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ORIGINAL RESEARCH ARTICLE

A Cross-Country Comparison of Rivaroxaban Spontaneous Adverse Event Reports and Concomitant Medicine Use with the Potential to Increase the Risk of Harm

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Abstract

Background Concerns with the safety profiles of the newer anticoagulants have been raised because of differences in treatment populations between pre-marketing studies (randomized controlled trials) and clinical practice. Little is known about the potential safety issues and the reporting in spontaneous adverse event databases associated with rivaroxaban.

Objectives To analyse spontaneous adverse event reports associated with the oral anticoagulant rivaroxaban from Australia, Canada and the USA; and to examine concomitant medicine use that may increase the risk of adverse events.

Methods Spontaneous adverse event report databases from Australia, Canada and the USA were examined for all reports of adverse events associated with rivaroxaban and concomitant medicines from 1 August 2005 to 31 March 2013. Disproportionality analysis (the proportional reporting ratio [PRR] and reporting odds ratio [ROR]) was conducted for quantitative detection of signals, using the US database.

Results There were 244 spontaneous adverse event reports associated with rivaroxaban from Australia, 536 from Canada and 1,638 from the USA. Reporting of haemorrhage (any type) was common, ranging from 30.7 % for Australia to 37.5 % for Canada. Gastrointestinal haemorrhage was the most commonly reported haemorrhage, accounting for 13.9 % of Australian, 16.4 % of Canadian and 11.1 % of US adverse event reports. Positive signals were confirmed in the US data (haemorrhage [any type] PRR 11.93, χ^2 4,414.78 and ROR 13.41, 95 % confidence interval [CI] 12.13–14.81; gastrointestinal haemorrhage PRR 12.52, χ^2 2,018.48 and ROR 13.15, 95 % CI 11.36–15.21). Reporting of concomitant use of medicines with the potential to increase bleeding risk ranged from 63.7 % in Australia to 89.2 % in Canada.

Conclusion A large proportion of adverse event reports for rivaroxaban were associated with use of concomitant medicines, which may have increased the risk of adverse events—in particular, haemorrhage. Increased awareness of a patient's comorbidity and associated medicine use is needed when rivaroxaban is used in clinical practice.

Key Points

Safety concerns, namely an increased risk of gastrointestinal bleeding with the newer anticoagulant rivaroxaban, have been raised

Examination of spontaneous adverse event reports from Australia, Canada and the USA showed that the reporting of haemorrhage—specifically, gastrointestinal haemorrhage—was common for rivaroxaban. Disproportionality analyses confirmed these positive signals for both haemorrhage and gastrointestinal haemorrhage with rivaroxaban

Across all three countries, over 60 % of rivaroxaban spontaneous adverse event reports had at least one potentially inappropriate concomitant medicine reported

Given the current lack of an antidote for rivaroxaban, this study highlights the importance of consideration of comorbidity and associated medicine use, particularly use of those medicines that may increase bleeding risk

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1 Introduction

Rivaroxaban is one of the newer oral anticoagulants that have been developed as an alternative to conventional anticoagulants for the prevention of arterial and venous thrombotic events (VTEs) [1, 2]. Clinical trial data and subsequent meta-analyses have reported rivaroxaban non-inferiority when compared with warfarin in terms of ischaemic stroke prevention (hazard ratio [HR] 0.88, 95 % confidence interval [CI] 0.74–1.03) in atrial fibrillation and a lower incidence of both haemorrhagic stroke (relative risk [RR] 0.58, 95 % CI 0.37–0.92) and mortality (RR 0.83, 95 % CI 0.70–1.00) [3, 4]. Compared with warfarin, rivaroxaban was associated with a decreased risk of fatal bleeding (RR 0.50, 95 % CI 0.31–0.79), whilst no change in the risk of major bleeding was observed [3]. However, the risk of gastrointestinal bleeding was increased with rivaroxaban (RR 1.46, 95 % CI 1.19–1.78) when compared with warfarin [4]. In VTE studies, rivaroxaban and warfarin were equipotent in terms of mortality and rates of recurrent VTE or pulmonary embolism [4].

Concerns with the safety profile of the newer anticoagulants have been raised, in part because of differences in treatment populations between pre-marketing randomized controlled trials (RCTs) and clinical practice [5]. Use in real-life patient populations includes older patients with multiple comorbidities and concomitant medicine use [5]. Further adding to safety issues with rivaroxaban is the lack of a specific antidote to reverse the anticoagulant effect in the event of haemorrhage [6]. This is potentially problematic, as rivaroxaban has clinically significant interactions with cytochrome P450 (CYP) 3A4 and P-glycoprotein inhibitors, resulting in increased plasma concentrations of rivaroxaban [6]. In addition, medicines commonly used in the older population where use of rivaroxaban is prevalent, including antithrombotics and nonsteroidal anti-inflammatory drugs (NSAIDs), may increase the risk of haemorrhagic adverse events [7].

Spontaneous adverse event reporting is a key post-marketing surveillance method, which involves voluntary submission of adverse events experienced by patients to a centralized database, by either the patients themselves or their health care providers. Potential adverse event signals can be generated from spontaneous adverse event reports when there is a series of reports involving the same medicine and the same adverse event [8]. The aims of this study were to analyse spontaneous adverse event reports for rivaroxaban from the national databases in Australia, Canada and the USA; to compare the adverse event reports for rivaroxaban between countries; and to examine the reporting of concomitant medicine use that may increase bleeding risk.

2 Methods

2.1 Data Source and Study Design

Spontaneous adverse event reports for rivaroxaban were obtained from the Australian Therapeutic Goods Administration's Database of Adverse Event Notifications for Medicines [9], Health Canada's Vigilance Adverse Reaction Online Database [10] and the US Food and Drug Administration Adverse Events Reporting System (FAERS) database [11]. These national adverse event report databases are all publicly available online. Reports were included from 1 August 2005 to 31 March 2013. International reports are included in the US FAERS database; however, we limited the analysis of this database to reports from the USA to avoid double counting.

2.2 Outcome Definition

We analysed the frequency of adverse event reports separately for all data sets, grouped by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC). Where a single report included more than one adverse event that was classified under the same MedDRA SOC classification, these were treated as one adverse event. Analyses were performed at the SOC level (including gastrointestinal disorders, nervous system disorders, vascular disorders and cardiac disorders) and at the MedDRA preferred term level, with the two most prevalent preferred terms within the SOC reported, and where the term 'haemorrhage' was reported, it was aggregated within each of the SOCs. Frequency of death was examined in the Canadian and US spontaneous adverse event reports; this variable is not available for individual reports in the Australian database, therefore the frequency of death was not reported for the Australian data.

We analysed the prevalence of reporting of potentially inappropriate concomitant medicines in the adverse event reports. The Australian Therapeutic Guidelines [12] and Australian Medicines Handbook [13] were used to categorize potentially inappropriate concomitant medicines into three groups: concomitant antithrombotics (warfarin, heparins, platelet aggregation inhibitors, direct thrombin inhibitors and direct factor Xa inhibitors; Anatomical Therapeutic Chemical (ATC) code B01A, excluding B01AF01—rivaroxaban); concomitant bleeding risk medicines (NSAIDs code M01A, selective serotonin reuptake inhibitors [SSRIs] code N06AB and oral [systemic] corticosteroids code H02A); and concomitant medicines with potentially clinically significant interactions (P-glycoprotein or CYP3A4 inhibitors, including systemic azole antifungals [codes J02AB and J02AC], macrolide antibiotics

code J01FA, human immunodeficiency virus [HIV] protease inhibitors code J05AE, cyclosporine code L04AD01, dronedarone code C01BD07, verapamil code C08DA01, amiodarone code C01BA01 and quinidine code C01BA01) [12, 13].

2.3 Statistical Analysis

We calculated the frequency of adverse events by MedDRA term as a proportion of all adverse event reports for rivaroxaban within each of the data sets. Recording of concomitant medicines is optional in spontaneous adverse event reports. This means it is possible that in some reports, patients were using potentially inappropriate concomitant medicines, but they weren't listed. To overcome this issue, we calculated the prevalence of potentially inappropriate concomitant therapy for each of the data sets, using the total number of adverse event reports where any concomitant medicines were reported as the denominator.

Two disproportionality analyses, the proportional reporting ratio (PRR) and the reporting odds ratio (ROR), were used to quantitate the strength of the association between reported adverse events and rivaroxaban from spontaneous adverse event reports [14, 15]. For this analysis, we focused on those adverse events that were of most concern from the clinical trials—namely, different types of haemorrhage [4]. The total number of individual adverse events reported by MedDRA terms is required for these disproportionality analyses. This information is publicly available in the US FAERS database but not in the Australian or Canadian databases. Therefore disproportionality analyses were only conducted within the FAERS data. An adverse event signal is detected with the PRR if the count of co-occurrences is ≥ 3 and the PRR is ≥ 2.0 with an associated χ^2 value of ≥ 4.0 [14]. A signal is detected with the ROR if the lower bound of the 95 % two-sided CI exceeds 1 [15]. Each adverse event report may contain multiple medicines and multiple adverse events, with the PRR and ROR calculated using each medicine/adverse event pair reported. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3 Results

There were 244 rivaroxaban adverse event reports submitted to the Australian database, 536 submitted to the Canadian database and 1,638 spontaneous adverse event reports in the US database during the study period. Table 1 describes the demographics of patients who reported an adverse event associated with rivaroxaban. The average age range was 71–73 years across all three databases. The proportion of reports involving men ranged from 30.2 % in Canada to 50.0 % in Australia.

The frequency and type of spontaneous adverse event reports for rivaroxaban are shown in Table 1. At the MedDRA SOC level, respiratory, gastrointestinal and vascular disorders were the most common for all countries. At the preferred term level, haemorrhage was common, particularly gastrointestinal haemorrhage, which ranged from 11.1 % of all adverse events reported with rivaroxaban in the USA to 16.4 % in Canada.

Approximately a third of all adverse event reports associated with rivaroxaban across all three countries reported haemorrhage (any type) as the outcome. Cardiac adverse event disorders ranged from 4.1 % of all adverse events reported in Canada to 8.2 % in Australia. Five percent of Canadian and 6.9 % of US reports of adverse events associated with rivaroxaban reported death as the outcome.

Disproportionality analyses within the US FAERS database found positive signals for gastrointestinal, nervous system and vascular haemorrhage associated with rivaroxaban use (Table 2). In accord, a positive signal was also detected for haemorrhage (all types). The signal strengths were similar for both types of disproportionality analyses. No signal was detected using either method for rivaroxaban and cardiac disorders, nor for rivaroxaban and myocardial infarction (Table 2).

Concomitant medicines were reported in 91 (37 %) of the 244 rivaroxaban adverse event reports in Australia, in 185 (34.5 %) of the 536 rivaroxaban adverse event reports in Canada and in 679 (41 %) of the 1,638 rivaroxaban adverse event reports in the USA. The average number of concomitant medicines per report was 3.8 ± standard deviation (SD) 3.1 in the Australian data set, 6.5 ± 6.8 in the Canadian data set and 5.5 ± 5.7 in the US data set.

Across all three countries, between 63.7 and 89.2 % of rivaroxaban adverse event reports mentioned the use of at least one potentially inappropriate medicine that may increase a patient's risk of experiencing adverse events, where concomitant medicines were recorded. The average number of potentially inappropriate medicines reported ranged from 1.34 (± 0.61) for Australia to 1.66 (± 1.02) for Canada (Table 3).

Concomitant administration of antithrombotic medicines with rivaroxaban was the most commonly reported potentially inappropriate medicine in all three countries, with prevalence ranging from 42.9 % of reports where concomitant medicines were recorded in Australia to 51.8 % of US reports where concomitant medicines were recorded. Aspirin was the most commonly reported antithrombotic in all countries (Table 3). Medicines that are associated with a potential to increase bleeding risk were the second most prevalent potentially inappropriate therapy

Table 1 Demographic characteristics and types of spontaneous adverse events reported by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) for rivaroxaban[a]

	Australia, $N = 244$	Canada, $N = 536$	USA, $N = 1{,}638$
Demographic characteristic			
Age [mean years ± SD, (*N*)]	72.8 ± 11.5 ($N = 75$)	70.6 ± 12.6 ($N = 297$)	71.0 ± 11.7 ($N = 842$)
Gender [% male]	50.0 %	30.2 %	36.5 %
Type of adverse event [N (%)]			
Gastrointestinal disorders	45 (18.4 %)	124 (23.1 %)	320 (19.5 %)
Gastrointestinal haemorrhage	34 (13.9%)	88 (16.4 %)	181 (11.1 %)
Nausea	6 (2.5 %)	6 (1.1 %)	16 (1.0 %)
Respiratory, thoracic disorders	45 (18.4 %)	154 (28.7 %)	337 (20.6 %)
Pulmonary embolism	24 (9.8 %)	116 (21.6 %)	235 (14.3 %)
Epistaxis	11 (4.5 %)	22 (4.1 %)	35 (2.1 %)
Nervous system disorders	25 (10.2 %)	53 (9.9 %)	261 (15.9 %)
Nervous system haemorrhage	4 (1.6 %)	4 (0.7 %)	34 (2.1 %)
Cerebrovascular accident	3 (1.2 %)	3 (0.6 %)	59 (3.6 %)
Vascular disorders	42 (17.2 %)	119 (22.2 %)	416 (25.4 %)
Vascular haemorrhage	14 (5.7 %)	51 (9.5 %)	101 (6.2 %)
Deep vein thrombosis	25 (10.2 %)	43 (8.0 %)	169 (10.3 %)
Cardiac disorders	20 (8.2 %)	22 (4.1 %)	109 (6.7 %)
Myocardial infarction	9 (3.7 %)	4 (0.7 %)	23 (1.4 %)
Atrial fibrillation	2 (0.8 %)	2 (0.4 %)	19 (1.2 %)
All haemorrhage	75 (30.7 %)	201 (37.5 %)	389 (23.7 %)
Death	NA	27 (5.0 %)	114 (6.9 %)

NA not applicable, *SD* standard deviation

[a] Frequencies are calculated as a proportion of all rivaroxaban spontaneous adverse event reports per country. Results are presented by SOC with a frequency of ≥5 % of reports in at least one of the adverse event reporting data sets. Within each of the SOCs, preferred terms that included haemorrhage were aggregated. The most prevalent two preferred terms within each SOC are reported

Table 2 Signal detection for rivaroxaban-associated adverse events in the US FDA Adverse Event Reporting System (FAERS) database

Type of adverse event	*N*	PRR (χ^2)	ROR (95 % CI)
Gastrointestinal disorders	436	1.47 (71.16)	1.53 (1.39–1.69)[a]
Gastrointestinal haemorrhage	191	12.52 (2,018.48)[a]	13.15 (11.36–15.21)[a]
Nervous system disorders	334	1.29 (22.59)	1.31 (1.18–1.47)[a]
Nervous system haemorrhage	62	17.62 (954.13)[a]	17.90 (13.92–23.01)[a]
Vascular disorders	443	5.76 (1,775.92)[a]	6.41 (5.80–7.08)[a]
Vascular haemorrhage	101	18.34 (1,637.90)[a]	18.83 (15.44–22.96)[a]
Cardiac disorders	127	0.81 (5.41)	0.81 (0.67-0.96)
Myocardial infarction	24	0.98 (<0.001)	0.98 (0.66–1.47)
All haemorrhage	438	11.93 (4,414.78)[a]	13.41 (12.13–14.81)[a]

CI confidence interval, *N* number of occurrences of the medicine/adverse event pair reported, *PRR* proportional reporting ratio, *ROR* reporting odds ratio

[a] Signal detected

recorded in all countries, accounting for from 20.9 % of Australian adverse event reports where concomitant medicines were recorded to 33.5 % of Canadian adverse event reports where concomitant medicine use with rivaroxaban was recorded (Table 3). NSAIDs were the most common concomitant bleeding-risk medicine reported in all three data sets, with prevalence of use ranging from 11.0 to 29.2 % of reports with concomitant medicines across all three countries. Medicines with the potential for drug–drug interactions (those that may increase the rivaroxaban

Table 3 Prevalence of potentially inappropriate concomitant therapy in rivaroxaban spontaneous adverse event reports[a]

	Australia, $N = 91$[a] [N (%)]	Canada, $N = 185$[a] [N (%)]	USA, $N = 679$[a] [N (%)]
Proportion of adverse event reports where potentially inappropriate therapy was reported	58 (63.7 %)	165 (89.2 %)	460 (67.7 %)
Count of potentially inappropriate therapy [mean number ± SD]	1.34 ± 0.61	1.66 ± 1.02	1.58 ± 0.81
Medication class			
Concomitant antithrombotic medicines	39 (42.9 %)	94 (51.0 %)	352 (51.8 %)
Aspirin	14 (15.4 %)	54 (29.2 %)	253 (37.3 %)
Warfarin	7 (7.7 %)	23 (12.4 %)	48 (7.1 %)
Clopidogrel	7 (7.7 %)	13 (7.0 %)	94 (13.8 %)
Enoxaparin	12 (13.2 %)	14 (7.6 %)	46 (6.7 %)
Concomitant bleeding-risk medicines	19 (20.9 %)	62 (33.5 %)	146 (21.5 %)
NSAIDs	10 (11.0 %)	54 (29.2 %)	95 (14.0 %)
SSRIs	4 (4.4 %)	20 (10.8 %)	49 (7.2 %)
Corticosteroids (systemic)	6 (6.6 %)	7 (3.8 %)	18 (2.7 %)
Concomitant medicines with potential drug–drug interactions	12 (13.2 %)	14 (7.6 %)	57 (8.4 %)
Amiodarone	2 (2.2 %)	2 (1.1 %)	37 (5.4 %)
Verapamil	6 (6.6 %)	–	143 (2.3 %)
Dronedarone	–	17 (3.1 %)	473 (7.7 %)
Diltiazem	2 (2.2%)	9 (4.9 %)	–

NSAID nonsteroidal anti-inflammatory drug, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitor

[a] The denominator is the total number of adverse event reports where at least one concomitant medicine was reported, for each country's adverse event reporting data set

plasma concentration and potentially increase bleeding risk) were reported in approximately 10 % of adverse event reports with concomitant medicines recorded across all three countries.

4 Discussion

This is the first study to conduct a cross-country comparison of spontaneous adverse event reports associated with the new oral anticoagulant rivaroxaban from Australia, Canada and the USA. We observed a high proportion of reports for haemorrhagic adverse events with use of rivaroxaban in the clinical setting from all three countries. Approximately a third of all spontaneous adverse event reports for rivaroxaban in all three countries studied were for some type of haemorrhage. Gastrointestinal haemorrhage was the most common haemorrhagic adverse event across all three countries examined, concordant with an increased risk of gastrointestinal bleeding reported in the ROCKET AF clinical trial with rivaroxaban [3, 4]. Disproportionality analysis of the US FAERS database confirmed positive signals for both haemorrhage and gastrointestinal haemorrhage.

The high prevalence of spontaneous adverse event reports of haemorrhage associated with rivaroxaban may be due to the high usage of concomitant medicines—in particular, potentially inappropriate concomitant medicines with the potential to increase the risk of bleeding. This is particularly pertinent given the current inability to monitor and reverse the anticoagulant effect of rivaroxaban and the observed haemorrhagic adverse events being reported in clinical practice. Across the three countries, approximately two thirds of reported rivaroxaban adverse event reports with concomitant medicines listed at least one concomitant medicine that may have placed the patient at increased risk of harm. This rate is considerably higher than that reported in spontaneous adverse event reports with dabigatran, where between a third and half of reports involving concomitant medicines included a potentially inappropriate medicine [16]. Whilst systematic reviews and meta-analyses have highlighted potential safety concerns with all newer oral anticoagulants, dabigatran may have been associated with increased awareness of safety issues (and potentially awareness of drug interactions) because of reports of an increased risk of adverse cardiovascular events [17]. This risk was not evident with rivaroxaban, either in the current study or in meta-analyses [17]. Further, the characteristics of the patient populations between those in clinical trials and those who receive rivaroxaban in clinical practice are likely to be different. The patients in clinical trials are generally younger and consequently less likely to have comorbid conditions, including renal or hepatic impairment, and they use fewer medicines. This limits the overall generalizability of safety and efficacy results obtained from RCTs and decreases the likelihood of

drug interactions and potential for adverse events [5, 18]. Clinically relevant subgroups of patients with atrial fibrillation who would be likely to use rivaroxaban and where the risk of both stroke and bleeding are increased include those aged 75 years or older, those with previous stroke or transient ischaemic attack, and those with renal dysfunction. The rivaroxaban ROCKET AF clinical trial targeted high-risk atrial fibrillation patients with a $CHADS_2$ score of $\geq$2; almost half had a prior stroke, and comorbidity was common [3]. The risk of adverse events is increased with increasing numbers of concomitant medicines, especially in older populations [19]. However, the exclusion criteria for the ROCKET AF trial included use of those medicines that may potentially increase bleeding risk [3], which were commonly reported with rivaroxaban in our study.

Concomitant antithrombotic medicines were the most prevalent potentially inappropriate medicine class across all countries, ranging from 42.9 to 51.8 % in rivaroxaban reports with concomitant medicines recorded. Aspirin was the most common concomitant antithrombotic medicine across all countries, with a prevalence ranging from 15.4 to 37.3 % in adverse event reports with concomitant medicines. This concomitant aspirin use is in concordance with the use of medicines at baseline during the ROCKET AF clinical trial, where 38 % of patients reported aspirin use at baseline of the trial [3]. In support of our findings that concomitant medicines may potentiate bleeding risk in clinical practice with rivaroxaban, a recent prospective analysis of the EINSTEIN clinical trial of patients with VTE reported that concomitant use of NSAIDs and aspirin in those receiving rivaroxaban was associated with 77 % (HR 1.77, 95 % CI 1.46–2.41) and 70 % (HR 1.7, 95 % CI 1.38–2.11) increased risks of clinically relevant bleeding, respectively [7]. Further, concomitant NSAID use was also associated with a 137 % (HR 2.37, 95 % CI 1.51–3.75) increased risk of major bleeding [7]. In addition, use of SSRIs in monotherapy has been shown to increase the risk of gastrointestinal bleeding by up to threefold [20].

Whilst the specific types of adverse events reported in the current study are similar to those observed in clinical trial results, whether these reports are a true reflection of all adverse events that are occurring in clinical practice or are an underrepresentation of those that are less severe (e.g. minor bleeds) with rivaroxaban remains unclear. Further, whether patients were truly concomitantly taking other medicines, particularly those with the potential to increase bleeding risk with rivaroxaban, was unable to be determined from the adverse event reports. For the reporting of an adverse medicine event, the Australian guidelines request information about any other medicines the patient was taking and the Canadian guidelines state that medicines should be classified as concomitant, drug used to treat adverse event or suspected cause of event [9, 10].

Medicines with established or clinically relevant potential interactions that may increase plasma levels of rivaroxaban and consequently increase bleeding risk were reported in 8.4–13.2 % of the adverse event reports where concomitant medicines were recorded. The most prevalent drug–drug interactions reported in the countries studied were medicines used to treat common cardiovascular comorbidities (including dronedarone, amiodarone, verapamil and diltiazem), where the likelihood of concomitant use with rivaroxaban may be high. Determining the clinical relevance of these interactions and quantification of the potential for serious adverse events are needed to understand the risk/benefit profile of their concomitant use.

Despite the limitations associated with the use of spontaneous adverse event reporting data, such as underreporting, reporting biases and varying report quality, many important safety signals have been identified using these data [21, 22]. Using these data, we were unable to fully ascertain whether the concomitant medicines reported were truly coadministered with rivaroxaban. However, in both the Australian and Canadian adverse event databases, it is clearly stated that reporters should include information on concomitant medicine use at the time of the adverse event [9, 10]. We were only able to conduct the disproportionality analysis in the US FAERS database, and other signals may have been observed with the inclusion of other spontaneous report data sets if available.

In terms of efficacy, rivaroxaban has been found to be at least noninferior to warfarin with regard to stroke prevention in patients with atrial fibrillation and prevention of VTE, and it may be a viable option for patients who have contraindications to warfarin or where international normalized ratio (INR) monitoring cannot be performed appropriately [4]. There has been rapid adoption of the newer anticoagulants into clinical practice. In a study of over 6,000 patients with atrial fibrillation over a 3-year period, novel anticoagulants accounted for 62 % of new prescriptions and 98 % of anticoagulant-related medicine costs, with patients at lower risk of adverse events being more likely to receive a newer oral anticoagulant [23].

5 Conclusion

The results of our study highlight the need for ongoing post-marketing surveillance of rivaroxaban, together with increased awareness of the potential for adverse events, particularly with the use of potentially inappropriate concomitant therapy. Many of these medicines are commonly used in the older patient population with multiple comorbidities, who may receive rivaroxaban for anticoagulation in clinical practice. Given the lack of an antidote, this study highlights the importance of consideration of comorbidity,

associated medicine use and the need for ongoing clinical monitoring of patients, including adherence, to facilitate appropriate and safe use in clinical practice.

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