## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Appropriateness of initial dose of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Non-Valvular Atrial Fibrillation in the United Kingdom: a Population-Based Observational Study using Primary Care Electronic Health Records |
| **AUTHORS** | García Rodríguez, Luis; Martín-Pérez, Mar; Vora, Pareen; Roberts, Luke; Balabanova, Yanina; Brobert, Gunnar; Fatoba, Samuel; Suzart-Woischnik, Kiliana; Schaefer, Bernhard; Ruigomez, Ana |

## VERSION 1 – REVIEW

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| **REVIEWER** | Martin H. Ellis MD<br>Meir Medical Center<br>Kfar Saba<br>Israel |
| **REVIEW RETURNED** | 08-May-2019 |

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| **GENERAL COMMENTS** | In this study the authors evaluate the "appropriteness" of initial dose of a NOAC in NVAF patinets in the UK using primary care ERs between 2011-2016.<br><br>A number of major concerns lead me to recommend rejecting the manuscript in its current form. After a number of revisions it would be suitable for submission as a brief communication or report.<br><br>Major concerns<br>1) The term "appropriateness" used throughout the paper imlies correctness and should be replaced by "label-consistent" or "recommended" or a similar term. The investigators are not in a position to judge whether the dose administered to any given patient was clinically appropriate or not given the database nature of the study.<br>2) The study is biased in a number of ways: only primary care prescribers were studied: what about patients for whom the prescription emanated from specialists such as cardiologists, neurologists, elder care specialists? Perhaps such prescribers would exhibit different patterns of prescription based on their clinical perspective. In the UK do all prescriptions originate with a PCP? This should be clarified<br>3)The data emanate from practices participating in two different databases: are these representative of practices in the UK? Perhaps the practitioners participating in these databases are more highly motivated/academic/experienced/university affiliated and thus more likely to comply with dosing recommendations and thus introduce bias. |

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| | 4) What is the nature of the "scientific committees" that approved the study? Are these ethics committees? If not, was ethics committee and Declaration of Helsinki approval obtained?<br>5) Around 40% of patients beginning a NOAC had previously received an anticoagulant (presumably a VKA). These patients represent s "survivor bias" in the study because they had a track record with anticoagulants and were considered eligible for a NOAC (patients with bleeding complications in the past may have been disqualified for NOACs by their physicians). A way of dealing with this could be a sensitivity analysis examining the previously treated patients<br>6) The aim of the study is not clear (indeed there is no "AIM" section to the paper): is is to look at simply the first dose of NOAC prescribed (as implied in the title), or the consistenly prescribed doses of NOACs ("overall" and "over time"-terms used variably in the paper)<br>7) The numbers and precentages in the text, tables and figures do not match and are presented in a confusing way. For example in the text on p 11: % patients eligible for standard dose apixaban=84.9%; %patients eligible for reduced dose apixaban=12.8%: total=97.7%. What about the remaining patinets. Similarly for the other drugs.<br>8) If 78.7% of patients eligible for standard dose received standard dose, how could 25.5% have recived reduced dose (total=104.2%). Similarly inconcsistincies are present for the other drugs.<br>9) What is the relationship between the figures given on p 11 nad the first paragraph on p 12? Unclear from the text<br>10) The studies referenced in the Discussion are not current and omit a number of papers relating to the issue of off-label dose reductions of NOACs. One (Thrombosis Research, 2018, 169;140) is of very similar size (N=26100) with results at variance to the current study- this should be discussed<br>11) The temptation to compare between the NOACs regarding "inappropriate" dose reduction should be resisted and is not legitimate in a retrospective database study of this nature -the patient groups are not matched (no HRs or adjusted HRs for different variables are provided) and unaccounted for between-group differences make comparisons illegitimate.<br>12) The speculation that there is less dose reduction among rivaroxaban patients because of fewer recommendations for dose reductions per label (only decreased renal function) cannot be substantiated and is not supported by data: an equally feasible explanation for the data is that physicians opt to treat sicker patients with the other NOACs because of some perceived advantage (effectiveness or safety) and as a result are more likely to dose-reduce<br>13) Are the data in Table 2 and Figure 1 meant to be the same? The numbers differ but the description of the data is the same. |

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| **REVIEWER** | Yana Vinogradova<br>University of Nottingham<br>United Kingdom |
| **REVIEW RETURNED** | 18-Jul-2019 |

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| **GENERAL COMMENTS** | The paper investigates the relative numbers of patients on different dosages of DOACs and, in particular, the proportion of patients on an appropriately prescribed standard or reduced dose. It is reassuring to see that the majority of patients are being prescribed the correct dose. The authors have improved the quality of their study, by using two databases and combining them.<br><br>Although the authors present their results clearly, the paper could be improved by reducing those parts of Results where they repeat at some length information concisely delivered in figures and tables. I also think that some implications covered in Discussion could be mentioned in the Abstract – for example the importance of monitoring or the need for more detailed research to identify those patient characteristics, which more commonly appear to influence doctors' prescribing decisions.<br><br>It would also be interesting to see descriptive statistics of the baseline characteristics for patients who were appropriately dosed, underdosed and overdosed, perhaps overall if individual DOACs resulted in numbers too small to comply with Data regulations. This information could be useful for people considering future research in the area.<br><br>A few comments in detail:<br><br>The abbreviation PCP is not common in the UK, so the term should be used either in full or given as general practice/practitioner.<br><br>Does the Supplementary figure include 'exclusions', i.e. patients who were prescribed different DOACs on the same date?<br><br>How did the authors assess initial daily dose? Was it simply taken from product information?<br><br>What were the rationale and selection criteria for patients on 6 months of DOAC? This information should appear in Methods and the Flow-chart. To support this analysis, the differences in baseline dosages between patients who had and who did not have DOAC prescriptions at 6 months of follow up should be reported.<br><br>The authors correctly consider the limitation of potentially overestimated dosage because of the prescribed number of days but they do not mention the possibility of underestimated dosage for the same reason. Did the authors look at the quantity/number of days/number of packs/ additional dosage information and the gap between prescriptions? This may have been beyond the scope of the study, but it should then be mentioned in the limitations. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer #1:

Comment 1: The term "appropriateness" used throughout the paper imlies correctness and should be replaced by "label-consistent" or "recommended" or a similar term. The investigators are not in a position to judge whether the dose administered to any given patient was clinically appropriate or not given the database nature of the study.

Authors' response: We acknowledge the reviewer's comment and recognise that the clinical context of NOAC dosing cannot be fully understood in a database study; however, we believe that "appropriateness" is a suitable term to use in the context of this study, especially as we provide a full definition of the term in the Methods section, i.e. that this was assessed in concordance with the approved EU label. Our analyses did not involve any degree of subjectivity or personal judgement of appropriateness outside of the definition that we have provided, and we feel it is implicit throughout the manuscript that a NOAC prescription dose was deemed appropriate (in line with the respective drug label) based only on the data recorded in the database. In the following sentence on page 5 of out manuscript (end of the Introduction section) we make it clear upfront that the aim of our study was to evaluate the level of 'appropriate' prescribing as the level of consistency with the approved drug label:

> "Therefore, using routinely-collected primary care electronic health records (EHRs), we conducted a large population-based study with the aim of evaluating the level of appropriate prescribing (consistency with the approved drug label) of standard and reduced dose NOACs in over 30,000 patients with NVAF initiating therapy with a NOAC between 2011 and 2016."

Comment 2: The study is biased in a number of ways: only primary care prescribers were studied: what about patients for whom the prescription emanated from specialists such as cardiologists, neurologists, elder care specialists? Perhaps such prescribers would exhibit different patterns of prescription based on their clinical perspective. In the UK do all prescriptions originate with a PCP? This should be clarified

Authors' response: It is possible that a patient's very first NOAC prescription may have been issued in secondary care, and in these cases the prescription would not have been captured in the database. Although GPs will enter information about their patients (into their electronic health record) that is received from letters or emails from a specialist, details on any medications that a specialist has prescribed will be entered as free text. All prescriptions recorded in the primary care databases are those that are issued by the GPs themselves (they are automatically recorded upon issue). However, we believe that the first NOAC prescription issued in primary care is unlikely to be a different dose to that issued by a specialist with expertise on this topic. The interesting question that the reviewer has could be the focus of separate study, yet beyond the scope of this current study. We acknowledge the need to cover this point in the manuscript and have now added the following text to the Discussion (page 14).

> "Additionally, although the very first NOAC prescription may have been issued in secondary care and this will not have been captured in the primary care databases, we believe it is unlikely that the first NOAC prescription issued in primary care would be a different dose to that issued by a specialist with the relevant expertise."

Comment 3: The data emanate from practices participating in two different databases: are these representative of practices in the UK? Perhaps the practitioners participating in these databases are more highly motivated/academic/experienced/university affiliated and thus more likely to comply with dosing recommendations and thus introduce bias.
Authors' response: Validation studies have shown that CPRD is broadly representative of the UK population in terms of age and sex, ethnicity and body mass index.[1] and that THIN is representative of the UK population in terms of demographics, prevalence of major health conditions prevalence and death rates adjusted for demographics and deprivation.[2]

While one can speculate that practitioners in these databases are highly motivated etc, and thereby more likely to comply with dosing recommendations, we are unaware of any study that has investigated this for any drug and so it is difficult to comment on this. If this was the case, this would not introduce bias in terms of the internal validity of our results (i.e. in terms of methods used), but at most would affect the generalisability of the results. If GPs in practices contributing to the database were to be more highly motivated and therefore more likely to comply with dosing recommendations, our findings would be an underestimation of the level of potential inappropriate dosing. However, it is worth noting that the decision to participate is at the practice level and not at the individual practitioner level, and therefore we believe a bias of this kind would be unlikely.

Comment 4: What is the nature of the "scientific committees" that approved the study? Are these ethics committees? If not, was ethics committee and Declaration of Helsinki approval obtained?
Authors' response: The scientific committees that approved the specific study were not ethics committees. Ethical approval is not required for individual studies using either THIN or CPRD-GOLD because this is covered by the original ethical approval for the ongoing collection of data from the participating general practices. Data collection for THIN was approved by the South East Multicentre Research Ethics Committee in 2003 and individual studies using THIN data do not require separate ethical approval if only anonymized THIN data is used. Similarly, the CPRD has been granted generic ethics approval for observational studies that make use of only anonymised data (Multiple Research Ethics Committee ref. 05/MRE04/87). We have added text in the 'Data source' section of our Methods (page 6 of our manuscript) to cover this point.
All CPRD studies require scientific approval from the UK's Medicines Health and Healthcare products Regulatory Agency (MHRA) Independent Scientific Advisory Committee (ISAC). The scientific committees that approve the study protocols for individual studies using either THIN or CPRD-GOLD are composed of experts in research involving primary care databases. They approve the study protocol in terms of it having a strong rationale to conduct the study, that the methods are valid in

addressing the research question, and that the research team have sufficient expertise in the use of the databases as well as sufficient knowledge of UK primary care practice.

Comment 5: Around 40% of patients beginning a NOAC had previously received an anticoagulant (presumably a VKA). These patients represent s "survivor bias" in the study because they had a track record with anticoagulants and were considered eligible for a NOAC (patients with bleeding complications in the past may have been disqualified for NOACs by their physicians). A way of dealing with this could be a sensitivity analysis examining the previously treated patients

Authors' response: At the reviewer's request we have performed additional analyses stratifying patients by whether they had previously used a VKA (i.e. non-naïve) or whether they had no previous use of a VKA (naïve). The results, which are shown in Tables A to D below, and clearly show that there is minimal difference in the level of appropriate dosing between naïve and non-naïve patients when considering all NOACs as a group (Table A), or when considering each individual NOAC (Tables B to D). We now present these data in Supplementary Table 4A to 4D in our manuscript, and refer to them in the Results section of our manuscript (page 11).

Table A. Appropriateness of the dose of the first NOAC prescription according to the EU drug label.

| ALL NOACs | Naïve patients N=14,807 (48.6%) | | Non-naive N=15,660 (51.4%) | | Total N=30,467 | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Appropriate dose | 11,924 | 80.5 | 12,293 | 78.5 | 24,217 | 79.5 |
| Inappropriate dose | 2883 | 19.5 | 3367 | 21.5 | 6250 | 20.5 |

Table B. Appropriateness of the dose of the first apixaban prescription according to the EU drug label.

| Apixaban | Naïve patients N=5774 (53.3%) | | Non-naive N=5060 (46.7%) | | Total N=10,834 | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Appropriate dose | 4405 | 76.3 | 3705 | 73.2 | 8110 | 74.9 |
| Inappropriate dose | 1369 | 23.7 | 1355 | 26.8 | 2724 | 25.1 |

Table C. Appropriateness of the dose of the first dabigatran prescription according to the EU drug label.

| Dabigatran | Naïve patients N=1827 (41.7%) | | Non-naive N=2554 (58.3%) | | Total N=4381 | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Appropriate dose | 1383 | 75.7 | 1875 | 73.4 | 3258 | 74.4 |
| Inappropriate dose | 444 | 24.3 | 679 | 26.6 | 1123 | 25.6 |

Table D. Appropriateness of the dose of the first rivaroxaban prescription according to the EU drug label.

| Rivaroxaban | Naïve patients N=7206 (47.2%) | | Non-naive N=8046 (52.8%) | | Total N=15,252 | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Appropriate dose | 6136 | 85.2 | 6713 | 83.4 | 12849 | 84.2 |
| Inappropriate dose | 1070 | 14.8 | 1333 | 16.6 | 2403 | 15.8 |

Comment 6: The aim of the study is not clear (indeed there is no "AIM" section to the paper): is is to look at simply the first dose of NOAC prescribed (as implied in the title), or the consistenly prescribed doses of NOACs ("overall" and "over time"-terms used variably in the paper)

Authors' response: The aim of the paper is mentioned in the last paragraph of the Introduction (page 5). However, to make this clearer to the reader, we have added the following text (shown in red) to the relevant sentence.

> "Therefore, using routinely-collected primary care electronic health records (EHRs), we conducted a large population-based study with the aim of evaluating the level of appropriate prescribing (consistency with the approved drug label) of standard and reduced dose NOACs in over 30,000 patients with NVAF initiating therapy with a NOAC between 2011 and 2016."

This additional text supports the study objective which is described in the first paragraph of the abstract.

Comment 7: The numbers and precentages in the text, tables and figures do not match and are presented in a confusing way. For example in the text on p 11: % patients eligible for standard dose apixaban=84.9%; %patients eligible for reduced dose apixaban=12.8%: total=97.7%. What about the remaining patinets. Similarly for the other drugs.

Authors' response: As shown in Table 2, there were a total of 10,834 patients prescribed apixaban, of which 9194 (84.9%) were eligible to receive the standard dose, 1385 (12.8%) were eligible to receive a reduced dose, and 255 (2.3%) were contraindicated. Similarly, Table 2 shows that for dabigatran, 1790 patients (40.9%) were eligible to receive the standard dose, 2357 (53.8%) were eligible to receive the reduced dose and 234 (5.3%) were contraindicated. With these clarifications, we trust that the reviewer will find the data presented in Table 2 clear. We have not included the number of patients who were contraindicated in the text in order to avoid unnecessary repetition with the data presented in Table 2.

Comment 8: If 78.7% of patients eligible for standard dose received standard dose, how could 25.5% have recived reduced dose (total=104.2%). Similarly inconcsistincies are present for the other drugs.

Authors' response: We would like to clarify that among patients who started on dabigatran and who were eligible to receive the standard dose, 78.7% were prescribed the standard dose and 21.3% were prescribed a reduced dose (78.7% + 21.3% =100%). This is stated in the following sentence on page 11 of our manuscript:

> "However, a quarter of apixaban patients (25.5%, 2344/9194) eligible to receive the recommended standard daily dose were prescribed a reduced dose, compared with 21.3% (381/1790) in the dabigatran cohort and 11.0% (1390/12,608) in the rivaroxaban cohort."

Comment 9: What is the relationship between the figures given on p 11 nad the first paragraph on p 12? Unclear from the text

Authors' response: The text under the subheading "Appropriateness of NOAC prescription among patients prescribed a standard or reduced dose" at the top of page 12 relates directly to Supplementary Figure 2. The denominator in these calculations is the number of patients actually prescribed a standard or reduced dose NOAC (as opposed to those eligible for standard or reduced dosing by the defined criteria, which is shown earlier in the manuscript). The data shown in both the text and the figure is the percentage of these patients in whom the prescribed NOAC dose was appropriate according to the label.

Comment 10: The studies referenced in the Discussion are not current and omit a number of papers relating to the issue of off-label dose reductions of NOACs. One (Thrombosis Research, 2018, 169;140) is of very similar size (N=26100) with results at variance to the current study- this should be discussed

Authors' response: We thank the reviewer for this comment and have now made reference to the study by Ellis et al[3] in the Introduction (page 5) and the Discussion (pages 14 and 15) of our manuscript. We have also made reference to the descriptive study by Fay et al[4] in the Introduction (page 5).

Comment 11: The temptation to compare between the NOACs regarding "inappropriate" dose reduction should be resisted and is not legitimate in a retrospective database study of this nature -the patient groups are not matched (no HRs or adjusted HRs for different variables are provided) and unaccounted for between-group differences make comparisons illegitimate.

Authors' response: This was a descriptive study and we report only descriptive statistics (numbers and percentages). The main objective was to look at the dosing of the first recorded NOAC prescription among patients with non-valvular atrial fibrillation, and we do not report HRs because we did not perform a time-to-event analysis (this would not be suitable to address the research question of interest). We report the percentage of the observed prescribing frequencies in the routine clinical practice. Matching of patients and statistical adjustments would be important if one is evaluating the outcomes between the drugs.

Comment 12. The speculation that there is less dose reduction among rivaroxaban patients because of fewer recommendations for dose reductions per label (only decreased renal function) cannot be substantiated and is not supported by data: an equally feasible explanation for the data is that physicians opt to treat sicker patients with the other NOACs because of some perceived advantage (effectiveness or safety) and as a result are more likely to dose-reduce.

Authors' response: We have speculated reasons for the lower percentage of inappropriate underdosing for rivaroxaban in order to suggest possible reasons for our findings, which is an expected component of any manuscript discussion. We are aware that substantiation of this postulated reason can only come from a more in-depth, possibly qualitative, research study. We have added the following text to the Discussion of our manuscript (page 15):

> "One can speculate that this finding may reflect the criteria for dose reduction for the former two NOACs with respect to apixaban and dabigatran although it is not possible to substantiate this with the current study design"

We agree with the reviewer's point that another possible explanation could have been that sicker patients may be more likely to be prescribed apixaban or dabigatran based on some perceived effectiveness or safety advantage. However, as shown in the table below, health status based on $CHA_2DS_2$-VASc score, HAS-BLED score, and the number of primary healthcare visits in the year before the start of NOAC therapy was similar between NOAC cohorts, and therefore this is unlikely to be an explanation for our findings.

Table: Distribution of $CHA_2DS_2$-VASc score, HAS-BLED score and number of GP visits among patients in the study according to the index NOAC.

| Characteristic | Apixaban N=10,834 | Dabigatran N=4381 | Rivaroxaban N=15,252 |
|---|---|---|---|
| $CHA_2DS_2$-VASc score | | | |
| 0 | 451 (4.2) | 252 (5.8) | 633 (4.2) |
| 1 | 727 (6.7) | 336 (7.7) | 1183 (7.8) |
| 2 | 1677 (15.5) | 739 (16.9) | 2387 (15.7) |
| 3 | 2187 (20.2) | 893 (20.4) | 3202 (21.0) |
| 4 | 5792 (53.5) | 2161 (49.3) | 7847 (51.4) |
| Mean (SD) | 3.7 (1.9) | 3.5 (1.9) | 3.6 (1.8) |
| HAS-BLED score | | | |
| 0 | 860 (7.9) | 361 (8.2) | 1282 (8.4) |
| 1 | 3600 (33.2) | 1425 (32.5) | 5430 (35.6) |
| 2 | 4024 (37.1) | (38.9) | 5795 (38.0) |
| 3 | 1878 (17.3) | 733 (16.7) | 2226 (14.6) |
| 4 | 472 (4.4) | 158 (3.6) | 519 (3.4) |
| Mean (SD) | | | |
| GP visits in the year before the index date (first recorded NOAC prescription) | 1.8 (1.0) | 1.8 (1.0) | 1.7 (1.0) |
| 0–3 | 106 (1.0) | 35(1.0) | 93 (0.6) |
| 4–9 | 995 (9.2) | 389 (8.9) | 1279 (8.4) |
| 10–19 | 3330 (30.7) | 1324 (30.2) | 4671 (30.6) |
| 20–29 | 2718 (25.1) | 1061 (24.2) | 3703 (24.3) |
| ≥30 | 3685 (34.0) | 1572 (35.8) | 5506 (36.1) |

Comment 13: Are the data in Table 2 and Figure 1 meant to be the same? The numbers differ but the description of the data is the same.

Authors' response: We can confirm that the data in last column (TOTAL) of Table 2 are the same as the Figure; however, to make this even clearer to the reader we have now added a footnote to Figure 2 as follows:

> "Note: Overdosed includes patients who received a higher dose than recommended plus patients who were contraindicated"

References

1. Herret et al 2015. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015 Jun;44(3):827-36. doi: 10.1093/ije/dyv098. Epub 2015 Jun 6.

2. Blak et al. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. Inform Prim Care. 2011;19(4):251–5.

3. Ellis MH et al. Appropriateness of non-vitamin K antagonist oral anticoagulant dose in patients with atrial fibrillation in Israel: A population-based study. Thromb Res. 2018 Sep;169:140-142. doi: 10.1016/j.thromres.2018.07.024

4. Fay et al. Oral anticoagulant prescribing patterns for stroke prevention in atrial fibrillation among general practitioners and cardiologists in three European countries. Eur H Journal; 37, Supplement 1 (August 2016) 510 (P2597 Abstract)

Reviewer #2:

Comment 1: Although the authors present their results clearly, the paper could be improved by reducing those parts of Results where they repeat at some length information concisely delivered in figures and tables. I also think that some implications covered in Discussion could be mentioned in the Abstract – for example the importance of monitoring or the need for more detailed research to identify those patient characteristics, which more commonly appear to influence doctors' prescribing decisions.

Authors' response: We thank the reviewer for these helpful comments. We have now reduced some of the text in the Results section where there is unnecessary repetitiveness with the data already presented in the Tables and Figures (page 10 [under the subheading 'Patient characteristics by daily dose at index NOAC prescription]. Additionally, we have added the following sentence to the Conclusion of the abstract:

> "Research into the patient characteristics that may influence inappropriate underdosing of NOACs in UK primary care is warranted."

We have also added text to cover this point in the last paragraph of the Discussion in the main body of the manuscript (page 16).

Comment 2: It would also be interesting to see descriptive statistics of the baseline characteristics for patients who were appropriately dosed, underdosed and overdosed, perhaps overall if individual DOACs resulted in numbers too small to comply with Data regulations. This information could be useful for people considering future research in the area.
Authors' response: We agree that this information would benefit researchers studying this topic in the future and now present the baseline characteristics for patients appropriately dosed, underdosed and overdosed as Supplementary Table 3. Please note that the former Supplementary Table 3 is now renamed to Supplementary Table 4. We make reference to these additional data in the Results section of our manuscript on page 11.

Comment 3: The abbreviation PCP is not common in the UK, so the term should be used either in full or given as general practice/practitioner.
Authors' response: We agree that the abbreviation PCP is not as common as GP in the UK and is more often used in studies where the prescriber includes nursing staff within the practice in addition to GPs. As GPs are likely to be the sole prescribers of NOACs in UK primary care, we have now replaced the term primary care practitioner (PCP) with general practitioner (GP) at the relevant places throughout the manuscript.

Comment 4: Does the Supplementary figure include 'exclusions', i.e. patients who were prescribed different DOACs on the same date?
Authors' response: We can confirm that in Supplementary Figure 1 these patients are removed during the step "Creation of mutually-exclusive cohorts in each database by assigning patients to only one cohort" (the second grey box in the figure).

Comment 5: How did the authors assess initial daily dose? Was it simply taken from product information?
Authors' response: We can confirm that daily dose was taken from the product instructions (quantity, pack size, number of tablets and posology) recorded for the first NOAC prescription within the databases, and we have now added a sentence to cover this aspect of our Methods on page 7 in the section "Renal function and other patient characteristics". To clarify further, daily dose was derived as the simple product of posology (text-based dosage instructions) value and the strength of the NOAC prescription. For NOACs, the posology from text-based dosage instructions usually has a value of 1 or 2; however, in the relatively small instances that other values were recorded, we manually reviewed the records of these patients. Additionally, in the very few instances that information on posology was missing, we assumed the following a posology of once a day for rivaroxaban, and twice a day for apixaban and dabigatran.

Comment 6: What were the rationale and selection criteria for patients on 6 months of DOAC? This information should appear in Methods and the Flow-chart. To support this analysis, the differences in

baseline dosages between patients who had and who did not have DOAC prescriptions at 6 months of follow up should be reported.

Authors' response: For the main research question there was no requirement for patients to still be on a NOAC at 6 months from the index date. The analysis looking at the dose of the NOAC prescription at 6 months among those patients with at least 6 months of follow-up and still using a NOAC at this time (Supplementary Table 4) was a sub-analysis. The rationale for choosing 6 months was to grant a minimum time for possible change in the initial dosing as well as to exclude, if any, use of the drug that was meant to be prescribed for short durations.

At the reviewer's request, we have added the baseline doses of the index NOAC for patients who had/did not have a NOAC prescription at 6 months (as shown in the Table below) as Supplementary material (Supplementary Table 6). We have also added the following sentence to the Results on page 14 of our manuscript:

> "Baseline doses of the index NOAC among patients who were, or who were not, continuous users of a NOAC at 6 months are shown in Supplementary Table 6)."

Table. Dose of the initial NOAC prescription among patients who had and who did not have NOAC prescriptions at 6 months of follow.

| Index NOAC | Patients with at least 6 months of follow-up and still prescribed a NOAC at 6 months | | Patients not prescribed a NOAC at 6 months (i.e. all remaining patients) | | Total | |
|---|---|---|---|---|---|---|
| Apixaban | N=6667 | | N=4167 | | N=10,834 | |
| | n | % | n | % | n | % |
| 5 mg | 2258 | 33.9 | 1515 | 36.4 | 3773 | 34.8 |
| 10 mg | 4409 | 66.1 | 2652 | 63.6 | 7061 | 65.2 |
| Dabigatran | N=2827 | | N=1554 | | N=4381 | |
| | n | % | n | % | n | % |
| 110 mg | 63 | 2.2 | 38 | 2.4 | 101 | 2.3 |
| 150 mg | 131 | 4.6 | 65 | 4.2 | 196 | 4.5 |
| 220 mg | 1290 | 45.6 | 776 | 49.9 | 2066 | 47.2 |
| 300 mg | 1343 | 47.5 | 675 | 43.4 | 2018 | 46.1 |
| Rivaroxaban | N=9750 | | N=5502 | | N=15,252 | |
| | n | % | n | % | n | % |
| 10 mg | 246 | 2.5 | 144 | 2.6 | 390 | 2.6 |
| 15 mg | 1648 | 16.9 | 1043 | 19.0 | 2691 | 17.6 |
| 20 mg | 7819 | 80.2 | 4272 | 77.6 | 12,091 | 79.3 |
| ≥30 mg | 37 | 0.3 | 43 | 0.8 | 80 | 0.5 |

Comment 7: The authors correctly consider the limitation of potentially overestimated dosage because of the prescribed number of days but they do not mention the possibility of underestimated dosage for the same reason. Did the authors look at the quantity/number of days/number of packs/ additional dosage information and the gap between prescriptions? This may have been beyond the scope of the study, but it should then be mentioned in the limitations.

Authors' response: We thank the reviewer for pointing out that we omitted to discuss the possibility of underestimated dosage, and have now added the following (red text) to this sentence in the Discussion (page 14):

> "Also, potential overdosing may have been overestimated because patients may have split a prescribed standard dose over more than one day, and likewise potential underdosing may have occurred if patients were instructed to spread out their prescribed medication, although we feel this is unlikely."

Regarding the second part of the reviewer's comment, we can confirm that daily dose was calculated based on the product instructions (quantity, pack size, number of tablets and posology). Further details on the calculation of daily dose are given in our response to
Comment 5. As the main analysis in our study related only to the first recorded NOAC prescription, gaps between subsequent prescriptions were not relevant.
In our sub-analysis we looked at whether the daily dose of the index NOAC was the same as the daily dose of the same NOAC when prescribed at 6 months. As we now clarify on page 13 of our Methods (under the subheading 'NOAC daily dose over time'), this analysis was performed among patients who were continuous users of a NOAC at 6 months, with continuous use defined as no gaps of more than 30 days between the end of a NOAC prescription and the start of the next.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Martin Ellis MD<br>Hematology Institute<br>Meir Medical Center, Kfar Saba<br>and<br>Sackler School of Medicine<br>Tel Aviv University, Tel Aviv<br>ISRAEL |
| **REVIEW RETURNED** | 12-Aug-2019 |

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| **GENERAL COMMENTS** | The authors have satisfactorily addressed by comments on the original version of the manuscript |

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| **REVIEWER** | Yana Vinogradova<br>University of Nottingham<br>United Kingdom |
| **REVIEW RETURNED** | 24-Aug-2019 |

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| **GENERAL COMMENTS** | I am happy with the response and changes to the paper. |