

Real-world experience: Effect of Apixaban on INR, More confusion to providers with inadvertent lab

Emad Elkholy (✉ emadelkholy86@yahoo.com)

King Abdullah Medical City

Rafal Brashi

Umm al-Qura University

Raghad Batrafi

Umm al-Qura University

salma Alhadrami

Umm al-Qura University

Braah Almutawakkil

Umm al-Qura University

Hashim Atallah

Taif University

Mohammed Mekkawy

Alexandria University

Ghada Shalaby

Zagazig University

mahmoud elragaal

Umm al-Qura University

Research Article

Keywords: Apixaban, DOAC monitoring, International Normalized Ratio(INR), anticoagulation monitoring

Posted Date: April 10th, 2023

DOI: <https://doi.org/10.21203/rs.3.rs-2687274/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Factor X inhibition can cause the prolongation of PT by acting on the common pathway factors. Although, Expensive and less available “calibrated anti-FXa” predicts DOAC plasma level had better than prothrombin time (PT) and the international normalized ratio (INR). Consecutive reports raise more attention to (PT/INR) abnormalities in clinical scenarios for the minority of patients on DOACs. This study focuses on studying the magnitude of the Apixaban effect on INR elevation, which may be of clinical significance.

Methods: This was a single-center, retrospective, observational analysis of adult patients who received at least 30 days of Apixaban. This study's primary outcome is to test the association between Apixaban use and significant INR elevation

Results: Five hundred Fifty-two patients have screened in the study .194 patients meet our study aim criteria, Apixaban use was associated with a significant rise in INR levels after Apixaban (1.54 ± 2.59) compared to the previous values (1.03 ± 0.62) $P < 0.001$. The mean rise was 0.58 (95% CI: 0.34-0.82, $p < 0.001$). Multiple linear regression showed insignificance of all other tested variables, like Age, Polypharmacy, Use of CYP inhibitors, baseline INR, or renal function.

Conclusion: Apixaban use is associated with a significant increase in INR in non-hospitalized patients, although the clinical outcomes of this observation are still understudied.

Although routine monitoring of INR for Apixaban is generally unadvised, it is pivotal for practitioners to understand the magnitude of this phenomenon, more research is warranted to describe the clinical importance and guidance for those coagulation assays in daily practice.

Take Home Message

Regular coagulation tests should not be used to monitor DOAC therapy, However, inadvertent INR testing for patient started on Apixaban more than 1 month was Higher than baseline (before use Apixaban), we tried to examine the phenomenon facing practitioner in daily practice.

Background

During the last decade, our practice of anticoagulation management had dramatic positive changes; direct oral anticoagulants (DOACs) have changed this area forever. (1) Health care Practitioners who had enormous experience and knowledge during managing their patients with Vitamin K antagonists for more than half a century had unprecedented options to treat their patients with DOACs, DOACs have proven to be at least as effective as VKAs, with far less serious bleeding, fixed doses, no routine monitoring, and less food and drug interactions. In addition, patients prefer the DOACs for their ease and simplicity. These factors were reflected in increased numbers of patients and many challenging populations groups that had never been treated are stepping in like frail, extremely aged, and cancer patients. (2-5)

These results in more questions raised, tons of researchers publishing new dilemmas, and monitoring which was an absolute advantage started to fire back not only for physicians but also for their patients, one of the major non-adherence reasons in a survey was lack of monitoring. The gap in monitoring efficacy and safety is broadening in comparison to VKAs.

The international normalized ratio (INR) is a routine lab in daily practice with multiple uses in different clinical scenarios. Although guidelines recommend against DOACs monitoring, multiple reports described the association of INR prolongation with different DOACs, especially rivaroxaban, and to less extent with Apixaban. (6,7) a case report of Apixaban toxicity reported INR > 20 . (8) Moreover, a retrospective study in Denmark linked INR increase to predict bleeding events. (9) One of the gaps we are facing about DOAC use, is trying to ignore having INR results.

The data around this association is limited and has limitations, the phenomenon is neither well described in literature nor it is applications. Our study aims to measure the frequency of INR lab orders for patients on Apixaban and the effect of Apixaban on INR prolongation in a stable outpatient population.

Methods

This study was a single-center retrospective Cohort study for 565 non-critically ill Hospitalized Patients who were already on Apixaban at KAMC and were admitted between January 1, 2019, and July 29, 2021. In addition, the data include all patients who were admitted between January 1, 2019, and July 29, 2021, and received a dose of Apixaban during their hospital admission.

We did not include patients who received warfarin or any direct thrombin inhibitor or other factor Xa inhibitors during the first 72 hours prior to or following Apixaban administration, any patient who did not get at least one lab investigation for INR before or after admission, and patients with a known history of coagulopathy Diseases, advanced right-sided heart failure, ESRD, any level of liver failure. Patients with a history of acute liver failure and Pregnant women were also excluded from our study.

Ethical approval is sought from the KAMC IRB committee, and all data is kept in a secure file and accessed by the research team only.

Patients' data were collected from the electronic medical records using a standardized proforma. Data collected included patient demographics (age, weight, Height, BMI, and gender), patient's past medical

history and did the patient was using Apixaban or not (indication of taking Apixaban, date of diagnosis, order date), and baseline laboratory results (INR without warfarin, PT without Warfarin). the use of aspirin or warfarin, the number of medications (patient considered polypharmacy), inhibitors, and inducers of the cytochrome CYP and P-gp were collected. Patient's INR was also collected pre and post (defined as INR before starting Apixaban and after), and INR post-Apixaban was collected with the nearest Patient encounter (at least 30 days after the first Apixaban prescription).

The prothrombin time (PT)/INR, PTT with heparin, and PTT without heparin, if available, serum creatinine were collected starting. Liver function tests were collected in addition to the CHADS score, Bleeding tendency or predisposition, Labile INR levels on warfarin, and if the patient has embolic or bleeding events were utilized, as well as the adverse events were considered. The CHA2DS2-VASc score for Stroke Risk Assessment in Atrial Fibrillation was categorized based on the total score obtained as i) low risk (score 0), moderate risk (score=1), and High risk (score=>2)(31).

Data Management and Statistical Analysis:

SPSS version 23 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics in the form of frequencies and percentages using suitable tables and figures will be used to represent categorical data. Shapiro–Wilk test was used to check the normality of the continuous variables, and that followed normal distribution were presented using mean and standard deviation, whereas those that didn't follow were presented using a median and interquartile range.

Comparison of continuous variables between categorical variables was evaluated using the Students' t' test or Mann-Whitney U test. The Analysis of Covariance (ANCOVA) method was used to evaluate the main and interaction effects of categorical variables on a continuous dependent variable while controlling for the effects of specified independent continuous variables that co-vary with the dependent. A p-value <0.05 will be considered statistically significant.

Results

Our analysis included 552 adult patients who received at least 30 days of Apixaban. After the exclusion criteria were applied, 338 patients (61 % of screened patients) had INR before starting on Apixaban of which, only 194 patients had INR on Apixaban also. Those 194 patients who were eligible for the analysis had (INR before and after starting the Apixaban). Demographics are presented in (Table 1)

Table 1	
Baseline Demographics	
Age	64 (21: 94)
Gender-male%	43 %
Weight	79 (40: 99)
BMI	30.9 (17: 52)
Comorbid n,(%)	
DM	135 (69.5%)
HTN	156 (80)
HF	94 (48 %)
Stroke	54 (27)
Vascular disease	88 (45.3)
CHA2DS2VASc mean	3.85
CHA2DS2VASc > 3	154 (79.3)
	68 (35)
HAS-BLED mean	2
HAS-BLED > 3	54 (29)
S.cr	1.22 (0.38: 3.9)
Crcl	79 ml/min (13:190)
Crcl <50 %	26
Concomitant Medications	
Polypharmacy (Meds> 5)	55 %
No medication mean	8 (1:17)
SAPT	58 (29.8)
DAPT	20 (10)
Apixaban dose	
5 mg	143
2.5 mg	51
Reduced dose (off-label dosing)	10
Strong P-gp inh	
Amiodarone	4
Concomitant CYP 3A4 Inducer	
Rifampicin	1

We observed statistically significant differences in the international normalized ratio (INR) before and after using Apixaban. The INR value significantly increased after using Apixaban (1.54 ± 2.59) compared to the previous values (1.03 ± 0.62). (Table -2) the mean rise was 0.58 (95% CI: 0.34-0.82, $p < 0.001$). (Figure 1)

Table 2					
Comparison of INR before and after using Apixaban					
	Mean	SD	t	df	P value
Baseline INR	1.03	0.62			
Post INR	1.54	2.59	-3.659	364	<0.001

The CHA2DS2-VASc calculation showed that 4.2% were in the low-risk category of Ischemic heart disease, whereas the majority fell in 87.1% of high risk

We used a Multivariate analysis of covariance (MANCOVA) model to eliminate the effects of covariates on INR value after Apixaban use. The analysis showed there were no statistically significant differences seen in INR after Apixaban after controlling factors like gender, BMI>25, Age>65, INR, Serum Creatinine, CHF, hypertension, diabetes Mellitus, stroke, vascular disease, bleeding tendency or predisposition and drug or alcohol use.

However, there were statistically significant differences observed in INR value after Apixaban use in patients who had embolism [$F(1, 330) = 15.254$, $p = <0.001$, partial η^2

$=0.047$] . and bleeding [$F(1, 330) = 8.481$, $p = 0.004$, partial $\eta^2 = 0.026$]

Discussion

Apixaban inhibits both free factor Xa and prothrombinase activity and clot-bound factor Xa activity(10, 23), which makes the INR unreliable for clinical interpretation since the mechanism is distinct from that of warfarin (12,13). The sensitivity of the PT varies widely from one DOAC to the next, and it can be affected by factors such as the reagent employed and the drug concentration in the plasma (14).

Clotting time measurements do not correlate to the same degree of anticoagulation as found with warfarin because both binding and unbound serine proteases are blocked. Apixaban is appealing because it has a predictable pharmacokinetic profile, numerous paths of elimination, an improved bleeding profile in comparison to warfarin, a lack of other serious side effects, and does not require frequent anticoagulation monitoring. (6,15,16).

The extent to which Apixaban affects the INR is unclear, and this lack of information might have unintended consequences for patient management. After excluding possible confounding factors, our findings showed that the INR significantly increased after Apixaban use. This increase was not associated with any factors like off-label dose, age, or baseline INR before starting. Previous studies have shown that Anti factor X DOACs have different effects on regular coagulation tests. Even so, Ofek et al. could build a model predicting Anti factor X level by using INR for rivaroxaban. the Apixaban's effect on the INR in hospitalized patients is small to moderate in vitro and preliminary observational studies (7).

Frost et al. examined the impact of treatment with rivaroxaban and Apixaban on coagulation tests in healthy subjects, which showed overall medication concentration was observed to affect the minimal increase in INR seen with Apixaban, although it was not predictive (18).

Another small study in Japan assessed clinical outcomes for cardioembolic stroke patients who were using DOACs, patients who had coagulation assay prolongation on presentation had a mild stroke and less large vessel occlusion(19). Finally a case report of an acute on top of chronic kidney disease, a patient who was admitted with INR 3.5, Apixaban drug was detectable in her blood after 10 days of discontinuation(20).

INR has been developed in the 1980s By the World health organization to standardize the practice of anticoagulation around the globe, it achieved widespread acceptance in the scientific community, not only for VKA management, but for other indications: Preoperative screening to assess the integrity of the extrinsic (factor VII) and common pathways (fibrinogen and factors II, V, and X) of coagulation, Coagulopathy evaluation, Assessment of liver function, and assessment of the nutritional status. (21-23)for VKA management, but for other indications: Preoperative screening to assess the integrity of the extrinsic (factor VII) and common pathways (fibrinogen and factors II, V, and X) of coagulation, Coagulopathy evaluation, Assessment of liver function, and assessment of the nutritional status. (21-23)

Our finding provides important background for estimating Apixaban's impact on the INR considering many other patient factors. Healthcare professionals (HCPs) need to be aware of the effect that DOACs have on routine coagulation test findings as these drugs gain popularity as a convenient therapeutic choice for patients. (24)

Our hospital collected both the prothrombin time (PT) and international normalized ratio (INR) despite evidence suggesting that INR is not a valid way to track anticoagulation when using DOACs. Possible causes include reasons rather than DOAC-specific monitoring are part of the hospital order set, treating patients with high-risk chest pain, guiding anticoagulation protocols, and "standard" laboratory testing for admission. The increase in INR could be influenced by a variety of conditions, including drugs that interact with one another and preexisting comorbidities. Incorrect

interpretation of this degree of elevation, on the other hand, might lead to improper treatment or reversal of anticoagulation, both of which are undesirable outcomes (24,30).

Due to the potential impact of many patient variables on Apixaban, not all-inclusive risk factors are important to take into consideration. Thus we considered co-factors such as age, gender, abnormal renal and liver function, serum creatinine, congestive heart failure, Hypertension, Diabetes Mellitus, stroke, vascular disease, bleeding tendency or predisposition, embolism, bleeding, and drug or alcohol use. In our analysis, we observed that factors such as abnormal renal and liver function, embolism, and bleeding showed a direct effect on INR increase.

Clinicians need to know if coagulation tests are impacted by Apixaban usage in addition to sufficient knowledge about the extent of anticoagulant action. Fibrinogen levels, as well as the PT and aPTT durations are routinely measured in the ER and some inpatient settings. Non-specialist doctors may misunderstand "abnormal results" from these tests since factor Xa inhibitors might impact their reliability. (32)

A factor Xa inhibitor may be responsible for the prolonged PT and aPTT in a sepsis patient rather than the sepsis itself. Many patients undergoing a "coagulation screen" will be taking Apixaban. Hence all acute care providers need to learn how these tests are affected. Although the chromogenic test has been shown to have a greater association between Apixaban levels and factor Xa activity, its application is currently limited due to availability and cost difficulties, whereas the PT assay is commonly accessible and easily conducted in most laboratories (21).

Although Apixaban shows a concentration-dependent PT lengthening, the tests are not reliable for quantitatively evaluating factor Xa inhibitory action owing to their low sensitivity and large reagent-dependent heterogeneity. Educating the doctors and specialists who are not primarily engaged in anticoagulation treatment but will encounter a growing number of patients inadvertently taking Apixaban will provide the greatest challenge. (33-35)

Limitations

We acknowledge the limitations in this study: It is a single-center study, and due to the retrospective nature of the study, we were unable to determine the exact timing of drug administration before blood samples influenced the results. Secondly, INR fluctuations can be influenced by a variety of variables while in the hospital, making it challenging to assess and account for all of them, our study excluded all possible known factors from the study but this is still a gap.

Another drawback of our study is that we did not investigate the possibility of all interactions between different drugs and the effect these interactions could have on INR levels in each patient. However, the application of this evaluation needs to be cautiously approached because there is a lack of evidence concerning the interactions of DOACs with other drugs.

Conclusion

Our findings showed that non-hospitalized patients taking Apixaban have a significantly higher INR. Many of the variables were found to interfere with our patients' ability to maintain an acceptable international normalized ratio (INR) had already been documented by other researchers, and therefore, their presence was not surprising or unexpected.

It is unclear how an elevated INR may manifest in a patient's clinical situation. A higher than usual INR may occur in patients using Apixaban; thus, the healthcare team must be aware of this possibility. Our findings have potential therapeutic implications, but more prospective studies are needed to corroborate our findings.

Abbreviations

INR: International Normalized Ratio

PT: Prothrombin Time

CYP: Cytochrome P

P-gp: P-glycoprotein

HCPs: Healthcare professionals

BMI: Body Mass Index

DOAC : Direct Oral Anticoagulant

VKA : Vitamin K antagonist

Declarations

Acknowledgements

I would like to thank all my teachers who have helped me to develop the fundamental and essential academic competence.

Author contributions

Study conception and design: Emad Elkholy, Mohammed Mekkawy Data collection: Rafal Brashi, Raghad Batrafi, Salma Alhadrami, Braah Almutawakkil, Hashim Atallah analysis and interpretation of results: Mohammed Mekkawy Draft manuscript preparation: Emad Elkholy, Mahmoud Elragaal, Ghada Shalaby. All authors reviewed the results and approved the final version of the manuscript

Funding

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was conducted at the King Abdullah Medial City (a tertiary hospital in Makkah, KSA) and was subject to approval from the King Abdullah Medial City Ethics Committee. The research has been performed in accordance with the Declaration of Helsinki. We confirm that all methods were performed in accordance with relevant guidelines and regulations. The King Abdullah Medial City Ethics Committee approved that written informed consent was waived due to the use of anonymous retrospective data.

Consent for publication

Not applicable

Competing interests :

Not applicable

References

1. Camm AJ, Accetta G, Ambrosio G, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. *Heart*. 2017;103(4):307-314. doi:10.1136/heartjnl-2016-309832
2. Hanley CM, Kowey PR. Are the novel anticoagulants better than warfarin for patients with atrial fibrillation? *J Thorac Dis*. 2015;7(2):165-171. doi:10.3978/j.issn.2072-1439.2015.01.23
3. Navar AM, Kolkailah AA, Overton R, et al. Trends in Oral Anticoagulant Use Among 436 864 Patients With Atrial Fibrillation in Community Practice, 2011 to 2020. *J Am Heart Assoc*. 2022;11(22):e026723. doi:10.1161/JAHA.122.026723
4. Roberti R, Iannone LF, Palleria C, et al. Direct Oral Anticoagulants: From Randomized Clinical Trials to Real-World Clinical Practice. *Front Pharmacol*. 2021;12:684638. Published 2021 May 26. doi:10.3389/fphar.2021.684638
5. Mitchell A, Snowball J, Welsh TJ, Watson MC, McGrogan A. Prescribing of direct oral anticoagulants and warfarin to older people with atrial fibrillation in UK general practice: a cohort study. *BMC Med*. 2021;19(1):189. Published 2021 Aug 31. doi:10.1186/s12916-021-02067-5
6. Kovacevic MP, Lupi KE, Wong A, Gilmore JF, Malloy R. Evaluation of the Effect of Apixaban on INR in the Inpatient Population. *J Cardiovasc Pharmacol Ther*. 2019;24(4):355-358. DOI: 10.1177/1074248419838502.
7. Ofek F, Bar Chaim S, Kronenfeld N, Ziv-Baran T, Berkovitch M. International Normalized Ratio Is Significantly Elevated With Rivaroxaban and Apixaban Drug Therapies: A Retrospective Study. *Clin Ther*. 2017 May;39(5):1003-1010. doi: 10.1016/j.clinthera.2017.04.007
8. Kahlon, N., Doddi, S., Ning, Y., Akpunonu, B., & Murphy, J. (2022). Elevated International Normalized Ratio Due to Apixaban in Patients With End-Stage Renal Disease on Hemodialysis. *Cureus*, 14(6). <https://doi.org/10.7759/cureus.25907>
9. Bhardwaj, P., Petersen, L. B., Binko, T. S., Petersen, J. R., & Fornitz, G. G. (2020). A slightly elevated international normalized ratio predicts bleeding episodes in patients treated with direct oral anticoagulants. *The Journal of International Medical Research*, 48(6). <https://doi.org/10.1177/0300060519894439>

10. Jiménez D, Yusen RD, Ramacciotti E. Apixaban: an oral direct factor-xa inhibitor. *Adv Ther.* 2012;29(3):187-201. doi:10.1007/s12325-012-0003-2
11. Nagakari K, Emmi M, Iba T. Prothrombin Time Tests for the Monitoring of Direct Oral Anticoagulants and Their Evaluation as Indicators of the Reversal Effect. *Clin Appl Thromb Hemost.* 2017;23(6):677-684. doi:10.1177/1076029616638506
12. Samuelson, B. T., & Cuker, A. (2017). Measurement and Reversal of the Direct Oral Anticoagulants. *Blood reviews*, 31(1), 77. <https://doi.org/10.1016/j.blre.2016.08.006>
13. Byon W, Garonzik S, Boyd RA, Frost CE. Apixaban: A Clinical Pharmacokinetic and Pharmacodynamic Review. *Clin Pharmacokinet.* 2019 Oct;58(10):1265-1279. doi: 10.1007/s40262-019-00775-z.
14. Dale BJ, Ginsberg JS, Johnston M, Hirsh J, Weitz JI, Eikelboom JW. Comparison of the effects of apixaban and rivaroxaban on prothrombin and activated partial thromboplastin times using various reagents [published correction appears in *J Thromb Haemost.* 2015 Mar;13(3):489]. *J Thromb Haemost.* 2014;12(11):1810-1815. doi:10.1111/jth.12720
15. Fareed J, Thethi I, Hoppensteadt D. Old versus new oral anticoagulants: focus on pharmacology. *Annu Rev Pharmacol Toxicol.* 2012;52:79-99. doi: 10.1146/annurev-pharmtox-010611-134633.
16. Helin TA, Pakkanen A, Lassila R, Joutsu-Korhonen L. Laboratory assessment of novel oral anticoagulants: method suitability and variability between coagulation laboratories. *Clin Chem.* 2013 May;59(5):807-14. doi: 10.1373/clinchem.2012.198788.
17. Adcock DM, Gosselin R. Direct Oral Anticoagulants (DOACs) in the Laboratory: 2015 Review. *Thromb Res.* 2015 Jul;136(1):7-12. doi: 10.1016/j.thromres.2015.05.001. Epub 2015 May 8. PMID: 25981138.
18. Frost C, Nepal S, Wang J, Schuster A, Byon W, Boyd RA, Yu Z, Shenker A, Barrett YC, Mosqueda-Garcia R, Lacreata F. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. *Br J Clin Pharmacol.* 2013 Nov;76(5):776-86. doi: 10.1111/bcp.12106.
19. Deguchi I, Osada T, Takao M, Takahashi S. Coagulation Assay and Stroke Severity upon Admission of Patients with Cardioembolic Cerebral Infarction during Direct Oral Anticoagulant Use. *Keio J Med.* 2021;70(4):93-99. doi:10.2302/kjm.2020-0019-OA
20. Robinson ZS, Harper NG. Apixaban Levels Detected in a Patient 10 Days From Last Known Dose While Experiencing Acute on Chronic Kidney Disease. *Ann Pharmacother.* 2021;55(5):687-688. doi:10.1177/1060028020962794
21. Stern R, Karlis V, Kinney L, Glickman R. Using the international normalized ratio to standardize prothrombin time. *J Am Dent Assoc.* 1997;128(8):1121-1122. doi:10.14219/jada.archive.1997.0369
22. Campbell SG, Magee K, Cajee I, et al. Is routine measurement of international normalized ratio necessary as part of the investigation of patients with cardiac-type chest pain? *World J Emerg Med.* 2021;12(3):221-224. doi:10.5847/wjem.j.1920-8642.2021.03.010
23. Fareed J, Thethi I, Hoppensteadt D. Old versus new oral anticoagulants: focus on pharmacology. *Annu Rev Pharmacol Toxicol.* 2012;52:79-99. doi: 10.1146/annurev-pharmtox-010611-134633.
24. Baglin T. The role of the laboratory in treatment with new oral anticoagulants. *J Thromb Haemost.* 2013 Jun;11 Suppl 1:122-8. <https://doi.org/10.1111/jth.12227>.
25. Frydman GH, Ellett F, Van Cott EM, et al. A New Test for the Detection of Direct Oral Anticoagulants (Rivaroxaban and Apixaban) in the Emergency Room Setting. *Crit Care Explor.* 2019;1(8):e0024. doi:10.1097/CCE.0000000000000024
26. Ciurus T, Sobczak S, Cichocka-Radwan A, Lelonek M. New oral anticoagulants - a practical guide. *Kardiochir Torakochirurgia Pol.* 2015;12(2):111-118. doi:10.5114/kitp.2015.52851
27. Adcock DM, Gosselin R. Direct Oral Anticoagulants (DOACs) in the Laboratory: 2015 Review. *Thromb Res.* 2015 Jul;136(1):7-12. doi: 10.1016/j.thromres.2015.05.001. Epub 2015 May 8. PMID: 25981138.
28. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory Assessment of the Anticoagulant Activity of Direct Oral Anticoagulants: A Systematic Review. *Chest.* 2017;151(1):127-138. doi:10.1016/j.chest.2016.08.1462
29. Helin TA, Pakkanen A, Lassila R, Joutsu-Korhonen L. Laboratory assessment of novel oral anticoagulants: method suitability and variability between coagulation laboratories. *Clin Chem.* 2013 May;59(5):807-14. doi: 10.1373/clinchem.2012.198788.
30. Summary of product characteristics, Eliquis (apixaban). Bristol-Myers Squibb/Pfizer. <http://www.ema.europa.eu>. [Accessed March 9, 2022].24
31. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines-CPG; Document Reviewers. 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. *Europace.* 2012;14(10):1385-413. doi: 10.1093/europace/eus305
32. Gabarin, N, Trinkaus, M, Selby, R, Goldberg, N, Hanif, H, Sholzberg, M. Coagulation test understanding and ordering by medical trainees: Novel teaching approach. *Res Pract Thromb Haemost.* 2022; 6:e12746. doi: 10.1002/rth2.12746
33. Siddaiah H, Patil S, Shelvan A, et al. Preoperative laboratory testing: Implications of "Choosing Wisely" guidelines. *Best Pract Res Clin Anaesthesiol.* 2020;34(2):303-314. doi:10.1016/j.bpa.2020.04.006

34. Long B, Long DA, Koyfman A. Emergency medicine misconceptions: Utility of routine coagulation panels in the emergency department setting. *Am J Emerg Med.* 2020;38(6):1226-1232. doi:10.1016/j.ajem.2020.01.057
35. van Veen JJ, Spahn DR, Makris M. Routine preoperative coagulation tests: an outdated practice?. *Br J Anaesth.* 2011;106(1):1-3. doi:10.1093/bja/aeq357

Figures

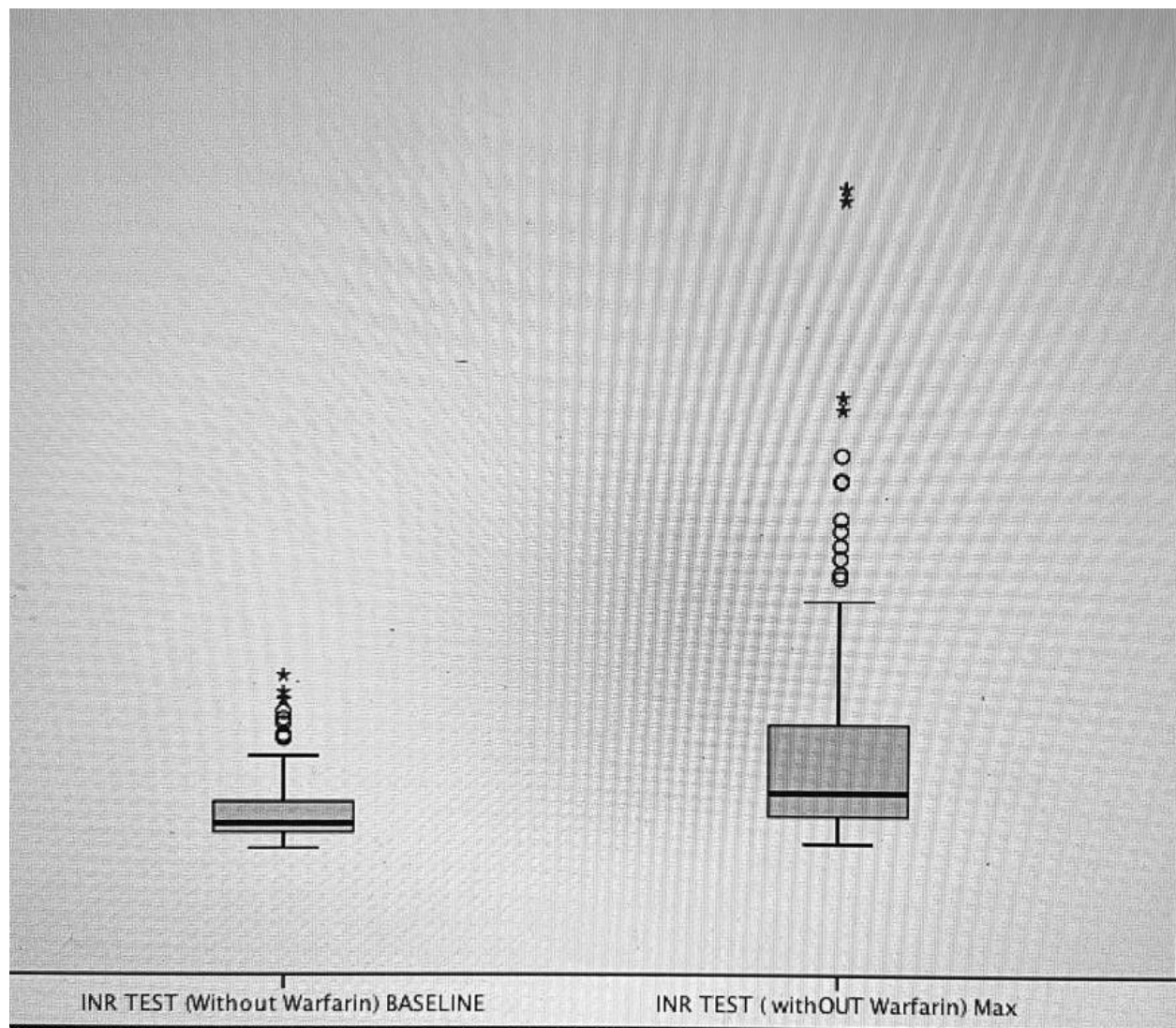


Figure 1

International Normalized Ratio Before and after apixaban