Prescribing More Stringent Design of Randomized Clinical Trials of Omega-3 Polyunsaturated Fatty Acids

To the Editor: We read with interest the carefully designed and executed comprehensive meta-analysis of the effects of omega-3 polyunsaturated fatty acids (PUFA) on coronary heart disease in randomized controlled trials (RCTs) and prospective cohort studies by Alexander et al[1] recently published in *Mayo Clinic Proceedings*. Together with the accompanying editorial by O'Keefe et al,[2] these authors make an important contribution to the discourse on the use of omega-3 PUFA and fish oil supplement therapy in patients with cardiovascular disease, which is currently confounded by the results of several previous underwhelming RCTs and meta-analyses.

In 2015, a review of only new evidence arising since 2008 was commissioned by the National Heart Foundation of Australia (NHFA).[3] That analysis confirmed the benefits of eating fish on the basis of evidence from cohort studies, but it could not confirm any benefit for fish oil from RCTs (except for triglyceride lowering and in heart failure). As a consequence, the NHFA has removed their recommendation to consume omega-3 fish oil supplements for cardiovascular health (not withstanding that fish consumption in Australia and in other countries such as the United States remains very low).

One major shortcoming of the NHFA review,[3] which also occurs in the current meta-analysis,[1] is the absence of discussion regarding the failure of most RCTs to recruit control groups with low baseline levels of the omega-3 PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), for example as reported by red blood cell membrane EPA + DHA analysis (ie, the omega-3 index). Some control groups exhibited quite high omega-3 PUFA levels, likely due to large variations in fish diet or other undocumented dietary sources. In our reexamination of the post-2008 RCTs considered in the NHFA review, we found that none of those studies excluded individuals who ate fish (at any level of intake), and only one measured omega-3 PUFA status before assignment to treatment group.[4] As we and others[5] have reported previously, the failure to prevent overlap between treatment and control group omega-3 PUFA level at baseline is a major confounder that flaws these RCTs and prevents valid assessments of outcomes and conclusions.

When you consider that cohort studies consistently reveal differences between those eating little or no fish on a regular basis and those eating fish regularly[1,3] and attribute the effects to omega-3 PUFA content of fish,[6] it is not surprising that RCTs, in which the control group is not equivalent to the lowest quintile or grouping according to fish intake, do not reproduce these very strong findings. Does an RCT of a new β-receptor blocker, or indeed any novel active agent, allow the active drug to be present randomly in the control group? Absolutely not!

There are other shortcomings in the design of RCTs that we have previously outlined[4]; however, we assert that if background omega-3 PUFA dietary intake and baseline red blood cell membrane PUFA measures were accounted for in each RCT recruitment, the outcome of the recent meta-analysis by Alexander et al[1] would likely be considerably more than the reported 6% reduction in risk. We therefore advocate that prospective randomized clinical trials include only patients who can be stratified and allocated to treatment groups on the basis of baseline-verified membrane PUFA content in red blood cells or other relevant tissues, in conjunction with documented dietary intake of preceding and continuing oral omega-3 PUFA sources. At the conclusion of treatments, each recruited group can be contrasted to respective baselines by molecular validation of potential cell membrane changes in omega-3 PUFA content.

We posit that systematic reviews that ostensibly pay strict attention to quality of recruitment and randomization within included RCTs should properly and systematically account for and discuss the quality of control groups in those trials and their adequate differentiation from treatment groups.

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In Reply I—Prescribing More Stringent Design of Randomized Clinical Trials of Omega-3 Polyunsaturated Fatty Acids

We thank Drs McLennan and Pepe for their insightful comments on our meta-analysis of randomized controlled trials (RCTs) and prospective cohort studies of eicosapentaenoic acid and docosahexaenoic acid (EPA+DHA) supplementation vs coronary heart disease (CHD) risk. The objectives of our research were to (1) estimate the summary association between EPA+DHA intake and CHD risk in prospective cohort studies and (2) examine the effects by dose, by specific CHD outcome, and among higher-risk populations (eg, individuals with elevated triglyceride levels). To this end, we evaluated the currently available and published data across the literature.

The authors raise 2 primary issues in their letter to the editor, both dealing with the design of individual RCTs, which is not the topic addressed in our meta-analysis but still is relevant for the discourse of the state of knowledge on this topic. The first is that there is an absence of discussion pertaining to the recruitment of control groups with low baseline levels of omega-3 EPA+DHA. However, the authors focus their attention on the National Heart Foundation of Australia review, not our meta-analysis. In fact, in our discussion section, we wrote that "most RCTs did not measure baseline intake of EPA+DHA from the diet nor track EPA+DHA intake from sources other than that supplemented during the course of study…." Therefore, it is not clear if the results from the individual trials have been impacted by background dietary EPA+DHA, particularly in the control group. If so, as the authors suggest, and as we indicated in our article, the effects of EPA+DHA on CHD risk may be more protective than what is reported in our meta-analysis. Although most studies undeniably include participants with varying baseline levels of EPA+DHA, the purpose of our meta-analysis was to evaluate the relative difference between individuals with EPA+DHA provision compared with those who did not receive supplemental EPA+DHA. Globally, levels of EPA+DHA in the general population have been considered low[1]; however, it is unclear whether the participants in the RCTs we analyzed have been recruited from a "healthier" source population with higher baseline levels of EPA+DHA. If so, effects of EPA+DHA supplementation may be attenuated toward the null value. Appropriately, the summary results from our meta-analyses of RCTs should be viewed as conservative.

From a methodological standpoint, it may not be pragmatic to evaluate CHD risk among individuals receiving EPA+DHA compared with an "exposure-free" (ie, no baseline level of EPA+DHA) control population. McLennan and Pepe ask the question of whether an RCT of a β-blocker, or any novel active agent, allows the active drug to be present in the control group. Although we agree with the their position that in most *drug* trials, the active agent may not—or should not—be present in the control group, EPA+DHA is a dietary factor, not an active drug.

Again, the aim of our meta-analysis was to estimate the *relative difference* of the effect of EPA+DHA on CHD risk based on the evaluation of participants receiving supplemental EPA+DHA compared with participants not receiving supplemental EPA+DHA. We fully submit that the control groups across the volume of RCTs include participants with varying levels of EPA+DHA. The reality is that we are not evaluating a drug or prescription medication per se but rather a dietary and nutritional constituent present in commonly consumed foods. Thus, the inherent methodology in published studies is a reflection of this fact (as is the case with most RCTs of dietary factors), and the findings across the literature should be interpreted in light of the challenges when attempting to isolate the effects of a single dietary factor on a complex and multifaceted outcome, such as CHD. In other words, unless the exposure is rare and uncommon in the dietary practice of large segments of the population, the control groups in most RCTs of dietary factors typically include participants with a baseline level of exposure. Indeed, McLennan and Pepe indicate that in our analyses, the prospective cohort studies consistently reveal reductions in CHD risk between those eating fish regularly compared with those who consume fish infrequently, and the RCTs do not reproduce these strong findings. This is discussed extensively in our article in which we indicate that prospective cohort studies enable us to evaluate unrestricted populations who may not have modified their dietary habits and medications on entry into the cohort. Furthermore, most prospective cohort studies are longer in duration than RCTs, include a larger study population, and evaluate dietary intake data that may be representative of lifelong eating habits. However, RCTs offer the methodological advantage of control for confounding through random allocation of exposure and a potentially more stringent and regulated follow-up for the occurrence of a CHD event. Each study design provides insight into the relationship between EPA+DHA and CHD, which is why we conducted separate meta-analyses by RCT and prospective cohort designs.