Tidsskriftet
DEN NORSKE LEGEFORENING

Omega-3 supplements do not prevent cardiovascular disease

KRONIKK

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There is little evidence that omega-3 supplements can prevent cardiovascular disease. We should therefore hold back on recommending and marketing omega-3 supplements as a preventive treatment.

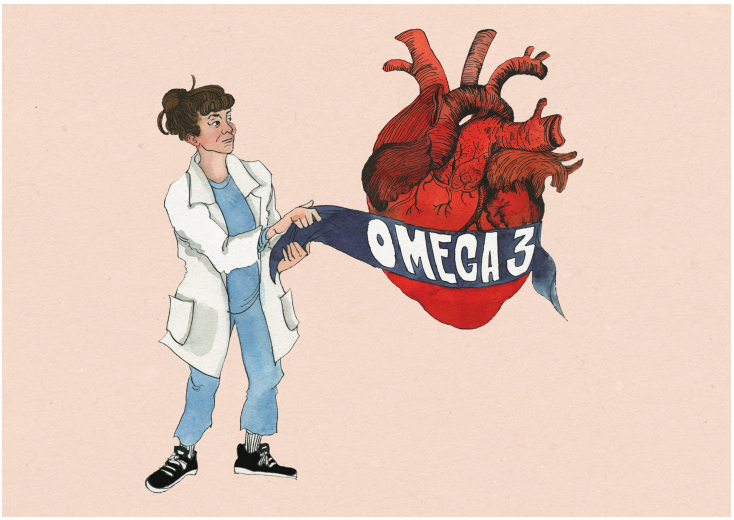

Illustration: Kjersti Synneva Moen

The last three years have seen the publication of results from several large randomised controlled trials on omega-3 supplements and cardiovascular disease (1–5). This has changed our understanding of omega-3 dietary supplements in cardiovascular prophylaxis and has

concentrated our focus on differences between the two most important marine omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Earlier trials dating back to the 1990s showed that after myocardial infarction, omega-3 supplements reduced the risk of further cardiovascular events. These findings have been key to the hypothesis that omega-3 supplements have a cardioprotective effect (6, 7). However, these trials were conducted before the introduction of present-day postinfarction treatments in clinical practice, including intensive lipid lowering therapy, appropriate blood pressure treatment, dual antiplatelet therapy, modern coronary revascularisation and heart failure treatment. Similar postinfarction omega-3 trials were conducted in the 2000s, but the results were neutral (8–10). This gave rise to speculations as to whether the beneficial effect of omega-3 disappears when the supplement is taken on top of modern treatments. However, these studies used the same low dose of omega-3 as in the 1990s (1 g/day), and this has raised the question of whether high-dose omega-3 supplements may be more effective.

Omega-3 for elderly patients after myocardial infarction

In 2012, a Norwegian multicentre trial was initiated by Oslo University Hospital and conducted in partnership with researchers at Akershus University Hospital, Stavanger University Hospital and Bærum Hospital (5). In this study, 1027 patients, between 70 and 82 years of age and who had recently experienced myocardial infarction, were randomised to either 1.8 g/day omega-3 (EPA/DHA) or placebo (corn oil). The results were presented as one of the main studies at the American Heart Association Scientific Sessions in November 2020 and attracted considerable attention. The main findings showed *no* difference in the incidence of new cardiovascular events (myocardial infarction, coronary revascularisation, stroke, hospitalisation for heart failure and death) between the group that received omega-3 and the placebo group (5).

Omega-3 as primary prophylaxis

Recently, highly reliable large-scale trials have also been conducted to study the effectiveness of omega-3 in patients *without* established heart disease. In one study involving approximately 26,000 healthy participants who were followed up over a period of 5 years, the omega-3 supplement (1 g/day) did not reduce the incidence of adverse cardiovascular events (myocardial infarction, stroke or cardiovascular death) or cancer (1). Similarly, another study that included almost 16,000 patients with diabetes but no established heart disease, found that the same dose of omega-3 taken as a dietary supplement had no preventive effect on adverse cardiovascular events (2).

Omega-3 for patients with hypertriglyceridemia

For many years, an omega-3 dietary supplement was the recognised treatment for patients with high triglyceride levels because such supplements had generally been proved to lower triglyceride levels by 20–30 % (11). Since hypertriglyceridemia is a cardiovascular risk factor independent of other established risk factors (including LDL cholesterol) (12), the belief was that the triglyceride reduction caused by omega-3 would translate into a beneficial effect on clinical endpoints. International guidelines have therefore been recommending a high-dose omega-3 supplement (2–4 g/day) for patients with hypertriglyceridemia. Consequently, medications that contain EPA and DHA have in Norway been pre-approved for subsidised prescription if dietary adjustments alone fail to have the desired effect in hypertriglyceridemia patients (11). It was not until recently that results were forthcoming from trials that were large enough to test if omega-3 supplements actually reduce adverse cardiovascular events in this group. In November 2020, the long-awaited results were published of a study that was both large enough to consider clinical endpoints and involved a sufficiently high dose of omega-3 (4). These results showed that for patients with hypertriglyceridemia and an elevated cardiovascular risk, the incidence of myocardial

infarction, unstable angina, coronary revascularisation or cardiovascular death was similar whether they were in the placebo group or in the group that received 4 g/day of an omega-3 supplement (EPA/DHA).

It appears that a very high dose of the ethyl-EPA *drug* may have a cardioprotective effect which has not been proved for standard omega-3 *dietary supplements*

The trial that has turned the whole field on its head is REDUCE-IT, which has attracted enormous attention since it was published in 2019 (3). REDUCE-IT tested the effect of administering a high dose of pure EPA (with an ethyl group, i.e. ethyl-EPA) to hypertriglyceridemia patients with and without established cardiovascular disease. The results showed a considerably lower incidence of adverse cardiovascular events on receiving 4 g/day ethyl-EPA compared to placebo. After following up more than 8,000 patients for an average period of 5 years, the incidence of myocardial infarction, coronary revascularisation, stroke or cardiovascular death was 25 % lower among patients who received omega-3. The effect was present for all primary endpoint components and across important subgroups. Based on these results, ethyl-EPA was recently approved as a prescription *drug* for the treatment of hypertriglyceridemia in the United States. However, the use of mineral oil as a placebo in REDUCE-IT has attracted criticism because the placebo group experienced a rise in LDL-cholesterol and CRP, which has not been found to be the case for the corn oil used in most other trials.

Based on new knowledge, Norway, where people are enthusiastic consumers of omega-3, should also hold back on recommending and marketing omega-3 dietary supplements as a preventive treatment for heart disease

How should we interpret the highly positive REDUCE-IT results in light of the other neutral studies? It appears that a very high dose of the ethyl-EPA *prescription drug* may have a cardioprotective effect which has not been proved for standard omega-3 *dietary supplements*. It is uncertain whether this difference is due to adverse effects of DHA and/or mineral oil, differences in dose or differences in the quality of the omega-3 fatty acids. This requires more research, and ideally a large-scale randomised controlled trial that tests the efficacy of ethyl-EPA in comparison with a corn oil placebo on cardiovascular endpoints.

Adverse effects of omega-3 supplements

In general, there are few adverse effects associated with taking omega-3 supplements, aside from light gastrointestinal problems such as reflux and nausea. There are therefore limited disadvantages to taking omega-3 as a dietary supplement. However, it is a worrying signal that several recent studies have observed an increased risk of atrial fibrillation (2–5). For the time being, this link must be considered uncertain. Further research is required, involving dedicated randomised trials with atrial fibrillation as the primary endpoint.

Conclusion

Countless observational studies have shown that higher levels of omega-3 in the body are associated with a lower risk of adverse cardiovascular events and other diseases. This association is probably caused by the fact that those who consume omega-3 in abundance are generally in better health, and that consumption of foods that are rich in omega-3 is beneficial. However, it now appears to be relatively certain, based on consistent findings from several large studies, that there is no place for over-the-counter omega-3 (DHA/EPA) dietary supplements in either primary or secondary prophylaxis for heart disease, including for patients with hypertriglyceridemia. In 2019, the European Medicines Agency removed its recommendation of omega-3 as a preventive treatment after myocardial infarction. Several meta-analyses, including a new Cochrane report from 2020, have also concluded that the cardioprotective effect of omega-3 supplements is very limited (13). Based on new knowledge, Norway, where people are enthusiastic consumers of omega-3 supplements,

should also hold back on recommending and marketing omega-3 dietary supplements as a preventive treatment for heart disease. This is particularly important in patients who already take multiple drugs, to avoid diminishing the focus on prophylactic treatments that actually reduce cardiovascular risk.

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Published: 12 April 2021. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.21.0033
Received 11.1.2021, first revision submitted 2.2.2021, accepted 8.2.2021.

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