Author's response to reviews

Title: Duration of Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention on Re-hospitalization for Acute Coronary Syndrome

Authors:

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Date: 5 December 2013

Author's response to reviews: see over
5 December 2013

Dr Fabrizio D’ascenzo

RE: MS 7962204631073473
Duration of Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention on Re-hospitalization for Acute Coronary Syndrome

Dear Editor:

Attached please find the revised version of our manuscript with title as “Duration of Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention on Re-hospitalization for Acute Coronary Syndrome.”

Thank you for providing us with this opportunity to revise the paper. We are very grateful for the reviewers’ and editor's helpful comments on reorganizing our paper. We also appreciate the time and effort you spent helping us as well. We have revised the text to clarify points suggested by the reviewers. We also had one professional native English editorial proof-read our manuscript for better clarity.

The revised manuscript now is a much stronger paper as a result of the reviewers’ and your suggestions. We hope you will find the changes satisfactory and this revised manuscript meets the high standard of BMC Cardiovascular Disorder.
Reviewer #1: COMMENTS FOR AUTHOR/S

Minor revisions:

1. Please fix spelling and grammatical errors throughout manuscript.

   **REPLY:** Thank you for the comment.

   We have fixed spelling and grammatical errors throughout manuscript.

2. Please address limitation of Taiwanese response to Clopidogrel vs. other populations (CYP2C19*2 prevalence)

   **REPLY:** We thank the reviewer for a very good suggestion.

   We have addressed limitation of Taiwanese response to Clopidogrel vs. other populations (CYP2C19*2 prevalence) in the **Discussion** section (page 18).

   “Thirdly, our findings may not be generalizable to non-Asian populations. Previous study has indicated that the cytochrome P450 (CYP) 2C19 poor metabolizers may exhibit less antiplatelet activity when they were exposed to the same clopidogrel regimen than other healthy volunteers. The variation of prevalence of CYP2C19 poor metabolizers in different populations (3-6% of Europeans and Africans, and 13-23% of Asians) thus need to be taken into account when interpreting our findings (17)”


3. Was there use of cilostazol and if so did this affect the outcome

   **REPLY:** Thank you for the comment.

   Based on the reimbursement criteria of Taiwan's National Health Insurance, cilostazol can only be used to treat peripheral vascular diseases (e.g. intermittent claudication), we thus retrieved the prevalence of peripheral vascular diseases in our study cohorts.

   We found that the prevalence of peripheral vascular diseases are very low and comparable in discontinuous and continuous users of all three cohorts (9-month: discontinuous 2.4% vs. continuous users 0.7%, p=0.05; 12-month: discontinuous 1.3% vs. continuous users 1.0%, p=0.65; 15-month: discontinuous 1.2% vs.
continuous users 1.2%, p=1.00). Therefore, we believed that the impact of use of cilostazol on the outcome could be very small.

Nevertheless, we have included this in the Discussion section (page 18). "...... our patients in the continuous and discontinuous groups were well balanced in terms of most baseline characteristics, including prevalence of peripheral vascular diseases."

4. In limitations it must be addressed that patients that discontinue any medication are generally at a higher risk of CV events (i.e. they are sicker) and thus reverse causation could be leading to these results - please emphasis this in the conclusions.

REPLY: Thank you for the good comment.

We agree with the reviewer that patients that discontinue any medication may be generally at a higher risk of CV events. Therefore, we collected a wide range of potential cardiovascular risk factors, including very detailed procedural characteristics and information on other concomitant medications. In general, patients in the continuous and discontinuous groups were well balanced in terms of most baseline characteristics. Nevertheless, our continuous users are sicker than discontinuous users (e.g. 12-month cohort: continuous clopidogrel users had higher prevalence of hypertension, multi-vessel disease, right coronary artery (RCA) stenosis, longer stent length, and smaller stent diameter). Therefore, the effect of reverse causation might be small in our study.
The manuscript by Shih-Chin Chen supports the use of clopidogrel for at least 12 months in ACS setting.

Major Compulsory Revisions

1. The authors have cited the ACC-AHA Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction. Worthy of mention are also the European Guidelines about NST-ACS (ESC, 2011) and STEMI (ESC 2012)

REPLY: Thank you for the comment.

We have included European Guidelines about NST-ACS (ESC, 2011) and STEMI (ESC 2012) in the Introduction section based on the reviewer's comment (page 7).

2. There is no mention on the use of GP IIb IIIa inhibitors during the index procedure. What about its use?

REPLY: Thank you for the comment.

We have added use of GP IIb IIIa inhibitors during the index procedure in Table 2.

Overall, the percentages of use of GP IIb IIIa inhibitors during the index procedure are approximately 2.4~4.3%. The use of GP IIb IIIa inhibitors between discontinuous and continuous users are comparable.

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<th>9 month</th>
<th>12 month</th>
<th>15 month</th>
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<tbody>
<tr>
<td></td>
<td>Dis continuous</td>
<td>Continuous</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>(n=292)</td>
<td>(n=452)</td>
<td></td>
</tr>
<tr>
<td>7 (2.4%)</td>
<td>15 (3.3%)</td>
<td>0.47</td>
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</table>

3. Among DES patients, the authors found a larger reduction in the hazard of ACS re-hospitalization for patients who received at least 12 months of clopidogrel but not 9 months of clopidogrel use. Is there any differences according to the type of DES used?
REPLY: We thank the reviewer for a very good suggestion.

We have compared the types of DES used between patients who received at least 9 and 12 months of clopidogrel use and no difference was found between these two groups.

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<thead>
<tr>
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<th>9 month</th>
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<tr>
<td></td>
<td>Dis continuous</td>
<td>Continuous</td>
</tr>
<tr>
<td>(n=292)</td>
<td>(n=452)</td>
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<tr>
<td>Paclitaxel</td>
<td>53 (18.2%)</td>
<td>103 (22.8%)</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>76 (26.0%)</td>
<td>134 (29.7%)</td>
</tr>
<tr>
<td>Zotarolimus</td>
<td>49 (16.8%)</td>
<td>105 (23.2%)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>12 (4.1%)</td>
<td>45 (10.0%)</td>
</tr>
<tr>
<td>EPC-capturing</td>
<td>11 (3.8%)</td>
<td>13 (2.9%)</td>
</tr>
</tbody>
</table>

4. Patients who received # 15 months of clopidogrel therapy were older than the discontinuous users. Could the authors explain this finding?

REPLY: Thank you for the comment.

In Taiwan, only 9 months of dual antiplatelet therapy would be covered by Taiwan’s National Health Insurance program for all patients discharged from an ACS hospitalization. Patients need pay out-of-pocket for dual antiplatelet therapy after finishing the 9-month therapy. Nevertheless, elderly are exempted from this restriction. Therefore, patients who continuously received more than 15 months of clopidogrel therapy were older than the discontinuous users.

5. There are no data about bleeding according to the duration of clopidogrel.

REPLY: Thank you for the comment.

As bleeding is not the main focus of our study, we have added this as one of our limitations in the Discussion section (page 19).

6. The manuscript focuses on the use of clopidogrel in the era of new antiplatelet agents (eg. prasugrel, ticagrelor). This is a limitation of the study.

REPLY: We agree with the reviewer that more new antiplatelet agents are available.

Nevertheless, prasugrel (currently not available) and ticagrelor (available July, 2013) are not reimbursed by Taiwan’s National Health Insurance program during our study period. We have added this as one of our limitations in the Discussion section (page 19).
The manuscript by Shih-Chin Chen supports the use of clopidogrel for at least 12 months in ACS setting.

**Major Compulsory Revisions**

1. **Competing interests:** Manuscripts should include a Competing interests section. This should be placed after the Conclusions/Abbreviations.

   **REPLY:** We have added a "Competing interest" section in our manuscript based on the editor's suggestion. (page 21)

2. **Authors' Contribution:** Please place the Authors' Contributions section after Competing interests. Please check the instructions for authors on the journal website for the correct format to use for Authors' Contributions.

   **REPLY:** We have added a "Authors' Contributions" section in our manuscript based on the editor's suggestion. (page 21)

3. **Acknowledgements:** Please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship.

   **REPLY:**

   We have added a "Acknowledgement" section in our manuscript based on the editor's suggestion. (page 21)

   We cannot express how much we appreciate the reviewers’ very thorough and thoughtful review of our paper. Their opinions and valuable suggestions inspired us to think the whole paper over carefully and strengthen the discussions. I hope that you will find this paper to be much improved and quite suitable for publication.

Sincerely yours,

Fei-Yuan Hsiao, Ph.D.
National Taiwan University, College of Medicine
Graduate Institute of Clinical Pharmacy