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Rivaroxaban compared with standard thromboprophylaxis after major orthopaedic surgery: co-medication interactions

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The XAMOS study confirmed the efficacy and safety of rivaroxaban seen in the phase III (RECORD) Regulation of Coagulation in Orthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism
- Rivaroxaban is metabolized via CYP3A4 and a substrate of P-gp; drugs affecting these pathways can influence the pharmacokinetics of rivaroxaban.
- Concomitant use of NSAIDs or PAIs with anticoagulants may increase bleeding risks.

WHAT THIS STUDY ADDS

- Concomitant CYP3A4/P-gp inhibitor/inducer use is infrequent in routine clinical practice.
- PAI users had overall higher incidences of symptomatic thromboembolic events compared with non-users.
- Concomitant PAI or NSAID use was associated with more bleeding events in both rivaroxaban and SOC patients, although the benefit–risk profile of rivaroxaban was maintained.

AIM

The aim of the present study was to analyse concomitant drug use and its association with outcome in patients (N = 17 701) receiving rivaroxaban or standard of care (SOC) for the prevention of venous thromboembolism after major orthopaedic surgery in the non-interventional, phase IV XAMOS (Xarelto® in the prophylaxis of post-surgical venous thromboembolism after elective major orthopaedic surgery of hip or knee) study.

METHODS

Concomitant drug use was at the discretion of the treating physician. Prespecified co-medications of interest were cytochrome P450 (CYP) 3A4/P-glycoprotein inhibitors/inducers, platelet aggregation inhibitors (PAIs) and nonsteroidal anti-inflammatory drugs (NSAIDs). Crude event incidences were compared between rivaroxaban and SOC groups.

RESULTS

CYP3A4/P-glycoprotein inhibitor/inducer use was infrequent, in contrast to PAI (~7%) and NSAID (~52%) use. Rivaroxaban was associated with a lower incidence of overall symptomatic thromboembolic events compared with SOC, regardless of co-medication use. In both treatment groups, PAI users, with higher age and prevalence of cardiovascular co-morbidities, had similar higher (>7-fold) incidences of symptomatic arterial but not venous thromboembolic events compared with non-users. NSAID use had no influence on thromboembolic events. However, odds ratios (ORs) for major bleeding events (European Medicines Agency definition) were higher in NSAID users compared with non-users in rivaroxaban [OR = 1.50; 95% confidence interval (CI) 1.06, 2.13] and SOC (OR = 1.70; CI 1.16, 2.49) groups. In PAI users, ORs for major bleeding events were no different from those of non-users in both the rivaroxaban (OR = 1.49; CI 0.84, 2.65) and SOC (OR = 1.46; CI 0.82, 2.62) groups.

CONCLUSIONS

Use of NSAIDs in XAMOS was frequent and associated with a higher frequency of bleeding events in patients receiving rivaroxaban or SOC, although the benefit–risk profile of rivaroxaban compared with SOC was maintained.

Introduction

Rivaroxaban, an oral, direct factor Xa inhibitor, is widely used for the prevention and treatment of several thromboembolic disorders [1]. The approval of rivaroxaban for the prevention of venous thromboembolism (VTE) in patients undergoing elective hip or knee replacement surgery was based on the outcomes of the phase III (RECORD) Regulation of Coagulation in Orthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism studies, in which rivaroxaban demonstrated superior efficacy and a similar safety profile to prophylactic regimens of enoxaparin [2–5]. More recently, the results from the XAMOS (Xarelto® in the prophylaxis of postsurgical venous thromboembolism after elective major orthopaedic surgery of hip or knee) study, a phase IV, non-interventional, observational study, have been published and provide evidence that the results of the phase III RECORD trials can be translated into routine clinical practice [6]. In unselected patients undergoing major orthopaedic surgery, rivaroxaban 10 mg once daily was associated with a significantly lower incidence of symptomatic thromboembolic events compared with other pharmacological thromboprophylaxis [standard of care (SOC)] [6]. Unlike randomized controlled trials, which select patients using prespecified and often strict inclusion and exclusion criteria, patients treated in routine clinical practice are likely to have other co-morbidities and to take other medications for acute or chronic conditions. A few concomitant medications have been identified that can lead to drug–drug interactions, affecting clinical outcomes when used concomitantly in patients treated with novel oral anticoagulants for VTE prevention; however, relevant data from routine clinical practice are limited.

Rivaroxaban is metabolized via the cytochrome P450 (CYP) enzymes 3A4/3A5 (accounting for ~18% of its elimination) as well as by CYP-independent mechanisms, and is a substrate of the efflux transport protein P-glycoprotein (P-gp) (accounting for ~30% of its elimination) [7]. Drugs that exhibit strong effects on these proteins therefore have the potential to influence the pharmacokinetics, and thus the safety and efficacy profile, of rivaroxaban [7, 8]. Consequently, strong inhibitors of both CYP3A4 and P-gp are not recommended for systemic concomitant use with rivaroxaban [9]. In addition, co-medications that affect the risk of bleeding, such as the commonly used nonsteroidal anti-inflammatory drugs (NSAIDs), or platelet aggregation inhibitors (PAIs), may influence clinical outcomes in patients receiving anticoagulant therapy, and are, therefore, also of considerable clinical interest [10, 11].

The aim of the present prespecified and exploratory subanalysis of the XAMOS study was to describe the use of co-medications in the latter study (i.e. routine clinical practice) and to explore the association of concomitant drug use with clinical outcomes in patients receiving rivaroxaban or SOC for VTE prevention after major orthopaedic surgery.

Methods

Study population and treatment

XAMOS was a non-interventional, open-label cohort study conducted in 252 centres in 37 countries [6]. Patients aged ≥18 years who were scheduled to undergo elective hip or knee replacement surgery (or fracture surgery in countries in which rivaroxaban was approved for this indication), and in whom a decision on pharmacological thromboprophylaxis had already been made, were eligible for inclusion in XAMOS. Exclusion criteria were based on the contraindications listed in the approved local product information for rivaroxaban 10 mg [9], and written informed consent was provided where necessary. The present study is registered with ClinicalTrials.gov (NCT00831714), and the study protocol was submitted to the European Medicines Agency (EMA) and approved by the appropriate independent ethics committee or an independent review board where required.

The use of rivaroxaban was recommended according to the approved 10 mg once-daily regimen in each country. SOC regimens included, but were not limited to, low molecular weight heparins, unfractionated heparin, fondaparinux, dabigatran etexilate, acetylsalicylic acid (ASA) and vitamin K antagonists. The type, duration and dose of pharmacological agents were determined by the attending physician before a patient was enrolled into the study. The use of co-medications was at the discretion of the treating physician. Of the 17 701 enrolled patients, 17 413 were included in the safety population – defined as patients who received at least one dose of a thromboprophylactic drug (rivaroxaban or SOC) [6].

Prespecified co-medications of interest

Because of their influence on the elimination pathway of rivaroxaban, inhibitors and inducers of CYP3A4 and/or P-gp were selected as one group of co-medications of interest. The corresponding drugs were selected in a step-wise approach, which included review of drugs listed in the draft guidance of the US Food and Drug Administration (FDA) for drug interaction studies [12], drugs listed at http://medicine.iupui.edu/clinpharm/DDIs/table.asp (as included on 9 December 2009) and selection of additional drugs from published reports. CYP3A4 inhibitors were categorized by strength of inhibition according to the available FDA guidance [12]. Subsequently, the World Health Organization (WHO) Drug Dictionary (version updated on 1 June 2009) was used to identify the corresponding Chemical Abstract Service (CAS) Registry Numbers for each compound, and, on the basis of this list, the WHO Drug Dictionary was searched to select the relevant drugs. We performed separate analyses for CYP3A4 and P-gp inhibitors, although several compounds belong to both lists. By contrast, we combined the lists for CYP3A4 and P-gp inducers because they were less frequently used and all identified P-gp inducers are also classified as CYP3A4 inducers.

PAIs and NSAIDs were selected as additional groups of co-medications because of their potential pharmacodynamic interaction with rivaroxaban and their effects on bleeding risk. These drugs were identified using the Anatomical Therapeutic Chemical (ATC) classification system. All drugs listed in the corresponding ATC classes B01AC (PAIs excluding heparin) and M01A (anti-inflammatory/antirheumatic products, nonsteroids) were initially selected and included in the primary analysis. Owing to the inevitable misclassification of some compounds following this procedure, a further analysis was performed that utilized the medications selected for the primary analysis but excluded some compounds belonging to ATC class M01AX. This was done because some compounds in this class, which were used in a total of 117 patients, lacked the potential for a pharmacodynamic interaction with rivaroxaban with an effect on bleeding risk (e.g. compounds such as chondroitin or glucosamine). The data for the latter analysis are presented in this study, with these 117 patients excluded.

Questions regarding the use of the prespecified co-medications (both pretrial use and concomitant use) were included in the Case Report Form and the information was recorded by the attending physician. In the present report, pretrial use of the prespecified co-medications was defined as at least one drug dose intake within 7 days before surgery, whereas concomitant use was defined as any use of these co-medications during the study period. Although both pretrial use and concomitant use of drugs were documented and are described here, the main objective of the present subanalysis was to assess the influence of concomitant use of the prespecified co-medications on the clinical outcomes during the study in patients receiving rivaroxaban or SOC. Therefore, further analyses on clinical outcomes focused on concomitant use of the prespecified co-medications only.

Outcome measures

The XAMOS study collected data on adverse events, including symptomatic thromboembolic events and bleeding events. The treating physicians reported events that were coded according to the standardized Medical Dictionary for Regulatory Activities (MedDRA; version 14.0).

Symptomatic arterial and venous thromboembolic events occurring within 3 months after surgery were identified and adjudicated. Data collected on bleeding events were differentiated as major and nonmajor bleeding events. The primary safety outcome was major bleeding as defined in the RECORD studies [13]: clinically overt bleeding that was fatal, occurred in a critical organ, necessitated reoperation, or was outside of the surgical site and associated with a fall in haemoglobin of $\geq$2 g dl^{-1} or required a transfusion of $\geq$2 units of blood. In addition, major bleeding events were defined in accordance with the EMA guidelines, which are similar to the RECORD major bleeding definition but with the inclusion of bleeding warranting treatment cessation and surgical site bleeding events associated with a fall in haemoglobin of $\geq$2 g dl^{-1} or leading to a transfusion of $\geq$2 units of blood or packed cells [14]. Bleeding events were defined as treatment-emergent events when they started on or after the day of the first dose and within 48 h after the last dose of thromboprophylactic drug.

Data analysis

The data presented are crude incidences in the rivaroxaban and SOC groups (safety population). Further analyses evaluating outcomes in subgroups are deemed as exploratory and descriptive; therefore, no statistical significance of the findings can be derived. Odds ratios (ORs) are given with 95% confidence intervals (CIs) within the context of the overall results to explore directional trends.

Results

A total of 17 701 patients were enrolled in the XAMOS study. The safety population included 17 413 patients – 8778 received rivaroxaban and 8635 received SOC (81.7% received low molecular weight heparins, 7.9% fondaparinux, 5.5% dabigatran etexilate and 4.9% other agents). In the safety population of the overall XAMOS study, the crude incidences of symptomatic

Table 1

Pretrial and concomitant use of medications in the XAMOS trial

	Rivaroxaban *N* = 8778 *n* (%)	SOC *N* = 8635 *n* (%)
Pretrial use		
CYP3A4 inhibitors	200 (2.3)	256 (3.0)
P-gp inhibitors	77 (0.9)	98 (1.1)
CYP3A4/P-gp inducers	67 (0.8)	73 (0.8)
PAIs	616 (7.0)	756 (8.8)
NSAIDs	1203 (13.7)	950 (11.0)
Concomitant use		
CYP3A4 inhibitors	227 (2.6)	318 (3.7)
P-gp inhibitors	88 (1.0)	115 (1.3)
CYP3A4/P-gp inducers	84 (1.0)	122 (1.4)
PAIs	539 (6.1)	653 (7.6)
NSAIDs	4732 (53.9)	4324 (50.1)

CYP3A4, cytochrome P450 3A4; NSAID, nonsteroidal anti-inflammatory drug; PAI, platelet aggregation inhibitor; P-gp, P-glycoprotein; SOC, standard of care.

thromboembolic events were 0.89% and 1.35% in the rivaroxaban and SOC groups, respectively (OR = 0.65; 95% CI 0.49, 0.87) as reported [6]. Treatment-emergent major bleeding events occurred in the overall study in 0.40% and 0.34% of patients in the rivaroxaban and SOC groups, respectively (OR = 1.19; 95% CI 0.73, 1.95; RECORD definition) as reported [6].

Pretrial and concomitant use of prespecified co-medications in XAMOS

The overall frequency of pretrial and concomitant co-medication use was similar between the rivaroxaban and SOC groups for all drugs of interest. In general, CYP3A4 inhibitors, P-gp inhibitors and CYP3A4/P-gp inducers were not frequently used either before the trial or as concomitant co-medications during the study treatment period (Table 1), and strong inhibitors of both CYP3A4 and P-gp (i.e. not recommended in the product label) were rarely used. The proportion of patients using these drugs as concomitant medications (between 1.0% and 3.7%; Table 1) was deemed too small for meaningful further analyses and comparison between users and non-users regarding patient characteristics and, most importantly, clinical outcomes. In the rivaroxaban group, a few patients were treated with co-medications that inhibited both CYP3A4 and P-gp before (0.9%) or during (1.0%) the study. Only one patient (1/8778; 0.01%) in the rivaroxaban group used a drug (itraconazole) that is not recommended in the product label owing to the fact that it is a strong inhibitor of both CYP3A4 and P-gp (both during and before the study); however, information on the route of administration (i.e. topical *vs*. systemic) was not documented.

PAIs were used frequently both before and during the study (7.0% and 6.1% in the rivaroxaban group; 8.8% and 7.6% for the SOC group; Table 1). ASA (*n* = 1029) was the most frequently used PAI, followed by clopidogrel (*n* = 87; Supplementary Table S1). NSAIDs were the most commonly used co-medications in both the pretrial and study periods, and there was a marked increase in the proportion of patients who took NSAIDs as concomitant co-medications during the study compared with pretrial use. In the rivaroxaban group, the proportion of patients who used NSAIDs increased from 13.7% in the pretrial phase to 53.9% during the study. Similarly, in the SOC group, the frequency increased from 11.0% to 50.1% (Table 1). The most frequently used NSAID was diclofenac (2403 users in total), followed by ketoprofen (1503 users in total) (Supplementary Table S1).

Characteristics of patients with and without use of PAIs or NSAIDs as concomitant medications

The overall demographic characteristics of patients were similar between the rivaroxaban and SOC groups (Table 2A,B). Patients with concomitant use of PAIs were older (a median age of 71 years for the rivaroxaban group and 73 years for the SOC group) compared with non-users (66 years and 67 years, respectively; Table 2A). Concomitant PAI users were more frequently male, and had a higher body mass index and a higher prevalence of co-morbidities affecting cardiovascular risk compared with PAI non-users in both the SOC and rivaroxaban groups (Table 2A). By contrast, the characteristics of patients with and without concomitant use of NSAIDs were similar. There was no difference in the frequency of co-morbidities affecting cardiovascular risk between users of NSAIDs and non-users (Table 2B).

Influence of concomitant use of PAIs and NSAIDs on thromboembolic events

Concomitant PAI users had notably higher incidences of total and arterial symptomatic thromboembolic events compared with PAI non-users in both the rivaroxaban and SOC treatment groups (Figure 1). PAI users in the SOC group had the highest incidence (2.91%) of total symptomatic thromboembolic events, which was more than twofold higher than in PAI non-users in this group (1.20%) (OR = 2.46; 95% CI 1.49, 4.05). Symptomatic arterial thromboembolic events occurred in 1.11% of PAI users *vs*. 0.16% of PAI non-users in the rivaroxaban group (OR = 7.09; 95% CI 2.68, 18.72); in the SOC group the incidences were 1.68% for PAI users *vs*. 0.22% for PAI non-users (OR = 7.94; 95% CI 3.70, 17.02) (Figure 1). Compared with SOC, rivaroxaban was associated with lower incidences of total, arterial and venous thromboembolic events both in PAI users and non-users (Figure 2A). For PAI users, the incidences of total symptomatic thromboembolic events in the rivaroxaban and SOC groups were 1.67% *vs*. 2.91% (OR = 0.57; 95% CI 0.25, 1.26), and for PAI non-users the incidences were 0.82% *vs*. 1.20% (OR = 0.68; 95% CI 0.49, 0.93) (Figure 2A).

Table 2A

Baseline demographics and clinical characteristics of patients with and without concomitant use of platelet aggregation inhibitors*

	PAI users		PAI non-users	
	Rivaroxaban (*N* = 539)	Standard of care (*N* = 653)	Rivaroxaban (*N* = 8196)	Standard of care (*N* = 7892)
Age, median, years (Q1–Q3)	71 (65–77)	73 (67–78)	66 (58–73)	67 (59–74)
Gender, %				
Male	46.2	45.3	36.7	36.2
Female	53.8	54.7	63.3	63.7
Body mass index, median, kg m^{-2} (Q1–Q3)	28.6 (25.9–32.0)	28.4 (25.4–32.3)	27.4 (24.6–30.9)	27.5 (24.6–30.9)
Concomitant diseases, %				
Hypertension	76.4	75.3	47.6	50.9
Hypercholesterolaemia	28.0	28.3	9.4	9.2
Diabetes	21.3	23.7	9.7	10.6
Arteriosclerosis	11.1	9.3	1.8	2.4
Cardiac failure	5.4	9.0	1.4	2.1
Atrial fibrillation	4.3	6.9	1.0	3.2
Coronary artery disease	3.2	4.1	0.3	0.3
Myocardial infarction	2.8	2.9	0.3	0.6

*Excluding patients who had incomplete or missing data for the start or stop dates for PAI use (concomitant medication use could not be confirmed in these patients). PAI, platelet aggregation inhibitor; Q, quartile.

Table 2B

Baseline demographics and clinical characteristics of patients with and without concomitant use of nonsteroidal anti-inflammatory drugs*

	NSAID users		NSAID non-users	
	Rivaroxaban (*N* = 4732)	Standard of care (*N* = 4324)	Rivaroxaban (*N* = 3842)	Standard of care (*N* = 3989)
Age, median, years (Q1–Q3)	66 (58–73)	67 (59–74)	67 (59–73)	69 (60–75)
Gender, %				
Male	36.8	37.5	38.1	36.0
Female	63.2	62.4	61.9	64.0
Body mass index, median, kg m^{-2} (Q1–Q3)	27.6 (24.8–31.2)	27.8 (25.0–31.2)	27.3 (24.5–30.5)	27.2 (24.4–30.6)
Concomitant disease, %				
Hypertension	50.0	53.4	48.6	52.8
Hypercholesterolaemia	11.3	11.5	9.7	10.2
Diabetes	9.9	11.5	11.0	12.2
Arteriosclerosis	2.1	3.0	2.7	3.2
Cardiac failure	1.7	2.6	1.6	2.8
Atrial fibrillation	1.1	3.3	1.4	3.8
Coronary artery disease	0.6	0.7	0.3	0.5
Myocardial infarction	0.4	0.9	0.6	0.8

*Excluding patients who had incomplete or missing data for the start or stop dates for NSAID use (concomitant medication use could not be confirmed in these patients). NSAID, nonsteroidal anti-inflammatory drug; Q, quartile.

The incidences of total, arterial and venous symptomatic thromboembolic events were similar between concomitant NSAID users and NSAID non-users in both the rivaroxaban and SOC treatment groups (Figure 1). Rivaroxaban was associated with a lower incidence of total symptomatic thromboembolic events compared with SOC in NSAID users (0.80% *vs.* 1.41%; OR = 0.57; 95% CI 0.38, 0.85) and NSAID non-users (0.86% *vs.* 1.25%; OR = 0.68; 95% CI 0.44, 1.06) (Figure 2B). Symptomatic venous thromboembolic events occurred in 0.57% of rivaroxaban-treated patients compared with 0.95% of SOC-treated patients in NSAID users (OR = 0.60; 95% CI 0.37, 0.98), and 0.62% *vs.* 1.05% in NSAID non-users (OR = 0.59; 95% CI 0.36, 0.98) (Figure 2B).

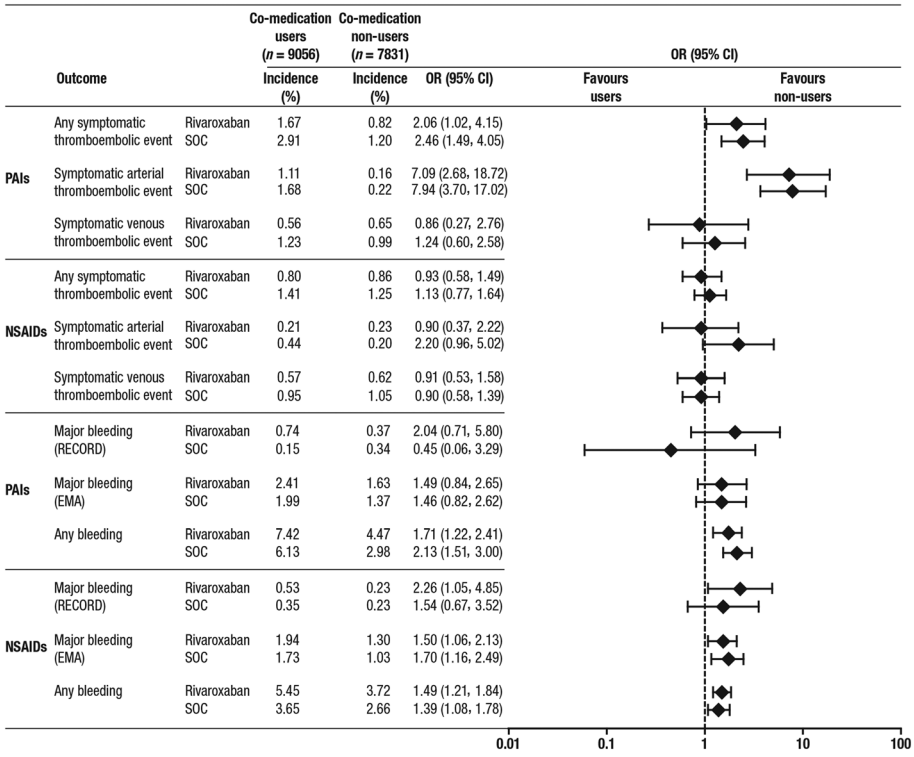

Figure 1

Association between user status for platelet aggregation inhibitors and nonsteroidal anti-inflammatory drugs and the incidence of thromboembolic events and treatment-emergent bleeding events in patients treated with rivaroxaban or standard of care. CI, confidence interval; EMA, European Medicines Agency; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PAI, platelet aggregation inhibitor; RECORD, Regulation of Coagulation in Orthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism; SOC, standard of care

Influence of concomitant use of PAIs and NSAIDs on bleeding events

PAI users had higher incidences of any treatment-emergent bleeding events compared with PAI non-users in both the rivaroxaban and SOC treatment groups (Figure 1). Separate analysis for the incidence of major bleeding (as defined in the RECORD studies) according to PAI or NSAID user status was limited owing to the small number of events observed in the corresponding subgroups (Figure 3). The OR for treatment-emergent major bleeding events, according to the EMA definition, for PAI users *vs*. PAI non-users was 1.49 (95% CI 0.84, 2.65) for the rivaroxaban group and 1.46 (95% CI 0.82, 2.62) for the SOC group (Figure 1). The incidence of any treatment-emergent bleeding events was higher in the rivaroxaban group (4.47%) than in the SOC group (2.98%) in PAI non-users (OR = 1.52; 95% CI 1.29, 1.80) (Figure 3A). In PAI users, any treatment-emergent bleeding event occurred in 7.42% of patients in the rivaroxaban group and 6.13% of patients in the SOC group (OR = 1.23; 95% CI 0.78, 1.93) (Figure 3A).

NSAID users had overall consistently higher incidences of treatment-emergent bleeding events compared with NSAID non-users in both treatment groups (Figure 1). The incidences of treatment-emergent major bleeding events according to the EMA definition were higher in NSAID users compared with NSAID non-users in both the rivaroxaban (OR = 1.50; 95% CI 1.06, 2.13) and SOC (OR = 1.70; 95% CI 1.16, 2.49) groups (Figure 1).

The incidences of treatment-emergent major bleeding events (RECORD or EMA definition) in the rivaroxaban group were similar or numerically higher than those seen in the SOC group, regardless of concomitant NSAID use status. Compared with the SOC group, the incidence of any treatment-emergent bleeding events was higher in the rivaroxaban group both in NSAID users (5.45% *vs*. 3.65%; OR = 1.52; 95% CI 1.24, 1.86) and NSAID non-users (3.72% *vs*. 2.66%; OR = 1.42; 95% CI 1.10, 1.83), consistent with the finding in the overall XAMOS safety population (Figure 3B).

Discussion

The present explorative subgroup analysis of the XAMOS study showed that the use of CYP3A4 inhibitors, P-gp inhibitors and CYP3A4/P-gp inducers was relatively low (<4%) in patients undergoing major orthopaedic surgery, both before and after surgery. Only one of the 8778 (0.01%) patients in the rivaroxaban group used a strong inhibitor of both CYP3A4 and P-gp (i.e. itraconazole) concomitantly, which is not recommended for systemic use with rivaroxaban according to the label

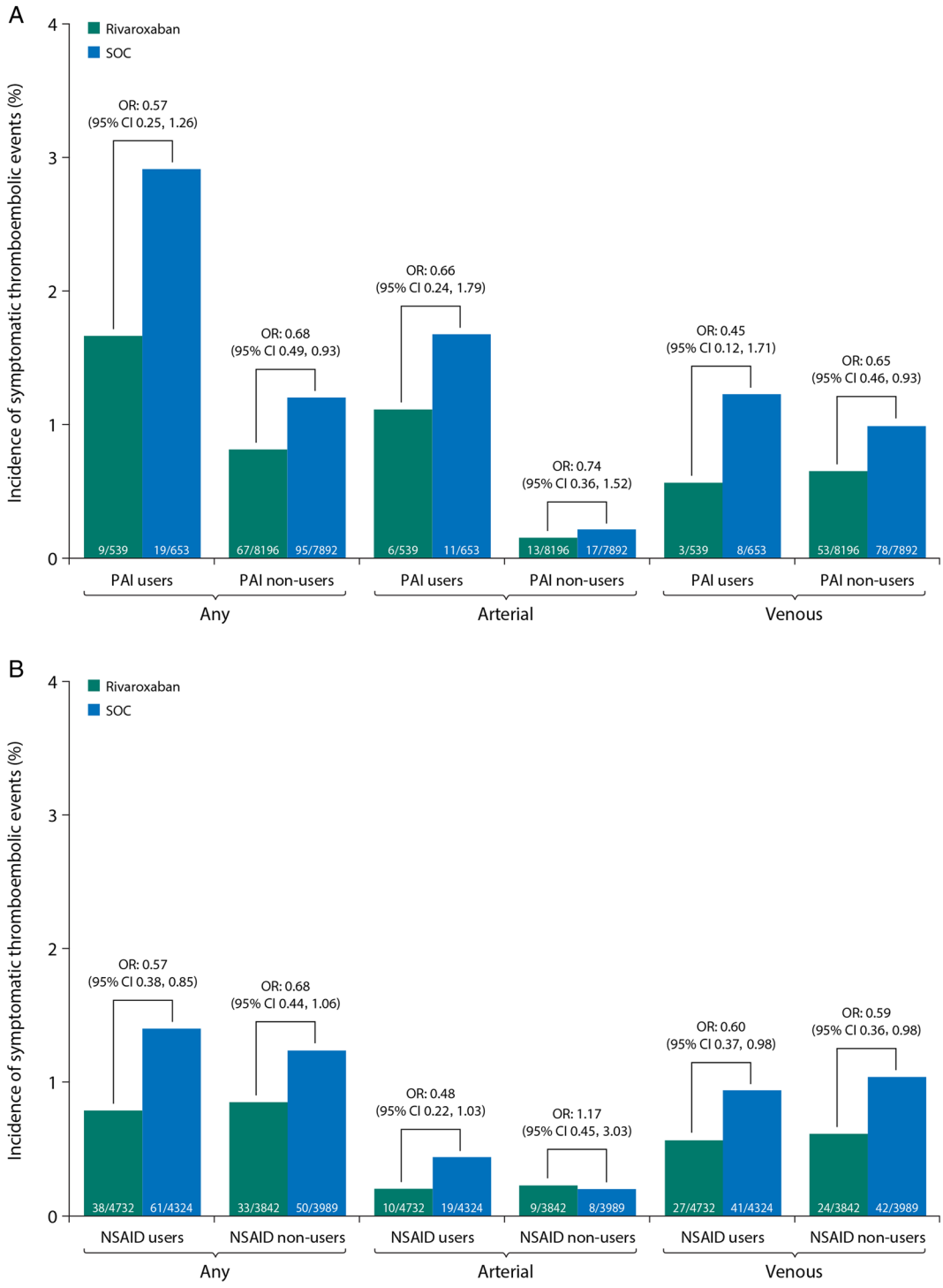

Figure 2

Incidence of symptomatic thromboembolic events (A) in platelet aggregation inhibitor users and non-users and (B) in nonsteroidal anti-inflammatory drug users and non-users. Data are given as crude incidences in the safety population. CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PAI, platelet aggregation inhibitor; SOC, standard of care

information [9]; however, this was probably not used systemically but as a topical treatment of onychomycosis of the foot. These findings indicate that, in the routine setting for major orthopaedic surgery, the overall risk for pharmacokinetic drug interactions with rivaroxaban attributable to this drug class is low owing to infrequent use. By contrast, pharmacodynamic (functional) interactions between anticoagulants (such as rivaroxaban) and NSAIDs and PAIs potentially affect the risk of bleeding [10, 11, 15], and are of greater clinical interest, given

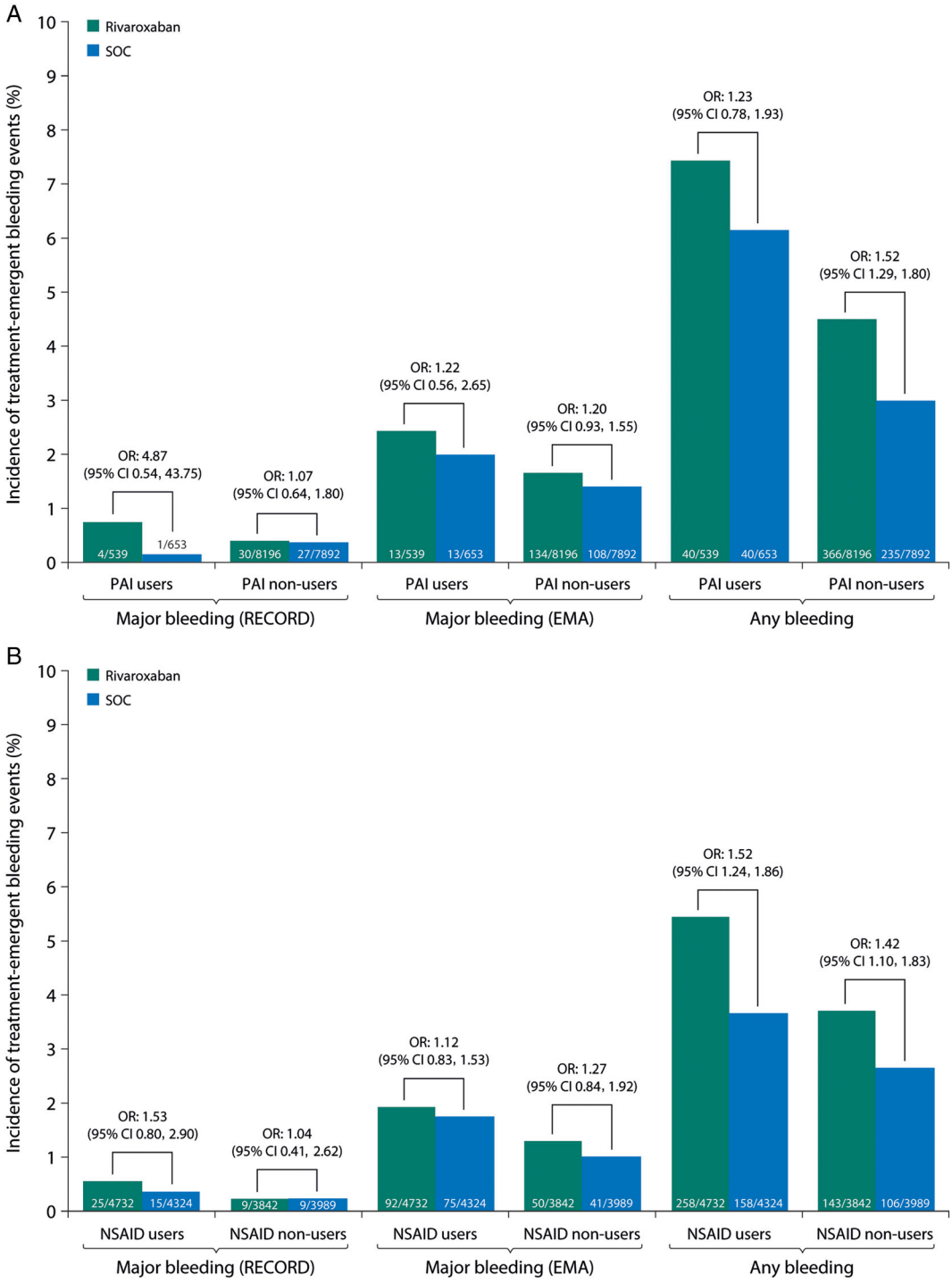

Figure 3

Incidence of treatment-emergent bleeding events (A) in platelet aggregation inhibitor users and non-users and (B) in nonsteroidal anti-inflammatory drug users and non-users. Data are given as crude incidences in the safety population. CI, confidence interval; EMA, European Medicines Agency; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PAI, platelet aggregation inhibitor; RECORD, Regulation of Coagulation in Orthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism; SOC, standard of care

that these drugs were – as expected – frequently used in XAMOS.

NSAIDs were the most commonly used co-medications, with an expected marked increase seen during the study (postsurgery; 53.9% for rivaroxaban and 50.1% for SOC) compared with pretrial use (13.7% for rivaroxaban and 11.0% for SOC). Overall, the incidences of total, arterial and venous symptomatic thromboembolic events were similar between NSAID users and NSAID non-users. In the rivaroxaban group, the incidence

of total symptomatic thromboembolic events was lower than in the SOC group in both NSAID users (0.80% *vs*. 1.41%; OR = 0.57; 95% CI 0.38, 0.85) and NSAID non-users (0.86% *vs*. 1.25%; OR = 0.68; 95% CI 0.44, 1.06). These results were consistent with the overall outcome in the XAMOS study, which showed that rivaroxaban 10 mg once daily was more effective than SOC thromboprophylaxis in reducing the incidence of symptomatic thromboembolic events [6]. It should be noted, however, that concomitant NSAID users had higher incidences of major bleeding (EMA definition) and any bleeding events compared with NSAID non-users in both treatment groups. In a pooled analysis of the RECORD1–4 studies, it was shown that, compared with the current non-interventional study, an even higher proportion of patients (i.e. 72% for the rivaroxaban and 73% for the enoxaparin regimen groups) [10]. In the RECORD1–4 pooled analysis, the overall relative rate ratios for any bleeding events for NSAID users *vs*. non-users were also increased to 1.22 in both the rivaroxaban (95% CI 0.99, 1.50) and enoxaparin (95% CI 0.98, 1.51) groups [10].

PAIs were also frequently used in XAMOS, both before and during the trial (6.1% and 7.0% in the rivaroxaban group; 8.8% and 7.6% in the SOC group, respectively), with ASA being the most frequently used PAI, followed by clopidogrel (total of 1029 and 87 users, respectively). There were higher incidences of total symptomatic thromboembolic events in PAI users compared with PAI non-users in both the rivaroxaban and SOC treatment groups. This finding was largely attributable to a higher incidence of symptomatic arterial thromboembolic events, which was 7–8-fold higher in PAI users compared with PAI non-users in both treatment groups. This observation might be related to the patient characteristics of concomitant PAI users; these patients were, on average, older and had more co-morbidities affecting cardiovascular risk, such as hypertension, diabetes, hypercholesterolaemia, heart failure and coronary artery disease. PAI users also had higher incidences of any treatment-emergent bleeding events compared with PAI non-users in both treatment groups. These data are also consistent with the direction of the results observed in the RECORD1–4 pooled analysis [10]. In the RECORD programme, a similar proportion (i.e. 9%) of the overall patient population had concomitant use of platelet function inhibitors or ASA. The rate ratio for any bleeding events for platelet function inhibitor users was also higher than for non-users: 1.32 (95% CI 0.85, 2.05) in the rivaroxaban group and 1.40 (95% CI 0.87, 2.25) in the enoxaparin group [10].

Recently, the randomized PeriOperative ISchemic Evaluation-2 (POISE-2) trial did not support the use of ASA in the perioperative period. POISE-2 randomized 10 010 patients undergoing noncardiac surgery and at risk of cardiovascular events to ASA 200 mg or placebo [16]. ASA exhibited no protective effect against major cardiovascular events or death in patients either continuing or starting ASA treatment during the perioperative period at 30 days [16]. Moreover, ASA significantly increased the risk of major bleeding (4.6% *vs*. 3.8%; hazard ratio = 1.23; 95% CI 1.01, 1.49; $P = 0.04$) [16]. Because patients at very high risk of cardiovascular events were either excluded or at least not well represented in this trial, it was not possible to assess whether temporary cessation of ASA is warranted in this patient group [17]. Thus, the question of whether ASA should be continued or withheld in patients undergoing noncardiac surgery (such as major orthopaedic surgery) and receiving VTE prophylaxis with either rivaroxaban or SOC remains uncertain and needs to be addressed in further studies [18].

Further analyses of other phase III studies with rivaroxaban have also demonstrated the influence of concomitant use of ASA or PAIs on the risk of bleeding complications [11]. In the EINSTEIN programme, which studied the treatment of VTE, concomitant use of rivaroxaban and ASA (up to 100 mg), clopidogrel (75 mg per day) or both was permitted if indicated [11]. The results from a pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies have shown that concomitant use of an NSAID or ASA is associated with an increased risk of clinically relevant and major bleeding [11]. In addition, in a recently published Danish cohort study of 150 900 patients with atrial fibrillation in routine clinical practice, NSAID use was associated with an independent risk of serious bleeding [19]. Collectively, these data demonstrate that the risk of bleeding is increased when NSAIDs or PAIs are used concomitantly with anticoagulants in different settings, including major orthopaedic surgery, as in XAMOS. The data also further highlight that these co-medications (including over-the-counter NSAIDs) should be used with caution.

It should be noted that this XAMOS subanalysis is descriptive in nature and is not powered to show any statistical differences between the comparison groups. Other limitations include the open-label, non-interventional, observational study design of XAMOS [20]. As with all observational studies, there can be potential bias in adverse event reporting (e.g. due to the 'Weber effect' [21]). In addition, because the XAMOS study included bleeding events starting on or after the day of the first dose of thromboprophylactic drug (6–10 h after surgery in the case of rivaroxaban), the potential effect of these co-medications on bleeding events during surgery or prior to surgery was not considered [6].

In summary, data from the present descriptive analysis of the XAMOS study show that the use of PAIs or NSAIDs was relatively common in routine clinical practice, whereas exposure to CYP3A4 and/or P-gp inhibitors or inducers was low. Interestingly, the study demonstrated that concomitant PAI users in both treatment groups had an increased risk of total and arterial symptomatic thromboembolic events. This finding is most likely to be attributable to confounding by underlying co-morbidities – i.e. a possible reflection of the increased

risk in patients taking PAIs. Importantly, both PAI and NSAID use was associated with an increased rate of treatment-emergent bleeding events. Thus, the present analysis further demonstrates that co-administration of PAIs or NSAIDs with pharmacological thromboprophylaxis in daily medical practice increases the risk of bleeding events, although the overall benefit–risk profile of rivaroxaban compared with SOC was maintained in patients exposed to these co-medications.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: RK, SH, GH, MRL, LGM, AS and AGGT had editorial support from Yong-Ling Liu for the submitted work; GH and AS have been employees of Bayer HealthCare Pharmaceuticals in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors

AGGT, SH, RK, LGM, GH, AS and MRL (Steering Committee Members) provided advice and recommendations on the effective operation of the XAMOS study, reviewed study progress, assisted in the analyses and interpretation of the data, and clarified logistical and ethical issues relating to the study when required. The adjudication committee (AGGT, SH, MRL, RK, and LGM) considered all thromboembolic events. All listed authors were involved in drafting the manuscript, revising the intellectual content and approving the submission draft.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1
List of platelet aggregation inhibitors and nonsteroidal anti-inflammatory drugs included in the analysis and their frequency of use