BMJ - Decision on Manuscript ID BMJ.2015.026464

Body: 21-May-2015

Dear Dr. Xian

Manuscript ID BMJ.2015.026464 entitled "Real-World Effectiveness of Warfarin among Ischemic Stroke Patients with Atrial Fibrillation: Findings from the Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) Study"

Thank you for sending us this paper and giving us the chance to consider your work, which we enjoyed reading.

Decision: We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise it as we suggest in the report below from the manuscript meeting: we are provisionally offering acceptance but will make the final decision when we see the revised version.

Deadline: Because we are trying to facilitate timely publication of manuscripts submitted to BMJ, your revised manuscript should be submitted by one month from todays date. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

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Yours sincerely

Jose Merino
jmerino@bmj.com,

Report from the Manuscript Meeting.

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

Present: Elizabeth Loder (chair), Rafael Perera (statistical consultant), Wim Weber, Tiago Villanueva, Georg Roeggla, José Merino. Written comments from Rebecca Burch and Rubin Minhas

Decision: provisional acceptance

Detailed comments from the meeting:

First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available below.

Please also respond to these additional comments by the committee:

1. This is a well written report. We were particularly happy to see the use of a patient-centered outcome measure.

2. The methodology is appropriate and well done. We have only a minor comment. The Propensity score inverse probability-weighting method works well when there is some overlap in the distribution of the variables used. If there is no overlap, the method could induce bias. Could you provide, perhaps as an appendix, data or figures on the age distribution of those treated with Coumadin vs. those not treated>

3. Please clarify in the manuscript, if this is the case, that warfarin was started before hospital discharge. If you had information on the timing when anticoagulation was started, that would also be useful.

REFEREE COMMENTS

Reviewer: 1

Recommendation:

Comments:
There are very few papers in which I have no major changes to propose. This is one of them. The authors investigated the prognosis of patients in the USA with AF who had a stroke and were

discharged on oral anticoagulation versus those who were not treated with warfarin. The study is based on a prospective registry (get-with-the –guidelines) which collects prospectively data from about 1/3 of stroke patients admitted to a hospital in the USA. The authors used Medicare claims to identify vascular endpoints and "time at home". As far as I can see this is the first study of its kind with data from USA hospitals. The strengths of the study are
1. Prospective design with publication of the methods
2. Application of patient centred outcomes (e.g. time at home)
3. Propensity matching
4. Sensitivity analyses in patients with and without NIHSS recorded
5. Extensive discussion of the possible shortcomings of the study
The authors might want to mention that the majority of population based studies are from the Danish Health Registry and (1) and that the rate of anticoagulation after stroke in AF patients has improved dramatically in the last 10 years (2).

1. Andersen KK, Olsen TS. Reduced poststroke mortality in patients with stroke and atrial fibrillation treated with anticoagulants: results from a Danish quality-control registry of 22,179 patients with ischemic stroke. Stroke. 2007 Feb;38(2):259-63. PubMed PMID: 17194876.
2. Weimar C, Benemann J, Katsarava Z, Weber R, Diener HC. Adherence and quality of oral anticoagulation in cerebrovascular disease patients with atrial fibrillation. Eur Neurol. 2008;60(3):142-8. PubMed PMID: 18628633.

Additional Questions:
Please enter your name: Hans-Christoph Diener

Job Title: Chairman

Institution: Department of Neurology, University Hospital Essen, Germany

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?: Yes

Funds for research?: Yes

Funds for a member of staff?: Yes

Fees for consulting?: Yes

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If you have any competing interests (please see BMJ policy) please declare them here: HCD received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, St. Jude, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth and Yamanouchi. Financial support for research projects was provided by AstraZeneca, GSK, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis and Talecris. The Department of Neurology at the University Duisburg-Essen re-ceived research grants from the German Research Council (DFG), German Ministry of Education and Research (BMBF), European Union, NIH, Bertelsmann Foundation and Heinz-Nixdorf Foundation. HCD has no ownership interest and does not own stocks of any pharmaceutical company.

Reviewer: 2

Recommendation:

Comments:
The authors report a study of antithrombotic therapy at the time of discharge for AF-related stroke and its association with subsequent time spent at home. Using linked data from the Get With the Guidelines—Stroke registry and Medicare claims, they performed a propensity-matched comparison of warfarin versus no oral anticoagulant therapy, and found that those prescribed warfarin had a lower risk of cardiovascular events and more time at home. This is a well-done and very nicely written paper on an important clinical topic. My main suggestion is for the authors to touch on the possibility that their findings may represent a substantial underestimate of the efficacy of warfarin therapy, since the authors relied on warfarin status at discharge, while recent work indicates that

50% of Medicare beneficiaries who are prescribed an oral anticoagulant fill only one prescription (PMID 25359164). It may well be that patients who have already had a stroke are more likely than the general population of AF patients to comply with warfarin therapy, but nevertheless it remains highly likely that many of the 88% of stroke patients who were given warfarin at discharge switched over to no oral anticoagulant therapy soon afterward. This would serve to attenuate the apparent effect of anticoagulant therapy on outcomes. On the other hand, it could be argued that the authors design represents an intention-to-treat comparison that reflects real-world effectiveness. My second suggestion is to elaborate more on whether presenting the benefit of warfarin in patient-centric terms, rather than traditional clinical descriptions of outcomes, may help improve adherence to proven anticoagulant therapy.
-- Hooman Kamel

Additional Questions:
Please enter your name: Hooman Kamel

Job Title: Assistant Professor

Institution: Weill Cornell Medical College

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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END

IMPORTANT
When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

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for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction

this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
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summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

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• RRR (relative risk reduction)
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point estimates and confidence intervals for the main results

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were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
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Date Sent: 21-May-2015