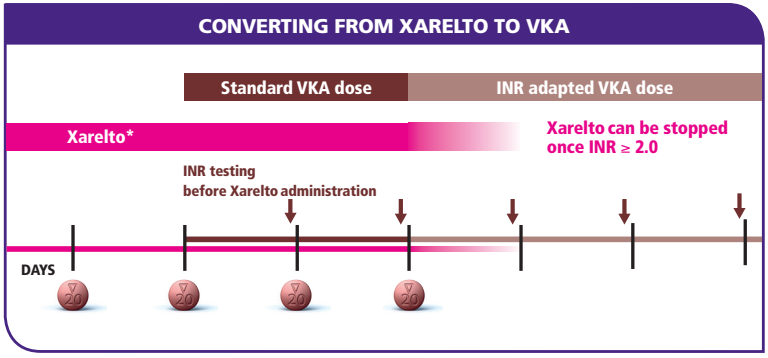
*See dosing recommendations for required daily dose

INR measurement is not appropriate to measure the anticoagulant activity of Xarelto, and therefore should not be used for this purpose. Treatment with Xarelto only does not require routine coagulation monitoring.

CONVERTING FROM XARELTO TO VKA

It is important to ensure adequate anticoagulation while minimising the risk of bleeding during conversion of therapy.

When converting to VKA, Xarelto and VKA should overlap until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing.



*See dosing recommendations for required daily dose

INR measurement is not appropriate to measure the anticoagulant activity of Xarelto. While patients are on both Xarelto and VKA the **INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Xarelto**. Once Xarelto has been discontinued, after 24 hours, INR values reliably reflect VKA dosing.

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO XARELTO

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Xarelto should be started at the time of discontinuation.
- 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 time of the next scheduled administration of the parenteral drug.

CONVERTING FROM XARELTO TO PARENTERAL ANTICOAGULANTS

The first dose of the parenteral anticoagulant should be given at the time the next Xarelto dose would have been taken.

POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING

Like all anticoagulants, Xarelto may increase the risk of bleeding.

Therefore Xarelto is contraindicated in patients:

- with clinically signficant active bleeding.
- with a lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or supected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh class B and C cirrhotic patients.
- receiving concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, dabigatran, apixaban etc) except under the circumstances of switching therapy to or from Xarelto or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- Xarelto is contraindicated during pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with Xarelto. Xarelto is contraindicated during breastfeeding. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

SEVERE SUB-GROUPS OF PATIENTS

Several sub-groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications.

Treatment decision in these patients should be done after assessment of treatment benefit against the risk of bleeding.

- *Patients with renal impairment:* See "dosing recommendations" for patients with moderate (creatinine clearance 30-49 ml/min) or severe (15-29 ml/min) renal impairment. Use of Xarelto is not recommended in patients with creatinine clearance <15 ml/min.
- *Patients concomitantly receiving other medicinal products:*
  - Use of Xarelto is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir).
  - Take care with drugs affecting haemostasis such as NSAIDs, acetylsalicylic acid, or platelet aggregation inhibitors.

- *Patients with other haemorrhagic risk factors:*

  As with other antithrombotics, Xarelto is not recommended in patients with an increased bleeding risk such as:

  - congenital or acquired bleeding disorders
  - uncontrolled severe arterial hypertension
  - other gastrointestinal disease that can potentially lead to bleeding complications
  - vascular retinopathy
  - bronchiectasis or history of pulmonary bleeding

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, Xarelto 15/20mg should be stopped at least 24 hours before the intervention if possible, and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding due to Xarelto should be assessed against the urgency of the intervention.

Xarelto should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established.

OVERDOSE

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg Xarelto and above. The use of activated charcoal to reduce absorption in case of overdose may be considered.

HOW TO MANAGE BLEEDING COMPLICATIONS

Should bleeding complications arise in a patient receiving Xarelto, the next Xarelto administration should be delayed or treatment discontinued as appropriate. Individualised bleeding management may include:

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement and haemodynamic support, blood product or component transfusion.
- For life-threatening bleeding that cannot be controlled with the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving Xarelto. Due to the high plasma protein binding Xarelto is not expected to be dialysable.

COAGULATION TESTING

Xarelto does not require routine coagulation monitoring. However, measuring Xarelto levels may be useful in exceptional situations where knowledge of Xarelto exposure may help to make clinical decisions, e.g. overdose and emergency surgery.

Anti-FXa assays with Xarelto-(rivaroxaban) specific calibrators to measure rivaroxaban levels are now commercially available. If clinically indicated haemostatic status can also be assessed by PT using Neoplastin as described in the SmPC.

The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated PT international normalised ratio (INR). Since the INR was developed to assess the effects of VKAs on the PT, it is therefore not appropriate to use the INR to measure activity of Xarelto. Dosing or treatment decisions should not be based on results of INR except when converting from Xarelto to VKA as described above.

Xarelto® ▼10 mg film-coated tablets (rivaroxaban) Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 10 mg rivaroxaban tablet. **Indication(s):** Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. **Posology and method of administration:** Dosage 10 mg rivaroxaban orally once daily with or without food; initial dose should be taken 6 to 10 hours after surgery provided haemostasis established. *Recommended treatment duration:* Dependent on individual risk of patient for VTE determined by type of orthopaedic surgery: for major hip surgery 5 weeks; for major knee surgery 2 weeks. Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants. ***Renal impairment:*** Mild & moderate (creatinine clearance 50-80ml/min & 30-49 ml/min respectively) – no dose adjustment necessary; severe (creatinine clearance 15-29ml/min) - limited data indicates rivaroxaban concentrations are significantly increased, use with caution. Patients with creatinine clearance < 15ml/min – use not recommended. ***Hepatic impairment:*** Do not use in patients with hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C patients. ***Paediatrics:*** Not recommended. **Contra-indications**: Hypersensitivity to active substance or any excipient; clinically significant active bleeding; hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breast feeding. **Warnings and precautions:** Not recommended in patients: undergoing hip fracture surgery; in patients receiving concomitant systemic treatment with strong CYP3A4 and P-gp inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; with severe renal impairment (creatinine clearance <15 ml/min). Increased risk of bleeding therefore careful monitoring for signs/symptoms of bleeding complications & anaemia required after treatment initiation: in patients with severe renal impairment (creatinine clearance 15 - 29 ml/min); or with moderate renal impairment (creatinine clearance 30 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; in patients treated concomitantly with medicinal products affecting haemostasis; in patients with congenital or acquired bleeding disorders; uncontrolled severe arterial hypertension; active ulcerative gastrointestinal disease (consider appropriate prophylactic treatment for at risk patients); recent gastrointestinal ulcerations; vascular retinopathy; recent intracranial or intracerebral haemorrhage; intraspinal or intracerebral vascular abnormalities; recent brain, spinal or ophthalmological surgery, bronchiectasis or history of pulmonary bleeding. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. If clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Take special care when neuraxial anaesthesia or spinal/epidural puncture is employed due to risk of epidural or spinal haematoma with potential neurologic complications. Xarelto contains lactose. **Interactions:** Concomitant use with strong inhibitors of both CYP3A4 & P-gp not recommended as increased rivaroxaban plasma concentrations to a clinically relevant degree are observed. Avoid co-administration with dronedarone. Use with caution in patients concomitantly receiving other anticoagulants, NSAIDs or platelet aggregation inhibitors due to the increased bleeding risk. Strong CYP3A4 inducers should be used concomitantly with caution as they may reduce rivaroxaban plasma concentrations.. **Pregnancy and breast feeding:** Contra-indicated. **Effects on ability to drive and use machines:** Adverse events like syncope and dizziness are common. Patients experiencing these effects should not drive or use machines. **Undesirable effects:** *Common:* anaemia, dizziness, headache, syncope, eye haemorrhage, tachycardia, hypotension, haematoma, epistaxis, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, pain in extremity, urogenital tract haemorrhage, fever, peripheral oedema, decreased general strength & energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Serious: cf. CI/Warnings and Precautions – in addition:* thrombocythemia, allergic reactions, occult bleeding/haemorrhage from any tissue (e.g. cerebral & intracranial, cutaneous & subcutaneous, haemoptysis, haemarthrosis, muscle) which may lead to complications (incl. compartment syndrome, renal failure, fatal outcome), abnormal hepatic function, renal impairment; hyperbilirubinaemia, jaundice, pseudoaneurysm formation following percutaneous intervention. Prescribers should consult SmPC in relation to full side effect information. **Overdose:** No specific antidote is available. **Legal Category:** POM. **Package Quantities and Basic NHS Costs:** 10 tablets: £21.00, 30 tablets: £63.00 and 100 tablets: £210.00. **MA Number(s):** EU/1/08/472/001-10 **Further information available from:** Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA, U.K. Telephone: 01635 563000. **Date of preparation:** June 2012.

Xarelto® is a trademark of the Bayer Group.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Bayer plc. Tel: 01635 563500, Fax: 01635 563703, Email: phdsguk@bayer.co.uk

Xarelto® ▼15 and 20 mg film-coated tablets (rivaroxaban) Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 15mg/20mg rivaroxaban tablet **Indication(s):** 1. Prevention of stroke & systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors such as congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischaemic attack (SPAF). 2. Treatment of deep vein thrombosis (DVT) & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). **Posology & method of administration:** *Dosage 1 (SPAF):* 20 mg orally *o.d.* with food. *Dosage 2 (DVT & PE):* 15 mg *b.i.d.* for 3 weeks followed by 20 mg *o.d.* for continued treatment & prevention of recurrent DVT & PE; take with food. Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants. ***Renal impairment:*** mild (creatinine clearance 50-80 ml/min) - no dose adjustment necessary; moderate (creatinine clearance 30-49 ml/min) & severe (creatinine clearance 15-29 ml/min; limited data indicates rivaroxaban plasma concentrations are significantly increased, use with caution) – *SPAF:* reduce dose to 15mg *o.d.*, DVT & PE: 15 mg *b.i.d.* for 3 weeks, thereafter 20mg *o.d.* Consider reduction from 20mg to 15mg o.d. if patient's bleeding risk outweighs risk for recurrent DVT & PE; Patients with creatinine clearance <15 ml/min - use not recommended. ***Hepatic impairment:*** Do not use in patients with hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C patients. ***Paediatrics:*** Not recommended. **Contra-indications:** Hypersensitivity to active substance or any excipient; clinically significant active bleeding; lesion or condition at significant risk of major bleeding (refer to SmPC); concomitant treatment with any other anticoagulant agent except under the circumstances of switching therapy to or from rivaroxaban or when unfractionated heparin is given at doses necessary to maintain a patent central venous or arterial catheter; hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breast feeding. **Warnings & precautions:** Clinical surveillance in line with anticoagulant practice is recommended throughout the treatment period. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Discontinue if severe haemorrhage occurs. In studies mucosal bleedings & anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment – haemoglobin/haematocrit testing may be of value to detect occult bleeding. Following sub-groups of patients are at increased risk of bleeding & should be carefully monitored after treatment initiation. Use with caution- in patients with severe renal impairment or with renal impairment concomitantly receiving potent inhibitors of CYP3A4 (PK models show increased rivaroxaban concentrations); in patients treated concomitantly with medicines affecting haemostasis. Use is not recommended in patients: with creatinine clearance <15 ml/min; with an increased bleeding risk (refer to SmPC); receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors; with prosthetic heart valves; with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. If invasive procedures or surgical intervention are required stop Xarelto use at least 24 hours beforehand. Restart use as soon as possible provided adequate haemostasis has been established. See SmPC for full details. Xarelto contains lactose. **Interactions:** Concomitant use with strong inhibitors of both CYP3A4 & P-gp not recommended as increased rivaroxaban plasma concentrations to a clinically relevant degree are observed. Avoid co-administration with dronedarone. Use with caution in patients concomitantly receiving other anticoagulants, NSAIDs or platelet aggregation inhibitors due to the increased bleeding risk. Strong CYP3A4 inducers should be used concomitantly with caution as they may reduce rivaroxaban plasma concentrations. **Pregnancy & breast feeding:** Contra-indicated. **Effects on ability to drive and use machines:** Adverse reactions like syncope (uncommon) & dizziness (common). Patients experiencing these effects should not drive or use machines. **Undesirable effects:** *Common:* anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, cutaneous & subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage, renal impairment, fever, peripheral oedema, decreased general strength & energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Serious: cf. CI/Warnings and Precautions – in addition:* thrombocythemia, allergic reactions, occult bleeding/haemorrhage from any tissue (e.g. cerebral & intracranial, haemarthrosis, muscle) which may lead to complications (incl. compartment syndrome, renal failure, fatal outcome), syncope, tachycardia, abnormal hepatic function, hyperbilirubinaemia, jaundice, vascular pseudoaneurysm. Prescribers should consult SmPC in relation to full side effect information. **Overdose:** No specific antidote is available. **Legal Category:** POM. **Package Quantities and Basic NHS Costs:** *15mg* – 28 tablets: £58.80, 42 tablets: £88.20, 100 tablets: £210.00; *20mg* – 28 tablets: £58.80, 100 tablets £210.00 **MA Number(s):** EU/1/08/472/011-21 **Further information available from:** Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA, U.K. Telephone: 01635 563000. Date of preparation: November 2012.

Xarelto® is a trademark of the Bayer Group.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Bayer plc. Tel: 01635 563500, Fax: 01635 563703, Email: phdsguk@bayer.co.uk

Bayer HealthCare

Date of preparation: November 2012
L.GB.10.2012.0781

What should I know about Xarelto®?

- Xarelto® thins the blood, which prevents you from dangerous blood clots.
- Xarelto® must be taken exactly as prescribed by your doctor. To ensure optimal protection from blood clots, **never skip a dose.**
- You must not stop taking Xarelto® without first talking to your doctor as your risk of blood clots may increase.
- Speak to your health care provider prior to any intake of other medication.
- Inform your health care providers about Xarelto® intake prior to any surgery or invasive procedure.

When should I seek advice from my health care provider?

When taking a blood thinner such as Xarelto® it is important to be aware of its possible side effects. Bleeding is the most common side effect. Do not start taking Xarelto® if you are at risk of abnormal bleeding, without first discussing this with your doctor.

Tell your health care provider right away if you have any signs or symptoms of bleeding such as the following:

- pain
- swelling or discomfort
- headache, dizziness or weakness
- unusual bruising, nosebleeds, bleeding of gums, bleeding from cuts that take a long time to stop
- menstrual flow or vaginal bleeding that is heavier than normal
- pink or brown urine, red or black stools
- coughing up blood, or vomiting blood or material that looks like coffee grounds.

How do I take Xarelto®?

- To ensure optimal protection, Xarelto®15mg and 20mg must be taken with food.

Date of preparation: November 2012
L.GB.10.2012.0954

PATIENT ALERT CARD

Xarelto® 15mg
Xarelto® 20mg

- **Keep this card with you at all times**
- **Present this card to every physician or dentist prior to treatment**

I am under anticoagulation treatment with Xarelto® (rivaroxaban)

Name: _____

Address: _____

_____

_____

Birth date: _____

Blood type: _____

Weight: _____

Other medications/conditions: _____

_____

_____

_____

_____

_____

_____

_____

In case of emergency, please notify:

Doctor's name: _____

Doctor's phone: _____

Doctor's stamp:

Please also notify:

Name: _____

Phone: _____

Relationship: _____

Information for health care providers:

- INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto®.

Annex D. Physician Questionnaire

Physician Questionnaire

Xarelto Risk Minimization Study

Study Introduction and Informed Consent

PPD an independent, nonprofit research firm engaging in numerous health and medicine research studies, is conducting a research study on behalf of Bayer HealthCare (BHC) and would like to invite you to participate. This study is being conducted as part of the ongoing safety and risk management process for Xarelto (rivaroxaban). This is not a marketing survey, but a scientific study conducted at the request of the European Medicines Agency (EMA), the drug regulatory body in the European Union (EU). The purpose of the study is to assess prescribers' understanding of and compliance with the safe use of Xarelto for the following two chronic indications:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
- Treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism following an acute deep vein thrombosis in adults. (This indication will be referred to as "**deep vein thrombosis treatment and secondary prevention"** throughout the questionnaire.)

You have been identified as a potential participant for this evaluation because you are a physician who treats patients who have, or who are at risk for developing these conditions. This questionnaire which takes 10 to 15 minutes to complete is being administered to approximately 1,200 physicians across several countries within the EU. Your answers will be treated with strict confidentiality. Any information provided will only be evaluated together with that of other respondents.

By completing and submitting this survey, you indicate that you have read the information provided above and voluntarily agree to participate in this study.

[The survey will be programmed online and a link will be provided to a contact page which will include the phone number for PPD should participants have a question about their rights as a study participant.]

C1. Do you agree to participate in the study?

- ☐ Yes, I agree to participate in this study.
- ☐ No, I do not agree to participate in this study.

[IF C1 = "No, I do not agree to participate in this study.",
THEN DISPLAY "You have indicated that you do not agree to participate in the study. Thank you for your time." TERMINATE SURVEY].

To confirm your eligibility to participate in this brief assessment, please answer the following question:

S1. In the past 6 months, have you prescribed Xarelto (rivaroxaban) to patients for either of the following indications?

(Tick all that apply.)

- ☐ Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
- ☐ Deep vein thrombosis treatment and secondary prevention in adults
- ☐ I have not prescribed Xarelto for either of these indications

[IF S1 = "I have not prescribed Xarelto for either of these indications",
THEN DISPLAY "It does not appear that you qualify for the survey. Thank you for your time and interest." AND TERMINATE SURVEY
ELSE DISPLAY "We have confirmed that you are eligible. We will now continue with the survey questions].

Physician Questionnaire

This questionnaire is designed to gain a better understanding of prescribers' knowledge about Xarelto for only the following two approved indications:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
- Deep vein thrombosis treatment and secondary prevention

Additionally, this assessment will be used to determine if the education materials regarding Xarelto, including the Prescriber Guide, are accurately understood and whether there are aspects of these materials that could be improved.

The first set of questions asks about your prescribing practices.

Q1. In the past 6 months, for how many patients have you prescribed Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation?

- ☐ 1 to 10
- ☐ 11 to 20
- ☐ 21 or more
- ☐ I have not prescribed Xarelto for this indication

Q2. In the past 6 months, for how many patients have you prescribed Xarelto for deep vein thrombosis treatment and secondary prevention?

- ☐ 1 to 10
- ☐ 11 to 20
- ☐ 21 or more
- ☐ I have not prescribed Xarelto for this indication

Q3. When did you write your <u>most recent</u> prescription for Xarelto for either of these indications?

(Tick one.)

- ☐ Less than 1 month ago
- ☐ 1 to 3 months ago
- ☐ 4 to 6 months ago
- ☐ I don’t know

Q4. Which of the following Xarelto treatment activities are you responsible for?

(Tick all that apply.)

- ☐ I initiate Xarelto treatment or convert treatment from or to Xarelto
- ☐ I write follow up (maintenance) prescriptions for Xarelto

The next questions ask about the use of Xarelto for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and deep vein thrombosis treatment and secondary prevention.

Q5. What is the most important risk associated with taking Xarelto?

(Tick one.)

- ☐ Neoplasia
- ☐ Hypertension
- ☐ Risk of bleeding*
- ☐ Immunosuppression
- ☐ I don't know

Q6. Which of the following populations are at an increased risk of experiencing serious side effect(s) associated with Xarelto?

(Tick Yes, No, or I don't know for each patient population listed)

Population	**Yes,** at higher risk	**No**, not at higher risk	**I don't know**
Patients with moderate or severe renal impairment	☐ *	☐	☐
Patients taking products that affect hemostasis such as NSAIDS, acetylsalicylic acid, platelet aggregation inhibitors	☐ *	☐	☐
Patients at risk of bleeding	☐ *	☐	☐
Patients with chronic constipation	☐	☐	☐

Q7. To which patient groups is Xarelto contraindicated?

(Tick all that apply.)

- ☐ Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child-Pugh class B and C*
- ☐ Patients who are pregnant or breastfeeding*
- ☐ Patients receiving concomitant treatment with any other anticoagulant such as unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives or oral anticoagulants except when switching therapy to or from Xarelto or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter*
- ☐ Patients with clinically significant active bleeding*
- ☐ I don't know

Q8. Xarelto (15 or 20 mg) must be taken….?

(Tick one.)

- ☐ On an empty stomach
- ☐ With food/on a full stomach*
- ☐ I don't know

Q9. Is routine coagulation monitoring required for patients taking Xarelto for these indications?

- ☐ Yes
- ☐ No*
- ☐ I don't know

Q10. In which of the following situations is INR monitoring needed?

(Tick all that apply.)

- ☐ When converting from vitamin K antagonist (VKA) (e.g., warfarin) to Xarelto*
- ☐ When converting from Xarelto to VKA*
- ☐ Continual INR monitoring is required for all patients taking Xarelto
- ☐ I don't know

Q11. Which of the following steps should be taken when converting patients from VKA (e.g., warfarin) to Xarelto?

(Tick all that apply.)

- ☐ Stop VKA without measuring INR
- ☐ For patients treated for prevention of stroke and systemic embolism, stop VKA and initiate Xarelto when INR is $\leq$ 3*
- ☐ For patients treated for deep vein thrombosis and secondary prevention, stop VKA and initiate Xarelto when INR is $\leq$ 2.5*
- ☐ I don't know

Q12. Which of the following steps should be taken when converting patients from Xarelto to VKA (e.g., warfarin)?

(Tick all that apply.)

- ☐ Overlap the two drugs until INR is ≥ 2.0*
- ☐ Measure INR but make sure it has been longer than 24 hours since the last dose of Xarelto*
- ☐ Stop Xarelto at any time
- ☐ Measure INR at any time of the day
- ☐ I don't know

Q13. Which of the following are true when converting from parenteral anticoagulants to Xarelto…?

(Tick all that apply.)

- ☐ Stop parenteral anticoagulants for a week prior to starting Xarelto
- ☐ 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*
- ☐ I don't know

Q14. 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)?

(Tick one.)

- ☐ One week prior to the procedure or surgical intervention
- ☐ At least 24 hours prior to the procedure or surgical intervention*
- ☐ It is not necessary to stop Xarelto for these procedures
- ☐ I don't know

Q15. 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.)

- ☐ Provide symptomatic treatment (e.g., mechanical compression, surgery)*
- ☐ Delay the next administration of Xarelto or discontinue Xarelto as appropriate*
- ☐ Provide hemodynamic support (e.g., blood transfusion)*
- ☐ Administer procoagulant reversal agent (for life-threatening bleeding)*
- ☐ Refer the patient to emergency care
- ☐ None of the above
- ☐ I don't know

[IF Q1 = "I have not prescribed Xarelto for this indication", SKIP TO intro text preceding Q18.

The following questions are about the indication for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Q16. What is the standard recommended dose of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation?

(Tick one.)

- ☐ 20 mg taken once a day*
- ☐ 15 mg taken once a day
- ☐ 10 mg taken once a day
- ☐ None of the above
- ☐ I don't know

Q17. 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?

(Tick one.)

- ☐ 20 mg taken once a day
- ☐ 15 mg taken once a day*
- ☐ 10 mg taken once a day
- ☐ None of the above
- ☐ I don't know

[IF Q2 = "I have not prescribed Xarelto for this indication", SKIP TO intro text preceding Q19.

The following question is about the indication for deep vein thrombosis treatment and secondary prevention in adult patients.

Q18. What is the standard recommended dose for patients receiving Xarelto for deep vein thrombosis treatment and secondary prevention?

(Tick one.)

- ☐ 20 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day
- ☐ 15 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day*
- ☐ 10 mg once a day
- ☐ None of the above
- ☐ I don’t know

In this next section, please tell us about any information you have received about Xarelto.

Q19. From which of the following sources did you receive information about Xarelto?

(Tick all that apply.)

- ☐ Xarelto Prescriber Guide
- ☐ Briefing from a company representative
- ☐ Discussion with a clinical expert
- ☐ The Summary of Product Characteristics for Xarelto
- ☐ Clinical trials published in the medical literature
- ☐ Other
- ☐ None of the above

Q20. How helpful were these sources to you in treating and educating your patients?

[ONLY DISPLAY RESPONSES THAT WERE CHECKED IN Q19; IF Q19 = "NONE OF THE ABOVE", SKIP TO Q21.]

	1 Not at all helpful	2	3	4	5 Extremely helpful
Xarelto Prescriber Guide	☐	☐	☐	☐	☐
Briefing from a company representative	☐	☐	☐	☐	☐
Discussion with a clinical expert	☐	☐	☐	☐	☐
Summary of Product Characteristics	☐	☐	☐	☐	☐
Medical Publications	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐

Q21. Have you received Xarelto Patient Alert Cards to provide to your patients?

☐ Yes
☐ No

[IF Q21 IS NO, SKIP TO Q24.]

Q22. Considering the Xarelto patients under your care, to how many did you provide a Patient Alert Card?

☐ Every one of my patients
☐ Most of my patients
☐ A few of my patients
☐ None of my patients

Q23. When would you discuss the information on the Patient Alert Card with your patients taking Xarelto?

(Tick all that apply.)

- ☐ When first prescribing Xarelto
- ☐ When a patient is facing an invasive procedure or surgical intervention
- ☐ When a patient has bleeding complications
- ☐ When a patient has a Xarelto related adverse event
- ☐ I do not use the Patient Alert Card
- ☐ Other

In this next section, please tell us a little about yourself and your clinical practice.

Q24. Which of the following <u>best</u> describes your specialty?

- ☐ General medicine
- ☐ Neurology
- ☐ Cardiology
- ☐ Haematology
- ☐ Accident & Emergency medicine
- ☐ Oncology
- ☐ Other

Q25. How many years have you been practicing medicine?

- ☐ 5 years or less
- ☐ 6 to 10 years
- ☐ 11 to 15 years
- ☐ 16 to 20 years
- ☐ 21 to 25 years
- ☐ More than 25 years

Q26. Are you…?

- ☐ Male
- ☐ Female

Q27. How would you characterise your practice?

(Tick all that apply.)

- ☐ General practice
- ☐ Hospital-based clinic
- ☐ Nursing home
- ☐ Other

Thank you for completing the questionnaire!

Reporting adverse events - Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Bayer plc. Tel.: PPD **Fax:** PPD
Email: PPD

If you would like additional information or have any questions about the prescribing guidelines or safety information related to Xarelto, please click to the link below to access the Xarelto Prescriber Guide.

[INSERT LINK]

Annex E. Patient Questionnaire

Xarelto Study
Patient Questionnaire 1

Thank you for agreeing to participate in this study!

Version 0.0

Questionnaire Instructions

- **Answer all of the questions by checking the box to the left of your answer**
- **You are sometimes told to skip over some questions in this questionnaire. When this happens, you will see an arrow with a note that tells you what question to answer next; like this:**

☑ Yes ➔ If yes, go to Question 1.
☐ No

This is the first of two questionnaires. Please complete this questionnaire before moving on to the second questionnaire (found in a separate envelope).

Please answer the following questions first to confirm that you are eligible for this study.

Q1. Are you 18 years of age or older?

- ☐ Yes
- ☐ No (If no, please speak with the study coordinator to confirm your eligibility.)

Q2. Have you taken Xarelto (also known as rivaroxaban) in the past 3 months?

- ☐ Yes, I have taken Xarelto in the past 3 months
- ☐ No, I have not taken Xarelto in the past 3 months
- ☐ I don't know

The purpose of this study is to learn more about your knowledge and understanding of the safety information related to Xarelto (rivaroxaban).

Please do not look at the Xarelto patient alert card while answering the following questions.

Q3. Are you currently taking Xarelto?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q4. Approximately how long have you been taking Xarelto?

Select the one answer that best applies to you.

- ☐ Less than 1 month
- ☐ Between 1 and 6 months
- ☐ More than 6 months but less than 1 year
- ☐ More than 1 year
- ☐ I don't know

Q5. How many prescription medications, including Xarelto, are you currently taking on a regular basis?

Select the one answer that best applies to you.

- ☐ I am taking only 1 prescription medication (Xarelto)
- ☐ 2 prescription medications
- ☐ 3 to 4 prescription medications
- ☐ 5 to 6 prescription medications
- ☐ More than 6 prescription medications
- ☐ I don't know

Q6. Xarelto is a prescription medicine used to thin the blood to prevent blood clots?

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q7. Before starting Xarelto, had you ever taken any prescription blood thinners (medications that thin the blood to prevent blood clots)?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q8. Where did you get <u>most</u> of your information about Xarelto?

Select the <u>one</u> answer that best applies to you.

- ☐ From my doctor
- ☐ From a specialist at the hospital
- ☐ From my pharmacist
- ☐ From a friend or family member
- ☐ From my carer
- ☐ From articles in newspapers or magazines
- ☐ From the Internet
- ☐ From the Xarelto Patient Alert Card and/or patient information leaflet
- ☐ Other, please specify _____

Like all medicines, Xarelto can cause side effects, although not everybody gets them.

The following questions are to learn more about your knowledge of side effect(s) that people who take Xarelto <u>could potentially</u> experience.

Please note that these questions are <u>not</u> asking about your own experiences while taking Xarelto.

If you have any questions or concerns about the information in the questionnaire, please talk with your health care professional.

Q9. Has your health care professional ever talked to you about the possible side effects of Xarelto?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q10. Blood thinning medications, such as Xarelto, may cause bleeding.
(Please remember that this question is asking about your knowledge in general and not about your own experience.)

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q11. Which of the following are possible signs or symptoms of bleeding while taking Xarelto? (Please remember that this question is asking about your knowledge in general and not about your own experience.)

Check the box Yes, No, or I don't know for each of the following items.

	Yes, this **may be** a sign or symptom of bleeding when taking Xarelto	**No**, this is **not** a sign or symptom of bleeding when taking Xarelto	**I don't know** if this is a sign or symptom of bleeding when taking Xarelto
Pain	☐	☐	☐
Swelling or discomfort	☐	☐	☐
Headache, dizziness, or weakness	☐	☐	☐
Unusual bruising	☐	☐	☐

Q12. I must not stop taking Xarelto at any time without consulting with my doctor.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q13. I need to speak to my doctor prior to any intake of other medication(s).

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q14. I need to inform my doctor or dentist about Xarelto intake prior to any kind of surgery or invasive procedure.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q15. I need to tell my doctor right away if I have any signs or symptoms of bleeding while taking Xarelto.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q16. Should Xarelto (15 mg and 20 mg tablets) be taken with food?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q17. What should you do to ensure Xarelto is effective in preventing blood clots?

Select all that apply.

- ☐ Take Xarelto exactly as prescribed by your Health Care Professional
- ☐ Take Xarelto only when you do not feel well
- ☐ Do not miss a dose of Xarelto
- ☐ I don't know

In this last section, please tell us a little information about yourself to help us describe the participants completing this questionnaire.

Q18. I was prescribed Xarelto for the following reason(s)…

Select all that apply.

- ☐ Prevention of stroke
- ☐ A blood clot in a vein
- ☐ I don't know
- ☐ Other, please specify: _____

_____

Q19. How old are you?

- ☐ 18-25 years
- ☐ 26-35 years
- ☐ 36-45 years
- ☐ 46-55 years
- ☐ 56-65 years
- ☐ 66-75 years
- ☐ 76-85 years
- ☐ 86 years or older

Q20. Are you …?

- ☐ Male
- ☐ Female

Q21. What is the highest level of education you have completed?

Select the one answer that best applies to you.

- ☐ Primary school education or less
- ☐ Secondary school education (e.g. GCSE/A level, Scottish Standard Grades/Highers)
- ☐ Professional or work-related college qualifications (e.g. Certificate of Higher Education, Diploma of Higher Education, foundation degree)
- ☐ Undergraduate university degree (e.g. BSc/BA)
- ☐ Postgraduate university degree (e.g. MSc/MA, MPhil, PhD)

You have now reached the end of the Patient Questionnaire 1. Please place your completed questionnaire back into the envelope and seal the envelope. Then, follow the instructions for completion of Patient Questionnaire 2.

Xarelto Study
Patient Questionnaire 2

Thank you for agreeing to participate in this study!

Version 0.0

This is the second of two questionnaires. Before you proceed, please make sure you have completed the first questionnaire (found in a separate envelope).

The purpose of the second questionnaire is to learn more about your understanding of important safety information related to Xarelto after reviewing the Xarelto Patient Alert Card.

Before you complete this questionnaire, please read through the attached Xarelto Patient Alert Card as if you just had received it for the first time from your doctor.

After you have read the Xarelto Patient Alert Card, please answer the following questions related to the safety information provided in the card.

Questionnaire Instructions

- **Answer all of the questions by checking the box to the left of your answer**
- **You are sometimes told to skip over some questions in this questionnaire. When this happens, you will see an arrow with a note that tells you what question to answer next; like this:**

☑ Yes ➔ If yes, go to Question 1.
☐ No

Q1. Xarelto is a prescription medicine used to thin the blood to prevent blood clots?

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q2. Blood thinning medications, such as Xarelto, may cause bleeding. (Please remember that this question is asking about your knowledge in general and not about your own experience.)

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q3. Which of the following are possible signs or symptoms of bleeding while taking Xarelto? (Please remember that this question is asking about your knowledge in general and <u>not</u> about your own experience.)

Check the box Yes, No, or I don't know for each of the following items.

	Yes, this **<u>may be</u>** a sign or symptom of bleeding when taking Xarelto	**No**, this is **<u>not</u>** a sign or symptom of bleeding when taking Xarelto	**<u>I don't know</u>** if this is a sign or symptom of bleeding when taking Xarelto
Pain	☐	☐	☐
Swelling or discomfort	☐	☐	☐
Headache, dizziness, or weakness	☐	☐	☐
Unusual bruising	☐	☐	☐

Q4. I must <u>not</u> stop taking Xarelto at any time without consulting with my doctor.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q5. I need to speak to my doctor prior to any intake of other medication(s).

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q6. I need to inform my doctor or dentist about Xarelto intake prior to any kind of surgery or invasive procedure.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q7. I need to tell my doctor right away if I have any signs or symptoms of bleeding while taking Xarelto.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q8. Should Xarelto (15 mg and 20 mg tablets) be taken with food?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q9. What should you do to ensure Xarelto is effective in preventing blood clots?

Select all that apply.

- ☐ Take Xarelto exactly as prescribed by your Health Care Professional
- ☐ Take Xarelto only when you do not feel well
- ☐ Do not miss a dose of Xarelto
- ☐ I don't know

The next section is about the Xarelto Patient Alert Card that you reviewed before completing the second questionnaire. The Xarelto Patient Alert Card contains important safety information about Xarelto.

Q10. Prior to today, had you received or been given the Patient Alert Card for Xarelto?

- ☐ Yes ➔ If yes, go to Question 11
- ☐ No ➔ If no, go to Question 15
- ☐ I don't remember ➔ If I don't remember, go to Question 15

Answer questions 11 to 14 only if you received a Patient Alert Card for Xarelto.

Q11. Prior to today, had you ever read the Patient Alert Card for Xarelto?

- ☐ Yes ➔ If yes, go to Question 13.
- ☐ No ➔ If no, go to Question 12
- ☐ I don't remember ➔ If I don't remember, go to Question 13

Q12. Is there a reason why you have not read the Patient Alert Card for Xarelto, prior to today?

Select all that apply.

- ☐ I haven't taken the medication yet
- ☐ Someone else explained it to me
- ☐ I lost the patient alert card
- ☐ I already knew the information
- ☐ I have not had the time yet
- ☐ I am not interested in reading it
- ☐ Other

Q13. How much of the time do you keep the Xarelto Patient Alert Card with you?

Select the one answer that best applies to you.

- ☐ All the time
- ☐ Some of the time
- ☐ None of the time
- ☐ I don't know

Q14. Who do you show the Patient Alert Card to?

Select the one answer that best applies to you.

- ☐ Every doctor or dentist that I visit
- ☐ No one, it is just for my information
- ☐ Only to healthcare professionals who ask for it
- ☐ I don't know

Q15. Prior to today, had someone explained the information in the Patient Alert Card for Xarelto to you?

Select all that apply.

- ☐ Yes, a doctor
- ☐ Yes, a nurse
- ☐ Yes, a pharmacist or someone at the chemists
- ☐ Yes, a friend, family member, or carer
- ☐ No
- ☐ I don't know

You have now reached the end of the second questionnaire. Thank you again for taking time to take part in this study!

If you have any questions about how to safely take Xarelto or about the potential side effects associated with Xarelto, you should talk with your healthcare professional.

Please place your completed questionnaire back into the envelope and seal the envelope. Then, notify the study coordinator that you are finished.

Annex F. Analysis Tables for Non-recruiting Physicians (Overall and by Country)

Table F-1. Physician and Practice Characteristics by Country and Overall: Non-Recruiting Physicians

Question	No. of Physicians (%)				
	UK n = 305	Germany n = 309	France n = 300	Spain n = 310	Overall N = 1,224
Which of the following best describe your specialty? (Q24)					
General medicine	85 (28%)	176 (57%)	171 (57%)	120 (39%)	552 (45%)
Neurology	22 (7%)	41 (13%)	0	44 (14%)	107 (9%)
Cardiology	69 (23%)	62 (20%)	54 (18%)	56 (18%)	241 (20%)
Haematology	33 (11%)	7 (2%)	16 (5%)	17 (5%)	73 (6%)
Accident & Emergency medicine	9 (3%)	2 (1%)	5 (2%)	23 (7%)	39 (3%)
Oncology	0	4 (1%)	30 (10%)	10 (3%)	44 (4%)
Other	84 (28%)	16 (5%)	24 (8%)	34 (11%)	158 (13%)
No answer	3 (1%)	1 (0%)	0	6 (2%)	10 (1%)
How many years have you been practicing medicine? (Q25)					
5 years or less	3 (1%)	2 (1%)	0	6 (2%)	11 (1%)
6 to 10 years	34 (11%)	14 (5%)	27 (9%)	54 (17%)	129 (11%)
11 to 15 years	73 (24%)	66 (21%)	58 (19%)	80 (26%)	277 (23%)
16 to 20 years	88 (29%)	71 (23%)	55 (18%)	64 (21%)	278 (23%)
21 to 25 years	63 (21%)	91 (29%)	74 (25%)	45 (15%)	273 (22%)
More than 25 years	41 (13%)	64 (21%)	86 (29%)	55 (18%)	246 (20%)
No answer	3 (1%)	1 (0%)	0	6 (2%)	10 (1%)

Question	No. of Physicians (%)				
	UK n = 305	Germany n = 309	France n = 300	Spain n = 310	Overall N = 1,224
Are you...? (Q26)					
Male	236 (77%)	248 (80%)	247 (82%)	180 (58%)	911 (74%)
Female	66 (22%)	60 (19%)	53 (18%)	124 (40%)	303 (25%)
No answer	3 (1%)	1 (0%)	0	6 (2%)	10 (1%)
How would you characterise your practice? (Q27) (Tick all that apply)					
General practice	139 (46%)	236 (76%)	204 (68%)	189 (61%)	768 (63%)
Hospital-based clinic	161 (53%)	80 (26%)	103 (34%)	177 (57%)	521 (43%)
Nursing home	0	5 (2%)	10 (3%)	10 (3%)	25 (2%)
Other	4 (1%)	2 (1%)	0	6 (2%)	12 (1%)
No answer	3 (1%)	1 (0%)	0	6 (2%)	10 (1%)

UK = United Kingdom.

Table F-2. Physician Prescribing Practices by Country and Overall: Non-Recruiting Physicians

Question	No. of Physicians (%)				
	UK n = 305	Germany n = 309	France n = 300	Spain n = 310	Overall N = 1,224
In the past 6 months, for how many patients have you prescribed Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation? (Q1)					
1 to 10	182 (60%)	79 (26%)	164 (55%)	175 (56%)	600 (49%)
11 to 20	64 (21%)	122 (39%)	77 (26%)	77 (25%)	340 (28%)
21 or more	37 (12%)	106 (34%)	46 (15%)	49 (16%)	238 (19%)
I have not prescribed Xarelto for this indication	22 (7%)	2 (1%)	13 (4%)	9 (3%)	46 (4%)
No answer	0	0	0	0	0
In the past 6 months, for how many patients have you prescribed Xarelto for deep vein thrombosis treatment and secondary prevention? (Q2)					
1 to 10	164 (54%)	168 (54%)	189 (63%)	127 (41%)	648 (53%)
11 to 20	35 (11%)	75 (24%)	37 (12%)	45 (15%)	192 (16%)
21 or more	27 (9%)	34 (11%)	33 (11%)	24 (8%)	118 (10%)
I have not prescribed Xarelto for this indication	79 (26%)	32 (10%)	40 (13%)	114 (37%)	265 (22%)
No answer	0	0	1 (0%)	0	1 (0%)
When did you write your most recent prescription for Xarelto for either of these indications? (Q3) (Tick one)					
Less than 1 month ago	211 (69%)	274 (89%)	232 (77%)	205 (66%)	922 (75%)
1 to 3 months ago	75 (25%)	27 (9%)	56 (19%)	78 (25%)	236 (19%)
4 to 6 months ago	13 (4%)	6 (2%)	9 (3%)	23 (7%)	51 (4%)
I don't know	6 (2%)	2 (1%)	3 (1%)	4 (1%)	15 (1%)
No answer	0	0	0	0	0

Question	No. of Physicians (%)				
	UK n = 305	**Germany n = 309**	**France n = 300**	**Spain n = 310**	**Overall N = 1,224**
Which of the following Xarelto treatment activities are you responsible for? (Q4) (Tick all that apply)					
I initiate Xarelto treatment or convert treatment from or to Xarelto	245 (80%)	297 (96%)	239 (80%)	264 (85%)	1045 (85%)
I write follow up (maintenance) prescriptions for Xarelto	195 (64%)	210 (68%)	224 (75%)	148 (48%)	777 (63%)
No answer	0	0	0	0	0

UK = United Kingdom.

Table F-3. Knowledge Questions by Country and Overall: Non-Recruiting Physicians

Question	No. of Physicians (%) (95% CI)				
	UK n = 305	Germany n = 309	France n = 300	Spain n = 310	Overall N = 1,224
What is the most important risk associated with taking Xarelto? (Q5) (Tick one)					
Neoplasia	2 (1%)	3 (1%)	8 (3%)	3 (1%)	16 (1%)
Hypertension	2 (1%)	2 (1%)	3 (1%)	10 (3%)	17 (1%)
Risk of bleeding*	285 (93%) (90%-96%)	292 (94%) (91%-97%)	264 (88%) (84%-91%)	280 (90%) (86%-93%)	1121 (92%) (90%-93%)
Immunosuppression	2 (1%)	2 (1%)	2 (1%)	2 (1%)	8 (1%)
I don't know	14 (5%)	10 (3%)	23 (8%)	15 (5%)	62 (5%)
No answer	0	0	0	0	0
Which of the following populations are at an increased risk of experiencing serious side effect(s) associated with Xarelto? (Q6)					
Patients with moderate or severe renal impairment					
Yes, at higher risk*	222 (73%) (67%-78%)	256 (83%) (78%-87%)	218 (73%) (67%-78%)	238 (77%) (72%-81%)	934 (76%) (74%-79%)
No, not at higher risk	39 (13%)	39 (13%)	64 (21%)	53 (17%)	195 (16%)
I don't know	44 (14%)	13 (4%)	16 (5%)	16 (5%)	89 (7%)
No answer	0	1 (0%)	2 (1%)	3 (1%)	6 (0%)

Question	No. of Physicians (%) (95% CI)				
	UK n = 305	**Germany n = 309**	**France n = 300**	**Spain n = 310**	**Overall N = 1,224**
Patients taking products that affect hemostasis such as NSAIDS, acetylsalicylic acid, platelet aggregation inhibitors					
Yes, at higher risk*	258 (85%) (80%-88%)	276 (89%) (85%-93%)	249 (83%) (78%-87%)	257 (83%) (78%-87%)	1040 (85%) (83%-87%)
No, not at higher risk	19 (6%)	27 (9%)	36 (12%)	40 (13%)	122 (10%)
I don't know	28 (9%)	5 (2%)	13 (4%)	10 (3%)	56 (5%)
No answer	0	1 (0%)	2 (1%)	3 (1%)	6 (0%)
Patients at risk of bleeding					
Yes, at higher risk*	283 (93%) (89%-95%)	287 (93%) (89%-95%)	265 (88%) (84%-92%)	274 (88%) (84%-92%)	1109 (91%) (89%-92%)
No, not at higher risk	12 (4%)	17 (6%)	20 (7%)	29 (9%)	78 (6%)
I don't know	10 (3%)	4 (1%)	12 (4%)	5 (2%)	31 (3%)
No answer	0	1 (0%)	3 (1%)	2 (1%)	6 (0%)
Patients with chronic constipation					
Yes, at higher risk	12 (4%)	15 (5%)	16 (5%)	19 (6%)	62 (5%)
No, not at higher risk*	169 (55%) (50%-61%)	236 (76%) (71%-81%)	185 (62%) (56%-67%)	215 (69%) (64%-74%)	805 (66%) (63%-68%)
I don't know	124 (41%)	57 (18%)	96 (32%)	74 (24%)	351 (29%)
No answer	0	1 (0%)	3 (1%)	2 (1%)	6 (0%)

Question	No. of Physicians (%) (95% CI)				
	UK n = 305	**Germany n = 309**	**France n = 300**	**Spain n = 310**	**Overall N = 1,224**
To which patient groups is Xarelto contraindicated? (Q7) (Tick all that apply)					
Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child-Pugh class B and C*	215 (70%)	271 (88%)	247 (82%)	250 (81%)	983 (80%)
Patients who are pregnant or breastfeeding*	243 (80%)	270 (87%)	249 (83%)	252 (81%)	1014 (83%)
Patients receiving concomitant treatment with any other anticoagulant such as unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives or oral anticoagulants except when switching therapy to or from Xarelto or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter*	202 (66%)	225 (73%)	227 (76%)	208 (67%)	862 (70%)
Patients with clinically significant active bleeding*	275 (90%)	294 (95%)	261 (87%)	277 (89%)	1107 (90%)
I don't know	18 (6%)	4 (1%)	10 (3%)	8 (3%)	40 (3%)
No answer	0	1 (0%)	0	2 (1%)	3 (0%)
Selected all four of the correct responses	159 (52%) (46%-58%)	192 (62%) (56%-68%)	175 (58%) (53%-64%)	177 (57%) (51%-63%)	703 (57%) (55%-60%)
Selected at least three of the four correct responses	225 (74%) (68%-79%)	268 (87%) (82%-90%)	248 (83%) (78%-87%)	237 (76%) (71%-81%)	978 (80%) (78%-82%)
Selected at least two of the four correct responses	264 (87%) (82%-90%)	296 (96%) (93%-98%)	271 (90%) (86%-93%)	273 (88%) (84%-91%)	1104 (90%) (88%-92%)
Selected at least one of the four correct responses	287 (94%) (91%-96%)	304 (98%) (96%-99%)	290 (97%) (94%-98%)	300 (97%) (94%-98%)	1181 (96%) (95%-97%)

Question	No. of Physicians (%) (95% CI)				
	UK n = 305	**Germany n = 309**	**France n = 300**	**Spain n = 310**	**Overall N = 1,224**
Xarelto (15 or 20 mg) must be taken….? (Q8) (Tick one)					
On an empty stomach	35 (11%)	64 (21%)	41 (14%)	69 (22%)	209 (17%)
With food on a full stomach*	140 (46%) (40%-52%)	192 (62%) (56%-68%)	198 (66%) (60%-71%)	187 (60%) (55%-66%)	717 (59%) (56%-61%)
I don't know	129 (42%)	52 (17%)	61 (20%)	52 (17%)	294 (24%)
No answer	1 (0%)	1 (0%)	0	2 (1%)	4 (0%)
Is routine coagulation monitoring required for patients taking Xarelto for these indications? (Q9)					
Yes	4 (1%)	12 (4%)	12 (4%)	13 (4%)	41 (3%)
No*	298 (98%) (95%-99%)	294 (95%) (92%-97%)	281 (94%) (90%-96%)	290 (94%) (90%-96%)	1163 (95%) (94%-96%)
I don't know	2 (1%)	1 (0%)	6 (2%)	4 (1%)	13 (1%)
No answer	1 (0%)	2 (1%)	1 (0%)	3 (1%)	7 (1%)
In which of the following situations is INR monitoring needed? (Q10) (Tick all that apply)					
When converting from vitamin K antagonist (VKA) (e.g., warfarin) to Xarelto*	163 (53%)	213 (69%)	158 (53%)	158 (51%)	692 (57%)
When converting from Xarelto to VKA*	220 (72%)	238 (77%)	252 (84%)	209 (67%)	919 (75%)
Continual INR monitoring is required for all patients taking Xarelto	4 (1%)	12 (4%)	11 (4%)	10 (3%)	37 (3%)
I don’t know	21 (7%)	6 (2%)	4 (1%)	9 (3%)	40 (3%)
No answer	1 (0%)	1 (0%)	0	2 (1%)	4 (0%)

Question	No. of Physicians (%) (95% CI)				
	UK n = 305	**Germany n = 309**	**France n = 300**	**Spain n = 310**	**Overall N = 1,224**
Selected both of the correct responses	102 (33%) (28%-39%)	157 (51%) (45%-57%)	119 (40%) (34%-45%)	75 (24%) (20%-29%)	453 (37%) (34%-40%)
Selected at least one of the two correct responses	281 (92%) (89%-95%)	294 (95%) (92%-97%)	291 (97%) (94%-99%)	292 (94%) (91%-97%)	1158 (95%) (93%-96%)
Which of the following steps should be taken when converting patients from VKA (e.g., warfarin) to Xarelto? (Q11) (Tick all that apply)					
Stop VKA without measuring INR	30 (10%)	43 (14%)	66 (22%)	39 (13%)	178 (15%)
For patients treated for prevention of stroke and systemic embolism, stop VKA and initiate Xarelto when INR is ≤ 3*	141 (46%)	148 (48%)	153 (51%)	182 (59%)	624 (51%)
For patients treated for deep vein thrombosis and secondary prevention, stop VKA and initiate Xarelto when INR is ≤ 2.5*	169 (55%)	231 (75%)	186 (62%)	172 (55%)	758 (62%)
I don't know	65 (21%)	17 (6%)	25 (8%)	25 (8%)	132 (11%)
No answer	1 (0%)	1 (0%)	0	3 (1%)	5 (0%)
Selected both of the correct responses	92 (30%) (25%-36%)	120 (39%) (33%-45%)	109 (36%) (31%-42%)	103 (33%) (28%-39%)	424 (35%) (32%-37%)
Selected at least one of the two correct responses	218 (71%) (66%-76%)	259 (84%) (79%-88%)	230 (77%) (71%-81%)	251 (81%) (76%-85%)	958 (78%) (76%-81%)
Which of the following steps should be taken when converting patients from Xarelto to VKA (e.g., warfarin)? (Q12) (Tick all that apply)					
Overlap the two drugs until INR is ≥ 2.0*	183 (60%)	190 (61%)	218 (73%)	177 (57%)	768 (63%)
Measure INR but make sure it has been longer than 24 hours since the last dose of Xarelto*	66 (22%)	129 (42%)	83 (28%)	92 (30%)	370 (30%)

Question	No. of Physicians (%) (95% CI)				
	UK n = 305	**Germany n = 309**	**France n = 300**	**Spain n = 310**	**Overall N = 1,224**
Stop Xarelto at any time	13 (4%)	30 (10%)	18 (6%)	34 (11%)	95 (8%)
Measure INR at any time of the day	8 (3%)	22 (7%)	8 (3%)	5 (2%)	43 (4%)
I don't know	71 (23%)	16 (5%)	26 (9%)	28 (9%)	141 (12%)
No answer	2 (1%)	1 (0%)	0	3 (1%)	6 (0%)
Selected both of the correct responses	27 (9%) (6%-13%)	49 (16%) (12%-20%)	43 (14%) (11%-19%)	21 (7%) (4%-10%)	140 (11%) (10%-13%)
Selected at least one of the two correct responses	222 (73%) (67%-78%)	270 (87%) (83%-91%)	258 (86%) (82%-90%)	248 (80%) (75%-84%)	998 (82%) (79%-84%)
Which of the following are true when converting from parenteral anticoagulants to Xarelto…? (Q13) (Tick all that apply)					
Stop parenteral anticoagulants for a week prior to starting Xarelto	5 (2%)	6 (2%)	6 (2%)	6 (2%)	23 (2%)
For patients with continuously administered parenteral anticoagulants such as intravenous unfractionated heparin, Xarelto should be started at time of drug discontinuation*	112 (37%)	174 (56%)	151 (50%)	146 (47%)	583 (48%)
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*	147 (48%)	176 (57%)	166 (55%)	174 (56%)	663 (54%)
I don't know	108 (35%)	34 (11%)	60 (20%)	58 (19%)	260 (21%)
No answer	2 (1%)	1 (0%)	1 (0%)	4 (1%)	8 (1%)
Selected both of the correct responses	67 (22%) (17%-27%)	80 (26%) (21%-31%)	82 (27%) (22%-33%)	75 (24%) (20%-29%)	304 (25%) (22%-27%)

Question	No. of Physicians (%) (95% CI)				
	UK n = 305	**Germany n = 309**	**France n = 300**	**Spain n = 310**	**Overall N = 1,224**
Selected at least one of the two correct responses	192 (63%) (57%-68%)	270 (87%) (83%-91%)	235 (78%) (73%-83%)	245 (79%) (74%-83%)	942 (77%) (74%-79%)
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)? (Q14) (Tick one)					
One week prior to the procedure or surgical intervention	32 (10%)	15 (5%)	54 (18%)	21 (7%)	122 (10%)
At least 24 hours prior to the procedure or surgical intervention*	214 (70%) (65%-75%)	273 (88%) (84%-92%)	204 (68%) (62%-73%)	243 (78%) (73%-83%)	934 (76%) (74%-79%)
It is not necessary to stop Xarelto for these procedures	7 (2%)	16 (5%)	22 (7%)	19 (6%)	64 (5%)
I don't know	50 (16%)	4 (1%)	20 (7%)	23 (7%)	97 (8%)
No answer	2 (1%)	1 (0%)	0	4 (1%)	7 (1%)
What are the most appropriate actions you should take if a patient taking Xarelto presents with a medically important bleeding complication? (Q15) (Tick all that apply)					
Provide symptomatic treatment (e.g., mechanical compression, surgery)*	242 (79%)	253 (82%)	211 (70%)	207 (67%)	913 (75%)
Delay the next administration of Xarelto or discontinue Xarelto as appropriate*	233 (76%)	257 (83%)	211 (70%)	209 (67%)	910 (74%)
Provide hemodynamic support (e.g., blood transfusion)*	228 (75%)	206 (67%)	183 (61%)	218 (70%)	835 (68%)
Administer procoagulant reversal agent (for life-threatening bleeding)*	159 (52%)	203 (66%)	122 (41%)	174 (56%)	658 (54%)
Refer the patient to emergency care*	241 (79%)	236 (76%)	231 (77%)	208 (67%)	916 (75%)
None of the above	0	2 (1%)	3 (1%)	3 (1%)	8 (1%)
I don't know	12 (4%)	2 (1%)	6 (2%)	5 (2%)	25 (2%)

Question	No. of Physicians (%) (95% CI)				
	UK n = 305	**Germany n = 309**	**France n = 300**	**Spain n = 310**	**Overall N = 1,224**
No answer	2 (1%)	1 (0%)	0	4 (1%)	7 (1%)
Selected all five of the correct responses	113 (37%) (32%-43%)	137 (44%) (39%-50%)	85 (28%) (23%-34%)	115 (37%) (32%-43%)	450 (37%) (34%-40%)
Selected at least four of the five correct responses	208 (68%) (63%-73%)	206 (67%) (61%-72%)	150 (50%) (44%-56%)	167 (54%) (48%-60%)	731 (60%) (57%-62%)
Selected at least three of the five correct responses	238 (78%) (73%-83%)	242 (78%) (73%-83%)	198 (66%) (60%-71%)	203 (65%) (60%-71%)	881 (72%) (69%-74%)
Selected at least two of the five correct responses	253 (83%) (78%-87%)	266 (86%) (82%-90%)	234 (78%) (73%-83%)	233 (75%) (70%-80%)	986 (81%) (78%-83%)
Selected at least one of the five correct responses	291 (95%) (92%-97%)	304 (98%) (96%-99%)	291 (97%) (94%-99%)	298 (96%) (93%-98%)	1184 (97%) (96%-98%)
What is the standard recommended dose of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation? (Q16) (Tick one)					
20 mg taken once a day*	213 (75%) (70%-80%)	242 (79%) (74%-83%)	176 (61%) (55%-67%)	208 (69%) (64%-74%)	839 (71%) (69%-74%)
15 mg taken once a day	33 (12%)	37 (12%)	60 (21%)	41 (14%)	171 (15%)
10 mg taken once a day	12 (4%)	20 (7%)	39 (14%)	40 (13%)	111 (9%)
None of the above	1 (0%)	4 (1%)	3 (1%)	4 (1%)	12 (1%)
I don't know	21 (7%)	3 (1%)	9 (3%)	4 (1%)	37 (3%)
No answer	3 (1%)	1 (0%)	0	4 (1%)	8 (1%)
Not applicable skip pattern - Q1 (Have not prescribed Xarelto for this indication)	22	2	13	9	46

Question	No. of Physicians (%) (95% CI) UK n = 305	Germany n = 309	France n = 300	Spain n = 310	Overall N = 1,224
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? (Q17) (Tick one)					
20 mg taken once a day	7 (2%)	10 (3%)	26 (9%)	16 (5%)	59 (5%)
15 mg taken once a day*	171 (60%) (54%-66%)	193 (63%) (57%-68%)	127 (44%) (38%-50%)	165 (55%) (49%-61%)	656 (56%) (53%-59%)
10 mg taken once a day	63 (22%)	80 (26%)	89 (31%)	89 (30%)	321 (27%)
None of the above	8 (3%)	18 (6%)	26 (9%)	20 (7%)	72 (6%)
I don't know	31 (11%)	5 (2%)	18 (6%)	5 (2%)	59 (5%)
No answer	3 (1%)	1 (0%)	1 (0%)	6 (2%)	11 (1%)
Not applicable skip pattern - Q1 (Have not prescribed Xarelto for this indication)	22	2	13	9	46
What is the standard recommended dose for patients receiving Xarelto for deep vein thrombosis treatment and secondary prevention? (Q18) (Tick one)					
20 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day	34 (15%)	67 (24%)	44 (17%)	42 (21%)	187 (19%)
15 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day*	151 (67%) (60%-73%)	175 (63%) (57%-69%)	159 (61%) (55%-67%)	97 (49%) (42%-57%)	582 (61%) (58%-64%)
10 mg once a day	14 (6%)	24 (9%)	41 (16%)	40 (20%)	119 (12%)
None of the above	1 (0%)	5 (2%)	3 (1%)	2 (1%)	11 (1%)
I don't know	25 (11%)	5 (2%)	13 (5%)	10 (5%)	53 (6%)
No answer	1 (0%)	1 (0%)	0	5 (3%)	7 (1%)

Question	No. of Physicians (%) (95% CI)				
	UK n = 305	Germany n = 309	France n = 300	Spain n = 310	Overall N = 1,224
Not applicable skip pattern - Q2 (Have not prescribed Xarelto for this indication)	79	32	40	114	265

CI = confidence interval; UK = United Kingdom.

Note 1: For each question the percentages reported for the response items were calculated using a denominator of the number of physicians who faced the question; thus physicians who did not face a question because of the skip pattern were not included in the denominator for that question.

Note 2: Exact 95% Confidence Intervals were computed using the Clopper-Pearson method for the proportion of correct responses for select questionnaire items.

Table F-4. Sources of Information About Xarelto by Country and Overall: Non-Recruiting Physicians

Question	No. of Physicians (%)				
	UK n = 305	Germany n = 309	France n = 300	Spain n = 310	Overall N = 1,224
From which of the following sources did you receive information about Xarelto? (Q19) (Tick all that apply)					
Xarelto Prescriber Guide	114 (37%)	171 (55%)	191 (64%)	207 (67%)	683 (56%)
Briefing from a company representative	167 (55%)	223 (72%)	204 (68%)	194 (63%)	788 (64%)
Discussion with a clinical expert	61 (20%)	91 (29%)	54 (18%)	94 (30%)	300 (25%)
The Summary of Product Characteristics for Xarelto	133 (44%)	235 (76%)	145 (48%)	145 (47%)	658 (54%)
Clinical trials published in the medical literature	84 (28%)	154 (50%)	66 (22%)	126 (41%)	430 (35%)
Other	49 (16%)	21 (7%)	10 (3%)	21 (7%)	101 (8%)
None of the above	22 (7%)	3 (1%)	10 (3%)	5 (2%)	40 (3%)
No answer	3 (1%)	1 (0%)	0	6 (2%)	10 (1%)

UK = United Kingdom.

Table F-5. Ratings of Sources of Information About Xarelto by Country and Overall: Non-Recruiting Physicians

Question	No. of Physicians (%)				
	UK n = 305	Germany n = 309	France n = 300	Spain n = 310	Overall N = 1,224
How helpful were these sources to you in treating and educating your patients? (Q20)					
Xarelto Prescriber Guide					
Not at all helpful	1 (1%)	1 (1%)	2 (1%)	0	4 (1%)
2	1 (1%)	4 (2%)	4 (2%)	5 (2%)	14 (2%)
3	17 (15%)	18 (11%)	36 (19%)	42 (20%)	113 (17%)
4	60 (53%)	74 (43%)	77 (40%)	98 (47%)	309 (45%)
Extremely helpful	35 (31%)	74 (43%)	72 (38%)	62 (30%)	243 (36%)
Not applicable skip pattern (Q19 item was not ticked)	191	138	109	103	541
Briefing from a company representative					
Not at all helpful	0	1 (0%)	4 (2%)	0	5 (1%)
2	6 (4%)	6 (3%)	9 (4%)	10 (5%)	31 (4%)
3	37 (22%)	35 (16%)	40 (20%)	57 (29%)	169 (21%)
4	103 (62%)	101 (45%)	95 (47%)	90 (46%)	389 (49%)
Extremely helpful	21 (13%)	80 (36%)	56 (27%)	37 (19%)	194 (25%)
Not applicable skip pattern (Q19 item was not ticked)	138	86	96	116	436

Question	No. of Physicians (%)				
	UK n = 305	**Germany n = 309**	**France n = 300**	**Spain n = 310**	**Overall N = 1,224**
Discussion with a clinical expert					
Not at all helpful	0	1 (1%)	0	0	1 (0%)
2	1 (2%)	2 (2%)	1 (2%)	1 (1%)	5 (2%)
3	10 (16%)	5 (5%)	5 (9%)	13 (14%)	33 (11%)
4	35 (57%)	43 (47%)	26 (48%)	46 (49%)	150 (50%)
Extremely helpful	15 (25%)	40 (44%)	22 (41%)	34 (36%)	111 (37%)
Not applicable skip pattern (Q19 item was not ticked)	244	218	246	216	924
Summary of Product Characteristics					
Not at all helpful	0	0	0	0	0
2	1 (1%)	6 (3%)	8 (6%)	5 (3%)	20 (3%)
3	27 (20%)	34 (14%)	32 (22%)	41 (28%)	134 (20%)
4	74 (56%)	100 (43%)	69 (48%)	67 (46%)	310 (47%)
Extremely helpful	31 (23%)	95 (40%)	36 (25%)	32 (22%)	194 (29%)
Not applicable skip pattern (Q19 item was not ticked)	172	74	155	165	566
Medical Publications					
Not at all helpful	0	0	0	0	0
2	2 (2%)	1 (1%)	3 (5%)	2 (2%)	8 (2%)
3	15 (18%)	25 (16%)	7 (11%)	18 (14%)	65 (15%)
4	48 (57%)	67 (44%)	29 (44%)	60 (48%)	204 (47%)
Extremely helpful	19 (23%)	61 (40%)	27 (41%)	46 (37%)	153 (36%)
Not applicable skip pattern (Q19 item was not ticked)	221	155	234	184	794

Question	No. of Physicians (%)				
	UK n = 305	**Germany n = 309**	**France n = 300**	**Spain n = 310**	**Overall N = 1,224**
Other					
Not at all helpful	1 (2%)	0	0	0	1 (1%)
2	3 (6%)	2 (10%)	1 (10%)	1 (5%)	7 (7%)
3	19 (39%)	6 (29%)	1 (10%)	4 (19%)	30 (30%)
4	21 (43%)	4 (19%)	3 (30%)	10 (48%)	38 (38%)
Extremely helpful	5 (10%)	9 (43%)	5 (50%)	6 (29%)	25 (25%)
Not applicable skip pattern (Q19 item was not ticked)	256	288	290	289	1123

UK = United Kingdom.

Table F-6. Physician's Experiences with Patient Alert Cards by Country and Overall: Non-Recruiting Physicians

Question	No. of Physicians (%)				
	UK n = 305	Germany n = 309	France n = 300	Spain n = 310	Overall N = 1,224
Have you received Xarelto Patient Alert Cards to provide to your patients? (Q21)					
Yes	89 (29%)	246 (80%)	119 (40%)	127 (41%)	581 (47%)
No	213 (70%)	62 (20%)	181 (60%)	176 (57%)	632 (52%)
No answer	3 (1%)	1 (0%)	0	7 (2%)	11 (1%)
Considering the Xarelto patients under your care, to how many did you provide a Patient Alert Card? (Q22)					
Every one of my patients	41 (45%)	131 (53%)	38 (32%)	38 (28%)	248 (42%)
Most of my patients	36 (39%)	80 (32%)	42 (35%)	59 (44%)	217 (37%)
A few of my patients	7 (8%)	32 (13%)	30 (25%)	25 (19%)	94 (16%)
None of my patients	5 (5%)	3 (1%)	9 (8%)	6 (4%)	23 (4%)
No answer	3 (3%)	1 (0%)	0	6 (4%)	10 (2%)
Not applicable skip pattern (Q21 was "No")	213	62	181	176	632

Question	No. of Physicians (%)				
	UK n = 305	**Germany n = 309**	**France n = 300**	**Spain n = 310**	**Overall N = 1,224**
When would you discuss the information on the Patient Alert Card with your patients taking Xarelto? (Q23) (Tick all that apply)					
When first prescribing Xarelto	85 (92%)	235 (95%)	100 (84%)	112 (84%)	532 (90%)
When a patient is facing an invasive procedure or surgical intervention	26 (28%)	72 (29%)	32 (27%)	39 (29%)	169 (29%)
When a patient has bleeding complications	19 (21%)	56 (23%)	18 (15%)	29 (22%)	122 (21%)
When a patient has a Xarelto related adverse event	21 (23%)	52 (21%)	24 (20%)	27 (20%)	124 (21%)
I do not use the Patient Alert Card	2 (2%)	4 (2%)	10 (8%)	5 (4%)	21 (4%)
Other	0	2 (1%)	3 (3%)	0	5 (1%)
No answer	3 (3%)	1 (0%)	0	6 (4%)	10 (2%)
Not applicable skip pattern (Q21 was "No")	213	62	181	176	632

UK = United Kingdom.

Note 1: For each question the percentages reported for the response items were calculated using a denominator of the number of physicians who faced the question; thus physicians who did not face a question because of the skip pattern were not included in the denominator for that question.

Annex G. Analysis Tables for Non-recruiting Physicians (Other Stratification Variables)

Table G-1. Knowledge Questions by Specialty: Non-Recruiting Physicians

Question	No. of Physicians (%)						
	General Medicine n = 552	Neurology n = 107	Cardiology n = 241	Haematology n = 73	Accident & Emergency Medicine n = 39	Oncology n = 44	Other N = 158
What is the most important risk associated with taking Xarelto? (Q5) (Tick one)							
Neoplasia	8 (1%)	0	1 (0%)	0	0	6 (14%)	1 (1%)
Hypertension	7 (1%)	0	5 (2%)	1 (1%)	1 (3%)	1 (2%)	2 (1%)
Risk of bleeding*	490 (89%)	104 (97%)	232 (96%)	70 (96%)	35 (90%)	34 (77%)	146 (92%)
Immunosuppression	5 (1%)	0	1 (0%)	1 (1%)	0	0	1 (1%)
I don't know	42 (8%)	3 (3%)	2 (1%)	1 (1%)	3 (8%)	3 (7%)	8 (5%)
No answer	0	0	0	0	0	0	0
Which of the following populations are at an increased risk of experiencing serious side effect(s) associated with Xarelto? (Q6)							
Patients with moderate or severe renal impairment							
Yes, at higher risk*	401 (73%)	84 (79%)	218 (90%)	57 (78%)	30 (77%)	22 (50%)	116 (73%)
No, not at higher risk	98 (18%)	16 (15%)	20 (8%)	15 (21%)	5 (13%)	19 (43%)	22 (14%)
I don't know	50 (9%)	7 (7%)	3 (1%)	1 (1%)	4 (10%)	3 (7%)	20 (13%)
No answer	3 (1%)	0	0	0	0	0	0

Question	No. of Physicians (%)						
	General Medicine n = 552	Neurology n = 107	Cardiology n = 241	Haematology n = 73	Accident & Emergency Medicine n = 39	Oncology n = 44	Other N = 158
Patients taking products that affect hemostasis such as NSAIDS, acetylsalicylic acid, platelet aggregation inhibitors							
Yes, at higher risk*	466 (84%)	99 (93%)	220 (91%)	69 (95%)	30 (77%)	34 (77%)	118 (75%)
No, not at higher risk	61 (11%)	7 (7%)	19 (8%)	3 (4%)	7 (18%)	9 (20%)	15 (9%)
I don't know	22 (4%)	1 (1%)	2 (1%)	1 (1%)	2 (5%)	1 (2%)	25 (16%)
No answer	3 (1%)	0	0	0	0	0	0
Patients at risk of bleeding							
Yes, at higher risk*	490 (89%)	102 (95%)	229 (95%)	68 (93%)	33 (85%)	38 (86%)	143 (91%)
No, not at higher risk	44 (8%)	3 (3%)	10 (4%)	4 (5%)	4 (10%)	4 (9%)	8 (5%)
I don't know	15 (3%)	2 (2%)	2 (1%)	1 (1%)	2 (5%)	2 (5%)	7 (4%)
No answer	3 (1%)	0	0	0	0	0	0
Patients with chronic constipation							
Yes, at higher risk	28 (5%)	3 (3%)	18 (7%)	5 (7%)	1 (3%)	4 (9%)	3 (2%)
No, not at higher risk*	352 (64%)	81 (76%)	172 (71%)	48 (66%)	29 (74%)	25 (57%)	92 (58%)
I don't know	169 (31%)	23 (21%)	51 (21%)	20 (27%)	9 (23%)	15 (34%)	63 (40%)

Question	No. of Physicians (%)						
	General Medicine n = 552	Neurology n = 107	Cardiology n = 241	Haematology n = 73	Accident & Emergency Medicine n = 39	Oncology n = 44	Other N = 158
No answer	3 (1%)	0	0	0	0	0	0
To which patient groups is Xarelto contraindicated? (Q7) (Tick all that apply)							
Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child-Pugh class B and C*	440 (80%)	87 (81%)	206 (85%)	66 (90%)	34 (87%)	35 (80%)	109 (69%)
Patients who are pregnant or breastfeeding*	455 (82%)	86 (80%)	212 (88%)	66 (90%)	29 (74%)	31 (70%)	130 (82%)
Patients receiving concomitant treatment with any other anticoagulant such as unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives or oral anticoagulants except when switching therapy to or from Xarelto or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter*	357 (65%)	90 (84%)	192 (80%)	59 (81%)	25 (64%)	29 (66%)	104 (66%)
Patients with clinically significant active bleeding*	491 (89%)	101 (94%)	228 (95%)	68 (93%)	36 (92%)	36 (82%)	142 (90%)
I don't know	22 (4%)	3 (3%)	3 (1%)	0	1 (3%)	4 (9%)	7 (4%)
No answer	0	0	0	0	0	0	0
Selected all four of the correct responses	288 (52%)	75 (70%)	164 (68%)	53 (73%)	19 (49%)	21 (48%)	79 (50%)

Question	No. of Physicians (%)						
	General Medicine n = 552	Neurology n = 107	Cardiology n = 241	Haematology n = 73	Accident & Emergency Medicine n = 39	Oncology n = 44	Other N = 158
Selected at least three of the four correct responses	431 (78%)	90 (84%)	209 (87%)	64 (88%)	29 (74%)	34 (77%)	116 (73%)
Selected at least two of the four correct responses	494 (89%)	95 (89%)	227 (94%)	69 (95%)	38 (97%)	36 (82%)	139 (88%)
Selected at least one of the four correct responses	530 (96%)	104 (97%)	238 (99%)	73 (100%)	38 (97%)	40 (91%)	151 (96%)
Xarelto (15 or 20 mg) must be taken….? (Q8) (Tick one)							
On an empty stomach	114 (21%)	14 (13%)	27 (11%)	13 (18%)	8 (21%)	10 (23%)	22 (14%)
With food on a full stomach*	294 (53%)	70 (65%)	171 (71%)	48 (66%)	25 (64%)	28 (64%)	78 (49%)
I don't know	144 (26%)	23 (21%)	43 (18%)	12 (16%)	6 (15%)	6 (14%)	58 (37%)
No answer	0	0	0	0	0	0	0
Is routine coagulation monitoring required for patients taking Xarelto for these indications? (Q9)							
Yes	20 (4%)	3 (3%)	6 (2%)	3 (4%)	1 (3%)	6 (14%)	2 (1%)
No*	525 (95%)	99 (93%)	235 (98%)	70 (96%)	37 (95%)	35 (80%)	156 (99%)
I don't know	6 (1%)	4 (4%)	0	0	0	3 (7%)	0
No answer	1 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (3%)	0	0 (0%)

Question	No. of Physicians (%)						
	General Medicine n = 552	Neurology n = 107	Cardiology n = 241	Haematology n = 73	Accident & Emergency Medicine n = 39	Oncology n = 44	Other N = 158
In which of the following situations is INR monitoring needed? (Q10) (Tick all that apply)							
When converting from vitamin K antagonist (VKA) (e.g., warfarin) to Xarelto*	282 (51%)	70 (65%)	172 (71%)	51 (70%)	16 (41%)	21 (48%)	75 (47%)
When converting from Xarelto to VKA*	426 (77%)	75 (70%)	176 (73%)	59 (81%)	33 (85%)	30 (68%)	117 (74%)
Continual INR monitoring is required for all patients taking Xarelto	18 (3%)	4 (4%)	6 (2%)	1 (1%)	3 (8%)	3 (7%)	2 (1%)
I don't know	18 (3%)	4 (4%)	5 (2%)	1 (1%)	0	3 (7%)	9 (6%)
No answer	0	0	0	0	0	0	0
Selected both of the correct responses	186 (34%)	45 (42%)	114 (47%)	38 (52%)	12 (31%)	12 (27%)	44 (28%)
Selected at least one of the two correct responses	522 (95%)	100 (93%)	234 (97%)	72 (99%)	37 (95%)	39 (89%)	148 (94%)
Which of the following steps should be taken when converting patients from VKA (e.g., warfarin) to Xarelto? (Q11) (Tick all that apply)							
Stop VKA without measuring INR	90 (16%)	10 (9%)	31 (13%)	9 (12%)	7 (18%)	10 (23%)	19 (12%)
For patients treated for prevention of stroke and systemic embolism, stop VKA and initiate Xarelto when INR is ≤ 3*	273 (49%)	69 (64%)	131 (54%)	47 (64%)	21 (54%)	22 (50%)	60 (38%)

Question	No. of Physicians (%)						
	General Medicine n = 552	Neurology n = 107	Cardiology n = 241	Haematology n = 73	Accident & Emergency Medicine n = 39	Oncology n = 44	Other N = 158
For patients treated for deep vein thrombosis and secondary prevention, stop VKA and initiate Xarelto when INR is ≤ 2.5*	344 (62%)	55 (51%)	170 (71%)	57 (78%)	22 (56%)	19 (43%)	88 (56%)
I don't know	58 (11%)	14 (13%)	14 (6%)	2 (3%)	4 (10%)	4 (9%)	35 (22%)
No answer	0	0	0	0	0	0	0
Selected both of the correct responses	191 (35%)	39 (36%)	95 (39%)	37 (51%)	12 (31%)	9 (20%)	40 (25%)
Selected at least one of the two correct responses	426 (77%)	85 (79%)	206 (85%)	67 (92%)	31 (79%)	32 (73%)	108 (68%)
Which of the following steps should be taken when converting patients from Xarelto to VKA (e.g., warfarin)? (Q12) (Tick all that apply)							
Overlap the two drugs until INR is ≥ 2.0*	335 (61%)	66 (62%)	163 (68%)	57 (78%)	26 (67%)	27 (61%)	90 (57%)
Measure INR but make sure it has been longer than 24 hours since the last dose of Xarelto*	176 (32%)	31 (29%)	69 (29%)	27 (37%)	13 (33%)	21 (48%)	33 (21%)
Stop Xarelto at any time	53 (10%)	9 (8%)	19 (8%)	3 (4%)	2 (5%)	5 (11%)	4 (3%)
Measure INR at any time of the day	23 (4%)	5 (5%)	9 (4%)	1 (1%)	0	1 (2%)	4 (3%)
I don't know	65 (12%)	10 (9%)	13 (5%)	4 (5%)	3 (8%)	3 (7%)	43 (27%)
No answer	0	0	0	0	0	0	0

Question	No. of Physicians (%)						
	General Medicine n = 552	**Neurology n = 107**	**Cardiology n = 241**	**Haematology n = 73**	**Accident & Emergency Medicine n = 39**	**Oncology n = 44**	**Other N = 158**
Selected both of the correct responses	63 (11%)	8 (7%)	25 (10%)	16 (22%)	5 (13%)	10 (23%)	13 (8%)
Selected at least one of the two correct responses	448 (81%)	89 (83%)	207 (86%)	68 (93%)	34 (87%)	38 (86%)	110 (70%)
Which of the following are true when converting from parenteral anticoagulants to Xarelto…? (Q13) (Tick all that apply)							
Stop parenteral anticoagulants for a week prior to starting Xarelto	9 (2%)	5 (5%)	3 (1%)	3 (4%)	0	1 (2%)	2 (1%)
For patients with continuously administered parenteral anticoagulants such as intravenous unfractionated heparin, Xarelto should be started at time of drug discontinuation*	252 (46%)	60 (56%)	139 (58%)	40 (55%)	13 (33%)	21 (48%)	57 (36%)
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*	271 (49%)	57 (53%)	158 (66%)	63 (86%)	21 (54%)	22 (50%)	70 (44%)
I don't know	136 (25%)	16 (15%)	19 (8%)	2 (3%)	12 (31%)	13 (30%)	60 (38%)
No answer	1 (0%)	0	0	0	0	0	0
Selected both of the correct responses	113 (20%)	29 (27%)	77 (32%)	34 (47%)	7 (18%)	12 (27%)	31 (20%)
Selected at least one of the two correct responses	410 (74%)	88 (82%)	220 (91%)	69 (95%)	27 (69%)	31 (70%)	96 (61%)

Question	No. of Physicians (%)						
	General Medicine n = 552	Neurology n = 107	Cardiology n = 241	Haematology n = 73	Accident & Emergency Medicine n = 39	Oncology n = 44	Other N = 158
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)? (Q14) (Tick one)							
One week prior to the procedure or surgical intervention	63 (11%)	8 (7%)	12 (5%)	4 (5%)	7 (18%)	9 (20%)	19 (12%)
At least 24 hours prior to the procedure or surgical intervention*	402 (73%)	86 (80%)	218 (90%)	67 (92%)	29 (74%)	31 (70%)	99 (63%)
It is not necessary to stop Xarelto for these procedures	44 (8%)	4 (4%)	7 (3%)	2 (3%)	1 (3%)	1 (2%)	5 (3%)
I don't know	43 (8%)	9 (8%)	4 (2%)	0	2 (5%)	3 (7%)	35 (22%)
No answer	0	0	0	0	0	0	0
What are the most appropriate actions you should take if a patient taking Xarelto presents with a medically important bleeding complication? (Q15) (Tick all that apply)							
Provide symptomatic treatment (e.g., mechanical compression, surgery)*	386 (70%)	85 (79%)	214 (89%)	61 (84%)	24 (62%)	24 (55%)	117 (74%)
Delay the next administration of Xarelto or discontinue Xarelto as appropriate*	369 (67%)	93 (87%)	211 (88%)	67 (92%)	20 (51%)	29 (66%)	119 (75%)
Provide hemodynamic support (e.g., blood transfusion)*	325 (59%)	82 (77%)	201 (83%)	64 (88%)	29 (74%)	27 (61%)	105 (66%)
Administer procoagulant reversal agent (for life-threatening bleeding)*	248 (45%)	70 (65%)	166 (69%)	57 (78%)	22 (56%)	18 (41%)	76 (48%)

Question	No. of Physicians (%)						
	General Medicine n = 552	Neurology n = 107	Cardiology n = 241	Haematology n = 73	Accident & Emergency Medicine n = 39	Oncology n = 44	Other N = 158
Refer the patient to emergency care*	433 (78%)	79 (74%)	166 (69%)	56 (77%)	30 (77%)	25 (57%)	125 (79%)
None of the above	3 (1%)	1 (1%)	1 (0%)	0	0	2 (5%)	1 (1%)
I don't know	7 (1%)	1 (1%)	6 (2%)	0	1 (3%)	4 (9%)	5 (3%)
No answer	0	0	0	0	0	0	0
Selected all five of the correct responses	148 (27%)	53 (50%)	122 (51%)	44 (60%)	13 (33%)	14 (32%)	55 (35%)
Selected at least four of the five correct responses	279 (51%)	72 (67%)	185 (77%)	56 (77%)	22 (56%)	17 (39%)	98 (62%)
Selected at least three of the five correct responses	363 (66%)	85 (79%)	204 (85%)	65 (89%)	25 (64%)	25 (57%)	112 (71%)
Selected at least two of the five correct responses	429 (78%)	94 (88%)	213 (88%)	67 (92%)	27 (69%)	29 (66%)	125 (79%)
Selected at least one of the five correct responses	542 (98%)	105 (98%)	234 (97%)	73 (100%)	38 (97%)	38 (86%)	152 (96%)
What is the standard recommended dose of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation? (Q16) (Tick one)							
20 mg taken once a day*	363 (67%)	79 (75%)	210 (88%)	52 (79%)	24 (69%)	17 (44%)	93 (65%)
15 mg taken once a day	98 (18%)	11 (10%)	12 (5%)	10 (15%)	5 (14%)	12 (31%)	23 (16%)

Question	No. of Physicians (%)						
	General Medicine n = 552	Neurology n = 107	Cardiology n = 241	Haematology n = 73	Accident & Emergency Medicine n = 39	Oncology n = 44	Other N = 158
10 mg taken once a day	53 (10%)	13 (12%)	13 (5%)	4 (6%)	5 (14%)	7 (18%)	15 (10%)
None of the above	6 (1%)	1 (1%)	2 (1%)	0	0	2 (5%)	1 (1%)
I don't know	19 (4%)	2 (2%)	3 (1%)	0	1 (3%)	1 (3%)	11 (8%)
No answer	0	0	0	0	0	0	0
Not applicable skip pattern - Q1 (Have not prescribed Xarelto for this indication)	13	1	1	7	4	5	15
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? (Q17) (Tick one)							
20 mg taken once a day	33 (6%)	7 (7%)	3 (1%)	2 (3%)	2 (6%)	7 (18%)	5 (3%)
15 mg taken once a day*	262 (49%)	65 (61%)	178 (74%)	47 (71%)	18 (51%)	14 (36%)	72 (50%)
10 mg taken once a day	181 (34%)	27 (25%)	41 (17%)	12 (18%)	9 (26%)	10 (26%)	41 (29%)
None of the above	32 (6%)	5 (5%)	12 (5%)	3 (5%)	5 (14%)	5 (13%)	10 (7%)
I don't know	30 (6%)	2 (2%)	6 (3%)	2 (3%)	1 (3%)	3 (8%)	15 (10%)
No answer	1 (0%)	0	0	0	0	0	0

Question	No. of Physicians (%)						
	General Medicine n = 552	Neurology n = 107	Cardiology n = 241	Haematology n = 73	Accident & Emergency Medicine n = 39	Oncology n = 44	Other N = 158
Not applicable skip pattern - Q1 (Have not prescribed Xarelto for this indication)	13	1	1	7	4	5	15
What is the standard recommended dose for patients receiving Xarelto for deep vein thrombosis treatment and secondary prevention? (Q18) (Tick one)							
20 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day	97 (22%)	10 (22%)	34 (18%)	14 (20%)	7 (21%)	12 (28%)	13 (11%)
15 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day*	260 (58%)	20 (44%)	128 (67%)	49 (71%)	24 (73%)	18 (42%)	83 (68%)
10 mg once a day	61 (14%)	12 (27%)	21 (11%)	6 (9%)	2 (6%)	9 (21%)	8 (7%)
None of the above	5 (1%)	1 (2%)	0	0	0	2 (5%)	3 (2%)
I don't know	26 (6%)	2 (4%)	8 (4%)	0	0	2 (5%)	15 (12%)
No answer	0	0	0	0	0	0	0
Not applicable skip pattern - Q2 (Have not prescribed Xarelto for this indication)	103	62	50	4	6	1	36

Note 1: For each question the percentages reported for the response items were calculated using a denominator of the number of physicians who faced the question; thus physicians who did not face a question because of the skip pattern were not included in the denominator for that question.
Note 2: 10 physicians who did not respond to Question 24 were excluded from this table.

Table G-2. Knowledge Questions by Whether or not Physicians Received Information From Xarelto Prescriber Guide: Non-Recruiting Physicians

Question	No. of Physicians (95 CI) Yes n = 683	No n=531
What is the most important risk associated with taking Xarelto? (Q5) (Tick one)		
Neoplasia	7 (1%)	9 (2%)
Hypertension	9 (1%)	8 (2%)
Risk of bleeding*	635 (93%)	476 (90%)
Immunosuppression	5 (1%)	3 (1%)
I don't know	27 (4%)	35 (7%)
No answer	0	0
Which of the following populations are at an increased risk of experiencing serious side effect(s) associated with Xarelto? (Q6)		
Patients with moderate or severe renal impairment		
Yes, at higher risk*	556 (81%)	372 (70%)
No, not at higher risk	99 (14%)	96 (18%)
I don't know	27 (4%)	61 (11%)
No answer	1 (0%)	2 (0%)
Patients taking products that affect hemostasis such as NSAIDS, acetylsalicylic acid, platelet aggregation inhibitors		
Yes, at higher risk*	613 (90%)	423 (80%)
No, not at higher risk	57 (8%)	64 (12%)
I don't know	12 (2%)	42 (8%)

Question	No. of Physicians (95 CI) Yes n = 683	No n=531
No answer	1 (0%)	2 (0%)
Patients at risk of bleeding		
Yes, at higher risk*	638 (93%)	465 (88%)
No, not at higher risk	31 (5%)	46 (9%)
I don't know	13 (2%)	18 (3%)
No answer	1 (0%)	2 (0%)
Patients with chronic constipation		
Yes, at higher risk	38 (6%)	24 (5%)
No, not at higher risk*	467 (68%)	332 (63%)
I don't know	177 (26%)	173 (33%)
No answer	1 (0%)	2 (0%)
To which patient groups is Xarelto contraindicated? (Q7) (Tick all that apply)		
Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child-Pugh class B and C*	593 (87%)	384 (72%)
Patients who are pregnant or breastfeeding*	591 (87%)	418 (79%)
Patients receiving concomitant treatment with any other anticoagulant such as unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives or oral anticoagulants except when switching therapy to or from Xarelto or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter*	502 (73%)	354 (67%)
Patients with clinically significant active bleeding*	645 (94%)	457 (86%)
I don’t know	8 (1%)	32 (6%)

Question	No. of Physicians (95 CI) Yes n = 683	No n=531
No answer	0	0
Selected all four of the correct responses	432 (63%)	267 (50%)
Selected at least three of the four correct responses	580 (85%)	393 (74%)
Selected at least two of the four correct responses	644 (94%)	454 (85%)
Selected at least one of the four correct responses	675 (99%)	499 (94%)
Xarelto (15 or 20 mg) must be taken….? (Q8) (Tick one)		
On an empty stomach	110 (16%)	98 (18%)
With food on a full stomach*	448 (66%)	266 (50%)
I don't know	125 (18%)	167 (31%)
No answer	0	0
Is routine coagulation monitoring required for patients taking Xarelto for these indications? (Q9)		
Yes	20 (3%)	21 (4%)
No*	658 (96%)	499 (94%)
I don't know	4 (1%)	9 (2%)
No answer	1 (0%)	2 (0%)
In which of the following situations is INR monitoring needed? (Q10) (Tick all that apply)		
When converting from vitamin K antagonist (VKA) (e.g., warfarin) to Xarelto*	416 (61%)	271 (51%)
When converting from Xarelto to VKA*	532 (78%)	384 (72%)
Continual INR monitoring is required for all patients taking Xarelto	19 (3%)	18 (3%)

Question	No. of Physicians (95 CI) Yes n = 683	No n=531
I don't know	7 (1%)	33 (6%)
No answer	0	0
Selected both of the correct responses	284 (42%)	167 (31%)
Selected at least one of the two correct responses	664 (97%)	488 (92%)
Which of the following steps should be taken when converting patients from VKA (e.g., warfarin) to Xarelto? (Q11) (Tick all th at apply)		
Stop VKA without measuring INR	93 (14%)	83 (16%)
For patients treated for prevention of stroke and systemic embolism, stop VKA and initiate Xarelto when INR is ≤ 3*	372 (54%)	251 (47%)
For patients treated for deep vein thrombosis and secondary prevention, stop VKA and initiate Xarelto when INR is ≤ 2.5*	472 (69%)	283 (53%)
I don't know	37 (5%)	94 (18%)
No answer	0	0
Selected both of the correct responses	270 (40%)	153 (29%)
Selected at least one of the two correct responses	574 (84%)	381 (72%)
Which of the following steps should be taken when converting patients from Xarelto to VKA (e.g., warfarin)? (Q12) (Tick all that apply)		
Overlap the two drugs until INR is ≥ 2.0*	460 (67%)	304 (57%)
Measure INR but make sure it has been longer than 24 hours since the last dose of Xarelto*	228 (33%)	142 (27%)
Stop Xarelto at any time	54 (8%)	41 (8%)

Question	No. of Physicians (95 CI) Yes n = 683	No n=531
Measure INR at any time of the day	24 (4%)	19 (4%)
I don't know	51 (7%)	90 (17%)
No answer	0	0
Selected both of the correct responses	96 (14%)	44 (8%)
Selected at least one of the two correct responses	592 (87%)	402 (76%)
Which of the following are true when converting from parenteral anticoagulants to Xarelto…? (Q13) (Tick all that apply)		
Stop parenteral anticoagulants for a week prior to starting Xarelto	9 (1%)	14 (3%)
For patients with continuously administered parenteral anticoagulants such as intravenous unfractionated heparin, Xarelto should be started at time of drug discontinuation*	358 (52%)	224 (42%)
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*	426 (62%)	236 (44%)
I don't know	104 (15%)	154 (29%)
No answer	1 (0%)	0
Selected both of the correct responses	212 (31%)	91 (17%)
Selected at least one of the two correct responses	572 (84%)	369 (69%)
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)? (Q14) (Tick one)		
One week prior to the procedure or surgical intervention	61 (9%)	61 (11%)
At least 24 hours prior to the procedure or surgical intervention*	559 (82%)	373 (70%)
It is not necessary to stop Xarelto for these procedures	28 (4%)	36 (7%)

Question	No. of Physicians (95 CI) Yes n = 683	No n=531
I don't know	35 (5%)	61 (11%)
No answer	0	0
What are the most appropriate actions you should take if a patient taking Xarelto presents with a medically important bleeding complication? (Q15) (Tick all that apply)		
Provide symptomatic treatment (e.g., mechanical compression, surgery)*	542 (79%)	369 (69%)
Delay the next administration of Xarelto or discontinue Xarelto as appropriate*	532 (78%)	376 (71%)
Provide hemodynamic support (e.g., blood transfusion)*	509 (75%)	324 (61%)
Administer procoagulant reversal agent (for life-threatening bleeding)*	408 (60%)	249 (47%)
Refer the patient to emergency care*	531 (78%)	383 (72%)
None of the above	3 (0%)	5 (1%)
I don't know	10 (1%)	14 (3%)
No answer	0	0
Selected all five of the correct responses	289 (42%)	160 (30%)
Selected at least four of the five correct responses	445 (65%)	284 (53%)
Selected at least three of the five correct responses	533 (78%)	346 (65%)
Selected at least two of the five correct responses	585 (86%)	399 (75%)
Selected at least one of the five correct responses	670 (98%)	512 (96%)

Question	No. of Physicians (95 CI) Yes n = 683	No n=531
What is the standard recommended dose of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation? (Q16) (Tick one)		
20 mg taken once a day*	512 (77%)	326 (64%)
15 mg taken once a day	88 (13%)	83 (16%)
10 mg taken once a day	44 (7%)	66 (13%)
None of the above	6 (1%)	6 (1%)
I don't know	11 (2%)	26 (5%)
No answer	0	0
Not applicable skip pattern - Q1 (Have not prescribed Xarelto for this indication)	22	24
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? (Q17) (Tick one)		
20 mg taken once a day	34 (5%)	25 (5%)
15 mg taken once a day*	410 (62%)	246 (49%)
10 mg taken once a day	154 (23%)	167 (33%)
None of the above	44 (7%)	28 (6%)
I don't know	19 (3%)	40 (8%)
No answer	0	1 (0%)
Not applicable skip pattern - Q1 (Have not prescribed Xarelto for this indication)	22	24

Question	No. of Physicians (95 CI) Yes n = 683	No n=531
What is the standard recommended dose for patients receiving Xarelto for deep vein thrombosis treatment and secondary prevention? (Q18) (Tick one)		
20 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day	98 (18%)	89 (22%)
15 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day*	365 (66%)	217 (54%)
10 mg once a day	60 (11%)	59 (15%)
None of the above	4 (1%)	7 (2%)
I don't know	22 (4%)	31 (8%)
No answer	0	0
Not applicable skip pattern - Q2 (Have not prescribed Xarelto for this indication)	134	128

Note 1: For each question the percentages reported for the response items were calculated using a denominator of the number of physicians who faced the question; thus physicians who did not face a question because of the skip pattern were not included in the denominator for that question.

Note 2: 10 physicians who did not respond to Question 19 were excluded from this table.

Table G-3. Knowledge Questions by Indication(s) for Which Physicians Prescribed Xarelto: Non-Recruiting Physicians

Question	No. of Physicians (%) SPAF only N=372	DVT only N=114	SPAF and DVT N=738
Which of the following steps should be taken when converting patients from VKA (e.g., warfarin) to Xarelto? (Q11) (Tick all that apply)			
Stop VKA without measuring INR	45 (12%)	19 (17%)	114 (15%)
For patients treated for prevention of stroke and systemic embolism, stop VKA and initiate Xarelto when INR is ≤ 3*	199 (53%)	51 (45%)	374 (51%)
For patients treated for deep vein thrombosis and secondary prevention, stop VKA and initiate Xarelto when INR is ≤ 2.5*	188 (51%)	72 (63%)	498 (67%)
I don't know	56 (15%)	15 (13%)	61 (8%)
No answer	2 (1%)	0	3 (0%)
Selected both of the correct responses	107 (29%)	34 (30%)	283 (38%)
Selected at least one of the two correct responses	280 (75%)	89 (78%)	589 (80%)
Which of the following steps should be taken when converting patients from Xarelto to VKA (e.g., warfarin)? (Q12) (Tick all that apply)			
Overlap the two drugs until INR is ≥ 2.0*	217 (58%)	70 (61%)	481 (65%)
Measure INR but make sure it has been longer than 24 hours since the last dose of Xarelto*	86 (23%)	33 (29%)	251 (34%)
Stop Xarelto at any time	30 (8%)	9 (8%)	56 (8%)
Measure INR at any time of the day	10 (3%)	1 (1%)	32 (4%)
I don't know	62 (17%)	12 (11%)	67 (9%)

Question	No. of Physicians (%) SPAF only N=372	DVT only N=114	SPAF and DVT N=738
No answer	3 (1%)	0	3 (0%)
Selected both of the correct responses	24 (6%)	9 (8%)	107 (14%)
Selected at least one of the two correct responses	279 (75%)	94 (82%)	625 (85%)
Which of the following are true when converting from parenteral anticoagulants to Xarelto…? (Q13) (Tick all that apply)			
Stop parenteral anticoagulants for a week prior to starting Xarelto	5 (1%)	5 (4%)	13 (2%)
For patients with continuously administered parenteral anticoagulants such as intravenous unfractionated heparin, Xarelto should be started at time of drug discontinuation*	160 (43%)	51 (45%)	372 (50%)
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*	172 (46%)	59 (52%)	432 (59%)
I don't know	107 (29%)	27 (24%)	126 (17%)
No answer	4 (1%)	0	4 (1%)
Selected both of the correct responses	74 (20%)	27 (24%)	203 (28%)
Selected at least one of the two correct responses	258 (69%)	83 (73%)	601 (81%)

DVT = deep vein thrombosis; SPAF = stroke prevention in atrial fibrillation.

Note: Indication categories are from physician experiences in the past six months as reported per response to screening question S1.

Note: For each question the percentages reported for the response items were calculated using a denominator of the number of physicians who faced the question; thus physicians who did not face a question because of the skip pattern were not included in the denominator for that question.

Table G-4. Knowledge Questions by Whether or not Physicians Responsible for Initiating Xarelto Treatment or Converting Treatment From or to Xarelto: Non-Recruiting Physicians

Question	No. of Physicians (%)	
	Yes n = 1,045	No n = 179
What is the most important risk associated with taking Xarelto? (Q5) (Tick one)		
Neoplasia	13 (1%)	3 (2%)
Hypertension	14 (1%)	3 (2%)
Risk of bleeding*	974 (93%)	147 (82%)
Immunosuppression	6 (1%)	2 (1%)
I don't know	38 (4%)	24 (13%)
No answer	0	0
Which of the following populations are at an increased risk of experiencing serious side effect(s) associated with Xarelto? (Q6)		
Patients with moderate or severe renal impairment		
Yes, at higher risk*	823 (79%)	111 (62%)
No, not at higher risk	162 (16%)	33 (18%)
I don't know	56 (5%)	33 (18%)
No answer	4 (0%)	2 (1%)
Patients taking products that affect hemostasis such as NSAIDS, acetylsalicylic acid, platelet aggregation inhibitors		
Yes, at higher risk*	908 (87%)	132 (74%)
No, not at higher risk	98 (9%)	24 (13%)
I don't know	35 (3%)	21 (12%)

Question	No. of Physicians (%) Yes n = 1,045	No n = 179
No answer	4 (0%)	2 (1%)
Patients at risk of bleeding		
Yes, at higher risk*	960 (92%)	149 (83%)
No, not at higher risk	60 (6%)	18 (10%)
I don't know	20 (2%)	11 (6%)
No answer	5 (0%)	1 (1%)
Patients with chronic constipation		
Yes, at higher risk	54 (5%)	8 (4%)
No, not at higher risk*	709 (68%)	96 (54%)
I don't know	277 (27%)	74 (41%)
No answer	5 (0%)	1 (1%)
To which patient groups is Xarelto contraindicated? (Q7) (Tick all that apply)		
Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child-Pugh class B and C*	860 (82%)	123 (69%)
Patients who are pregnant or breastfeeding*	878 (84%)	136 (76%)
Patients receiving concomitant treatment with any other anticoagulant such as unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives or oral anticoagulants except when switching therapy to or from Xarelto or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter*	757 (72%)	105 (59%)
Patients with clinically significant active bleeding*	967 (93%)	140 (78%)
I don’t know	21 (2%)	19 (11%)

Question	No. of Physicians (%) Yes n = 1,045	No n = 179
No answer	3 (0%)	0
Selected all four of the correct responses	621 (59%)	82 (46%)
Selected at least three of the four correct responses	858 (82%)	120 (67%)
Selected at least two of the four correct responses	962 (92%)	142 (79%)
Selected at least one of the four correct responses	1021 (98%)	160 (89%)
Xarelto (15 or 20 mg) must be taken….? (Q8) (Tick one)		
On an empty stomach	176 (17%)	33 (18%)
With food on a full stomach*	640 (61%)	77 (43%)
I don't know	225 (22%)	69 (39%)
No answer	4 (0%)	0
Is routine coagulation monitoring required for patients taking Xarelto for these indications? (Q9)		
Yes	35 (3%)	6 (3%)
No*	997 (95%)	166 (93%)
I don't know	7 (1%)	6 (3%)
No answer	6 (1%)	1 (1%)
In which of the following situations is INR monitoring needed? (Q10) (Tick all that apply)		
When converting from vitamin K antagonist (VKA) (e.g., warfarin) to Xarelto*	613 (59%)	79 (44%)
When converting from Xarelto to VKA*	794 (76%)	125 (70%)
Continual INR monitoring is required for all patients taking Xarelto	32 (3%)	5 (3%)

Question	No. of Physicians (%) Yes n = 1,045	No n = 179
I don't know	23 (2%)	17 (9%)
No answer	4 (0%)	0
Selected both of the correct responses	409 (39%)	44 (25%)
Selected at least one of the two correct responses	998 (96%)	160 (89%)
Which of the following steps should be taken when converting patients from VKA (e.g., warfarin) to Xarelto? (Q11) (Tick all that apply)		
Stop VKA without measuring INR	151 (14%)	27 (15%)
For patients treated for prevention of stroke and systemic embolism, stop VKA and initiate Xarelto when INR is ≤ 3*	556 (53%)	68 (38%)
For patients treated for deep vein thrombosis and secondary prevention, stop VKA and initiate Xarelto when INR is ≤ 2.5*	685 (66%)	73 (41%)
I don't know	82 (8%)	50 (28%)
No answer	5 (0%)	0
Selected both of the correct responses	388 (37%)	36 (20%)
Selected at least one of the two correct responses	853 (82%)	105 (59%)
Which of the following steps should be taken when converting patients from Xarelto to VKA (e.g., warfarin)? (Q12) (Tick all that apply)		
Overlap the two drugs until INR is ≥ 2.0*	679 (65%)	89 (50%)
Measure INR but make sure it has been longer than 24 hours since the last dose of Xarelto*	322 (31%)	48 (27%)
Stop Xarelto at any time	85 (8%)	10 (6%)

Question	No. of Physicians (%) Yes n = 1,045	No n = 179
Measure INR at any time of the day	40 (4%)	3 (2%)
I don't know	95 (9%)	46 (26%)
No answer	6 (1%)	0
Selected both of the correct responses	127 (12%)	13 (7%)
Selected at least one of the two correct responses	874 (84%)	124 (69%)
Which of the following are true when converting from parenteral anticoagulants to Xarelto…? (Q13) (Tick all that apply)		
Stop parenteral anticoagulants for a week prior to starting Xarelto	19 (2%)	4 (2%)
For patients with continuously administered parenteral anticoagulants such as intravenous unfractionated heparin, Xarelto should be started at time of drug discontinuation*	530 (51%)	53 (30%)
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*	602 (58%)	61 (34%)
I don't know	176 (17%)	84 (47%)
No answer	8 (1%)	0
Selected both of the correct responses	282 (27%)	22 (12%)
Selected at least one of the two correct responses	850 (81%)	92 (51%)
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)? (Q14) (Tick one)		
One week prior to the procedure or surgical intervention	91 (9%)	31 (17%)
At least 24 hours prior to the procedure or surgical intervention*	842 (81%)	92 (51%)
It is not necessary to stop Xarelto for these procedures	46 (4%)	18 (10%)

Question	No. of Physicians (%) Yes n = 1,045	No n = 179
I don't know	59 (6%)	38 (21%)
No answer	7 (1%)	0
What are the most appropriate actions you should take if a patient taking Xarelto presents with a medically important bleeding complication? (Q15) (Tick all that apply)		
Provide symptomatic treatment (e.g., mechanical compression, surgery)*	806 (77%)	107 (60%)
Delay the next administration of Xarelto or discontinue Xarelto as appropriate*	800 (77%)	110 (61%)
Provide hemodynamic support (e.g., blood transfusion)*	739 (71%)	96 (54%)
Administer procoagulant reversal agent (for life-threatening bleeding)*	593 (57%)	65 (36%)
Refer the patient to emergency care*	780 (75%)	136 (76%)
None of the above	6 (1%)	2 (1%)
I don't know	16 (2%)	9 (5%)
No answer	7 (1%)	0
Selected all five of the correct responses	414 (40%)	36 (20%)
Selected at least four of the five correct responses	647 (62%)	84 (47%)
Selected at least three of the five correct responses	778 (74%)	103 (58%)
Selected at least two of the five correct responses	863 (83%)	123 (69%)
Selected at least one of the five correct responses	1016 (97%)	168 (94%)

Question	No. of Physicians (%) Yes n = 1,045	No n = 179
What is the standard recommended dose of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation? (Q16) (Tick one)		
20 mg taken once a day*	755 (75%)	84 (50%)
15 mg taken once a day	135 (13%)	36 (21%)
10 mg taken once a day	84 (8%)	27 (16%)
None of the above	9 (1%)	3 (2%)
I don't know	20 (2%)	17 (10%)
No answer	7 (1%)	1 (1%)
Not applicable skip pattern - Q1 (Have not prescribed Xarelto for this indication)	35	11
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? (Q17) (Tick one)		
20 mg taken once a day	47 (5%)	12 (7%)
15 mg taken once a day*	600 (59%)	56 (33%)
10 mg taken once a day	259 (26%)	62 (37%)
None of the above	59 (6%)	13 (8%)
I don't know	36 (4%)	23 (14%)
No answer	9 (1%)	2 (1%)
Not applicable skip pattern - Q1 (Have not prescribed Xarelto for this indication)	35	11

Question	No. of Physicians (%) Yes n = 1,045	No n = 179
What is the standard recommended dose for patients receiving Xarelto for deep vein thrombosis treatment and secondary prevention? (Q18) (Tick one)		
20 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day	165 (20%)	22 (18%)
15 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day*	529 (63%)	53 (44%)
10 mg once a day	94 (11%)	25 (21%)
None of the above	6 (1%)	5 (4%)
I don't know	38 (5%)	15 (12%)
No answer	6 (1%)	1 (1%)
Not applicable skip pattern - Q2 (Have not prescribed Xarelto for this indication)	207	58

Note1: For each question the percentages reported for the response items were calculated using a denominator of the number of physicians who faced the question; thus physicians who did not face a question because of the skip pattern were not included in the denominator for that question.

Annex H. Analysis Tables for Recruiting Physicians (Overall and by Country)

Table H-1. Physician and Practice Characteristics by Country and Overall: Recruiting Physicians

Question	No. of Physicians (%)				
	UK n = 7	Germany n = 10	France n = 7	Spain n = 11	Overall N = 35
Which of the following best describe your specialty? (Q24)					
General medicine	1 (14%)	0	0	0	1 (3%)
Neurology	0	2 (20%)	0	0	2 (6%)
Cardiology	1 (14%)	6 (60%)	7 (100%)	6 (55%)	20 (57%)
Haematology	3 (43%)	0	0	5 (45%)	8 (23%)
Accident & Emergency medicine	0	0	0	0	0
Oncology	0	0	0	0	0
Other	2 (29%)	2 (20%)	0	0	4 (11%)
No answer	0	0	0	0	0
How many years have you been practicing medicine? (Q25)					
5 years or less	0	0	0	0	0
6 to 10 years	1 (14%)	0	0	6 (55%)	7 (20%)
11 to 15 years	2 (29%)	3 (30%)	1 (14%)	1 (9%)	7 (20%)
16 to 20 years	1 (14%)	3 (30%)	3 (43%)	0	7 (20%)
21 to 25 years	0	2 (20%)	2 (29%)	0	4 (11%)
More than 25 years	3 (43%)	2 (20%)	1 (14%)	4 (36%)	10 (29%)
No answer	0	0	0	0	0

Question	No. of Physicians (%)				
	UK n = 7	Germany n = 10	France n = 7	Spain n = 11	Overall N = 35
Are you...? (Q26)					
Male	4 (57%)	9 (90%)	6 (86%)	7 (64%)	26 (74%)
Female	3 (43%)	1 (10%)	1 (14%)	4 (36%)	9 (26%)
No answer	0	0	0	0	0
How would you characterise your practice? (Q27) (Tick all that apply)					
General practice	3 (43%)	4 (40%)	0	10 (91%)	17 (49%)
Hospital-based clinic	4 (57%)	6 (60%)	7 (100%)	10 (91%)	27 (77%)
Nursing home	0	0	0	0	0
Other	0	0	0	2 (18%)	2 (6%)
No answer	0	0	0	0	0

UK = United Kingdom.

Table H-2. Physician Prescribing Practices by Country and Overall: Recruiting Physicians

Question	No. of Physicians (%)				
	UK n = 7	Germany n = 10	France n = 7	Spain n = 11	Overall N = 35
In the past 6 months, for how many patients have you prescribed Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation? (Q1)					
1 to 10	3 (43%)	0	1 (14%)	3 (27%)	7 (20%)
11 to 20	1 (14%)	3 (30%)	3 (43%)	6 (55%)	13 (37%)
21 or more	3 (43%)	6 (60%)	2 (29%)	2 (18%)	13 (37%)
I have not prescribed Xarelto for this indication	0	1 (10%)	1 (14%)	0	2 (6%)
No answer	0	0	0	0	0
In the past 6 months, for how many patients have you prescribed Xarelto for deep vein thrombosis treatment and secondary prevention? (Q2)					
1 to 10	4 (57%)	3 (30%)	2 (29%)	2 (18%)	11 (31%)
11 to 20	1 (14%)	1 (10%)	1 (14%)	1 (9%)	4 (11%)
21 or more	1 (14%)	5 (50%)	2 (29%)	0	8 (23%)
I have not prescribed Xarelto for this indication	1 (14%)	1 (10%)	2 (29%)	8 (73%)	12 (34%)
No answer	0	0	0	0	0

Question	No. of Physicians (%)				
	UK n = 7	**Germany n = 10**	**France n = 7**	**Spain n = 11**	**Overall N = 35**
When did you write your most recent prescription for Xarelto for either of these indications? (Q3) (Tick one)					
Less than 1 month ago	7 (100%)	10 (100%)	7 (100%)	10 (91%)	34 (97%)
1 to 3 months ago	0	0	0	1 (9%)	1 (3%)
4 to 6 months ago	0	0	0	0	0
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Which of the following Xarelto treatment activities are you responsible for? (Q4) (Tick all that apply)					
I initiate Xarelto treatment or convert treatment from or to Xarelto	7 (100%)	10 (100%)	7 (100%)	11 (100%)	35 (100%)
I write follow up (maintenance) prescriptions for Xarelto	5 (71%)	5 (50%)	4 (57%)	4 (36%)	18 (51%)
No answer	0	0	0	0	0

UK = United Kingdom.

Table H 3. Knowledge Questions by Country and Overall Recruiting Physicians

Question	No. of Physicians (%) (95% CI)				
	UK n = 7	Germany n = 10	France n = 7	Spain n = 11	Overall N = 35
What is the most important risk associated with taking Xarelto? (Q5) (Tick one)					
Neoplasia	0	0	0	0	0
Hypertension	0	0	0	0	0
Risk of bleeding*	7 (100%) (59% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	35 (100%) (90% - 100%)
Immunosuppression	0	0	0	0	0
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Which of the following populations are at an increased risk of experiencing serious side effect(s) associated with Xarelto? (Q6)					
Patients with moderate or severe renal impairment					
Yes, at higher risk*	7 (100%) (59% - 100%)	9 (90%) (55% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	34 (97%) (85% - 100%)
No, not at higher risk	0	1 (10%)	0	0	1 (3%)
I don't know	0	0	0	0	0
No answer	0	0	0	0	0

Question	No. of Physicians (%) (95% CI)				
	UK n = 7	**Germany n = 10**	**France n = 7**	**Spain n = 11**	**Overall N = 35**
Patients taking products that affect hemostasis such as NSAIDS, acetylsalicylic acid, platelet aggregation inhibitors					
Yes, at higher risk*	7 (100%) (59% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	10 (91%) (59% - 100%)	34 (97%) (85% - 100%)
No, not at higher risk	0	0	0	1 (9%)	1 (3%)
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Patients at risk of bleeding					
Yes, at higher risk*	7 (100%) (59% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	35 (100%) (90% - 100%)
No, not at higher risk	0	0	0	0	0
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Patients with chronic constipation					
Yes, at higher risk	1 (14%)	0	0	1 (9%)	2 (6%)
No, not at higher risk*	6 (86%) (42% - 100%)	10 (100%) (69% - 100%)	5 (71%) (29% - 96%)	8 (73%) (39% - 94%)	29 (83%) (66% - 93%)
I don't know	0	0	2 (29%)	2 (18%)	4 (11%)
No answer	0	0	0	0	0

Question	No. of Physicians (%) (95% CI) UK n = 7	Germany n = 10	France n = 7	Spain n = 11	Overall N = 35
To which patient groups is Xarelto contraindicated? (Q7) (Tick all that apply)					
Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child-Pugh class B and C*	6 (86%)	10 (100%)	7 (100%)	11 (100%)	34 (97%)
Patients who are pregnant or breastfeeding*	7 (100%)	10 (100%)	6 (86%)	11 (100%)	34 (97%)
Patients receiving concomitant treatment with any other anticoagulant such as unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives or oral anticoagulants except when switching therapy to or from Xarelto or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter*	5 (71%)	9 (90%)	7 (100%)	11 (100%)	32 (91%)
Patients with clinically significant active bleeding*	7 (100%)	10 (100%)	7 (100%)	11 (100%)	35 (100%)
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Selected all four of the correct responses	5 (71%) (29% - 96%)	9 (90%) (55% - 100%)	6 (86%) (42% - 100%)	11 (100%) (72% - 100%)	31 (89%) (73% - 97%)
Selected at least three of the four correct responses	6 (86%) (42% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	34 (97%) (85% - 100%)
Selected at least two of the four correct responses	7 (100%) (59% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	35 (100%) (90% - 100%)
Selected at least one of the four correct responses	7 (100%) (59% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	35 (100%) (90% - 100%)

Question	No. of Physicians (%) (95% CI)				
	UK n = 7	**Germany n = 10**	**France n = 7**	**Spain n = 11**	**Overall N = 35**
Xarelto (15 or 20 mg) must be taken….? (Q8) (Tick one)					
On an empty stomach	0	1 (10%)	0	1 (9%)	2 (6%)
With food on a full stomach*	7 (100%) (59% - 100%)	8 (80%) (44% - 97%)	7 (100%) (59% - 100%)	10 (91%) (59% - 100%)	32 (91%) (77% - 98%)
I don't know	0	1 (10%)	0	0	1 (3%)
No answer	0	0	0	0	0
Is routine coagulation monitoring required for patients taking Xarelto for these indications? (Q9)					
Yes	0	0	0	0	0
No*	7 (100%) (59% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	35 (100%) (90% - 100%)
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
In which of the following situations is INR monitoring needed? (Q10) (Tick all that apply)					
When converting from vitamin K antagonist (VKA) (e.g., warfarin) to Xarelto*	6 (86%)	8 (80%)	6 (86%)	10 (91%)	30 (86%)
When converting from Xarelto to VKA*	4 (57%)	9 (90%)	5 (71%)	8 (73%)	26 (74%)
Continual INR monitoring is required for all patients taking Xarelto	0	0	1 (14%)	0	1 (3%)
I don't know	0	0	0	0	0
No answer	0	0	0	0	0

Question	No. of Physicians (%) (95% CI)				
	UK n = 7	**Germany n = 10**	**France n = 7**	**Spain n = 11**	**Overall N = 35**
Selected both of the correct responses	3 (43%) (10% - 82%)	7 (70%) (35% - 93%)	4 (57%) (18% - 90%)	7 (64%) (31% - 89%)	21 (60%) (42% - 76%)
Selected at least one of the two correct responses	7 (100%) (59% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	35 (100%) (90% - 100%)
Which of the following steps should be taken when converting patients from VKA (e.g., warfarin) to Xarelto? (Q11) (Tick all that apply)					
Stop VKA without measuring INR	0	0	0	0	0
For patients treated for prevention of stroke and systemic embolism, stop VKA and initiate Xarelto when INR is ≤ 3*	4 (57%)	8 (80%)	5 (71%)	8 (73%)	25 (71%)
For patients treated for deep vein thrombosis and secondary prevention, stop VKA and initiate Xarelto when INR is ≤ 2.5*	6 (86%)	10 (100%)	7 (100%)	9 (82%)	32 (91%)
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Selected both of the correct responses	3 (43%) (10% - 82%)	8 (80%) (44% - 97%)	5 (71%) (29% - 96%)	6 (55%) (23% - 83%)	22 (63%) (45% - 79%)
Selected at least one of the two correct responses	7 (100%) (59% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	35 (100%) (90% - 100%)
Which of the following steps should be taken when converting patients from Xarelto to VKA (e.g., warfarin)? (Q12) (Tick all that apply)					
Overlap the two drugs until INR is ≥ 2.0*	4 (57%)	10 (100%)	7 (100%)	10 (91%)	31 (89%)
Measure INR but make sure it has been longer than 24 hours since the last dose of Xarelto*	3 (43%)	6 (60%)	2 (29%)	5 (45%)	16 (46%)

Question	No. of Physicians (%) (95% CI)				
	UK n = 7	**Germany n = 10**	**France n = 7**	**Spain n = 11**	**Overall N = 35**
Stop Xarelto at any time	0	0	0	0	0
Measure INR at any time of the day	0	1 (10%)	0	0	1 (3%)
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Selected both of the correct responses	0 (0% - 41%)	6 (60%) (26% - 88%)	2 (29%) (4% - 71%)	4 (36%) (11% - 69%)	12 (34%) (19% - 52%)
Selected at least one of the two correct responses	7 (100%) (59% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	35 (100%) (90% - 100%)
Which of the following are true when converting from parenteral anticoagulants to Xarelto…? (Q13) (Tick all that apply)					
Stop parenteral anticoagulants for a week prior to starting Xarelto	0	0	0	0	0
For patients with continuously administered parenteral anticoagulants such as intravenous unfractionated heparin, Xarelto should be started at time of drug discontinuation*	5 (71%)	7 (70%)	7 (100%)	11 (100%)	30 (86%)
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*	6 (86%)	10 (100%)	6 (86%)	9 (82%)	31 (89%)
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Selected both of the correct responses	4 (57%) (18% - 90%)	7 (70%) (35% - 93%)	6 (86%) (42% - 100%)	9 (82%) (48% - 98%)	26 (74%) (57% - 88%)

Question	No. of Physicians (%) (95% CI)				
	UK n = 7	**Germany n = 10**	**France n = 7**	**Spain n = 11**	**Overall N = 35**
Selected at least one of the two correct responses	7 (100%) (59% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	35 (100%) (90% - 100%)
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)? (Q14) (Tick one)					
One week prior to the procedure or surgical intervention	0	0	0	0	0
At least 24 hours prior to the procedure or surgical intervention*	7 (100%) (59% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	35 (100%) (90% - 100%)
It is not necessary to stop Xarelto for these procedures	0	0	0	0	0
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
What are the most appropriate actions you should take if a patient taking Xarelto presents with a medically important bleeding complication? (Q15) (Tick all that apply)					
Provide symptomatic treatment (e.g., mechanical compression, surgery)*	7 (100%)	10 (100%)	7 (100%)	10 (91%)	34 (97%)
Delay the next administration of Xarelto or discontinue Xarelto as appropriate*	6 (86%)	10 (100%)	7 (100%)	10 (91%)	33 (94%)
Provide hemodynamic support (e.g., blood transfusion)*	6 (86%)	10 (100%)	7 (100%)	11 (100%)	34 (97%)
Administer procoagulant reversal agent (for life-threatening bleeding)*	4 (57%)	10 (100%)	6 (86%)	9 (82%)	29 (83%)
Refer the patient to emergency care*	6 (86%)	9 (90%)	6 (86%)	11 (100%)	32 (91%)
None of the above	0	0	0	0	0
I don't know	0	0	0	0	0

Question	No. of Physicians (%) (95% CI)				
	UK n = 7	**Germany n = 10**	**France n = 7**	**Spain n = 11**	**Overall N = 35**
No answer	0	0	0	0	0
Selected all five of the correct responses	4 (57%) (18% - 90%)	9 (90%) (55% - 100%)	5 (71%) (29% - 96%)	9 (82%) (48% - 98%)	27 (77%) (60% - 90%)
Selected at least four of the five correct responses	6 (86%) (42% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	9 (82%) (48% - 98%)	32 (91%) (77% - 98%)
Selected at least three of the five correct responses	6 (86%) (42% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	34 (97%) (85% - 100%)
Selected at least two of the five correct responses	6 (86%) (42% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	34 (97%) (85% - 100%)
Selected at least one of the five correct responses	7 (100%) (59% - 100%)	10 (100%) (69% - 100%)	7 (100%) (59% - 100%)	11 (100%) (72% - 100%)	35 (100%) (90% - 100%)
What is the standard recommended dose of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation? (Q16) (Tick one)					
20 mg taken once a day*	7 (100%) (59% - 100%)	9 (100%) (66% - 100%)	6 (100%) (54% - 100%)	11 (100%) (72% - 100%)	33 (100%) (89% - 100%)
15 mg taken once a day	0	0	0	0	0
10 mg taken once a day	0	0	0	0	0
None of the above	0	0	0	0	0
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Not applicable skip pattern - Q1 (Have not prescribed Xarelto for this indication)	0	1	1	0	2

Question	No. of Physicians (%) (95% CI)				
	UK n = 7	**Germany** n = 10	**France** n = 7	**Spain** n = 11	**Overall** N = 35
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? (Q17) (Tick one)					
20 mg taken once a day	0	1 (11%)	0	0	1 (3%)
15 mg taken once a day*	6 (86%) (42% - 100%)	8 (89%) (52% - 100%)	6 (100%) (54% - 100%)	11 (100%) (72% - 100%)	31 (94%) (80% - 99%)
10 mg taken once a day	1 (14%)	0	0	0	1 (3%)
None of the above	0	0	0	0	0
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Not applicable skip pattern - Q1 (Have not prescribed Xarelto for this indication)	0	1	1	0	2

Question	No. of Physicians (%) (95% CI)				
	UK n = 7	**Germany** n = 10	**France** n = 7	**Spain** n = 11	**Overall** N = 35
What is the standard recommended dose for patients receiving Xarelto for deep vein thrombosis treatment and secondary prevention? (Q18) (Tick one)					
20 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day	0	1 (11%)	0	0	1 (4%)
15 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day*	6 (100%) (54% - 100%)	8 (89%) (52% - 100%)	5 (100%) (48% - 100%)	3 (100%) (29% - 100%)	22 (96%) (78% - 100%)
10 mg once a day	0	0	0	0	0
None of the above	0	0	0	0	0
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Not applicable skip pattern - Q2 (Have not prescribed Xarelto for this indication)	1	1	2	8	12

UK = United Kingdom.

Note 1: For each question the percentages reported for the response items were calculated using a denominator of the number of physicians who faced the question; thus physicians who did not face a question because of the skip pattern were not included in the denominator for that question.

Note 2: Exact 95% Confidence Intervals were computed using the Clopper-Pearson method for the proportion of correct responses for select questionnaire items.

Table H-4. Sources of Information About Xarelto by Country and Overall: Recruiting Physicians

Question	No. of Physicians (%)				
	UK n = 7	Germany n = 10	France n = 7	Spain n = 11	Overall N = 35
From which of the following sources did you receive information about Xarelto? (Q19) (Tick all that apply)					
Xarelto Prescriber Guide	7 (100%)	9 (90%)	6 (86%)	11 (100%)	33 (94%)
Briefing from a company representative	5 (71%)	8 (80%)	7 (100%)	9 (82%)	29 (83%)
Discussion with a clinical expert	5 (71%)	7 (70%)	5 (71%)	7 (64%)	24 (69%)
The Summary of Product Characteristics for Xarelto	7 (100%)	9 (90%)	6 (86%)	6 (55%)	28 (80%)
Clinical trials published in the medical literature	7 (100%)	8 (80%)	7 (100%)	10 (91%)	32 (91%)
Other	0	1 (10%)	1 (14%)	1 (9%)	3 (9%)
None of the above	0	1 (10%)	0	0	1 (3%)
No answer	0	0	0	0	0

UK = United Kingdom.

Table H-5. Ratings of Sources of Information About Xarelto by Country and Overall: Recruiting Physicians

Question	No. of Physicians (%)				
	UK n = 7	Germany n = 10	France n = 7	Spain n = 11	Overall N = 35
How helpful were these sources to you in treating and educating your patients? (Q20)					
Xarelto Prescriber Guide					
Not at all helpful	0	0	0	0	0
2	0	2 (22%)	1 (17%)	0	3 (9%)
3	1 (14%)	0	2 (33%)	3 (27%)	6 (18%)
4	4 (57%)	4 (44%)	2 (33%)	4 (36%)	14 (42%)
Extremely helpful	2 (29%)	3 (33%)	1 (17%)	4 (36%)	10 (30%)
Not applicable skip pattern (Q19 item was not ticked)	0	1	1	0	2
Briefing from a company representative					
Not at all helpful	0	0	0	1 (11%)	1 (3%)
2	0	2 (25%)	1 (14%)	0	3 (10%)
3	1 (20%)	0	1 (14%)	3 (33%)	5 (17%)
4	3 (60%)	4 (50%)	4 (57%)	5 (56%)	16 (55%)
Extremely helpful	1 (20%)	2 (25%)	1 (14%)	0	4 (14%)
Not applicable skip pattern (Q19 item was not ticked)	2	2	0	2	6

Question	No. of Physicians (%)				
	UK n = 7	Germany n = 10	France n = 7	Spain n = 11	Overall N = 35
Discussion with a clinical expert					
Not at all helpful	0	1 (14%)	0	0	1 (4%)
2	0	1 (14%)	0	0	1 (4%)
3	0	1 (14%)	1 (20%)	1 (14%)	3 (13%)
4	4 (80%)	2 (29%)	3 (60%)	4 (57%)	13 (54%)
Extremely helpful	1 (20%)	2 (29%)	1 (20%)	2 (29%)	6 (25%)
Not applicable skip pattern (Q19 item was not ticked)	2	3	2	4	11
Summary of Product Characteristics					
Not at all helpful	0	0	1 (17%)	0	1 (4%)
2	0	2 (22%)	0	0	2 (7%)
3	1 (14%)	0	0	3 (50%)	4 (14%)
4	4 (57%)	3 (33%)	3 (50%)	3 (50%)	13 (46%)
Extremely helpful	2 (29%)	4 (44%)	2 (33%)	0	8 (29%)
Not applicable skip pattern (Q19 item was not ticked)	0	1	1	5	7

Question	No. of Physicians (%)				
	UK n = 7	Germany n = 10	France n = 7	Spain n = 11	Overall N = 35
Medical Publications					
Not at all helpful	0	0	0	0	0
2	0	2 (25%)	0	0	2 (6%)
3	0	0	0	0	0
4	5 (71%)	1 (13%)	2 (29%)	4 (40%)	12 (38%)
Extremely helpful	2 (29%)	5 (63%)	5 (71%)	6 (60%)	18 (56%)
Not applicable skip pattern (Q19 item was not ticked)	0	2	0	1	3
Other					
Not at all helpful	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	1 (100%)	1 (33%)
4	0	0	1 (100%)	0	1 (33%)
Extremely helpful	0	1 (100%)	0	0	1 (33%)
Not applicable skip pattern (Q19 item was not ticked)	7	9	6	10	32

UK = United Kingdom.

Table H-6. Physician's Experiences with Patient Alert Cards by Country and Overall: Recruiting Physicians

Question	No. of Physicians (%)				
	UK n = 7	Germany n = 10	France n = 7	Spain n = 11	Overall N = 35
Have you received Xarelto Patient Alert Cards to provide to your patients? (Q21)					
Yes	7 (100%)	9 (90%)	6 (86%)	11 (100%)	33 (94%)
No	0	1 (10%)	1 (14%)	0	2 (6%)
No answer	0	0	0	0	0
Considering the Xarelto patients under your care, to how many did you provide a Patient Alert Card? (Q22)					
Every one of my patients	4 (57%)	6 (67%)	2 (33%)	2 (18%)	14 (42%)
Most of my patients	1 (14%)	3 (33%)	2 (33%)	6 (55%)	12 (36%)
A few of my patients	2 (29%)	0	2 (33%)	3 (27%)	7 (21%)
None of my patients	0	0	0	0	0
No answer	0	0	0	0	0
Not applicable skip pattern (Q21 was "No")	0	1	1	0	2
When would you discuss the information on the Patient Alert Card with your patients taking Xarelto? (Q23) (Tick all that apply)					
When first prescribing Xarelto	7 (100%)	9 (100%)	6 (100%)	10 (91%)	32 (97%)
When a patient is facing an invasive procedure or surgical intervention	1 (14%)	2 (22%)	3 (50%)	4 (36%)	10 (30%)
When a patient has bleeding complications	1 (14%)	3 (33%)	3 (50%)	4 (36%)	11 (33%)
When a patient has a Xarelto related adverse event	1 (14%)	2 (22%)	3 (50%)	4 (36%)	10 (30%)
I do not use the Patient Alert Card	0	0	0	0	0

Question	No. of Physicians (%)				
	UK n = 7	Germany n = 10	France n = 7	Spain n = 11	Overall N = 35
Other	0	0	0	0	0
No answer	0	0	0	0	0
Not applicable skip pattern (Q21 was "No")	0	1	1	0	2

UK = United Kingdom.

Note 1: For each question the percentages reported for the response items were calculated using a denominator of the number of physicians who faced the question; thus physicians who did not face a question because of the skip pattern were not included in the denominator for that question.

Annex I. Analysis Tables for Patients (Overall and by Stratification Variables)

Table I-1. Patient Demographics by Country and Overall

Question	No. of Patients (%)				
	UK n = 118	Germany n = 94	France n = 107	Spain n = 108	Overall N = 427
How old are you …? (Q19)					
18-25 years	4 (3%)	1 (1%)	0	0	5 (1%)
26-35 years	6 (5%)	2 (2%)	3 (3%)	1 (1%)	12 (3%)
36-45 years	9 (8%)	1 (1%)	5 (5%)	2 (2%)	17 (4%)
46-55 years	20 (17%)	12 (13%)	21 (20%)	7 (6%)	60 (14%)
56-65 years	16 (14%)	11 (12%)	30 (28%)	17 (16%)	74 (17%)
66-75 years	30 (25%)	27 (29%)	25 (23%)	34 (31%)	116 (27%)
76-85 years	26 (22%)	26 (28%)	16 (15%)	36 (33%)	104 (24%)
86 years or older	5 (4%)	4 (4%)	1 (1%)	8 (7%)	18 (4%)
No answer	2 (2%)	10 (11%)	6 (6%)	3 (3%)	21 (5%)
Are you …? (Q20)					
Male	53 (45%)	50 (53%)	60 (56%)	59 (55%)	222 (52%)
Female	62 (53%)	33 (35%)	40 (37%)	40 (37%)	175 (41%)
No answer	3 (3%)	11 (12%)	7 (7%)	9 (8%)	30 (7%)

Question	No. of Patients (%)				
	UK n = 118	**Germany n = 94**	**France n = 107**	**Spain n = 108**	**Overall N = 427**
What is the highest level of education you have completed? (Q21) Select the one answer that best applies to you					
Primary school education or less	12 (10%)	7 (7%)	15 (14%)	51 (47%)	85 (20%)
Secondary school education (e.g. GCSE/A level, Scottish Standard Grades/Highers)	46 (39%)	39 (41%)	23 (21%)	13 (12%)	121 (28%)
Professional or work-related college qualifications (e.g. Certificate of Higher Education, Diploma of Higher Education, foundation degree)	34 (29%)	22 (23%)	46 (43%)	15 (14%)	117 (27%)
Undergraduate university degree (e.g. BSc/BA)	17 (14%)	15 (16%)	9 (8%)	24 (22%)	65 (15%)
Postgraduate university degree (e.g. MSc/MA, MPhil, PhD)	6 (5%)	2 (2%)	8 (7%)	2 (2%)	18 (4%)
No answer	3 (3%)	9 (10%)	6 (6%)	3 (3%)	21 (5%)

UK = United Kingdom.

Note: For patients with multiple responses for Q21, only the highest, indicated education level was used in this analysis.

Table I-2. Patient's Xarelto Background by Country and Overall

Question	No. of Patients (%)				
	UK n = 118	Germany n = 94	France n = 107	Spain n = 108	Overall N = 427
Are you currently taking Xarelto? (Q3)					
Yes	114 (97%)	84 (89%)	102 (95%)	104 (96%)	404 (95%)
No	4 (3%)	5 (5%)	2 (2%)	3 (3%)	14 (3%)
I don't know	0	0	1 (1%)	0	1 (0%)
No answer	0	5 (5%)	2 (2%)	1 (1%)	8 (2%)
Approximately how long have you been taking Xarelto? (Q4) Select the one answer that best applies to you.					
Less than 1 month	22 (19%)	17 (18%)	23 (21%)	3 (3%)	65 (15%)
Between 1 and 6 months	59 (50%)	27 (29%)	33 (31%)	32 (30%)	151 (35%)
More than 6 months but less than 1 year	13 (11%)	9 (10%)	12 (11%)	18 (17%)	52 (12%)
More than 1 year	23 (19%)	37 (39%)	36 (34%)	54 (50%)	150 (35%)
I don't know	1 (1%)	0	2 (2%)	0	3 (1%)
No answer	0	4 (4%)	1 (1%)	1 (1%)	6 (1%)
How many prescription medications, including Xarelto, are you currently taking on a regular basis? (Q5) Select the one answer that best applies to you.					
I am taking only 1 prescription medication (Xarelto)	23 (19%)	9 (10%)	12 (11%)	10 (9%)	54 (13%)
2 prescription medications	13 (11%)	10 (11%)	15 (14%)	8 (7%)	46 (11%)
3 to 4 prescription medications	27 (23%)	30 (32%)	38 (36%)	27 (25%)	122 (29%)
5 to 6 prescription medications	21 (18%)	27 (29%)	17 (16%)	23 (21%)	88 (21%)

Question	No. of Patients (%)				
	UK n = 118	**Germany n = 94**	**France n = 107**	**Spain n = 108**	**Overall N = 427**
More than 6 prescription medications	32 (27%)	11 (12%)	23 (21%)	38 (35%)	104 (24%)
I don't know	2 (2%)	1 (1%)	2 (2%)	2 (2%)	7 (2%)
No answer	0	6 (6%)	0	0	6 (1%)
Before starting Xarelto, had you ever taken any prescription blood thinners (medications that thin the blood to prevent blood clots)? (Q7)					
Yes	73 (62%)	48 (51%)	62 (58%)	73 (68%)	256 (60%)
No	40 (34%)	45 (48%)	41 (38%)	32 (30%)	158 (37%)
I don't know	4 (3%)	1 (1%)	4 (4%)	2 (2%)	11 (3%)
No answer	1 (1%)	0	0	1 (1%)	2 (0%)
I was prescribed Xarelto for the following reason(s) (Q18) Select all that apply.					
Prevention of stroke	44 (37%)	42 (45%)	52 (49%)	65 (60%)	203 (48%)
A blood clot in a vein	68 (58%)	37 (39%)	46 (43%)	30 (28%)	181 (42%)
I don't know	2 (2%)	1 (1%)	8 (7%)	5 (5%)	16 (4%)
Other	24 (20%)	12 (13%)	15 (14%)	17 (16%)	68 (16%)
No answer	2 (2%)	12 (13%)	6 (6%)	2 (2%)	22 (5%)

UK = United Kingdom.

Table I-3. Sources of Xarelto Information by Country and Overall

Question	No. of Patients (%)				
	UK n = 118	Germany n = 94	France n = 107	Spain n = 108	Overall N = 427
Where did you get most of your information about Xarelto? (Q8) Select the one answer that best applies to you.					
From my doctor	39 (33%)	33 (35%)	22 (21%)	42 (39%)	136 (32%)
From a specialist at the hospital	56 (47%)	42 (45%)	68 (64%)	68 (63%)	234 (55%)
From my pharmacist	2 (2%)	2 (2%)	4 (4%)	3 (3%)	11 (3%)
From a friend or family member	0	1 (1%)	1 (1%)	3 (3%)	5 (1%)
From my career	0	1 (1%)	0	0	1 (0%)
From articles in newspapers or magazines	0	2 (2%)	1 (1%)	0	3 (1%)
From the Internet	2 (2%)	4 (4%)	3 (3%)	3 (3%)	12 (3%)
From the Xarelto Patient Alert Card and/or patient information leaflet	24 (20%)	12 (13%)	15 (14%)	8 (7%)	59 (14%)
Other	2 (2%)	3 (3%)	12 (11%)	1 (1%)	18 (4%)
No answer	0	1 (1%)	2 (2%)	0	3 (1%)
Has your health care professional ever talked to you about the possible side effects of Xarelto? (Q9)					
Yes	70 (59%)	36 (38%)	45 (42%)	52 (48%)	203 (48%)
No	40 (34%)	43 (46%)	59 (55%)	53 (49%)	195 (46%)
I don't know	8 (7%)	13 (14%)	3 (3%)	3 (3%)	27 (6%)
No answer	0	2 (2%)	0	0	2 (0%)

UK = United Kingdom.

Note: Some patients provided multiple responses for Q8.

Table I-4. Patient Alert Card Experience by Country and Overall

Question	No. of Patients (%)				
	UK n = 118	Germany n = 94	France n = 107	Spain n = 108	Overall N = 427
Prior to today, had you received or been given the Patient Alert Card for Xarelto? (S2Q10)					
Yes -> If yes, go to Question 11	76 (64%)	44 (47%)	53 (50%)	29 (27%)	202 (47%)
No -> If no, go to Question 15	38 (32%)	45 (48%)	50 (47%)	67 (62%)	200 (47%)
I don't remember -> If I don't remember, go to Question 15	3 (3%)	2 (2%)	1 (1%)	7 (6%)	13 (3%)
No answer	1 (1%)	3 (3%)	3 (3%)	5 (5%)	12 (3%)
Prior to today, had you read the Patient Alert Card for Xarelto? (S2Q11)					
Yes -> If yes, go to Question 13	74 (96%)	32 (68%)	48 (86%)	20 (59%)	174 (81%)
No -> If no, go to Question 12	2 (3%)	9 (19%)	6 (11%)	8 (24%)	25 (12%)
I don't know	0	3 (6%)	1 (2%)	1 (3%)	5 (2%)
No answer	1 (1%)	3 (6%)	1 (2%)	5 (15%)	10 (5%)
Not applicable skip pattern S2Q10 (answered 'No' or 'I don't Remember')	41	47	51	74	213
Is there a reason why you have not read the Patient Alert Card for Xarelto, prior to today? (S2Q12) Select all that apply.					
I haven't taken the medication yet	0	1 (8%)	0	0	1 (3%)
Someone else explained it to me	2 (67%)	4 (33%)	1 (14%)	5 (38%)	12 (34%)
I lost the patient alert card	0	0	0	1 (8%)	1 (3%)
I already knew the information	0	0	1 (14%)	2 (15%)	3 (9%)
I have not had the time yet	0	2 (17%)	2 (29%)	1 (8%)	5 (14%)
I am not interested in reading it	0	0	1 (14%)	0	1 (3%)

Question	No. of Patients (%)				
	UK n = 118	Germany n = 94	France n = 107	Spain n = 108	Overall N = 427
Other	0	2 (17%)	1 (14%)	2 (15%)	5 (14%)
No answer	1 (33%)	3 (25%)	1 (14%)	4 (31%)	9 (26%)
Not applicable skip pattern S2Q10 (answered 'No' or 'I don't Remember')	41	47	51	74	213
Not applicable skip pattern S2Q11 (answered 'Yes' or 'I don't Remember')	74	35	49	21	179
How much of the time do you keep the Xarelto Patient Alert Card with you? (S2Q13) Select the one answer that best applies to you.					
All the time	57 (74%)	36 (77%)	40 (71%)	18 (53%)	151 (71%)
Some of the time	14 (18%)	7 (15%)	4 (7%)	5 (15%)	30 (14%)
None of the time	5 (6%)	2 (4%)	9 (16%)	7 (21%)	23 (11%)
I don't know	1 (1%)	0	1 (2%)	0	2 (1%)
No answer	0	2 (4%)	2 (4%)	4 (12%)	8 (4%)
Not applicable skip pattern S2Q10 (answered 'No' or 'I don't Remember')	41	47	51	74	213
Who do you show the Patient Alert Card to? (S2Q14) Select the one answer that best applies to you.					
Every doctor or dentist that I visit	67 (87%)	36 (77%)	41 (73%)	14 (41%)	158 (74%)
No one, it is just for my information	2 (3%)	2 (4%)	3 (5%)	2 (6%)	9 (4%)
Only to healthcare professionals who ask for it	9 (12%)	8 (17%)	12 (21%)	14 (41%)	43 (20%)
I don’t know	1 (1%)	1 (2%)	0	2 (6%)	4 (2%)
No answer	0	2 (4%)	3 (5%)	3 (9%)	8 (4%)

Question	No. of Patients (%)				
	UK n = 118	**Germany n = 94**	**France n = 107**	**Spain n = 108**	**Overall N = 427**
Not applicable skip pattern S2Q10 (answered 'No' or 'I don't Remember')	41	47	51	74	213
Prior to today, had someone explained the information in the Patient Alert Card for Xarelto to you? (S2Q15) Select all that apply.					
Yes, a doctor	62 (53%)	48 (51%)	39 (36%)	42 (39%)	191 (45%)
Yes, a nurse	23 (19%)	5 (5%)	11 (10%)	2 (2%)	41 (10%)
Yes, a pharmacist or someone at the chemists	15 (13%)	3 (3%)	9 (8%)	2 (2%)	29 (7%)
Yes, a friend, family member, or carer	3 (3%)	1 (1%)	1 (1%)	0	5 (1%)
No	34 (29%)	32 (34%)	50 (47%)	58 (54%)	174 (41%)
I don’t know	1 (1%)	4 (4%)	4 (4%)	5 (5%)	14 (3%)
No answer	2 (2%)	5 (5%)	5 (5%)	2 (2%)	14 (3%)

UK = United Kingdom.

Note 1: S2 indicates the second survey, so S2Q10 is question 10 from the second survey.

Note 2: Portions of patient responses not in compliance with the skip pattern instructions were omitted.

Note 3: Some patients provided multiple responses for Q14.

Table I-5. Patient Knowledge Before and After Reading the Patient Alert Card:

UK, Germany, and France

	No. of Patients (%)					
	UK (n = 118)		Germany(n = 94)		France(n = 107)	
Question	Initial Survey	After PAC Review	Initial Survey	After PAC Review	Initial Survey	After PAC Review
Xarelto is a prescription medicine used to thin the blood to prevent blood clots? (Q6)						
Yes, this is true*	115 (97%) (93% - 99%)	116 (98%) (94% - 100%)	94 (100%) (96% - 100%)	93 (99%) (94% - 100%)	100 (93%) (87% - 97%)	106 (99%) (95% - 100%)
No, this is not true	1 (1%)	1 (1%)	0	0	1 (1%)	0
I don't know	2 (2%)	0	0	0	5 (5%)	1 (1%)
No answer	0	1 (1%)	0	1 (1%)	1 (1%)	0
Blood thinning medications, such as Xarelto, may cause bleeding. Please remember that this question is asking about your knowledge in general and not about your own experience. (Q10)						
Yes, this is true*	101 (86%) (78% - 91%)	111 (94%) (88% - 98%)	76 (81%) (71% - 88%)	84 (89%) (81% - 95%)	82 (77%) (67% - 84%)	98 (92%) (85% - 96%)
No, this is not true	6 (5%)	1 (1%)	3 (3%)	2 (2%)	4 (4%)	3 (3%)
I don't know	11 (9%)	5 (4%)	14 (15%)	7 (7%)	20 (19%)	6 (6%)
No answer	0	1 (1%)	1 (1%)	1 (1%)	1 (1%)	0

Question	No. of Patients (%)					
	UK (n = 118)		Germany(n = 94)		France(n = 107)	
	Initial Survey	After PAC Review	Initial Survey	After PAC Review	Initial Survey	After PAC Review
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)						
Pain						
Yes, this may be*	33 (28%) (20% - 37%)	77 (65%) (56% - 74%)	12 (13%) (7% - 21%)	40 (43%) (32% - 53%)	14 (13%) (7% - 21%)	57 (53%) (43% - 63%)
No, this is not	30 (25%)	7 (6%)	23 (24%)	19 (20%)	34 (32%)	19 (18%)
I don't know	41 (35%)	21 (18%)	41 (44%)	20 (21%)	42 (39%)	19 (18%)
No answer	14 (12%)	13 (11%)	18 (19%)	15 (16%)	17 (16%)	12 (11%)
Swelling or discomfort						
Yes, this may be*	50 (42%) (33% - 52%)	84 (71%) (62% - 79%)	17 (18%) (11% - 27%)	44 (47%) (36% - 57%)	21 (20%) (13% - 28%)	64 (60%) (50% - 69%)
No, this is not	17 (14%)	4 (3%)	17 (18%)	15 (16%)	25 (23%)	13 (12%)
I don't know	38 (32%)	18 (15%)	41 (44%)	23 (24%)	45 (42%)	20 (19%)
No answer	13 (11%)	12 (10%)	19 (20%)	12 (13%)	16 (15%)	10 (9%)
Headache, dizziness, or weakness						
Yes, this may be*	66 (56%) (46% - 65%)	85 (72%) (63% - 80%)	27 (29%) (20% - 39%)	50 (53%) (43% - 64%)	34 (32%) (23% - 41%)	78 (73%) (63% - 81%)
No, this is not	9 (8%)	4 (3%)	13 (14%)	11 (12%)	25 (23%)	9 (8%)
I don't know	35 (30%)	19 (16%)	39 (41%)	20 (21%)	40 (37%)	15 (14%)

Question	No. of Patients (%)					
	UK (n = 118)		Germany(n = 94)		France(n = 107)	
	Initial Survey	After PAC Review	Initial Survey	After PAC Review	Initial Survey	After PAC Review
No answer	8 (7%)	10 (8%)	15 (16%)	13 (14%)	8 (7%)	5 (5%)
Unusual bruising						
Yes, this may be*	85 (72%) (63% - 80%)	98 (83%) (75% - 89%)	53 (56%) (46% - 67%)	66 (70%) (60% - 79%)	57 (53%) (43% - 63%)	84 (79%) (70% - 86%)
No, this is not	4 (3%)	1 (1%)	6 (6%)	8 (9%)	18 (17%)	5 (5%)
I don't know	22 (19%)	12 (10%)	24 (26%)	13 (14%)	24 (22%)	10 (9%)
No answer	7 (6%)	7 (6%)	11 (12%)	7 (7%)	8 (7%)	8 (7%)
I must not stop taking Xarelto at any time without consulting with my doctor. (Q12)						
Yes, this is true*	109 (92%) (86% - 96%)	111 (94%) (88% - 98%)	82 (87%) (79% - 93%)	84 (89%) (81% - 95%)	96 (90%) (82% - 95%)	100 (93%) (87% - 97%)
No, this is not true	5 (4%)	4 (3%)	2 (2%)	2 (2%)	4 (4%)	2 (2%)
I don't know	4 (3%)	2 (2%)	10 (11%)	1 (1%)	0	1 (1%)
No answer	0	1 (1%)	0	7 (7%)	7 (7%)	4 (4%)
I need to speak to my doctor prior to any intake of other medication(s). (Q13)						
Yes, this is true*	92 (78%) (69% - 85%)	109 (92%) (86% - 96%)	82 (87%) (79% - 93%)	86 (91%) (84% - 96%)	97 (91%) (83% - 95%)	104 (97%) (92% - 99%)
No, this is not true	10 (8%)	4 (3%)	6 (6%)	1 (1%)	2 (2%)	1 (1%)
I don't know	16 (14%)	5 (4%)	6 (6%)	4 (4%)	2 (2%)	2 (2%)
No answer	0	0	0	3 (3%)	6 (6%)	0

	No. of Patients (%)					
	UK (n = 118)		Germany(n = 94)		France(n = 107)	
Question	Initial Survey	After PAC Review	Initial Survey	After PAC Review	Initial Survey	After PAC Review
I need to inform my doctor or dentist about Xarelto intake prior to any kind of surgery or invasive procedure. (Q14)						
Yes, this is true*	115 (97%) (93% - 99%)	117 (99%) (95% - 100%)	93 (99%) (94% - 100%)	92 (98%) (93% - 100%)	98 (92%) (85% - 96%)	106 (99%) (95% - 100%)
No, this is not true	0	0	1 (1%)	0	2 (2%)	0
I don't know	3 (3%)	1 (1%)	0	0	1 (1%)	1 (1%)
No answer	0	0	0	2 (2%)	6 (6%)	0
I need to tell my doctor right away if I have any signs or symptoms of bleeding while taking Xarelto. (Q15)						
Yes, this is true*	108 (92%) (85% - 96%)	115 (97%) (93% - 99%)	79 (84%) (75% - 91%)	88 (94%) (87% - 98%)	91 (85%) (77% - 91%)	102 (95%) (89% - 98%)
No, this is not true	1 (1%)	2 (2%)	2 (2%)	1 (1%)	4 (4%)	1 (1%)
I don't know	9 (8%)	1 (1%)	3 (3%)	3 (3%)	6 (6%)	3 (3%)
No answer	0	0	10 (11%)	2 (2%)	6 (6%)	1 (1%)
Should Xarelto (15 mg and 20 mg tablets) be taken with food? (Q16)						
Yes*	79 (67%) (58% - 75%)	99 (84%) (76% - 90%)	44 (47%) (36% - 57%)	66 (70%) (60% - 79%)	59 (55%) (45% - 65%)	83 (78%) (68% - 85%)
No	22 (19%)	11 (9%)	23 (24%)	14 (15%)	16 (15%)	5 (5%)
I don't know	17 (14%)	7 (6%)	16 (17%)	11 (12%)	26 (24%)	19 (18%)
No answer	0	1 (1%)	11 (12%)	3 (3%)	6 (6%)	0

Question	No. of Patients (%)					
	UK (n = 118)		Germany(n = 94)		France(n = 107)	
	Initial Survey	After PAC Review	Initial Survey	After PAC Review	Initial Survey	After PAC Review
What should you do to ensure Xarelto is effective in preventing blood clots? (Q17) Select all that apply.						
Take Xarelto exactly as prescribed by your Health Care Professional*	106 (90%)	110 (93%)	76 (81%)	88 (94%)	91 (85%)	105 (98%)
Take Xarelto only when you do not feel well	1 (1%)	1 (1%)	0	0	2 (2%)	1 (1%)
Do not miss a dose of Xarelto*	51 (43%)	62 (53%)	39 (41%)	47 (50%)	52 (49%)	52 (49%)
I don't know	1 (1%)	3 (3%)	4 (4%)	3 (3%)	5 (5%)	2 (2%)
No answer	3 (3%)	0	10 (11%)	2 (2%)	7 (7%)	0
Selected both of the correct responses	43 (36%) (28% - 46%)	55 (47%) (37% - 56%)	35 (37%) (27% - 48%)	45 (48%) (37% - 58%)	47 (44%) (34% - 54%)	51 (48%) (38% - 58%)
Selected at least one of the two correct responses	114 (97%) (92% - 99%)	117 (99%) (95% - 100%)	80 (85%) (76% - 92%)	90 (96%) (89% - 99%)	96 (90%) (82% - 95%)	106 (99%) (95% - 100%)

PAC - Patient Alert Card; UK = United Kingdom.

Spain and Overall

	No. of Patients (%)			
	Spain (n = 108)		Overall (N = 427)	
Question	Initial Survey	After PAC Review	Initial Survey	After PAC Review
Xarelto is a prescription medicine used to thin the blood to prevent blood clots? (Q6)				
Yes, this is true*	102 (94%) (88% - 98%)	107 (99%) (95% - 100%)	411 (96%) (94% - 98%)	422 (99%) (97% - 100%)
No, this is not true	0	0	2 (0%)	1 (0%)
I don't know	6 (6%)	0	13 (3%)	1 (0%)
No answer	0	1 (1%)	1 (0%)	3 (1%)
Blood thinning medications, such as Xarelto, may cause bleeding. Please remember that this question is asking about your knowledge in general and not about your own experience. (Q10)				
Yes, this is true*	84 (78%) (69% - 85%)	99 (92%) (85% - 96%)	343 (80%) (76% - 84%)	392 (92%) (89% - 94%)
No, this is not true	4 (4%)	1 (1%)	17 (4%)	7 (2%)
I don't know	20 (19%)	5 (5%)	65 (15%)	23 (5%)
No answer	0	3 (3%)	2 (0%)	5 (1%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)				
Pain				
Yes, this may be*	19 (18%) (11% - 26%)	67 (62%) (52% - 71%)	78 (18%) (15% - 22%)	241 (56%) (52% - 61%)
No, this is not	33 (31%)	13 (12%)	120 (28%)	58 (14%)

Question	No. of Patients (%)			
	Spain (n = 108)		Overall (N = 427)	
	Initial Survey	After PAC Review	Initial Survey	After PAC Review
I don't know	47 (44%)	18 (17%)	171 (40%)	78 (18%)
No answer	9 (8%)	10 (9%)	58 (14%)	50 (12%)
Swelling or discomfort				
Yes, this may be*	30 (28%) (20% - 37%)	65 (60%) (50% - 69%)	118 (28%) (23% - 32%)	257 (60%) (55% - 65%)
No, this is not	23 (21%)	10 (9%)	82 (19%)	42 (10%)
I don't know	44 (41%)	20 (19%)	168 (39%)	81 (19%)
No answer	11 (10%)	13 (12%)	59 (14%)	47 (11%)
Headache, dizziness, or weakness				
Yes, this may be*	41 (38%) (29% - 48%)	77 (71%) (62% - 80%)	168 (39%) (35% - 44%)	290 (68%) (63% - 72%)
No, this is not	16 (15%)	5 (5%)	63 (15%)	29 (7%)
I don't know	43 (40%)	17 (16%)	157 (37%)	71 (17%)
No answer	8 (7%)	9 (8%)	39 (9%)	37 (9%)
Unusual bruising				
Yes, this may be*	64 (59%) (49% - 69%)	85 (79%) (70% - 86%)	259 (61%) (56% - 65%)	333 (78%) (74% - 82%)
No, this is not	10 (9%)	5 (5%)	38 (9%)	19 (4%)
I don't know	28 (26%)	12 (11%)	98 (23%)	47 (11%)

Question	No. of Patients (%)			
	Spain (n = 108)		Overall (N = 427)	
	Initial Survey	After PAC Review	Initial Survey	After PAC Review
No answer	6 (6%)	6 (6%)	32 (7%)	28 (7%)
I must not stop taking Xarelto at any time without consulting with my doctor. (Q12)				
Yes, this is true*	102 (94%) (88% - 98%)	106 (98%) (93% - 100%)	389 (91%) (88% - 94%)	401 (94%) (91% - 96%)
No, this is not true	1 (1%)	1 (1%)	12 (3%)	9 (2%)
I don't know	5 (5%)	0	19 (4%)	4 (1%)
No answer	0	1 (1%)	7 (2%)	13 (3%)
I need to speak to my doctor prior to any intake of other medication(s). (Q13)				
Yes, this is true*	98 (91%) (84% - 95%)	104 (96%) (91% - 99%)	369 (86%) (83% - 90%)	403 (94%) (92% - 96%)
No, this is not true	1 (1%)	0	19 (4%)	6 (1%)
I don't know	9 (8%)	1 (1%)	33 (8%)	12 (3%)
No answer	0	3 (3%)	6 (1%)	6 (1%)
I need to inform my doctor or dentist about Xarelto intake prior to any kind of surgery or invasive procedure. (Q14)				
Yes, this is true*	98 (91%) (84% - 95%)	105 (97%) (92% - 99%)	404 (95%) (92% - 97%)	420 (98%) (97% - 99%)
No, this is not true	2 (2%)	0	5 (1%)	0
I don't know	6 (6%)	0	10 (2%)	2 (0%)
No answer	2 (2%)	3 (3%)	8 (2%)	5 (1%)

Question	No. of Patients (%)			
	Spain (n = 108)		Overall (N = 427)	
	Initial Survey	After PAC Review	Initial Survey	After PAC Review
I need to tell my doctor right away if I have any signs or symptoms of bleeding while taking Xarelto. (Q15)				
Yes, this is true*	100 (93%) (86% - 97%)	106 (98%) (93% - 100%)	378 (89%) (85% - 91%)	411 (96%) (94% - 98%)
No, this is not true	0	0	7 (2%)	4 (1%)
I don't know	6 (6%)	0	24 (6%)	7 (2%)
No answer	2 (2%)	2 (2%)	18 (4%)	5 (1%)
Should Xarelto (15 mg and 20 mg tablets) be taken with food? (Q16)				
Yes*	73 (68%) (58% - 76%)	96 (89%) (81% - 94%)	255 (60%) (55% - 64%)	344 (81%) (76% - 84%)
No	6 (6%)	2 (2%)	67 (16%)	32 (7%)
I don't know	26 (24%)	8 (7%)	85 (20%)	45 (11%)
No answer	3 (3%)	2 (2%)	20 (5%)	6 (1%)
What should you do to ensure Xarelto is effective in preventing blood clots? (Q17) Select all that apply.				
Take Xarelto exactly as prescribed by your Health Care Professional*	98 (91%)	106 (98%)	371 (87%)	409 (96%)
Take Xarelto only when you do not feel well	1 (1%)	2 (2%)	4 (1%)	4 (1%)
Do not miss a dose of Xarelto*	43 (40%)	42 (39%)	185 (43%)	203 (48%)
I don't know	2 (2%)	0	12 (3%)	8 (2%)

	No. of Patients (%)			
	Spain (n = 108)		Overall (N = 427)	
Question	Initial Survey	After PAC Review	Initial Survey	After PAC Review
No answer	2 (2%)	2 (2%)	22 (5%)	4 (1%)
Selected both of the correct responses	37 (34%) (25% - 44%)	42 (39%) (30% - 49%)	162 (38%) (33% - 43%)	193 (45%) (40% - 50%)
Selected at least one of the two correct responses	104 (96%) (91% - 99%)	106 (98%) (93% - 100%)	394 (92%) (89% - 95%)	419 (98%) (96% - 99%)

PAC - Patient Alert Card.

Table I-6. Patient Knowledge Change After Reviewing Patient Alert Card by Country and Overall

Overall

Overall					
Initial Survey	**After Reviewing Patient Alert Card**				
Xarelto is a prescription medicine used to thin the blood to prevent blood clots? (Q6)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	408 (96%)	0	0	3 (1%)	411 (96%)
No, this is not true	1 (0%)	1 (0%)	0	0	2 (0%)
I don't know	12 (3%)	0	1 (0%)	0	13 (3%)
No answer	1 (0%)	0	0	0	1 (0%)
Total	422 (99%)	1 (0%)	1 (0%)	3 (1%)	427 (100%)
Blood thinning medications, such as Xarelto, may cause bleeding. Please remember that this question is asking about your knowledge in general and not about your own experience. (Q10)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	331 (78%)	1 (0%)	6 (1%)	5 (1%)	343 (80%)
No, this is not true	13 (3%)	3 (1%)	1 (0%)	0	17 (4%)
I don't know	46 (11%)	3 (1%)	16 (4%)	0	65 (15%)
No answer	2 (0%)	0	0	0	2 (0%)
Total	392 (92%)	7 (2%)	23 (5%)	5 (1%)	427 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Pain	Yes, this may be	No, this is not	I don't know	No answer	Total

Overall					
Initial Survey	**After Reviewing Patient Alert Card**				
Yes, this may be*	76 (18%)	0	0	2 (0%)	78 (18%)
No, this is not	56 (13%)	47 (11%)	11 (3%)	6 (1%)	120 (28%)
I don't know	95 (22%)	7 (2%)	66 (15%)	3 (1%)	171 (40%)
No answer	14 (3%)	4 (1%)	1 (0%)	39 (9%)	58 (14%)
Total	241 (56%)	58 (14%)	78 (18%)	50 (12%)	427 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Swelling or discomfort	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	114 (27%)	1 (0%)	0	3 (1%)	118 (28%)
No, this is not	36 (8%)	30 (7%)	12 (3%)	4 (1%)	82 (19%)
I don't know	88 (21%)	7 (2%)	69 (16%)	4 (1%)	168 (39%)
No answer	19 (4%)	4 (1%)	0	36 (8%)	59 (14%)
Total	257 (60%)	42 (10%)	81 (19%)	47 (11%)	427 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Headache, dizziness, or weakness	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	166 (39%)	2 (0%)	0	0	168 (39%)
No, this is not	33 (8%)	20 (5%)	5 (1%)	5 (1%)	63 (15%)

Overall					
Initial Survey	**After Reviewing Patient Alert Card**				
I don't know	83 (19%)	4 (1%)	65 (15%)	5 (1%)	157 (37%)
No answer	8 (2%)	3 (1%)	1 (0%)	27 (6%)	39 (9%)
Total	290 (68%)	29 (7%)	71 (17%)	37 (9%)	427 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Unusual bruising	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	254 (59%)	1 (0%)	3 (1%)	1 (0%)	259 (61%)
No, this is not	20 (5%)	12 (3%)	4 (1%)	2 (0%)	38 (9%)
I don't know	54 (13%)	2 (0%)	39 (9%)	3 (1%)	98 (23%)
No answer	5 (1%)	4 (1%)	1 (0%)	22 (5%)	32 (7%)
Total	333 (78%)	19 (4%)	47 (11%)	28 (7%)	427 (100%)
I must not stop taking Xarelto at any time without consulting with my doctor. (Q12)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	370 (87%)	6 (1%)	1 (0%)	12 (3%)	389 (91%)
No, this is not true	9 (2%)	2 (0%)	1 (0%)	0	12 (3%)
I don't know	16 (4%)	1 (0%)	2 (0%)	0	19 (4%)
No answer	6 (1%)	0	0	1 (0%)	7 (2%)
Total	401 (94%)	9 (2%)	4 (1%)	13 (3%)	427 (100%)
I need to speak to my doctor prior to any intake of other medication(s). (Q13)					

Overall					
Initial Survey	**After Reviewing Patient Alert Card**				
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	361 (85%)	0	2 (0%)	6 (1%)	369 (86%)
No, this is not true	11 (3%)	5 (1%)	3 (1%)	0	19 (4%)
I don't know	25 (6%)	1 (0%)	7 (2%)	0	33 (8%)
No answer	6 (1%)	0	0	0	6 (1%)
Total	403 (94%)	6 (1%)	12 (3%)	6 (1%)	427 (100%)
I need to inform my doctor or dentist about Xarelto intake prior to any kind of surgery or invasive procedure. (Q14)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	398 (93%)	0	1 (0%)	5 (1%)	404 (95%)
No, this is not true	4 (1%)	0	1 (0%)	0	5 (1%)
I don't know	10 (2%)	0	0	0	10 (2%)
No answer	8 (2%)	0	0	0	8 (2%)
Total	420 (98%)	0	2 (0%)	5 (1%)	427 (100%)
I need to tell my doctor right away if I have any signs or symptoms of bleeding while taking Xarelto (Q15)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	370 (87%)	1 (0%)	3 (1%)	4 (1%)	378 (89%)
No, this is not true	4 (1%)	2 (0%)	1 (0%)	0	7 (2%)
I don't know	20 (5%)	1 (0%)	3 (1%)	0	24 (6%)

Overall					
Initial Survey	**After Reviewing Patient Alert Card**				
No answer	17 (4%)	0	0	1 (0%)	18 (4%)
Total	411 (96%)	4 (1%)	7 (2%)	5 (1%)	427 (100%)
	Should Xarelto (15 mg and 20 mg tablets) be taken with food? (Q16)				
	Yes	No	I don't know	No answer	Total
Yes*	247 (58%)	1 (0%)	4 (1%)	3 (1%)	255 (60%)
No	35 (8%)	25 (6%)	5 (1%)	2 (0%)	67 (16%)
I don't know	47 (11%)	5 (1%)	33 (8%)	0	85 (20%)
No answer	15 (4%)	1 (0%)	3 (1%)	1 (0%)	20 (5%)
Total	344 (81%)	32 (7%)	45 (11%)	6 (1%)	427 (100%)
	What should you do to ensure Xarelto is effective in preventing blood clots? (Q17) Select all that apply.				
	Selected both correct responses	Selected one correct response	Selected response but none correct	No answer	Total
Selected both correct responses	137 (32%)	24 (6%)	0	1 (0%)	162 (38%)
Selected one correct response	47 (11%)	183 (43%)	0	2 (0%)	232 (54%)
Selected response but none correct	3 (1%)	3 (1%)	4 (1%)	1 (0%)	11 (3%)
No answer	6 (1%)	16 (4%)	0	0	22 (5%)
Total	193 (45%)	226 (53%)	4 (1%)	4 (1%)	427 (100%)

France

France					
Initial Survey	**After Reviewing Patient Alert Card**				
Xarelto is a prescription medicine used to thin the blood to prevent blood clots? (Q6)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	100 (93%)	0	0	0	100 (93%)
No, this is not true	1 (1%)	0	0	0	1 (1%)
I don't know	4 (4%)	0	1 (1%)	0	5 (5%)
No answer	1 (1%)	0	0	0	1 (1%)
Total	106 (99%)	0	1 (1%)	0	107 (100%)
Blood thinning medications, such as Xarelto, may cause bleeding. Please remember that this question is asking about your knowledge in general and not about your own experience. (Q10)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	80 (75%)	1 (1%)	1 (1%)	0	82 (77%)
No, this is not true	2 (2%)	2 (2%)	0	0	4 (4%)
I don't know	15 (14%)	0	5 (5%)	0	20 (19%)
No answer	1 (1%)	0	0	0	1 (1%)
Total	98 (92%)	3 (3%)	6 (6%)	0	107 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Pain	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	14 (13%)	0	0	0	14 (13%)

France					
Initial Survey	**After Reviewing Patient Alert Card**				
No, this is not	14 (13%)	15 (14%)	3 (3%)	2 (2%)	34 (32%)
I don't know	21 (20%)	4 (4%)	16 (15%)	1 (1%)	42 (39%)
No answer	8 (7%)	0	0	9 (8%)	17 (16%)
Total	57 (53%)	19 (18%)	19 (18%)	12 (11%)	107 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Swelling or discomfort	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	20 (19%)	0	0	1 (1%)	21 (20%)
No, this is not	12 (11%)	11 (10%)	1 (1%)	1 (1%)	25 (23%)
I don't know	24 (22%)	2 (2%)	19 (18%)	0	45 (42%)
No answer	8 (7%)	0	0	8 (7%)	16 (15%)
Total	64 (60%)	13 (12%)	20 (19%)	10 (9%)	107 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Headache, dizziness, or weakness	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	34 (32%)	0	0	0	34 (32%)
No, this is not	15 (14%)	8 (7%)	1 (1%)	1 (1%)	25 (23%)
I don't know	25 (23%)	1 (1%)	13 (12%)	1 (1%)	40 (37%)

France					
Initial Survey	**After Reviewing Patient Alert Card**				
No answer	4 (4%)	0	1 (1%)	3 (3%)	8 (7%)
Total	78 (73%)	9 (8%)	15 (14%)	5 (5%)	107 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Unusual bruising	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	56 (52%)	0	1 (1%)	0	57 (53%)
No, this is not	11 (10%)	4 (4%)	2 (2%)	1 (1%)	18 (17%)
I don't know	16 (15%)	0	7 (7%)	1 (1%)	24 (22%)
No answer	1 (1%)	1 (1%)	0	6 (6%)	8 (7%)
Total	84 (79%)	5 (5%)	10 (9%)	8 (7%)	107 (100%)
I must not stop taking Xarelto at any time without consulting with my doctor. (Q12)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	91 (85%)	2 (2%)	0	3 (3%)	96 (90%)
No, this is not true	3 (3%)	0	1 (1%)	0	4 (4%)
I don't know	0	0	0	0	0
No answer	6 (6%)	0	0	1 (1%)	7 (7%)
Total	100 (93%)	2 (2%)	1 (1%)	4 (4%)	107 (100%)
I need to speak to my doctor prior to any intake of other medication(s). (Q13)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total

France					
Initial Survey	**After Reviewing Patient Alert Card**				
Yes, this is true*	96 (90%)	0	1 (1%)	0	97 (91%)
No, this is not true	0	1 (1%)	1 (1%)	0	2 (2%)
I don't know	2 (2%)	0	0	0	2 (2%)
No answer	6 (6%)	0	0	0	6 (6%)
Total	104 (97%)	1 (1%)	2 (2%)	0	107 (100%)
I need to inform my doctor or dentist about Xarelto intake prior to any kind of surgery or invasive procedure. (Q14)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	98 (92%)	0	0	0	98 (92%)
No, this is not true	1 (1%)	0	1 (1%)	0	2 (2%)
I don't know	1 (1%)	0	0	0	1 (1%)
No answer	6 (6%)	0	0	0	6 (6%)
Total	106 (99%)	0	1 (1%)	0	107 (100%)
I need to tell my doctor right away if I have any signs or symptoms of bleeding while taking Xarelto (Q15)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	90 (84%)	0	1 (1%)	0	91 (85%)
No, this is not true	2 (2%)	1 (1%)	1 (1%)	0	4 (4%)
I don't know	5 (5%)	0	1 (1%)	0	6 (6%)
No answer	5 (5%)	0	0	1 (1%)	6 (6%)
Total	102 (95%)	1 (1%)	3 (3%)	1 (1%)	107 (100%)

France					
Initial Survey	**After Reviewing Patient Alert Card**				
	Should Xarelto (15 mg and 20 mg tablets) be taken with food? (Q16)				
	Yes	No	I don't know	No answer	Total
Yes*	56 (52%)	0	3 (3%)	0	59 (55%)
No	9 (8%)	4 (4%)	3 (3%)	0	16 (15%)
I don't know	13 (12%)	1 (1%)	12 (11%)	0	26 (24%)
No answer	5 (5%)	0	1 (1%)	0	6 (6%)
Total	83 (78%)	5 (5%)	19 (18%)	0	107 (100%)
	What should you do to ensure Xarelto is effective in preventing blood clots? (Q17) Select all that apply.				
	Selected both correct responses	Selected one correct response	Selected response but none correct	No answer	Total
Selected both correct responses	40 (37%)	7 (7%)	0	0	47 (44%)
Selected one correct response	8 (7%)	41 (38%)	0	0	49 (46%)
Selected response but none correct	2 (2%)	1 (1%)	1 (1%)	0	4 (4%)
No answer	1 (1%)	6 (6%)	0	0	7 (7%)
Total	51 (48%)	55 (51%)	1 (1%)	0	107 (100%)

Germany

Germany					
Initial Survey	**After Reviewing Patient Alert Card**				
Xarelto is a prescription medicine used to thin the blood to prevent blood clots? (Q6)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	93 (99%)	0	0	1 (1%)	94 (100%)
No, this is not true	0	0	0	0	0
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Total	93 (99%)	0	0	1 (1%)	94 (100%)
Blood thinning medications, such as Xarelto, may cause bleeding. Please remember that this question is asking about your knowledge in general and not about your own experience. (Q10)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	74 (79%)	0	1 (1%)	1 (1%)	76 (81%)
No, this is not true	3 (3%)	0	0	0	3 (3%)
I don't know	6 (6%)	2 (2%)	6 (6%)	0	14 (15%)
No answer	1 (1%)	0	0	0	1 (1%)
Total	84 (89%)	2 (2%)	7 (7%)	1 (1%)	94 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Pain	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	11 (12%)	0	0	1 (1%)	12 (13%)

Germany					
Initial Survey	**After Reviewing Patient Alert Card**				
No, this is not	6 (6%)	16 (17%)	0	1 (1%)	23 (24%)
I don't know	21 (22%)	0	19 (20%)	1 (1%)	41 (44%)
No answer	2 (2%)	3 (3%)	1 (1%)	12 (13%)	18 (19%)
Total	40 (43%)	19 (20%)	20 (21%)	15 (16%)	94 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Swelling or discomfort	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	16 (17%)	0	0	1 (1%)	17 (18%)
No, this is not	3 (3%)	10 (11%)	2 (2%)	2 (2%)	17 (18%)
I don't know	19 (20%)	1 (1%)	21 (22%)	0	41 (44%)
No answer	6 (6%)	4 (4%)	0	9 (10%)	19 (20%)
Total	44 (47%)	15 (16%)	23 (24%)	12 (13%)	94 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Headache, dizziness, or weakness	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	26 (28%)	1 (1%)	0	0	27 (29%)
No, this is not	4 (4%)	7 (7%)	1 (1%)	1 (1%)	13 (14%)
I don't know	19 (20%)	0	19 (20%)	1 (1%)	39 (41%)

Germany					
Initial Survey	**After Reviewing Patient Alert Card**				
No answer	1 (1%)	3 (3%)	0	11 (12%)	15 (16%)
Total	50 (53%)	11 (12%)	20 (21%)	13 (14%)	94 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Unusual bruising	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	51 (54%)	1 (1%)	1 (1%)	0	53 (56%)
No, this is not	0	4 (4%)	1 (1%)	1 (1%)	6 (6%)
I don't know	13 (14%)	0	10 (11%)	1 (1%)	24 (26%)
No answer	2 (2%)	3 (3%)	1 (1%)	5 (5%)	11 (12%)
Total	66 (70%)	8 (9%)	13 (14%)	7 (7%)	94 (100%)
I must not stop taking Xarelto at any time without consulting with my doctor. (Q12)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	74 (79%)	1 (1%)	0	7 (7%)	82 (87%)
No, this is not true	1 (1%)	1 (1%)	0	0	2 (2%)
I don't know	9 (10%)	0	1 (1%)	0	10 (11%)
No answer	0	0	0	0	0
Total	84 (89%)	2 (2%)	1 (1%)	7 (7%)	94 (100%)
I need to speak to my doctor prior to any intake of other medication(s). (Q13)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total

Germany					
Initial Survey	**After Reviewing Patient Alert Card**				
Yes, this is true*	78 (83%)	0	1 (1%)	3 (3%)	82 (87%)
No, this is not true	4 (4%)	1 (1%)	1 (1%)	0	6 (6%)
I don't know	4 (4%)	0	2 (2%)	0	6 (6%)
No answer	0	0	0	0	0
Total	86 (91%)	1 (1%)	4 (4%)	3 (3%)	94 (100%)
I need to inform my doctor or dentist about Xarelto intake prior to any kind of surgery or invasive procedure. (Q14)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	91 (97%)	0	0	2 (2%)	93 (99%)
No, this is not true	1 (1%)	0	0	0	1 (1%)
I don't know	0	0	0	0	0
No answer	0	0	0	0	0
Total	92 (98%)	0	0	2 (2%)	94 (100%)
I need to tell my doctor right away if I have any signs or symptoms of bleeding while taking Xarelto (Q15)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	75 (80%)	0	2 (2%)	2 (2%)	79 (84%)
No, this is not true	1 (1%)	1 (1%)	0	0	2 (2%)
I don't know	2 (2%)	0	1 (1%)	0	3 (3%)
No answer	10 (11%)	0	0	0	10 (11%)
Total	88 (94%)	1 (1%)	3 (3%)	2 (2%)	94 (100%)

Germany					
Initial Survey	**After Reviewing Patient Alert Card**				
Should Xarelto (15 mg and 20 mg tablets) be taken with food? (Q16)					
	Yes	No	I don't know	No answer	Total
Yes*	41 (44%)	1 (1%)	1 (1%)	1 (1%)	44 (47%)
No	11 (12%)	10 (11%)	1 (1%)	1 (1%)	23 (24%)
I don't know	7 (7%)	2 (2%)	7 (7%)	0	16 (17%)
No answer	7 (7%)	1 (1%)	2 (2%)	1 (1%)	11 (12%)
Total	66 (70%)	14 (15%)	11 (12%)	3 (3%)	94 (100%)
What should you do to ensure Xarelto is effective in preventing blood clots? (Q17) Select all that apply.					
	Selected both correct responses	Selected one correct response	Selected response but none correct	No answer	Total
Selected both correct responses	29 (31%)	5 (5%)	0	1 (1%)	35 (37%)
Selected one correct response	14 (15%)	31 (33%)	0	0	45 (48%)
Selected response but none correct	0	1 (1%)	2 (2%)	1 (1%)	4 (4%)
No answer	2 (2%)	8 (9%)	0	0	10 (11%)
Total	45 (48%)	45 (48%)	2 (2%)	2 (2%)	94 (100%)

Spain

Spain					
Initial Survey	**After Reviewing Patient Alert Card**				
Xarelto is a prescription medicine used to thin the blood to prevent blood clots? (Q6)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	101 (94%)	0	0	1 (1%)	102 (94%)
No, this is not true	0	0	0	0	0
I don't know	6 (6%)	0	0	0	6 (6%)
No answer	0	0	0	0	0
Total	107 (99%)	0	0	1 (1%)	108 (100%)
Blood thinning medications, such as Xarelto, may cause bleeding. Please remember that this question is asking about your knowledge in general and not about your own experience. (Q10)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	79 (73%)	0	2 (2%)	3 (3%)	84 (78%)
No, this is not true	4 (4%)	0	0	0	4 (4%)
I don't know	16 (15%)	1 (1%)	3 (3%)	0	20 (19%)
No answer	0	0	0	0	0
Total	99 (92%)	1 (1%)	5 (5%)	3 (3%)	108 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Pain	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	19 (18%)	0	0	0	19 (18%)

Spain					
Initial Survey	**After Reviewing Patient Alert Card**				
No, this is not	18 (17%)	11 (10%)	2 (2%)	2 (2%)	33 (31%)
I don't know	28 (26%)	2 (2%)	16 (15%)	1 (1%)	47 (44%)
No answer	2 (2%)	0	0	7 (6%)	9 (8%)
Total	67 (62%)	13 (12%)	18 (17%)	10 (9%)	108 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Swelling or discomfort	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	28 (26%)	1 (1%)	0	1 (1%)	30 (28%)
No, this is not	13 (12%)	6 (6%)	3 (3%)	1 (1%)	23 (21%)
I don't know	22 (20%)	3 (3%)	17 (16%)	2 (2%)	44 (41%)
No answer	2 (2%)	0	0	9 (8%)	11 (10%)
Total	65 (60%)	10 (9%)	20 (19%)	13 (12%)	108 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Headache, dizziness, or weakness	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	41 (38%)	0	0	0	41 (38%)
No, this is not	10 (9%)	2 (2%)	2 (2%)	2 (2%)	16 (15%)
I don't know	24 (22%)	3 (3%)	15 (14%)	1 (1%)	43 (40%)

Spain					
Initial Survey			**After Reviewing Patient Alert Card**		
No answer	2 (2%)	0	0	6 (6%)	8 (7%)
Total	77 (71%)	5 (5%)	17 (16%)	9 (8%)	108 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Unusual bruising	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	63 (58%)	0	1 (1%)	0	64 (59%)
No, this is not	7 (6%)	3 (3%)	0	0	10 (9%)
I don't know	14 (13%)	2 (2%)	11 (10%)	1 (1%)	28 (26%)
No answer	1 (1%)	0	0	5 (5%)	6 (6%)
Total	85 (79%)	5 (5%)	12 (11%)	6 (6%)	108 (100%)
I must not stop taking Xarelto at any time without consulting with my doctor. (Q12)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	100 (93%)	1 (1%)	0	1 (1%)	102 (94%)
No, this is not true	1 (1%)	0	0	0	1 (1%)
I don't know	5 (5%)	0	0	0	5 (5%)
No answer	0	0	0	0	0
Total	106 (98%)	1 (1%)	0	1 (1%)	108 (100%)
I need to speak to my doctor prior to any intake of other medication(s). (Q13)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total

Spain					
Initial Survey	**After Reviewing Patient Alert Card**				
Yes, this is true*	95 (88%)	0	0	3 (3%)	98 (91%)
No, this is not true	1 (1%)	0	0	0	1 (1%)
I don't know	8 (7%)	0	1 (1%)	0	9 (8%)
No answer	0	0	0	0	0
Total	104 (96%)	0	1 (1%)	3 (3%)	108 (100%)
I need to inform my doctor or dentist about Xarelto intake prior to any kind of surgery or invasive procedure. (Q14)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	95 (88%)	0	0	3 (3%)	98 (91%)
No, this is not true	2 (2%)	0	0	0	2 (2%)
I don't know	6 (6%)	0	0	0	6 (6%)
No answer	2 (2%)	0	0	0	2 (2%)
Total	105 (97%)	0	0	3 (3%)	108 (100%)
I need to tell my doctor right away if I have any signs or symptoms of bleeding while taking Xarelto (Q15)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	98 (91%)	0	0	2 (2%)	100 (93%)
No, this is not true	0	0	0	0	0
I don't know	6 (6%)	0	0	0	6 (6%)
No answer	2 (2%)	0	0	0	2 (2%)
Total	106 (98%)	0	0	2 (2%)	108 (100%)

Spain					
Initial Survey	**After Reviewing Patient Alert Card**				
Should Xarelto (15 mg and 20 mg tablets) be taken with food? (Q16)					
	Yes	No	I don't know	No answer	Total
Yes*	71 (66%)	0	0	2 (2%)	73 (68%)
No	3 (3%)	2 (2%)	1 (1%)	0	6 (6%)
I don't know	19 (18%)	0	7 (6%)	0	26 (24%)
No answer	3 (3%)	0	0	0	3 (3%)
Total	96 (89%)	2 (2%)	8 (7%)	2 (2%)	108 (100%)
What should you do to ensure Xarelto is effective in preventing blood clots? (Q17) Select all that apply.					
	Selected both correct responses	Selected one correct response	Selected response but none correct	No answer	Total
Selected both correct responses	31 (29%)	6 (6%)	0	0	37 (34%)
Selected one correct response	9 (8%)	56 (52%)	0	2 (2%)	67 (62%)
Selected response but none correct	1 (1%)	1 (1%)	0	0	2 (2%)
No answer	1 (1%)	1 (1%)	0	0	2 (2%)
Total	42 (39%)	64 (59%)	0	2 (2%)	108 (100%)

United Kingdom

United Kingdom					
Initial Survey	**After Reviewing Patient Alert Card**				
Xarelto is a prescription medicine used to thin the blood to prevent blood clots? (Q6)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	114 (97%)	0	0	1 (1%)	115 (97%)
No, this is not true	0	1 (1%)	0	0	1 (1%)
I don't know	2 (2%)	0	0	0	2 (2%)
No answer	0	0	0	0	0
Total	116 (98%)	1 (1%)	0	1 (1%)	118 (100%)
Blood thinning medications, such as Xarelto, may cause bleeding. Please remember that this question is asking about your knowledge in general and not about your own experience. (Q10)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	98 (83%)	0	2 (2%)	1 (1%)	101 (86%)
No, this is not true	4 (3%)	1 (1%)	1 (1%)	0	6 (5%)
I don't know	9 (8%)	0	2 (2%)	0	11 (9%)
No answer	0	0	0	0	0
Total	111 (94%)	1 (1%)	5 (4%)	1 (1%)	118 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Pain	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	32 (27%)	0	0	1 (1%)	33 (28%)

United Kingdom					
Initial Survey	**After Reviewing Patient Alert Card**				
No, this is not	18 (15%)	5 (4%)	6 (5%)	1 (1%)	30 (25%)
I don't know	25 (21%)	1 (1%)	15 (13%)	0	41 (35%)
No answer	2 (2%)	1 (1%)	0	11 (9%)	14 (12%)
Total	77 (65%)	7 (6%)	21 (18%)	13 (11%)	118 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Swelling or discomfort	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	50 (42%)	0	0	0	50 (42%)
No, this is not	8 (7%)	3 (3%)	6 (5%)	0	17 (14%)
I don't know	23 (19%)	1 (1%)	12 (10%)	2 (2%)	38 (32%)
No answer	3 (3%)	0	0	10 (8%)	13 (11%)
Total	84 (71%)	4 (3%)	18 (15%)	12 (10%)	118 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Headache, dizziness, or weakness	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	65 (55%)	1 (1%)	0	0	66 (56%)
No, this is not	4 (3%)	3 (3%)	1 (1%)	1 (1%)	9 (8%)
I don't know	15 (13%)	0	18 (15%)	2 (2%)	35 (30%)
No answer	1 (1%)	0	0	7 (6%)	8 (7%)

United Kingdom					
Initial Survey	**After Reviewing Patient Alert Card**				
Total	85 (72%)	4 (3%)	19 (16%)	10 (8%)	118 (100%)
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)					
Unusual bruising	Yes, this may be	No, this is not	I don't know	No answer	Total
Yes, this may be*	84 (71%)	0	0	1 (1%)	85 (72%)
No, this is not	2 (2%)	1 (1%)	1 (1%)	0	4 (3%)
I don't know	11 (9%)	0	11 (9%)	0	22 (19%)
No answer	1 (1%)	0	0	6 (5%)	7 (6%)
Total	98 (83%)	1 (1%)	12 (10%)	7 (6%)	118 (100%)
I must not stop taking Xarelto at any time without consulting with my doctor. (Q12)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	105 (89%)	2 (2%)	1 (1%)	1 (1%)	109 (92%)
No, this is not true	4 (3%)	1 (1%)	0	0	5 (4%)
I don't know	2 (2%)	1 (1%)	1 (1%)	0	4 (3%)
No answer	0	0	0	0	0
Total	111 (94%)	4 (3%)	2 (2%)	1 (1%)	118 (100%)
I need to speak to my doctor prior to any intake of other medication(s). (Q13)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	92 (78%)	0	0	0	92 (78%)

United Kingdom					
Initial Survey	**After Reviewing Patient Alert Card**				
No, this is not true	6 (5%)	3 (3%)	1 (1%)	0	10 (8%)
I don't know	11 (9%)	1 (1%)	4 (3%)	0	16 (14%)
No answer	0	0	0	0	0
Total	109 (92%)	4 (3%)	5 (4%)	0	118 (100%)
I need to inform my doctor or dentist about Xarelto intake prior to any kind of surgery or invasive procedure. (Q14)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	114 (97%)	0	1 (1%)	0	115 (97%)
No, this is not true	0	0	0	0	0
I don't know	3 (3%)	0	0	0	3 (3%)
No answer	0	0	0	0	0
Total	117 (99%)	0	1 (1%)	0	118 (100%)
I need to tell my doctor right away if I have any signs or symptoms of bleeding while taking Xarelto (Q15)					
	Yes, this is true	No, this is not true	I don't know	No answer	Total
Yes, this is true*	107 (91%)	1 (1%)	0	0	108 (92%)
No, this is not true	1 (1%)	0	0	0	1 (1%)
I don't know	7 (6%)	1 (1%)	1 (1%)	0	9 (8%)
No answer	0	0	0	0	0
Total	115 (97%)	2 (2%)	1 (1%)	0	118 (100%)
Should Xarelto (15 mg and 20 mg tablets) be taken with food? (Q16)					
	Yes	No	I don't know	No answer	Total

United Kingdom					
Initial Survey	**After Reviewing Patient Alert Card**				
Yes*	79 (67%)	0	0	0	79 (67%)
No	12 (10%)	9 (8%)	0	1 (1%)	22 (19%)
I don't know	8 (7%)	2 (2%)	7 (6%)	0	17 (14%)
No answer	0	0	0	0	0
Total	99 (84%)	11 (9%)	7 (6%)	1 (1%)	118 (100%)
What should you do to ensure Xarelto is effective in preventing blood clots? (Q17) Select all that apply.					
	Selected both correct responses	Selected one correct response	Selected response but none correct	No answer	Total
Selected both correct responses	37 (31%)	6 (5%)	0	0	43 (36%)
Selected one correct response	16 (14%)	55 (47%)	0	0	71 (60%)
Selected response but none correct	0	0	1 (1%)	0	1 (1%)
No answer	2 (2%)	1 (1%)	0	0	3 (3%)
Total	55 (47%)	62 (53%)	1 (1%)	0	118 (100%)

Table I-7. Patient Open Text Responses

Country	Free Response
Where did you get most of your information about Xarelto? (Q8) Other, please specify:	
France	PPD
Germany	
Spain	
UK	
I was prescribed Xarelto for the following reason(s) (Q18) Other, please specify:	
France	PPD

Country	Free Response
Germany	PPD

I was prescribed Xarelto for the following reason(s) (Q18) Other, please specify:

Germany	PPD

Country	Free Response
Spain	PPD

I was prescribed Xarelto for the following reason(s) (Q18) Other, please specify:

Spain	PPD

Country	Free Response
	PPD
UK	

I was prescribed Xarelto for the following reason(s) (Q18) Other, please specify:

UK	PPD

Country	Free Response
	PPD

Table I-8. Characteristics of Participants and Decliners

Variable	No. of Patients (%)	
	Completed[a] n = 427	Declined n = 41
Age		
18-25 years	5 (1.2%)	0
26-35 years	12 (2.8%)	1 (2.6%)
36-45 years	19 (4.4%)	1 (2.6%)
46-55 years	59 (13.8%)	2 (5.1%)
56-65 years	77 (18.0%)	3 (7.7%)
66-75 years	118 (27.6%)	13 (33.3%)
76-85 years	119 (27.9%)	12 (30.8%)
86 years or older	18 (4.2%)	7 (17.9%)
Missing	0	2
Sex		
Female	191 (44.7%)	19 (48.7%)
Male	236 (55.3%)	20 (51.3%)
Missing	0	2

Variable	No. of Patients (%)	
	Completed[a] n = 427	Declined n = 41
Indication for which Xarelto was prescribed		
Atrial Fibrillation	289 (67.7%)	27 (71.1%)
Deep Vein Thrombosis And Secondary Prevention	138 (32.3%)	11 (28.9%)
Missing	0	3

[a] Data are based on screening information collected by the sites at recruitment which may be different than patient self-reported responses to the questionnaire.

Table I-9. Patient Knowledge Before and After Reading the Patient Alert Card by Previous Experience With Taking Prescription Anti-Coagulants

	No. of Patients (%)			
	Have Taken (n = 256)		Have Not Taken (n = 158)	
Question	**Initial Survey**	**After PAC Review**	**Initial Survey**	**After PAC Review**
Xarelto is a prescription medicine used to thin the blood to prevent blood clots? (Q6)				
Yes, this is true*	247 (96%)	252 (98%)	155 (98%)	158 (100%)
No, this is not true	2 (1%)	1 (0%)	0	0
I don't know	7 (3%)	0	3 (2%)	0
No answer	0	3 (1%)	0	0
Blood thinning medications, such as Xarelto, may cause bleeding. Please remember that this question is asking about your knowledge in general and not about your own experience. (Q10)				
Yes, this is true*	210 (82%)	234 (91%)	126 (80%)	147 (93%)
No, this is not true	8 (3%)	3 (1%)	8 (5%)	3 (2%)
I don't know	37 (14%)	14 (5%)	23 (15%)	8 (5%)
No answer	1 (0%)	5 (2%)	1 (1%)	0
Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and not about your own experience. (Q11)				
Pain				
Yes, this may be*	43 (17%)	146 (57%)	33 (21%)	89 (56%)
No, this is not	81 (32%)	39 (15%)	38 (24%)	17 (11%)
I don't know	104 (41%)	43 (17%)	60 (38%)	32 (20%)
No answer	28 (11%)	28 (11%)	27 (17%)	20 (13%)

	No. of Patients (%)			
	Have Taken (n = 256)		Have Not Taken (n = 158)	
Question	**Initial Survey**	**After PAC Review**	**Initial Survey**	**After PAC Review**
Swelling or discomfort				
Yes, this may be*	69 (27%)	154 (60%)	47 (30%)	97 (61%)
No, this is not	52 (20%)	27 (11%)	29 (18%)	14 (9%)
I don't know	105 (41%)	49 (19%)	56 (35%)	28 (18%)
No answer	30 (12%)	26 (10%)	26 (16%)	19 (12%)
Headache, dizziness, or weakness				
Yes, this may be*	104 (41%)	179 (70%)	62 (39%)	106 (67%)
No, this is not	34 (13%)	14 (5%)	28 (18%)	13 (8%)
I don't know	97 (38%)	42 (16%)	53 (34%)	25 (16%)
No answer	21 (8%)	21 (8%)	15 (9%)	14 (9%)
Unusual bruising				
Yes, this may be*	158 (62%)	203 (79%)	98 (62%)	124 (78%)
No, this is not	22 (9%)	12 (5%)	15 (9%)	6 (4%)
I don't know	58 (23%)	25 (10%)	33 (21%)	18 (11%)
No answer	18 (7%)	16 (6%)	12 (8%)	10 (6%)
I must not stop taking Xarelto at any time without consulting with my doctor. (Q12)				
Yes, this is true*	234 (91%)	242 (95%)	146 (92%)	148 (94%)
No, this is not true	5 (2%)	6 (2%)	5 (3%)	3 (2%)
I don't know	12 (5%)	1 (0%)	5 (3%)	2 (1%)

	No. of Patients (%)			
	Have Taken (n = 256)		Have Not Taken (n = 158)	
Question	**Initial Survey**	**After PAC Review**	**Initial Survey**	**After PAC Review**
No answer	5 (2%)	7 (3%)	2 (1%)	5 (3%)
I need to speak to my doctor prior to any intake of other medication(s). (Q13)				
Yes, this is true*	220 (86%)	244 (95%)	138 (87%)	147 (93%)
No, this is not true	11 (4%)	2 (1%)	7 (4%)	4 (3%)
I don't know	20 (8%)	6 (2%)	12 (8%)	5 (3%)
No answer	5 (2%)	4 (2%)	1 (1%)	2 (1%)
I need to inform my doctor or dentist about Xarelto intake prior to any kind of surgery or invasive procedure. (Q14)				
Yes, this is true*	239 (93%)	251 (98%)	154 (97%)	157 (99%)
No, this is not true	4 (2%)	0	0	0
I don't know	6 (2%)	1 (0%)	3 (2%)	0
No answer	7 (3%)	4 (2%)	1 (1%)	1 (1%)
I need to tell my doctor right away if I have any signs or symptoms of bleeding while taking Xarelto. (Q15)				
Yes, this is true*	231 (90%)	250 (98%)	139 (88%)	149 (94%)
No, this is not true	3 (1%)	1 (0%)	2 (1%)	3 (2%)
I don't know	10 (4%)	1 (0%)	11 (7%)	5 (3%)
No answer	12 (5%)	4 (2%)	6 (4%)	1 (1%)
Should Xarelto (15 mg and 20 mg tablets) be taken with food? (Q16)				
Yes*	151 (59%)	207 (81%)	96 (61%)	128 (81%)
No	37 (14%)	16 (6%)	28 (18%)	14 (9%)

	No. of Patients (%)			
	Have Taken (n = 256)		Have Not Taken (n = 158)	
Question	**Initial Survey**	**After PAC Review**	**Initial Survey**	**After PAC Review**
I don't know	55 (21%)	30 (12%)	27 (17%)	13 (8%)
No answer	13 (5%)	3 (1%)	7 (4%)	3 (2%)
What should you do to ensure Xarelto is effective in preventing blood clots? (Q17) Select all that apply.				
Take Xarelto exactly as prescribed by your Health Care Professional*	222 (87%)	244 (95%)	140 (89%)	153 (97%)
Take Xarelto only when you do not feel well	3 (1%)	2 (1%)	1 (1%)	2 (1%)
Do not miss a dose of Xarelto*	116 (45%)	120 (47%)	64 (41%)	79 (50%)
I don't know	5 (2%)	4 (2%)	5 (3%)	2 (1%)
No answer	13 (5%)	3 (1%)	8 (5%)	1 (1%)
Selected both of the correct responses	100 (39%)	113 (44%)	58 (37%)	76 (48%)
Selected at least one of the two correct responses	238 (93%)	251 (98%)	146 (92%)	156 (99%)

PAC = Patient Alert Card.

Note: 12 patients indicated that they did not know about ever taking any prescription blood thinners. One patient did not respond.

Signature Page - Qualified Person Responsible for Pharmacovigilance (QPPV)

Study Title	Xarelto (Rivaroxaban) Risk Minimisation Plan Evaluation: Patient and Physician Knowledge of Key Safety Messages
Product	Rivaroxaban, BAY59-7939
Indication	Prevention of venous thromboembolism Prevention of stroke in patients with atrial fibrillation Treatment of venous thromboembolism
Sponsor's Name and Address:	Bayer Healthcare AG, 51368 Leverkusen, Germany
IMPACT Study Number:	16167
EU PAS Register Number	ENCEPP/SDPP/3911
Development phase:	Post-Authorization
Study Type:	PASS
Investigator:	PPD

Function:	Qualified Person Responsible for Pharmacovigilance
Name:	PPD
Title:	
Address:	Bayer Pharma AG, D-13353 Berlin, Germany

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature: Oct. 20th, 2015, PPD

Confidentiality statement:

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