Author’s response to reviews

Title: Effect of Eicosapentaenoic acid/Docosahexaenoic acid on Coronary High-intensity Plaques Detected with Non-contrast T1-Weighted Imaging (The AQUAMARINE EPA/DHA Study): study protocol for a randomized controlled trial

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Dear Professor Jean Joel R Bigna, MD, MPH

Associate Editor

Trials

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Enclosed please find the revised version of our manuscript entitled “Effect of Eicosapentaenoic acid/Docosahexaenoic acid on Coronary High-intensity Plaques Detected with Non-contrast T1-Weighted Imaging(The AQUAMARINE EPA/DHA Study): study protocol for a randomized controlled trial“ which we are returning for consideration for publication in Trials. We appreciate the favorable review and the opportunity to improve our manuscript. Our responses to the reviewers’ comments are attached.

All authors have read and approved submission of the manuscript. The manuscript has not been published and is not being considered for publication elsewhere in whole or part in any language except as an abstract.

We hope that our revised manuscript is now suitable for publication in Trials.

Thank you for considering our paper. We look forward to receiving your reply.

Sincerely yours,

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Editor requests

1) The title should indicate that this is a protocol for randomized controlled trial.

(Response)

Thank you for your comment. We revised the title of our manuscript as follows.

Effect of Eicosapentaenoic acid/Docosahexaenoic acid on Coronary High-intensity Plaques Detected with Non-contrast T1-Weighted Imaging (The AQUAMARINE EPA/DHA Study): study protocol for a randomized controlled trial

2) Study design. By definition, randomized controlled trials are prospective in their design. The term “prospective” is not necessary.

3) Study design. Precise that this is a triple arm, parallel group, randomized controlled trial.

4) Study design. “…adjusting for age, gender, presence or absence of type 2 diabetes mellitus, and PMR of the primary coronary lesion measured with non-contrast T1WI.” What does it means this sentence? Is the randomization stratified or minimized on these variables? If yes, this should be reported like that. Otherwise, clarifications are needed.

5) Study design. Design should include the allocation ratio.

6) Study design. What is the framework: superiority, equivalence, non inferiority, exploratory?

(Response)
Thank you for your comment. In response to your comment (2-6), we have revised STUDY DESIGN as follows (page 9, line 10 – page 10, line1).

STUDY DESIGN

This is a triple arm, parallel group, randomized controlled, open-label, superiority trial examining the effect of 12 months of EPA/DHA on coronary HIPs in patients with CAD between May 2014 and April 2018. Eligible subjects are randomly assigned to the 2 gram/day EPA/DHA group, 4 gram/day EPA/DHA group, or no treatment group (allocation rate 1:1:1). The randomization stratified on following variables (age, gender, presence or absence of type 2 diabetes mellitus, and PMR of the primary coronary lesion measured with non-contrast T1WI) (Figure 1, Table1).

7) Trial status. Report the trial status at this time or when the recruitment started.

Thank you for your comment. We add the information when the recruitment started (Recruitment started at August 2015.) (page 23, line 3).

Reviewer reports:

Reviewer #1: I have a number of concerns about this manuscript which largely related to the trial design rather than the manuscript itself.

1. Aims of the study: The authors mention the JELIS trial (reference 17) as evidence of a beneficial effect of supplementation with omega-3 fatty acids on the risk of major vascular events. However, they ignore a large number of studies indicating no effect of omega-3 fatty acid supplementation on vascular events [Wen YT, Dai JH, Gao Q. Effects of Omega-3 fatty acid on major cardiovascular events and mortality in patients with coronary heart disease: a meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2014 May;24(5):470-5]. Against a background of several negative cardiovascular outcome trials it is difficult to see how this trial of 150 people assessing an imaging measure is going to change practice. Furthermore there are a number of large on-going trials assessing omega-3 fatty acid supplementation which are not mentioned, such as the VITAL study and the ASCEND trial which together include over 30,000 people randomized to 1 gram of omega-3 fatty acid supplement or placebo. There remains the possibility that the higher doses of omega-3 fatty acids planned in this study might have additional effects but that argument needs to be made explicitly.

(Response)
Thank you for your suggestion. In response to your comment, we have revised our manuscript as follows (page 7, line 14 – page 8, line 6).

In experimental study, EPA/DHA treatments significantly attenuated the development and destabilization of atherosclerotic plaques.[17] Although meta-analysis failed to demonstrate the inhibitory effect of cardiovascular events by n-3 PUFAs supplementation, the effects of high dose n-3 PUFAs on cardiovascular outcome should be discussed (most previous and on-going studies use 1g EPA/DHA).[18] Indeed, higher dose EPA (1.8g) could reduce the risk of cardiovascular diseases in patients who resist LDL-cholesterol lowering by statins. [19] And a previous human studies have investigated the effect of high dose EPA on plaque stability or plaque component. [20, 21] Therefore, the present study focused on the effects of high dose administration of EPA/DHA on coronary plaques.

2. Sample size: The sample size calculation looks optimistic. The suggestion is that fewer than 4 out of 50 people in each group will drop out. There is no plan for a run-in period so the number of drop outs might be larger than this.

(Response)

After starting registration, more than 70 people have been registered and there are no cases that drop out due to drug side effects or other reasons. We estimate that probability that more than 4 out of 50 people in each group will drop out is low. This is a single-center study, which is a limitation of the study but may have an advantage of patients follow-up.

3. Blinding: Why not have a placebo controlled study? If a blinded study is not possible then at least those grading the images need to be blinded. This is not discussed.

(Response)

As you pointed out, the evaluation of the image is done blindly, which has been clarified in the revised manuscript (page 17, lines 7-11)

4. Assessments: Is it really necessary to do both cardiac MR and coronary angiography? This seems to be exposing people to unnecessary radiation when the cardiac MR is the main outcome.

(Response)
Thank you for your comment. For plaque detection, we used co-registration images to facilitate confirmation of the anatomical position of high-intensity lesions on T1W images and the coronary vessel on coronary CT. These methods used to evaluate MR plaque images in this study. And our research is conducted on patients who have already identified high risk plaques by MRI, we believe that to perform coronary CT after one-year follow-up under informed consent is acceptable.

5. Recruitment: How many people with CAD have High Intensity Plaques? How many people will need to be screened with cardiac MR to find a potentially eligible individual with this lesion?

(Response)

In our previous report, we investigated that High Intensity Plaque is approved by more than 50% in patient with CAD, we estimate that we will be able to find the patients if we screen 300-400 patients with CAD.

6. Study organisation: How will this study be organised? Who is the sponsor? Is it registered with a trials registry? How many centres will be involved?

(Response)

The research group consists of researchers and statisticians at National Cerebral and Cardiovascular Center, Suita, Japan and independent data monitoring committee. We add STUDY ORGANIZATION in the manuscript (page19, lines 11-14). Funding for the study was provided by Takeda Pharmaceutical Co., Ltd. Funding No.OME-IIT-001 (142CR1-002) (page 25, lines3-5). This clinical trial was registered on the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN 000015316) at 2 October 2014 (page 5, lines 15-17). This study is single center study, we add this point (page9, line10).

7. Exclusion criteria: Why are individuals with higher LDL-cholesterol or diabetes plus HbA1c over 8% excluded? It might be quite hard to find individuals with the High Intensity Plaque and strict exclusion criteria might make it even more difficult to recruit. How is "clinically significant renal impairment defined"?

(Response)

Our goal is to assess the effect of EPA/DHA on coronary HIPs in patients with CAD under controlled LDL levels by statin treatment. For that reason, we exclude the patients with higher
LDL Cholesterol levels. The reason why excluded uncontrolled diabetic patients is our preliminary data shows that HIP exacerbates frequently in diabetic patients. We define renal impairment as less than estimated glomerular filtration rate 40 ml/min. In response to your comment, we added the definition (page12, lines 7-8). Thank you for your comment.

Reviewer #2: I would like to thank the authors for their efforts. It was interesting to review this manuscript about "Effect of Eicosapentaenoic acid/Docosahexaenoic acid on Coronary High-intensity Plaques Detected with Non-contrast T1-Weighted Imaging: The AQUAMARINE EPA/DHA Study"

Thank you for your favorable comment.

I do have some comments;

Page 7, line 47; "We will study the change in PMR of coronary HIPs detected using CMR after 12 months of EPA/DHA therapy."…. Why 12 months in particular? Could we also report 3 and 5 years. In the prior experimental series, some studies report it at 3 years for effect to appear.

(Response)

As you pointed out, we also believe that a longer follow-up period is desirable. However, in previous reports to assess the effects of high dose EPA on coronary plaques using imaging modalities revealed that one year administration change the plaque phenotypes (References 20, 21). For that reason, we set the F/U period to one year in this study.

Page 8, line 31-38; "adjusting for age, gender, presence or absence of type 2 diabetes mellitus, and PMR of the primary coronary lesion measured with non-contrast T1WI" and although you mentioned later on page 14 that "dynamic allocation is used in order to ensure an even allocation of factors that may influence the evaluation of the efficacy of anti-hypertensive medications" which is a good point, I would like to include hypertension variable in the randomization process itself as it is a known risk factor for cerebrovascular and cardiovascular events.

(Response)

Thank you for your comment. In our previous work (References 24), the relationship between HIP and hypertension is relatively weak compared to the relationship with diabetes. For that reason, we did not include hypertension as the allocation factor in this study.
Page 9, line 9; Please explain why "presence of bleeding" is exclusion criterion in your manuscript.

(Response)

Because we thought that antiplatelet action of omega-3 fatty acids may promote bleeding, we exclude the patients who have active bleeding.

Page 9, line 54; "received instructions for lifestyle modification.. Can you add time frame, for example "for at least 3 month"??

(Response)

All of the subjects participating in this study are patients who have already received treatment and a 3-6 months lifestyle modification at our hospital. We have clarified this issue in the revised manuscript.

Page 11, line 15-19; "inappropriate for study participation in the opinion of the Principal Investigator or Investigator"; What do you mean by the word "inappropriate" as this may represent a bias in itself and What about performance status (PS); did all patients, even with poor PS, will be recruited??

(Response)

Thank you for your suggestion. To avoid bias, we deleted the eighth exclusion criteria.

Page 12, line 9-42; I prefer to avoid redundancy in the 2ry endpoints…So we can combine point 5 and 7 to be" Change and Percent change...." Similarly point 4 and 6 together

(Response)

As you pointed out, we have corrected that point.

Page 13, line 9-12; LDL diameter Measured by what??

(Response)

Thank you for your comment. We measure LDL diameter by LipoprintTM system (Quantimetrix). We added it to our manuscript (page12, lines 7-8).
Page 15, line 15 and 41; please write the meaning of PDF and CRF.

(Response)

We add the meaning of these abbreviations (PDF: portable document format, CRF: case report form) (page 16, lines 7 and 15).

Page 16, line 2; "Plaque to myocardium ratio (PMR): Below 1.1 / 1.1 or higher in non-contrast T1-weighted CMR images of the main lesion"…. Why this cutoff point?? please add to the manuscript

(Response)

Thank you for your comment. From our previous studies, a cut-off point of PMR that separates high risk from intermediate risk is 1.3-1.4 (references 24 and 26). We have corrected the cutoff value (1.35) and added the reason to the manuscript (page17, lines4-6).

Page 18, line 28; what are the adverse events you are looking for? Is there any particular classification for AE eg minor and major...etc. Some papers will report adverse events based on "Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0" that I think will be helpful and more scientific way to represent any adverse events

(Response)

In this trial, we are reporting Adverse Events (AEs) strictly. We added that method briefly in our manuscript (page 20, line 9 – page 21, line 14). In future research, we would like to consider using CTCAE. Thank you for your suggestion.

Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.
Reporting of AEs

When an AE occurs, the principal investigator or investigator must promptly take appropriate measures and follow up all subjects experiencing an AE until the symptoms resolve, or any clinically significant abnormal laboratory values have returned to the values at the start, addition, or switching of the investigational product, or there is a satisfactory explanation for the change (for adverse events that are permanent or irreversible), regardless of whether the causal relationship of the AE with the investigational product. All AEs will be documented in the CRF. The following information will be documented for each AE: event term; dates of onset and disappearance; frequency; severity; causal relationship between the event and the investigational product (not related or related); action taken for the investigational product; outcome of event; and seriousness. For AEs that are considered not related to the investigational product, the reason for ruling out the causality should be documented in the comment column of the CRF.

Page 19, line 9; Typo! "Optimal management", please correct.

(Response)

Thank you for your comment. We have corrected the term (page 22, line 2).