

## **Reviewer's report**

**Title:** Cilostazol Improves Endothelial Function in Acute Cerebral Ischemia Patients: A Doubleblind Placebo Controlled Trial with Flow-mediated Dilation Technique

**Version: 0 Date:** 13 Jul 2017

**Reviewer:** Mark Harrigan

### **Reviewer's report:**

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The authors report a randomized trial comparing aspirin to cilostazol treatment of patients with acute ischemic stroke. Patients within 7 days of their stroke were treated with one or the other drug in a blinded fashion for 90 days. Cilostazol appeared to improve endothelial function as measured by flow-mediated dilation. There was a significantly higher rate of adverse events in the cilostazol group, which was mainly due to significant headaches in about a third of the subjects getting cilostazol. The study is significantly limited by the omission of a normal control arm and L-arginine levels at T1.

1. A healthy control group should have been included in this study, to determine if a recent ischemic stroke produces any changes in the parameters of interest. There is growing evidence that local ischemia can produce systemic effects, and a healthy control group might have also shed some light on the disparities of various studies of cilostazol mentioned in the Discussion.
2. How were the doses of cilostazol and aspirin selected? This should be included in the Methods section.
3. "Reverse" correlation is used throughout the manuscript. I believe the authors intend to use "inverse."

4. Include the percentages of patients on statin therapy prior to study enrollment in Table 1. This medication is thought to play an important role in atherosclerotic disease and could impact results. As such, the imbalance of statin therapy in Table 3 is a concern and deserves mention in the limitations section.
5. There are important differences in percentage of patients with hypertension and diabetes mellitus in favor of cilostazol. These deserve mention in the limitations section.
6. The significant differences in the T0 and T1 FMD could reflect differences in the baseline values. The baseline FMD in the aspirin group is larger than the baseline in the cilostazol group, despite not being significantly different. It is possible that the FMD curve plateaus. This deserves discussion. Inclusion of normal values may have shed light on the issue.
7. The phrase "dose associated relationship" is used in paragraph 1 of the discussion. This is confusing given that the doses of aspirin and cilostazol were fixed.
8. The last sentence of paragraph 1 and 2 are hard to follow and need re-worked.
9. In paragraph 4 of the discussion the sentence that starts with "In the case of hypercholesterolemia..." needs a citation.
10. In the discussion there is a sentence that states that "L arginine acts as a substrate for L arginine synthesis". This appears to be a mistake.
11. The data on L-arginine supports the notion of the "L-arginine paradox" but sheds little insight in the the paradox. Basically, the lower the initial L-arginine concentration is, the greater the FMD response in patients getting cilostazol. The part of the Discussion covering this is confusing and can be tightened up along the lines of, "Our data shows the paradox, but doesn't explain it...."

**Are the methods appropriate and well described?**

If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**

If not, please specify which controls are required in your comments to the authors.

No

**Are the conclusions drawn adequately supported by the data shown?**

If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**

If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

**Quality of written English**

Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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