PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry
AUTHORS	Apenteng, Patricia; Gao, Haiyan; Hobbs, Richard; Fitzmaurice, David

VERSION 1 – REVIEW

REVIEWER	Eitaro Kodani Department of Internal Medicine and Cardiology, Nippon Medical School, Tama-Nagayama Hospital Tokyo, Japan.
REVIEW RETURNED	14-Aug-2017

GENERAL COMMENTS	This manuscript by Apenteng al. focused on the real-world status of anticoagulation therapy in patients with newly diagnosed atrial fibrillation (AF) in United Kingdom (UK). Authors demonstrated that an increasing trend of non-vitamin K agonist oral anticoagulant (NOAC) use was found in four cohort of different year along with a decreasing trend of antiplatelet (AP) use. These findings seems reasonable since NOAC is recommended, whereas AP is not, in the current ESC guidelines for the management of AF. Therefore, dissemination of these information would be valuable for physicians who are involved in the management of patients with AF. Overall manuscript seems written very well. However, this reviewer has several questions. Authors may want to consider several issues as below. Major comments; One of important findings of this study is thought that a decreasing trend of the proportion of no-anticoagulant (AC) use was fond in four cohort of different year in UK. This appears to be a little strange for readers in other countries. Although authors provided Table 5 concerning the reasons for no-AC use in high-risk patients, it is difficult to fully understand the reason. As authors mention in discussion, no-AC use is further scope for improvement, especially in patients who are eligible for anticoagulation therapy but not receiving any AC. 1) Authors may want to provide baseline characteristics of patients not receiving AC by cohort as well as Table 3. 2) Logistic regression analysis should be performed to clarify the relation between no- AC use and baseline characteristics. Authors may want to provide odds ratios for no-AC use as well as Table 4. Minor comments; 1) Although corresponding year of each cohort is described in abstract, there in no explanation in main text. In addition, description

	of the corresponding year of cohort 3 is wrong. It may be 2013 to 2014. 2) Because corresponding year of each cohort is important to understand the trend of anticoagulation therapy, it should be described in Table 1 as well as Figure 1. 3) In footnote of Table 1, please do not repeat “patients missing”. Authors may want to find some way to write more simply. 4) In Table 2, it seems better to describe patient numbers in the first line as those in other tables. 5) In Figures 1 and 2, some of patient numbers in each cohort are different from those in Table 1.

REVIEWER	Carlos Aguilar Department of Haematology Hospital General Santa Bárbara Soria (Spain)
REVIEW RETURNED	28-Aug-2017

GENERAL COMMENTS	The paper is an interesting analysis of the GARFIELD database, it is well written and the results are relevant to be reported. Some minor comments to the manuscript could be made: - It is obvious from figure 1 that the prescription of dabigatran remains steady over periods C2 to C5 whereas the use of direct FXa inhibitors has increased over time which is consistent with data reported elsewhere and clinical practice worldwide. Perhaps some type of comment on this respect would be welcome. - Perhaps the authors should further stress the growing role of primary care in NOAC prescription. - It is interesting that a significant part of the patients are prescribed both oral anticoagulants plus antiplatelet agents at disease onset. This is surprising and is mentioned by the authors in their discussion. - On the other hand it also surprising that still today roughly 1 in 10 high risk patients do not receive any antithrombotic treatment and this proportion has remained stable over the period assessed. The reasons for not prescribing such therapy (other than patient refusal) are not really convincing. This issue is also addressed but perhaps some more emphasis should be made on it and some comments on such reasons to refrain from prescribing oral anticoagulants would be desirable. - It is also of note that half low-risk individuals are on some type of antithrombotic therapy (3 in 4 of them on oral anticoagulants) when there is not a clear recomendation to do so. This tendency has been reduced over time but it is so high yet; perhaps the more favorable bleeding risk profile of the NOACs might have had an influence on this change in practice. Please make some comment on this. . - The authors have emphasized antithrombotic patterns with both low (0) and high (≥2) risk CHA2DS2-VASc score but little attention is paid to those with a score of 1. In this group is where the increment in NOAC prescription has seemed to increase more steeply and where the use of antiplatelet agents has been reduced the most. Could you please pay some more attention to this subset of patients?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

This manuscript by Apenteng al. focused on the real-world status of anticoagulation therapy in patients with newly diagnosed atrial fibrillation (AF) in United Kingdom (UK). Authors demonstrated that an increasing trend of non-vitamin K agonist oral anticoagulant (NOAC) use was found in four cohort of different year along with a decreasing trend of antiplatelet (AP) use. These findings seems reasonable since NOAC is recommended, whereas AP is not, in the current ESC guidelines for the management of AF. Therefore, dissemination of these information would be valuable for physicians who are involved in the management of patients with AF. Overall manuscript seems written very well. However, this reviewer has several questions. Authors may want to consider several issues as below.

Major comments;
One of important findings of this study is thought that a decreasing trend of the proportion of no-anticoagulant (AC) use was fond in four cohort of different year in UK. This appears to be a little strange for readers in other countries. Although authors provided Table 5 concerning the reasons for no-AC use in high-risk patients, it is difficult to fully understand the reason. As authors mention in discussion, no-AC use is further scope for improvement, especially in patients who are eligible for anticoagulation therapy but not receiving any AC.

Response: There was an increase in the proportion of patients not receiving any antithrombotic therapy over the study period; this may reflect the fact that patients have no therapy instead of antiplatelet therapy which fits with the 2014 guidelines. Regarding reasons for no-AC use in high-risk patients, as this is an observational study we can only report the data we found. It is acknowledged in our discussion that there is a need to elucidate the reasons why some high-risk patients for not receive anticoagulation.

1) Authors may want to provide baseline characteristics of patients not receiving AC by cohort as well as Table 3.

Response: We have provided a table of baseline characteristics of patients not receiving AC by cohort (Table 5) and added related text to the manuscript on page 7.

2) Logistic regression analysis should be performed to clarify the relation between no- AC use and baseline characteristics. Authors may want to provide odds ratios for no-AC use as well as Table 4.

Response: We have provided a table of No AC use versus AC in relation to baseline characteristics (Table 6) and added related text to the manuscript on page 7.

Minor comments;
1) Although corresponding year of each cohort is described in abstract, there is no explanation in main text. In addition, description of the corresponding year of cohort 3 is wrong. It may be 2013 to 2014.

Response: We thank the reviewer for pointing this out – the correct year relating to cohort 3 was 2013 to 2014. This has now been corrected in the manuscript. The corresponding years for each cohort is described in the main text first paragraph of results.

2) Because corresponding year of each cohort is important to understand the trend of anticoagulation therapy, it should be described in Table 1 as well as Figure 1.

Response: We have added the corresponding year for each cohort to Table 1 and Figure 1.

3) In footnote of Table 1, please do not repeat “patients missing”. Authors may want to find some way to write more simply.

Response: We have now simplified this (see Table 1).

4) In Table 2, it seems better to describe patient numbers in the first line as those in other tables.

Response: We thank the reviewer for pointing this out. We have added the patient numbers to the header like in the other tables.

5) In Figures 1 and 2, some of patient numbers in each cohort are different from those in Table 1.

Response: Please note patient numbers in Figures 1 and 2 represents the total population in each cohort excluding unknown treatment. The patient numbers have been double checked and corrections made where necessary.

Reviewer 2

The paper is an interesting analysis of the GARFIELD database, it is well written and the results are relevant to be reported. Some minor comments to the manuscript could be made:

- It is obvious from figure 1 that the prescription of dabigatran remains steady over periods C2 to C5 whereas the use of direct FXa inhibitors has increased over time which is consistent with data reported elsewhere and clinical practice worldwide. Perhaps some type of comment on this respect would be welcome.

Response: We have added a comment to the third sentence of the first paragraph of the discussion. It now reads “There was a notable increase in the use of NOACs ± AP (C2 1.3%, C3 8.0%, C4 23.0%, 43.3%), with the main increase in NOAC prescribing being driven by the prescribing of FXa inhibitors;”

- Perhaps the authors should further stress the growing role of primary care in NOAC prescription.

Response: We are not in a position to comment on this based on the data we have.

- It is interesting that a significant part of the patients are prescribed both oral anticoagulants plus antiplatelet agents at disease onset. This is surprising and is mentioned by the authors in their discussion.

Response: We thank the reviewer for the comment.

- On the other hand it also surprising that still today roughly 1 in 10 high risk patients do not receive any antithrombotic treatment and this proportion has remained stable over the period assessed. The reasons for not prescribing such therapy (other than patient refusal) are not really convincing. This issue is also addressed but perhaps some more emphasis should be made on it and some comments on such reasons to refrain from prescribing oral anticoagulants would be desirable.

Response: As this is an observational study we can only report what we found and cannot really speculate on the reasons for this.

- It is also of note that half low-risk individuals are on some type of antithrombotic therapy (3 in 4 of them on oral anticoagulants) when there is not a clear recommendation to do so. This tendency has been reduced over time but it is so high yet; perhaps the more favorable bleeding risk profile of the NOACs might have had an influence on this change in practice. Please make some comment on this.

Response: We have added a comment on this – This may be due to clinicians' perception of stroke risk as all participants were deemed by the recruiting clinician to have an investigator determined risk factor for stroke (page 9).

- The authors have emphasized antithrombotic patterns with both low (0) and high (≥2) risk CHA2DS2-VASc score but little attention is paid to those with a score of 1. In this group is where the increment in NOAC prescription has seemed to increase more steeply and where the use of antiplatelet agents has been reduced the most. Could you please pay some more attention to this subset of patients?

Response: We have addressed this by adding a sentence to paragraph 2 of the discussion (page 8)– "For patients with a CHA2DS2-VASc score of 1, there was a notable increase in AC prescribing from C2 to C5 and a steep decline in the use of AP only."

VERSION 2 – REVIEW

REVIEWER	Eitaro Kodani Department of Internal Medicine and Cardiology, Nippon Medical School, Tama-Nagayama Hospital Tokyo, Japan.
REVIEW RETURNED	01-Oct-2017

GENERAL COMMENTS	This revised manuscript by Apenteng et al. focused on the real-world status of anticoagulation therapy in patients with newly diagnosed atrial fibrillation (AF) in United Kingdom (UK). Authors have revised appropriately according to the reviewers' suggestions. It appears to be better.

REVIEWER	carlos aguilar Department of Haematology. Hospital General Santa Bárbara. Soria. Spain
REVIEW RETURNED	01-Oct-2017

GENERAL COMMENTS	I think changes made to the paper are satifactory enough to recommend publication