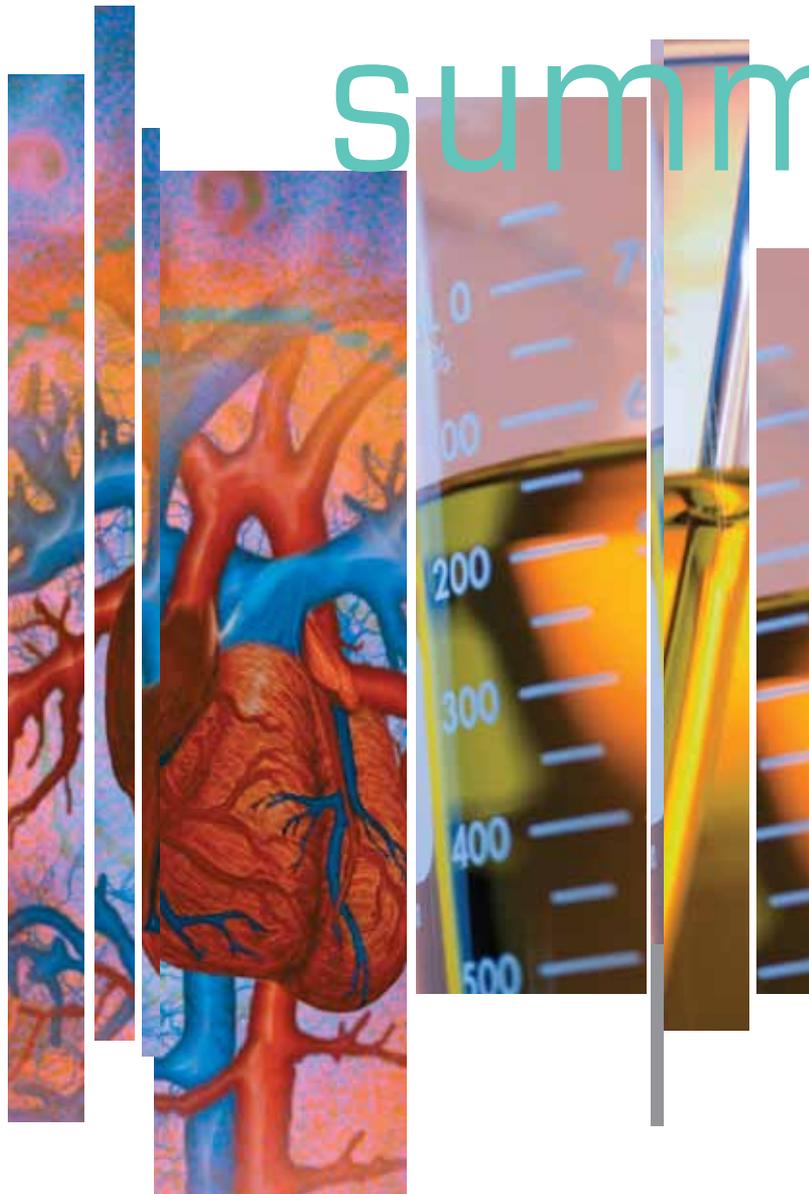


SCIENTIFIC BACKGROUND INFORMATION ON

MARINOL[®]

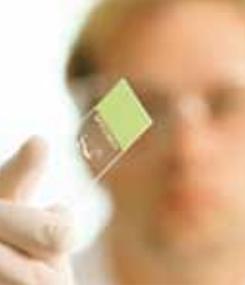
Cardiovascular Health

summary



Marinol[®]

Stepan[®]
Lipid Nutrition
The Natural Way to Better Health



Marinol® - Fish Oil Prevents Cardiovascular Disease

For several years now, it has been clear that consumption of fish oil can prevent recurrent heart disease. Specifically, these health benefits have been attributed to the fish omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (figure 1). Many international health agencies, including the American Heart Association and the United Kingdom National Health Service, advise daily consumption of 500mg EPA and DHA for healthy people and 1g EPA and DHA for heart attack survivors. This advice is based on the result of several important human clinical trials showing beneficial effects from fish oil on recurrent cardiovascular disease. The most important one, the GISSI-Prevenzione trial, clearly showed a 30% lower risk of cardiovascular death in heart disease patients after daily consumption of fish oil (figure 2).

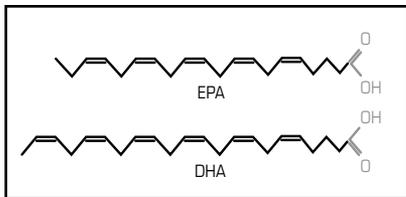


Figure 1

Chemical structures of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

There is also evidence that fish oil has preventive effects against cardiovascular disease in healthy

people. Results from a meta-analysis of cohort studies showed that an increase in fish consumption of one portion/day decreased cardiovascular mortality risk by 35%. Especially the risk of sudden death seems to be reduced when people take fish oil regularly. Finally, in a study with hypercholesterolemic patients using statins, supplementation of 1.8g EPA reduced coronary events such as myocardial infarction and unstable angina by 19%.

The health benefits of fish oil in regards to cardiovascular disease may be explained by its favorable effects on:

- blood lipids
- atherosclerosis, endothelial function and inflammation
- thrombosis
- blood pressure
- arrhythmia

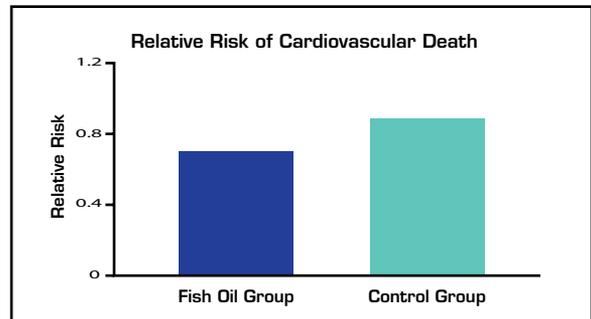


Figure 2

Relative risk of cardiovascular death in myocardial infarction survivors taking 1g/day of fish oil or not receiving fish oil supplementation

GISSI-Prevenzione investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999; 354: 447-55

Blood Lipids

Increased concentrations of the blood lipids cholesterol and triglycerides are well-known risk factors for cardiovascular disease. By now, it is scientifically accepted that fish oil reduces the levels of triglycerides in the blood and may thereby reduce cardiovascular risk. This beneficial effect is seen in people with normal and high blood lipid concentrations. EPA and DHA seem to reduce triglycerides to a similar extent. The mechanism by which they do so is still subject to further research, but they probably reduce the production and secretion of triglycerides by the liver.

Research also suggests that fish oil is capable of further reducing total cholesterol concentrations in patients receiving statin treatment. In addition, some studies indicate that fish oil is capable of increasing the "good" HDL-cholesterol.

Atherosclerosis, Endothelial Function and Inflammation

Atherosclerosis is one of the pathological processes leading to cardiovascular disease. Observational studies suggest that consumption of fish is associated with a significantly reduced progression of atherosclerosis in women with coronary artery disease. Indeed, a beneficial effect of fish (oil) on carotid plaques and intima-media thickness, both measures of atherosclerosis, is seen in randomized trials. Fish oil supplementation also directly improves arterial elasticity, an important marker of atherosclerosis.

Endothelial function plays an important role in the development of atherosclerosis. Several trials have shown that fish oil improves endothelial function, demonstrated by an improved flow-mediated dilation and a reduction in markers such as thrombomodulin and adhesion molecules. These effects are most probably explained by actions of EPA and DHA on inflammation. It is suggested that DHA especially may increase endogenous nitric oxide production, which improves vasodilation. This presents a primary mechanism responsible for improvement in endothelial function.

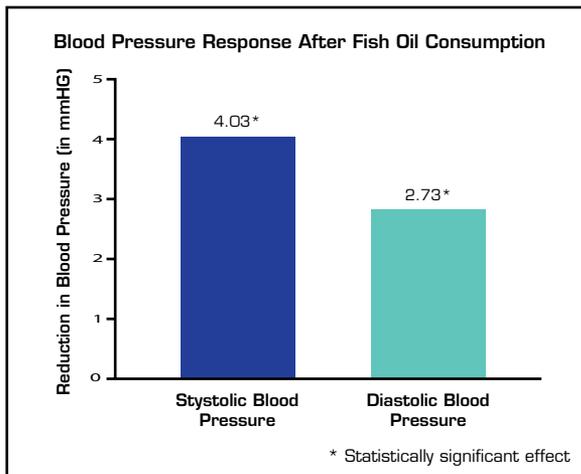


Figure 3

Reduction in systolic (SBP) and diastolic blood pressure (DBP) after fish oil supplementation in subjects with hypertension. Meta-analysis from double blind trials

Geleijnse et al. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *J Hypert* 2002;20:1493-1499

Furthermore, there is evidence that EPA and DHA are incorporated into atherosclerotic plaques and increase their stability. Stable plaques are less prone to rupture, making consequent thrombosis and occlusion of the blood vessel less likely. It is also known that EPA and DHA preserve beneficial vasorelaxant prostacyclins at the expense of vasoconstrictive thromboxanes, which improve vascular function. Finally, a recent study indicates that EPA and DHA may stimulate resolvins, protective compounds that enhance resolution of blood clots.

Thrombosis

Thrombosis is the process of blood clot formation. If thrombosis is excessively stimulated inside a blood vessel, the blood clot can become large and block the blood flow. This may, in turn, lead to myocardial infarction or stroke. Blood platelets are important mediators in thrombosis as they are part of the blood clot, but also secrete many thrombotic factors. It is known that fish oil can reduce blood clotting, among other things, by reducing the clotting activity of platelets.

People with diets rich in fish or fish oils, such as the Greenland Eskimos, have reduced platelet aggregation, increased bleeding time and thereby a lower chance of clot formation and a lower risk of cardiovascular disease. EPA and DHA lead to the formation of anti-thrombotic cytokines and eicosanoids at the expense of pro-thrombotic factors. Also, fish oil seems to favorably affect blood clotting factors such as von Willebrand factor and thrombomodulin.

Blood Pressure

High blood pressure is a common major risk factor for cardiovascular disease. A meta-analysis has shown that fish oil supplementation reduces blood pressure in different populations. The effect was stronger in elderly people and in subjects with hypertension (figure 3). The reduction of blood pressure is partially explained by similar mechanisms such as the effect on thrombosis and endothelial function. The production of vasodilating eicosanoids may reduce systemic vascular resistance, reducing ventricular afterload, which improves diastolic function and decreases blood pressure.

Arrhythmia

Arrhythmia (irregular heartbeat) is the most common cause of sudden cardiac death. Dietary supplementation with omega-3 EPA and DHA has been shown to have a beneficial effect on arrhythmia. Low heart rate variability, a predictive marker for arrhythmia, is improved with EPA and DHA supplementation in heart disease patients and in healthy men. A recent meta-analysis has shown that fish oil reduces heart rate, leading to a reduced risk for sudden cardiac death.

This beneficial effect of EPA and DHA may be explained by the incorporation of these fatty acids into the heart cell membranes, thereby changing the responsiveness of the heart. Also, the reduction in blood pressure as described above would benefit heart rate by improving ventricular efficiency. Finally, it has been suggested that EPA and DHA affect sodium and calcium currents through the heart cell membranes, which control heart rhythm.

Conclusions

Cardiovascular disease is a long-term and complex process, involving many different factors. It is clear that EPA and DHA influence these factors throughout the development of cardiovascular disease. Their different actions on inflammation and blood pressure may minimize atherosclerosis. They help stabilize plaques and may prevent them from rupturing. In the case that plaque rupture still occurs, they help limit the size of the blood clot. Finally, the beneficial effects on arrhythmia may help the heart recover from a reduction in blood flow through a (near) obstruction. Dietary supplementation with fish oil therefore reduces the risk of cardiovascular disease, as well as intermittent phases, such as high blood pressure and atherosclerosis.

Marinol® Helps to:

- reduce cardiovascular risk
- reduce triglyceride levels
- prevent atherosclerosis
- improve endothelial function
- reduce thrombosis
- reduce high blood pressure
- prevent irregular heartbeat

Suggested Reading

Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 2002;106:2747-2757.

Wang C, Harris W, Chung M et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr* 2006;84:5-17.

He K, Song Y, Daviglius M et al. Accumulated evidence on fish consumption and coronary heart disease mortality. A meta-analysis of cohort studies. *Circulation* 2004;109:2705-2711.

Yokoyama M, Origasa H, Matsuzaki M et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomized open-label, blinded endpoint analysis. *The Lancet* 2007;369:1090-1098.

De Roos B, Mercer DK, Wainwright C, Thies F. Effect of long chain n-3 PUFA on endothelial activation, endothelial function and atheromatous plaque stability. *Curr Nutr Food Sci* 2005;1:167-177.

Ueshima H, Stamler J, Elliott P et al. Food omega-3 fatty acid intake of individuals (total, linolenic acid, long-chain) and their blood pressure. INTERMAP Study. *Hypertension* 2007;50:313-319.

Mozaffarian D, Geelen A, Brouwer IA et al. Effect of fish oil on heart rate in humans. A meta-analysis of randomized controlled trials. *Circulation* 2005;112:1945-1952.

Mori TA, Woodman RJ. The independent effects of eicosapentaenoic acid and docosahexaenoic acid on cardiovascular risk factors in humans. *Curr Opin Clin Nutr Metab Care* 2006;9:95-104.



STEPAN LIPID NUTRITION USA
100 West Hunter Avenue
Maywood, New Jersey 07607
Phone: +1 201 845 3030

STEPAN LIPID NUTRITION EUROPE
Museumlaan 16
1541 LP, Koog aan de Zaan
The Netherlands
Phone: +31 (0) 75 727 10 00

www.lipidnutrition.com
Email: food.health@stepan.com

*Stepan Lipid Nutrition is the business name of Stepan Specialty Products LLC and BV. All trademarks owned by Stepan Specialty Products LLC.