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.

Andrea Messori, PharmD
Valeria Fadda, PharmD
Dario Maratea, PharmD
HTA Unit
ESTAV Toscana Centro

Regional Health Service
Firenze, Italy

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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.

FIGURE 1. Trial sequential analysis for a relative risk reduction of 25% of postoperative atrial fibrillation after an isolated coronary artery bypass grafting procedure in 7 trials that included 304 patients reporting postoperative atrial fibrillation. Parameters are $\alpha = .05$ (2-sided), $\beta = .20$ (power = 80%), and event frequency in the control group of 33.5%, with odds ratio as measure effects for each study. The cumulated z curve (blue) crosses the trial sequential monitoring boundary (red curve), indicating evidence for a beneficial effect of 25% relative risk reduction provided by the intervention. PUFA, Polyunsaturated fatty acid.

In conclusion, the TSA as we have performed it confirms the results of our previous meta-analysis on the protective effect of preoperative n-3 PUFA supplementation for POAF prevention after an isolated CABG.

Simona Costanzo, MS, PhD
Augusto Di Castelnuovo, MS, PhD
Licia Iacoviello, MD, PhD
Laboratorio di Epidemiologia
Genetica ed Ambientale
Laboratori di Ricerca
Fondazione di Ricerca e Cura
"Giovanni Paolo II"
Università Cattolica
Campobasso, Italy

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RESPONSE TO STAGED PERCUTANEOUS CORONARY INTERVENTION AND MINIMALLY INVASIVE VALVE SURGERY: RESULTS OF A HYBRID APPROACH TO CONCOMITANT CORONARY AND VALVULAR DISEASE

Reply to the Editor:

We greatly appreciate the insightful comments of Cheema and Roberts¹ concerning our recent article, which evaluated a hybrid approach of staged percutaneous coronary intervention followed by minimally invasive valve surgery (MIVS) in patients with concomitant coronary and valvular

disease.² We concur with their comments that mortality and morbidity rates in valve surgery are highly correlated with the case load of the individual surgeon. At the time our data were gathered, each surgeon on average had more than 20 years of experience and was performing approximately 200 valve cases per year. We therefore do not believe that lack of surgical experience played a role in the outcomes.

Cheema and Roberts¹ were also concerned that 61 of 65 hybrid patients had undergone percutaneous coronary intervention of the left anterior descending coronary artery (LAD) before MIVS, and that only 55.5% of the stents used were drug eluting, contending that perhaps these patients might have been better served with a left internal thoracic artery graft to the LAD. In our study, 25 patients (38.5%) did have bare metal stents placed. These patients were more likely to have single-vessel disease, were older, and did not have a lesion involving the proximal LAD. Thus all the patients with a proximal LAD lesion had drug-eluting stents placed, not bare metal. A meta-analysis of 9 randomized, controlled trials that enrolled 1210 patients with proximal LAD lesions, comparing those who had a left internal thoracic artery graft to the LAD with those with a drug-eluting stent, demonstrated no differences in survival at 30 days, 1 year, or 5 years.³ We therefore believe that the patients in our study were treated appropriately.

Another concern mentioned by Cheema and Roberts¹ was that the mitral valve repair rate in the MIVS group was 58%, and that "perhaps the lack of adequate exposure inherent to a 4- to 5-cm incision compromised the ability to attain a satisfactory repair." Although we agree that in the hands of a high-volume surgeon a P2 prolapse can have a high repair rate, those were not the type of patients we encountered. Our patient population