PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Warfarin treatment among Finnish patients with atrial fibrillation: retrospective registry study based on primary health care data
AUTHORS	Hallinen, Taru; Soini, Erkki; Asseburg, Christian; Kuosmanen, Pekka; Laakkonen, Ari

VERSION 1 - REVIEW

REVIEWER	Dr Chris Arden GPSI Cardiology Southampton United Kingdom
REVIEW RETURNED	13-Oct-2013

GENERAL COMMENTS	I have not performed a detailed statistical analysis on the article, this may be worth considering?

- Reviewer 1 provided a marked PDF copy of the manuscript with comments. This is available upon request to the Publisher.

REVIEWER	Arlene Gallagher Clinical Practice Research Datalink (CPRD), UK
REVIEW RETURNED	22-Oct-2013

GENERAL COMMENTS	This paper is generally well written and clear. The limitations about generalisability have been addressed. Further comments: 1. The study population consists of patients diagnosed with AF, assessing the frequency of warfarin use. 53.7% were not treated with warfarin at all. This should be discussed. 2. There is no information on how long the patients had AF. Might there be differences in the TTR for those recently diagnosed? 3. Were any patients excluded from the analyses? Patients with a history of certain conditions (e.g. intracranial bleed) may be treated differently. 4. The average age was 74, but what were the minima and maxima? Were some very young or very old patients included? 5. Only 474 of the 1271 patients were identified as continuously using warfarin. More discussion is needed about this. 6. The target range is for chronic AF, but the description of the cohort only mentions AF in general. Can the authors be sure they were chronic AF patients? If not, how does this affect the results/conclusions? 7. What does figure 1 add to the story? Since we do not know the duration of AF or the range of ages, there may be other causes that

	explain why more patients had died in the subgroups with poorer treatment balance. What can be said about the no warfarin group with regard to this? 8. Figure 2 would benefit from including the numbers of patients involved. Are all 1271 patients included in each bar? 9. Are two measurements enough to calculate TTR well? Would the results differ markedly if the minimum requirement was three? 10. The authors conclude that this population mimic those in recent clinical trials. This is interesting as other papers have shown population based studies to differ from clinical trial results (e.g. Gallagher et al, Journal of Thrombosis and Haemostasis 2008). More discussion is needed about this. 11. There is no mention of scientific or ethical approval.

REVIEWER	Amelia Adcock West Virginia University USA
REVIEW RETURNED	28-Oct-2013

GENERAL COMMENTS	Important data; meaningful date. Largest disadvantage is the absence of any comment/estimation on cost of break-through strokes/systemic embolism in a)pts on warfarin/novel anti-coags and (perhaps more importantly) b) Pts NOT on anticoagulation, especially if the conclusion is that warfarin pts are associated with higher out pt costs in general as compared to non-warfarin users. The cost of thrombolembolism should at least be addressed, if possible (even imperfectly through admission diagnosis codes). Also I don't understand if any cost of an in-patient stay was included or not I think they were thrown out (along with nursing visit home cost) because of difficulties deciphering why they were hospitalized, etc but I would suggest clarification and addressing more explicitly in discussion. Would expand on the fact that overall, pts with acceptable INR more than 70% of the time only applies to roughly half of the patients i.e. as many other studies have shown, only 50 % of patients utilizing warfarin enjoy reasonable protection from thrombolism. Factors alluded to in this more protected population were in this study (in line with previous studies) were those with more frequent INR checking but this was also the same population who used more out patient financial resources (probably because they had tighter INR control). Would like to see authors discuss why they think this is and here again, comment on the fact that if the high TTR's have less clinical events, their increased out patient resource use is negated (if that is true)

REVIEWER	Milka Hauta-aho Department of Pharmacology, Drug Development, and Therapeutics, University of Turku, Finland
REVIEW RETURNED	29-Oct-2013

GENERAL COMMENTS	1. The study objectives in the abstract are different from the objectives listed in the article summary (article focus) and in

	the introduction chapter. It is not explicit what the research questions are and, most likely because of this, the rest of the manuscript is lacking coherence. 2. See the comment 1 concerning about the study objective. The study design should be clearly stated (e.g. cohort/ cross-sectional study etc). “Registry study” states the data source, not the design. I don’t think it is necessary to mention statistical analysis method in the methods section of the abstract. The conclusion section could put the results and the significance of them in the greater context. 3. See the comments 1 and 2 about the study questions and the design. It is unclear what questions are to be answered and what was meant to be the study design. For investigating the one-year period prevalence of warfarin use in AF patients, the most appropriate design would be cross sectional study. Cohort study would be appropriate design for investigating the quality of warfarin use in AF patients and the use of health care resources in primary care. Considering this study as a cohort study, there are numerous problems with the design. Firstly, two different cohort entry criteria have been applied, which may have caused combining two different populations. Secondly, warfarin exposure was defined only for continuous warfarin users (using INR measurement as a proxy for warfarin therapy), which may result in including INR measurements from the time when warfarin was not used in the analysis biasing the results (there are other indications for measuring INR than monitorin warfarin therapy though these are less common). Therefore, the fixed follow-up time should not have been used either. Thirdly, even though most patients had numerous INR measurements during the study period, the minimum number of INR measurements for calculating TTR was two over the study period. No clinician would estimate the quality of warfarin therapy based on two measurements. Fourthly and also clinically thinking, this study population should have been categorized in initiators of warfarin therapy and long-term warfarin users, and these groups should have been analyzed separately. Patients with heart valve replacement cannot be considered as typical AF patients and therefore, they should have been excluded from the analysis. Having all these different patient groups in TTR analysis must have skewed the results. Also, the rationale of examining the mortality after the end of the study period is not reported. Another concern is the cost analysis. Can comparing warfarin users with non-users without the reason for the health care service use bring any reliable knowledge on the costs associated with AF treatment, especially when it was clear that warfarin users had more comorbidities than non-users? What is the rationale comparing warfarin users and non-users without matching? The applicability of these results is questionable. 4. Why the INR measurement practice is explained? Is there any validation studies made on the use of patient administration system data for research purposes? Mediatri

	is the name of the software used in some primary health care centers, not the name of the database (compare GPRD in UK for instance). The time of or the method for collecting information on comorbidities is not described. 5. There is no mention whether data use was accepted by local authorities or the deidentification of the data prior to hand-over to the researchers as the law in Finland provides in case the data can be handled without personal identification codes. 10. There are results without a corresponding study question or a mention in the methods section reported in the results section, for instance, the use of other antithrombotic medication after the end of the study period. Also, the data on INR measurements (p. 19, lines 3-25) would be more readable if it was presented in a table. 15. I would highly recommend checking by a professional. There are many expressions that can be recognized as literal translations from Finnish to English and which just don't read well. This is a study investigating the use of warfarin in AF patients, the quality of warfarin therapy and the outpatient health care costs of AF patients. The topic is important as warfarin is widely used oral anticoagulant and recently new anticoagulants have been introduced on the market as alternatives for warfarin. Thus, there is a need for examining the quality and costs of warfarin therapy. This knowledge is essential when comparing different drug therapies. However, I have major concerns mostly about the research questions and the study design. That is why I find it difficult to rely on the validity of the results and cannot recommend the manuscript " Warfarin treatment among Finnish patients with atrial fibrillation: retrospective registry study based on primary health care data" for publication.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Dr Chris Arden
Institution and Country GPSI Cardiology
Southampton
United Kingdom
Please state any competing interests or state 'None declared': None declared.

Please find attached original article with a few highlighted comments.

I have not performed a detailed statistical analysis on the article, this may be worth considering?

We wish to thank the reviewer for helpful comments. We have incorporated suggested changes into the manuscript.

To be more specific, we explained
• the term "continuous warfarin use" earlier in the text
• mention of the coverage of the database. Due to the mostly publicly funded health care system in Finland, the database should include all patients who have been diagnosed with AF.
• why the population consisted of almost equal numbers of men and women although the prevalence

of AF is higher among men (i.e. the gender distribution among aged Finnish population is skewed: more than 60% of elderly inhabitants in the municipality are women)
• that we do not know the reason why some individually defined INR-target ranges deviate from those recommended for patients with chronic AF or mechanical heart valves but assume these to be related to individual tailoring of warfarin treatment (e.g. perhaps the patients are known to develop adverse events already at INR-ranges considered normal)
• Conclusion and discussion section was expanded.

Reviewer Name Arlene Gallagher
Institution and Country Clinical Practice Research Datalink (CPRD), UK
Please state any competing interests or state 'None declared': None Declared

This paper is generally well written and clear. The limitations about generalisability have been addressed.

Thank you!

Further comments:
1. The study population consists of patients diagnosed with AF, assessing the frequency of warfarin use. 53.7% were not treated with warfarin at all. This should be discussed.

We have now commented on this in the discussion section.

2. There is no information on how long the patients had AF. Might there be differences in the TTR for those recently diagnosed?

Unfortunately we did not have diagnosis dates and therefore could not assess this.

3. Were any patients excluded from the analyses? Patients with a history of certain conditions (e.g. intracranial bleed) may be treated differently.

No, we did not exclude any patients. We wanted to presents average results for the whole AF cohort.

4. The average age was 74, but what were the minima and maxima? Were some very young or very old patients included?
The minimum age was 3 and maximum age was 111. This may suggest that all deaths have not been updated into the database. To see whether these potential outliers would have impact on the results we reanalyzed TTR and total costs for a patient cohort excluding patients younger than 50 years and older than 100 years. The results varied only a little and therefore no changes we made to the manuscript.

5. Only 474 of the 1271 patients were identified as continuously using warfarin. More discussion is needed about this.

We have now commented on this in the discussion section.

6. The target range is for chronic AF, but the description of the cohort only mentions AF in general. Can the authors be sure they were chronic AF patients? If not, how does this affect the results/conclusions?

No, unfortunately we cannot ascertain that the patients had chronic AF. However, Finnish treatment guidelines recommend oral anticoagulation for all AF patients provided that their CHA2DS2-VASc≥1 and from that perspective the results or conclusions should not change even though we cannot classify the patients according to their AF type.

7. What does figure 1 add to the story? Since we do not know the duration of AF or the range of ages, there may be other causes that explain why more patients had died in the subgroups with poorer treatment balance. What can be said about the no warfarin group with regard to this?

We agree. The reason for including the figure was simply the fact that we found the observation of higher mortality among patients with lower TTR interesting. We do not know whether the deteriorating condition of patients prior to their death leads to lower TTR or whether the lower TTR increases mortality. This would be an interesting subject for further study. We have added this comment into discussion section.

8. Figure 2 would benefit from including the numbers of patients involved. Are all 1271 patients included in each bar?

Patient numbers were added to figure 2.

9. Are two measurements enough to calculate TTR well? Would the results differ markedly if the minimum requirement was three?

We agree that two measurements may not be enough to calculate TTR well. This definition was applied as the “minimum” approach so as to include the maximum number of patients in the estimation. Due to the potential problems in this definition, we performed similar assessment for patients using warfarin regularly during one year period. With this definition the TTRs were approximately 8-9% higher. We assume that the TTR with minimum of three measurements would be somewhere in between the TTRs obtained with minimum of two measurements and regular warfarin use for one year period. We have now clarified these issues in the discussion section.

10. The authors conclude that this population mimic those in recent clinical trials. This is interesting as other papers have shown population based studies to differ from clinical trial results (e.g. Gallagher et al, Journal of Thrombosis and Haemostasis 2008). More discussion is needed about this.

We have not performed a literature review regarding other real-life studies on warfarin use and therefore cannot assess whether our results differ from other studies. It seems, however, that the study by Gallagher et al. included only patients with chronic AF whereas our study included all patients with atrial fibrillation which may explain the differences. We have not expanded this in the discussion because we felt that it would be outside the scope of our manuscript.

11. There is no mention of scientific or ethical approval.

According to Finnish laws ethical committee approval or informed consent was not required because we did not contact patients and only anonymized data was used in the analyses. This has now been explained in the methods section.

Reviewer Name Amelia Adcock
Institution and Country West Virginia University
USA

Please state any competing interests or state ‘None declared’: None

Comments:

Important data; meaningful date.

Thank you!

Largest disadvantage is the absence of any comment/estimation on cost of break-through strokes/systemic embolism in a)pts on warfarin/novel anti-coags and (perhaps more importantly) b) Pts NOT on anticoagulation, especially if the conclusion is that warfarin pts are associated with higher out pt costs in general as compared to non-warfarin users. The cost of thrombolembolism should at least be addressed, if possible (even imperfectly through admission diagnosis codes).

It is true that our manuscript lacks the costs associated with stroke/systemic embolism events. The objective of our study was not to assess the effectiveness of warfarin in the prevention of these outcomes but rather to assess the quality of care (using % time spent in target INR-range) and roughly estimate how much primary health care resources are used in warfarin monitoring. All costs associated with specialized health care (e.g. stroke/systemic embolism and severe bleeding events) were excluded from the assessment and data regarding these events were not even collected (since this would have required registry data from another service provider). However, we acknowledge that this would be a meaningful and important question for further research.

Also I don't understand if any cost of an in-patient stay was included or not I think they were thrown out (along with nursing visit home cost) because of difficulties deciphering why they were hospitalized, etc but I would suggest clarification and addressing more explicitly in discussion.

Yes, we excluded primary health care inpatient stays and nurse visits from the cost assessment. This was done because these resources would only in rare occasions be expected to be directly related to warfarin use, and we did not have access to the number of nurse home visits. The primary health care hospitals typically provide long-term treatment for such elderly patients who cannot be managed in less intensive care settings. Also home nursing services are seldom needed solely due to warfarin INR-monitoring. We sought to control for the use of these services by including the number of inpatient days and the use of home services (yes / no) in the regression models. The use of these services might lower the use of other analyzed outpatient services. These aspects are now clarified in the manuscript.

Would expand on the fact that overall, pts with acceptable INR more than 70% of the time only applies to roughly half of the patients i.e. as many other studies have shown, only 50 % of patients utilizing warfarin enjoy reasonable protection from thrombolism. Factors alluded to in this more protected population were in this study (in line with previous studies) were those with more frequent INR checking but this was also the same population who used more out patient financial resources (probably because they had tighter INR control). Would like to see authors discuss why they think this is and here again, comment on the fact that if the high TTR's have less clinical events, their increased out patient resource use is negated (if that is true)

We have now commented on this in the discussion section.

Thank you

Reviewer Name Milka Hauta-aho
Institution and Country Department of Pharmacology, Drug Development, and Therapeutics, University of Turku, Finland
Please state any competing interests or state 'None declared': None declared.

1. The study objectives in the abstract are different from the objectives listed in the article summary (article focus) and in the introduction chapter. It is not explicit what the research questions are and, most likely because of this, the rest of the manuscript is lacking coherence.

It is true that the wording in abstract, article summary and introduction differ. The main reason for this is the word limitation for the abstract i.e. 250 words. Since the reader is likely to read the 'article focus' first to see whether the article is of interest, we have elaborated the objectives in more detail there. However, we do not feel that the stated objectives are "different" in the sense that it would make the manuscript incoherent. We can remove extra words in the 'article focus' and 'introduction' to make the wording match that in the abstract, but in our opinion that would not improve the manuscript.

2. See the comment 1 concerning about the study objective. The study design should be clearly stated (e.g. cohort/ cross-sectional study etc). "Registry study" states the data source, not the design. I don't think it is necessary to mention statistical analysis method in the methods section of the abstract. The conclusion section could put the results and the significance of them in the greater context.

Our study is a real-life study utilizing institutional data. The study could be categorized as a cohort study (i.e., a cohort of people with AF in Joensuu area within a defined period) for which health care resource use and INR measurements for warfarin users was followed over one year time period. However, the term "registry study" has been widely used to describe this type of study and we consider this to be more informative than the term "cohort study".

We disagree with the suggestion to remove the statistical analysis method from the methods section. By stating the method we inform the reader in a short and concise way that we acknowledge that there are differences in patient characteristics between warfarin users and non-users and that we analyzed the impact of these differences on costs. (See comment 3 below regarding non-matched warfarin users and non-users)

3. See the comments 1 and 2 about the study questions and the design. It is unclear what questions are to be answered and what was meant to be the study design. For investigating the one-year period prevalence of warfarin use in AF patients, the most appropriate design would be cross sectional study. Cohort study would be appropriate design for investigating the quality of warfarin use in AF patients and the use of health care resources in primary care.

Please see the above response. The key objective of the study was not to estimate one-year period prevalence of warfarin use in AF-patients (neither the abstract, 'article focus' or introduction states this as the objective, so we do not really understand this comment). We state the frequency of warfarin use i.e. what proportion of all patients used warfarin (continuously or with interruptions) according to our data during the one year period. If we are not mistaken, cross-sectional study would evaluate warfarin use prevalence only at one single time point (i.e. not during one year). With this definition, the warfarin use prevalence in the studied municipality would have been 51.8% in June 2012. When warfarin use frequency was defined based on analyzable TTR during one year, the proportion dropped to 46.3% as described in the manuscript.

Considering this study as a cohort study, there are numerous problems with the design. Firstly, two different cohort entry criteria have been applied, which may have caused combining two different populations.

We do not understand what is meant by “two different cohort entry criteria” here. Our patient sample consisted of all AF patients in the municipality and the only entry criterion was the diagnosis of AF in the database. We also analyzed subgroups of the AF cohort defined with specific criteria (e.g. for TTR: no warfarin, warfarin, continuous warfarin use).

Secondly, warfarin exposure was defined only for continuous warfarin users (using INR measurement as a proxy for warfarin therapy), which may result in including INR measurements from the time when warfarin was not used in the analysis biasing the results (there are other indications for measuring INR than monitorin warfarin therapy though these are less common). Therefore, the fixed follow-up time should not have been used either.

This comment is a bit unclear. Warfarin exposure was defined using different methods in the study. What concerns the group with continuous warfarin use, the allowed maximum gap in INR-tests was 8 weeks. This means that any problems related to including INR measurements from time when warfarin was not used, would have occurred at maximum 8 weeks prior to true warfarin treatment initiation. We think that this is unlikely to impact the results in any way. On the other hand, patients with individually defined target ranges in our patient cohort were using warfarin with certainty as these target ranges were taken from “warfarin sheet” of the patient records. The fixed follow-up time was used for practical reasons, i.e. this assessment is based on real-life patient registry with no fixed end-dates and there is simply no other choice than to constrain the analysis time period somehow. For practical reasons, we wanted to have full view of the AF cohort during a calendar year.

Thirdly, even though most patients had numerous INR measurements during the study period, the minimum number of INR measurements for calculating TTR was two over the study period. No clinician would estimate the quality of warfarin therapy based on two measurements.

As has been reported in the manuscript, time in target INR range has been estimated with various methods. Time in target INR range can be estimated when at least two successive INR test results exist and therefore this was chosen as the “minimum” approach so as to include the maximum number of patients in the estimation. As pointed by the reviewer this approach may not be clinically relevant and therefore similar assessment has been performed for patients using warfarin regularly during the observation period (i.e. continuous use based on clinical rationale, clinical guidelines and Current Care Criteria). This change resulted in improving TTR-estimates, yet significantly smaller number of patients actually considered to receive warfarin treatment.

Fourthly and also clinically thinking, this study population should have been categorized in initiators of warfarin therapy and long-term warfarin users, and these groups should have been analyzed separately. Patients with heart valve replacement cannot be considered as typical AF patients and therefore, they should have been excluded from the analysis. Having all these different patient groups in TTR analysis must have skewed the results.

We did not see any reason to exclude patients with heart valves since they had AF, we had individually defined target INR-ranges in our database and therefore we were able to assess TTR based on INR-targets for this specific group. The reviewer makes a strong statement in claiming that our results are skewed especially considering the fact that our results are in line with other published estimates in this patient population. If we would have excluded patients with AF diagnosis, we would not have all patients in our cohort (i.e. a complete population). Furthermore, our TTR-subgroups in specific analyses were mutually exclusive.

Too see whether treatment initiation would have a large impact on the results we analyzed TTR among patients without INR measurements during three months prior to start of the follow-up period (supposedly warfarin initiators) and the obtained TTR values differed only slightly (~1%) from the TTRs reported in the manuscript or TTRs for patients with INR measurements three months prior to follow-up period.

Also, the rationale of examining the mortality after the end of the study period is not reported.

The mortality after the end of study period was presented in the manuscript simply because we found the observation of higher mortality among patients with lower TTR interesting. Our data does not enable the assessment of causal relationships regarding TTR and probability of death but this would be an interesting question for further study. This has now been added to the discussion section.

Another concern is the cost analysis. Can comparing warfarin users with non-users without the reason for the health care service use bring any reliable knowledge on the costs associated with AF treatment, especially when it was clear that warfarin users had more comorbidities than non-users? What is the rationale comparing warfarin users and non-users without matching? The applicability of these results is questionable.

Precisely because of these reasons we used the generalized linear regression model to compare the costs between warfarin users and non-users. The performed regression analysis seeks to control for the differences in the explanatory variables (i.e. patient characteristics) included in the model. However, the regression analysis cannot control for the potential differences in the severity of comorbid illnesses (no matter the chosen method, we cannot control for this, because we lack the needed information) or unknown confounders. This has been stated as a limitation in the discussion section.

4. Why the INR measurement practice is explained? Is there any validation studies made on the use of patient administration system data for research purposes? Mediatri is the name of the software used in some primary health care centers, not the name of the database (compare GPRD in UK for instance). The time of or the method for collecting information on comorbidities is not described.

It is our understanding that INR-monitoring practices vary in different countries (and even in different Finnish municipalities) and therefore, in our opinion, it is only appropriate to give some background information for the readers. To our knowledge there are no validation studies regarding patient administration system data for research purposes for Finnish primary health care registries. Despite potential limitations in patient databases, e.g. Finnish local or national secondary health care databases are widely used for research purposes although they in many cases ignore primary health care and have similar issues regarding the follow-up time, comorbidities, etc. The comorbidity information was collected from the database using ICD-10 codes.

Mediatri is a product of Mediconsult Oy. Mediconsult uses terms “Mediatri patient information system” and Finnish equivalent of “Mediatri database” (in Finnish “Mediatri-tietokanta”) in their internet pages. We added the first term into the manuscript.

5. There is no mention whether data use was accepted by local authorities or the deidentification of the data prior to hand-over to the researchers as the law in Finland provides in case the data can be handled without personal identification codes.

Explanation has now been added in the methods section. The patients were not contacted and

anonymous patient data has been used in the statistical assessments and therefore no ethical approval or informed patient consent was required.

10. There are results without a corresponding study question or a mention in the methods section reported in the results section, for instance, the use of other antithrombotic medication after the end of the study period. Also, the data on INR measurements (p. 19, lines 3-25) would be more readable if it was presented in a table.

Yes, that is true. These data were not our research questions but we preferred to give an overall description of the patients and used anticoagulants. These results can be removed, if necessary.

15. I would highly recommend checking by a professional. There are many expressions that can be recognized as literal translations from Finnish to English and which just don't read well.

The manuscript has already been proofread by a native English speaker prior to submission to BMJ Open. It would be beneficial to pinpoint the expressions that are considered problematic if any changes are needed.

The changes to the manuscript on the basis of reviewer comments were not proofread (but can be if necessary).

This is a study investigating the use of warfarin in AF patients, the quality of warfarin therapy and the outpatient health care costs of AF patients. The topic is important as warfarin is widely used oral anticoagulant and recently new anticoagulants have been introduced on the market as alternatives for warfarin. Thus, there is a need for examining the quality and costs of warfarin therapy. This knowledge is essential when comparing different drug therapies. However, I have major concerns mostly about the research questions and the study design. That is why I find it difficult to rely on the validity of the results and cannot recommend the manuscript " Warfarin treatment among Finnish patients with atrial fibrillation: retrospective registry study based on primary health care data" for publication.

VERSION 2 – REVIEW

REVIEWER	Arlene Gallagher Clinical Practice Research Datalink (CPRD), UK
REVIEW RETURNED	31-Dec-2013

GENERAL COMMENTS	The authors have satisfactorily addressed all of my original comments. Additional comments, based on the new additions to the manuscript: 1. Page 11. Why would warfarin prescribing not be a primary reason for primary care visits in Finland? We expect this could happen in the UK. 2. The authors have added a statement about ethical approval, but have not stated if there is a generic approval in Finland for the use of anonymous patient data, and if so, what it is called. 3. The information on warfarin is based upon prescribing data. As with many databases of this kind, a limitation should be added about prescribing versus dispensing versus confirmed use. 4. In the discussion, page 22, the authors should avoid starting a sentence with the word 'because'. 5. A relatively small proportion of the patients used warfarin for the entire follow-up period. It would be interesting to know whether there

	was any other healthcare setting in which they may have received a prescription, e.g. hospital.

REVIEWER	Amelia Adcock West Virginia university United States
REVIEW RETURNED	02-Jan-2014

GENERAL COMMENTS	Bottom line = warfarin use among studied population of Af is associated with higher cost as compared to non-users. I still think this statement fails to take into account the potential cost savings among users by preventing costly hospitalization and or increased morbidity with prevention of strokes. I know you compared the outpatient costs of both groups and given the electronic review only it was not possible to follow patients and assess for cardioembolic strokes in untreated vs warfarin users. However, such analyses exist at least generically, and would be an interesting and very relevant in the real world sense comparison when considering true costs of warfarin vs no anticoag especially when you consider the less than ideal percent of warfarin users among the afib patients in your cohort

VERSION 2 – AUTHOR RESPONSE

Reviewer Name Arlene Gallagher
Institution and Country Clinical Practice Research Datalink (CPRD), UK
Please state any competing interests or state 'None declared': None Declared

The authors have satisfactorily addressed all of my original comments.

Additional comments, based on the new additions to the manuscript:

1. Page 11. Why would warfarin prescribing not be a primary reason for primary care visits in Finland? We expect this could happen in the UK.

Answer: We meant to state that warfarin treatment is not expected to be the primary reason why patients need institutional care or home nursing services. This has now been clarified.

2. The authors have added a statement about ethical approval, but have not stated if there is a generic approval in Finland for the use of anonymous patient data, and if so, what it is called.

Answer: The use of anonymous patient registry data is allowed in Finland but it doesn't have a particular name. The Finnish law defines circumstances in which ethical approval and patient consent is required (and anonymous patient registry data does not fulfill those criteria).

3. The information on warfarin is based upon prescribing data. As with many databases of this kind, a limitation should be added about prescribing versus dispensing versus confirmed use.

Answer: This has been added in the discussion section.

4. In the discussion, page 22, the authors should avoid starting a sentence with the word 'because'.

Answer: We are not sure if we were able to locate this sentence but one 'because' was changed.

5. A relatively small proportion of the patients used warfarin for the entire follow-up period. It would be interesting to know whether there was any other healthcare setting in which they may have received a prescription, e.g. hospital.

Answer: It is possible that warfarin use is initiated in a hospital setting. Here we assessed warfarin use based on INR-testing and therefore the place of prescription would not be expected to impact the results.

Reviewer Name Amelia adcock
Institution and Country West Virginia university
United States
Please state any competing interests or state 'None declared': None declared

Bottom line = warfarin use among studied population of Af is associated with higher cost as compared to non-users. I still think this statement fails to take into account the potential cost savings among users by preventing costly hospitalization and or increased morbidity with prevention of strokes. I know you compared the outpatient costs of both groups and given the electronic review only it was not possible to follow patients and assess for cardioembolic strokes in untreated vs warfarin users. However, such analyses exist at least generically, and would be an interesting and very relevant in the real world sense comparison when considering true costs of warfarin vs no anticoag especially when you consider the less than ideal percent of warfarin users among the afib patients in your cohort

Answer: We agree that reduced risk of stroke and other complications would impact costs in secondary health care. However, this was outside the scope of this study and therefore we cannot draw any valid conclusions about the potential cost-savings related to these complications. We added a sentence to emphasize the exclusion of these costs in our study.