PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Coronary and Mortality Risk of Novel Anti-Thrombotic Agents: a Meta-analysis of Large Randomised Trials
AUTHORS	Mak, KoonHou

VERSION 1 - REVIEW

REVIEWER	Vic Hasselblad Duke Clinical Research Institute USA I have no conflict of interest.
REVIEW RETURNED	02-Jul-2012

GENERAL COMMENTS	The purpose of a meta-analysis is to combine similar studies with common endpoints across reasonably similar populations. If the studies do not meet this criterion, then the inclusion criteria must be changed so that the studies do meet it. If, after segregating the studies, it appears that the results are quite similar regardless of the population, then it might make sense to give an overall result. Some specific comments follow: P. 5: why were studies restricted to those with a total size > 1000? If you are worried about the stability of the estimates, then the number of events is the critical item. I did notice that the event rates could vary by a factor of nearly 100, which is indicative of some major differences. P. 5: Why were different doses of the same study drug combined? It makes some sense but it seems like you need a reason. P. 5: You indicated that the bleeding definitions are different, which is confirmed by the results. This may be an issue that cannot be handled quantitatively, but the results could be described. P. 6: the funnel plots are nice but I don't think they are necessary. Tests for publication bias are not especially powerful for small numbers of studies, but reporting the results you obtained is worthwhile. Figure 3D (and others): one flaw with CMA is that it does not handle zero counts well on the graphs. For example, in Figure 3D the point estimate for APPRAISE 1 is infinity, but the plot shows it as 4.80 (the result of adding fractional counts to the cells). I would be nice if the plot did not even show a point estimate, but was instead a line with an arrow head on the right, starting at 0.20.

REVIEWER	Diener, Hans-Christian University Hospital Essen, Neurology
REVIEW RETURNED	09-Jul-2012

GENERAL COMMENTS	This paper is a very well conducted meta-analysis of the risks of mortality and coronary events as well as major bleeding complications with the new anticoagulants. The data on MI and death are solid. The data on major bleeds suffer from the fact that this endpoint was defined in a different way in different studies. The study showed a higher incidence of MIs with dabigatran and a lower rate with rivaroxaban. Despite the increase in MI risk mortality was significantly reduced with dabigatran compared to control. My major criticism is the fact that no conclusions for the use of the new anticoagulants for a clinician are provided. In patients with AF, should a treating physician avoid dabigatran because of a very small increase in the risk of MI and expose him to a much higher risk of ischemic stroke? In addition the author needs to point out that firm conclusion can only be drawn from properly powered randomised trials. Only in cases were these results are inconclusive meta-analysis should be used and interpreted. The author frequently uses the term “trend”. This is statistically incorrect. A difference is either significant or not. 1. Page 4: “looms the dark cloud of higher rate of MI” is a very unscientific term. 2. I feel not very comfortable with using major bleeds (due to the different definitions). Could this replaced by fatal bleeds, in which there is no doubt about the definition)? 3. Figure 2A-D: please add the overall numbers across all trials in the last line 4. Page 9: The author mentions the lack of an antidote for the new anticoagulants. These are under development for dabigatran and apixaban. In addition there was no difference in outcome of intracranial bleeds and emergency surgery with dabigatran compared to warfarin the RE-LY trial despite the lack of an antidote 5. The author needs to point out that in some trials silent infarcts were counted as MIs, and in other trials not.

REVIEWER	Masatsugu Hori President Osaka Medical Center for Cancer and Cardiovascular Diseases Japan
REVIEW RETURNED	11-Jul-2012

THE STUDY	To Authors: This manuscript presents a meta-analysis of large randomized trials for new oral anticoagulants, antithrombin inhibitors (ximelagatran and dabigatran) and anti-Xa inhibitors (rivaroxaban and apixaban). The authors demonstrated that the risk for MI/ACS is higher for the antithrombin inhibitors whereas it is lower for anti-Xa inhibitors. They also showed that all-cause mortality is lower among those receiving novel antithrombotic agents. The present meta-analysis is providing the useful information reflecting the pharmacological characteristics

	of the specific subsets of the new oral anticoagulants, however, the reviewer concerns several issues which should be responded by the authors. 1) The present meta-analysis was performed using a fixed-effects model. The authors should justify why the fixed-effects model was used given the fact that heterogeneity was observed for some analysis and trials differ in indication, population and comparator. Wouldn't the random-effects model been more appropriate? 2) In the present study, only studies with more than 1000 subjects were included. What is the rational of this inclusion criterion? This may cause the bias in drawing the conclusion. How many full-published trials were excluded from this study, and what was the effect of this exclusion on the conclusion? 3) In the Methods, the authors defined that the primary outcome is acute coronary events comprising of either MI or ACS. They included cardiac death in this primary outcome, however, cardiac death is not always associated with coronary events. Death from heart failure and arrhythmogenic death may be included in "cardiac death". Why is cardiac death pooled with MI/ACS? 4) The authors pool all dosages of one drug. There might be lower dosages not considered to be clinically effective and pooling of these data implies a bias forward non-inferiority in disfavor of the respective drug. The most appropriate way would be to look at each dosage of one drug separately to potentially detect dose-dependent effects and to exclude dosages that are considered not clinically effective. 5) In Fig.2C, the numbers of events may be those of major bleeding, not of MI/ACS. They are all identical with in Fig. 3C. In Fig.4C, the number of events (641) in the ATLAS ACS2 TIMI51 include all-cause mortality (245), MI and stroke as a composite endpoint. All figures should be checked again for clarification. 6) In Conclusion, the risk for MI/ACS was higher for ximelagatran, but it is not significant. Thus, the description "The risk for MI/ACS was significantly higher for oral direct thrombin inhibitors" is not appropriate. Minor comments: p.3 l.6 Article summary; ant-thrombotic→anti-thrombotic p.8 l.4 "while" should be deleted. p.8 l.17 follow→following

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. Rationale of including studies with >1000 subjects

Randomized controlled clinical trials with >1000 subjects are likely to be well-conducted with higher quality including independent clinical event adjudication and monitoring and safety committees. As such, this arbitrary number was chosen and was reflected in the Title as "large randomised trials." In smaller clinical trials, the individual endpoints may not be adequately described, especially when information on each patient was not available. Indeed, of the 269 studies identified, only 10 of them were excluded because of this criterion (Figure 1). These were early exploratory short-term studies with limited reporting of the outcomes of interest. Furthermore, there are newer oral anti-thrombotic agents that are being investigated.

2. Combining different doses of the same drugs

Different doses of the same drug were used especially in Phase II trials. The numbers in each group

was small and not the doses studied were used in Phase III trials. As such, it was appropriate to combine them together, which the Reviewer felt that it was sensible. So, the phrase " … as the numbers of patients and events in each of the doses were small, especially in phase II studies" has been added in the Methods section

3. Bleeding risks
With the expansion of the Figure 3, the combination of anti-thrombotic agents with antiplatelet agents accounted for the increase in major bleeding complications. The discussion has been expanded in the second paragraph of page 9 and page 10, including the recommendation to exercise caution when combining these agents.

4. Funnel plots
The Reviewer agreed that the Funnel plots were useful and worth reporting. Since they were briefly referred to in the text, no change was made.

5. Figure 3D
As requested by the Reviewer, the point estimate for APPRAISE I has been removed.

Reviewer 2

I would like to express my gratitude for his kind and favourable comments.

1. Recommendation to the clinician
I agree with the Reviewer that some form of recommendation should be made based on the results. It is not the intention to dissuade clinicians from using anti-thrombotic agents. The difference in risk profile may assist the practitioner in choosing an appropriate agent. As such, the following sentence "Therefore, based on these findings, those with heightened coronary risk, the use of anti-Xa agents may be preferable to direct thrombin inhibitors" has been added to the end of the first paragraph of the Discussion. In conjunction with his next point, the reader is advised to exercise caution in interpreting the findings.

2. Drawing firm conclusion
Although this limitation has been stated in the Article Summary section, it is now highlighted in the last paragraph of the Discussion of the revised manuscript.
"As with any results from meta-analyses, a firm conclusion can only be drawn from well-conducted, adequately powered randomised trials."

3. Use of the word "trend"
As suggested by the Reviewer, the word "trend" has been changed to "non-statistically significant" or "statistically insignificant."

4. Unscientific term
The phrase "… looms the dark cloud of higher rate of myocardial infarction …" has been changed to "Amidst the enthusiasm of favorable results, higher rates of myocardial infarction (MI) among patients receiving dabigatran initially reported in the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial(1) have generated concern regarding the overall effectiveness of this agent.

5. Use of major bleeding complications
Unfortunately, I do not have source data to differentiate identify fatal bleeding complications.

6. Total number of subjects in Figures 2A to 2D
As requested, the total number of subjects has been included in Figures 2A to 2D.

7. Bleeding complication and antidote
Both assays and antidotes are being developed for these new anti-thrombotic agents. However, they are not routinely available in clinical practice. In addition, there has been bleeding risk signals in the real world practice (Harper P, Young L, Merriman E. Bleeding risk with dabigatran in the frail elderly. N Engl J Med 2012; 366:864-866). Detailed discussion of this subject, ie; assays and antidote, is beyond the scope of the paper.

8. Silent myocardial infarction
This limitation was elaborated in the Discussion section.
“Silent MI may be actively sought out for in some studies, especially after revascularisation procedures, with routine electrocardiography or cardiac enzyme assays. But this approach may not be adopted in other trials. While this difference could have accounted for variation observed among studies, it was less likely to impact on results within a study.”

Reviewer 3

1. Statistical modeling
I have performed the analysis using both fixed- and random-effects models (with 95% confidence interval in parenthesis), and the results were fairly comparable, except for coronary events among those receiving ximelagatran.

Outcome/Drug Fixed-effects P-value Random-effects P-value
Coronary events
Ximelagatran 1.08 (0.73-1.61) 0.700 1.65 (0.56-4.87) 0.368
Dabigatran 1.30 (1.04-1.63) 0.021 1.30 (1.04-1.63) 0.021
Rivaroxaban 0.78 (0.69-0.89) <0.001 0.78 (0.69-0.89) <0.001
Apixaban 0.94 (0.82-1.07) 0.333 0.94 (0.82-1.07) 0.333
Major bleeding
Ximelagatran 0.97 (0.76-1.25) 0.827 0.99 (0.64-1.54) 0.974
Dabigatran 0.90 (0.80-1.001) 0.052 0.99 (0.71-1.38) 0.932
Rivaroxaban 1.15 (1.003-1.31) 0.046 1.57 (0.84-2.94) 0.157
Apixaban 0.94 (0.82-1.07) 0.333 0.91 (0.59-1.41) 0.661
All-cause mortality
Ximelagatran 0.92 (0.76-1.10) 0.356 0.92 (0.76-1.10) 0.356
Dabigatran 0.89 (0.80-0.99) 0.039 0.89 (0.80-0.99) 0.039
Rivaroxaban 0.82 (0.74-0.90) <0.001 0.82 (0.74-0.90) <0.001
Apixaban 0.91 (0.82-0.99) 0.038 0.91 (0.82-0.99) 0.038

As recommended by the Reviewer, I have changed the overall analysis to the random-effects model. In addition, I have included the analysis of each of the groups based on the indication for use. Since in these sub-groups, the selection criteria and doses are fairly similar, the fixed-effects model was used, except for apixaban in the context of atrial fibrillation. Since the control groups were different, antiplatelet agent and warfarin, the random-effects model was used instead. As such, the following amendment has been made in the revised manuscript.

“The associations between risk of each of the outcomes in the control groups (baseline risk); acute coronary events, major bleeding complications and all-cause mortality, with the corresponding odds ratio of the use of each of the anti-thrombotic agents for each of the indication of use; namely venous thromboembolism prophylaxis, treatment of thromboembolism, prevention of thromboembolism among those with non-valvular atrial fibrillation and acute coronary syndromes, were evaluated with a linear fixed-effects meta-regression model. For studies using dissimilar agents in the control group,

the random-effects model was applied instead. In the overall results, the random-effects model was used."

2. Rationale of including studies with >1000 subjects
Please refer to Response 1 of Reviewer 1.

3. Myocardial infarction /Acute coronary syndromes
Indeed in the Methods section, coronary events included myocardial infarction, acute coronary syndromes, and cardiovascular death. Unfortunately, data provided from the publications categorized these events differently. As such, the entire group could be renamed as coronary events and cardiovascular death. However, only 4 of the 28 trials included in the study used cardiovascular event or death as outcome measures. So the term "coronary events" (which was used in the methods section) is used instead. The Figure Legends and Titles have been changed.

4. Pooling of dosages of each drug
Please refer to Response 2 of Reviewer 1. Furthermore, individual information of each patient was not available.

5. Figure errors
I would like to thank the Reviewer for his astute observation. The numbers in Figure 2C have been corrected. As requested, the numbers for all-cause mortality for ATLAS ACS2/ TIMI 51in Figure 4C has been checked with the original article and it is correct.

6. Conclusion
As recommended by the Reviewer, the conclusion in the Abstract has been modified in the revised manuscript.
"The risk for MI/ACS was significantly higher for dabigatran but not significantly higher for ximelagatran."

7. Spelling errors
Thank you again for pointing out the typographical errors. They have been corrected in the revised draft.

The manuscript has not been published previously in print or electronic format and is not under consideration by another publication or electronic medium. None of the paper's contents have been previously published. I have met the full criteria and requirements for authorship. The manuscript has been read and approved the final version of the manuscript. Should the paper be accepted for publication, an exclusive licence on a worldwide basis to the BMJ Publishing Group Ltd to permit this article to be published in BMJ editions and any other BMJPGL products and sublicences such use and exploit all subsidiary rights, as set out in the licence. I did not receive any support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work. However, I was an Event Adjudicator of the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial.

VERSION 2 – REVIEW

REVIEWER	Vic Hasselblad Duke UNiversity I have no conflicts of interest.
REVIEW RETURNED	21-Aug-2012

- The reviewer completed the checklist but made no further comments.

REVIEWER	Masatsugu Hori President, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan
REVIEW RETURNED	29-Aug-2012

GENERAL COMMENTS	The revised manuscript well responded to the Reviewer's comments. Particularly, the author applied the random-effects model for studies using dissimilar agents in the control group. The Reviewer recognized much improvement of the analysis in the revised manuscript. The Reviewer has some minor concerns about wording. Several expressions; p.7 l.24, 49, p.8 l.43 "non-statistically significant" →"insignificant" or "statistically insignificant" may be better p.9 l.10 hightened → "high" may be better p.10 l.35 exercised → "paid" may be better