BMJ - Decision on
Manuscript ID
BMJ.2017.041508

Body: 16-Nov-2017

Dear Dr. Kumar

Manuscript ID BMJ.2017.041508 entitled "Ischaemic stroke, haemorrhage and mortality in elderly patients with chronic kidney disease receiving anticoagulation for atrial fibrillation: a population-based study from UK primary care"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Georg Roeggla
groggla@bmj.com

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Manuscript meeting 09.11.2017

Elizabeth Loder (chair), Doug Altman (stats), Wim Weber, Jose Merino, John Fletcher, Georg Roggla, Tiago Villanueva, Rubin Minhas

Decision: Ask for revision.

The committee was interested in the topic of your research. The following concerns were mentioned:

- The committee thought the clinical implications of your findings could be discussed in more detail.
- The abbreviations make it difficult to read your paper.
- 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)?
- 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 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?
- If outcome ascertainment only began after the 60 day point, then you are missing people who died during the 60 days.

- 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.
- Were some people in the non-exposed cohort in fact prescribed anticoagulants after the 60 day period? How was this handled?
- Shouldn't the propensity score have included history of previous ischemic stroke or TIA? It looks like only previous haemorrhagic stroke was included.
- 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.
- 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?
- Is this the final word?
- Are the reported associations confounded by indication?
- Table 1 shows systematic differences between those receiving anticoagulation and those that did not (more women, more taking almost every type of medication).
- Blood pressure is not included in the adjustment (though diagnosed hypertension is).
- 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.
- When you have such a small cohort you will inevitably have very small numbers of events. What are the absolute rates?
- Then mortality reduction is based on small numbers and marginally significant.
- 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.
- 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.

Please excuse the delayed decision mail. We had to discuss a few statistical issues after the manuscript meeting-see the last two issues on the list above.

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to the additional comments by the committee.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

In this study, Kumar and coworkers assessed associations between anticoagulation, ischemic stroke, gastrointestinal and cerebral hemorrhage and all-cause mortality in older people with AF and CKD. For this purpose, they undertook a propensity-matched population based retrospective cohort analysis. Overall, about 7000 pts with CKD (GFR <50ml/min) and new diagnosed AF were included; 2400 were anticoagulated within 60 days of AF diagnosis that were matched with patients not anticoagulated after AF diagnosis. Unexpectedly, rates/100-person years for ischemic stroke were higher in anticoagulated patients (4.6 vs 1.5). On the other hand, rates/100-person years of hemorrhage were higher in anticoagulated patients compared to non-anticoagulated subjects (1.5 vs 0.4). In comparison to non-anticoagulated pts., HR for ischemic stroke, hemorrhage and all-cause mortality was 2.6 (CI 2.0-3.38), 2.42 (1.44-4.05) and 0.82 (0.74-0.091) in anticoagulated pts. The authors conclude, that anticoagulating older people with AF and coexisting CKD is perhaps associated with an increased risk of stroke and hemorrhage but a lowered risk of all-cause mortality. They call for adequately powered randomized trials in this patient-population (older pts with AF and CKD) to provide more clarity on best clinical management.
This is a very interesting study and the topic is of high clinical relevance for daily clinical practice. However, I do have several questions and comments:

- 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.
- Additionally, separate analyzes on gastrointestinal and cerebral hemorrhages should be provided to enable better interpretation of results.
- 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.
- 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?).
- 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.
- 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?
- Figure 1 can perhaps be deleted and relevant information can be included into the text.
- It would be of interest to present results also for the different substances used.
- 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.
- 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?).
- 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.
- 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).
- Statistical review should be performed

Additional Questions:
Please enter your name: T Rizos

Job Title: Neurologist

Institution: Heidelberg University

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: Received consulting honoraria, speakers honoraria and travel support from BMS Pfizer, Boehringer Ingelheim, Bayer HealthCare and Daiichi Sankyo.

Reviewer: 2

Recommendation:

Comments:
TO THE EDITOR
Kumar et al. investigate the effects of anticoagulation versus no anticoagulation among newly diagnosed atrial fibrillation (AF) patients aged 65 years or older, with moderate renal dysfunction. To this end, they retrospectively analyse an 11-year data base from the England and Wales General Practitioners Research and Surveillance Centre. The AA compare the rates of ischaemic strokes, gastrointestinal or cerebral haemorrhages, and all-cause deaths among 2424 newly diagnosed AF patients started on anticoagulation versus those of 2424 newly diagnosed AF patients on no anticoagulation. The pairs were matched by propensity score. Over a median follow-up of 1.4 years, the rates of stroke and haemorrhage were significantly increased, whereas mortality was significantly lower, among anticoagulated patients. The AA conclude that randomised controlled trials (RCT) of anticoagulation versus none are needed in this patient population.
An important implication of the present analysis is the need to conduct RCTs in this common patient population. Although not entirely novel, the study is the largest of its kind to report on individual ischaemic, bleeding and fatal outcomes. Within the limitations of a retrospective observational analysis, it appears well conducted and is

clearly presented. Because it is not prospective and randomised, my main requests are: i) to substitute the term 'risk' with 'rate', and ii) to explain how the diagnosis of new AF was made. Other lesser suggestions are in my comments to the AA.

MAJOR COMMENTS FOR THE AA

1. 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').
2. METHODS, pg 6: Can the AA explain how the diagnosis of recent onset atrial fibrillation was made among anticoagulated and non anticoagulated patients?
3. 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.
4. METHODS, pg 7, line 28: Explain how the diagnosis of ischaemic stroke was made.
5. Pg 9, line 24: '4848' instead of '8484'?

MINOR COMMENTS FOR THE AA

TITLE, line 4: To improve clarity, 'newly started on' instead of 'receiving'?
ABSTRACT, line 38: To improve clarity, add 'and 4543 were not' after 'diagnosis' (or similar).
ABSTRACT, line 39: To improve clarity, add 'or none' after 'anticoagulant'.
INTRODUCTION, pg 6, line 23: 'anticoagulated or not for newly diagnosed AF' instead of 'anticoagulated for AF'.
METHODS, pg 7, line 53: Briefly explain what the index of multiple deprivation is.
RESULTS, pg 8, line 44: Repeat the three inclusion criteria here (new AF, age 65 or above, eGFR <50 ml/min/1.73m2).
RESULTS, pg 8, line 52: Briefly describe the comparator group.
RESULTS, pg 8, line 55: Add 'Before matching' (or similar) at the start of the paragraph.
TABLES 1 and 2 and FIGURE 1: complete the list of abbreviations.
TABLE 2: provide units after '50' (third box of last line). Replace 'NA' (third to last box in last line)?

Additional Questions:

Please enter your name: Felicita Andreotti

Job Title: Consultant Cardiologist, University Professor

Institution: Catholic University Hospital in Rome

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: During the past 3 years I have received speaker or consulting fees from Actelion, Amgen, Bayer, Boehringer-Ingelheim, BMS/Pfizer, Daiichi Sankyo and Menarini International Foundation. I have received institutional funds to conduct research projects.