20-Jun-2016

Dear Dr. Odutayo


Thank you for submitting this paper, which we discussed at a recent manuscript meeting. We would be happy to publish a revision that addresses the comments of reviewers and editors at the end of this letter. We hope you find all comments helpful

Please revise and submit within one month.

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And finally, we also require a copy of the manuscript with changes highlighted. Please upload this file with file designation 'Revised Manuscript Marked copy'.

Many thanks again. We look forward to seeing your revised paper

With best wishes

Alison Tonks
Clinical editor BMJ
atonks@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. Members of the committee were: Wim Weber [chair], Elizabeth Loder, Jamie Kirkham [statistical adviser], Kristina Fister, Georg Roeggla, Tiago Villanueva, Jessamy Bagenal, Amy Price, Jose Merino, Alison Tonks.

Decision: provisional acceptance subject to satisfactory revision

Detailed comments from the meeting:

This is a clear and interesting paper. The findings are not strictly new, but the size and scale of the work are a valuable addition.

Specific comments that come up during discussions:

* Please add a sentence or two discussion your choice of method for quality assessment. It seems a little unorthodox to us since you don't use standard instruments.

* Does your search needed updating? [only to March 2015 currently].

* Please also add detail about exclusions. Eg. You excluded studies that did not report which co variables they adjusted for, and also excluded unadjusted studies. Could either of these exclusions introduce bias? How may were excluded for each of these reasons? [the flow chart details only one of them]
*Please consider adding supplementary figure 1 [flow chart] to the main paper.
* Some of the later funnel plots have very few studies in them - are they valid? Please review.

FURTHER INFORMATION

Essential Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)

3. Patient confidentiality forms when appropriate (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality).

4. Competing interests statement (see http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests)

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10. Patient involvement statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research).

11. Please ensure the paper complies with The BMJ’s style, as detailed below:

   a. Title: this should include the study design eg “systematic review and meta-analysis.”

   b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.

   c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

   d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

   e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/.

   f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vii) unanswered questions and future research

   g. Footnotes and statements

REVIEWERS' COMMENTS

Reviewer(s)’ Comments to Author:

Reviewer: 1

Recommendation:
treatments were not very effective at treating AF, or that AF is not the cause of the non-stroke outcomes. You can address this issue, and with the rhythm control options they had available there was no benefit over rate control.

Additional Questions:

Please enter your name: Casper N. Bang
Job Title: MD. PhD.
Institution: Roskilde University Hospital, Denmark

If you have any competing interests (please see BMJ policy) please declare them here: none

Reviewer: 2
Recommendation:

Comments:

Review comments for manuscript BMJ.2016.033290 'Atrial fibrillation and the risks of cardiovascular disease, renal disease and death: a meta-analysis' by Odutayo et al.

Odutayo et al. summarized the evidence from prospective observational studies regarding the association of atrial fibrillation (AF) with a variety of cardiovascular outcomes, renal disease and mortality. The authors performed an impressive and well-reported effort to summarize this evidence, which will be helpful for researchers and decision makers to get a complete overview of the risks associated with the significant population burden of AF. I think the paper is of interest to the BMJ readers, if the following issues can be addressed or clarified:

1. Page 5, Methods: the authors should report their search strategy, so others can replicate or build on this. The search strategy can be supplemented online.
2. Page 5, Methods: describe the study selection criteria (inclusion/exclusion) under a separate header, and explain why you chose to exclude studies with <100 participants and <6 months follow-up.
3. Page 5, Data Extraction and Quality Assessment:
4. Page 5, Methods: the authors correctly address the potential sources of bias regarding adjusting for potential confounders in multivariable analysis and the method of AF diagnosis at baseline. However, for complete study quality assessment the authors should consider providing details regarding the following: I) Selection of exposed (AF) and unexposed (Controls) participants; if Controls were likely to have other health issues, it has to be considered how this affects the reported relative risk and to what extent this can be projected onto the general population. II) Completeness of follow-up data; if for some reason a larger portion of Controls were lost to follow-up than AF patients, this might bias the reported relative risk. III) Outcome ascertainment during follow-up; was it possible that AF patients were more closely monitored for outcomes than Controls, for example using routine administrative data rather than a regularly monitored prospective cohort study? This might bias the reported association for outcomes other than mortality.
5. Page 6, line 13: explain why studies that did not report the covariates were excluded. Are these studies presumably of less quality than studies that were minimally adjusted or unadjusted?
6. Page 6, line 16: I agree to distinguish between 'minimally' adjusted and 'adequately' adjusted relative risks. However, does it not depend on the outcome of interest regarding which variables should be minimally included as covariates? Age and gender are standard, but for example where CVD history is relevant for ischemic events, for stroke we know that the CHA2DS2-VASc risk factors are associated with stroke. Different risk factors will be relevant for heart failure, bleeding, and other outcomes. With your method, does it mean that the outcome-specific known risk factors are taken in account for the 'adequately' adjusted relative risk, rather than 'minimally'?
7. Page 6, line 19: should "adequately adjusted" also include adjustment for certain treatments, depending on the outcome of interest? For example, in recent studies many AF patients will be on oral anticoagulation, which will lower the relative risk of a stroke.
8. Page 8, line 6: clarify which statistical tests were used to test for trend.
9. Page 8, line 7: clarify why AF type and % oral anticoagulation were not used for stratified analysis, as both had >9 studies.
10. Page 14, Discussion: the paper could benefit from more extensive discussion of the results. Two examples: I) relative risks found in general population studies were typically larger than in specific settings. This could be related to the selection of the Controls and the proportion of AF patients treated with effective evidence-based therapies. II) the potential publication bias for reporting stroke incidence, and the lower relative risk after removing the studies that were causing most of the heterogeneity, are important findings. Many scientific papers and funding proposals are based on the same presumptions regarding the risk for stroke in AF, typically referencing the Framingham study and other well-known prospective cohort studies. However, your finding might indicate that this risk is actually lower, or has become lower in recent studies due to higher rates of oral anticoagulation use. Can you explore the latter and comment more specifically on this issue in the Discussion?
11. Page 17: If AF is simply a marker and not a cause of these outcomes, many risk factors are at play. However, hypertension deserves special attention as typically 70-80% of AF patients have hypertension, and it is also an important risk factor for all reported outcomes. Please add this consideration to the Discussion.
12. Page 17: If AF is a marker, but has significant associations with all of these outcomes, this might also indicate that the selected observational studies are inadequately correcting for the real causes. Please discuss as a methodological issue, or limitation.
13. Page 17: If AF has a causal relation with the outcomes, treatment of AF should lower their incidence, please discuss whether there is any evidence for this. Previous rhythm vs. rate control trials (AFFIRM, RACE, others) have addressed this issue, and with the rhythm control options they had available there was no benefit over rate control. These studies also assessed other outcomes than stroke. These results meant that either the rhythm control treatments were not very effective at treating AF, or that AF is not the cause of the non-stroke outcomes. You can
include more recent evidence to discuss this.

14. Page 17: another important AF—specific scenario for illustration: the new oral anticoagulants are at least as effective at preventing stroke and cause fewer bleedings than warfarin. However, warfarin might prevent some more myocardial infarctions, one of your non-stroke outcomes.

15. Page 17: a next research step could be to use your absolute risk increases for AF patients to determine what types of interventions or strategies need to be tested next to further reduce their burden of disease, please comment.

Additional Questions:
Please enter your name: Robby Nieuwlaat
Job Title: Assistant Professor
Institution: McMaster University

If you have any competing interests [please see BMJ policy] please declare them here:

Reviewer: 3

Recommendation:

Comments:
The Authors conducted a systematic review and meta-analysis to examine the relationship between atrial fibrillation (AF) and the development of cardiovascular disease, renal disease and death. The results of this meta-analysis involving 9,620,130 participants (6% with AF) demonstrated that AF was associated with increased risk of all-cause mortality, cardiovascular mortality, major cardiovascular events (MACE), stroke, ischemic stroke, ischaemic heart disease (IHD), sudden cardiac death (SCD), heart failure (HF), and chronic kidney disease (CKD).

The increased risk of death and stroke in patients with AF is already well-known and cardiovascular diseases such as hypertension and heart failure are common co-morbidities in this population, as is CKD. It is important to highlight that multiple risk factor management (blood pressure control, rate/rhythm control to prevent/reduce risk of HF, weight, smoking, alcohol intake, diet (all to reduce cardiovascular risk)) is essential in AF patients, as the Authors conclude, although stroke prevention will necessarily remain a key treatment goal.

* Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers? Is a general journal the right place for it?

Yes. This is a very comprehensive systematic review and meta-analysis and the Authors should be congratulated on this. In my opinion, the paper is of sufficient interest/importance to general readers to warrant publication in the BMJ. However, the majority of the results are contained in the very extensive Supplementary Tables (9 Tables) and Figures (23 Figures) and I feel that this impedes the readability and understanding of the results. I'm not sure how this can be rectified though or how many Supplementary Tables and Figures the journal allows.

* Scientific reliability
Research Question - clearly defined and appropriately answered?
Yes

Overall design of study - adequate ?
N/A

Participants studied - adequately described and their conditions defined?
N/A

Methods - adequately described? Complies with relevant reporting standard - Eg CONSORT for randomised trials ?
Ethical ?
Yes, overall.

How were the outcomes of congestive heart failure, peripheral arterial disease and CKD defined in the studies?

Please provide a clear rationale for why American Heart Association estimates of the incidence of cardiovascular mortality, IHD, HF, SCD were used, and Centers for Disease Control and Prevention estimates were used to calculate the absolute risk increase for each vascular outcome?

MOOSE checklist should be included.

Results - answer the research question? Credible? Well presented?
Yes, but the vast majority of the results are contained in Supplementary Tables (9 Tables) and Figures (23 Figures)

Since the Table of characteristics of the included studies is not included in the main manuscript it would be helpful to add a short paragraph summarising these in the Results section.

Please explain what Figure 1 represents in the text in the Results section.

The I-squared statistics are very high, demonstrating substantial heterogeneity and this calls into question the validity of combining the data, although the results reported were broadly similar when studies were excluded until heterogeneity (I-squared statistic) was less than 50%.

Page 10, lines 18-19 "...relative risk of major..." does not make sense. Please clarify.

In Figure 3, when stratified by age, the age groups are overlapping, 64 and 71 appear in 2 groups. It is not clear to me what the other figures in square brackets on the left hand side for CHD and stroke represent.
Confidence intervals should be written in the format (1.36 to 2.60) within parentheses, using the word "to" rather than as (1.36, 2.60).

Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear?
Yes

The proportion of patients on anticoagulation will likely affect all the outcomes of interest (particularly all-cause mortality, stroke (ischemic and hemorrhagic). The implications of this on the findings should be considered further and discussed.

References - up to date and relevant? Any glaring omissions?
Yes up to date and relevant.

A reference(s) to a clinical guideline(s) would be more appropriate than reference 5 in the Introduction. It would be better if you did not reference just one of the NOAC clinical trials (currently reference 4) but included a reference(s) which summarised the findings of VKA trials (e.g., Hart et al, 2007) and NOAC trials (e.g., Ruff et al, 2014); there are many others to choose from.

The references in the text should be given as numbers in square brackets or superscript throughout not a mixture of the two.

The references from 19 onwards are missing from the main reference list.

Abstract/summary/key messages/What this paper adds - reflect accurately what the paper says?
Yes

Additional comments:
Was this systematic review registered (e.g., PROSPERO)? If so, please provide the details.

Additional Questions:
Please enter your name: Deirdre Lane
Job Title: Senior Lecturer in Cardiovascular Health
Institution: University of Birmingham

If you have any competing interests (please see BMJ policy) please declare them here: DAL has received investigator-initiated educational grants from Bayer Healthcare, Bristol Myers Squibb and Boehringer Ingelheim, has been a speaker for Boehringer Ingelheim, Bayer, and Bristol Myers Squibb/ Pfizer, and consulted for BMS and Boehringer Ingelheim.

Reviewer: 4
Recommendation:
Comments:
This is a wide-ranging systematic review and meta-analysis to evaluate the impact of AF on a spectrum of CVD, not just stroke/thromboembolism.
In general, the review is well-conducted and well-reported.

Major comments
There is no reference in the entire manuscript to risk prediction of stroke/thromboembolism which is the focus of management in AF using scores such as CHADS2 or CHA2DS2-VASc. The derivation and validation studies for these scores (which are widely used) suggest different absolute stroke rates based on baseline characteristics, which seems to be in conflict with the conclusion of this study. What may have caused this difference?

What is the implication for future risk prediction in AF?

Minor Comments
The background section in the abstract states "a wide range of cardiovascular outcomes". Renal disease is not classically included in CVD. Why is it included here?

Why are Congestive Heart Failure and Chronic Kidney Disease together in the results section? Please separate these two unrelated categories.

Additional Questions:
Please enter your name: Dr Amitava Banerjee
Job Title: Senior Clinical Lecturer in Clinical Data Science and Honorary Consultant Cardiologist
Institution: University College London

If you have any competing interests (please see BMJ policy) please declare them here: No competing interests

Reviewer: 5
Recommendation:
Comments:
This paper is exceptionally clear, well organized, and important in that it evaluates the critical question of additional cardiovascular risk in patients with AF. I'll leave the methodology review to others more qualified to comment on statistics. However, the underlying question goes straight to the heart of patients' needs. AF may be picked up as an incidental finding on EKG in a patient with no other cardiovascular history - this has actually happened twice in my family. The initial question, then, is what does this mean? What are the implications?

The clinicians' reflex is stroke prevention, as the authors clearly point out. I've seen variation in clinicians' aggression in restoring sinus rhythm, the depth of their advice on the overall implications of the diagnosis, and patients' willingness and ability to receive and understand counsel. More information is sometimes better and I imagine usually doesn't hurt, and this study adds to that information.

The discussion of the implications for clinicians is excellent in that it addresses identifying the possibility of AF as a prognostic marker for other conditions, and the importance of primary prevention and risk management. I could ask for strengthening these statements by including clear recommendations for how to communicate this risk information to patients and how to follow up - regular follow-up visits and testing protocols come to mind - but I really think clinicians are going to understand the implications for their patients regardless. If the methodology is deemed sound, I'd like to see this paper published.

Thanks for the opportunity to review.

Additional Questions:
Please enter your name: Michael Kahn
Job Title: Patient Reviewer
Institution: n/a

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 6

Recommendation:
Comments:
This paper reports on a large systematic review and meta-analysis of studies reporting the association of atrial fibrillation with cardiovascular disease, renal disease and death. The authors are to be congratulated on assembling 100 cohort studies involving over 9.5 million participants. The paper is well written and provides interesting (although not particularly novel) information about the relative risks of adverse outcomes associated with atrial fibrillation.

As the authors acknowledge, their analyses are limited by substantial heterogeneity between the included studies and by the lack of individual patient data.

The prevalence of atrial fibrillation amongst the participants was 14.8% overall and varied substantially between the analyses for different endpoints (5.4% to 15.5%). It would be useful to illustrate the considerable variation in the prevalence of atrial fibrillation between individual studies (currently only available as numbers in the on-line supplement).

The heterogeneity might partly reflect variation in endpoint definitions between the studies and over time (e.g. impact of troponin on diagnosis of myocardial infarction) but the authors provide little information about this aspect of their systematic review. Did the authors document variation in endpoint definitions and can they comment on the extent to which this may have contributed to heterogeneity between studies?

The authors used American estimates for the incidence of cardiovascular mortality and other cardiovascular events to translate relative risks into estimates of absolute risk. Can the authors comment on the extent to which this might limit generalisability of the absolute risk estimates to other populations?

Some of the analyses suggest that atrial fibrillation is associated with very large increases in the risk of adverse cardiovascular outcomes, but these risks likely reflect the particular populations under study. For example, only 6 of the 100 studies reported on the association between atrial fibrillation and heart failure (RR 4.99). Can the authors comment on the extent to which their findings are generalizable to a wider unselected population of patients with atrial fibrillation, particularly as sensitivity analyses were not done for some outcomes?

The authors conclude that additional interventions to reduce cardiovascular risk (beyond the use of anticoagulation to reduce the risk of stroke) are warranted in patients with atrial fibrillation, but also correctly state that they have only demonstrated a statistical association between atrial fibrillation and adverse cardiovascular outcomes. Can the authors comment on the extent to which the increased risks of adverse outcomes in patients with atrial fibrillation are likely to be modifiable?

The reference notation in the paper appears inconsistent. For example, in line 7 on page 4, the authors refer to reference 5 (super script) and reference 4 (in brackets). The text suggests that reference 5 relates to a guideline, but reference 5 in the main reference list is a research paper. Please can the authors review and correct the referencing in the paper.

Minor point:
The abbreviation CHF (page 6, line 7) is not defined until line 11.

Rob Henderson
Nottingham University Hospitals
Additional Questions:
Please enter your name: Robert Henderson

Job Title: Consultant Cardiologist

Institution: Nottingham University Hospitals

If you have any competing interests (please see BMJ policy) please declare them here:

Date Sent: 20-Jun-2016