

LETTERS TO THE EDITOR

THE DOG DIDN'T BARK**To the Editor:**

The interesting article, "Outcome and prognostic factors of pleural mesothelioma after surgical diagnosis and/or pleurodesis"¹ recently published in the *Journal* again illustrates the universally lethal course of this disease.

During the last 60 years, hundreds of thousands of young patients worldwide have undergone prophylactic pleurodesis, typically for recurrent spontaneous pneumothorax. These patients have then risked the "normal" exposure to asbestos fibers suffered by the general population. Surprisingly, Middleton and colleagues² state, "No documented cases of pleural malignancy after instillation of talc exist."

This seems extraordinary. Although it seems counterintuitive, whatever the mechanism, the significance of this cannot be overlooked and raises an important question. Should a young individual with evidence of asbestos-related pleural disease also be free to consider pleurodesis to prevent subsequent development of mesothelioma?

Vincent Acton, FRANZCR
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1. Baud M, Strano S, Dechartres A, Jouni R, Triponez F, Chouaid C, et al. Outcome and prognostic factors of pleural mesothelioma after surgical diagnosis and/or pleurodesis. *J Thorac Cardiovasc Surg.* 2013;145:1305-11.

The Editor welcomes submissions for possible publication in the Letters to the Editor section that consist of commentary on an article published in the *Journal* or other relevant issues. Authors should: • Include no more than 500 words of text, three authors, and five references. • Type with double-spacing. • See <http://jtcvs.ctsnetjournals.org/misc/ifora.shtml> for detailed submission instructions. • Submit the letter electronically via jtcvs.editorialmanager.com. Letters commenting on an article published in the *JTCVS* will be considered if they are received within 6 weeks of the time the article was published. Authors of the article being commented on will be given an opportunity of offer a timely response (2 weeks) to the letter. Authors of letters will be notified that the letter has been received. Unpublished letters cannot be returned.

2. Middleton EA, Daniel JC, Knox KS, Williams K. PET positive pleural plaques decades after pleurodesis: mesothelioma? *Southwest J Pulm Crit Care.* 2011;2:9-16.

<http://dx.doi.org/10.1016/j.jtcvs.2013.04.045>

Reply to the Editor:

We thank Dr Acton for his interest in our work. Although some long-term survivors exist, prognosis of non-surgically treated malignant pleural mesothelioma remains poor. This raises the question of identification of subset of patients more likely to benefit from an aggressive approach, including extensive surgery. On the other hand, with respect to his provocative thoughts about the possible effect of talc in preventing mesothelioma, some consideration is in order.

Talc has been used effectively as a pleurodesis agent for several decades. After some early concerns about possible occurrence of malignancy, no cases have been reported of lung cancer or mesothelioma. Talc used for pleural symphysis is asbestos free and consists of large particles, to prevent risks of embolization, pneumonia, or adult respiratory distress syndrome. Indication for talc pleurodesis are mainly malignant effusion and, to a lesser extent, pneumothorax.

We know of no precise estimate regarding the number of patients with long life expectancy (those with pneumothorax) treated by talc pleurodesis worldwide in the last decades, although we are not fully convinced by Dr Acton's estimate of hundreds of thousands. If his estimate is accurate, the hypothesis of possible protective effect of talc against mesothelioma would certainly be real, considering the annual incidence of mesothelioma (approximately 1.5/100,000). Even if the estimate is 10-fold superior to the real number, however, the lack of documentation of cases of mesothelioma in patients treated by talc pleurodesis still suggests some considerations.

Talc is the most effective sclerosing agent, and the most widely used in malignant pleural effusion. The mechanisms of talc-induced pleurodesis are complex and not fully understood: diffuse inflammation, pleural coagulation-fibrinolysis imbalance favoring the formation of adhesions, recruitment and proliferation of fibroblasts, and collagen production occur after instillation of sclerosing agents.¹ Normal pleural mesothelial cells play a major role, releasing several mediators, including interleukin-8, transforming growth factor- β and basic fibroblast growth factor, and it has been pointed out that relative preservation of the pleural cavity (without massive tumoral infiltration) is a major predictor of the success of pleurodesis.¹ Nevertheless, it has been suggested that clinical improvement of patients with malignant pleural effusion after talc pleurodesis is not related only to the control of effusion. It has been shown that pleural fluid of patients receiving talc pleurodesis has increased levels of endostatin relative to control samples.² Normal pleural mesothelial cells would be the origin of this increase, with a resultant shift in the balance to local angiostasis rather than angiogenesis.² Furthermore, in vitro experiments have suggested that, at a therapeutically achievable concentration, talc induces significant apoptosis in malignant mesothelioma³ and lung adenocarcinoma⁴ cells, but not in normal pleural mesothelial cells.³

These properties of talc seem extremely intriguing. Preclinical studies to determine effects in asbestos-related nonneoplastic pleural disease would be interesting, with the aim of assessing the possible action of talc in preventing evolution toward mesothelioma. Appropriate nonhuman models remain to be determined.

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<http://dx.doi.org/10.1016/j.jtcvs.2013.05.021>

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

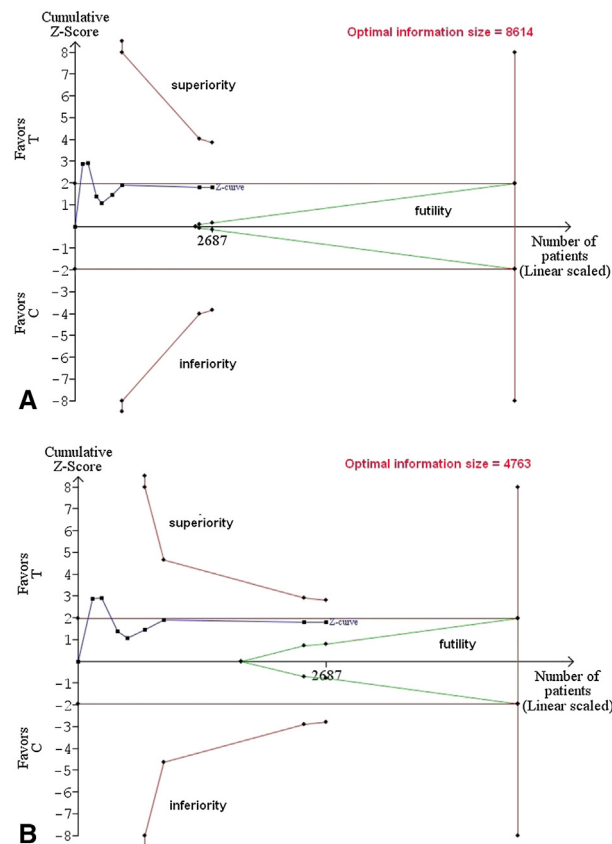


FIGURE 1. Application of trial sequential analysis to interpret the results of 8 placebo-controlled trials evaluating preoperative n-3 polyunsaturated fatty acids to prevent postoperative atrial fibrillation in heart surgery (A and B, expected 15% and -20% relative risk reductions, respectively). In 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.