Author's response to reviews

Title: Effects of Fish Oil Supplementation on Inflammatory Markers in Chronic Heart Failure: A Meta-analysis of Randomized Controlled Trials

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Version: 2 Date: 25 July 2012

Author's response to reviews: see over
Dear Prof. Marinette Lacson and Michel Noutsias,

Thank you for your kind email and the instructive comments to improve our previous manuscript (MS: 2049788316709069). These comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and addressed your suggestions and revised the manuscript. We hope this version can meet with the Journal’s criteria and be published in the BMC Cardiovascular Disorders.

Thank you very much!

Sincerely yours,

Xiaoying Li
Revision

Associate Editor's comment
After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further. We advise you to seek the assistance of a fluent English speaking colleague, or to have a professional editing service correct your language. Please ensure that particular attention is paid to the abstract.

Authors’ response
Thanks for your comment and helpful advice. We do realize that the language editing is needed for our manuscript. Therefore, we focused on the language editing during the whole revision process and got some help from a colleague who is a native English speaker. Particular attention has been paid to the abstract as requested by the editor and the corrections of the manuscript have been highlighted in red in the revised version. Hopefully, the revised manuscript can meet the journal’s criteria.

Reviewer 1's report
Title: Effects of Fish Oil Supplementation on Inflammatory Markers in Chronic Heart Failure: A Meta-analysis of Randomized Controlled Trials
Version: 1 Date: 6 May 2012
Reviewer: Petar Otasevic
Reviewer's report:

1. In abstract the authors state that 7 studies were identified, whereas in the rest of the manuscript and in the figures we have 8 studies. Please correct or advise.

Authors’ response
We agree that there is a little confusion as described in the formal manuscript regarding the number of studies included in the meta-analysis. Actually, we identified 8 records through searching process. However, 2 articles by Moertl D. et al. published in 2011 (reference 24 and 25) reported the outcomes of different inflammatory markers from the same study population (one paper of hsCRP, the other of TNF-a and IL-6). Therefore, the 8 records we identified were from 7 trials. At the same time, the study by Moertl D. included two intervention groups of different doses of fish oil (a higher dose group of 3360 mg/d and a lower dose group of 840 mg/d), which we included in our study separately. Therefore, we got 8 study arms included in this meta-analysis. The above information has been clarified during the revision of the manuscript, as modified in the Abstract and Study characteristics sections.

2. Having in mind the limitations of the study, this reviewer would recommend that conclusions should reflect this issue i.e. they should be more defensive.
Authors’ response
We agree with Dr. Otasevic’s opinion that the limitation of our meta-analysis is that only a handful of studies were identified and that there is obvious heterogeneity between the studies which may limit data interpretation. Particular problem is that data on statin use are lacking in most studies. The above limitation has been pointed out in the section of Discussion. We do feel we should temper our tongue when come to the conclusion and be more moderate and defensive. So, during the revision we modified the section of Conclusion according to Dr. Otasevic’s advice.

In the Abstract section, as:
Limited evidence suggests anti-inflammation may be a potential mechanism underlying the beneficial effects of fish oil for chronic heart failure. Further large-scale and adequately powered clinical trials are needed to confirm these effects.

In the Conclusion section, as:
In conclusion, our meta-analysis, by pooling the limited trials available currently, indicates that additional supplementation with fish oil may reduce the circulating levels of TNF-α, IL-1 and IL-6 in patients with CHF, although the levels of hsCRP, sICAM-1 and sVCAM-1 were not significantly affected. Also, greater reduction of TNF-α and IL-6 might be seen in patients who take fish oil in a higher dose or for a longer duration. These results suggested that anti-inflammation might be a possible mechanism underlying the potential beneficial effects of fish oil supplementation to patients with CHF. Additionally, large-scale randomized controlled trials with adequate power are warranted in the future to confirm these effects.

3. Background and discussion sections should be considerably shortened. Discussion should also be better focused only on problem of the inflammation in CHF patients.

Authors’ response
During the revision process, we took Dr. Otasevic’s helpful advice and tried to shorten the Background and Discussion sections and focus the Discussion section mainly on problem of inflammation in CHF patients. Hopefully, these modifications can make the manuscript seems more clear and simplified.

Reviewer 2’s report
Title: Effects of Fish Oil Supplementation on Inflammatory Markers in Chronic Heart Failure: A Meta-analysis of Randomized Controlled Trials
Version: 1 Date: 10 June 2012
Reviewer: Gerasimos Filippatos
Reviewer's report:

1. Does the formulation of fish oil play any role in the results?

Authors’ response
We agree with Dr. Filippatos’ opinion that the formulation of fish oil may influence the effects of fish oil on inflammatory markers in CHF. In fact, in our analysis, we tried to test this hypothesis concerning whether the ratio between EPA and DHA may play a role. However, no significant influence has been detected by either meta-regression analysis or subgroups analysis according to the ratio of EPA and DHA. During the revision process, we further extended this concern to explore whether the DHA or EPA doses applied in each study arms influenced the results. Firstly, we extracted the doses of EPA and DHA from the included studies (as shown in Table 1). Then, we performed meta-regression and subgroup analysis (using the median of the doses as cut-off value) to investigate the influence of the doses of DHA and EPA on the outcomes (as shown in Table 3). However, the results of these studies didn’t suggest significant influence of EPA or DHA dose on the effects of fish oil on TNF-a and IL-6. Therefore, based on the above results, our meta-analysis didn’t support the hypothesis that the formulation of fish oil (dose of EPA, DHA or the ratio between EPA and DHA) play a role in the final results.

2. In several of the studies presented in the manuscripts other parameters besides the inflammatory markers have been performed. Is the direction of the change in the same direction as the inflammatory markers? (ie improvement if inflammatory markers decrease, no change if they don’t change).

Authors’ response
As indicated by Dr. Filippatos, it was really true that the trials included in our study reported many other parameters besides the inflammatory markers that we have been focusing on. We totally understand the importance of the concern of Dr. Filippatos that whether effects of fish oil on these parameters were paralleled with its effects on inflammatory markers. If it turned out to be the case, we may infer that anti-inflammation seem to be a kind of important mechanism underlying fish oil’s role in CHF. However, there are some practical issues which kept us from exploring the above concern. First, as shown in our manuscript, many included studies measured more than 1 inflammatory markers in our study; besides, changes of these markers were not consistent even in the same study after fish oil supplementation. Second, there isn’t a generally accepted golden marker of inflammation which we can mainly depend on and can be chosen as a marker of inflammatory status in CHF. Third, various other parameters other than inflammatory markers were investigated in the included trials, including body weight, hemoglobin, neurohormonal markers, autonomic markers, episodes of arrhythmias, cardiac function as indicated by echocardiograph, markers of endothelial function, functional capacity as indicated by the cardiopulmonary exercise test, and markers of platelet activation and coagulation. These markers were all related to the development, progression and prognosis of CHF; however, they were all surrogate markers and most of their roles in CHF have not been well established. Basically, we believe it was most convincing if the change of a generally accepted inflammatory marker of CHF (which doesn’t exit yet) following fish oil supplementation is paralleled with hard clinical outcomes (e.g. hospitalization
or death due to heart failure, which were not investigated in the included trials). For above reasons, based on the trials available now, we are afraid we can’t give a satisfactory answer to the concern raised by Dr. Filippatos, although we hope this issue can be addressed in the future studies.

3. It is not clear if the severity of the disease plays any role in the results. Are the results different if we start from a higher level of inflammatory markers?

Authors’ response
We agree with Dr. Filippatos’s opinion that the severity of the disease may influence the effects of fish oil on inflammatory markers in CHF. Actually, by meta-regression and subgroup analysis, we tried to explore the influence of mean baseline NYHA function and baseline LVEF on the effects of fish oil on TNF-a and IL-6. But these results turned to be negative. For the baseline levels of the inflammatory markers, we agree with Dr. Filippatos’s opinion that this may have significant impact on the effects of fish oil on the inflammatory markers in CHF. And it’s very helpful advice because we didn’t address this issue in the first draft of the manuscript. Following Dr. Filippatos’s suggestion, we extracted the baseline levels of the aforementioned inflammatory markers as in Table 2 (newly added). And then we performed meta-regression and subgroup analysis according to the baseline levels of TNF-a and IL-6. Although these analyses didn’t reach a significant result, we noticed that reduction of TNF-a following fish oil supplementation seemed to be more remarkable in those study arms with a higher baseline TNF-a (SMD: -0.85, 95% CI -1.51, -0.18 for higher baseline TNF-a group; SMD: -0.33, 95% CI -0.82, -0.17 for lower baseline TNF-a group; p=0.22); similarly, reduction of IL-6 also seemed to be more remarkable in those study arms with a higher baseline IL-6 (SMD: -1.23, 95% CI -1.93, -0.54 for higher baseline TNF-a group; SMD: -0.31, 95% CI -1.27, 0.65 for lower baseline TNF-a group; p=0.13), as indicated in Table 3.

4. Effect of statins and other background therapy?

Authors’ response
We agree that statins and many other background therapies may have very important influence on the effects of fish oil supplementation on inflammatory markers in CHF. For statins, many included trials lack the baseline data of its usage. Although we tried our best to contact the authors of the included study for the missing data, it turned out that few data can be acquired. As a result, only 4 study arms reported the usage of statins, and the percentages of patients varied significantly, from 0 to 83%. So, we feel it difficult to perform a subgroup analysis based on so little available data. We know that’s an important limitation. For other CHF background therapies, we assessed whether usage of beta-blockers or ACEI/ARB will influence the results. However, the results of meta-regression and subgroup analysis didn’t find a significant influence of these medications on the final results. But in our point of view, these negative results may result from the limited number of included study arms, and future studies are
needed to further explore the influence of CHF background medication on fish oil’s anti-inflammatory effect.

Other Parts of Revision

In the Discussion section, we cited our recently published meta-analysis of fish oil supplementation on cardiac function and functional capacity when summarizing the potential of fish oil in CHF, as stated in the revised manuscript “Besides, our recent published meta-analysis also indicated that fish oil supplementation can favorably affect the cardiac function and functional capacity in CHF patients 33”.

Thanks very much!

Yours sincerely

Xiaoying Li