

## Research

## Should patients with cardiovascular disease take fish oil?

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∞ See related articles, pages 150, 157 and 177

The scientific community and the public have been fascinated by epidemiologic data showing the beneficial effects that a diet rich in fish oils can have on cardiovascular disease. As a result, several clinical trials have been performed that have examined the effects of omega-3 polyunsaturated fatty acids (the active ingredient in fish oils) on cardiovascular disease.<sup>1-6</sup>

The most important trial of the effects of polyunsaturated fatty acids on cardiovascular outcomes, the GISSI-Prevenzione trial, tested omega-3 polyunsaturated fatty acids in patients who had survived a myocardial infarction in the past 3 months.<sup>6</sup> The primary outcome was a composite of death, nonfatal myocardial infarction and stroke. This trial showed a modest, but statistically significant, reduction in the risk of the primary outcome among patients who received omega-3 polyunsaturated fatty acids. Interestingly, a subgroup analysis showed that much of the observed reduction in mortality was due to a reduction in sudden cardiac deaths. The GISSI-Prevenzione trial was not designed to evaluate sudden cardiac death specifically, and the results of these analyses have to be interpreted cautiously. However, this report generated interest in the antiarrhythmic potential of omega-3 polyunsaturated fatty acids.<sup>6</sup>

Experimental work in animal models has shown that omega-3 fatty acids affect the electrophysiological properties of the heart. Stabilization of cell membranes and suppression of arrhythmia have been identified as possible mechanisms that could reduce sudden death.<sup>7</sup> In the last few years, 3 small, well-executed randomized clinical trials have been published that evaluated the antiarrhythmic effects of omega-3 fatty acids.<sup>8-10</sup> The patient population included in these recent trials was quite different from that included in the GISSI-Prevenzione trial. These trials included patients with implantable cardioverter defibrillators who had sustained ventricular tachycardia or fibrillation. These patients had a variety of cardiac conditions, and most had left ventricular systolic dysfunction that was moderately severe. It is also likely that the mechanism of ventricular arrhythmia was different between the 2 patient populations. After myocardial infarction, patients are more likely to have arrhythmia related to recurrent ischemia, and patients with implantable cardioverter defibrillators are more likely to have scar-related ventricular tachycardia. Thus, these trials tested the effects of omega-3 fatty acids on cardiac arrhythmia in a clinical setting that was quite different from that of the GISSI-Prevenzione trial.

## Key points of the article

- The 3 randomized controlled trials evaluated by Jenkins and colleagues failed to convincingly demonstrate a beneficial effect of omega-3 fatty acids in preventing ventricular arrhythmia.
- There is weak evidence from other meta-analyses that omega-3 fatty acids prevent ventricular arrhythmia and cardiovascular mortality.
- Health Canada currently does not approve omega-3 fatty acids for prevention of cardiovascular outcomes.
- There is insufficient evidence to recommend the routine use of omega-3 fatty acids.

What did the 3 recent trials show? As demonstrated by a meta-analysis in this issue,<sup>11</sup> these trials failed to convincingly demonstrate a beneficial effect of omega-3 fatty acids in preventing ventricular arrhythmia. Pooling the data from these trials provides no further evidence that omega-3 fatty acids reduce discharge of implantable cardioverter defibrillators or mortality.<sup>11</sup> What have we learned from these trials? It is unlikely that fatty acids reduce ventricular arrhythmia in patients with implantable cardioverter defibrillators. However, because arrhythmia markers may be very different early after myocardial infarction, this finding does not disprove the hypothesis that polyunsaturated fatty acids reduce arrhythmic death in patients after myocardial infarction.

In an attempt to make sense of all available data about the effect of omega-3 fatty acids on heart disease, Hooper and colleagues performed a comprehensive meta-analysis of nearly 100 randomized controlled trials and prospective cohort studies that were published before 2002. This meta-analysis, which included over 600 000 patients, showed no clear benefit of omega-3 fatty acids on reducing total mortality or combined cardiovascular events.<sup>12</sup> More recently, Yokoyama and colleagues reported on the outcome of the Japan EPA Lipid Intervention study, a primary prevention trial of omega-3 fatty acids that included 18 645 patients with a total cholesterol of 6.5 mmol/L or greater (these patients were not included in the meta-analysis by Hooper and colleagues).<sup>13</sup> Yokoyama and colleagues reported a statistically

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significant 19% reduction in the primary outcome of any major coronary event (a composite outcome that included sudden cardiac death, fatal and nonfatal myocardial infarction, and other nonfatal events including unstable angina pectoris, angioplasty, stenting or coronary artery bypass grafting). They found no effect on total or sudden death.<sup>13</sup>

At present, there is only weak evidence that omega-3 fatty acids prevent ventricular arrhythmia and somewhat stronger (but not fully convincing) evidence that they prevent cardiovascular mortality. Although they are approved in some countries, Health Canada currently does not approve omega-3 fatty acids for prevention of cardiovascular outcomes. However, this does not mean that we should stop performing research on the role of omega-3 fatty acids in the prevention and treatment of cardiovascular diseases. We agree with a recently published report from the National Heart, Lung and Blood Institute that encourages researchers to continue evaluating omega-3 fatty acids.<sup>14</sup> Several interesting, large randomized controlled trials are either being planned or are already underway. These include a study of the role of omega-3 fatty acids in patients with heart failure and a trial focused on the outcome of sudden death among patients after myocardial infarction trial as well as major studies involving patients with diabetes.<sup>14</sup> Ultimately, these trials will create a clear picture of the appropriate role of omega-3 fatty acids in the prevention of cardiovascular outcomes.

What should clinicians do? Because omega-3 fatty acids are not approved as pharmaceuticals in Canada, they cannot be prescribed. Preparations of concentrated omega-3 fatty acids are available over the counter as health foods, and are quite widely used and recommended by some physicians. Clearly, there is no evidence to support the use of omega-3 fatty acids in protection against ventricular arrhythmia in any patient population. One could be cautiously optimistic that patients may benefit from omega-3 fatty acids if they are taken preventatively or after a myocardial infarction, but we feel that the evidence is not sufficiently persuasive to recommend their routine use as either a health food or a pharmaceutical.

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