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SUPPLEMENTATION OF N-3 POLYUNSATURATED FATTY ACIDS TO PREVENT POSTOPERATIVE ATRIAL FIBRILLATION IN PATIENTS SUBJECTED TO HEART SURGERY

To the Editor:

The debate on the effectiveness of n-3 polyunsaturated fatty acids (PUFAs) in cardiovascular disease has recently been fueled by the publication of 3 meta-analyses.¹⁻³ Furthermore, attempts to apply trial sequential analysis (TSA) to these issues have also contributed to the debate.^{4,5}

With regard to secondary prevention of cardiovascular disease, the meta-analysis by Kwak and colleagues¹ found no proof of

effectiveness for PUFAs. Later, a TSA that was based on the same data provided a stronger negative conclusion in terms of proof of no effectiveness (futility).⁴ Likewise, with regard to the role of PUFAs to prevent atrial fibrillation, a meta-analysis showing no effectiveness was published,² followed by a TSA indicating futility.⁵

In this framework, the meta-analysis by Costanzo and associates³ recently published in the *Journal* has been focused on the preoperative supplementation of PUFAs to prevent postoperative atrial fibrillation in

heart surgery. The results of this meta-analysis were borderline, because most effectiveness indices were at the limits of statistical significance.

In an attempt to clarify the uncertainty surrounding the effectiveness of PUFAs for this indication, we undertook a TSA aimed at reexamining the same 8 trials evaluated by Costanzo and associates.³ Our analysis considered the end point of postoperative atrial fibrillation. Main assumptions included 2-sided testing, risk of type 1 error of 5%, and power of

FIGURE 1. Application of trial sequential analysis to interpret the results of 8 placebo-controlled trials evaluating preoperative n-3 polyunsaturated fatty acids to prevent postoperative atrial fibrillation in heart surgery (A and B, expected 15% and -20% relative risk reductions, respectively). In both graphs, the z curve (blue) is composed of consecutive segments that correspond to individual trials; trials are plotted in chronologic order from left to right. The x-axis indicates the cumulative number of patients; the starting point of the z curve is by definition at x = 0 (inclusion of no trials). At the cumulative number of 2687 included patients (8 trials), the curve is still in an inconclusive area, because none of the boundaries of superiority or inferiority or futility have been reached. The information-size analysis estimates that at least 8614 or 4763 patients (A and B, respectively) would be needed to reach a conclusion in terms of superiority or inferiority or futility. Red lines are the boundaries for superiority or inferiority; green lines are the boundaries for futility; horizontal brown lines indicate the traditional limits of statistical significance ($z = 1.96$ or -1.96). T, Treatment, C, control.

80%. The intervention effect was set at an anticipated 15% or 20% relative risk reduction, with the event rate in the control group assumed to be 30% (equal to the overall rate in the 8 control groups). As usual, the main result of TSA was expressed through the graph of cumulative z curve. With reference to this graph, the boundaries for concluding superiority or inferiority or futility were calculated according to the O'Brien-Fleming α -spending function. Our analysis was done with a specific statistical software package (TSA Viewer; Copenhagen Trial Unit, Copenhagen, Denmark).

Application of TSA to these 8 randomized trials generated an inconclusive result (Figure 1). In particular, our analysis estimated that the optimal information size would be 8614 or 4763 patients (according to the assumptions of relative risk reduction of 15% or 20%, respectively). At the cumulative number of 2687 patients (those included in the 8 trials published thus far), the z curve remained, in both graphs, quite far from intercepting the boundary of superiority but at the same time did not reach the futility area.

In the light of the current evidence, the conclusion that PUFAs are effective for this clinical indication is not justified; on the other hand, neither can the conclusion of a proven ineffectiveness of PUFAs be made. Unless further positive trial results are made available, uncertainty remains regarding the effectiveness of PUFAs for this indication. Overall, if one considers that a clear proof of ineffectiveness has been obtained for two other important indications of PUFAs,^{4,5} the overall picture of the therapeutic role of these agents seems to be extremely weak.

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Reply to the Editor:

In their letter, Messori and colleagues described their performance of a trial sequential analysis (TSA) to interpret better the results of a meta-analysis we recently published in the *Journal*, "Prevention of postoperative atrial fibrillation in open heart surgery patients by preoperative supplementation of n-3 polyunsaturated fatty acids: An updated meta-analysis."¹ After application of TSA to the same 8 trials included in our study¹ and another meta-analysis on the same topic,² they state that the results are inconclusive but tend more toward proof of no effectiveness of n-3 polyunsaturated fatty acid (PUFA) supplementation for preventing postoperative atrial fibrillation (POAF) after heart surgery.

Although the findings of Messori and colleagues appear to be reliable,

one should consider that in our meta-analysis on the effect of preoperative n-3 PUFA supplementation in POAF prevention after cardiac surgery,¹ several sources of heterogeneity were found, in particular the type of surgery or of placebo. For this reason, we performed both sensitivity and subgroup analyses to investigate the source of heterogeneity among studies and focused on the type of cardiac surgery.¹ The novelty of our meta-analysis was the effect of the preoperative supplementation of n-3 PUFAs on POAF, in a specific heart surgical procedure such as coronary artery bypass grafting (CABG). Data on patients who underwent isolated CABG were extracted from 7 studies (1028 patients), and a significant protection of 34% was observed with a fixed-effects model (odds ratio 0.66, 95% confidence interval 0.50–0.87; $P = .003$; $I^2 = 26\%$; $P = 0.23$).¹ We concluded that the preoperative supplementation of n-3 PUFAs to patients undergoing isolated CABG significantly prevents the occurrence of POAF.

We have now reexamined, with the TSA suggested by Messori and colleagues, the 7 trials performed on isolated CABG. This analysis was performed according to the O'Brien-Fleming α -spending function and considering the assumptions of the 2-sided testing, the risk of type 1 error as 5%, the power as 80%, the event frequency assigned to the controls as 33.5% (the pooled frequency in the 7 control groups, 172 POAF events in 513 patients), and the relative risk reduction of 25% (TSA Viewer; Copenhagen Trial Unit, Copenhagen, Denmark).^{2,3} Figure 1 shows the main result of TSA, expressed through the graph of the cumulative z curve and the threshold for a statistically significant treatment effect. The cumulative z curve crosses the trial sequential monitoring boundary for benefit, indicating a beneficial effect of almost 25% relative risk reduction of POAF in the intervention arm.