No. 1

The present study was conducted to prove that fish oil failed in all measures of CVD prevention or improving. The format of this article was completed.

Some suggestions:

1. The present study aimed to show that fish oil had no preventive effect in high risk people with CVD. This theme was opposite with common view and the evidences which were used in the study was not convincing.
2. In the study, it contained 3 groups (group I 34, group II 16and group III 15). The number of participant in each group was too little. Besides, why each group had different number of participant?
3. How long did each group's participants consume specified oil? Where did these oils which were used in the study come from?
4. Why choose "Biologic Age Compared to Physical Age" as the study results measurement index? What relationship did this parameter have with CVD?
5. I think paired t-test was not very suitable for this study's data analysis. Because paired t-test required sample size greater than 50.

Regard to readers comments:

This article may be rejected. I think the medical research paper should be conducive to medical progress or improve human health. It was obviously that this paper does not meet this requirement. The evidences are far from enough to support author's view. The design of this experiment was not reasonable and rigorous. Classic is hard to knock down. Do not want to be famous to challenge classic with unconvincing evidence.

No. 2

Manuscript FNS #2700839 attempts to clarify the effect of fish oils in aortic stiffness and explain their failure in improving CVD outcomes. A few comments from a cardiovascular point of view:

It is now accepted that a major therapeutic goal when encountering a patient with hyperlipidemias is the effective lowering of low density lipoprotein cholesterol (LDL). LDL levels are a major risk factor for coronary artery disease. The evidence showing that reducing total cholesterol (TC) and LDL-C can prevent CVD is strong and compelling, based on results from multiple randomized controlled trials (RCTs). To date, the only well-established therapy is statins, which have been extensively studied through numerous randomized clinical trials. On the other hand, fish oil reduces triglycerides by

30%, but the effects on other lipoproteins are trivial in their magnitude. Although the role of TG as a risk factor for CVD has been strongly debated, recent data strongly favor the role of TG-rich lipoproteins as a risk factor for CVD. **There is no conclusive data that justify fish oil prescription in daily clinical practice and its effects on CVD outcomes are not yet clarified**. In addition, most high risk patients take n-3 fatty acids in combination with statins, which consistently show reduction in cardiovascular mortality. This controversy is further reflected in the recent European Society of Cardiology guidelines on the management of hyperlipidemias. The expert panel gives n-3 fatty acid intake a rather weak indication. It should be noted that the administration of n-3 is clinically safe and no major interaction with other medication has been recorded.

With regards to the role of the endothelium, it is now common knowledge that its dysfunction contributes to the genesis of atherosclerosis. Therefore it is believed that 'biological age' is reflected in the arterial stiffness. Pulse wave velocity is a noninvasive method for the measurement of arterial stiffness. Carotid-femoral PWV is the 'gold standard' for measuring aortic stiffness. In addition, a substantial proportion of patients at intermediate risk could be reclassified into a higher or lower CV risk, when arterial stiffness is measured.

With regards to manuscript methodology and results, it would be appropriate to see a Table illustrating patients' demographics and other risk factors. Moreover, atherosclerosis is a multifactorial disease, thus, **a multivariate analysis is required in order to clarify the detrimental effect of PEOs on arterial stiffness.** Especially the effect of age and diabetes cannot be overlooked.

Specific comments:

p.1, Introduction,l.17: the author should differentiate between omega-3 FA in general and omega-3 FA in fish oil. i.e. linolenic acid is an omega-3 FA functioning differently than EPA or DHA.

p.5, paragraph 3.1, l.27: ‘thiobarbituric acid reactive substances’ is abbreviated as (TBARS).

All in all, I have my reservations on how valid are the claims of the author regarding the negative health effects of fish oils.