PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Direct oral anticoagulant therapies for atrial fibrillation: changing profiles of newly treated patients
AUTHORS	Huiart, Laetitia Ferdynus, Cyril Renoux, Christel Beaugrand, Amélie Lafarge, Sophie Bruneau, Léa Suissa, Samy Maillard, Olivier

VERSION 1 – REVIEW

REVIEWER	Yuji Murakawa Teikyo University School of Medicine, Mizonokuchi Hospital Japan
REVIEW RETURNED	27-Jun-2017

GENERAL COMMENTS	This study offers an insight into physicians' viewpoint in terms of anticoagulant strategy for patients with atrial fibrillation. If findings are not surprising, these observations are important for further comparison with anticoagulant strategy in other countries.

REVIEWER	Inmaculada Hernandez University of Pittsburgh, USA
REVIEW RETURNED	21-Jul-2017

GENERAL COMMENTS	This manuscript evaluated the use of DOACs and VKAs using French National Health Administrative Database. Its main strength is the use of this nation-wide data base; its major weakness is likely the unavailability of diagnosis codes in the dataset, and the subsequent need to define NVAF based on medication use. I highly encourage the authors to do a time trend analysis to formally test the change in DOAC uptake overtime, and to further refine their statistical analyses. Nevertheless, the manuscript is beautifully written. I commend the authors for their work. Major comments: -I suggest the authors perform a trend analysis to formally assess the time trends in DOAC use. They can use a regression model where outcome is the penetration of DOACs and covariates include month, indicator variables for different periods (for example, period after dabigatran was approved for reimbursement, period after rivaroxaban was), and the interactions between these periods and

	month. Such analysis would enable them to formally address how the use (slope) of DOACs changed overtime, and whether it differed between different periods. Then authors can comment on potential changes in level of DOAC use and in slope. -I am not sure I understand well the methods: "a logistic regression stratified by calendar year of anticoagulant initiation" means "5 logistic regressions, one for each year", right? I would rephrase the sentence to improve clarity. -I am confused about what analyses were done to populate figures 3, 4, 5. What is the reference category for HAS-BLED >2 ? Why CHA2DS2-VASc >2 and CHA2DS2-VASc =1 were used as two levels, when the mean in the sample is of 3.9? I think these figures take a bit too much space for what they show, but I understand it is an editorial decision if the editor prefers authors to collapse them, or simply report all odds ratio in a table. In any case, please make clear the levels of each variable. -I can see table 3 for the 2 sensivity analysis cohorts but not for the base case sample. Can you add this table for the base case sample to the main text, and maybe collapse figures or drop them? -I think the discussion could benefit from some changes, for example: a) I am missing a discussion of why the uptake of DOACs is so high in French, if the health authorities recommend VKA as first line therapy. Moreover, I think the authors should comment on the paradox that, whereas the European guidelines place DOACs as first line therapy and French do not, uptake of DOACs in France seems to be higher than in other countries. b) I do not think US is the best country to compare uptake DOACs in France to. Difference in out-of-pocket expenses for DOACs vs VKAs is considerably larger in the US than France, and 2 health care systems are much different. c) many papers (not only Desai et al) have shown that patients on DOACs are sicker than those on warfarin. Many authors have attributed this to potential risk-aversion of prescribers to the bleeding risk with DOACs. I think this is a point worth discussing. (I acknowledge the authors then mention the warnings, but I think they could elaborate a bit more on the risk-aversion issue). d) There were warnings released for bleeding risk by all major agencies, including FDA, EMA; not only French agency. e) Page 13 line 10: I am not sure if DOACs being preferred by only one third of prescribers actually proves the previous point the authors make. Minor comments: -Title: I suggest changing the title to something that captures the study of trends in DOAC uptake/use, and also captures the use of the French National Health Administrative Database. -Page 4 line 43: I believe authors are defining "availability of a NOAC" as having being approved by the French health authorities for reimbursement. In any case, please revise whether edoxaban is also available according to your definition at the time of manuscript revision, and update this sentence in such case. -Page 5 line 48: I would say: "The benefit-risk ratio of DOACs nevertheless varies across individual agents, and also according to patient profile". -Page 6 line 13: Not sure if reference is the same one used in line 17. Please add reference otherwise -Study covariates: I would suggest adding the definition in the supplemental material (treatment or hospital discharge codes used to define them).

	-What is the rationale behind controlling for corticosteroids? -Page 8 line 43: I would suggest removing "irrelevant for DOAC users". This may be true, but it is relevant for VKA users, and they are also included in the study. (I understand these are new oral anticoagulant users, so probably it would not affect otherwise, but I would still drop those words. -Page 10 line 18: Rivaroxaban is misspelled. -(Throughout results): Please double check journal's policy in case I am wrong, but I am mostly used to seeing SD with capital letters. -Page 12 line 34: Not sure "thus" is the correct connector. -Figure 2 panel a: two series are redundant. Maybe the authors could simply display one panel, with 4 series: dabigatran, rivaroxaban, apixaban and total DOACs. -Figure 3: Please capitalize HAS-BLED in the legend to be consistent. -Figures 3,4,5. Please specify in the Y axis whether the OR shows DOACs vs VKA initiation or viceversa. I understand it shows VKA vs DOACs initiation because of the results; however, the figure titles say "Associated with DOAC vs VKA initiation". Please correct this in the title of Figure 3,4,5 if I am right. -I am confused as of why Figure 3 shows unadjusted odds ratio but figures 4, 5 show adjusted odds ratio. -I suggest merging table 1 and 2 into one, so that it is easier to see how patients in each of the individual DOACs compare with those on warfarin. -Page 15 line 45: In my opinion, it is a bit too far-fetched to say that DOACs can challenge the sustainability of the French healthcare system, at a time when treatments for diseases with similar prevalence are 3 or more times more expensive than DOACs… I suggest the authors consider rephrasing the last paragraph of the paper. -Page 15 line 53: Can the authors explain why they consider the cost-effectiveness of DOACs is uncertain? There are many studies assessing their cost-effectiveness.

REVIEWER	MAURA French National Health Insurance (Assurance Maladie/CNAMTS-TS)
REVIEW RETURNED	11-Aug-2017

GENERAL COMMENTS	The authors analyzed nationwide data from the French national Health administrative database and describe trends and patterns of use of oral anticoagulants, direct oral anticoagulant (DOAC) *versus* vitamin K antagonists, over the period 2011-2015 in nonvalvular atrial fibrillation new users. Overall, a significant channeling of DOACs over VKAs towards a healthier and younger population was observed as well as a early and steady increase in the use of DOAC in France. The main strengths of the study are: a) Nationwide, large size descriptive study, b) Important topic and good case study of adoption of a new drug in newly treated patients; c) Underscores the important issue of channeling for further

	observational studies assessing the risk-benefit of DOAC *versus* VKA (especially using these data). Main Weaknesses: a) Identification of nonvalvular atrial fibrillation: the authors favored sensitivity over specificity which is questionable for this type of study. b) Despite French data has never been published on the topic so far, many studies have reported channeling of new over old drug towards healthier patients or preferential prescribing of the new drugs by specialists, including with DOAC *versus* VKA. Differences between characteristics of each DOAC *versus* VKA new users should be highlighted as well as the potential mechanism underlying the observed channeling and their corresponding consequences on the management of AF patients. c) Doubts remain on the extent to which the authors really know the database they have used. <u>Title.</u> The type of data used, the geographic region and time frame should be specified. <u>Introduction</u> The first sentence of the objective section should mention that it is a *French* cohort based on claims data. <u>Study design and source of data</u> - "…*approximately 63 million inhabitants, which corresponds to 93% of the French population*" This information is incorrect. Please read and add these references and correct: * Bezin J et al, The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017;26(8):954-962. * Tuppin P et al, Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique. 2017 Jul 26. pii: S0398-7620(17)30431-5. doi:

	10.1016/j.respe.2017.05.004 - "*However, no clinical diagnosis is provided in this database for outpatient consultations with general practitioners and specialists"* Not only for general practitioners and specialists. The French database does not contain any diagnosis for ambulatory care, whatever the healthcare provider, as well as clinical information such as smoking, weight, body mass index or results from lab tests. Please modify. <u>Cohort definition</u> - "*we define a cohort of all patients …and December 31, 2015*" From the previous section, we learnt that the NHIS is divided in several schemes, providing health insurance coverage to nearly 63 million inhabitants. Do we have to understand that authors included all warfarin/DOAC new users from the 63 Million persons? - Why was the entire class of calcium channel agonists considered as rate-control treatment and not only nondihydropyridine calcium channel antagonists (additionally the later should not be use in heart failure)? - Here it is unclear whether patients had to be incident of both oral anticoagulants and antiarrhythmic agent/rate control treatment to be included. Please clarify in this section. - "*Lastly, we excluded patients who had undergone lower limb orthopedic surgery within 30 days of inclusion*?" How did the authors deal with pulmonary embolism and deep vein thrombosis indications? Have the patients treated for such conditions not been excluded? If so, this is a major limitation that should be clearly stated. Especially because the proportion of VKA *versus* DOAC patients treated for DVT/PE may be very different. <u>Exposure</u> - Are the authors sure that phenindione and tioclomarol were still used in France over the study period. The reviewer would be curious to see % of patients initiating these three VKAs over the study period. Please check again. <u>Study covariates</u> - Please provide the definition of all covariates (ATC, ICD-10 codes) in supplementary materials.

	In particular, how did the authors define renal failure by using claims data? Discuss this general limitation. - "*exposure to treatment other than anticoagulants…was identified in the three months prior cohort entry*". However in France a 90-pill pack size can be delivered for chronic preventive therapy such as antihypertensive drugs or oral hypoglycemic agents. Could the authors reassure the reader on the consistency of exposure assessment? - Please justify the choice of comedications. Why PPI were not reported instead of corticosteroids? Could the authors also distinguish aspirin used as an NSAID from aspirin prescribed as antiplatelet agent. - "*We also determined whether …by a general practitioner, a cardiologist*". However it is not possible to precisely and fully identify cardiologist prescribers in the French healthcare database as only private cardiologists can be. In the database, hospital cardiologists i.e., those working in French public hospital, are drown in a group of salaried workers or employed practitioner which includes all specialists working in public hospital. The authors must have assumed that they were all cardiologists. This limitation should be mentioned or results should clearly distinguish private cardiologist from salaried workers. <u>Data analysis</u> - "*Further we define two other cohorts… regardless of other potential concomitant therapies*." Overall, in these sensitivity analyses, despite first and questionable restriction to RC treatment other than BB, the authors seem to have favored sensibility over specificity. Why? This seems not to be in line with the objective that is to describe patterns of use in AF patients. The authors could have identified AF by using previous history of AF diagnosis (ICD-10 codes diagnosis from hospital discharge or French long-term chronic diseases, ALD from the ambulatory setting)? This limitation should be extensively discussed and the authors should be more specific when identifying AF patients. Fully identifying AF in claims data is challenging. Recently an algorithm to identify AF in the NHIS was published (Billionnet et al, PDS 2017). As a sensitivity analysis, the authors could apply this algorithm and compare the patients' numbers and characteristics obtained; at least they should discuss how using it could have led to the same or different results.

	Results - Please modify "*rivorixaban*". - Table 1 and 2: * These tables should be merged so that VKA patients can be compared to each DOAC patients. * More importantly, as mentioned by the authors, reimbursement of dabigatran (but also rivaroxaban) for the treatment of NVAF began in July 2012 (August 2012). Year 2011 is therefore very different in terms of DOAC use in AF. Furthermore several DOAC doses (dabigatran 150/rivaroxaban 15 mg and 20mg) were not available until July 2012, apixaban 2.5 and 5mg until January 2014. This is an important limitation: what is the rationale for bringing together data for year 2011 with those of 2012-2015? - "*Patients who received DOACs had less comorbidities and were on average younger than those who were prescribed VKAs"*; This is no longer the case when you compare VKA- and apixaban-newly treated patients. Please clarify this point and comment differences between each DOAC and VKAs with the corresponding discussion. - "*The negative association was not reinforced…in 2015, likely due the fact that a larger proportion of patients received apixaban*." This is an important point to develop and discuss. - Can the authors develop the results shown in Figure 5 but not detailed in the Result section? - Figure 1: "*Patients with lower limb orthopaedic surgery within 30 days before or after date of inclusion*". In the methods section, it is mentioned "within 30 days of inclusion". Please clarify. - Figure 2: Could the authors describe and comment the decrease in the number of newly treated rivaroxaban patients between October 2015 and December 2015. - Figure 3, 4 and 5: As DOACs were not marketed (or available) for AF in France before July 2012, could the authors explain why results from 2011 are shown here. Discussion - "This convergence of results is surprising", P12 then "the speed of adoption of DOAC is similar to that described for other new drugs", P13.

	These statements might seem to be contradictory. Please clarify. The authors should also discuss 1) the observed differences in terms of prescribers' perception of (each) DOAC safety *versus* VKA, regarding the channeling ; 2) the potential combined effect of marketing campaigns of the three pharmaceutical companies, as not only one but three DOACs were launched over the study period, regarding the sharp and steady increase. - As importantly, could the authors analyze the consistency (or not) of their results in terms of patients characteristics with those published by other authors using the NHIS for the same time frame (Bouillon *et al*, Lancet Haematol. 2015; Maura *et al*, Circulation 2015, Maura *et al*, PDS 2017). - The trends of dabigatran are different from those of other DOACs. The authors should further discuss its steady decrease, especially in light of EMA safety warnings. - "*the fact that DOAC initiation is...warning issued by different health agencies in France*", P14; It would have been observed just after the warning only but channeling already existed at the time of DOAC introduction and remained three years after the warning. This should be deleted and more discussion added about prescribers' perception of DOAC safety *versus* VKA in terms of lack of antidote or ability to readily or continually monitor the extent of anticoagulation. If possible, compare with other published example of new drugs launch on the French market. - "*insofar as the results our sensitive analyses are consistent...are not sensitive.*", P15; Please see above comments on identification of AF. And please modify. <u>Conclusion</u> - "could potentially challenge the French health care system" Please tone down.

REVIEWER	Professor Marion Bennie University of Strathclyde Glasgow Scotland
REVIEW RETURNED	27-Aug-2017

GENERAL COMMENTS	BMJ – AF use in France This is a nice descriptive analysis of initial use of oral

	anticoagulants in a large population based study (good national coverage) drawing out some key observations on the use of DOACs in relation to VKAs. Interesting to see the variation by prescriber group. The limitation section acknowledges the absence of clinical diagnostic and monitoring data. However would wish to see some commentary on any potential impact of the results of the differential prescribing physician (cardiologist vs GP) on potential recording and thus analysis of co-morbidities and any impact on generation of CHA2DS2-VASc2 score e.g. CHF, diabetes, hypertension i.e are the specialists dealing with a different cohort of patients ? There is minimal discussion / concluding statement on any variation in population sub cohorts across the DOACs – maybe helpful for this to be more explicit if no variation except renal failure as a patient characteristic . Page 8 – line 22 – what is the definition of renal failure used in the study as a key result in regard to use of DOAC ?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 - Reviewer Name: Yuji Murakawa
Q1 This study offers an insight into physicians' viewpoint in terms of anticoagulant strategy for patients with atrial fibrillation. If findings are not surprising, these observations are important for further comparison with anticoagulant strategy in other countries.
A1 The authors thank the reviewer for his comment

Reviewer 2 - Reviewer Name: Inmaculada Hernandez
Institution and Country: University of Pittsburgh, USA
Please state any competing interests: None declared
GC This manuscript evaluated the use of DOACs and VKAs using French National Health Administrative Database. Its main strength is the use of this nation-wide data base; its major weakness is likely the unavailability of diagnosis codes in the dataset, and the subsequent need to define NVAF based on medication use. I highly encourage the authors to do a time trend analysis to formally test the change in DOAC uptake overtime, and to further refine their statistical analyses. Nevertheless, the manuscript is beautifully written. I commend the authors for their work.
GA The authors thank the reviewer for his comment
This review was very detailed and helped us a lot to improve the manuscript. We sincerely thank the reviewer for his in-depth work.
Major comments
Q1 -I suggest the authors perform a trend analysis to formally assess the time trends in DOAC use. They can use a regression model where outcome is the penetration of DOACs and covariates include month, indicator variables for different periods (for example, period after dabigatran was approved for reimbursement, period after rivaroxaban was), and the interactions between these periods and month. Such analysis would enable them to formally address how the use (slope) of DOACs changed overtime, and whether it differed between different periods. Then authors can comment on potential changes in level of DOAC use and in slope.
A1 Many thanks for this comment. This is a great idea that, we hope, is improving the manuscript.
We performed a trend/change point analysis using a segmented regression model. We added the paragraph in the method section to describe the model and variables tested.

We also mentioned the results in the result section and modified figure 2 to show the significant change points in the trend analysis.

Q2 -I am not sure I understand well the methods: “a logistic regression stratified by calendar year of anticoagulant initiation” means “5 logistic regressions, one for each year”, right? I would rephrase the sentence to improve clarity.

A2 We apologise for the confusion. The rephrasing of the reviewer is exact. This change has been made in the manuscript.

“To identify independent predictors of initial anticoagulant choice, we performed a multivariate analysis using 5 logistic regression models, one for each calendar year of anticoagulant initiation”

Q3 -I am confused about what analyses were done to populate figures 3, 4, 5. What is the reference category for HAS-BLED >2 ?

A3 The figures 3 corresponds to the crude odds ratio and confidence intervals computed in the computed per calendar year separately for HAS-BLED and CHA2DS2-VASc.

Figures 4, 5 correspond to the adjusted odds ratio and confidence intervals obtained in the 5 regression logistic models computed per calendar year and adjusted for the covariates specified in the legend. This 2 figures (4 and 5) are issued from the same statistical models. We do admit that this is confusing.

We propose to the reviewer to suppress figures 4 and 5 and to replace it by a table (Table 3 in the former version/ Table 2 in the new version of the paper). Figure 3 may be the most illustrative one and we suggest to keep it as such, if this is ok for the reviewer (after correcting to clarify the reference value for HAS-BLED). Legend was clarified.

Q4 Why CHA2DS2-VASc >2 and CHA2DS2-VASc =1 were used as two levels, when the mean in the sample is of 3.9?

A4 CHA2DS2-VASc was used as 3 levels: 0, 1 and >= 2. This was not based on statistical considerations but followed the French guidelines of anticoagulant therapy in Atrial Fibrillation (score=0 no AC treatment, score = 1 – discussion of AC treatment, score>= 2 – indication of treatment). This was done as well to provide comparable data as in other papers such as Loo et al, BJCP 2017

Q5 I think these figures take a bit too much space for what they show, but I understand it is an editorial decision if the editor prefers authors to collapse them, or simply report all odds ratio in a table. In any case, please make clear the levels of each variable.

A5 As discussed in A3, we propose that figure 4 and 5 should be removed and replaced by a table, if this is fine for the reviewer and editor. Levels of variables were clarified on figure 3.

Q6 -I can see table 3 for the 2 sensivity analysis cohorts but not for the base case sample. Can you add this table for the base case sample to the main text, and maybe collapse figures or drop them?

A6 As suggested, we suppressed figure 4 and 5 and replaced it by table 3 for the main cohort.

Q7 -I think the discussion could benefit from some changes, for example:

a) I am missing a discussion of why the uptake of DOACs is so high in French, if the health authorities recommend VKA as first line therapy. Moreover, I think the authors should comment on the paradox that, whereas the European guidelines place DOACs as first line therapy and French do not, uptake of DOACs in France seems to be higher than in other countries.

A7 Early after the first EMA approval in 2008, NOAC prescriptions have differed across EU countries. France reported high rates of prescription since the early years after initial marketing authorization although other countries did not. In France, although recommendations have been issued, prescribers are still free to prescribe, contrarily to other countries with a more regulated approach. The underlying hypothesis is that physician perceive DOACs to be simpler to use and maybe more effective. A sentence was added in the discussion.

Q8 b) I do not think US is the best country to compare uptake DOACs in France to. Difference in out-of-pocket expenses for DOACs vs VKAs is considerably larger in the US than France, and 2 health care systems are much different.

A8 We agree with the reviewer with this comment. We discussed the difference between the 2 systems. The striking result is that although systems are really different, results are similar. The US results are interesting as it was one of the first available. We added UK as a comparison.

Q9 c) many papers (not only Desai et al) have shown that patients on DOACs are sicker than those on warfarin. Many authors have attributed this to potential risk-aversion of prescribers to the bleeding risk with DOACs. I think this is a point worth discussing. (I acknowledge the authors then mention the warnings, but I think they could elaborate a bit more on the risk-aversion issue).

A9 Many papers have shown that DOACs are less sick than VKA user which indeed may be likely due to the perception of DOACs by physician. We added a sentence on the evolution of the efficacy/safety perception evolving over time.

Q10 d) There were warnings released for bleeding risk by all major agencies, including FDA, EMA; not only French agency.

A10 This is true. We mentioned them in the paper.

Q11 e) Page 13 line 10: I am not sure if DOACs being preferred by only one third of prescribers actually proves the previous point the authors make.

A11 The sentence was clarified and modified to discuss this point. New sentence “Indeed, a recent study indicates that DOACs were considered equal or preferred to VKAs by respectively 48.5% and 33.3% of surveyed physicians”

Minor comment

Q12 -Title: I suggest changing the title to something that captures the study of trends in DOAC uptake/use, and also captures the use of the French National Health Administrative Database.

A12 The title has been changed to “Trends in initiation of direct oral anticoagulant therapies for atrial fibrillation in the French Health Insurance databases”

Q13 -Page 4 line 43: I believe authors are defining “availability of a NOAC” as having being approved by the French health authorities for reimbursement. In any case, please revise whether edoxaban is also available according to your definition at the time of manuscript revision, and update this sentence in such case.

A13 Edoxaban was approved by the European agency in june 2015, however reimbursement is not available in France for this indication.

The sentence has been modified to “This is particularly the case for apixaban, which was the most recent DOAC available at the time of the study” to clarify this point.

Q14 -Page 5 line 48: I would say: “The benefit-risk ratio of DOACs nevertheless varies across individual agents, and also according to patient profile”.

A14 Thank you for this comment. The sentence was modified as suggested

Q15 -Page 6 line 13: Not sure if reference is the same one used in line 17. Please add reference otherwise

A15 We confirm that the reference provided is corresponding to these 2 sentences.

Q16 -Study covariates: I would suggest adding the definition in the supplemental material (treatment or hospital discharge codes used to define them).

A16 We added a table in the supplementary material to summarize what type of data where used to define the different variables used. This will certainly clarify how the variables have been defined. The lists of ATC and ICD-10 codes would take more than 30 pages and would not show the combination used. We believe this may not be very useful for the reader and the solution found is more informative. This question is left to the editor.

Q17 -What is the rationale behind controlling for corticosteroids?

A17 Many medications could have been described. Some choices had to be made. These choices were made so that the drugs presented would help to describe the population. Corticosteroids have important interactions with anticoagulants and is one of numerous treatment that might influence to choice of the anticoagulant therapy. The choice is questionable and other drugs may have been of interest. This was provided for descriptive purpose only and did not influence the rest of the analysis.

Q18 -Page 8 line 43: I would suggest removing "irrelevant for DOAC users". This may be true, but it is relevant for VKA users, and they are also included in the study. (I understand these are new oral anticoagulant users, so probably it would not affect otherwise, but I would still drop those words.

A18 The sentence was modified as suggested

Q19 -Page 10 line 18: Rivaroxaban is misspelled.

A19 Thank you for tis correction. The text was corrected

Q20 -(Throughout results): Please double check journal's policy in case I am wrong, but I am mostly used to seeing SD with capital letters.

A20 We did not find it mentioned in the journal policy, however we found it in articles in open BMJ, therefore we made the changes in the manuscript.

Q21 -Page 12 line 34: Not sure "thus" is the correct connector.

A21 Thank you for this comment. "Thus" was replaced by "Indeed"

Q22 -Figure 2 panel a: two series are redundant. Maybe the authors could simply display one panel, with 4 series: dabigatran, rivaroxaban, apixaban and total DOACs.

A22 We agree with the reviewer comment. We tried in a previous version to present the figure as suggested but this appeared to be quite confusing for the readers. We did not find a way to summarize all the curves on the same figure without adding confusion. Therefore, if this is OK for the reviewer and the editor, we would like to leave the curves as it is.

Q23 -Figure 3: Please capitalize HAS-BLED in the legend to be consistent.

A23 Figure 3 has been corrected in accordance

Q24 -Figures 3,4,5. Please specify in the Y axis whether the OR shows DOACs vs VKA initiation or viceversa. I understand it shows VKA vs DOACs initiation because of the results; however, the figure titles say "Associated with DOAC vs VKA initiation". Please correct this in the title of Figure 3,4,5 if I am right.

A24 The figure has been clarified following this comment. A new version is provided

Q25 -I am confused as of why Figure 3 shows unadjusted odds ratio but figures 4, 5 show adjusted odds ratio.

A25 We suppressed figure 4 and 5. Figure 3 is unadjusted as the score do account for most of the covariates. The 2 scores are not accounting for the same covariates, therefore presenting adjusted results would have required to adjust for different covariates in the 2 models and would have made the figure difficult to read. Adjusted results (not shown) provide very similar results.

Q26 -I suggest merging table 1 and 2 into one, so that it is easier to see how patients in each of the individual DOACs compare with those on warfarin.

A26 We fully agree. The 2 table are now merged into table 1

Q27 -Page 15 line 45: In my opinion, it is a bit too far-fetched to say that DOACs can challenge the sustainability of the French healthcare system, at a time when treatments for diseases with similar prevalence are 3 or more times more expensive than DOACs… I suggest the authors consider rephrasing the last paragraph of the paper.

A27 We agree and rephrased this part of the manuscript.

Q28 -Page 15 line 53: Can the authors explain why they consider the cost-effectiveness of DOACs is uncertain? There are many studies assessing their cost-effectiveness.

A28 Maybe the wording was not appropriate. We meant that results of cost-effectiveness studies depended on the context/characteristics of the patients. We suppressed this part of the sentence to clarify the paragraph.

Reviewer 4 – Reviewer Name: Professor Marion Bennie

Q1 This is a nice descriptive analysis of initial use of oral anticoagulants in a large population based study (good national coverage) drawing out some key observations on the use of DOACs in relation to VKAs. Interesting to see the variation by prescriber group.

A1 Thank you for this general comment

Q2 The limitation section acknowledges the absence of clinical diagnostic and monitoring data. However would wish to see some commentary on any potential impact of the results of the differential prescribing physician (cardiologist vs GP) on potential recording and thus analysis of co-morbidities and any impact on generation of CHA2DS2-VASc2 score e.g. CHF, diabetes, hypertension i.e are the specialists dealing with a different cohort of patients ?

A2 A limitation of our database, is the absence of diagnostic codes filled by physician outside the hospital setting. Comorbidities were constructed mainly in hospital diagnostic codes and prescriptions. Therefore we think that comorbidities definition were not influenced by the different coding of the different physicians.

Q3 There is minimal discussion / concluding statement on any variation in population sub cohorts across the DOACs – maybe helpful for this to be more explicit if no variation except renal failure as a patient characteristic.

A3 We fully agree that is an interesting point. However, as this was not the objective of this paper we did not conduct these analysis. We focused on renal failure as this is a relative contraindication of some of the drugs under study are was deemed important.

Q4 Page 8 – line 22 – what is the definition of renal failure used in the study as a key result in regard to use of DOAC ?

A4 A table was added in the supplementary section to clarify how variables were defined. In the case of renal failure, hospital discharge diagnostic codes, long duration disease (specific to France) and procedures (any kind of dialysis) were used.

Reviewer 3 - Reviewer Name: MAURA

Institution and Country: French National Health Insurance (Assurance Maladie/CNAMTS-TS)

Please state any competing interests: None declared

Q1 The authors analyzed nationwide data from the French national Health administrative database and describe trends and patterns of use of oral anticoagulants, direct oral anticoagulant (DOAC) versus vitamin K antagonists, over the period 2011-2015 in nonvalvular atrial fibrillation new users. Overall, a significant channeling of DOACs over VKAs towards a healthier and younger population was observed as well as a early and steady increase in the use of DOAC in France.

The main strengths of the study are:

a) Nationwide, large size descriptive study,

b) Important topic and good case study of adoption of a new drug in newly treated patients;

c) Underscores the important issue of channeling for further observational studies assessing the risk-benefit of DOAC versus VKA (especially using these data).

Main Weaknesses:

a) Identification of nonvalvular atrial fibrillation: the authors favored sensitivity over specificity which is questionable for this type of study.

b) Despite French data has never been published on the topic so far, many studies have reported channeling of new over old drug towards healthier patients or preferential prescribing of the new drugs by specialists, including with DOAC versus VKA. Differences between characteristics of each DOAC versus VKA new users should be highlighted as well as the potential mechanism underlying the observed channeling and their corresponding consequences on the management of AF patients.

c) Doubts remain on the extent to which the authors really know the database they have used.

A1 The authors thank the reviewer for this general comments and for the strengths identified in the study.

Regarding weaknesses, A) sensitivity was indeed favoured in order to provide a comprehensive description of the prescription practices. A more restrictive approach may have restricted the sample to a sub-sample selected more severe, or treated in a more hospital based context and therefore less representative of the general population approach. We acknowledge that if we had been conducting an effectiveness study, we may have restricted the sample to limit indication bias. It is not an issue in this descriptive study.

B) We fully agree with this comment. This is particularly the case for apixaban. However, because of the study period data on apixaban are scarce and more follow-up would be needed to better describe temporal trend for this drug

C) We would appreciate to discuss this item on a more factual basis

Q2 Title.

The type of data used, the geographic region and time frame should be specified.

A2 The title has been modified to account for reviewer 2 and reviewer 4 comment. We propose to following title adding some of the precision requested, while maintaining the title at a reasonable length: “Trends in initiation of direct oral anticoagulant therapies for atrial fibrillation in the French Health Insurance databases”

Q3 Introduction

The first sentence of the objective section should mention that it is a French cohort based on claims data.

A3 We agree. The text was modified in accordance to this comment.

Q4 Study design and source of data

- “7approximately 63 million inhabitants, which corresponds to 93% of the French population”

This information is incorrect. Please read and add these references and correct:

* Bezin J et al, The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017;26(8):954-962.

* Tuppin P et al, Value of a national administrative database to guide public decisions: From the système national d’information interrégimes de l’Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique. 2017 Jul 26. pii: S0398-7620(17)30431-5. doi: 10.1016/j.respe.2017.05.004

A4 Thank you for the precision. The coverage is indeed better than the one stated in the text. This has been corrected in the text. 63 has been replaced by 66 million and 93% of coverage replaced by 99% (99.8 in ref Bezin et al.). Our data corresponded to a former version of the database.

- Numbers and coverage of the NHIS have been modified in the text according to the first reference mentioned by the reviewer.

Q5 - “However, no clinical diagnosis is provided in this database for outpatient consultations with general practitioners and specialists” Not only for general practitioners and specialists. The French database does not contain any

diagnosis for ambulatory care, whatever the healthcare provider, as well as clinical information such as smoking, weight, body mass index or results from lab tests. Please modify.

A5 The sentence initially written corresponded to the diagnosis that would have been interested for our study and it was not meant to describe the database as a whole. We would rather focus on the data that would have been useful for the study (and for example, used in a recent paper of our group Loo et al. BJCP 2017), rather than a complete description of the database. We have modified “outpatient consultations with general practitioners and specialists” to “consultations by health professionals in an ambulatory care setting”.

Q6 Cohort definition

- “we define a cohort of all patients _and December 31, 2015”

From the previous section, we learnt that the NHIS is divided in several schemes, providing health insurance coverage to nearly 63 million inhabitants. Do we have to understand that authors included all warfarin/DOAC new users from the 63 Million persons?

A6 The reviewer understood correctly the text written.

Q7 - Why was the entire class of calcium channel agonists considered as rate-control treatment and not only nondihydropyridine calcium channel antagonists (additionally the later should not be use in heart failure)?

A6 Thank you for this comment. Indeed, we did not use the entire class. We added in the text the list of drugs. We are sorry that this was removed at some stage in the preparation of the paper. It indeed create confusion for the reader. We clarified this point in the revised version of the manuscript.

Q8 - Here it is unclear whether patients had to be incident of both oral anticoagulants and antiarrhythmic agent/rate control treatment to be included. Please clarify in this section.

A8 The text was modified in clarify this point. Patients had to be exposed to an AR agent/rate control treatment and to receive a new treatment for an anticoagulant therapy in a defined time window. We selected all first anticoagulant treatments in the study period and defined as first treatment the ones that were not associated with a previous anticoagulant therapy. We tried to clarify this point in the manuscript.

Q9 - "Lastly, we excluded patients who had undergone lower limb orthopedic surgery within 30 days of inclusion?"

How did the authors deal with pulmonary embolism and deep vein thrombosis indications? Have the patients treated for such conditions not been excluded? If so, this is a major limitation that should be clearly stated. Especially because the proportion of VKA versus DOAC patients treated for DVT/PE may be very different.

A9 Thank you for this comment. This is a limitation. The exclusion criteria limited the number of patient receiving a treatment for the prevention of DVT/PE. The curves of drug use before the authorisation of DOAC for AF shows a limited use. The proportion of patients that have an DVT code in their follow-up is 4.5% and it should not affect the results

Q10 Exposure

- Are the authors sure that phenindione and tioclomarol were still used in France over the study period. The reviewer would be curious to see % of patients initiating these three VKAs over the study period. Please check again.

A10 Our analysis was prepared on a database called EGB (Echantillon Général des Bénéficiaires) which corresponds to a random sample (ratio 1/97) of the large database used in this study. In the EGB, we identified 139 subjects receiving TIOCLOMAROL and 116 subjects receiving PHENINDIONE.

In the statistical program used, we kept these 2 treatments, although in the final database for this article, there are no patients receiving any of these 2 drugs. This can obviously be removed from the text, if the reviewer believes it makes the text clearer.

Q11 Study covariates

- Please provide the definition of all covariates (ATC, ICD-10 codes) in supplementary materials.

A11 We added a table in the supplementary material to summarize what type of data where used to define the different variables used. This will certainly clarify how the variables have been defined. The lists of ATC and ICD-10 codes would take more than 30 pages and would not show the combination used. We believe this may not be very useful for the reader and the solution found is more informative. This question is left to the editor.

Q12 In particular, how did the authors define renal failure by using claims data? Discuss this general limitation.

A12 As answered in the previous comment, a table was added in the supplementary section to clarify how variables were defined. In the case of renal failure, hospital discharge diagnostic codes, long duration disease (specific to France) and procedures (any kind of dialysis) were used. It is clearly known, renal failure is a challenging disease to identify in a health administrative database. The percentage of patients with renal failure is likely to be underestimated. However, there are no reasons to believe that this underestimation would be different according to the treatment or years of initiation.

Q13 - “exposure to treatment other than anticoagulants_was identified in the three months prior cohort entry”. However in France a 90-pill pack size can be delivered for chronic preventive therapy such as antihypertensive drugs or oral hypoglycemic agents. Could the authors reassure the reader on the consistency of exposure assessment?

A13 Three-months is defined as 30.5 days x 3, corresponding to 91.5 and therefore capturing a 90 day prescription. We hope the reviewer is reassured.

Q14 - Please justify the choice of comedications. Why PPI were not reported instead of corticosteroids? Could the authors also distinguish aspirin used as an NSAID from aspirin prescribed as antiplatelet agent.

A14 We agree that many medications could have been described. Some choices had to be made. These choices were made so that the drugs presented would help to describe the population. This article is not aiming to assessing haemorrhagic outcomes and therefore, due to the limited space available, we did not present data on PPI. Corticosteroids have important interactions with anticoagulants and is one of numerous treatment that might influence to choice of the anticoagulant therapy. The choice is questionable and other drugs may have been of interest.

To date we have not conducted a full description of the use of aspirin depending on the dosage used. This task requires some important computational work and may only add limited information to this study. Therefore, the distinction between the different indications of Aspirin has not been conducted.

Q15 - “We also determined whether _by a general practitioner, a cardiologist”.

However it is not possible to precisely and fully identify cardiologist prescribers in the French healthcare database as only private cardiologists can be. In the database, hospital cardiologists i.e., those working in French public hospital, are drown in a group of salaried workers or employed practitioner which includes all specialists working in public hospital. The authors must have assumed that they were all cardiologists. This limitation should be mentioned or results should clearly distinguish private cardiologist from salaried workers.

A15 This is true but additional elements should be accounted for. 1- this is true for cardiologists but also for GPs working in hospital; 2- only a 1/3 of cardiologists are working in a hospital based setting; 3- most importantly, the prescriber was used only for the 1st prescription which was mostly issued outside a hospital setting. Indeed, regarding prescriptions of anticoagulant therapy in our study, 75.2% of prescribers were practicing in a private community setting, 7.3% in a private hospital setting, less than 1% were individually identified from a public hospital setting and the information was not available for 17.5% of prescribers.

This confirms as well that we capture a non-selected AF population and not only hospital based AF diagnosis in line with our objective.

Q16 Data analysis

- “Further we define two other cohorts_ regardless of other potential concomitant therapies.” Overall, in these sensitivity analyses, despite first and questionable restriction to RC treatment other than BB, the authors seem to have favored sensibility over specificity. Why? This seems not to be in line with the objective that is to describe patterns of use in AF patients. The authors could have identified AF by using previous history of AF diagnosis (ICD-10 codes diagnosis from hospital discharge or French long-term chronic diseases, ALD from the ambulatory setting)? This limitation should be extensively discussed and the authors should be more specific when identifying AF patients. Fully identifying AF in claims data is challenging. Recently an algorithm to identify AF in the NHIS was published (Billionnet et al, PDS 2017). As a sensitivity analysis, the authors could apply this algorithm and compare the patients’ numbers and characteristics obtained; at least they should discuss how using it could have led to the same or different results.

A16 This is an interesting comment and we thank the reviewer for rising this point. However, in health databases studies, the algorithms used to define a disease are clearly dependant on the objective of the study. In our study, our objective was to describe the drugs used at the initiation of treatment and the characteristics of users. Most of AF are diagnosed and treated initially outside a hospital setting. Therefore restricting the cohort to patients who had a previous hospitalisation for AF

would have been a too restrictive approach and would have selected a sub-sample not representative of our target population. Long duration disease codes (ALD) are an effective way to identify patient with a specific disease in an ambulatory setting, however these codes are lacking sensitivity as a substantial proportion of patient are not reported in the system. Moreover, the ALD declaration may be delayed in time and therefore not capture the initial treatment. We fully acknowledge that the algorithm published by Billionnet et al. may be very useful for effectiveness/safety study on DOACs where a more restrictive approach is needed. In our study, however, using such an algorithm would not have allowed to describe the characteristics of patients and prescriber already included in the algorithm (i.e: age, prescriber, sex…). It would have overrepresented patients who had an hospitalisation or diagnostic tests, which may sometimes have occur after the initial AC prescriptions (delay in access to specialists/holter…) in the general population. This approach is not in line with our objectives in the present study.

Q17 Results

- Please modify “rivorixaban".

A17 Thank you for the correction also mentioned by reviewer 2

Q18 - Table 1 and 2:

* These tables should be merged so that VKA patients can be compared to each DOAC patients.

A18 The table were merged. We do agree that it makes the table section clearer.

Q19 * More importantly, as mentioned by the authors, reimbursement of dabigatran (but also rivaroxaban) for the treatment of NVAF began in July 2012 (August 2012). Year 2011 is therefore very different in terms of DOAC use in AF. Furthermore several DOAC doses (dabigatran 150/rivaroxaban 15 mg and 20mg) were not available until July 2012, apixaban 2.5 and 5mg until January 2014. This is an important limitation: what is the rationale for bringing together data for year 2011 with those of 2012-2015?

A19 We agree with the reviewer. However we believe this is rather a very interesting results in our study. Even though dabigatran was reimbursed for AF in July 2012, it was approved in this indication by the French authorities in August 2011. Physician clearly didn’t all wait until the reimbursement of the drug for AF. This appears clearly on Figure 2, with a first increase after August 2011 and another increase after the decision of reimbursement in 2012. Reviewer 2 suggested to fit a segmented regression model to adjust for the time line events (time of marketing of each drug, security warning…). This was a very interesting comment. These models were fitted and added to the manuscript and respond to this question.

Q20 - “Patients who received DOACs had less comorbidities and were on average younger than those who were prescribed VKAs”;

This is no longer the case when you compare VKA- and apixaban-newly treated patients. Please clarify this point and comment differences between each DOAC and VKAs with the corresponding discussion.

- “The negative association was not reinforced_in 2015, likely due the fact that a larger proportion of patients received apixaban.” This is an important point to develop and discuss.

A20 I do apologize for answering these 2 questions together. We fully agree that it seems that the arrival of apixaban on the market has had a large impact on the results in 2015 and the changes in trends. However, because there are only a short period of availability of apixaban in our data, it is premature to draw firm conclusion. We added a sentence in the discussion section.

Q21 - Can the authors develop the results shown in Figure 5 but not detailed in the Result section?

A21 In accordance with reviewer 2 comments, figure 5 has been suppressed and replaced by table 2 (new table 2), this should answer of question of reviewer 3

Q22 - Figure 1: “Patients with lower limb orthopaedic surgery within 30 days before or after date of inclusion”. In the methods section, it is mentioned “within 30 days of inclusion”. Please clarify

A22 We clarified this point by modifying the method section to “within +/- 30 days.”

Q23 - Figure 2: Could the authors describe and comment the decrease in the number of newly treated rivaroxaban patients between October 2015 and December 2015.

A23 This corresponds either to a general diminution of DOACs following a draft guidance by the HAS in September 2015. In the change point model, we identified a significant change in trends at this time corresponding to the HAS guidance and reduction in reimbursement of dabigatran and associated with an increase in apixaban at this point in time (change point models were added in the method and result section).

Q24 - Figure 3, 4 and 5: As DOACs were not marketed (or available) for AF in France before July 2012, could the authors explain why results from 2011 are shown here.

A24 This is discussed above. Drugs are being used after their approval, and clearly before being reimbursed.

Q25 - "This convergence of results is surprising", P12 then "the speed of adoption of DOAC is similar to that described for other new drugs", P13.

These statements might seem to be contradictory. Please clarify.

A25 This was not meant to be contradictory. One sentence is corresponding to the fact that similar patterns are observed across different health care system. The other sentence is referring to a comparison between different drugs. We modified the text in an attempt to clarify this point.

Q26 The authors should also discuss 1) the observed differences in terms of prescribers' perception of (each) DOAC safety versus VKA, regarding the channeling ; 2) the potential combined effect of marketing campaigns of the three pharmaceutical companies, as not only one but three DOACs were launched over the study period, regarding the sharp and steady increase.

A26 We fully agree on the interest of the comment of the reviewer and indeed the marketing campaigns would be very interesting to study. However this goes beyond the scope of our study. We added a segmented regression model to better identify the change points in the drug use trends.

Q27 - As importantly, could the authors analyze the consistency (or not) of their results in terms of patients characteristics with those published by other authors using the NHIS for the same time frame (Bouillon et al, Lancet Haematol. 2015; Maura et al, Circulation 2015, Maura et al, PDS 2017).

A27 We agree on these interesting comparison. In Maura et al Circulation in 2015, the authors propose a comparison of outcome events in NvAF in a new user cohort defined between July and November 2012. The time period is short and corresponds at the early post-marketing period of dabigatran and rivaroxaban. We can notice that cohort entry definition were different and render difficult the comparison for the same period. Moreover Maura et al used a propensity score matching approach. It will however be definitely relevant to make comparisons with this paper while studying the safety and efficacy of the DOACs in the database.

In Bouillon et al published in 2015, the authors propose a safety study in the exclusively population of switchers from VKAs to DOACs between January 2011 and November 2012. We can notice that year 2011 was included in the study period as we did in our paper. Swithers and new users are difficult to compare. Once again, it could be more relevant to discuss this paper in a future study dealing with the safety of DOACs in the database.

In PDS in 2017, Maura et al have studied the adherence with DOACs in a NvAF new users cohort defined between January 2013 and June 2013. The restricted time period limits the relevance of the comparison.

We will definitely use these papers to compare results of safety analysis in a future paper.

Q28 - The trends of dabigatran are different from those of other DOACs. The authors should further discuss its steady decrease, especially in light of EMA safety warnings.

A28 We believe that the addition of the segmented regression model may clarify this point as it identifies the significant change points and the changes in patterns of drug use.

Q29 - "the fact that DOAC initiation is…warning issued by different health agencies in France", P14;

It would have been observed just after the warning only but channeling already existed at the time of DOAC introduction and remained three years after the warning. This should be deleted and more

discussion added about prescribers' perception of DOAC safety versus VKA in terms of lack of antidote or ability to readily or continually monitor the extent of anticoagulation. If possible, compare with other published example of new drugs launch on the French market.

A29 We agree that the channeling may have occurred on a broader time period. However our results suggest that it was reinforced after the warning. Here again, we believe that the addition of the segmented regression model may clarify this point as it identifies the significant change points and the changes in patterns as reported now in the method and result section. We acknowledge that the addition of the segmented regression models makes the discussion on the changes over time much easier to explain factually and we thank again the previous reviewer for the suggestion. We hope that it provides a clearer view to the 3rd reviewer as well.

Q30 - "insofar as the results our sensitive analyses are consistent…are not sensitive.", P15; Please see above comments on identification of AF. And please modify.

A30 Please see answer to previous comment to justify the selection process.

Q31 - "could potentially challenge the French health care system"

Please tone down.

A31 This point was modified in the text.

VERSION 2 – REVIEW

REVIEWER	Inmaculada Hernandez University of Pittsburgh, USA
REVIEW RETURNED	16-Oct-2017

GENERAL COMMENTS	The authors have done an excellent job reviewing this paper and have adequately addressed the numerous comments raised by all reviewers. I have no further comments

REVIEWER	MAURA French national health insurance (CNAMTS, Assurance Maladie)
REVIEW RETURNED	31-Oct-2017

GENERAL COMMENTS	The authors have positively answered to several of our questions regarding the first version of the manuscript and they have added a segmented regression model very helpful to assess and comments the OAC trends. However, it still remains two major limitations still not addressed (or at least discussed) by the authors among our comments; they are related to their expertise of the French claims data, so please, again, discuss: 1) French claims data use: 1.1) concerning the quality of data used, Tuppin et al. have reported important differences between the completeness of French data according to type of scheme regarding date of data use; in particular data of RSI and MSA schemes do not include long duration disease data before 2016 and 2014, respectively. Also, restrictions apply to variables such as vital status and refined ATC coding (please see Table 2 of Tuppin P et al, Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique. 2017 Oct;65 Suppl 4:S149-S167). However authors stated they used data from all schemes ("99% of

	the French population"), especially to identify comorbidities from long duration disease data (as displayed in the supplementary table). Did the authors actually include all OAC new users from the 66 M persons living in France? If so, completeness of data was not the same for the different schemes used; 1.2.) % of GP as first prescriber found in this study are not in line with the data reported on the same database (around 25% versus 60% reported here, see Maura et al. 2017 Pharmacoepidemiol. and Drug safety or Maura et al, Circulation 2015) for year 2012/2013; although differential inclusion/exclusion criteria between these studies might have explained this result, this is concerning especially because the category of hospital practitioners did not appear here as first prescribers? (% hospi. pract. reported in Maura et al. around 30%). As a consequence the same applies to cardiologists specialty. Additionally, can the authors explained data at the back of the Table 1 in "Suppl. Material, sensitivity analysis, cohort 2":"among GP…among cardiologists"? Can the authors reassure on a potential flawed identification of OAC first-prescribers in the French claims data? 2) Identification of nonvalvular atrial fibrillation: 2.1.) The authors still have not indicated how they managed patients with recent DVT/PE, another indication of DOAC therapy that may account for around 25% of incident treatment (see Billionnet et al, Pharmacoepidemiol. and Drug safety); if not, characteristics displayed in Table 2 might also reflect those of DVT/PE patients and this must be discussed ; 2.2.) The authors still have not properly discussed the method used to identify AF: a) Specificity: why no utilization of previous history of AF diagnosis via ICD-10 codes diagnosis from hospital discharge or French long duration disease, at least as sensitivity analysis; b) as a consequence relevance of their sensitivity analyses (SA) is questionable, especially in view of the differences in nature/% of first prescriber between the main analysis and SA, notably versus SA2, "patients newly treated with an anticoagulant therapy regardless of other potential concomitant therapies"; as a consequence the sentence "we can be confident that our findings are not too sensitive to the definition of AF" should be deleted and SA reported modified. Other comments : 1) Still curious about authors comments on consequences of the observed channeling on the management of AF patients in France. 2) Discuss the difference in the observed channelling DOAC versus VKA in light of apixaban data regarding patients' age/severity (in abstract and discussion). 3) Use of PPI would have been interesting to add and comment, especially because DOAC therapy was shown to increase GI bleeding versus warfarin

VERSION 2 – AUTHOR RESPONSE

Manuscript ID bmjopen-2017-018180.R1 entitled "Trends in initiation of direct oral anticoagulant therapies for atrial fibrillation in a national population-based cross sectional study from the French Health Insurance databases".

Editorial Requirements:
- Please add the study design to the title.
As suggested, we added “a national population-based cross sectional study” to the title.

Reviewer(s)' Comments to Author:

Reviewer: 2
Reviewer Name: Inmaculada Hernandez
Institution and Country: University of Pittsburgh, USA
Please state any competing interests: None declared

Please leave your comments for the authors below
The authors have done an excellent job reviewing this paper and have adequately addressed the numerous comments raised by all reviewers. I have no further comments

We thank the reviewer for this comment and also for previous questions and comments that helped improving the manuscript.

Reviewer: 3
Reviewer Name: MAURA
Institution and Country: French national health insurance (CNAMTS, Assurance Maladie)
Please state any competing interests or state: None declared

Please leave your comments for the authors below

The authors have positively answered to several of our questions regarding the first version of the manuscript and they have added a segmented regression model very helpful to assess and comments the OAC trends.
However, it still remains two major limitations still not addressed (or at least discussed) by the authors among our comments; they are related to their expertise of the French claims data, so please, again, discuss:

1) French claims data use:
1.1) concerning the quality of data used, Tuppin et al. have reported important differences between the completeness of French data according to type of scheme regarding date of data use; in particular data of RSI and MSA schemes do not include long duration disease data before 2016 and 2014, respectively.
The RSI and MSA schemes correspond to 5 and 6 % of the population, respectively, as described in Tuppin et al. Long disease duration codes have several limitation, one of which is mentioned by the reviewer. This is why we did not use ‘long duration disease’ to define atrial fibrillation in our study.
We used long duration disease to define several covariates. However, we never use long duration of disease as the only mean to define a covariate, due to the limitation of such codes. In order to create a bias, covariates would have to be different in the different schemes but the pattern of drug use (for DOAC, VKA and as well or the other drugs used to define the covariate) should also differ.

Of note, this issue was not addressed in the revised version of the manuscript as it was not asked by the reviewer in the previous version of his review.

The following paragraph has been added in the discussion section:

"We did not use long duration diseases codes to define AF as these codes have various limitation, for example their use has been shown to differ between the different insurance schemes included in the database41 and there was an important discrepancy between them and hospital discharge codes. These long duration disease codes were only used to define some covariates but only in combination with drugs delivery and/or hospital codes."

Also, restrictions apply to variables such as vital status and refined ATC coding (please see Table 2 of Tuppin P et al, Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique. 2017 Oct;65 Suppl 4:S149-S167).
We agree with the reviewer that restrictions apply to vital status. However, our study is a cross-sectional study where we are only interested in the initiation of treatment and we don't follow up patients. We don't use the "vital status" variable to define cohort entry or in any other part of the study. Cohort entry is only defined by the delivery of drugs and by Hospitalisations.
With respect to refined ATC codes, it is unclear how it would affect our study (table 2 from Tuppin et al. is not clear on this point either). Indeed, we selected drugs using the first 5 digits only of ATC codes and the select all drugs into these categories by listing all "Codes Identifiant de Presentation" (13 digit CIP codes – available in the French database); then we selected, in these lists, the drugs to include to define the different covariates. We accounted for the changes of codes that occurred over time. As stated in Tuppin et al.: "drug dispensing is recorded by means of a reliable coding system, comprising precise information not subject to recall bias: CIP code available for each product and each packaging by mean of an automated….."

However authors stated they used data from all schemes ("99% of the French population"), especially to identify comorbidities from long duration disease data (as displayed in the supplementary table).
As suggested in the initial review of our manuscript, we already corrected the 99% to 93% in the previous revised version submitted. As previously discussed (please refer to question 1.1), long duration disease codes are never used on their own, and are not used to define cohort entry.

Did the authors actually include all OAC new users from the 66 M persons living in France? If so, completeness of data was not the same for the different schemes used;
Please note that this point has already been discussed in the first round of revision. Maybe our answer was unclear and we apologize for this. We confirm that we selected all OAC new users. We used at this stage only a combination of drugs to select patients. It is not clear why the completeness of drug recording (First 5 digit of ATC and CIP codes) should be differential between the different schemes.

1.2.) % of GP as first prescriber found in this study are not in line with the data reported on the same database (around 25% versus 60% reported here, see Maura et al. 2017 Pharmacoepidemiol. and Drug safety or Maura et al, Circulation 2015) for year 2012/2013; although differential inclusion/exclusion criteria between these studies might have explained this result, this is concerning especially because the category of hospital practitioners did not appear here as first prescribers? (% hospi. pract. reported in Maura et al. around 30%). As a consequence the same applies to cardiologists specialty. Additionally, can the authors explained data at the back of the Table 1 in "Suppl. Material, sensitivity analysis, cohort 2":"among GP…among cardiologists"? Can the authors reassure on a potential flawed identification of OAC first-prescribers in the French claims data?
We agree with the reviewer that percentages reported in our study differ from those reported in two other studies using the same database. These differences are expected because of the differences in drugs studied and study populations. First, in the two studies cited by the reviewer (Maura et al.,2015

and 2017) drugs are different from those included in our study: dabigatran and rivaroxaban only in Maura, all NOACs and VKAs in our study. Second, the study populations are also very different: our study population comprised all patients with a first OAC prescription whether or not they had been hospitalised for AF whereas in the different papers by Maura et al., patients were selected if they had been hospitalised (only hospitalisation for AF in one case, AF or deep vein thrombosis in the other) or selected using a specific algorithm which, among others, comprised holter, electrocardiogramm, or private cardiologist prescriber. Therefore, the population selected in the two papers by Maura was a highly selected population including more patients hospitalised or treated by a cardiologist and the percentage of GP prescriber was low which is not surprising. In contrast, the percentage of GP prescribers is expected to be much higher in our study, based on our selection criteria. In fact, similar percentages between our study and the two studies cited by Maura would have raised questions about potential flaws in the selection process of the studies compared. To "reassure on a potential flaw", we selected a new sample (from the same data) who had a hospitalisation for AF before anticoagulant delivery. In this design, which is closer to that of Maura, in 2013, first prescription of dabigatran was done by GP in 23.3% of case for dabigatran, and in 27.15% of cases for rivaroxaban. These proportions are close to that reported by Maura et al.

2) Identification of nonvalvular atrial fibrillation:
2.1.) The authors still have not indicated how they managed patients with recent DVT/PE, another indication of DOAC therapy that may account for around 25% of incident treatment (see Billionnet et al, Pharmacoepidemiol. and Drug safety); if not, characteristics displayed in Table 2 might also reflect those of DVT/PE patients and this must be discussed;
Patients with recent DVT/PE correspond to 36445 patients i.e. 4.4% of our sample. The sample selection is different from that of Billonnet, as previously discussed (see previous point). Patients with DVT/VTE are more likely to have gone through hospitalisation.
We provide for information a table excluding these patients. Results are similar whether these patients are included or not.
We added a paragraph in the discussion section. We did not include the table in the text for space issue, but we can add it if the editor find it useful.

Table 1 excluding DVT/PE patients

Table 1 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation (2011-2015) – excluding DVT/PE patients

	VKA*			
	N = 475,651	Dabigatran		
	N = 94,094	Rivaroxaban		
	N = 164,928	Apixaban		
	N = 43,328			
Demographic characteristics				
Mean age (sd†)	75.6 (11.8)	74.1 (11.3)	73.0 (11.5)	76.2 (11.1)
Male	50.0%	52.3%	52.3%	49.6%
Clinical characteristics‡				
High blood pressure	95.2%	92.1%	92.3%	94.7%
Ischemic heart disease	28.5%	19.7%	17.3%	17.6%
Heart failure	28.2%	18.8%	15.2%	21.4%
Diabetes	23.6%	19.9%	19.7%	20.8%
Cancer	16.2%	13.9%	12.7%	11.0%
Renal failure	10.4%	2.3%	2.3%	4.1%
Liver failure	1.7%	0.7%	0.7%	0.6%
Dementia	4.9%	3.1%	2.8%	3.3%

History of ischemic stroke		9.7%	8.3%	6.0%	9.0%			
History of bleeding	0.4%	0.3%	0.2%	0.4%				
HAS-BLED score, mean (sd)		2.7 (0.9)		2.4 (0.9)		2.4 (0.9)		2.5 (0.9)
CHA2DS2- VASc2, mean (sd)		3.9 (1.5)		3.5 (1.5)		3.3 (1.4)		3.7 (1.4)
Other treatments at cohort entry§								
Aspirin	46.3%	43.3%	41.1%	43.7%				
Nonsteroidal anti-inflammatory drugs			13.7%	16.6%	16.9%	13.0%		
Antiplatelet Agents (other than Aspirin)			15.9%	12.1%	10.9%	12.3%		
Corticosteroids	13.6%	12.2%	12.6%	12.0%				
Prescriber of first anticoagulant								
General Practitioner	64.1%	50.1%	51.6%	50.3%				
Cardiologist	23.0%	39.0%	38.6%	38.0%				
Other specialist	4.6%	4.4%	4.6%	4.6%				
Unknown	8.3%	6.5%	5.2%	7.1%				

* Vitamin K agonist; † Direct oral anticoagulants; ‡ sd: standard deviation; § defined in the 12 months prior to cohort entry; ‖ defined in the 3 months prior to cohort entry

2.2.) The authors still have not properly discussed the method used to identify AF:
a) Specificity: why no utilization of previous history of AF diagnosis via ICD-10 codes diagnosis from hospital discharge or French long duration disease, at least as sensitivity analysis;
Although the suggested analysis would be of interest in another context, the objective of our study was not to restrict our study to patients with AF who were hospitalised but to study trends of DOACs initiation in a non-selected population of patients with AF. Therefore we believe that this analysis would not be relevant in our study. Moreover, some limitations of ALD codes are discussed above by the reviewer himself.

b) as a consequence relevance of their sensitivity analyses (SA) is questionable, especially in view of the differences in nature/% of first prescriber between the main analysis and SA, notably versus SA2, “patients newly treated with an anticoagulant therapy regardless of other potential concomitant therapies”; as a consequence the sentence “we can be confident that our findings are not too sensitive to the definition of AF” should be deleted and SA reported modified.

In fact, the proportion of GP prescribers is similar. The proportion of specialists is different: in SA2 other specialist increases and comprises mainly prescriptions delivered by orthopaedic surgeons and to a lesser extent, anesthesiologists. This is expected as we are not selecting only AF in SA2.
We changed the sentence to “we can be confident that our findings regarding the choice of the initial therapy and the patients’ characteristics are not too sensitive to the definition of AF”.

Other comments :
1) Still curious about authors comments on consequences of the observed channeling on the management of AF patients in France.
We thank the reviewer for this comment, however we are not too sure on what we add to what was previously discussed.
2) Discuss the difference in the observed channelling DOAC versus VKA in light of apixaban data regarding patients' age/severity (in abstract and discussion).
We believe that data on apixaban will need to be confirmed with more recent data to ensure that this is not an effect in the first year of availability. This is mentioned p12 of the manuscript.
3) Use of PPI would have been interesting to add and comment, especially because DOAC therapy was shown to increase GI bleeding versus warfarin

Although this is not the focus of our study, we added the PPI use in table 1 of the paper to answer this comment.

VERSION 3 – REVIEW

REVIEWER	MAURA CNAMTS, France
REVIEW RETURNED	21-Dec-2017

GENERAL COMMENTS	Il would like to thank very much the authors for properly answering all my comments. I have no further questions. Here are some remarks that do no need to be addressed by the authors: - I found disappointing to learn that the authors had written to the BMJ Open editors between R1 and R2 to mention that I had "an undeclared conflict of interest and [was] currently working on the same topic, using the same data". I do not consider that working on the same quite large subject on the same database can prevent me from giving the best and the most objective review. Besides, due to the fully open peer review process of BMJ Open, the authors (and BMJ Open editors) had my name/affiliations since the very beginning of this review process. Fortunately, OAC therapy is not my only topic of research and our work on OAC adherence and persistence were already published earlier this year. Finally I'm quite happy to have the chance to review this paper and that other research teams can currently work on the topic of French patterns of use of DOAC, especially based on the French healthcare data; - I found very low the percentage (4%) of DVT/PE identified and DVT patients may not be "more likely to have gone through hospitalization", PE does; - "the objective of our study was not to restrict our study to patients with AF who were hospitalized" and "First, in the two studies cited by the reviewer (Maura et al.,2015 and 2017) drugs are different from those included in our study: dabigatran and rivaroxaban only in Maura, all NOACs and VKAs in our study. Second, the study populations are also very different: our study population comprised all patients with a first OAC prescription whether or not they had been hospitalised for AF whereas in the different papers by Maura et al., patients were selected if they had been hospitalised (only hospitalisation for AF in one case, AF or deep vein thrombosis in the other) or selected using a specific algorithm which, among others, comprised holter, electrocardiogramm, or private cardiologist prescriber" * First, in Maura et al, 2015 we also have included VKA patients; in your study dabigatran and rivaroxaban patients account for around 264,000 patients versus only nearly 43,700 apixaban patients. * Second, I agree with you on the differences between our cohorts. However, our objective was not to restrict our studies to patients with hospitalized AF either. It was to identify AF patients with the highest specificity, hospitalization or not. That's why we use both LTD diagnoses (allowing identify FA from the ambulatory setting) and our algorithm (also including some covariates you used to identify AF patients in your study such as delivery of antiarrhythmic agent or a rate control treatment), to identify AF patients in the group of

	patients with NO hospitalization for AF or for DVT/PE or for orthopedic procedures. Of course, the non-hospitalized, LTD AF patients identified this way were then added to the hospitalized AF patients in our final cohorts. That's why, as a sensitivity analysis, of this type of paper untitled "Trends in initiation of direct oral anticoagulant therapies FOR ATRIAL FIBRILLATION in a national population-based cross-sectional study", it might have been relevant to describe it as an alternative exists. I agree that due to the limitations of including all French schemes, you were not able to perform such analyses.