BMJ - Decision on
Manuscript ID
BMJ.2018.046115

Body: 22-Oct-2018

Dear Dr. Hao

Manuscript ID BMJ.2018.046115 entitled "Clopidogrel plus aspirin versus aspirin alone for the treatment of acute minor ischemic stroke or high-risk TIA: A systematic review and meta-analysis"

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.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Thanks!

Georg Roeggla
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Report from The BMJ's manuscript committee meeting

Manuscript meeting 18.10.2018

John Fletcher (chair), Jamie Kirkham (stats), Elizabeth Loder, Jose Merino, Sophie Cook, Georg Roggla, Tiago Villanueva, Daoxin Yin.

Decision: ask for Revision

The committee was interested in the topic of your research. The following issues were discussed:

• The committee thought that this study addresses an important clinical question.
• There is an important point about outcomes. We think that this review looks at both prevention of ischemic stroke and risk of haemorrhage: the benefits seem to outweigh the risks. The increase in bleeding is mostly in minor haemorrhages. It is a false equivalence to consider ischemic stroke and minor GI bleeding in the same category. Bleeding episodes in POINT were more likely to happen after 2 weeks of treatment while the benefit in stroke was seen before that time. The timing analysis is therefore important. We are dealing with short-term treatment with DAPT to maximize benefit and minimize risks.

• You obtained additional data from the trialists regarding absolute number of certain outcomes. You present in table 2 the aggregated number of outcomes. Could you provide these for each trial?
• What do you mean by this: "As the POINT study enrolled a diverse, multi-national population who underwent contemporary stroke management, to calculate absolute effects, we applied the relative risks to the baseline risks from this trial (e.g., 6.4% risk for recurrent stroke)"? We assume that you added the baseline risk because the rate of stroke, MI or death from ischemic vascular causes in the ASA group was 11.7% in CHANCE (done in many centres in China) but only 6.5% in POINT (done mostly in the US but also Australia, NZ and Europe). Presumably the baseline risk is higher in China because other factors that contribute to recurrent stroke or TIA (lipids, BP) are more aggressively managed in the countries where POINT was carried out.
• Could you provide, with figure 3, a "blow-up" of the 0-21 day timeframe to give us greater detail about timing of stroke and adverse outcomes?
• In this review you took the search strategy from a previous review which you judged to be comprehensive and then updated this search to 2018. However only 2 of the 14 eligible studies proved to be eligible for this new review. This may well be a valid approach but we think we need more details on why 12 were excluded in terms of the differences between previous/current reviews.

Please respond to the comments by the committee.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
Hao and colleagues present a meta-analysis of three trials of dual antiplatelet therapy vs. standard acetylsalicylic acid monotherapy after minor stroke or high-risk TIA. The research question is timely and the methods used appear appropriate. However, due to the numbers of subjects included they essentially summarise two large well-known trials, such that it is questionable whether a meta-analysis adds sufficient value to justify lumping together trials. One key insight the authors deliver is how strikingly similar many effect estimates are in these two trials.

I offer the following major comments:

1. A key open question is the optimal duration of dual antiplatelet therapy after stroke. The authors mention "separating survival curves" several times. I assume they mean incidence curves as the main outcome was not death. They do not show incidence curves. If anyhow possible such curves must be shown, optimally complemented by curves of risk over time.

2. It is unclear what the etiologies in the trials included in this meta-analysis were. Lacunar, large-vessel disease, arterio-arterial embolic and cryptogenic all have different pathophysiologies that may well result in differential effect of dual antiplatelet therapy. It is likely that most arterio-arterial embolic strokes have not been included as they will often have received unfractionated heparin. Lacunar strokes are associated with cerebral microbleeds, in which case antiplatelet agents may be relatively contraindicated. The authors should state clearly what the

etiologies were and, if possible, show key results by etiology. If they cannot, they must discuss this important weakness.

I offer the following minor comments:

1. There are grammatical and spelling errors throughout that should be corrected. There are painful oversights such as omitted words and abruptly ending sentences that should be corrected.

2. On page 19 the authors state that their review provide high quality evidence. In my view they do not provide evidence but rather summarise the evidence provided by others. This should be amended.

3. The authors cite the Small Subcortical Strokes trial to strengthen their point that there be no benefit for dual antiplatelet therapy initiated after the first two weeks after stroke. However, this trial investigated lacunar infarcts. It should be justified how the present analysis and this trial are comparable.

Additional Questions:
Please enter your name: Raimund Pechlaner

Job Title: Resident

Institution: Medical University of Innsbruck

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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: none

Reviewer: 2

Recommendation:

Comments:
This is a high quality systematic review with meta-analysis on the important topic of dual antiplatelet therapy for patients with minor ischaemic stroke and transient

ischaemic attack, now that the NIH-funded POINT trial has concluded with data supporting the earlier dramatic Chinese CHANCE trial. The advantage of the updated review by including POINT is the precision of the estimates of benefits and harms, and of the survival curve diversions indicating that most of the benefits of dual antiplatelet therapy (aspirin and clopidogril) occurs in the first 10 days, which will guide clinicians in managing treatment to maximise benefits over harms (major intracrainial and extracranial haemorrhage). In addition, worse case scenario sensitivity analyses were undertaken over missing outcomes, showing no material alteration of the estimates. The data are well presented and discussed, with estimates supported by a grading of the quality of the evidence.
I found it difficult to fault the review.

Additional Questions:
Please enter your name: Craig Anderson

Job Title: Executive Director

Institution: The George Institute China

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: I have received a research grant to my institution from Takeda China. I have received honorarium and travel reimbursement for attending an Advisory Board meeting for Amgen. I have received honorarium and travel reimbursement from Takeda and Boehringer Ingelheim for speaking at a symposium. None of these companies has any of the products or therapies related to the topic covered in the manuscript

Reviewer: 3

Recommendation:

Comments:
BMJ.2018.046115 – review by Hanne Christensen
Hao et al

Looks at ASA + clopidogrel versus ASA alone in TIA, minor stroke, including only three trials FASTER, CHANCE and POINT, finds reduction of risk of recurrent ischaemic events at the price of haemorrhage.
Methodologically I find no flaws, the analysis and search process is described according to standards and the report is clear and transparent.
However, I do not think that the research question asked is to the point as to clinical needs, which is also reflected by the background section which only focuses on benefit. The uncertainty in this field is focused on harms and not on benefit: I do not think that anybody based on existing literature for years have really been able to doubt if double platelets reduced risk of ischaemic stroke better than single, the question has been at what price of haemorrhage, especially intracranially.
I do not think that the current review really contributes to this as it is: from a clinically point of view the right questions that have not been asked.
There are two main issues still discussed in this field:
1) Choice of investigated IMP: today clopidogrel is first choice in this group of patients in many countries – there is little debate if clopidogrel is superior to ASA, so the real burning issue is if ASA + clopidogrel is superior to clopidogrel. The opposite is stated in the MS; but this is not the case outside of US at the moment. However, there is little data on this question.
2) Haemorrhagic complications (especially ICH): The question in clinical practice is if the price in haemorrhagic complications is worth paying for the reduction in recurrent ischaemic events, and lack of data on long term outcome to better understand harms.
The authors could have compared single platelet versus double or triple platelet to better cover these issues or another solution to better cover the area based on clinical relevance e.g. I think it is concerning that TARDIS was not included – at least based on the clinical.
One of the devils in the detail of systematic reviews remains the selection criteria: these decide if the research question is really what is clinically relevant – as well as if all relevant/useful literature in the field will be included. The majority of studies are for various reasons – including the time of the planning of the trials – based on ASA as gold standard.
It is stated in section 2: what this study adds
'Pooled data from 3 trials established and important benefit of dual therapy begun within 24 hours of presentation in reducing recurrent stroke by approximately 2%'
Comment: this benefit could be observed individually at least in Chance and Point (did not check Faster); the comparator is (ASA) is not stated, nor that this is not universal standard anymore. The very close balance of benefit and harms – underlined by the diverging results in trials as to ICH – is not touched and results to a significant driven by the surprisingly low rates of ICH in Chance – my opinion is that including TARDIS as to harms would have changes the safety profile. The risk of ICH in double platelets is generally reported at the level of NOACs, and this is not nothing.
..'Serious extracranial bleeding in this setting is uncommon, and any increase with dual therapy is likely to be small.
Discontinuation of dual therapy within 10 days of initiation is likely to maximize benefits and reduce harms.'..
Comments: Extracranial bleeding is not a major issue with double platelets. The included trials used treatment for 90 days, TARDIS (not included) looked at 30 days and reported excess bleeding in group receiving both ASA and clopidogrel. Most likely bleeding rates are lower the shorter the treatment period, but this has not yet been determined.
This box is concluding beyond data, and does not have sufficient focus on patient safety.
Conclusively: There are no methodological concerns, however, the analysis is not addressed towards the clinical needs in the area not does it take patient safety

issues sufficiently into account. Further, not all relevant studies are included; a large not-included study might have changes conclusions as to harms.

Additional Questions:
Please enter your name: Hanne Christensen

Job Title: Professor

Institution: University of Copenhagen

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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