n-3 Fatty Acids from Fish and Plants
Primary and Secondary Prevention of Cardiovascular Disease

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KEY POINTS

- Animal studies, epidemiological studies, and clinical trials have shown that fish and fish oil may reduce sudden death by preventing cardiac arrhythmias.
- n-3 fatty acids have an antithrombotic effect through the diminution of thromboxane A₂ that produces platelet aggregation and vasoconstriction.
- Eicosapentaenoic and docosahexaenoic acids have been shown to inhibit atherosclerosis, probably because of their suppression of cellular growth factors that inhibit the proliferation of smooth muscle cells.
- n-3 fatty acids lower very low-density lipoprotein and triglyceride through depression of synthesis of triglyceride in the liver. n-3 fatty acids also suppress postprandial lipemia, which reduces chylomicron remnants that are considered atherogenic.
- Fish oil does not adversely affect glucose control in patients with diabetes.
- n-3 fatty acids have been uniformly associated with a mild decrease in systolic blood pressure and, at times, a decrease in diastolic blood pressure.
- The intake of n-3 fatty acids should be increased to prevent coronary heart disease.

1. INTRODUCTION

Fish and fish oils contain the very long-chained and highly polyunsaturated n-3 fatty acids (in this chapter, the terms n-3 and omega-3 are used interchangeably), which are derived from phytoplankton, the base of the food chain in oceans, lakes, and rivers (1). Phytoplankton synthesize the n-3 fatty acids eicosapentaenoic (20:5) (EPA) and docosahexaenoic (22:6) (DHA), which are subsequently incorporated into fish, shellfish, and sea mammals. The plants synthesize an n-3 fatty acid, linolenic acid (18:3), which can be converted by the body to EPA and more slowly to DHA (2,3). The n-3 fatty acids have profound biological and biochemical effects in the body. Despite a wealth of scientific information (a review listed more than 120 references about cardiovascular effects alone (4), clinical interest in n-3 fatty acids has not been high in the United States.
despite considerable attention to their use in Europe and Japan. This chapter focuses on the considerable and underappreciated potential benefits of the n-3 fatty acids in cardiovascular disease (CVD).

In the 1950s, it was discovered that polyunsaturated vegetable oils containing the n-6 linoleic acid had a pronounced plasma cholesterol-lowering effect, but the mechanism of this action has remained obscure (1). At that time, it was noted that fish oil, which was also polyunsaturated, had a similar hypocholesterolemic effect. No mention was made of the fact that fish oil contained very long-chain n-3 fatty acids (C20:5 and C22:6) and that these might act differently than the n-6 fatty acids of vegetable oils, such as linoleic acid (C18:2). These early data about fish oil laid fallow until the pioneering observations of Dyerberg and Bang focused special attention on the n-3 fatty acids EPA (20:5) and DHA (22:6), which are found in marine oils (5). Dyerberg and Bang observed a lower coronary mortality among the Greenland Eskimos, whose diet was especially rich in marine oils compared to Danish people, who consumed a diet high in saturated fat (6). It was later discovered that not only did these n-3 fatty acids lower cholesterol, but they had a profound plasma triglyceride-lowering effect, especially in hypertriglyceridemic patients (7–9). Over two decades of research in humans, animals, perfused organs, and tissue cultures have firmly documented the mechanisms of the hypolipidemic actions of these n-3 fatty acids from fish and, furthermore, have demonstrated that these fatty acids have many other beneficial effects in CVD.

This chapter focuses on seven different areas of research that will help to answer the question about the potential benefits of n-3 fatty acids from fish oil for primary and secondary prevention of CVD. These benefits are listed below and are subsequently discussed in detail. We first discuss how n-3 fatty acids will prevent further events in those patients who already have coronary heart disease (CHD) (secondary prevention). This is especially relevant to staving off fatal arrhythmias of the heart and thrombosis. Then, we discuss how n-3 fatty acids might prevent coronary disease in healthy individuals, especially in those who possess certain risk factors.

2. ANTIARRHYTHMIC ACTIONS

2.1. Animal Studies

Sudden death from ventricular arrhythmias is a much-dreaded complication in patients with CHD. Several experimental studies have addressed this problem with the use of n-3 fatty acids from fish oil. McLennan et al. (10) used coronary artery ligation in the rat to produce an in vivo model of ventricular fibrillation and myocardial infarction (MI). They found that the number of ventricular ectopic beats and duration of tachycardia or fibrillation was increased in rats that were fed sheep kidney fat (a saturated fat) compared to rats that were fed tuna fish oil, a rich source of n-3 fatty acids. The rats that were fed tuna fish oil had a significantly reduced incidence and severity of arrhythmias. In another animal study, ventricular fibrillation was prevented by fish oil during both the occlusion of the coronary artery and reperfusion of the heart (11).

In other experiments, Hallaq et al. (12) used isolated neonatal cardiac myocytes (from hearts of 1-d-old rats) as a model for the study of cardiac arrhythmogenic factors that are modified by n-3 fatty acids. They incubated isolated myocytes (for 3–5 d) in a