Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
0(0) 1–9

DOI: 10.1177/0300060519894439
journals.sagepub.com/home/imr
SAGE

Slightly elevated international normalized ratio predicts bleeding episodes in patients treated with direct oral anticoagulants

Priya Bhardwaj[1], Louise Breum Petersen[1], Tomas Sorm Binko[2], Jan Roland Petersen[1] and Gitte Gleerup Fornitz[1]

Abstract

Introduction: Patients treated with direct oral anticoagulants (DOACs) are at increased bleeding risk. It is therefore of increasing interest to identify predictors of bleeding episodes to increase safety during treatment with DOACs.

Methods: This retrospective cohort study systematically reviewed medical records of 235 patients treated with either apixaban, rivaroxaban or dabigatran for non-valvular atrial fibrillation or venous thromboembolism and collected data on the international normalized ratio (INR) and all bleeding episodes.

Results: INR $\geq$ 1.5 was significantly associated with increased risk of minor and major bleeding events in patients treated with direct factor Xa inhibitors. This association was not present in patients treated with dabigatran. However, a high negative predictive value was identified for INR $<$ 1.5 for all drugs. The relative risks of bleeding episodes in patients with INR $\geq$ 1.5 and INR $<$ 1.5 were 5.1 and 0.20, respectively.

Conclusions: Our results demonstrate a strong correlation between INR and risk of bleeding episodes during DOAC treatment. INR $<$ 1.5 was a strong negative predictor for low bleeding risk independent of indication or choice of drug, and INR $\geq$ 1.5 was associated with increased risk of bleeding episodes in patients treated with direct factor Xa-inhibitors.

[1]Department of Cardiology, Slagelse Hospital, Region Seeland – Denmark
[2]Department of Cardiology, Amager Hospital, Capital Region – Denmark

Corresponding author:
Gitte Gleerup Fornitz, Slagelse Hospital Ingemansvej 30 Slagelse, 4200 Denmark.
Email: gitte.fornitz@live.dk

Keywords
Direct oral anticoagulants, factor Xa inhibitors, thrombin inhibitor, international normalized ratio, minor bleeding, major bleeding

Date received: 24 August 2019; accepted: 21 November 2019

Introduction

Direct oral anticoagulants (DOACs) are effective alternatives to anticoagulation with vitamin K antagonists (e.g., warfarin) for the prevention and treatment of thromboembolic disorders. In addition, DOACs have been demonstrated to be superior and non-inferior to warfarin for both stroke prevention and bleeding risk.[1–4] DOACs are increasingly used worldwide for treatment and prevention of venous thromboembolisms (VTEs) and for prevention of stroke in patients with non-valvular atrial fibrillation (NVAF). Currently, many scientific societies recommend DOACs instead of warfarin as anticoagulants in patients with atrial fibrillation.[5,6]

The DOACs consist of the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban, rivaroxaban, edoxaban and betrixaban. DOACs are prescribed as fixed-dose management either once or twice daily, with dosages determined by creatinine clearance, body weight, age and use of concomitant drugs.[7–9] This is possible because of the predictable pharmacodynamics and pharmacokinetic properties of DOACs compared with warfarin. A key benefit of DOACs is that they do not require routine laboratory monitoring, and although they are non-inferior in terms of bleeding risk compared with vitamin K antagonists, a risk of internal bleeding still exists.[10] No studies have investigated whether quantitative or qualitative measurement of DOACs is associated with increased bleeding risk. The international normalized ratio (INR) is highly related to thrombotic and bleeding episodes in patients treated with warfarin, despite a large variation of values.[11]

Treatment with apixaban and rivaroxaban have recently been described to cause a significant elevation of the INR (rivaroxaban more so than apixaban).[12] In this real-world retrospective study, we explored if this elevation of INR might have any clinical impact in patients treated with DOACs according to the current guidelines.

Material and methods

Study design and population

A retrospective cohort study was conducted at an outpatient thrombocardiology clinic. The 235 subjects were enrolled from the department of coagulation from 1 June 2013 to 31 December 2016.

Medical records were thoroughly inspected by one resident and reviewed by two senior cardiologists. The subjects were divided according to the specific drug they were treated with. The INR, hemoglobin level and any documentation of minor or major bleeding events were recorded. The assay used for INR measurement in all patients was the Owren type PT procedure and the results were converted to an INR (O-INR) level. INR measurements were all performed at a single laboratory.

Inclusion criteria

Treatment was with one of the three DOACs apixaban, rivaroxaban or dabigatran, all of which were licensed in Denmark during the study period. The subjects were patients with

NFAF or VTE treated with DOACs in our outpatient clinic according to current guidelines. All patients had normal liver parameters and the DOAC doses were adjusted according to renal parameters.

Exclusion criteria

Severe non-compliance or availability of less than two INR samples during follow-up.

Ethical considerations

Approval to store patient data was granted by the Danish Data Protection Agency.

Informed consent

Informed consent was not needed due to the retrospective study design.

Outcomes

The primary outcomes were INR levels and bleeding events. We hypothesized from our pilot study that a cut-off INR of ≥ 1.5 could predict bleeding events in patients treated with DOACs according to current guidelines, independent of the indication. Bleeding events were categorized as minor and major according to the International Society of Thrombosis and Haemostasis criteria for non-surgical patients.[13] Anemia that could be attributed to other conditions was not regarded as a bleeding complication.

Statistical analyses

Data were analyzed using standard software. We evaluated associations between variables with the χ^2 test. Values of $p < 0.05$ were considered statistically significant. The relative risk (RR) was used to compare the risk of bleeding in patients with high and low INR.

Results

The medical records of 235 patients were thoroughly inspected. We observed minor or major bleeding episodes in 73 patients (31.1%). No bleeding episodes occurred in the remaining 162 patients (68.9%) (Figure 1).

Fifty-one (69.9%) of the 73 patients experiencing bleeding had an INR ≥ 1.5, whereas only 22 patients (30.1%) patients with bleeding had INRs < 1.5 (Figure 1). Using a cut-off value of INR ≥ 1.5, we found that INR was significantly associated

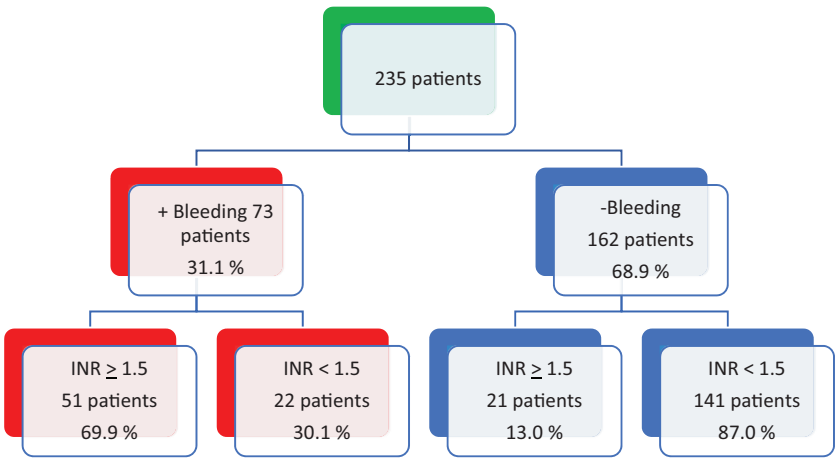

Figure 1. Distribution of bleeding and INR in the study population.

with increased risk of minor or major bleeding episodes in patients treated with direct Xa inhibitors. This association was not observed for patients treated with dabigatran (Figure 2).

Of the 162 patients, 141 (68.9%) who did not experience bleeding had an INR < 1.5 (87.0%), and only 21 patients (13.0%) had an INR ≥ 1.5 (Figure 1). Table 1 shows the data for the study population categorized according to drug treatment. The association between INR ≥ 1.5 and bleeding was more apparent in patients treated with rivaroxaban than other drugs ($p = 0.02$). By contrast, in patients with INRs < 1.5 who did not experience bleeding the association was

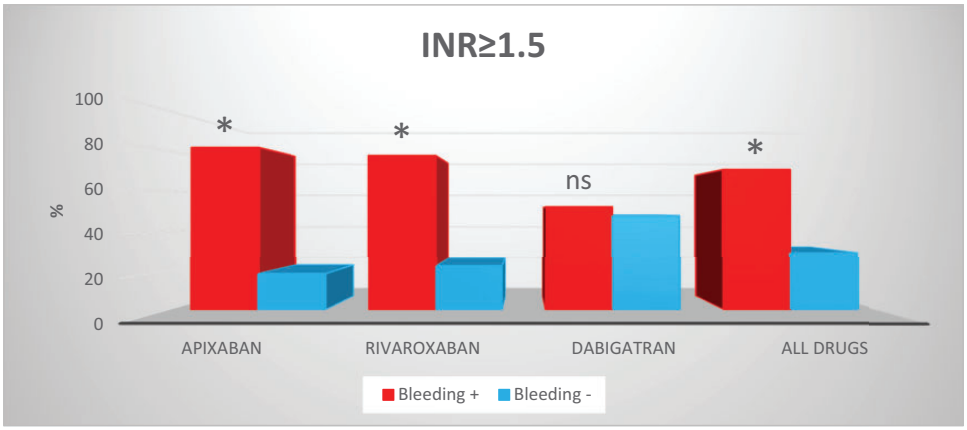

Figure 2. Bleeding events in patients with INR ≥ 1.5.
Bleeding: Bleeding +; No bleeding: Bleeding −; *$p = 0.001$ for association between INR ≥ 1.5 and bleeding during treatment with specific drug; ns: non-significant.

Table 1. Association between INR and bleeding in patients treated with different drugs.

	Apixaban		Rivaroxaban		Dabigatran		All drugs	
	%	n	%	n	%	n	%	n
INR ≥ 1.5								
Bleeding +	17.7	18	30.9*	21	18.5	12	21.7	51
Bleeding −	3.9	4	8.8	6	16.9	11	8.9	21
INR < 1.5								
Bleeding +	10.8	11	8.8	6	7.7	5	9.4	22
Bleeding −	67.6	69	51.5	35	56.9	37	60.0	141
Total	100	102	100	68	100	65	100	235
Positive predictive value	81.8		77.8		52.2		70.8	
Negative predictive value	86.3		85.4		88.1		86.5	
	RR							
RR of bleeding INR ≥ 1.5	5.1							
RR of bleeding INR < 1.5	0.2							

Bleeding: Bleeding +; No bleeding: Bleeding −.
RR: Relative Risk; *$p = 0.02$ rivaroxaban association versus association for all drugs.

Table 2. Association between INR and bleeding events according to magnitude of INR.

Drug	INR≥1.5	INR<1.5
All drugs		
Bleeding + % (CI)	70.8 (69.5–71.0)*	13.5
Bleeding − % (CI)	29.2	86.5 (85.6–87.4)*
Apixaban		
Bleeding + % (CI)	81.8 (78.0-85.6)*	13.8
Bleeding − % (CI)	18.2	86.2 (84.3–88.2)*
Rivaroxaban		
Bleeding + % (CI)	77.8 (74.1–81.4)*	14.6
Bleeding − % (CI)	22.2	85.4 (82.4–88.3)*
Dabigatran		
Bleeding + % (CI)	52.2 (47.5–56.9)**	11.9
Bleeding − % (CI)	47.8	88.1 (84.8–91.6)*

Bleeding: Bleeding +; No bleeding: Bleeding −.
*p<0.001: INR↑ and bleeding +; **p = ns: INRn and bleeding−.
INR↑ = INR≥1.5; INRn = INR<1.5; CI: 95% confidence interval.

slightly stronger for apixaban, although this difference was not statistically significant (Table 1).

The positive predictive (PPV) and negative predictive values (NPV) using a cut-off INR $\geq$ 1.5 were 81.8% and 86.3% for apixaban, respectively; 52.2% and 88.1% for dabigatran, respectively; and 77.8% and 85.4% for rivaroxaban, respectively.

The RR of bleeding in patients treated with all drugs with INRs $\geq$ 1.5 was 5.1 and the RR for bleeding in patients with INRs < 1.5 was 0.20.

Using the cut-off of INR $\geq$ 1.5 appears to be of clinical importance. Table 2 shows the correlation between INR and bleeding categorized by the magnitude of INR for different drugs.

We found that bleeding events during apixaban treatment occurred in 81.8% of patients with INRs $\geq$ 1.5, whereas bleeding episodes were only observed in 13.8% of patients with INRs < 1.5. The same pattern was observed in patients treated with rivaroxaban: 77.8% of patients with INRs $\geq$ 1.5 experienced bleeding events, while only 14.6% of patients with INRs < 1.5 did. However, we found no correlation between INR $\geq$ 1.5 and bleeding events in patients treated with dabigatran (Table 2).

Irrespectively of the drug used, INR < 1.5 was found to have a strong negative predictive value for the absence of bleeding events during treatment. We observed no bleeding episodes in 86.2% of patients treated with apixaban whose INRs were < 1.5. Only 13.8% of apixaban-treated patients with INRs < 1.5 experienced bleeding. Similar trends were observed for treatment with rivaroxaban (no bleeding: 85.4% versus bleeding: 14.6%) and dabigatran (no bleeding: 88.1% versus bleeding: 11.9%) (Table 2).

Figure 2 illustrates the significantly increased risk of bleeding episodes in patients with INRs $\geq$ 1.5 during treatment with apixaban and rivaroxaban. No association with INR was identified in patients treated with dabigatran treatment.

Figure 3 shows that almost no bleeding episodes occurred in individuals with INRs < 1.5 irrespective of the drug used.

Discussion

In patients treated with warfarin, associations between INR and thrombotic and

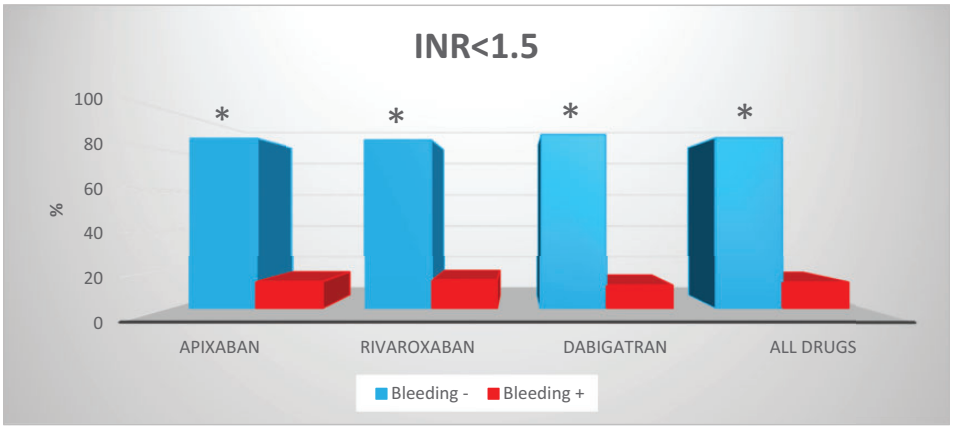

Figure 3. Bleeding events in patients with INR<1.5.
Bleeding: Bleeding +; No bleeding: Bleeding −; *p = 0.001 for association between INR<1.5 and no bleeding during treatment with specific drug.

bleeding events are well established despite large variation in INR values. The relation of INR to clinical events during DOAC treatment has not been investigated, as patients are fully anticoagulated on a fixed dose regime. However, a clinical case report described a potential association between INR and apixiban.[14]

Our study is the first to clarify the clinical significance of slightly elevated INRs during DOAC treatment. To simplify the prediction of future bleeding episodes, we did not stratify patients according to clinical indications (NVAF and VTE), instead hypothesizing that a useful predictor of bleeding episodes during DOAC treatment would only be affected by the drug used, and not by the indication. Furthermore, DOAC dosing is adjusted according to age, drug interactions and renal parameters.

Whether subgroup analyses of patients according to indications, dosage, age, drug interactions and renal parameters would affect our results was not possible to clarify in this study. Such questions will need to be addressed in our future prospective studies.

We found that an INR $\geq$ 1.5 was significantly associated with an increased risk of bleeding events during treatment with direct factor Xa inhibitors and that such associations were slightly stronger for rivaroxaban than apixaban. No such association was identified in patients treated with dabigatran.

This observation was supported by the finding that an INR $\leq$1.5 was a strong negative predictor of bleeding risk in patients treated with DOACs independent of indication (NVAF and VTE). In patients treated with dabigatran, previously studies demonstrated a correlation between diluted thrombin time or activated partial thromboplastin time and plasma concentrations of anti-Xa, and that these biomarkers were more sensitive than INR.[15] Patients treated with factor Xa inhibitors showed a significant correlation between INR and plasma concentration of anti-Xa.[14–16] However, none of these studies correlated the clinical outcome (bleeding) to these biomarkers as we did in this study. In agreement with previous data, we found that the correlation between INR and bleeding in patients treated with dabigatran was not significant.

Rivaroxaban and apixaban bind directly to factor Xa and inhibit both free and clot-bound factor Xa as well as prothrombinase activity, resulting in a very effective decrease in thrombin formation. However, it is possible that not all factor Xa inhibitors influence prothrombinase activity to the same extent, and this might explain our observation that the association between INR $\leq$1.5 and bleeding episodes was a little stronger for rivaroxaban than apixaban. These observations are supported by a newly published study,[12] which observed that DOACs elevated INR significantly (rivaroxaban more so than apixaban), and that no other factors other than the drugs themselves affected INR. We observed almost no bleeding episodes in patients with INRs $\leq$1.5, indicating that an INR $<$ 1.5 was a strong negative predictor for bleeding and an indicator of the safety of DOACs.

Our observations are corroborated by pharmacodynamic studies. The therapeutic maximum plasma concentration (Cmax) of rivaroxaban is in the range pf 173 to 274 $\mu g\ L^{-1}$. Plasma rivaroxaban levels of 200 $\mu g\ L^{-1}$, 400 $\mu g\ L^{-1}$, and 600 $\mu g\ L^{-1}$ were associated with mean INRs of 1.28, 1.55 and 1.85, respectively. Similarly, a plasma rivaroxaban level of 305 $\mu g\ L^{-1}$ was associated with a mean INR $<$ 1.4.

At therapeutic concentrations of rivaroxaban (173–274 $\mu g\,L^{-1}$), INR rarely exceeds 1.5 and may even be in the reference range ($\leq$1.2). In the case of supratherapeutic plasma levels, INR may increase to $\geq$ 1.5 if the plasma concentration of rivaroxaban exceeds 400 $\mu g\ L^{-1}$. Indeed, in our study we observed no significant association between an INR of 1.3 to 1.4 and bleeding events. We found that a cut-off value of INR $\geq$ 1.5 was significantly associated with increased risk of bleeding events.[17,18] This might explain why we observed a correlation between bleeding episodes and INR $\geq$ 1.5.

The value of INR as a prognostic test in clinical practice will depend on the NPV and PPV of the threshold INR level. We reported a NPV of 86.5% and a PPV of 70.8% for the pooled data for all drugs using a cut-off of INR $\geq$ 1.5 (Table 1). Applying the incidence of bleeding events reported in large clinical studies (14.5%–14.9%),[19] the NPV and PPV would be 98% and 44%, respectively. It seems plausible that the PPV would be higher with longer follow-up, as the bleeding event did not occur until later during follow-up for most patients.

According to the pharmacodynamic studies, the INR assay may be used to detect supratherapeutic concentrations of DOACs. Because Cmax is reached within 1 to 4 hours after administration, the INR must be performed at or close to Cmax, otherwise INR levels may not reach $\geq$ 1.5.

Of 73 patients with bleeding episodes, 22 experienced bleeding despite their INRs of $<$ 1.5. Elevated INR is one of several causes of bleeding during DOAC treatment. Other causes (i.e., vulnerable blood vessels in diverticular disease, tumors and gingivitis) may be unrelated to the level of INR.

Our study demonstrated a higher frequency of bleeding events than other studies. This might be explained by the inclusion of minor bleeding episodes, whereas other studies only included major bleeding episodes.

In this study, the time of administration of DOACs was unknown. Therefore, we may not have captured the Cmax, which might influence our results to a minor degree. All INRs were measured between 8 am and 12 pm.

Our study does not answer when an increase in INR will appear after starting DOAC treatment. We therefore suggest frequent control of INR during the first year, at least until prospective studies have clarified the clinical impact.

The present study had some limitations. The design was retrospective and levels of anti-IIa (for dabigatran) and specific anti-Xa activity (for rivaroxaban and apixaban)

are not routinely used in Denmark and thereby were not available in this study.

The study also had several strengths. It was a real-life observation study. All patients were seen by doctors specialized in cardiology. Medical records were scrutinized for potential alternative causes of bleeding events, including thrombocytopenia, heart insufficiency, hematological disease, chronic renal insufficiency, trauma and cancer. Furthermore, we included minor bleeding episodes, which theoretically might be the first signs of upcoming major bleeding episodes.

Conclusions

We reported a statistically significant correlation between a cut-off INR ≥ 1.5 and increased risk of bleeding events in patients treated with direct factor Xa inhibitors. Furthermore, we found that an INR < 1.5 was a strong negative predicative test for the safety of DOACs.

There is no clearly established therapeutic range for any given DOAC. Routine assessment of the intensity of the anticoagulation of DOACs is not recommended. Because the INR assay is a widely accessible low-cost assay, it is highly valuable in clinical practice to measure the INR level in patients treated with DOACs frequently during the first year to reduce morbidity and mortality until more appropriate coagulation assays are appropriate.

To predict supratherapeutic concentrations, we propose confirmation using the Xa test in patients with an INR ≥ 1.5, at least until prospective studies of INR and bleeding episodes have been conducted, and results from our prospective study are available.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authorship addendum stating the role and contribution of each author

- Priya Bhardwaj: Data collection, data analysis, protocol writing, manuscript writing
- Louise Breum Petersen: Data collection, manuscript writing
- Tomas Storm Binko: Data collection, protocol writing, manuscript writing
- Jan Roland Petersen: Data analysis, protocol writing, manuscript writing
- Gitte Gleerup Fornitz: Data analysis, protocol writing, manuscript writing.

Declaration of conflicting interest

The authors whose names are listed immediately below certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

1. Priya Bhardwaj
2. Louise Breum Petersen
3. Tomas Storm Binko
4. Jan Roland Petersen
5. Gitte Gleerup Fornitz

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Gitte Gleerup Fornitz https://orcid.org/0000-0003-1235-9216

References

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2009; 361:

1139–1151. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa0905561.
2. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *N Engl J Med* 2011; 365: 883–891. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1009638.
3. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2011; 365: 981–992. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1107039.
4. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2013; 369: 2093–2104. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1310907.
5. Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation *Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; 33: 2719–2747. Available from: https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehs253.
6. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015; 17: 1467–1507. Available from: https://academic.oup.com/europace/article-lookup/doi/10.1093/europace/euv309.
7. CHMP. Eliquis, INN-apixaban [Internet]. [cited 2018 Sep 17]. Available from: www.ema.europa.eu/contact.
8. CHMP. Pradaxa, INN-dabigatran etexilate [Internet]. [cited 2018 Sep 17]. Available from: www.ema.europa.eu/contact.
9. CHMP. Xarelto, INN-rivaroxaban [Internet]. [cited 2018 Sep 17]. Available from: www.ema.europa.eu/contact.
10. Eikelboom JW, Quinlan DJ, Hirsh J, et al. Laboratory Monitoring of Non–Vitamin K Antagonist Oral Anticoagulant Use in Patients With Atrial Fibrillation. *JAMA Cardiol* 2017; 2: 566–574. Available from: http://cardiology.jamanetwork.com/article.aspx?doi=10.1001/jamacardio.2017.0364.
11. Harenberg J. Laboratory determination of old and new targeted anticoagulant agents for prevention of bleeding and thrombotic events in cancer patients. *Thromb Res* 2016; 140(Suppl 1): S165–S167. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27067972.
12. Ofek F, Bar Chaim S, Kronenfeld N, et al. International Normalized Ratio Is Significantly Elevated With Rivaroxaban and Apixaban Drug Therapies: A Retrospective Study. *Clin Ther* 2017; 39: 1003–1010. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28476405.
13. Kaatz S, Ahmad D, Spyropoulos AC, et al. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost* 2015; 13: 2119–2126. Available from: http://doi.wiley.com/10.1111/jth.13140.
14. Guadarrama DS, DeMarinis SM and Sweeney JD. Coagulation assays in a case of apixaban overdose. *Blood Coagul Fibrinolysis* 2018; 29: 231–235.
15. Samuelson BT, Cuker A, Siegal DM, et al. Laboratory assessment of the aniticoagulant activity of direct oral anticoagulants. A systematic review. *Chest* 2017; 151: 127–138.
16. Gosswlin R, Grant RP and Adcock DM. Comparison of the effect of the anti-Xa direct oral anticoagulants apixaban, edoxaban, and rivaroxaban on coagulation assays. 2016; 38: 505–513.
17. Hillarp A, Baghaei F, Fagerberg Blixter I, et al. Effects of the oral, direct factor Xa inhibitor rivaroxaban on commonly used coagulation assays. *J Thromb Haemost* 2011; 9: 133–139.
18. Helin TA, Pakkanen A, Lassila R, et al. Laboratory assessment of novel oral anticoagulants: method suitability and variability between coagulation laboratories. *Clin Chem* 2013; 59: 807–814. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23378569.
19. Halperin JL and Dorian P. Trials of novel oral anticoagulants for stroke prevention in patients with non-valvular atrial fibrillation. *Curr Cardiol Rev* 2014; 10: 297–302. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24821657.