PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Oral anticoagulation therapy use in patients with atrial fibrillation after the introduction of non-vitamin K antagonist oral anticoagulants: findings from the French healthcare databases, 2011-2016
AUTHORS	MAURA, Géric; Billionnet, Cécile; Drouin, Jérôme; Weill, Alain; Neumann, Anke; Pariente, Antoine

VERSION 1 - REVIEW

REVIEWER	Marco Proietti Istituto di Ricerche Farmacologiche Mario Negri, Italy Consulting activity for Boehringer Ingelheim
REVIEW RETURNED	31-Oct-2018

GENERAL COMMENTS	The paper presented deals with an important issue, even though already extensively reported in several other cohorts. Notwithstanding, national data are still needed to completely assess a larger view of the current use of OAC drugs, after all NOACs are steadily and consistently entered in the current use of all physicians treating AF patients. Nevertheless, a number of issues should be taken into consideration. I got serious concerns about the study design. First of all, it's not clear why the authors choose to investigate only those three specific years and not the entire spectrum of years available. Secondly, the identification of two different cohorts doesn't allow to obtain a clear vision of the problem and doesn't clearly help in elucidating the objectives stated by the authors. Further, even the description of how the two cohorts have been defined is not completely clear and methods section should be revised for much clarity. Another point of criticism is the use of CHA2DS2-VASc and HAS-BLED score to evaluate the appropriateness of prescription. In particular the last one should not be used to evaluate the type or dose of OAC in any case, since it does not have to be used as a determinant of OAC prescription. The last part of the results should be revised for much clarity since doesn't read really well. Further, I would have liked to see at least a regression analysis regarding the clinical predictors of different types of OAC therapy. Those data would have helped to substantiate better the clinical profile of OAC types users. The absence of these data also limited the comparison to other data in the Discussion section, that in general appears to be

	lacking of comparison to a large number of studies that are not cited and discussed (for example larger European studies as EORP-AF). Lastly, to add more interest data about discontinuation and adverse events (stroke, major bleeding and death) over the long term follow up should be added to provide a full picture of current epidemiology about AF patients in France. Minor The acronym DOAC should be avoided. Indeed, in Europe and European Society of Cardiology the term "NOACs": non-vitamin K antagonist oral anticoagulants should be preferred. Lastly, the text should be largely revised for proper use of english and typos (particularly about acronyms clearly reported in french).

REVIEWER	Geoffrey Barnes University of Michigan
REVIEW RETURNED	25-Nov-2018

GENERAL COMMENTS	Maura and colleagues describe the use of oral anticoagulants for AF patients over the 5 year period 2011-2016 since DOACs have been introduced. They showed that OAC use for AF patients increased modestly (+16%) with a decline in antiplatelet use. In general, the data is well presented and informative. It is limited by simple statistics, without significant adjustment for other factors that may influence anticoagulant prescribing. But the analysis is appropriate for the goal of the project, in my opinion. The simple use of CHADS-VASc and HAS-BLED to determine if full/reduce dose DOAC is appropriate has certain limitations. Can this be added to the limitations paragraph? Table 2 - can you clarify if "prosthetic valve" is bioprosthetic, mechanical, or both? It would be most useful to just examine mechanical as these are contraindicated with DOAC therapy Figure 3 - this is a really nice way to visualize potential under-prescribing based on CHADS-VASc and HAS-BLED scores.

VERSION 1 – AUTHOR RESPONSE

Responses to comments from reviewer 1.

Reviewer Name: Marco Proietti Institution and Country: Istituto di Ricerche Farmacologiche Mario Negri, Italy Please state any competing interests or state ‘None declared’: Consulting activity for Boehringer Ingelheim

The paper presented deals with an important issue, even though already extensively reported in several other cohorts. Notwithstanding, national data are still needed to completely assess a larger view of the current use of OAC drugs, after all NOACs are steadily and consistently entered in the current use of all physicians treating AF patients.

Nevertheless, a number of issues should be taken into consideration.

We would like to thank the reviewer very much for his positive comment and his very detailed review of our work that has helped us to improve precision and clarity of the entire manuscript. We hope that our responses and the corresponding revised version of the manuscript will satisfy him.

I got serious concerns about the study design.

First of all, it's not clear why the authors choose to investigate only those three specific years and not the entire spectrum of years available.

The primary objective of this study was to assess the trend in OAC coverage in patients identified as having AF following the introduction of NOAC therapy in France. To address this issue, the study period had to include data from the year preceding the first reimbursement of NOAC therapy as a reference or starting point, which were then compared to the most recent data available. We chose as starting point the last year before reimbursement of NOAC therapy for stroke prevention in France, i.e. year 2011, and 2011 OAC coverage was compared to that of 2016, the most recent data available at the time of writing the study protocol. We added OAC coverage for year 2013 as an intermediate point, as this year represented the first calendar year for which the first two NOACs were available (all days of the year) in France, i.e. a pivotal year for the pharmacological management of AF by oral anticoagulants.

We have entirely modified the “Study populations and study designs” sub-section of the Methods section to more clearly describe this point, as follows:

“A study population was defined for each objective. Two study populations were defined; one for each objective.

FirstTo answer the first objective, in a repeated cross-sectional study was performed to describe the trends in OAC use following the introduction of NOAC in AF patients. , patients Patients with AF were identified for each of the following calendar years: in 2011 (as none of the NOACs was available for stroke prevention in France), 2013 (first calendar year with both rivaroxaban and dabigatran reimbursed for stroke prevention in July 2012) and 2016 (the most recent data available at the time of writing the study protocol; dabigatran, rivaroxaban and apixaban were all reimbursed for stroke prevention in France, as apixaban was reimbursed from January 2014 onwards). OAC coverage was also calculated for year 2013 as this year represented the first calendar year for which the first two NOACs were available in France, i.e. a pivotal year for the pharmacological management of AF by oral anticoagulants. For each of these calendar years, a patient was considered to have AF when at least one diagnosis of AF (ICD-10 code I48) was identified from discharge and LTD diagnoses in the SNIIRAM-PMSI database in the calendar year considered or during the previous 5 years. Patients with no continuous ‘Régime général’ health insurance coverage for at least six years before the calendar year considered were excluded.

Second, a retrospectiveTo answer the second objective, a population-based cohort study was performed including patients with AF among those initiating DOAC therapy in 2015-2016. First, OAC new users were identified among To be included in this cohort, patients with continuous ‘Régime général’ health insurance coverage had to be identified as DOAC new users: as those with at least one reimbursement for DOAC therapy in 2015-2016 and no reimbursement for any OAC (VKA or NOAC) in the previous 24 months. The patient’s index date was the date of first DOAC reimbursement identified during the 2015-2016 period. Second, the cohort of NOAC news users was restricted to those treated for AF: (…).”

Secondly, the identification of two different cohorts doesn’t allow to obtain a clear vision of the problem and doesn’t clearly help in elucidating the objectives stated by the authors.

The aims of this study were: 1) to describe trends in OAC coverage in AF patients after introduction of NOAC therapy for stroke prevention in France; 2) to report current patterns of OAC use in AF patients in France, with particular focus on NOAC therapy.

First, we therefore performed a repeated cross-sectional study to address the primary objective: a moderate increase in OAC use was observed over the 2011-2016 study period, with consistent results across the various subgroups.

Second, patterns of use of OAC therapies were described on the basis of the most recent data available in the French healthcare databases. We extensively described the clinical characteristics of OAC new users and then searched for potential inappropriate use of NOAC therapies, including the emerging issue of NOAC underdosing. For these analyses, we preferred the incident use setting to prevalent use to describe more comparable clinical settings by aligning AF patients at a uniform point in time of their clinical work-up, i.e. initiation of anticoagulation therapy. Moreover, it provides a better framework in terms of possible subsequent public health actions, when needed. These investigations were designed to address the secondary objective by providing a detailed description of current OAC new users and defining areas of possible improvement in terms of the prescription of OAC therapies.

We have modified the “study population and study design” sub-section to clarify this twofold study objective and the corresponding design choices (see above).

Further, even the description of how the two cohorts have been defined is not completely clear and methods section should be revised for much clarity.

We agree and, as shown above, the “study population and study design” sub-section has been rewritten accordingly.

Another point of criticism is the use of CHA2DS2-VASc and HAS-BLED score to evaluate the appropriateness of prescription. In particular the last one should not be used to evaluate the type or dose of OAC in any case, since it does not have to be used as a determinant of OAC prescription.

We agree that, as mentioned in the ESC guidelines, the CHA2DS2-VASc and HAS-BLED scores have been proposed to help to inform the choice of antithrombotic agent and the management strategy in clinical practice.

In addition to the use of CHA2DS2-VASc score to define patients at risk of stroke, we also used a definition independent of these scores for sensitivity analysis, i.e. patients aged over 75 with a history of stroke. Results were provided together with comparison of selected baseline characteristics between patients with potential underdosing and those also presenting a low risk of bleeding, but who were prescribed standard dose NOAC.

Regarding HAS-BLED score, the 2012 ESC guidelines (applicable for the 2015-2016 study period as the next ESC guidelines were published at the end of 2016) recommended, in their “Recommendations for prevention of thromboembolism in non-valvular AF” table (Camms et al, Eur Heart J 2012; P 2730), that the standard dose of dabigatran and rivaroxaban “should be considered for most patients in preference to [their reduced dose] with the latter dose recommended” in several clinical situations, including “patients with “high bleeding risk (HAS-BLED score ≥3)”. However, we acknowledge that the use of the HAS-BLED score to evaluate NOAC underdosing presents certain limitations. We have therefore consolidated the Discussion section as follows:

“Thirdly, identification of inappropriate underdosing at NOAC initiation was also indirectly assessed by using stroke and bleeding risk scores computed from claims data. Important medical data such as the patient’s weight, glomerular filtration rate renal function and exact alcohol consumption are not available in the French healthcare databases, which may have led to underestimation of the HAS-BLED score and therefore to overestimation of the proportion of patients potentially underdosed at

initiation. These missing clinical data may also explain the prescription of reduced dose NOAC at treatment initiation in clinical practice. Furthermore, the agreement between these empirical scores in patients with AF and the prescriber-assessed stroke and bleeding risk is a subject of discussion. [61] Consequently, the rate of inappropriate underdosing should be interpreted with caution and must be confirmed by further studies. (…)"

The last part of the results should be revised for much clarity since doesn't read really well.

We fully agree and this sub-section has been rewritten to improve clarity, as follows:

"Among the 116,391 NOAC new users with AF with a CHA2DS2-VASc score ≥2, 42.9% (N=49,935) of patients were prescribed a reduced dose at initiation, and 29.1% (N=33,845) were prescribed a reduced dose although they also had an HAS-BLED score <3. This meant meaning that nearly 1 in 3 NOAC new users with AF and at risk of stroke were therefore potentially prescribed an inappropriately reduced dose of NOAC at initiation. This The proportion of patients potentially underdosed was 33% (N=24,281) and 14.5% when defining patients at risk of stroke as patients in patients with a CHA2DS2-VASc score ≥4 and 14.5% in patients and aged 75 and over with a history of ATE, respectively (Figure 3).

Among the patients with no criterion justifying dose reduction, i.e. patients with HAS-BLED<3 only, these proportions were 39.3%, 51.9% and 58.4%, respectively. Differences in baseline characteristics were observed in patients with HAS-BLED <3 according to the type of NOAC dose prescribed, e.g. patients with reduced-dose NOAC DOAC were older and frailer than those with standard-dose NOAC DOAC (Supplementary Table 2 3)."

Further, I would have liked to see at least a regression analysis regarding the clinical predictors of different types of OAC therapy. Those data would have helped to substantiate better the clinical profile of OAC types users.

The absence of these data also limited the comparison to other data in the Discussion section, that in general appears to be lacking of comparison to a large number of studies that are not cited and discussed (for example larger European studies as EORP-AF).

We agree and, in addition to the descriptive statistics provided in Table 1, we have performed regression analyses assessing the clinical predictors for being treated by NOAC therapy versus VKA. More specifically, we performed negative binomial regression analysis for each NOAC therapy and each baseline characteristic to assess the association between baseline characteristics and the choice of NOAC therapy compared to VKA therapy, while adjusting for age and sex. The results are shown in Table A below.

After adjustment for age and sex, for each NOAC therapy, each of the baseline characteristics considered was significantly associated with the choice of NOAC therapy versus VKA therapy. Characteristics associated with bleeding risk, such as older age, renal impairment, history of bleeding or bleeding predisposition, and treatment with a concomitant drug increasing the risk of bleeding at OAC initiation, were strong predictors of being treated with VKA therapy versus NOAC therapies. Being a woman (after adjusting for age) and being treated by NSAIDs or antiarrhythmic drugs were the only predictors positively associated with NOAC prescription.

These results have been added to Results section in the manuscript and as Supplementary Table 2.

Table A. Age- and sex-adjusted association between baseline characteristics and the choice of NOAC therapy compared to VKA therapy in OAC new users

Baseline characteristics	Dabigatran *vs* VKA				Rivaroxaban *vs* VKA				Apixaban *vs* VKA			
	RR*	*95% CI*		p-value†	RR*	*95% CI*		p-value†	RR*	*95% CI*		p-value†
Female sex	1.11	1.05	1.17	***	1.03	1.00	1.07	*	1.07	1.04	1.09	***
Age (years)												
18-54 (Ref)	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
55-64	0.87	0.78	0.98	*	0.92	0.87	0.97	**	0.97	0.92	1.02	
65-74	0.86	0.77	0.95	**	0.89	0.84	0.94	***	0.98	0.93	1.03	
75-79	0.73	0.65	0.81	***	0.77	0.73	0.82	***	0.91	0.87	0.96	***
80-84	0.58	0.52	0.65	***	0.65	0.61	0.68	***	0.83	0.79	0.87	***
85-89	0.44	0.39	0.49	***	0.50	0.48	0.54	***	0.74	0.70	0.77	***
>=90	0.28	0.25	0.32	***	0.37	0.35	0.40	***	0.61	0.57	0.65	***
Deprivation index												
quintile 1 (least deprived) (Ref)	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
quintile 2	0.97	0.91	1.05		0.94	0.92	0.97	***	0.97	0.95	1.00	*
quintile 3	0.99	0.93	1.07		0.90	0.87	0.92	***	0.94	0.92	0.97	***
quintile 4	0.96	0.89	1.03		0.85	0.83	0.87	***	0.90	0.88	0.93	***
quintile 5 (most deprived)	1.00	0.94	1.07		0.85	0.83	0.87	***	0.91	0.89	0.93	***
Overseas departments	1.60	1.41	1.82	***	0.83	0.77	0.89	***	0.77	0.72	0.83	***
First prescriber's specialty												
Hospital practitioner (Ref)	1.00	1.00	1.00		1.00	1.00	1.00		1.00	1.00	1.00	
General practitioner	1.37	1.29	1.46	***	1.16	1.10	1.23	***	1.00	0.96	1.04	
Private cardiologist	2.92	2.76	3.08	***	1.80	1.70	1.90	***	1.65	1.59	1.71	***
Private orthopedic surgeon	1.96	1.20	3.21	**	1.48	1.20	1.81	***	1.32	1.07	1.61	**
Other private specialist	1.07	0.93	1.24		1.12	1.04	1.21	**	1.03	0.97	1.10	
From CHA_2DS_2-VASc score												
Heart Failure	0.52	0.49	0.54	***	0.70	0.68	0.71	***	0.77	0.75	0.78	***
Antihypertensive drugs	0.60	0.57	0.63	***	0.74	0.72	0.76	***	0.80	0.78	0.82	***
Diabetes	0.67	0.63	0.71	***	0.76	0.74	0.77	***	0.80	0.79	0.82	***

ATE	0.85	0.79	0.92	***	0.71	0.68	0.74	***	0.90	0.88	0.92	***
Vascular diseases	0.47	0.42	0.53	***	0.63	0.61	0.66	***	0.71	0.67	0.74	***
From HAS-BLED score												
Abnormal renal function	0.17	0.15	0.19	***	0.31	0.30	0.33	***	0.40	0.38	0.42	***
Abnormal liver function	0.46	0.39	0.54	***	0.58	0.54	0.62	***	0.60	0.57	0.64	***
Bleeding predisposition	0.53	0.47	0.59	***	0.63	0.60	0.65	***	0.70	0.67	0.72	***
Major bleeding	0.23	0.20	0.26	***	0.36	0.33	0.39	***	0.41	0.38	0.45	***
Alcohol abuse	0.55	0.48	0.62	***	0.69	0.65	0.72	***	0.68	0.65	0.72	***
Drug-drug interactions	0.22	0.20	0.24	***	0.36	0.34	0.37	***	0.40	0.37	0.43	***
Parenteral anticoagulants	0.04	0.03	0.06	***	0.07	0.06	0.07	***	0.07	0.06	0.07	***
Antiplatelets drugs	0.34	0.31	0.37	***	0.49	0.47	0.51	***	0.56	0.53	0.60	***
NSAIDs	1.80	1.43	2.28	***	1.24	1.12	1.38	***	1.18	1.06	1.32	**
Other comorbidities												
Valvular heart diseases	0,25	0,20	0,31	***	0,40	0,36	0,45	***	0,47	0,41	0,54	***
Ischemic heart diseases	0.51	0.46	0.56	***	0.65	0.63	0.67	***	0.74	0.71	0.77	***
Frailty (proxies)	0.48	0.45	0.51	***	0.58	0.55	0.61	***	0.64	0.62	0.66	***
Dementia or Parkinson's disease	0.66	0.60	0.72	***	0.82	0.78	0.85	***	0.77	0.75	0.80	***
Psychiatric disorders	0.74	0.70	0.78	***	0.86	0.84	0.88	***	0.86	0.84	0.88	***
Smoking	0.56	0.52	0.60	***	0.71	0.69	0.74	***	0.74	0.71	0.76	***
Comedications												
Antiarrhythmics or cardiac glycosides	1.42	1.35	1.50	***	1.22	1.19	1.25	***	1.18	1.16	1.20	***
Lipid-lowering agents	0.76	0.71	0.81	***	0.81	0.79	0.84	***	0.90	0.87	0.92	***
Oral corticosteroids	0.85	0.80	0.91	***	0.94	0.91	0.97	***	0.94	0.91	0.96	***
Antiulcer agents	0.61	0.56	0.66	***	0.73	0.71	0.75	***	0.78	0.75	0.81	***
Polymedication (≥5 ATC classes)	0.37	0.35	0.40	***	0.55	0.54	0.57	***	0.60	0.59	0.62	***
Polymedication (≥10 ATC classes)	0.33	0.30	0.36	***	0.49	0.46	0.52	***	0.54	0.51	0.57	***

NOAC: Non vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist; OAC: oral anticoagulant; RR: Relative risk; IC; Confidence interval; ATE: arterial thromboembolic events (ischaemic stroke, arterial systemic embolism or transient ischaemic attack); NSAIDs: non-steroidal anti-inflammatory drugs

* RR determined using negative binomial regression analysis adjusting for age and sex(except for age and sex covariates, adjusted for sex and for age only, respectively).

† p-values : *** $p < 0{,}001$; ** $p < 0{,}01$; * $p < 0{,}05$

Reading example: Age and sex being equal, frailty reduced the probability for a prescription of dabigatran (instead of VKA) by 52% (1 minus the estimated RR of 0.48). For rivaroxaban and apixaban, this reduction was 42% and 36%, respectively.

Finally, we agree that EORP-AF Pilot General registry data offer a unique opportunity for indirect comparison of our nationwide DOAC patterns of use with those of other European countries. Younger age and non-valvular heart diseases were also found to be clinical predictors for being treated with NOAC in South countries (Greece, Italy, Portugal) as reported in Lip GY et al, Europace 2015. This point and this reference were added to the Discussion section as follows:

“This study demonstrated channelling of NOAC therapy towards patients at lower risk of stroke and bleeding when considering all patients with AF, in line with what has become a common feature reported worldwide in clinical practice by many observational studies on the current patterns of use of NOACs [15,42–45]. In particular, data from EORP-AF registry showed that younger age and non-valvular heart diseases were also found to be clinical predictors for being treated with NOAC in other South countries (Greece, Italy, Portugal) [46] However NOAC therapy is (…).”

Lastly, to add more interest data about discontinuation and adverse events (stroke, major bleeding and death) over the long term follow up should be added to provide a full picture of current epidemiology about AF patients in France.

We fully agree with the reviewer that discontinuation data are of interest regarding the potential inappropriate use during the first year of OAC treatment in AF patients. We have therefore calculated the one-year discontinuation rates for each OAC therapy. The results have been added to Table 2 instead of the less precise item “≤5 reimbursements”.

Regarding adverse events (stroke, major bleeding and death), it must be noted that this study was not designed to compare real-life effectiveness and safety of NOAC therapies versus VKA therapy. Furthermore, such a study would have required careful consideration of covariate selection and much more sophisticated statistical analyses for adjustment.

Minor

The acronym DOAC should be avoided. Indeed, in Europe and European Society of Cardiology the term "NOACs": non-vitamin K antagonist oral anticoagulants should be preferred.

Lastly, the text should be largely revised for proper use of english and typos (particularly about acronyms clearly reported in french).

We have replaced DOAC by NOAC and typos have been careful checked.

Responses to comments from reviewer 2.

Reviewer Name: Geoffrey Barnes

Institution and Country: University of Michigan Please state any competing interests or state ‘None declared’: None declared.

Maura and colleagues describe the use of oral anticoagulants for AF patients over the 5 year period 2011-2016 since DOACs have been introduced. They showed that OAC use for AF patients increased modestly (+16%) with a decline in antiplatelet use.

In general, the data is well presented and informative. It is limited by simple statistics, without significant adjustment for other factors that may influence anticoagulant prescribing. But the analysis is appropriate for the goal of the project, in my opinion.

First of all, we would like to thank the reviewer very much for his positive comment. At the request of the first reviewer, we have now added the results of regression analysis performed to assess clinical

predictors of OAC treatment choice. These results have been added to Manuscript as Supplementary Table 2.

The simple use of CHADS-VASc and HAS-BLED to determine if full/reduce dose DOAC is appropriate has certain limitations. Can this be added to the limitations paragraph?

We fully agree with the reviewer that, in clinical practice, the choice of the type of DOAC dose cannot be exclusively based on the use of these clinical scores, which is why we also used a definition independent of these scores as sensitivity analysis to define patients at risk of stroke, i.e. patients aged 75 and over with a history of stroke. The HAS-BLED score may have been underestimated, as a comprehensive assessment of abnormal renal function or alcohol consumption is challenging on the basis of claims data. We have therefore consolidated the Discussion section as follows:

“Thirdly, identification of inappropriate underdosing at NOAC initiation was also indirectly assessed by using stroke and bleeding risk scores computed from claims data. Important medical data such as the patient’s weight, glomerular filtration rate renal function and exact alcohol consumption are not available in the French healthcare databases, which may have led to underestimation of the HAS-BLED score and therefore to overestimation of the proportion of patients potentially underdosed at initiation. These missing clinical data may also explain the prescription of reduced dose NOAC at treatment initiation in clinical practice. Furthermore, the agreement between these empirical scores in patients with AF and the prescriber-assessed stroke and bleeding risk is a subject of discussion. [61] Consequently, the rate of inappropriate underdosing should be interpreted with caution and must be confirmed by further studies. (…)”

Table 2 - can you clarify if "prosthetic valve" is bioprosthetic, mechanical, or both? It would be most useful to just examine mechanical as these are contraindicated with DOAC therapy

Unfortunately, bioprosthetic and mechanical valves cannot be distinguished in the available French healthcare data. We agree with the reviewer and we have added this information in Table 2. However, note that this result is presented in the sub-section entitled “Contraindications or non-approved indication/dose” and none of the NOAC therapies are indicated in valvular AF, irrespective of the type of valvular disease.

Figure 3 - this is a really nice way to visualize potential under-prescribing based on CHADS-VASc and HAS-BLED scores.

We thank the reviewer for this comment.

VERSION 2 – REVIEW

REVIEWER	Marco Proietti Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
REVIEW RETURNED	20-Jan-2019

GENERAL COMMENTS	I do appreciate the changes provided by the authors. In particular, the changes in study design description made the manuscript clearer and more understandable. Notwithstanding, I think that other changes are needed to the manuscript. First of all, the paper referenced to compare the data provided about the factors associated with NOACs use in the EORP study is not the proper one. Indeed, the paper cited described only a part of the EORP Pilot study. Furthermore, in the EORP AF Programme, the Pilot study was followed by a Long-Term study that described the more contemporary use of NOACs, that covers the 2013-2016 years. Since the description of clinical characteristics of NOACs prescription is related to 2015-2016 years, I believe that the authors should analyse and reference this more recent paper (doi: 10.1093/europace/eux301). Second, I believe that the authors should better underline and stress the concept that HAS-BLED score is not designed to evaluate prescription of OAC type and dosage. Even though in their answers they report the 2012 ESC guidelines, in the 2016 ones is clearly addressed that the HAS-BLED score should not be used for this purpose and this approach was further endorsed by the following guidelines.

VERSION 2 – AUTHOR RESPONSE

Responses to comments from reviewer.

Reviewer Name: Marco Proietti

Institution and Country: Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below I do appreciate the changes provided by the authors. In particular, the changes in study design description made the manuscript clearer and more understandable.

We thank the reviewer for this comment.

Notwithstanding, I think that other changes are needed to the manuscript.

First of all, the paper referenced to compare the data provided about the factors associated with NOACs use in the EORP study is not the proper one. Indeed, the paper cited described only a part of the EORP Pilot study. Furthermore, in the EORP AF Programme, the Pilot study was followed by a Long-Term study that described the more contemporary use of NOACs, that covers the 2013-2016 years. Since the description of clinical characteristics of NOACs prescription is related to 2015-2016

years, I believe that the authors should analyse and reference this more recent paper (doi: 10.1093/europace/eux301).

We agree and the reference has been deleted and replaced by Boriani G et al, Europace 2018. The Discussion section has been modified accordingly, as follows:

“In particular, data from the ESC-sponsored ‘EURObservational Research Programme on AF’ (EORP-AF) General Long-Term Registry showed that younger age and, having fewer risk factors or a history of non-valvular heart diseases were also found to be clinical predictors for being treated with NOACs vs. VKAs in other South countries (Greece, Italy, Portugal) [46] [46].”

Second, I believe that the authors should better underline and stress the concept that HAS-BLED score is not designed to evaluate prescription of OAC type and dosage. Even though in their answers they report the 2012 ESC guidelines, in the 2016 ones is clearly addressed that the HAS-BLED score should not be used for this purpose and this approach was further endorsed by the following guidelines.

This point has been added and clearly underlined in the Discussion section, as follows:

“Consequently, the rate of inappropriate underdosing should be interpreted with caution and must be confirmed by further studies. However, NOAC misuse and underdosing have also been reported in a French prospective field study based on patients’ medical charts [63]. Of note, as INR values were not available in the databases, underdosing with VKA therapy was not assessed in this study, but has been frequently reported and must not be overlooked [53,64]. In addition, as stated in the 2016 ESC guidelines [7], HAS-BLED score is not designed to evaluate prescription of NOAC type and dosage and no longer must be used for this purpose in clinical practice. Finally (…)”

VERSION 3 – REVIEW

REVIEWER	Marco Proietti Istituto di Ricerche Farmacologiche Mario Negri IRCCS
REVIEW RETURNED	05-Feb-2019

GENERAL COMMENTS	The authors addressed the remaining remarks.