

Marine Lipids and Atherosclerosis: A Review

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Marine lipids rich in omega-3 fatty acids have been shown to beneficially modify plasma lipid concentrations and decrease platelet aggregation. The combined lipid-lowering and antithrombotic effects of marine omega-3 fatty acids make this natural food source an ideal intervention to potentially prevent and possibly regress atherosclerosis. The bleeding-time prolongation, reduction in platelet aggregation, and decrease in blood pressure with dietary omega-3 fatty acids are believed to be secondary to a change in prostaglandin substrates. Whereas vegetable omega-6 fatty acids serve as substrates for highly reactive thromboxane A₂, marine lipids serve as substrates for the weakly active thromboxane A₃. The net result is prostaglandin synthesis that favors less platelet aggregation and reduced vasoconstriction. The hypolipidemic effect of marine lipids, though of an uncertain mechanism, causes approximately a 10% reduction in total cholesterol and a 40% lowering of triglycerides and, unlike vegetable oils, does not lower HDL cholesterol. The recent development of a marine lipid concentrate allows practical omega-3 fatty acid supplementation for the majority of the adult population to be superimposed on the standard Western diet.

INTRODUCTION

The low incidence of coronary heart disease in Greenland Eskimos has stimulated considerable interest in fish consumption as a protective measure against the development of atherosclerosis. Compared with Western populations, the Eskimos have lower plasma-lipid levels, a decreased frequency of hypertension, and prolonged bleeding times—characteristics that were initially felt to be genetically determined.¹⁻³ It has recently been shown, however, that these characteristics are related to their diet, which consists of cold-water fish, seal, and whale meat; all three are high in the marine omega-3 series of polyunsaturated fats. The marine omega-3 series, eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), was originally classified with the structurally similar vegetable oil omega-6 series of

polyunsaturated fats; their differences in hypolipidemic activity and antithrombotic effect have only recently been recognized. This review will discuss the latest information regarding marine omega-3 fatty acids and the reasons that they are presently a focus of investigation into the prevention of coronary artery disease.

THEORY OF ATHEROSCLEROSIS

The prevailing "response to injury" hypothesis of atherosclerosis suggests that platelets contribute to lesion formation by releasing a potent growth factor, which stimulates the proliferation of arterial smooth-muscle cells that can subsequently accumulate lipid and become foam cells. Foam cells are also believed to be derived from monocytes. Monocytes can form fatty streaks, one of the earliest findings in the development of atherosclerosis. Like platelets, monocytes adhere to the arterial endothelium and release growth factors that stimulate smooth-muscle proliferation (Figure 1). Marine lipids may reduce the adherence of monocytes to the arterial wall, an effect of omega-3 fatty acids that has been recently shown to occur in neutrophils. Therefore, marine lipids may retard the development of atherosclerosis by both inhibiting platelet aggregation and, possibly, decreasing monocyte adherence to arterial endothelium.

INHIBITION OF PLATELET AGGREGATION

The prolonged bleeding time observed in subjects receiving increased amounts of dietary omega-3 fatty acids appears to result from changes in prostaglandin synthesis (Table 1). The omega-6 series of polyunsaturated fats derived from vegetable oils (safflower, sunflower, soy bean, and corn oils) serve as substrates for the formation of two potent prostaglandins that modulate platelet aggregation, thromboxane A₂ and prostaglandin I₂ (prostacyclin). Thromboxane A₂ is produced in the platelets and promotes their aggregation and vasoconstriction. Prostacyclin, on the

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TABLE I
IMPORTANT DIETARY FATTY ACIDS

Name	Carbon Atoms	Saturation
Stearic acid	(18)	(Saturated)
Oleic acid	(18:1,9)	(Monosaturated)
Linoleic acid	(18:2,9,12)	(W6)
Alpha-linolenic acid	(18:3,9,12,15)	(W3)
Gamma-linolenic acid	(18:3,6,9,12)	(W6)
Arachidonic acid	(20:4,5,8,11,14)	(W6)
Eicosapentaenoic acid	(20:5,5,8,11,14,17)	(W3)

other hand, is synthesized in endothelial cells of arteries and veins, inhibits platelet aggregation, and is a vasodilator. The omega-3 fatty acids appear to compete favorably with omega-6 fatty acids, producing a combination of prostaglandins that retards platelet aggregation and promotes vasodilation. Omega-3 fatty acid consumption produces diminished amounts of proaggregatory thromboxane A₂

with the formation of only small amounts of an apparently biologically inactive or weakly active thromboxane A₃, whereas the prostacyclin effects are maintained or amplified (Figure 2). The net effects of these changes is a reduction in platelet aggregation and a prolongation of bleeding time.

The bleeding tendencies of the Greenland Eskimos were first noted in the 1930s, but prolongation of bleeding time in non-Eskimo subjects fed a high fish diet was not recognized until recently. Thorngren and Gustafson⁴ studied ten Swedish men

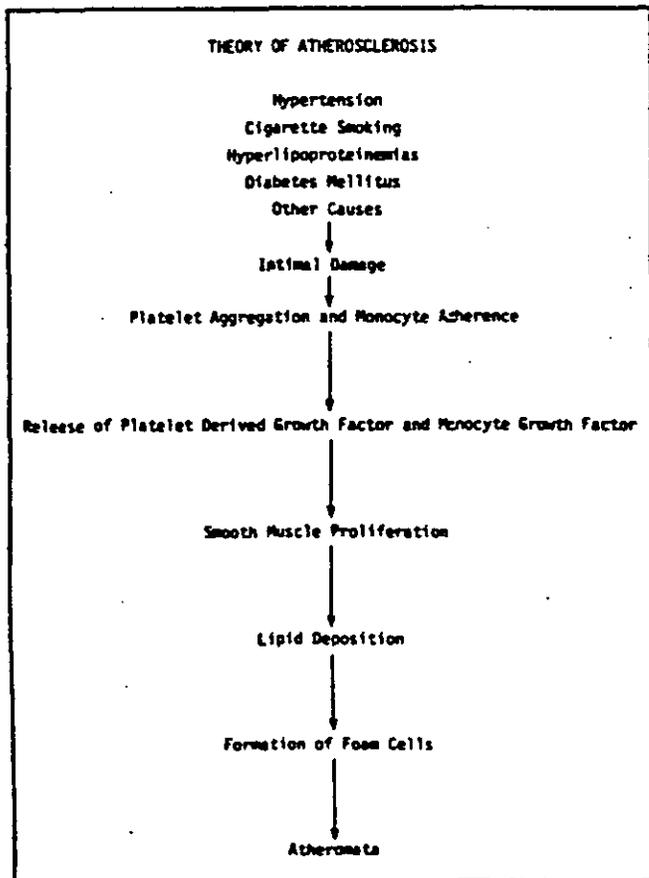


Figure 1. Sequence of events of the endothelial injury hypothesis of atherosclerosis.

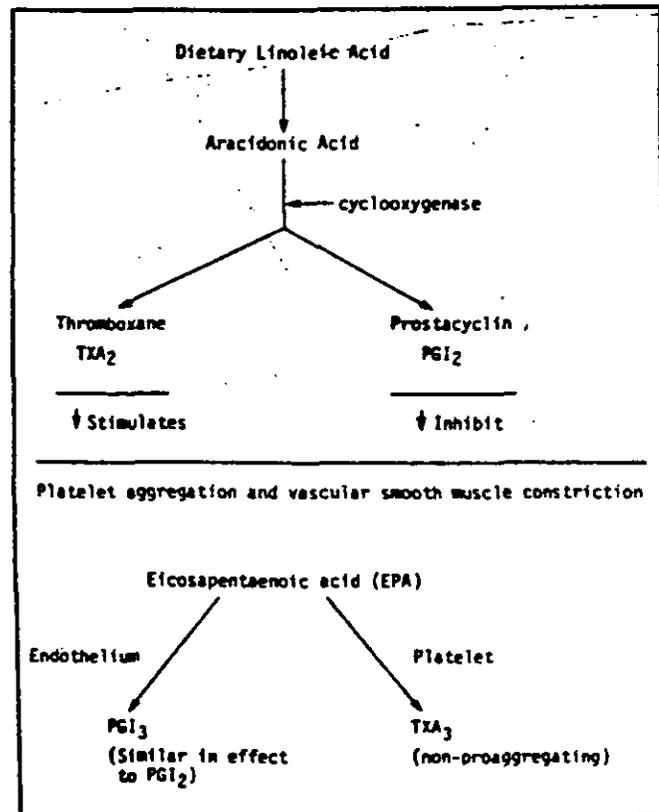


Figure 2. Prostaglandin production from the omega-6 linoleic acid compared with the omega-3 eicosapentaenoic acid.

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who were fed a diet that consisted mainly of mackerel and salmon, for a total of 2 to 3 g of EPA daily. After six weeks of this diet, there was a reduction in platelet aggregation to adenosine diphosphate, collagen, and epinephrine, as well as a prolongation of bleeding time. These results were also verified in healthy volunteers, using cod liver oil or marine lipid concentrate capsules as the source of EPA.⁵ These studies also demonstrated an increase in platelet survival time, a 15% reduction in platelet count, a 75% decrease in platelet factor 4, and a 30% lowering of plasma thromboglobulin.⁶ All of these additional effects contribute to an antithrombotic effect and bleeding-time prolongation. The thrombocytopenia appears to be transient, with the platelet count returning to baseline after three months of fish oil therapy.⁷ Additional studies have noted a modest reduction in serum viscosity.⁸ These same results have been achieved in patients with ischemic heart disease. The combined results of all these studies revealed a bleeding-time prolongation in the range of two to four minutes, a 25% to 50% increase.⁹⁻¹⁰

Aspirin also prolongs bleeding time, but it does so by inhibiting the enzyme cyclooxygenase, which converts arachidonic acid to thromboxane A₂ and prostacyclin. The net result is a decrease of thromboxane A₂ production by irreversibly inhibiting the cyclooxygenase present in platelet membranes and, at the same time, an only temporary inhibition of prostacyclin production by the vessel wall.

As might be predicted, the combination of aspirin and a high fish diet has been shown to prolong the bleeding time. The increase, however, exceeds the prolongation expected from adding the individual effects.¹⁰ Among the explanations for this finding is the possibility that aspirin inhibition of cyclooxygenase may not fully block the conversion of omega-3 fatty acids to prostacyclin I₃ or that the bleeding-time prolongation cannot be fully explained by the altered balance of prostaglandin derivatives. Since the mechanisms of these effects of the fish diet and aspirin on hemostasis seem to differ, the combination of these two agents may provide an interesting preventive and therapeutic modality for atherosclerosis.

NEUTROPHIL AND MONOCYTE ENDOTHELIAL ADHERENCE

In a study in seven healthy subjects given a daily dose of EPA 3.2 g and DHA 2.2 g, using marine lipid concentrate, adherence of neutrophils to bovine endothelial cell monolayers pretreated with leukotriene B was inhibited completely, and the chemotactic response was also markedly reduced.¹¹ This study suggests that fish oil may have an anti-inflammatory response by inhibiting adherence and chemotaxis of white cells. These findings also have implications for effects on the development of atherosclerosis, which may be stimulated by mono-

cyte adherence following endothelial damage, with subsequent release of a growth factor causing smooth-muscle proliferation and the formation of foam cells.

HYPOLIPEMIC EFFECT

Of the three classes of fatty acids, the saturated fatty acids (stearic, palmitic) have a potent hypercholesterolemic effect, the monosaturated fatty acids have a neutral or mild cholesterol-lowering effect, and the polyunsaturated fatty acids have a moderate hypocholesterolemic effect. The two classes of polyunsaturated fatty acids are the omega-6 vegetable oils, of which linoleic and arachidonic acids are most common, and the omega-3 marine oils, of which eicosapentaenoic and docosahexanoic acids are the most prominent. Alpha-linolenic acid (linseed oil) is also an omega-3 fatty acid, but studies have shown that humans are incapable of converting this fatty acid to EPA in sufficient quantities. Omega-3 fatty acids are not interconvertible, and both types can compete with each other for the enzyme cyclooxygenase for conversion to various prostaglandin derivatives. When the cholesterol-lowering ability of polyunsaturated fats was first noted, the difference in the lipid-lowering activity of these two series of fatty acids went unrecognized. With increased use of dietary polyunsaturated fatty acids, more information became available regarding the potentially harmful side effects of this class of fatty acids. Polyunsaturated fats of the omega-6 series were found to enhance cholesterol gallstone formation, decrease immune function, produce unstable lipid factors in cell membrane, and, although reducing low-density lipoprotein (LDL) cholesterol level, also lowered the beneficial high-density lipoprotein (HDL) cholesterol concentration. Although the safety of the omega-3 fatty acids is yet to be fully established, epidemiologic evidence suggests that populations such as the Eskimos, who consume a large quantity of the omega-3 series compounds daily, do not suffer from these possibly untoward effects.

The differences in lipid-lowering activity of acids of the omega-6 series and the omega-3 series were not recognized until Harris and associates¹² compared salmon oil with vegetable oil in healthy volunteers. This study demonstrated an equally significant fall in serum cholesterol level in both groups, but the salmon oil-diet group also experienced a marked reduction in triglyceride concentrations. Other studies have verified the significant lowering effect of omega-3 fatty acids on triglyceride-rich lipoproteins very-low-density lipoproteins [VLDL] and chylomicrons.^{13,14} Although the triglyceride-lowering effect is present in healthy volunteers, the most marked reduction has been noted in type IV and type V hyperlipoproteinemias.¹⁵

The precise mechanism of lipid lowering by omega-3 polyunsaturated fats is not known. How-

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In type II diabetes

Tolinase[®]

(tolazamide) 100, 250, & 500 mg tablets
One tablet...one day's therapy

TOLINASE [®] Tablets tolazamide		
Suggested Initial Dosage		
	Patient Criteria	TOLINASE Dose
No previous hypoglycemic agent	FBS* level lower than 200 mg% (fast)	100 mg/day single dose
	FBS* level greater than 200 mg% (fast)	250 mg/day single dose
	Malnourished, underweight, elderly, or poor dietary habits	100 mg/day single dose
Transfer from other hypoglycemic agents	From chlorpropamide 250 mg/day [†] or tolbutamide more than 1 g/day	250 mg/day single dose
	From tolbutamide 1 g or less/day, or acetohexamide 250 mg/day	100 mg/day single dose
Transfer from insulin	From less than 20 U/day	250 mg/day single dose
	From 20-40 U/day	250 mg/day single dose
	From more than 40 U/day	Reduce insulin dosage 50%; begin TOLINASE Tablets 250 mg/day

*See complete prescribing information. [†]Fasting blood sugar
[†]See package insert for special precautions when transferring patients from chlorpropamide

CONTRAINDICATIONS

- TOLINASE Tablets are contraindicated in patients with:
- Known hypersensitivity or allergy to the drug.
 - Diabetic ketoacidosis, with or without coma.
- This condition should be treated with insulin.
- Type I diabetes mellitus as sole therapy

SPECIAL WARNINGS ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the data generated by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying common complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 18 [Suppl 2]: 747-828, 1979).

UGDP reported that patients treated for 8 to 9 years with diet plus a fixed dose of tolazamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolazamide was associated based on the increase in cardiovascular mortality. Thus, limiting the opportunity for the study to show an increase in overall mortality. Despite reservations regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be advised of the potential risks and advantages of TOLINASE and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolazamide) was included in this study, it is prudent from a safety standpoint to caution that this warning may apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS - General

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection and dosage and instructions are important to avoid hypoglycemic episodes. Patients with renal or hepatic insufficiency, elderly debilitated or malnourished patients, and those with alcohol or planetary insufficiency, are particularly susceptible to hypoglycemia. Hypoglycemia may be difficult to recognize in the elderly and in those taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: This may occur in diabetic patients exposed to stress such as fever, trauma, infection or surgery. It may then be necessary to discontinue TOLINASE and administer insulin.

Adverse Reactions of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Information for Patients - Patients should be informed of the potential risks and advantages of TOLINASE and of alternative modes of therapy. They also should be informed about the importance of adherence to dietary restrictions, of a regular exercise program, and of regular testing of urine and/or blood glucose. The signs of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Laboratory Tests - Response to TOLINASE Tablets should be monitored by frequent urine glucose tests and periodic blood glucose tests. Measurement of glycosylated hemoglobin levels may be helpful in some patients.

Drug Interactions - The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including monoamine oxidase-inhibitory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, acetaminophen, mefenamic acid, and other salicylic acid derivatives.

Certain drugs tend to produce hypoglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and alcohol.

Pregnancy - TOLINASE should be used during pregnancy only if clearly related benefit should be used during pregnancy to maintain blood glucose as close to normal as possible. Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonatal born to mothers who were receiving a sulfonylurea drug at the time of delivery. TOLINASE should be discontinued at least two weeks before the expected delivery date.

Nursing Mothers - Some sulfonylurea drugs are known to be secreted in human milk. Insulin therapy should be considered.

Patients Use - Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypoglycemia: See Precautions and Overdosage sections. Gastrointestinal reactions: Cholinergic reactions may occur rarely. TOLINASE Tablets should be discontinued if this occurs. Gastrointestinal disturbances, e.g., nausea, epigastric burning, and heartburn are the most common reactions (1% of patients). They tend to be self-

limited and may disappear when dosage is reduced. **Dermatologic Reactions:** Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions occurred in 0.4% of patients. These may be transient and may disappear despite continued use of TOLINASE. If skin reactions persist, the drug should be discontinued. **Porphyria:** Cutaneous porphyria and photosensitivity reactions have been reported with sulfonylureas. **Hematologic Reactions:** Leukopenia agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia and pancytopenia have been reported with sulfonylureas. **Metabolic Reactions:** Hepatic porphyria and gallstone-like reactions have been reported with sulfonylureas. However, disulfiram-like reactions have been reported very rarely. **Miscellaneous:** Headache, fatigue, dizziness, vertigo, nausea, and headache have infrequently been reported.

OVERDOSAGE

Overdosage of sulfonylureas, including TOLINASE Tablets, can produce hypoglycemia. If hypoglycemia is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate which will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

HOW SUPPLIED

- TOLINASE Tablets are available in the following strengths and package sizes:
- 100 mg (scored, round, white) Unit-of-Use bottles of 100 NDC 0009-0070-02
 - 250 mg (scored, round, white) Bottles of 200 NDC 0009-0114-04
 - 250 mg (scored, round, white) Bottles of 1000 NDC 0009-0114-02
 - 500 mg (scored, round, white) Unit-of-Use bottles of 100 NDC 0009-0114-05
 - 500 mg (scored, round, white) Unit-Dose package of 100 NDC 0009-0114-06
 - 500 mg (scored, round, white) Unit-of-Use bottles of 100 NDC 0009-0477-08

Caution: Federal law prohibits dispensing without prescription. Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in well closed containers with safety closures. Keep container tightly closed.

For additional product information see your Upjohn representative.

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ever, studies indicate that inhibition of apoprotein B production rather than enhanced clearance is the probable mechanism of decreased VLDL plasma triglyceride concentrations. Several studies that have examined the lipid-lowering effects of omega-3 fatty acids have found a 10% to 20% reduction in total cholesterol level, a 30% to 60% reduction in triglyceride contents, and, unlike the omega-6 fatty acids, a 5% increase in HDL cholesterol level. The increased HDL cholesterol level appears to be a result of an increase in the HDL₂ fraction, believed to be the most protective compound against the development of coronary artery disease.¹⁶

ANTIHYPERTENSIVE EFFECT

The antihypertensive effect of marine omega-3 fatty acids is also believed to be secondary to the change in prostaglandin derivatives, from the potent vasoconstrictor thromboxane A₂ to the weakly active thromboxane A₃. However, a reduction in norepinephrine levels has been noted as well. In one study

with ingestion of omega-3 fatty acids, 15 healthy volunteers were placed on a high EPA mackerel diet or a low EPA herring diet.¹⁷ Both diets were equivalent in calories and total polyunsaturated fat content. In the mackerel diet group, there was a significant 10% reduction in both systolic and diastolic pressures, while the herring diet group did not display any significant change. In another study, eight healthy volunteers were given 40 mL/d of cod liver oil for 25 days.⁵ At the end of the study period, there was a significant fall in both blood pressure and blood pressure response to norepinephrine. At present, there have been no studies on the effects of marine lipids on blood pressure response in hypertensive patients.

THE PREVENTION OF ATHEROSCLEROSIS

Although intimal hyperplasia and atherosclerosis are believed to be separate clinical entities, excessive platelet aggregation is presumed to contribute to both processes. Fibrous intimal hyperplasia is the

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most common cause of late graft failure after aorto-coronary bypass surgery.¹⁸ Antiplatelet agents such as aspirin and dipyridamole have been shown to prolong vein graft patency.¹⁹ In a group of mongrel dogs who underwent jugular vein grafting between femoral arteries and were also given cod liver oil supplementation and a high cholesterol diet, there was significantly less intimal hyperplasia in the harvested veins six weeks later in the cod liver oil group compared with controls.²⁰ This animal study supports the use of marine lipids to prevent graft failure in patients who have undergone venous aortocoronary or femoropopliteal bypass grafting. Intimal hyperplasia is believed to be a significant cause of restenosis of coronary arteries following angioplasty. The use of marine lipids to improve graft survival after venous bypass or to prevent restenosis after coronary angioplasty has yet to be explored.

Although the use of marine lipids to prevent coronary artery disease has yet to be conclusively proven, a retrospective study suggests that dietary fish consumption may markedly reduce the risk of myocardial infarction.²¹ In the Netherlands, information about a group of 852 middle-age men was collected in 1960 by a careful dietary history. After 20 years of follow-up, 78 men had died of coronary disease. An inverse dose-response relation was observed between fish consumption in 1960 and death from coronary disease. The mortality from coronary heart disease was more than 50% lower among those who ate at least 30 g/d of fish as compared with those who did not eat fish. The conclusion of this study was that as little as two fish dishes per week may help prevent coronary artery disease (Table II).

MARINE LIPID CONCENTRATE

For most of the Western population, the Eskimo diet of fish, seal, and whale may be tolerable only for relatively brief periods of time. Cod liver oil contains high quantities of EPA and DHA. However, in order to ingest adequate amounts of these omega-3 fatty acids, vitamin A and D toxicity may occur. Recently, a commercial marine lipid concentrate has been developed that provides varying amounts of omega-3 fatty acids. There are three brands on the American market, MaxEPA, Shaklee EPA, and Res-q-1,000. Each of these brands provides about 300-500 mg EPA and DHA per capsule (Table II). Studies have shown that these capsules are an effective means of utilizing omega-3 fatty acids to lower plasma lipoproteins and blood pressure and to prolong bleeding time. Saynor and colleagues,⁷ using 20 capsules/d of marine lipid concentrate, found a statistically significant reduction in total cholesterol and triglyceride levels, an increase in HDL cholesterol content, and a prolongation of bleeding time. The study also noted a marked reduction in nitrate use among patients with ischemic heart disease. This study was neither controlled nor randomized. A study recently completed in this institution compared the effects of marine lipid concentrate with olive oil in a double-blind, randomized fashion.²² In the marine lipid concentrate group, there was a 13% reduction in total cholesterol compared with baseline or olive oil group, ($P < .025$), a 40% decrease in triglycerides ($P < .005$), a 5% increase in HDL (not significant), a 7% reduction in systolic blood pressure ($P < .005$), and an 8% decrease in diastolic blood pressure ($P < .01$). Compliance, as determined by capsule counting, was excellent, and neither group reported significant adverse reactions. Therefore, marine lipid concentrate capsules, which lack the toxicity of cod liver oil, can supply adequate amounts of omega-3 fatty acids to potentially retard atherosclerosis.

CONCLUSION

The combined hypolipidemic and antithrombotic effects of marine omega-3 fatty acids have evoked interest in these fatty acids as potential agents to retard atherosclerosis development. For patients with elevated serum cholesterol and triglyceride concentrations, marine lipids are an ideal means with which to lower these plasma lipoproteins. The blood pressure-reducing effect of omega-3 fatty acids has yet to be explored in patients with hypertension. For patients who already have atherosclerotic coronary or peripheral artery disease, the potential use of marine lipids to inhibit venous graft closure or restenosis following coronary angioplasty, alone, or in conjunction with other antiplatelet agents, deserves further study. Regression of atherosclerosis, once considered an impossibility, is a

TABLE II
 CONTENT OF OMEGA-3 FATTY ACIDS*

	Total Fat (g)	EPA (g)	DHA (g)
Fish			
Whitefish (lake)	6.0	0.3	1.0
Trout (brook)	2.7	0.2	0.2
Tuna (albacore)	4.9	0.3	1.0
Cod (atlantic)	0.7	0.1	0.2
Perch (white)	2.5	0.2	0.1
Salmon (pink)	3.4	0.4	0.6
Fish Oils			
Cod liver oil	100	9.8	9.5
Salmon oil	100	8.0	11.1
Marine Lipid Concentrates			
MaxEPA	100	17.8	11.6
Shaklee EPA	100	28.0	8.0
Res-q-1,000	100	30.0	22.0

* 100 g (3.5 oz), edible portion, raw.
 Derived from United States Department of Agriculture information.

process that may be a result of the unique combination of effects of marine omega-3 fatty acids.

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ISOPTIN[®]

(verapamil HCl/Knoll)

80 mg and 120 mg scored, film-coated tablets

Contraindications: Severe left ventricular dysfunction (see Warnings), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction < 30% or moderate to severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. (See Precautions.) Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before ISOPTIN is used. (Note interactions with digoxin under Precautions.) ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild and controlled by decrease in ISOPTIN dose). Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations may disappear even with continued treatment, however, four cases of hepatocellular injury by verapamil have been proven by rechallenge. Periodic monitoring of liver function is prudent during verapamil therapy. Patients with atrial flutter or fibrillation and an accessory AV pathway (e.g. W-P-W or L-G-L syndromes) may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion, which has been used safely and effectively after ISOPTIN. Because of verapamil's effect on AV conduction and the SA node, 1st AV block and transient bradycardia may occur. High grade block, however, has been infrequently observed. Marked 1st or progressive 2nd or 3rd AV block requires a dosage reduction or, rarely, discontinuation and institution of appropriate therapy depending upon the clinical situation. Patients with hypertrophic cardiomyopathy (IHSS) received verapamil in doses up to 720 mg/day. It must be appreciated that this group of patients had a serious disease with a high mortality rate and that most were refractory or intolerant to propranolol. A variety of serious adverse effects were seen in this group of patients including sinus bradycardia, 2nd AV block, sinus arrest, pulmonary edema and/or severe hypotension. Most adverse effects responded well to dose reduction and only rarely was verapamil discontinued. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use at 1/3 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, dose surveillance of vital signs and clinical status should be carried out. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patients should be carefully monitored to avoid over- or under-digitalization. ISOPTIN may have an additive effect on lowering blood pressure in patients receiving oral antihypertensive agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Clinical experience with the concomitant use of ISOPTIN and short- and long-acting nitrates suggest beneficial interaction without undesirable drug interactions. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR < 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%), elevations of liver enzymes have been reported (See Warnings.) The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: ecchymosis, bruising, gynecomastia, psychotic symptoms, confusion, paresthesia, insomnia, somnolence, equilibrium disorder, blurred vision, syncope, muscle cramp, shakiness, claudication, hair loss, macules, spotty menstruation. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in round, scored, film-coated tablets containing either 80 mg or 120 mg of verapamil hydrochloride and embossed with "ISOPTIN 80" or "ISOPTIN 120" on one side and with "KNOLL" on the reverse side. Revised August, 1984. 2385



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