Reviewer's report

Title: Recent findings on the health effects of omega-3 fatty acids and statins, and their interactions. Do statins inhibit omega-3?

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Reviewer: George E. Billman

Reviewer's report:

The authors have provided an excellent analysis of recent randomized controlled trials of omega-3 polyunsaturated fatty acids (n-3 PUFAs). As the authors note that majority of more recent trial have not confirmed the cardiovascular benefits of n-3 PUFAs reported in the previous trials. They then center on the possible effects of the increased use of statins for the management of cardiovascular disease for apparent diminished efficacy of n-3 PUFAs in the more recent trials. Specifically, they propose that the negative/neutral finding resulted from negative interaction between the statins and n-3 PUFAs - statins counteract the actions n-3 PUFAs - and in themselves increase rather than decrease the risk of adverse cardiovascular events. The authors also suggest that n-3 PUFAs may only have benefits in n-3 PUFA deficient patients. They conclude by presenting a few mechanisms by which statins could adversely affect cardiovascular health. The authors' hypothesis is interesting and clinically important. this hypothesis certainly merits further investigation. However, an important limitation of the present review is the authors somewhat selective sampling of the literature.

Major Compulsory Revisions:

1. The authors also need to discuss recent clinical and animal studies that not only failed to confirm a beneficial effect of n-3 PUFA but report that this treatment increased rather than decreased adverse cardiovascular events. For example, Burr et al. (Eur J Clin Nutr 57:193-200, 2003) reported that n-3 PUFAs increased, rather than decreased, all cause mortality (15% increase over 9 year follow-up period, with a 54% increase in sudden death). In a similar manner, Raitt and co-workers (JAMA 293:2884-2891, 2005) reported that fish oil supplements not only did not reduce ICD events or mortality but also increased arrhythmic events in the subgroup of patients (67%) who received an ICD with ventricular tachycardia as an indication. [The authors have presented this study but have not addressed this possible proarhythmic effects reported in sub-group of the patients, that admittedly was not confirmed in subsequent studies] Heart failure patients (NYHA class II and III) with the highest RBC n-3 PUFA levels also exhibited an increased risk for ventricular arrhythmias that required anti-tachycardic therapy (Am Heart J 155:971-977, 2008). Finally, and perhaps most importantly with regards to the authors hypothesis concerning the negative interactions, are some recent animals studies. Coronel et al. (Cardiovasc Res 73:386-394, 2007) found that dietary n-3 PUFA increased the incidence of VF during regional ischemia in isolated pig heart preparations. More recently,
Billman et al. (Circulation Arrhythm Electrophysiol 5:553-560, 2012) using a well-characterized canine model of sudden cardiac found that n-3 PUFA treatment (1-4 d g/day for 3 months) produced large increases in the omega-3 index of both red blood cell and cardiac tissue yet not only failed to prevent ischämically-induced ventricular fibrillation but actually significantly increased the susceptibility to malignant arrhythmias in low risk dogs (both dogs with and without myocardial infarction -MI). Long-term dietary n-3 PUFA treatment induced ventricular tachyarrhythmias in one third of the post MI dogs that had been previously been shown to be resistant arrhythmias while two non-infarcted dogs died spontaneously during the 3-month n-3 PUFA treatment. This latter observation is particularly noteworthy, as these non-infarcted dogs would normally exhibit a negligible risk for sudden death. Statins were not used in either the porcine or canine study. Thus, statins mediated inferences with the action of n-3 PUFA can not explain the possible pro-arrhythmic actions of n-3 PUFAs in these studies.

Minor Essential Revisions:

1. Page 2, line 12: either the results were significant or there were not, eliminate the phrase about “borderline non-significant protection”

2. Page 2, lines 13-15: should a read as “Finally, no significant protection was reported in tow large RCTs (JELIS and GISSI) that combined a statin with n-3 treatment – suggesting a possible reciprocal inhibition.” To what GISSI are you referring, GISSI-HF?

3. Page 2, line 20: should read as “The inhibition of the effects of n-3 by stains…”

4. Page 3, line 1: should read as “Until 2005, studies consistently provided clear evidence….”

5. Page 4, line 3-4: either the results were significant or there were not, eliminate the phrase about “borderline non-significant protection”

6. Page 4, 4 lines from bottom of the page: “…and reported a non-significant effect…”

7. Page 4, last line: should read as “either group” not “neither group”.

8. Page 5, line 10: “an ICD” not “a ICD”

9. Page 5, lines 16-17: should read as “…to detect protection…”

10. Page 8, first two lines. Same problem concerning “borderline significant differences”.

11. Page 8, line 18: should read as “…trial with single group receiving p only the placebo.”

12. Page 9, line 4: should read as “…was not protective.” Delete “at all”.

13. Page 9, line 12: should read as “…in any biological mechanisms…”

14. Page 10, line 3: How was “lower cognitive function” assessed in a dog? Should merely state what test was impaired rather than speculate on a dog’s ability to think.

15. Page 11, line 3: should read as “Finally, this negative action on the central nervous system probably explains…”

16. Page 11, lines 14-15: should read as “… it is time to reassess the benefits …”

17. Page 12, first paragraph: A similar argument can be made concerning the n-3 PUFA studies. A potential conflict of interest is also possible for n-3 PUFAs, as there is a huge and growing market for n-3 PUFA supplements.

18. Page 13, 4 lines from the bottom of the page: “total innocuousness” this statement is not correct. n-3 PUFAs may have negative effect in certain patient populations - see the first discussion point listed above.

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No Conflicts of Interest.