

## FISH OIL TO PREVENT HEART DISEASE: THE EVIDENCE AND THE CONTROVERSY

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*Ong HT. Fish oil to prevent heart disease: the evidence and the controversy. Malaysian Family Physician. 2006;1(2&3):65-66*

In November 2002, the American Heart Association, after a comprehensive review, announced that fish oil reduces heart disease and recommended that patients consume daily 1gram of marine derived omega-3 fatty acids (comprising eicosapentaenoic acid, EPA, and docosahexaenoic acid, DHA).<sup>1</sup> Yet, the *BMJ* recently published a report suggesting that fish oil is of no value in heart disease.<sup>2</sup> What are we to believe, and does omega-3 really protects against heart disease?

### THE EVIDENCE

The idea that fish oil may be useful came about because communities that consume large quantities of fish, such as the Eskimos and Japanese, seem to have a low incidence of heart disease. Further research showed that even in the same community, those who eat more fish are better off. A 30-year follow up study of men in Chicago showed that those men who consume 35 g or more of fish daily had a 38% lower risk of heart disease mortality.<sup>3</sup> Similarly, in 85,000 women followed for 16 years, those who take fish 2 to 4 times a week had a 31% lower risk of death from heart disease compared to those rarely eating fish.<sup>4</sup> A 12-year study of 43,671 men showed that those eating fish 1 to 3 times a month had a 43% lower risk of strokes compared to those eating fish less than once a month.<sup>5</sup>

The next step in trying to confirm the protective effect of fish oil calls for concrete evidence from randomised placebo-controlled trials. In 1999, the Italian GISSI investigators reported their trial of over 11,000 heart patients given fish oil, vitamin E, both or neither.<sup>6</sup> After 3.5 years, the risk of death, heart attacks or stroke was reduced with fish oil by 10%, and the risk of dying of heart disease was reduced by 17%. Vitamin E was found to be of no benefit. In 1999, von Schacky reported a placebo-controlled study on 233 patients with angiographic coronary artery disease given fish oil supplements for 2 years.<sup>7</sup> In patients on fish oil, 29% of the coronary vessel segments saw a reduction of narrowing, with 71% of segments having an increase in their obstruction severity. This compares with only 15% of the diseased segments improving in the placebo group, and 85% of segments

seeing an increase in narrowing. This difference between the fish oil group and the placebo group is statistically significant ( $p < 0.05$ ).

Since many of the fish oil trials enrolled small number of patients, pooling these studies may provide a clearer idea of the appropriateness of treatment. In 2002, Bucher and colleagues reported their meta-analysis of 11 trials, in which 7951 patients were put on fish oil and 7588 patients were in the control group.<sup>8</sup> The risk of fatal heart attacks was reduced by 30% ( $p < 0.001$ ), and overall death rates reduced by 20% ( $p < 0.001$ ) in the treated group. The highly significant p values strongly support the conclusion of the authors that omega-3 fatty acids are beneficial for patients with coronary disease. In April 2005, Studer and colleagues reviewed 97 studies that enrolled 276,116 patients studying whether different lipid lowering medicines or dietary changes had an effect on mortality rates.<sup>9</sup> Only those receiving the statins and fish oil saw a significant reduction of overall mortality, with a reduction of 13% with statins and 23% with fish oil. Writing in the March 2006 issue of the *American Heart Journal*, Defilippis and Sperling conclude that fish-derived, and even plant-derived, omega-3 fatty acids favourably affect cardiovascular health.<sup>10</sup>

### THE CONTROVERSY

A review article by Hooper and colleagues, released online in March 2006 in the *BMJ*, suggested that fish-derived (DHA and EPA) and plant-derived (alpha-linolenic acid, ALA) omega-3 oils have no effect on heart disease or mortality rates.<sup>2</sup> The reason this differing conclusion was reached is because this review included a study by Burr, the DART-2 study, which suggested that fish oil in fact increases cardiac death.<sup>11</sup> If the DART-2 trial had been excluded, Hooper would have results similar to that of the others and showed that fish oil significantly reduced mortality by 17%. The methodology of the DART-2 trial was strongly criticized by many, including a report of the Agency for Healthcare Research and Quality of the United States government, prepared by the Tufts-New England Medical Centre.<sup>12</sup> Patients on the fish-oil arm were either

advised to eat more oily fish or else given fish oil capsules. Recruitment was spread out over 6 years, but was interrupted and ceased for 12 months due to funding shortage. DART-2 reported a follow-up of 3-9 years on 3,114 patients. However, assessment of compliance in the treatment arm with plasma EPA levels was carried out only once, 6 months after initiation of dietary advice to increase fish intake in the first phase of the trial, in 68 patients. Thus it is not clear whether the other 3,046 patients, especially those in the second phase, actually followed the prescribed treatment over the trial period. The study suggested that patients on fish oil capsules, rather than those consuming fatty fish, had an adverse cardiovascular outcome. Given the recent withdrawal of Seven Seas cod liver oil capsules from the European market, the possibility of dioxin contamination of the fish oil capsules used in the Welsh study must be contemplated. Dart-2 also found that fruit intake is of no value in heart disease, again contrary to most other researchers. It is thus reasonable to give less emphasis to the results of DART-2, compared to the large number of patients studied in the other papers.

## CONCLUSION

It is reasonable to conclude that the evidence thus far still supports the contention that fish derived omega-3 fatty acids, EPA and DHA, are good for heart patients. But this controversy tells us something about the medical research, and the acquisition and application of medical knowledge.

Being scientists, doctors try to perform studies as rigorously as possible with randomised, placebo-controlled trials and using tests of statistical significance. But since the studies are on humans, with all their individual differing habits and inconsistencies, different results are produced by different researchers. And so while medicine is a science, in that the trials are scientifically conducted, the interpretation of the results, and in particular its application for the individual patient, is very much an art. A good doctor, like the good artist, must spend much time, energy and effort sieving through the good from the not so good

data before coming out with the correct picture. Only by keeping an unbiased, inquisitive mind can the evidence be reviewed to solve the problem at hand. Almost always, the balance of data will favour a particular stand. In this day when newspapers are full of medical articles, a family physician has to be educated, interested and inquisitive to be a source of accurate and relevant information for the patients.

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