Author's response to reviews

Title: Prognostic significance of endothelial dysfunction in patients undergoing percutaneous coronary intervention in the era of drug-eluting stents

Authors:

Motoki Kubo (k.moto.39@gmail.com)
Toru Miyoshi (miyoshit@cc.okayama-u.ac.jp)
Hiroki Oe (hirokioe@gmail.com)
Yuko Ohno (he17805@s.okadai.jp)
Kazufumi Nakamura (ichibun@cc.okayama-u.ac.jp)
Hiroshi Ito (itomd@md.okayama-u.ac.jp)

Version: 3
Date: 10 August 2015

Author's response to reviews: see over
Dear Editors;

Re: Resubmission of manuscript for publication (MS: 1958524473169284)

We would like to thank you and the reviewers for your time and effort in reviewing our manuscript titled “Prognostic significance of endothelial dysfunction in patients undergoing percutaneous coronary intervention in the era of drug-eluting stents”. We appreciate the valuable and detailed comments provided by the reviewers. We have followed these suggestions and revised the manuscript accordingly. Text that we changed or inserted in response to the reviewers’ comments is shown in red font in the revised manuscript. In the pages that follow are our point-by-point responses to the comments of the reviewers.

We hope that our revised manuscript is now acceptable for publication in BMC Cardiovascular Disorders and we look forward to hearing from you.

Yours sincerely,

Toru Miyoshi

Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan

Tel: +81 86 235 7351

Fax: +81 86 222 7353

E-mail: miyoshit@cc.okayama-u.ac.jp
Response to the Reviewer #1

-Please clarify the number of patients excluded according the different exclusion criteria. The overall time of enrollment is very long, I think that the study population is highly selected.

Response: To clarify this point, we added the following paragraph at the start of the Results section (see below). Additionally, a flow diagram showing patients’ acceptance into the study was added (Figure 1).

“A flow diagram of this study is shown in Figure 1. Of 632 patients who underwent PCI from August 2008 to February 2014, we excluded 494 patients without FMD data. Of the 138 remaining patients, 58 patients were excluded because of acute coronary syndrome (n = 24), coronary artery bypass graft (n = 16), FMD measured over 1 week after PCI (n = 16), and lost to follow-up (n = 2). Finally, 80 patients were analyzed.”

-You enrol 80 patients from among 138 with stable CAD. Please clarify the reasons to exclude the other 58 patients.

Response: This clarification has been added at the start of the Results section.

“Of 632 patients who underwent PCI from August 2008 to February 2014, we excluded 513 patients without FMD data. Of the 138 remaining patients, 58 patients were excluded because of acute coronary syndrome (n = 24), coronary artery bypass graft (n = 16), FMD measured over 1
week after PCI (n = 16), and lost to follow-up (n = 2).”

-Please, clarify the experience of the team performing the FMD measurement. It is performed by only one technician and/or physician? Please clarify variability between observations.

Response: We added a sentence to the Methods section to clarify this point.

“An experienced technician blinded to the clinical data of the study participants measured FMD and intra- and inter-observer correlation coefficients were high (>0.9).”

-Several reports suggested that ACE inhibitors are able to modulate endothelial function. Especially, it has been observed a significant difference between A2R blockers and ACE-I. Similarly, some studies suggested a difference between ACE-Inhibitors (Am J Cardiovasc Drugs. 2011;11:189). Please clarify this issue. Please clarify the number of patients in ACE-I and in A2R blockers. Please, clarify the type of ACE-I

Response: We have added the following text to the results section in response to this point.

“There was no difference in prescription rates for angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) between the two FMD groups. Additionally, there was no difference in the type of ACE inhibitors between the two groups.”

Additionally, we have added these data to Table 1 and have added a paragraph in the Discussion to discuss this issue (the 5th paragraph of the Discussion).
-A similar consideration should be done for statins. Please clarify type and dose of statins.

Response: We have added the following text to the results section.

“There was also no difference in the type of statins between the two groups.”

Additionally, we have added these data to Table 1 and have added a paragraph in the Discussion to discuss this issue (the 5th paragraph in the Discussion).

-Endpoints: the composite endpoint is not usual? Why you include critical limb ischaemia? In addition the definition of all endpoints is missing. How you assess cardiac death? You include type 2 MI in you definition? You include type 4 MI in you definition? How you define stroke? Ischaemic stroke only or also intracranial haemorragic strok?

Response: In response to this point, we added the relevant information to the Methods section. Definition and assessment of endpoints were performed based on the statement from the American College of Cardiology/American Heart Association Task Force.\(^1\) Myocardial infarction was defined as type 1 or type 2 myocardial infarction according to the Third Universal Definition of Myocardial Infarction.\(^2\) All elective coronary revascularizations were undertaken only if the invasive fractional flow reserve of a coronary lesion was 0.80 or less.\(^3\) Definition of stroke included both ischemic and hemorrhagic types, while in this study only ischemic stroke was documented. Peripheral vascular intervention was documented in a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards.\(^1\) Critical limb ischemia needs emergency vascular intervention. Therefore, we included critical
limb ischemia as a cardiovascular endpoint in this study.

References


-It was present a independent reviewer to assess adverse events? This reviewer was blinded to FMD measurements?

Response: The following text has been added to the Methods section.

“Data regarding primary and secondary outcomes were carefully collected from clinical charts and the diagnosis was confirmed by an investigator who was blinded to FMD data.”

-You observed 19 adverse evets due to new lesions. This is a very high number?

Do you perform angiographic follow-up? Please clarify the clinical presentation. It is after stress test? It is for ACS? Nevertheless, you reported only one MI adverse event.

Response: The following text has been added to the methods section.

“All elective coronary revascularizations were undertaken only if the invasive fractional flow
reserve of a coronary lesion was 0.80 or less.”

Additionally, the following text has been added to the results section.
“Of 19 patients undergoing coronary revascularization due to new lesions, two patients in the low FMD group were hospitalized for unstable angina, but were not diagnosed as having myocardial infarction.”

- Why you did not consider hospital admission for ACS in your endpoints?
Response: In this study, patients who underwent PCI included those without myocardial infarction. Of 19 patients undergoing coronary revascularization due to new lesions, two patients in the low FMD group were hospitalized for unstable angina, but were not diagnosed as having myocardial infarction. We have added this information in the Results section.

-Discussion: endothelial function may be really important after BVS implantation.
I well know that in your study population BVS are not implanted. Nevertheless, a sentence in the discussion may improve the interest in the paper.
Response: We have added a new paragraph of text about this issue in the final paragraph in the Discussion.
1) In Abstract, it says "The incidence of all cardiovascular disease was significantly lower in the low FMD group with a median value of <4.2% than the high FMD group (60 % vs. 25% p < 0.01). According to Table 3 it should read the opposite (higher in low FMD group).

Response: We have corrected it.

2) In Results, it says "Patients with low FMD had lower -LDL cholesterol levels compared with the high FMD group (p = 0.03). These data do not match the data in Table 1 for LDL-cholesterol.

Response: We have corrected it as follows in the Results section.

“Patients with low FMD had lower high-density lipoprotein (HDL) cholesterol levels than those with high FMD (p = 0.04).”