To:

Editorial Office

BMJ

BMJ.2017.041508 Ischaemic stroke, haemorrhage and mortality in elderly patients with chronic kidney disease newly started on anticoagulation for atrial fibrillation: a population-based study from UK primary care

Dear Dr Röggla,

Thank you very much for considering our article and giving us the opportunity to submit a revised manuscript. We would also like to thank the reviewers and the manuscript committee for their highly constructive and insightful feedback. We have attempted to address all the points raised by the reviewers and the committee below. For your convenience, we have provided an annotated version highlighting changes requested in red as well as a clean copy of the revised manuscript.

We are also providing this letter, which incorporates a copy of the reviewers' comments with our point-by-point responses.

Reviewer 1:

Within the overall-cohort, only 35% of pts with new AF were anticoagulated. It would be of interest and importance to learn more about reasons for this notable low number.

We thank the reviewer for highlighting this important point. The rate of anticoagulation in this little-studied cohort of patients varies greatly in the literature. While our figure of 35% may indeed seem surprising to some, across the medical specialities nephrologists, cardiologists and general practitioners have *no* clear guidance about what is best for their patients in this clinical setting, especially when considering CKD patients who do not require renal replacement therapy. Broadly speaking, it is harder to keep patients with CKD in the therapeutic range using warfarin (Szummer K, Gasparini A, Eliasson S, Ärnlöv J, Qureshi AR, Bárány P, Evans M, Friberg L, Carrero JJ. Time in Therapeutic Range and Outcomes After Warfarin Initiation in Newly Diagnosed Atrial Fibrillation Patients With Renal Dysfunction. J Am Heart Assoc. 2017 Mar 1;6(3). pii: e004925.), and the benefits of doing so are very hard to define, while the potential harm is significant (Burlacu A, Genovesi S, Ortiz A, Kanbay M, Rossignol P, Banach M, Malyszko J, Goldsmith D, Covic A. The quest for equilibrium: exploring the thin red line between bleeding and ischaemic risks in the management of acute coronary syndromes in chronic kidney disease patients. Nephrol Dial

Transplant. 2017 Mar 27). Thus, any new evidence to help understand this confused and perplexing clinical dilemma is needed urgently, and nothing more so than a properly conducted randomised clinical trial.

Our anti-coagulation rate is in fact higher than in a paper published earlier this year in Kidney International (Keskar V, McArthur E, Wald R, et al. The association of anticoagulation, ischemic stroke, and hemorrhage in elderly adults with chronic kidney disease and atrial fibrillation. *Kidney international* 2017;91(4):928-36) of 23%, though somewhat lower than Jun et al (Jun M, James MT, Ma Z, et al. Warfarin Initiation, Atrial Fibrillation, and Kidney Function: Comparative Effectiveness and Safety of Warfarin in Older Adults With Newly Diagnosed Atrial Fibrillation. *American journal of kidney diseases* 2017;69(6):734-43.) in which the rate was 45%. To this end, we have included a line in the discussion which highlights our anticoagulation rate of 35%, comparing it to the published literature:

In our cohort, 35% were in receipt of an anticoagulant prescription though there is variation from 23%-45% in the published literature.[21 30 31]

Additionally, separate analyses on gastrointestinal and cerebral hemorrhages should be provided to enable better interpretation of results.

We thank the reviewer for making this suggestion. Our study lacks the statistical power to undertake analyses of gastrointestinal and cerebral bleeds separately. Nevertheless, we were able to demonstrate the expected finding of an association between major gastrointestinal and cerebral bleeding with anticoagulation. A large, multi-centre, randomised controlled trial may be better powered to further analyse this association by type of bleed. We have added a line in the limitations paragraph of our discussion acknowledging this:

Our study lacked the statistical power to undertake sub-analyses for gastrointestinal and cerebral bleeds separately.

What was the reason to define exposure to anticoagulation within 60 days? This time period appears quite wide to me and it could be speculated, that events occurred before starting anticoagulation, hence influencing results.

We thank the reviewer for asking us to clarify this important point. We considered this point at length and consulted previous literature before choosing to define exposure to anticoagulation within 60 days of diagnosis. In our experience of working with the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database, a two-month window allows for capture of most prescribing made at the time of diagnosis: With this definition, we were able to detect prescriptions that occurred from

primary care following prescriptions issued from hospital. Using a shorter cut-off, of say 30 days, would have been too restrictive as many patients may receive their first month's prescription of an anticoagulant from the hospital and we would have missed the repeat prescriptions issued in primary care.

We have added the following justification in the manuscript:

Almost all anticoagulant prescriptions in the UK are issued from primary care and are therefore captured in the RCGP RSC database. The exception to this is where the anticoagulant is initiated during a hospital attendance. We selected the 60-day period to allow for the transfer of anticoagulant prescribing to primary care where it had been initiated in secondary care.

Including also pts who received heparin compounds is not helpful in my point of view and these patients should be deleted; in particular, also because no information on the degree of therapy/medication is provided (i.e.: full dose for anticoagulation or low dose regimes?).

We agree entirely that including heparin-based compounds would be inappropriate if low-dose regimens were included. However, we ensured that we only considered patients in receipt of a prescription for heparin who were on full dose regimens for anticoagulation and we therefore feel that these patients should remain in the study. Moreover, full dose long-term heparin is used in CKD. We have clarified this in the methods section:

Anticoagulants included vitamin K antagonists, direct oral anticoagulants and heparin-based compounds (full dose for anticoagulation).

While TIA is often falsely diagnosed, I would recommend to include only definite ischemic stroke as an endpoint. Moreover, more information on the definition and procedure to diagnose the chosen endpoints has to be provided and information on the severity of these event would be desirable.

We thank the reviewer for this recommendation and request for further clarification.

In the UK, patients can only be registered with a single primary care provider / General Practice and records of all secondary care events are sent to the patient's general practitioner. Diagnoses are coded into the primary care record so the UK primary care records provide a robust list of a patient's diagnoses both made in both primary and secondary care.

We opted to use both ischaemic stroke and TIA as outcomes as these are both very relevant in this clinical setting, both reported on in previous studies. Moreover, there is the potential for overlap in the recording of these diagnoses in Read clinical coding so using both is most representative of thromboembolic events. Notably, in UK primary care, the correct coding of transient ischaemic attack is financially incentivised, improving the robustness of recording.

The chosen endpoints were identified from a comprehensive list of established Read codes (reference 43), which was inclusive for ischaemic stroke and TIA.

The clinical descriptors in this study, which was based in primary care (to achieve large numbers) were all coded in a standardised and consistent fashion. As such, there is no access to patient-level information such as severity. This is a limitation of the previous studies in this setting, too, providing a further need for an RCT. We have acknowledged this limitation in the discussion:

Severity of stroke is not readily available from the primary care record and so this could not be assessed.

What was the definition for cerebral hemorrhage? Is it about intracranial or intracererbral hematomas? Were traumatic bleeds included? Were subdural/subarachnoid hemorrhages included or were only intraparenchymal hematomas included?

We used previously published Read codes (reference 43) to identify the endpoints of intracranial haemorrhage, including both intra-axial and extra-axial (extradural, subdural and subarachnoid haemorrhage) events. Bleeds specifically coded as traumatic bleeds were not included. Indeed, we have adopted the same approach as previous studies have in this setting so meaningful comparisons can be made.

Figure 1 can perhaps be deleted and relevant information can be included into the text.

We thank for the reviewer for asking us to reconsider the inclusion of figure 1. We have reflected on this and feel that the flow diagram aids the reader in understanding how we arrived at our study cohort. As pointed out by the manuscript committee, it is important to outline how our study cohort was derived from the initial 2.73 million patients. Nevertheless, we are open to editorial guidance on the suitability of the figure for publication and will reassess our position if there is a strong preference from the editorial team.

It would be of interest to present results also for the different substances used.

We agree with the reviewer that it would have been very interesting to undertake separate analyses considering vitamin K antagonists and direct oral anticoagulants separately. However, our study lacks the statistical power to perform these analyses, given the relatively few patients on direct oral anticoagulants. In the intervening time between submission of this article and receiving the first decision from the BMJ, a very interesting systematic review has investigated this very issue (Kimachi M, Furukawa TA, Kimachi K et al. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD011373. DOI: 10.1002/14651858.CD011373.pub2) Randomised controlled trials are undoubtedly needed in this area and they can be designed to further investigate the differences in using warfarin and direct oral anticoagulants.

We have added this reference and expanded upon this in our discussion:

Lastly, despite our large cohort, the proportion of patients receiving direct oral anticoagulants was small and so a comparison with vitamin K antagonists could not be undertaken. Future RCTs will provide clarity on this little-studied management conundrum.[67]

According to your data (table 1), 60% (!) of OAC patients received additional antiplatelets. This appears unexpectedly high to me. Moreover, Aspirin is stated as an extra variable in table 1 which confuses me.

Using the recent review, based on the 2016 European Society of Cardiology (and other) guidelines for anti-coagulation in a variety of cardiological settings, it is clear that there is a dearth of quality evidence about the nature, type, duration and other aspects of anti-platelet, and other anti-coagulant strategies in chronic kidney disease patients. (Burlacu A, Genovesi S, Ortiz A, Kanbay M, Rossignol P, Banach M, Malyszko J, Goldsmith D, Covic A. The quest for equilibrium: exploring the thin red line between bleeding and ischaemic risks in the management of acute coronary syndromes in chronic kidney disease patients. Nephrol Dial Transplant. 2017 Mar27. doi: 10.1093/ndt/gfx041.). Part of this uncertainty extends to whether, when, and for how long it is prudent to combine two modes of anti-thrombotic therapy in this clinical setting. A full discussion of this important point is beyond the scope of this manuscript.

We thank the reviewer for pointing out the possible confusion caused by the variable names in table 1 and have clarified these using “antiplatelet agents excluding aspirin” and “aspirin”.

Information on the time of CKD diagnosis (at what time was the GFR assessed?) should be provided (before/after AF diagnosis? During follow up? Prior to any hospital admission?).

All patients entered into the study had an established diagnosis of CKD prior to their new onset AF. We used the CKD-EPI equation to calculate eGFR and all patients in the study had more than 1 eGFR value.

Some limitations are mentioned very well, but it should be made more clearly that adherence data were not available and the consequence regarding data interpretation should be made more clearly to readers.

We thank the reviewer for the praise pertaining to the discussion of the limitations of our study. We agree that more detail is required to explain the implications of data interpretation in the absence of adherence data and have added the following:

Our work is based on dispensed anticoagulation prescriptions but there were no data on patient adherence so our findings should be interpreted with caution pending further research.

Last sentence discussion: Instead of recommending a personalized approach with regard to starting OAC or not in AF patients with CKD, it should be referred to existent guidelines and current recommendations on this topic (though reliable data are sparse).

We shall of course strongly suggest following those guidelines that exist, but the argument for personalisation has to rest on the knowledge that there has been systematic and organised exclusion of patients with CKD from most large series and studies, and thus, guideline statements are not applicable without significant extrapolation. This may not be wise, as CKD patients both clot and bleed more (Burlacu A, Genovesi S, Ortiz A, Kanbay M, Rossignol P, Banach M, Malyszko J, Goldsmith D, Covic A. The quest for equilibrium: exploring the thin red line between bleeding and ischaemic risks in the management of acute coronary syndromes in chronic kidney disease patients. Nephrol Dial Transplant. 2017 Mar27. doi: 10.1093/ndt/gfx041.) We have acknowledged the lack of guidelines in the conclusion as follows:

Meanwhile, given the present lack of present guidelines, the decision to initiate anticoagulant therapy in patients with new-onset atrial fibrillation should be made on a personalised patient-level basis, weighing up the known risks and potential benefits, and where possible taking into account patients' wishes.

Reviewer 2:

Because the study is not prospective and randomised, I suggest to substitute the term 'risk' (that indicates a cause-effect relation) with the term 'rate' (more appropriate for the observed association). E.g. pg 3, line 25; pg 4, line 52 (twice); pg 9, line 57; pg 10, lines 23-24 (twice); pg 11, line 18 (consider 'in the rate of ischaemic' for 'in ischaemic'); pg 13, line 4-5 (consider 'a possible increase' for 'an increase').

We agree with the reviewer that using the term rate is more precise than the term risk in the context of our study and have amended this throughout the manuscript as suggested.

METHODS, pg 6: Can the AA explain how the diagnosis of recent onset atrial fibrillation was made among anticoagulated and non anticoagulated patients?

In the UK, patients can only be registered with a single primary care provider General Practice and records of all secondary care events are sent to the patient's general practitioner. Diagnoses are coded into the primary care record so the UK primary care records provide a robust list of a patient's diagnoses. One of the key primary care pay for performance targets is quality of AF diagnosis recording, improving the accuracy of the records that we interrogated for this study.

We used a comprehensive list of Read codes to identify patients with new-onset of atrial fibrillation (reference 42). These were based on codes related to many aspects of AF diagnosis such as ECG findings, formal diagnostic codes or coding related to AF clinics in primary or secondary care (process of care codes). We have expanded on the use of primary care records in our manuscript as follows:

AF was defined by Read Codes[40] from the primary care database utilising diagnostic and process of care codes to maximise case identification.[41] In the UK, patients can only be registered with a single primary care provider / general practice and records of all secondary care events are sent to the patient's general practitioner. Diagnoses are coded into the primary care record, so the UK primary care records provide a robust list of a patient's diagnoses made in both primary and secondary care.

METHODS, pg 6, line 54: Explain why the commonly used Cockcroft Gault (CG) formula was not applied. If possible, provide information based on CG estimates, as the CG method is the one used in the major phase III anticoagulation trials.

The high-level recommendation from KDIGO CKD guidelines 2012 is to use CKD-Epi formula for the estimated derivation of kidney function (Stevens PE, Levin A; Kidney

Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013 Jun 4;158(11):825-30. doi:10.7326/0003-4819-158-11-201306040-00007). It is correct to say that many pharmacodynamic studies are done in a regulatory setting using CG, and also correct to say that this is very unfortunate practice, as there is the potential for a serious mis-alignment of CKD grading using these two approaches, but no doubt that the best contemporary clinical practice mandates use of the CKD-Epi formula which for some decades now superceded CG.

METHODS, pg 7, line 28: Explain how the diagnosis of ischaemic stroke was made.

In the UK, patients can only be registered with a single primary care provider / General Practitioner and records of all secondary care events are sent to the GPs. Diagnoses are coded into the primary care record so the UK primary care records provide a robust list of a patient's diagnoses both in primary and secondary care. We used a comprehensive list of Read codes to identify ischaemic stroke and TIA and the financial incentivisation for primary care practices to record these correctly improves the robustness. Nevertheless, we have acknowledged in the discussion that misclassification bias cannot be excluded given that we were unable to review neuroimaging:

Misclassification bias may have occurred as we were unable to review electrocardiograms and neuroimaging.

Pg 9, line 24: '4848' instead of '8484'?

We apologise for this typing error and have corrected this to read as 4848.

TITLE, line 4: To improve clarity, 'newly started on' instead of 'receiving'?

We thank this reviewer for this title suggestion. We agree that it adds clarity and have adjusted it as suggested to read as follows:

Ischaemic stroke, haemorrhage and mortality in elderly patients with chronic kidney disease newly started on anticoagulation for atrial fibrillation: a population-based study from UK primary care

ABSTRACT, line 38: To improve clarity, add 'and 4543 were not' after 'diagnosis' (or similar).

We thank the reviewer for this suggestion. We agree that this improves clarity and have added this to our abstract as suggested:

We identified 6,977 patients with CKD and newly diagnosed AF, of whom 2,434 were anticoagulated within 60 days of diagnosis and 4,543 were not.

ABSTRACT, line 39: To improve clarity, add 'or none' after 'anticoagulant'.

Thank you for suggesting we add this detail which makes our methodology even more clear to the reader:

We matched 2,434 pairs using propensity scores by exposure to anticoagulant or none and followed for a median of 506 days.

INTRODUCTION, pg 6, line 23: 'anticoagulated or not for newly diagnosed AF' instead of 'anticoagulated for AF'.

We thank for this reviewer for this recommendation which we have incorporated as suggested:

Given the paucity of trial-based data, the conflicting outcome data from the small number of studies, and the lack of specific clinical practice guidelines in this important and frequently occurring clinical setting, the objective of the present study was to further explore the association between ischaemic stroke, haemorrhage and mortality in a large population of older patients with CKD anticoagulated or not for newly diagnosed AF.

METHODS, pg 7, line 53: Briefly explain what the index of multiple deprivation is.

We agree with the reviewer that a brief explanation of the index of multiple deprivation, widely used in UK health research, will benefit the global readership in understanding its role in our study. We have added the following to the methods:

The socioeconomic status measure, Index of Multiple Deprivation (IMD), is derived from patient postcode and is the official national measure of deprivation. The IMD score provides a combined measure of household income, education, healthcare provision, and living environment for the UK at small spatial scales.[46]

RESULTS, pg 8, line 44: Repeat the three inclusion criteria here (new AF, age 65 or above, eGFR <50 ml/min/1.73m2).

We thank the reviewer for this suggestion which serves as an important reminder to the reader and helps to understand the results presented:

A total of 6,977 patients met the inclusion criteria of being aged 65 years and older with a new diagnosis of AF and eGFR of <50 ml/min/1.73m^2 (Figure 1).

RESULTS, pg 8, line 52: Briefly describe the comparator group.

We thank the reviewer for raising this point. However, in the following paragraph, we do describe the similarities and differences between the anticoagulated and non-anticoagulated groups. We feel further comments at line 52 prior to the subsequent paragraph will disrupt the flow of our manuscript but we are happy to reconsider our position if there is a strong editorial opinion on this issue.

RESULTS, pg 8, line 55: Add 'Before matching' (or similar) at the start of the paragraph.

We thank the reviewer for this suggestion which we have incorporated as follows:

Before matching, patients prescribed anticoagulants tended to be younger (mean 81.7 years vs. 83.2 years), female (54.7%) and not current smokers (8.6% vs. 12.1%) compared to those not anticoagulated (Table 1).

TABLES 1 and 2 and FIGURE 1: complete the list of abbreviations.

We thank the reviewer for these suggestions which we have incorporated, thereby providing a comprehensive list of abbreviations for the tables and figures.

TABLE 2: provide units after '50' (third box of last line). Replace 'NA' (third to last box in last line)?

We have rectified this accordingly by defining the units as part of the Figure legend and removing 'NA'.

Manuscript committee:

The committee thought the clinical implications of your findings could be discussed in more detail.

We agree with the committee that the clinical implications of our work need further discussion to highlight how important our findings are and we have expanded upon this as follows:

The main clinical implications of the findings are that there is significant uncertainty about the best approach to initiating and managing anti-coagulation in the setting of new-onset AF in non-dialysis CKD. There are few reports, and these are discordant in terms of their main

findings with both reduced stroke[31], no impact on stroke[21 30] and increased stroke in the present study. The most pressing need therefore exists for a real-world RCT comparing either no anti-coagulation (placebo), versus vitamin K antagonist, or, a hybrid approach, of placebo versus direct oral anticoagulant versus vitamin K antagonist.[67]

Meanwhile, given the present lack of present guidelines, the decision to initiate anticoagulant therapy in ND-CKD patients with new-onset AF should be made on a personalised patient-level basis, weighing up the known risks and potential benefits, and where possible taking into account patients' wishes.

The abbreviations make it difficult to read your paper.

We thank the committee for this observation and agree with this statement. We have removed the abbreviations 'AF', 'ND-CKD', 'ESRD', 'VKA', 'GI', 'TIA' and 'DOAC' which we agree improves the readability of our manuscript.

What is the rationale for the 60 day window above and beyond the unconvincing point that this was used in a previous study (reference 31)?

We thank the reviewer for asking us to clarify this important point. We considered this point at length and consulted previous literature before choosing to define exposure to anticoagulation within 60 days of diagnosis. In our experience of working with the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database, a two-month window allows for capture of most prescribing made at the time of diagnosis. With this definition, we were able to detect prescriptions that occurred from primary care following prescriptions issued from hospital. Using a shorter cut-off, of say 30 days, would have been too restrictive as many patients may receive their first month's prescription of an anticoagulant from the hospital and we would have missed the repeat prescriptions issued in primary care.

We have added the following justification in the manuscript:

Exposure was defined as receipt of an anticoagulant prescription within 60 days of atrial fibrillation diagnosis. Almost all anticoagulant prescriptions in the UK are issued from primary care and are therefore captured in the RCGP RSC database. The exception to this is where the anticoagulant is initiated during a hospital attendance. We selected the 60-day period to allow for the transfer of anticoagulant prescribing to primary care where it had been initiated in secondary care.

Please discuss novelty, especially regarding your ref 31, https://www.ncbi.nlm.nih.gov/pubmed/28017326 and the recent Cochrane review http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011373.pub2/full.

We thank the committee for giving us the opportunity to further discuss the novelty of our study. We have attempted to clarify the point that given the findings of our study are in conflict with other studies, there is an urgent need for an RCT to be undertaken in this clinical setting:

The main clinical implications of the findings are that there is significant uncertainty about the best approach to initiating and managing anti-coagulation in the setting of new-onset atrial fibrillation in non-dialysis CKD. There are few reports, and these are discordant in terms of their main findings with both reduced stroke, no impact on stroke and increased stroke in the present study. Similarly, the impact of anticoagulation on all-cause mortality is unclear, with reports of no impact, increased and reduced mortality in this study. The most pressing need therefore exists for a real-world RCT comparing either no anti-coagulation (placebo), versus vitamin K antagonist, or, a hybrid approach, of placebo versus direct oral anticoagulant versus vitamin K antagonist.[67]

As well as adding the Cochrane review in the text above, we referenced it in response to a comment from reviewer 1. This interesting systematic reviewed the efficacy and safety of direct oral anticoagulants versus warfarin among AF patients with CKD, rather than comparing versus no anticoagulation as we did in the present study.

We were unclear about the point at which participants were included in the study and the period of time during which outcome events were ascertained. Were outcome events that occurred in the 60 day window included?

We thank the committee for pointing out that the precise details of study design are not clear to the reader in the manuscript's current form and apologise for this. We have added a section 'Study Design' to make the method much clearer:

Study design

Anticoagulated patients entered the study (the time at which outcome ascertainment began) on the day of receipt of their first anticoagulant prescription within 60 days of their newly diagnosed atrial fibrillation. Patients who received anticoagulation were propensity matched in a 1:1 ratio with those who were not anticoagulated, who were alive at the time of the first dispensed prescription of their matched counterpart. To mitigate the effect of immortal time bias, the date the non-anticoagulated patient entered the study coincided with the date of

atrial fibrillation diagnosis plus the time between their matched counterpart's atrial fibrillation diagnosis and date of first anticoagulant prescription (Figure 2).[31 42]

If outcome ascertainment only began after the 60 day point, then you are missing people who died during the 60 days.

We thank the reviewer for asking us to further explain this point. The new 'Study design' section along with the new Figure 2, we hope, clarifies at exactly what time point outcome ascertainment began. All patients were alive at the time of first anticoagulant prescription, and the non-anticoagulated matched counterpart was alive at the time of their matched counterpart's first anticoagulant prescription

And if the events in this window are not included in the analysis, isn't there a problem of immortal time bias? Maybe I am just confused. A timeline would help.

We thank the committee for posing this important question and the excellent suggestion to include a timeline. Avoidance of immortal time bias was at the very heart of the study design and we followed methodology used previously (Reference 31). The new 'Study design' section along with the timeline (Figure 2), we hope, clarifies at exactly what time point outcome ascertainment began.

Were some people in the non-exposed cohort in fact prescribed anticoagulants after the 60 day period? How was this handled?

We thank the committee for raising this point. We handled this issue by censoring non-exposed patients at the time of their first anticoagulant prescription, as have previous studies (reference 30). We have added a line in the text to make this far clearer to the reader:

Non-anticoagulated patients were censored at the time of receipt of first anticoagulant prescription.[30]

Shouldn't the propensity score have included history of previous ischemic stroke or TIA? It looks like only previous haemorrhagic stroke was included.

We thank the committee for raising this point. We did include this important factor in our propensity score with reference to it in Table 1. However, we inadvertently omitted this in our methods section and apologise for this oversight. This has now been rectified as follows:

Clinical variables included smoking status, eGFR, co-morbidities at baseline (myocardial infarction, coronary artery disease, cardiac failure, type 2 diabetes mellitus, hypertension, history of previous stroke/TIA, previous cerebral or gastrointestinal bleed, peripheral artery

disease), and drugs at baseline (antiplatelet agents, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), lipid lowering drugs, beta blockers, aspirin, potassium-sparing diuretics, supraventricular and ventricular antiarrhythmic agents, thiazide diuretics, calcium channel blockers, alpha blockers, loop diuretics, insulin, metformin, cardiac glycosides).

The anticoagulated group seems considerably on more intense treatment with drugs that are associated with decreased mortality (e.g. beta-blockers, ACE inhibitors, metformin, etc.), and those differences are not completely evened out with propensity matching.

We agree with this observation made by the committee. However, following propensity score matching there were no significant differences between the two groups with a standardised mean difference of less than 0.1 across all clinical and demographic variables. Indeed, the differences were not *completely* evened out but a standardised mean difference of less than 0.1 is considered to be non-significant and the highest standard possible for propensity matching. An RCT is the only way to improve upon this and we have pressed for this throughout our manuscript.

How would one interpret the fact that AC leads to more strokes but fewer deaths? How does one convey the information? How severe were the strokes? Was the lower death rate despite higher strokes due to fewer fatal strokes? Were these in the "worse than death" category?

It is not possible to comment from these Read codes derived data on the severity of strokes suffered. From other data, series and publications, it is clear that CKD is associated with an increased risk of both ischaemic and haemorrhagic stroke. In addition to shared risk factors, this higher cerebrovascular risk is mediated by several CKD-associated mechanisms including platelet dysfunction, coagulation disorders, endothelial dysfunction, inflammation, and increased risk of atrial fibrillation. CKD can also modify the effect of treatments used in acute stroke and in secondary stroke prevention. We feel (but this is speculative) that there were more non-fatal strokes in these CKD patients and RCTs will be better placed to assess this possibility.

Is this the final word?

This is very much not the final word in this topic but the paradoxical findings of our study of increased stroke, increased gastrointestinal and cerebral haemorrhage but reduced mortality, make it clear that an RCT is needed. In addressing the point above with regards to

further discussing the clinical implications of our findings, we feel we have now made it clear that this work is not the final word but should inform future trials.

The main clinical implications of the findings are that there is significant uncertainty about the best approach to initiating and managing anti-coagulation in the setting of new-onset atrial fibrillation in non-dialysis CKD. There are few reports, and these are discordant in terms of their main findings with both reduced stroke, no impact on stroke and increased stroke in the present study. Similarly, the impact of anticoagulation on all-cause mortality is unclear, with reports of no impact, increased and reduced mortality in this study. The most pressing need therefore exists for a real-world RCT comparing either no anti-coagulation (placebo), versus vitamin J antagonist, or, a hybrid approach, of placebo versus direct oral anticoagulant versus vitamin K antagonist.[67]

Are the reported associations confounded by indication?

The committee raise an important point. We have expanded upon this in the text in the limitations section to emphasise that the reported associations may be confounded by indication and that our important findings need to be further explored:

Despite well-matched groups after propensity-score matching, we cannot exclude that the reported associations were confounded by indication. It is possible that those anticoagulated had an inherent increased baseline rate of stroke. Furthermore, an assumption was that patients were adequately anticoagulated within the therapeutic range of international normal ratio (INR) when receiving warfarin, though this may be harder to achieve consistently in severe CKD.[66]. Robust RCTs are therefore needed to explore whether the reported associations in the present study are indeed causal.

Table 1 shows systematic differences between those receiving anticoagulation and those that did not (more women, more taking almost every type of medication).

We thank the committee for raising this point. We agree with this observation and outlined these systematic differences in the results section. The purpose of propensity score matching was to take these differences into account and we achieved this as best as the methodology permitted, as the standardised mean difference was less than 0.1 across all clinical and demographic variables in the model. Nevertheless, we do not dispute that RCTs are needed to further explore our findings. The following text added in response to another remark from the committee also serves to address this:

Despite well-matched groups after propensity-score matching, we cannot exclude that the reported associations were confounded by indication. It is possible that those anticoagulated had an inherent increased baseline rate of stroke. Furthermore, an assumption was that patients were adequately anticoagulated within the therapeutic range of international normal ratio (INR) when receiving warfarin, though this may be harder to achieve consistently in severe CKD.[66]. Robust RCTs are therefore needed to explore whether the reported associations in the present study are indeed causal.

Blood pressure is not included in the adjustment (though diagnosed hypertension is).

It would not be possible to gather a representative and meaningful "blood pressure" value in these acutely unwell patients, who spent time in hospital, and, in the community. Accordingly, we felt it more robust to fall back on established standardised (coded) definitions for hypertension diagnosis.

This looks big but actually it's quite small, the actual final cohort from the 5 million is only 6000. You used propensity score matching which in theory might give a more accurate result, but the loss of power to achieve matching is massive, hence the matched cohorts are only 2000 each. So you claim 5 million but match 2000 odd pts against each other.

Inevitably, with age, CKD, new onset AF selection criteria, there are far fewer patients left to study for the purposes of this investigation.

The General Practice database covers a cohort of 2.73 million patients from 110 General Practices across England and Wales. Inevitably, with age, CKD, new onset AF selection criteria, there are far fewer patients left to study for the purposes of this investigation. We outline in Figure 1 how we arrived at our study cohort and where patients were lost at each stage. This is typical of the other studies in this setting.

When you have such a small cohort you will inevitably have very small numbers of events. What are the absolute rates?

We had included the absolute rates for stroke, cerebral and gastrointestinal haemorrhage and deaths in the results section:

The crude rates for ischaemic stroke and haemorrhage were 4.6 and 1.2 following anticoagulation, and 1.5 and 0.4 in non-anticoagulated individuals per 100 person-years, respectively.

Then mortality reduction is based on small numbers and marginally significant.

We agree with this observation by the committee. Nevertheless, the association that we report between anticoagulation and mortality in the present study is in line with the Keskar et al report published in Kidney International earlier this year (Reference 30). The paradoxical nature of our findings (increased ischaemic stroke, cerebral and gastrointestinal bleeding) despite the lower rate of mortality should provide the impetus for an RCT.

Kaplan-Meier plots in Figure 2 have a false zero and thus are visually misleading. They would look fine if plotted the other way up as recommended by Pocock et al when outcome events are not common. Also, it's desirable to show numbers at risk at the start and, say, every 2 years.

We thank the committee for this observation. On reflection, we agree that following the recipe described in Pocock et al is desirable and we have adjusted the survival curves. We have also added the numbers of at risk population each year on the survival curves.

You should say how closely they matched on propensity scores. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet 2002:359:1686-1689.

We have clarified how closely matching was on propensity scoring for each variable by ensuring that the standardised mean difference is reported. It was less than 0.1 in all cases which is considered to represent adequate matching within the confines of this methodology.

Thank you for considering our re-submitted manuscript for publication.

Yours sincerely,

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