Simvastatin, but not Atorvastatin, is associated with higher peak Rivaroxaban serum levels and bleeding

Xin Qin Soh (e0309138@u.nus.edu)
National University of Singapore https://orcid.org/0000-0003-2575-4530
Doreen Su-Yin Tan
National University of Singapore
Eric Chun Yong Chan
National University of Singapore

Research Article

Keywords: Atrial Fibrillation, Bleeding, Rivaroxaban, Simvastatin

Posted Date: April 18th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1539231/v1

Abstract

Aims In a previous study, Singaporean Asians were found to have lower rivaroxaban plasma concentrations than Caucasians. This expanded study attempts to identify predictors associated with bleeding and stroke and systemic embolism (SSE) in Singaporean Asians taking rivaroxaban and apixaban.

Methods A total of 134 Singaporean patients on either rivaroxaban or apixaban for non-valvular atrial fibrillation were included for this study. Baseline characteristics were recorded at recruitment while bleeding and SSE events were recorded during a 1-year follow-up. Characteristics of patients with or without bleeds were compared using relevant statistical tests. Multivariable regression that included covariates with $p < 0.1$ from an initial univariable regression was performed to analyze predictors that resulted in higher risk of bleeding in patients.

Results Median creatinine clearance (CrCl) was significantly lower in patients on rivaroxaban who experienced bleeds as compared to patients who did not experience bleeds (61.5 vs 70.8 mL/min, $p = 0.047$), while concomitant simvastatin use was found to be independently associated with a six-fold increased risk of bleeding [Adjusted OR = 6.14 (95% CI: 1.18 – 31.97), $p = 0.031$] for rivaroxaban after controlling for body mass index, CrCl and having experienced a previous SSE.

Conclusion Our findings suggest that concomitant use of simvastatin with rivaroxaban may be associated with bleeding events in an Asian cohort. Further studies using physiologically-based pharmacokinetic modeling are required to investigate the drug-drug interactions between these drugs.

1. Introduction

Direct oral anticoagulants (DOACs) are mainstay drugs in anticoagulation therapy for non-valvular atrial fibrillation (NVAF), the most prevalent form of atrial fibrillation (AF) [1]. NVAF is associated with a five-fold increased risk of ischemic stroke [2, 3] and up to 1.9-fold increased risk of mortality [3] as compared to the healthy population. As a result of DOACs' non-inferiority compared to warfarin in preventing stroke and systemic embolism (SSE) and significantly superior safety profile in AF patients [4], existing guidelines recommend the use of DOACs over warfarin for eligible patients [5–7]. Furthermore, unlike warfarin, routine monitoring for DOACs is not required due to their better efficacy-to-safety ratio, predictable anticoagulant effects [8] and pharmacokinetics [9].

The US Food and Drug Administration previously approved rivaroxaban and apixaban, two direct oral factor Xa inhibitors [10, 11], for use in SSE prevention in patients with AF in 2011 and 2012 respectively [4]. The recommended dose for rivaroxaban is 20 mg daily, decreased to 15 mg daily for patients with moderate-severe renal impairment [5]. The recommended dose for apixaban is 5 mg twice daily, decreased to 2.5 mg twice daily if patients have any two of (1) serum creatinine $\geq$ 1.5 mg/dL, (2) $\geq$ 80 years old, and (3) body weight $\leq$ 60 kg [5]. Unlike warfarin, these labeled indications recommend a fixed dose regimen for both DOACs.

Studies have, however, demonstrated high inter-individual variability in drug concentrations amongst patients on DOACs and suggested association between peak and trough of drug concentrations with bleeding and SSE events respectively [12–14]. This inter-individual variability may be altered by various factors, including other co-morbidities or the use of concomitant medications. Furthermore, Weber et al illustrated the bleeding risk from the use of DOACs in AF patients with chronic kidney disease [15], while concomitant use of rivaroxaban and apixaban with inhibitors of CYP3A4 enzyme, P-glycoprotein (P-gp) transporters, or both, have been associated with high DOAC concentrations in AF patients [16].

Ng et al demonstrated that Singaporeans had lower steady state rivaroxaban concentrations than Caucasians [17], while another Taiwanese study also identified lower rivaroxaban concentrations in their population as compared to published Western literature [18], thus suggesting potential differences in clinical disposition towards DOACs for the Asian population. However, an expanded retrospective cohort study involving 1700 Singaporeans revealed a prevalence of bleeding to be higher than published literature for rivaroxaban (manuscript to be published), seemingly a contradiction to the study by Ng et al. Furthermore, a three-fold increase in SSE with apixaban was observed in comparison to warfarin. Therefore, it seems that there may be other factors at play that result in conflicting observations. Hence, we aim to identify the correlation between the peak and trough concentrations of DOACs with bleeding or SSE in an Asian population, and to characterize other potential predictors that could also contribute to these complications.

2. Methods

Study population

This multicenter, prospective, observational study in NVAF patients treated with rivaroxaban or apixaban was carried out in the National Heart Center Singapore and Khoo Teck Puat Hospital, and approved by the Domain Specific Review Board (Study reference number: 2017/00815). Patients were recruited between 5 October 2017 and 6 February 2020. After providing their signed informed consent, NVAF patients who were at least 21 years of age and on rivaroxaban or apixaban for at least 3 continuous days were included in the study. Pregnant or breastfeeding women or women who had given birth in the past 90 days and patients enrolled in another drug or device study were excluded. A total of 106 rivaroxaban and 40 apixaban patients were recruited. The choice and dose of DOAC prescription was based on their physician’s discretion.

Baseline characteristics including gender, ethnicity, age, height, weight, smoking history, alcohol consumption, serum creatinine, co-morbidities and concomitant medications were recorded. Body mass index (BMI) and CHA_2DS_2-VASc scores were computed based on the collected records. Creatinine clearance (CrCl) was estimated via the Cockcroft-Gault equation [19]. Patients were followed up by phone at week 2, months 1, 3, 6 and 12. At each check-point, patients were interviewed on compliance and clotting or bleeding events.

Determination of drug plasma concentrations

Trough plasma samples were obtained at 24 hours or 12 hours after last administered dose of rivaroxaban or apixaban respectively. Peak plasma samples were obtained on the same day of trough plasma samples, at 3 hours after intake of medication with food.

Plasma concentrations for rivaroxaban and apixaban were measured using high performance liquid chromatography-mass spectrometry (HPLC-MS). The lower limits of quantification (LLOQ) and upper limits of quantification (ULOQ) were 5 ng/mL and 1000 ng/mL for rivaroxaban, and 1 ng/mL and 500 ng/mL for apixaban.

Measured plasma concentrations below the LLOQs of the analytical methods were set to half of the LLOQ (LLOQ/2) of the respective analytical methods

Determination of clinical endpoints of bleeding and SSE

Bleeding events were categorized into major and minor bleeding, by the International Society on Thrombosis and Haemostasis (ISTH) criteria [20]. Major bleeding was defined as (1) fatal bleeding, or (2) bleeding in a critical area or organ, for example intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome, or (3) bleeding causing a fall in hemoglobin level of ≥ 20 g L^{-1} (1.24 mmol L^{-1}) or leading to transfusion of ≥ 2 units of whole blood or red cells. Minor bleeding was defined as any overt bleeding that did not fall under the ISTH major bleeding criteria.

Major bleeding and SSE events were adjudicated by the study team comprising a cardiologist and a cardiology specialist pharmacist based on doctors' diagnoses obtained from electronic medical records (EMRs). Minor bleeding events were likewise obtained from EMRs or based on clinical signs and symptoms self-reported by patients during the follow-up phone interviews.

Statistical analysis

For the descriptive analysis, Shapiro-Wilk test was used to determine normality of the variables for $n < 50$, while Kolmogorov-Smirnov test was used to determine normality of the variables for $n \geq 50$. Normally distributed continuous variables were reported as mean and standard deviation (SD). Ordinal variables and non-normally distributed continuous variables were reported as median and inter-quartile range (IQR) values. Categorical variables were reported as frequencies and percentages.

For the analysis for plasma concentrations and bleeding events, patients were categorized into four classes (Class I, II, III and IV) based on equal quartiles of the populations' range of plasma concentrations adapted from Testa et al [12, 13], with Class I corresponding to the group of patients whom plasma concentrations fall within the lowest quartile and Class IV corresponding to the group of patients whom plasma concentrations fall within the highest quartile.

Statistical tests were performed using the Independent-sample's t-test for normally distributed continuous variables, Mann-Whitney U test for ordinal variables and non-normally distributed continuous variables, and Chi-square test or Fisher's exact test for categorical variables, to identify predictors for bleeding and SSE events.

Univariable logistic regression was performed to estimate relative risk for bleeding and SSE. Results were reported as odds ratio (OR) and 95% confidence interval (CI). Multivariable logistic regression was performed for covariates with a p-value < 0.1 from the univariable analysis to adjust for confounders.

Statistical analyses were performed with the IBM SPSS Statistics 27 for Windows. A p-value of < 0.05 was considered to be statistically significant.

3. Results

Out of 146 patients recruited for the study, 134 patients (91.8%) were included (97 patients taking rivaroxaban, 37 patients taking apixaban). Patients who were lost to follow-up, had their DOAC changed, stopped or down-titrated were excluded (Fig. 1).

Baseline demographics of all 146 patients are reported in Table 1. Patient characteristics were similar for rivaroxaban and apixaban patients. Three patients out of 134 included for analysis experienced SSE events (2.2%), while 33 experienced bleeds (24.6%).

Table 1 Demographics of patients on rivaroxaban and apixaban

	Rivaroxaban		Apixaban		Total
Patients, *N*	106		40		146
Daily dose, n (%)	15mg daily	25 (23.6)	2.5mg BD	6 (15.0)	
	20mg daily	81 (76.4)	5mg BD	34 (85.0)	
Gender, n (%)					
Male	77 (72.6)		32 (80.0)		109 (74.7)
Female	29 (27.4)		8 (20.0)		37 (25.3)
Age (years), mean ± SD	64.1 ± 9.5		66.4 ± 7.4		64.7 ± 9.0
BMI (kg/m^2), median (IQR)	26.0 (23.5 – 30.3)		26.2 (22.8 – 28.2)		26.0 (23.4 – 29.7)
CrCl (mL/min), median (IQR)[a]	71.0 (55.2 – 85.2)		61.9 (46.0 – 77.1)		67.7 (54.1 – 85.0)
Previous major bleed, n (%)	7 (6.6)		2 (5.0)		9 (6.2)
Previous SSE, n (%)	17 (16.0)		9 (22.5)		26 (17.8)
CHA_2DS_2-VASc, median (IQR)	2 (2 – 3)		3 (2 – 4)		2 (2 – 3)
SSE, n (%)[b]	2 (2.1)		1 (2.7)		3 (2.2)
Bleeds, n (%)[b]	29 (29.9)		4 (10.8)		33 (24.6)
ISTH major bleeds	2 (2.1)		0 (0.0)		2 (1.5)
ISTH minor bleeds	27 (27.8)		4 (10.8)		31 (23.1)

Abbreviations: *BD* twice daily, *SD* standard deviation, *BMI* body mass index, *IQR* inter-quartile range, *CrCl* creatinine clearance, *SSE* stroke and systemic embolism, *ISTH* International Society on Thrombosis and Haemostasis.

[a] There were missing data for this variable in the dataset. Median (IQR) for this variable is presented based on available data (Rivaroxaban: *N* = 102; Apixaban: *N* = 34).

[b] There were patients excluded for this variable. n (%) for this variable is presented based on included patients (Rivaroxaban: *N* = 97; Apixaban: *N* = 37).

We compared the characteristics of patients with and without bleeding events for both DOACs. For the rivaroxaban cohort, CrCl and concomitant use of simvastatin were statistically significant factors associated with bleeding (p = 0.047 and 0.024 respectively) (Table 2). Further information on the frequencies of patients who bled in each individual class is described in Supplementary Table S1. We did

not carry out further analyses for the apixaban cohort because there were no significant factors associated with bleeding in the cohort (Supplementary Table S2).

Table 2 Comparison of characteristics between patients with and without bleeds in the rivaroxaban group

	Patients without bleed	Patients with bleed	p-value
Patients, *N*	68	29	
Peak plasma concentration (ng/mL), median (IQR)	180.98 (109.12 – 271.98)	182.58 (149.90 – 267.06)	0.457
Trough plasma concentration (ng/mL), median (IQR)	29.26 (13.54 – 52.61)	33.50 (19.53 – 43.21)	0.828
Peak concentration (Classes), n (%)			0.254
Class I	28 (41.2)	8 (27.6)	
Class II – IV	40 (58.8)	21 (72.4)	
Trough concentration (Classes), n (%)			0.824
Class I	37 (54.4)	17 (58.6)	
Class II – IV	31 (45.6)	12 (41.4)	
Gender, n (%)			0.336
Male	28 (84.8)	23 (79.3)	
Female	5 (15.2)	6 (20.7)	
Age, median (IQR)	66.0 (59.0 – 70.0)	64.0 (57.5 – 69.0)	0.484
BMI (kg/m^2), median (IQR)	27.4 (24.4 – 31.2)	25.1 (22.6 – 28.7)	0.059*
CrCl (mL/min), median (IQR)[a]	70.8 (57.7 – 85.8)	61.5 (49.4 – 79.8)	**0.047****
Previous SSE, n (%)	15 (22.1)	2 (6.9)	0.086*
Previous major bleed, n (%)	6 (8.8)	0 (0.0)	0.174
Antiplatelets, n (%)	8 (11.8)	5 (17.2)	0.521
Amiodarone, n (%)	5 (7.4)	3 (10.3)	0.693
Angiotensin receptor blockers, n (%)[b]			
Losartan	5 (7.4)	2 (6.9)	1.000
Telmisartan	3 (4.4)	0 (0.0)	0.548
Valsartan	8 (11.8)	2 (6.9)	0.718
Combined total	16 (23.5)	4 (13.8)	0.412
HMG-CoA reductase inhibitors, n (%)[c]			

Atorvastatin	43 (63.2)	14 (48.3)	1.000
Rosuvastatin	0 (0.0)	2 (6.9)	0.069*
Simvastatin	4 (5.9)	7 (24.1)	**0.024****
Combined total	47 (69.1)	23 (79.3)	0.336

Abbreviations: *IQR* inter-quartile range, *BMI* body mass index, *CrCl* creatinine clearance, *SSE* stroke and systemic embolism, *HMG-CoA* 3-hydroxy-3-methylglutaryl coenzyme A.

**p-value < 0.05.

*p-value < 0.10.

[a] There were missing data for this variable in the dataset. Median (IQR) for this variable is presented based on available data (Without bleed: *N* = 66; With bleed: *N* = 28).

[b] No use of any angiotensin receptor blocker was considered the reference group.

[c] No use of any HMG-CoA reductase inhibitor was considered the reference group.

Table 3 shows the multivariable analysis for risk of bleeding with rivaroxaban. After controlling for BMI, CrCl and previous SSE, concomitant use of simvastatin (compared with patients not on statins) remained as the only significant predictor of bleeding [Adjusted OR = 6.14 (95% CI: 1.18–31.97), p = 0.031]. Although not statistically significant, patients with previous SSE events seemed to have a four-fold lower risk of bleeding [Adjusted OR = 0.25 (95% CI: 0.05–1.27), p = 0.094].

Table 3 Results for multivariable analysis for risk of bleeding in the rivaroxaban group

	Patients without bleed	Patients with bleed	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio[ab] (95% CI)
Patients, *N*	68	29		
Class I peak plasma concentration, n (%)	28 (41.2)	8 (27.6)	Ref	
Class II-IV peak plasma concentration, n (%)	40 (58.8)	21 (72.4)	1.84 (0.71 – 4.74)	
Class I trough plasma concentration, n (%)	37 (54.4)	17 (58.6)	Ref	
Class II-IV trough plasma concentration, n (%)	31 (45.6)	12 (41.4)	0.84 (0.35 – 2.03)	
BMI (kg/m^2), median (IQR)	27.4 (24.4 – 31.2)	25.1 (22.6 – 28.7)	0.92 (0.84 – 1.01)*	0.91 (0.80 – 1.03)
CrCl (mL/min), median (IQR)[c]	70.8 (57.7 – 85.8)	61.5 (49.4 – 79.8)	0.98 (0.96 – 1.00)*	0.99 (0.96 – 1.02)
Previous SSE, n (%)	15 (22.1)	2 (6.9)	0.26 (0.06 – 1.23)*	0.25 (0.05 – 1.27)*
No HMG-CoA reductase inhibitor, n (%)	21 (30.9)	6 (20.7)	Ref	Ref
Atorvastatin, n (%)	43 (63.2)	14 (48.3)	1.14 (0.38 – 3.39)	1.40 (0.41 – 4.73)
Rosuvastatin, n (%)	0 (0.0)	2 (6.9)	NA[d]	NA[d]
Simvastatin, n (%)	4 (5.9)	7 (24.1)	**6.13 (1.33 – 28.21)****	**6.14 (1.18 – 31.97)****

Abbreviations: *CI* confidence interval, *BMI* body mass index, *IQR* inter-quartile range, *CrCl* creatinine clearance, *SSE* stroke and systemic embolism, *HMG-CoA* 3-hydroxy-3-methylglutaryl coenzyme A.

**p-value < 0.05.

*p-value < 0.10.

[a] Adjusted for BMI, CrCl, previous SSE, concomitant use of atorvastatin, rosuvastatin or simvastatin.

[b] There were missing data for CrCl in the dataset. Multivariable regression was performed on available data (Without bleed: *N* = 66; With bleed: *N* = 28).

[c] There were missing data for this variable in the dataset. Median (IQR) for this variable is presented based on available data (Without bleed: *N* = 66; With bleed: *N* = 28).

[d] As the cell count for patients without bleed and with concomitant use of rosuvastatin is 0, the denominator of the odds ratio equation is 0 resulting in a very large odds ratio.

Comparing rivaroxaban plasma concentrations in patients with or without concomitant simvastatin use, median peak rivaroxaban plasma concentration in simvastatin patients was significantly higher compared to patients not on simvastatin (Table 4). Trough plasma concentrations were not significantly different between groups.

Table 4 Comparison of peak and trough plasma concentrations between patients taking rivaroxaban with or without concomitant use of simvastatin

	Patients without concomitant use of simvastatin	**Patients with concomitant use of simvastatin**	**p-value**
Patients, *N*	86	11	
Peak plasma concentration (ng/mL), median (IQR)	180.42 (116.81 – 250.26)	241.25 (177.10 – 374.47)	**0.047****
Trough plasma concentration (ng/mL), median (IQR)	30.44 (14.11 – 48.18)	44.41 (17.90 – 68.40)	0.224

Abbreviations: *IQR* inter-quartile range.

**p-value < 0.05.

There was no statistically significant difference in median rivaroxaban plasma concentrations with or without concomitant use of atorvastatin (Supplementary Table S3). There were too few patients with concomitant use of rosuvastatin for comparison to be done.

Table 5 Trough plasma concentration of DOACs of the study population and individual patients who experienced SSE events

Patient	Drug	Trough concentration (ng/mL)	Percentage of population's median trough concentration[a]	CHA_2DS_2-VASc	SSE event
Study population (*N* = 134)	Rivaroxaban	31.0 (2.5 – 133.7)[b]	Ref	2 (2 – 4)[c]	-
	Apixaban	90.7 (0.5 – 215.5)[b]	Ref	3 (2 – 3)[c]	-
	Combined	-	-	2 (2 – 3)[c]	-
Patient 1	Rivaroxaban	2.5	8.1%	5	Ischemic stroke
Patient 2	Rivaroxaban	8.3	26.8%	2	NSTEMI
Patient 3	Apixaban	15.0	16.5%	1	LAA thrombus

Abbreviations: *SSE* stroke and systemic embolism, *NSTEMI* non-ST-elevation myocardial infarction, *LAA* left atrial appendage.

[a] Calculated as (patient's trough concentration) ÷ (population's median trough concentration for patient's drug) x 100%.

[b] Data is presented as median (range).

[c] Data is presented as median (inter-quartile range)

Table 5 describes the trough concentrations and CHA_2DS_2-VASc scores of the three patients with SSE. These patients had low trough plasma concentrations of between 8.1% and 26.8% of the populations' median concentrations for the respective DOACs. No further analyses were carried out to compare these patients as there were too few events for substantial comparison.

4. Discussion

The present study is, to the best of our knowledge, the first study that highlights a six-fold increased risk of bleeding when rivaroxaban and simvastatin were used together. We propose that there could be two possible explanations for the observation of increased bleeding with concomitant simvastatin.

Firstly, approximately 18% and 14% of rivaroxaban is metabolized by CYP3A4 and CYP2J2 respectively [21], while P-gp was reported to contribute to its renal elimination [21–23]. In addition, the human organic anion transporter 3 (OAT3) was demonstrated to play a pivotal role in the renal clearance of rivaroxaban via its basolateral uptake in proximal tubular cells [24]. A previous study predicted that systemic exposure of rivaroxaban and bleeding risk could be increased due to inhibition of OAT3 by benzofuran antiarrhythmic agents [25].

Several studies had been carried out to understand the inhibitory potential of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors (statins) on liver enzymes and drug transporters. Yang et al demonstrated that simvastatin exhibited CYP3A4 inhibition with a half-maximal inhibitory concentration (IC_{50}) value of 3.10 μM [26], while another study demonstrated a greater than 85% reduction of CYP2J2 activity by simvastatin at 30 μM [27]. Simvastatin is also known to inhibit P-gp with IC_{50} values between 8.9 to 49 μM [28, 29] and shown to have some inhibitory effects on OAT3 with IC_{50} values between 32.3 and 48.1 μM [30–32]. Thus, we postulate that simvastatin could potentially decrease the hepatic and renal clearances of rivaroxaban, potentially leading to more bleeding. This is further supported by significantly higher median peak plasma concentration in patients co-prescribed with simvastatin in this study.

Secondly, lower low-density lipoprotein cholesterol (LDL-C) levels may result in higher bleeding risk [33]. While LDL-C was not measured in our study, the use of simvastatin has been reported to decrease the LDL-C levels by 28.3 to 45.8% [34]. It was posited that low LDL-C levels could be negatively associated with platelet activation [33], and that platelet aggregation might be impaired due to depletion of cholesterol [35]. Taken together, decreased platelet activation and aggregation might have contributed to the observed increased risk of bleeding in patients co-prescribed with simvastatin. Further studies involving LDL-C measurements would need to be carried out to substantiate this postulation.

While the event rate for rosuvastatin was too small for a convincing analysis, a question arises as to why a similar significance was not observed for concomitant use of atorvastatin which also decreases LDL-C levels in patients [34] and was similarly shown to inhibit CYP3A4 [26], P-gp [28] and OAT3 [30, 31] in various studies? One possible explanation is the weaker inhibitory potencies of atorvastatin against CYP3A4-mediated metabolism and P-gp-mediated transport with IC_{50} values of 48.0 μM [26] and between 271 and 356 μM [28], respectievly. Considering the relatively more potent inhibition of CYP3A4 and P-gp by simvastatin, the interaction with rivaroxaban was more pronounced culminating in higher peak rivaroxaban plasma concentrations observed in this study.

Another finding was that median CrCl was significantly lower in patients taking rivaroxaban who experienced bleeds as compared to those who did not. This is supported by two possible explanations.

Firstly, an increased risk of bleeding independent of anticoagulant use in patients with renal impairment was identified by Del-Carpio et al in a meta-analysis [36]. As CrCl can estimate glomerular filtration rate which is used as a measurement of renal function [37], it may be inferred that patients with lower CrCl have poorer renal function which potentially contributes to bleeding risk.

Secondly, poorer renal function may also have decreased the elimination of some concomitant medications that may have interactions with rivaroxaban, for example, simvastatin which is partially cleared by the renal route [38]. This would translate to a potentially larger extent of inhibition of liver enzymes or drug transporters that are crucial in the elimination of rivaroxaban and may thus contribute to bleeding risk. This may also explain the likely collinearity between use of simvastatin and CrCl, as CrCl

was a significant predictor for bleeding in the univariable analysis, but was no longer a significant predictor when modeled with other factors including use of simvastatin, while simvastatin was identified to be the only significant predictor for bleeding after controlling for BMI, CrCl and previous SSE.

Interestingly, patients with a previous SSE were associated with a four-fold lower risk of bleeding, albeit not statistically significant. We postulate that patients who had previously experienced SSE events have a higher risk of clotting at baseline based on the pathophysiology of embolism, and hence have lower bleeding risk.

While statistical tests were not performed to characterize the relationship between trough plasma concentrations and SSE events due to the small sample size of patients who experienced a SSE event during follow-up, we observed that these patients belonged to the lowest class for trough plasma concentrations, with one patient whose trough plasma concentration fell below the LLOQ of the HPLC-MS assessment. This observation is supported by a previous study by Testa et al [13]. DOACs are reversible, competitive inhibitors of factor Xa with short half-lives [39, 40]. Thromboembolism can occur in a period where plasma concentrations are below the necessary thresholds for sufficient inhibitory activity to maintain adequate anticoagulation. This should be verified in larger studies.

We acknowledge that this study has its limitations. Firstly, the ability to detect significant relationship between DOAC plasma concentrations and SSE events is limited by the small sample size. This is especially apparent for the apixaban group which only consisted of 37 patients included for analysis, and only 1 patient experienced an SSE. To counter issues with small sample size, we included patients whose plasma concentrations were below the LLOQ by estimating their plasma concentrations to LLOQ/2 to provide more data points for the analysis. As only a small percentage of recorded plasma concentrations was below the LLOQ, this method of estimation is unlikely to be biased [41]. Future studies could be designed to address the issue of extremely low trough plasma concentrations and how that should be best handled. This would be important in associative studies correlating trough concentrations and risk of SSEs when investigating the acceptable lower limits for trough concentrations. This would have important clinical interpretation and use.

Secondly, we assumed that the recorded plasma concentrations of the DOACs stay constant throughout the 1-year follow-up. The most likely reason for fluctuating plasma concentrations could be attributed to poor adherence to DOACs because a one year timeframe is too short for significant changes in the disposition of DOACs. We made the best possible effort to ascertain medication adherence during the follow-up calls, and were able to ascertain that the adherence rate was over an impressive 90%. Thus we do not think that poor adherence could have contributed to the observed outcome of low plasma concentrations and thus SSEs.

5. Conclusion

This study demonstrated an increased risk of bleeding in Asian patients taking simvastatin concomitantly with rivaroxaban, suggesting potential clinically relevant pharmacokinetic and

pharmacodynamic interactions between the two drugs. This interaction was not observed with atorvastatin. Current European guideline suggests no notable anticipated effects of atorvastatin on the area-under-the-curve of rivaroxaban, and does not recommend a need for dose adjustment of the DOAC [8], while simvastatin was not mentioned. We suggest that the drug-drug interactions between rivaroxaban and simvastatin should be further investigated in a larger, focused patient cohort, using physiologically-based pharmacokinetic modeling or otherwise. The mechanistic explanation of the interaction could hold important clues towards concomitant use of drugs of similar disposition profile, particularly when DOAC effects or plasma concentrations are not routinely measured nor readily accessible.

Declarations

Acknowledgement

The authors wish to extend their thanks to Ms Lin Yingying (Khoo Teck Puat Hospital) for her help with data collection and data preparation for this study.

Competing interests

The authors have no conflicts of interest to declare.

Funding

The authors declare that there was no funding obtained for this study.

Ethics and patient consent

Ethics approval was obtained from the Domain Specific Review Board (Study reference number: 2017/00815). Informed consent by participants was obtained prior to data collection.

Authorship contributions

Participated in research design: Soh, Tan and Chan

Performed data analysis: Soh

Wrote of contributed to the writing of the manuscript: Soh, Tan and Chan

Data availability statement

The datasets generated during and/or analysed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

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Figures

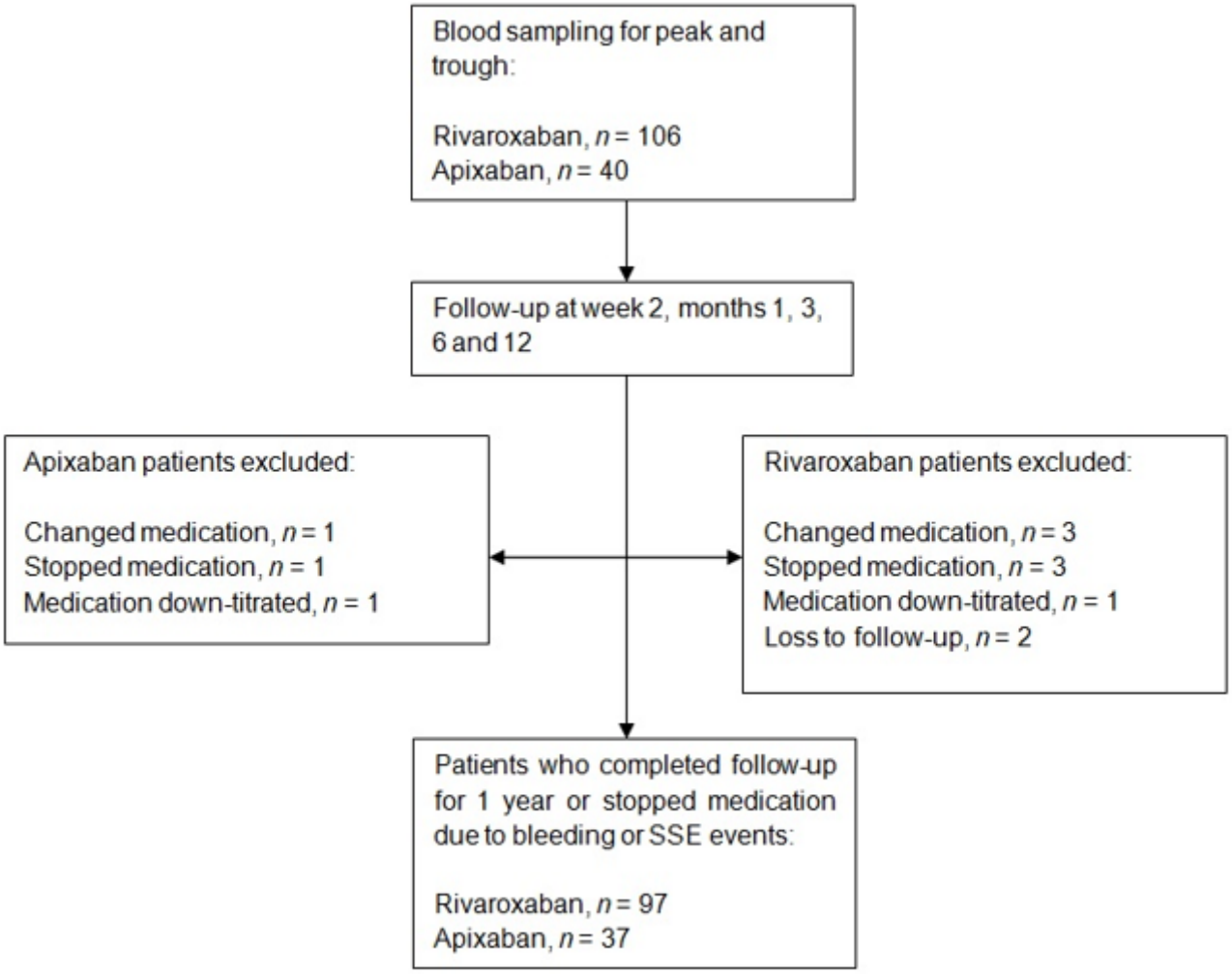

Figure 1

Flowchart of inclusion and exclusion of subjects

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