REVIEW

# Coronary Heart Disease: How Do the Benefits of ω-3 Fatty Acids Compare with Those of Aspirin, Alcohol/Red Wine, and Statin Drugs?

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**ABSTRACT:** At the present time the primary cause of death of most Americans is cardiovascular disease. Approximately 20 million Americans are currently being treated with some form of statin drugs as a means to lower their blood cholesterol levels, and many of these same people also consume some combination of omega-3 FA, aspirin, and alcohol/red wine because of clinical data indicating that each of these, taken alone, seems to improve mortality. Recent studies with omega-3 FA have demonstrated a positive impact on mortality from coronary heart disease as well as from "all causes," and this article compares their metabolic benefits with those of aspirin, alcohol/red wine, and statin drugs. The article suggests that these four compounds may have synergistic qualities and that clinical trials to study this possibility are warranted.

Paper no. J11416 in *JAOCS 83*, 985–997 (December 2006).

**KEY WORDS:** Alcohol, aspirin, coronary heart disease, health benefits, omega-3 fatty acids, red wine, statin drugs.

Coronary artery disease (CAD) is a condition in which the walls of the arteries supplying blood to the heart muscle become thickened with fibrous plaques, comprising cholesterol, calcium, and abnormal cells, that are deposited in the inner lining of the arteries. These plaques or lesions can protrude into the arterial lumen and reduce blood flow to the heart or remain hidden in the wall of the vessel. When lesions extend into the lumen, they can decrease oxygen supply to the heart, which is uncompensated by the endogenous vasodilatory system (1,2), resulting in angina and/or intermittent myocardial ischemia. These plaques are subject to sudden rupture and trigger a clotting event in the artery that can cause acute obstruction of the lumen. This process can expose underlying collagen of the arterial wall to circulating platelets, which are activated and aggregate to form a plug. This platelet aggregation eventually can lead to thrombus formation. If these lesion/thrombus complexes block a coronary artery, a heart attack occurs. If the blockage occurs in vessels that lead into the brain, the subject has a stroke, whereas clots occurring in the leg lead to the development of intermittent claudication. Chronic bacterial or viral infections, abnormal serum cholesterol and homocysteine metabolism, and high blood pressure are all contributory factors in the development of atherosclerosis *via* a number of pathways that lead to actual physical damage to the endothelium. The cascade of events leading to cardiovascular occlusion often starts with an inflammatory response in the arterial wall. This inflammatory response is then followed by platelet aggregation at the site of injury and concomitant alterations in clot removal (fibrinolysis).

*Inflammation*. Chronic low levels of inflammation of the vascular endothelium are known to cause atherosclerosis, the process underlying cardiovascular disease (CVD) that includes CHD, myocardial infarction (MI), and ischemic stroke (IS) as well as peripheral vascular disease (PVD) (3). Vascular inflammation can be induced in a number of ways including infection, trauma, and cardiovascular shearing forces and has been associated with the production of several acute-phase proteins. These proteins play a key role in the prevention of CVD by providing necessary compounds to immune cells, which destroy bacteria and viruses, thereby allowing for the repair of damaged tissue, including endothelial cells.

A number of physiological changes occur in the body as a result of inflammation. The changes include an increase in the concentration of circulating interleukin-6 (IL-6), which regulates the hepatic production of C-reactive protein (CRP). CRP is an acute-phase reactive protein that circulates at low levels but is rapidly released from the liver to 1,000 times the normal level in the circulation in response to acute inflammation, infection, and tissue injury (4). Whereas CRP has historically been used as a biomarker for inflammation, its role in the inflammation process is still poorly understood. CRP levels show a strong positive correlation with parameters associated with risk factors for CVD, including blood pressure, total cholesterol, TG, and fibrinogen, whereas an inverse correlation has been shown to occur with high-density lipoprotein (HDL) cholesterol (5), an indicator of cardiovascular health.

Many studies (6–13) have shown a strong, positive correlation between CRP, systemic inflammation, and both CHD and PVD. The degree of inflammation in these individuals correlates with disease severity. Madsen *et al.* (14) have shown that patients who have one or more arteries with a 50% or greater blockage have significantly higher CRP levels in their blood than do patients with no significant blockages. They also concluded that inflammatory conditions probably exist in patients with stable CAD. According to Ridker *et al.* (15), baseline CRP levels were higher among men who had MI (1.51 vs. 1.13

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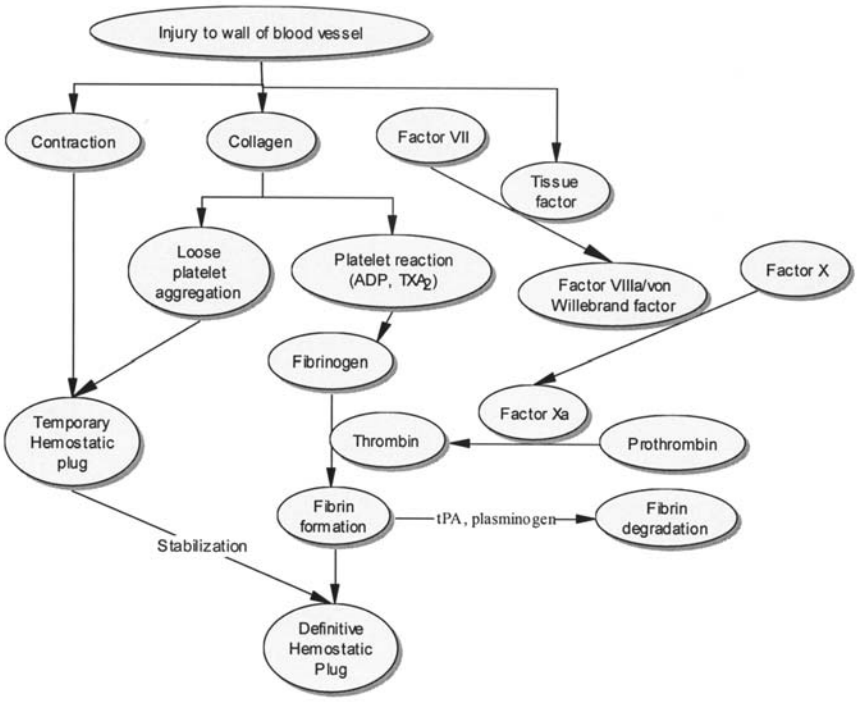



**SCHEME 1**

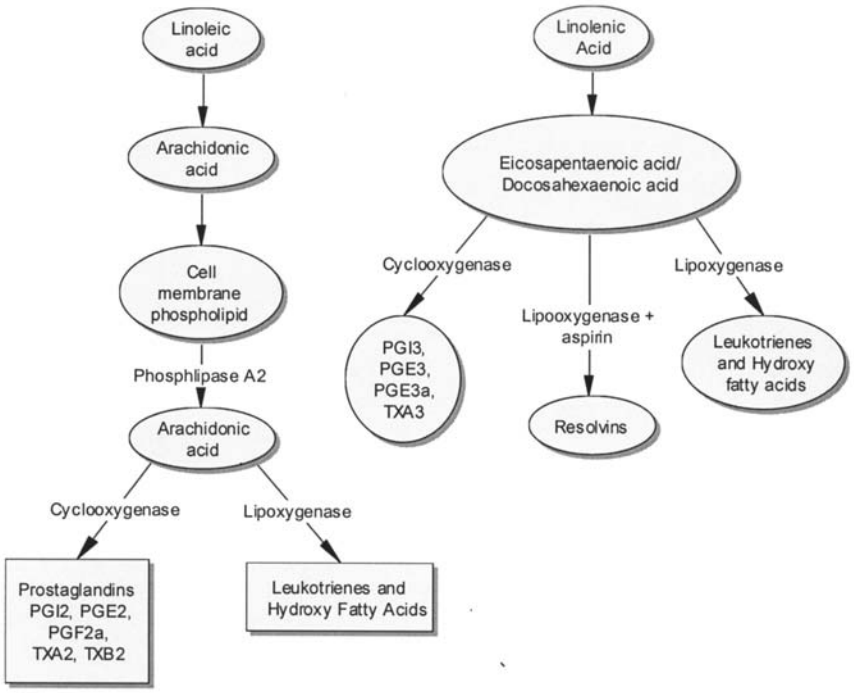
mg/L, $P < 0.001$) or IS (1.38 vs 1.13 mg/L, $P = 0.02$), but not those with venous thrombosis (1.26 vs. 1.13 mg/L, $P = 0.34$). The men with the highest CRP levels had three times the risk of MI (relative risk, 2.9; $P < 0.001$) and two times the risk of IS (relative risk 1.9, $P = 0.02$) compared with men in the lowest quartile. Risks were stable over long periods, were not modified by smoking, and were independent of other lipid and nonlipid-related risk factors. The authors concluded that baseline plasma concentration of CRP could be used to predict the risk of future MI and strokes.

In autopsies of patients who have died from MI, inflammation is evident from the accumulation of monocytes and macrophages at the sites of plaque rupture. These observations suggest that serum CRP levels may reflect the development and progression of atherosclerosis. With the recent development of highly sensitive assays, it is possible to evaluate the role of CRP as a risk factor for CVD (7,8,11,12,14). Other markers of inflammation such as IL-6, tumor necrosis factor alpha (TNF-α), and monocyte-chemotactic protein-1 (MCP-1) are, to varying extents, related to cardiovascular risk factors (16).

The vascular inflammatory process is complex and leads to thrombus formation, angiogenesis, arterial thickening, and atherosclerosis (16–18). One of the first steps in the development of atherosclerosis involves the adhesion of the immune cells known as leukocytes to the vascular endothelium. Stimulation of immune cell function is associated with inflammation. Interactions between immune and inflammatory cells are mediated in large part by a class of proteins termed interleukins (IL). These proteins promote cell growth, differentiation, and functional activation. TNF-α, IL-1, and IL-6 are the most important cytokines produced by monocytes and macrophages. Production of appropriate amounts of these cytokines plays a critical role in the response to infection, although overproduction of compounds like TNF-α can be dangerous and lead to pathological responses. Monocyte adhesion to the endothelium, which is activated by various stimuli, results in the expression of adhesion molecules such as vascular cell adhesion molecule (VCAM)-1 and E-selectin (18,19). Interaction with the endothelium causes the monocytes to infiltrate the endothelial barrier, generate chemotactic factors, and attract other leukocytes to the site, provoking inflammatory reactions (17–20).

*Hemopoiesis, platelet aggregation, and fibrinolysis.* As highlighted in Scheme 1,when damage is done to the lining of blood vessels a series of events involving hemopoiesis and platelet aggregation is initiated that can lead to the formation of a clot and cessation of blood flow. The principal reaction in the clotting of blood is the formation of insoluble fibrin from soluble plasma fibrinogen. The transformation of fibrinogen to fibrin is catalyzed by thrombin, which is made from its circulating precursor, prothrombin, mediated by the action of activated factor X (Stuart Prower factor). A protein cofactor VIII/VIIIa (antihemophilic factor/von Willebrand factor) helps in activation of factor X. The extrinsic system is triggered by the release of tissue thromboplastin, a protein phospholipid mixture that activates factor VII (Proconvertin) (21), which is shown in Scheme 1. The initial reaction in the intrinsic system involves conversion of inactive factor XII (Hageman factor) to active factor XIIa (not shown in Scheme 1).

Fibrinogen is an acute-phase protein like CRP that circulates in blood and increases with the severity of atherosclerosis and PVD (22). Univariate analysis of a large, nested case-control study has reported that plasma levels of total cholesterol,




**SCHEME 2**

low-density lipoprotein (LDL) cholesterol, TG, apolipoprotein B (ApoB) 100, fibrinogen, CRP, and the total cholesterol/HDL cholesterol ratio were significantly higher among men who subsequently developed PVD. In multivariate analysis, CRP was the strongest nonlipid predictor of increased risk, but, according to Ridker *et al.* (23), elevation of the fibrinogen levels was also associated with elevated risk.

Platelets play important roles in hemostasis, with activated platelets adhering to injured vessel walls and then initiating platelet aggregation (24). At the same time platelets have cytotoxic effects on endothelial cells that are manifested by increased levels of $Ca^{2+}$ and decreased levels of EDRF (endothelial cell relaxing factor/nitric oxide). EFA, as precursors of eicosanoid metabolites, play a key physiological role in the process of platelet aggregation as well as inflammation. Eicosanoids are hormones that are made from ω-3 (linolenic acid, LNA) or ω-6 (linoleic acid, LA; arachidonic acid, AA) FA, which have divergent effects on hemopoiesis. AA found in platelets and vessel wall cells is liberated from phospholipids by phospholipase $A_2$ and is converted to thromboxane $A_2$ ($TXA_2$) *via* cyclo-oxygenase (COX1), which causes platelet aggregation and vasoconstriction. On the other hand, AA can also be converted into prostaglandin $I_2$ ($PGI_2$) (COX2), an antagonist of $TXA_2$. Dietary ω-3 FA, such as LNA, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), promote inhibition of platelet aggregation and are anti-inflammatory. Currently, the most common PUFA found in Western diets is the ω-6 FA, LA. Scheme 2 shows the pathways for eicosanoid production from the ω-6 FA AA and from the ω-3 FA LNA.

An anticlotting mechanism prevents clotting in the vasculature. The active forms of factors IX, X, and XI comprise the active components of the plasminogen (fibrinolytic) system. The lytic enzymes that are formed break down both fibrin and fibrinogen and leave fibrinogen degradation products that inhibit thrombin formation.

## OMEGA-3 FA AND CHD

A number of studies have shown that dietary ω-3 FA play a preventive role in CHD (25). The Diet and Reinfraction Trial (DART) study was a major, early investigation that examined the relationship between dietary intake of ω-3 FA and prevention of second MI (26). In this study 1,015 men were advised to eat at least two servings of fatty fish per week and 1,018 men were advised to avoid eating fish. After a 2-yr period, those who consumed fish showed a 29% reduction in "all-cause" mortality but no reduction in the incidence of MI. The Gruppo Italiano per lo Studio della Sopravviv enza nell' Infarto micocardico (GISSI)-Prevenzione Study (27) was the largest prospective, randomized, controlled evaluation of the effect of ω-3 FA on health. In this study 11,324 subjects with known CHD were randomized to receive either 300 mg of vitamin E, 850 mg of ω-3 FA, both, or neither. After 3 1/2 yr, the group that received the ω-3 FA supplement showed a reduction in Sudden Cardiac Death (SCD) (45%) and a reduction in "all causes" of mortality (20%) (28). A meta-analysis of 11 randomized, controlled trials conducted between 1966 and 1999, and including 7,951 subjects with heart disease, further revealed that dietary and nondietary ω-3 FA reduced overall mortality and, specifically, mortality caused by MI and SCD. The U.S. Physician's Health Study surveyed approximately 20,000 male physicians and initially demonstrated no apparent associ-

ation of fish consumption or ω-3 FA supplementation with the risk of MI, SCD, or total cardiovascular mortality (6,15). However, a reanalysis of the results revealed a significant inverse relationship between blood levels of ω-3 FA and the risk of SCD in men with no history of CHD (29). Furthermore, men who consumed fish at least once a week had a 50% reduction in the risk of SCD and a significant reduction in "all-causes" of mortality (30). In another study (31), consumption of 5.5 g of ω-3 FA per month (equivalent to one weekly serving of a fatty fish) was associated with a 50% reduction in the risk of primary cardiac arrest. Finally, The U.S. Nurses' Health Study (32), which analyzed the diets of 84,688 female nurses, provided evidence for the protective effects of fish and α-LNA and showed that the higher consumption levels of fish and α-LNA acid were associated with a decreased risk of CHD and CHD-related deaths (32). An important fish oil study that dealt with a specific patient population was the Shunt Occlusion Trial (SOT), which involved 610 subjects who received 4 g/d of fish oil or a control. The end point in this study was graft occlusion status at the end of 1 yr. Significantly better results were obtained with subjects who received the fish oil supplements (33).

*Inflammation.* When Western diets are supplemented with ω-3 FA, these FA partially replace AA, an ω-6 FA, in the membranes of erythrocytes, platelets, endothelial cells, and monocytes. This dietary supplementation subsequently alters eicosanoid metabolism leading to a decrease in the levels of prostaglandin $E_2$ ($PGE_2$), which is an inducer of pain, vasodilation, and fever, and leukotriene $B_4$ ($LTB_4$), which is a weak inducer of inflammation and a weak chemotactic agent. An increase also occurs in $LTB_5$, which is a weak inducer of inflammation and a chemotactic agent (14). Thus, supplementation with ω-3 FA modulates eicosanoid metabolism in a beneficial manner in regards to immune function.

Khalfoun *et al.* (34) examined the effects of EPA and DHA on the production of IL-6 by stimulated and unstimulated human endothelial cells and showed that both of these FA significantly reduced the production of IL-6, although EPA was more effective than DHA. AA supplementation was ineffective at suppressing IL-6 production even at high levels (34). This is important since IL-6 has been shown to stimulate the production of CRP. Omega-3 FA have also been shown to suppress the synthesis of IL-1, which increases leukocyte adhesion by inducing the expression of adhesion molecules and promotes endothelial protein permeability (35).

Recent studies by Madsen *et al.* (14,36) have shown an inverse relationship between fish oil consumption and CRP levels. In a study of 269 patients who had been referred for coronary angiography, CRP levels were significantly higher in patients with increased levels of stenosis. Those subjects who had lower levels of CRP had higher levels of DHA in their granulocytes.

*Hemopoiesis, platelet aggregation, and fibrinolysis.* Historical references have indicated that diets containing ω-3 FA have a major effect on blood clotting and bleeding time. Saynor *et al.* (37) demonstrated that low dosages of fish oil (1.8 g EPA/d) do not have an effect on bleeding time, whereas higher dosages (4 g/d) significantly increase bleeding time. Omega-3 FA seem to accomplish this *via* a number of mechanisms. Diets that are rich in ω-3 FA are associated with decreased levels of $TXA_2$, a platelet aggregator and vasoconstrictor, and increased levels of $PGI_3$, an active vasodilator and inhibitor of platelet aggregation (38).

Omega-3 FA also have an impact on other hemostatic markers that are related to blood clotting. In a study by Johansen *et al.* (39) patients were pretreated with either 5.1 g of ω-3 FA/d (group 1) or corn oil (group 2) for 6 mon. After 6 mon, group 1 patients had lower median values of von Willebrand factor/VIIIa (128 vs. 147%) and soluble thrombomodulin (24.9 vs. 32.5 ng/mL) relative to group 2. In a subsequent 4-wk study period, group 1 continued its ω-3 dietary regime, whereas group 2 received a 4-wk treatment of 5.1 g of ω-3 FA/day. Tissue plasminogen activator (t-PA) antigen decreased (*P* values for differences between group 1 and group 2 were 0.001), indicating that ω-3 FA supplementation leads to a decrease in hemostatic markers of atherosclerosis. In other studies, dietary ω-3 supplementation has been shown to suppress the capacity of monocytes to synthesize IL-1 and TNF. IL-1 potentiates coagulant activity *via* increased production of plasminogen activator inhibitor (PAI) and endothelin, and by promotion of eicosanoid synthesis (35).

Omega-3 FA have been shown to have an impact on platelet function in a number of studies. α-LNA has inhibitory effects on the clotting activity of platelets and on their response to thrombin (40,41). α-LNA has also been suggested to affect CHD *via* stimulation of a decrease in platelet aggregation (42). It has been suggested that α-LNA may act by reducing the formation of platelet-activating factor, a phospholipid that causes platelet aggregation (43). Saynor *et al.* (37) found that subjects who received 4 g/d of fish oil had a decrease in platelet count. The impact of fish oil on platelet activity was also shown in the GISSI trial (27) involving men who recently recovered from a MI. Long-term fish oil consumption (1 g/d) significantly reduced death from CVD, nonfatal events, and stroke. Fish oil modulates platelet function by decreasing $TXA_2$ synthesis (44).

*Cholesterol/lipoproteins/TG.* Omega-3 FA have been shown to prevent and rapidly reverse carbohydrate-induced hypertriglyceridemia (45). Fish oil has been shown to increase very low density lipoprotein (VLDL) catabolism (46–48), decrease hepatic secretion of VLDL, and inhibit VLDL-cholesterol and TG synthesis in the liver. A large body of evidence from both epidemiological and clinical studies has shown that this effect is dose dependent and is achievable by diet. In a study by Harris *et al.* (49), administration of 4 g/d of omega-3 FA in an ethyl ester form to patients with severe hypertriglyceridemia reduced LDL levels by nearly 30%, VLDL by 32%, cholesterol by 10%, and TAG by 45% whereas HDL cholesterol increased by 13%. Lower intakes (1 g/d) of EPA and DHA usually have not lowered fasting TG but have been shown to reduce postprandial TG levels (50).

*Blood pressure.* A number of human trials have shown that increased intake of dietary ω-3 FA is associated with a reduction in blood pressure (51–54). Hypertensive patients have

been shown to have a dose–response effect with ω-3 FA consumption (52). In a meta-analysis of 36 studies it was shown that a median dosage of 3.7 g/d of fish oil reduced systolic/diastolic blood pressure by 2.1/1.6 mm Hg (55). In a separate meta-analysis that examined 31 studies and involved 1,356 patients, 5.6 g/d fish oil was found to reduce blood pressure by 3.4/2.0 mm Hg (38). Clinical trials have shown no effect on normotensive patients (56). α-LNA has independently been shown to reduce blood pressure in clinical studies (57,58); however, when DHA is compared with EPA, DHA has a greater effect on blood pressure (59).

*Arrhythmia: SCD.* In the United States, SCD accounts for 50 to 60% of the mortality from acute MI and causes 250,000 deaths/yr (55). In the GISSI Prevenzione trial, it was shown that, in general, dietary ω-3 FA consumed over the length of the study were more directly correlated with decreased mortality due to a reduction in SCD (60). Supportive data have been reported by Engelstein and Zipes (61), who showed that when seafood consumption is increased there is a decrease in primary cardiac arrest (PCA), with 5.5 g/mon leading to a 50% decrease in PCA, a 5% increase in red blood cell membrane phospholipid ω-3 FA, and a 70% reduction in risk of PCA. Mortality statistics from the United States and United Kingdom indicate that up to 80% of SCD cases are due to ventricular fibrillation (62)

The benefit of fish oil/ω-3 FA in the prevention of fatal ventricular arrhythmia has been established in both experimental animals and humans (61,63,64). Rat studies have shown that canola oil decreases ventricular fibrillation, and the authors suggested that ALA increase was the cause (63). A recent review of studies concluded that ALA is also effective at reducing ventricular fibrillation (65).

Leaf *et al.* (66) reviewed the recent research related to the clinical prevention of SCD by ω-3 FA and postulated that ω-3 FA alter ion channels in cardiac cells, thereby leading to a reduction in arrhythmias. Kang and Leaf (67,68) showed that ω-3 FA make the heart less excitable by modulating the conductance of sodium ion channels. The prevention of ischemia-induced ventricular fibrillation was confirmed in a study using intravenous infusions of emulsions of ω-3 FA in nonanesthetized dogs. First, it was discovered that the FFA with negatively charged carboxylic acid groups could inhibit L-type $Ca^{2+}$ currents (69,70). By inhibiting the entry of $Ca^{2+}$ through L-type calcium channels in the heart, the FA prevented the overload of $Ca^{2+}$ in the cytosol of the heart, thereby preventing arrhythmia. These FA also affected the conductance of other channels. Leaf and Kang (71,72) repeated these experiments with cultured neonatal cardiomyocytes and showed that the treated cells were more electrically stable. This electrophysiological effect results from the ability of ω-3 FA to block the fast voltage dependent sodium channels and L-type $Ca^{2+}$ channels (66).

## ALCOHOL AND CHD

Light or moderate alcohol intake (one to two drinks, or less than 30 g alcohol per day) has been associated with a substantial decrease in CHD-related and all-cause mortality (73–78), and a decrease in CHD risk (73,75,79–82). The consumption of even small amounts of alcohol (one drink, or approximately 12–15 g of pure alcohol/wk) appears to be protective against CVD (74). In analyzing the intake of types of alcoholic beverages, Gronback *et al.* (75) in the Copenhagen Heart Study looked at 6,051 men and 7,234 women between the ages of 30 and 74 yr and found that wine, but not beer or spirits, was associated with a decrease in mortality from both cardiovascular and cerebrovascular diseases as well as from all causes of mortality (75). In a study of 21 countries, Renaud and Ruf (83) showed that wine intake was very negatively correlated with CHD. In a more recent study, Renaud *et al.* (84) considered 34,014 middle-aged men from eastern France, of whom 23% were teetotalers and 77% drank some wine. Those who consumed moderate amounts (2–5 glasses/d) were monitored and found to have a 24–31% reduction in mortality from all causes.

*Inflammation.* Evidence from animal and human studies indicates that ethanol has a direct and profound effect on inflammation (85). Zairis *et al.* (86) suggested that alcohol protects against CHD through an anti-inflammatory mechanism. In this connection, Imhof *et al.* (87) reported that alcohol consumption in men shows a U-shaped association with the serum concentration of the inflammatory biomarker, CRP. These authors proposed that IL-6, one of the main regulators of the genes that encode for acute-phase reactants, could be the link between ethanol and inflammation since moderate ethanol consumption seems to inhibit the production of IL-6. High concentrations of IL-6 have been reported to be present in heavy drinkers (88). A review by Stewart *et al.* (85) suggested that nonethanolic components in certain alcoholic beverages such as red wine also have a significant impact on inflammation. Resveratrol, which is present in red wine, has been shown to be both anti-inflammatory and cardioprotective, particularly in animal models of myocardial ischemia and MI.

Sierksma *et al.* (89) have studied the effect of alcoholic and nonalcoholic beer on inflammation in a randomized diet-controlled intervention study. In this 6-wk study, four glasses (three glasses for women) of beer with dinner gave a greater decrease (35%) in plasma CRP and fibrinogen when compared with alcohol-free beer (12%), thus emphasizing the substantial effect that alcohol has on CRP levels. The effect on CRP was significant in women, but not significant in men, though the sample size was small. Mezzano and Martinez (90) did not detect an effect of moderate red wine drinking on CRP in healthy male students, thus confirming data presented by Sierksma *et al.* (89). Interestingly, the baseline CRP values were quite high in the study by Sierksma *et al.,* and this suggests that only those with high-baseline CRP values would benefit from the anti-inflammatory (CRP-lowering) effect of moderate ethanol drinking.

*Hemopoiesis, platelet aggregation, and fibrinolysis.* Alcohol is generally regarded as a potent, but transitory, inhibitor of platelet aggregation, although the effects of alcohol on platelet function are complex. Thrombin-induced platelet aggregation is reduced by both red wine and white wine (91). A more detailed explanation of possible mechanisms has been reported in

the Caerphilly Heart study, which indicated that alcohol intake was associated with an increased sensitivity of platelets to aggregation when they were exposed to thrombin, whereas ADP- or collagen-induced aggregation of platelets was diminished with alcohol consumption (92).

Fibrinolysis is elevated in subjects who consume alcohol. Rimm *et al.* (93) reported that an intake of 30 g of alcohol was associated with a 1.25 ng/dL increase in t-PA antigen concentration and a 1.4% increase in plasminogen concentration (93). Urquiaga and Leighton (94) conducted an interventional study using 21 groups of male volunteers to evaluate the effects of red wine (240 mL/d) supplemented for 1 mon with a Mediterranean diet or Occidental diet on biochemical, physiological, and clinical parameters related to atherosclerosis and other chronic diseases. When compared with the Occidental diet, the Mediterranean diet was associated with an improvement in hemostatic cardiovascular risk factors, including lower levels of plasma fibrinogen, factor VII coagulant activity (proconvertin, a coagulation factor formed in the kidney), and factor VIII coagulant activity (antihemophilic factor), and with a longer bleeding time. Red wine supplementation of both diets resulted in a further decrease in plasma factor VIIc and in increase in PAI-1 and t-PA antigen (94).

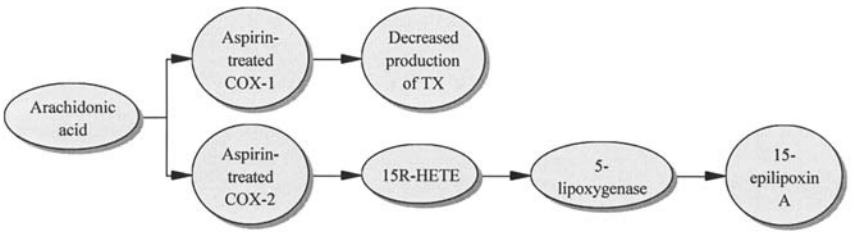
*Cholesterol/lipoproteins/TG.* One of the major risk factors for CHD is an abnormal lipoprotein profile, which is defined as an elevated level of LDL relative to that of HDL (95). Low concentrations of alcohol in the blood elevate HDL cholesterol levels (95). However, TG levels are also increased by alcohol consumption (96). The main anti-atherogenic function of HDL is to promote a "reversal" of cholesterol transport. The three early steps of in this process involve cholesterol efflux from the cell, plasma cholesterol esterification by the plasma enzyme lecithin:cholesterol acyl transferase, and cholesteryl ester transfer to ApoB-containing lipoproteins. Sierksma *et al.* (97) have shown that in healthy middle-aged men and postmenopausal women, moderate alcohol consumption concomitantly increases serum HDL cholesterol levels and stimulates efflux of cholesterol from the cell. Early work suggested that alcohol consumption increased only one type of HDL (HDL 3) cholesterol and that this type was not involved in reverse cholesterol transport. Recently it has been shown that both HDL cholesterol forms (HDL 2 and HDL3) contribute equally in regards to the reversal of cholesterol transport (98). Alcohol also has been shown to reduce apolipoprotein A (ApoA) (99). This is significant since ApoA plays a key role in atherosclerosis and is a major risk factor for CHD (100).

*Blood pressure.* A number of studies indicate that alcohol consumption affects blood pressure. Epidemiological data have shown higher blood pressure readings with increasing alcohol consumption (101). Moderate drinkers have lower blood pressure levels than heavy drinkers (102). Marques-Vidal *et al.* (103) showed that male binge drinkers from Northern Ireland who drank primarily on weekends had acute increases in blood pressure in comparison with long-term regular drinkers. No fluctuations in blood pressure were noted in French drinkers who regularly consumed alcohol.

*Nutraceutical properties of wine.* Red wine and white wine possess an average of 200 and 40 mg per glass of phenols, respectively, which are derived from grapes. The phenols in wine are categorized as nonflavonoids and flavonoids. The nonflavonoid phenols include hydroxybenzoate, hydroxycinnamates, and stilbenes, whereas flavonoids consist of flavonols, flavan-3-ols, and anthocyanins. Polyphenols, which are derivatives of phenol that contain many phenols joined together, and their metabolites have antioxidant, antithrombotic, anti-inflammatory, and anticancer effects (104). Tannins are non-flavonoid examples of polyphenols found in wine. Polyphenols act as free-radical scavengers and hence have strong antioxidant properties. Red wine and its phenolic compounds prevent the oxidative modification of human LDL (105). Experimental meals with wine have been shown to increase the total antioxidant capacity of the diner's plasma (106). Wine is thought to have a positive impact on lipoproteins because it contains significant levels of polyphenolic antioxidants that protect LDL from oxidation. This is significant since LDL is thought to have its most negative impact in its oxidized form (107). Flavonoids are reported to inhibit adhesion of immune cells to endothelial cells and to down-regulate gene expression of inflammatory mediators (108,109).

## ASPIRIN AND CHD

Aspirin, in a variety of doses, has been shown to reduce the risk of CVD under certain conditions. The prophylactic benefit of aspirin has been shown in a number of large studies (110–113). In a meta-analysis that involved over 100,000 patients, of whom 70,000 were considered to be "high risk," aspirin reduced the risk of nonfatal heart attacks by approximately one-third, nonfatal strokes by one-third, and vascular death by one-sixth (114). Aspirin's impact occurs with both genders. The U.S. Physician's Health Study (110) involved 22,071 male physicians who showed a 44% reduction in having an initial MI when they were placed on 325 mg aspirin once every other day, although the benefit was limited to physicians over the age of 50. In the Women's Health Study (113), 39,876 healthy female health professionals were monitored for 10 yr. Regular low-dose aspirin therapy reduced their stroke risk (17%) but did not decrease the number of heart attacks or cardiovascular deaths among all of the women. However, the subgroup of women who were 65 yr old or older showed a reduced risk of developing CVD, IS, or heart attacks. Another large study that observed how aspirin affected women's health was the Women's Health Initiative Observational Study (115). This study initially observed 93,676 women who were between 50 and 79 yr old. A subpopulation ($n$ = 8,928) of this group had stable CVD, and 46% of this subpopulation reported taking aspirin. Thirty per cent of these women took 81 mg/d whereas 70% took 325 mg/d. The group that took aspirin showed a lower "all cause" mortality rate (8.7%) when compared with those who did not (17%). Women who took either the 81-mg dose or the 325-mg dose showed similar mortality rates with regard to all-cause mortality and cardiovascular events. The CVD-related




**SCHEME 3**

mortality rate was 25% lower for the women who had taken aspirin. Other interesting observations from the group taking aspirin included a nonsignificant (11%) reduction in strokes and no change in MI. Aspirin's impact on evolving MI was shown in the Second International Study of Infarct Survival (116) in which 17,000 men and women were studied to determine the effect of aspirin administration within 24 h of the onset of MI symptoms. Experimental subjects received 162 mg of aspirin whereas the control group received placebos. Five weeks after the initial treatment, the experimental group showed a significant reduction in vascular mortality (23%), nonfatal reinfarction (49%), and nonfatal stroke (46%).

*Inflammation, hemopoiesis and platelet aggregation.* Numerous studies have shown that aspirin has anti-inflammatory effects that are related to CHD. Ridker *et al.* (15) studied the interaction between aspirin intake, CRP levels, and MI and found that aspirin intake was directly related to decreased CRP levels. These findings were corroborated by Ikonomidis *et al.* (117), who showed that aspirin reduced circulating levels of IL-6 and CRP in patients with CHD. Kennon *et al.* (118) also studied the effect of aspirin on CRP in patients with unstable angina. They concluded that aspirin had a significant effect on the acute-phase inflammatory response to myocardial injury.

Aspirin has an impact on inflammation *via* interference in the biosynthesis of PG. AA is normally used to produce $PGG_2$, $PGH_2$, and $TXA_2$ *via* the action of the COX enzyme. The COX1 and COX2 forms of this enzyme play key roles in platelet aggregation and inflammatory response, respectively. Aspirin completely inactivates COX1 and causes COX2 to synthesize a less active metabolite of AA (15*R*-hydroxyeicosatetraenoic acid). This leads to a decrease in the production of $TXA_2$. This is critical since $TXA_2$, in response to a variety of stimuli (collagen, thrombin, etc.), amplifies the platelet aggregation response (119). Scheme 3 summarizes the effect of aspirin on $TXA_2$ and 15-epilipoxin A (15-epi-LXA), which is attributable to its effects on the two forms of cyclooxygenase, COX-1 and COX-2.

Aspirin initiates the biosynthesis of anti-inflammatory mediators known as 15-epi-LXA, which are produced by endothelial cells and leukocytes (120,121). Aspirin also initiates the production of anti-inflammatory 5-epi-LXA, with smaller doses of aspirin (81 mg/d) giving the highest increase (0.25 ± 0.63 ng/mL) when compared with 325 mg/d (0.16 ± 0.71 ng/mL) and 650 mg/d (0.01 ± 0.75 ng/mL).

*Endothelial functions.* Aspirin has been shown to ameliorate endothelial dysfunction in atherosclerotic vessels. It has been suggested that aspirin positively modulates acetylcholine-induced peripheral vasodilation in patients with atherosclerosis (1221).

*Antioxidant activity.* Aspirin is a powerful antioxidant that can directly scavenge hydroxyl radicals (123), and it plays an important role in limiting the oxidation of both lipoproteins and fibrinogen (124,125). Aspirin may help decrease the progression of atherosclerosis by protecting LDL from oxidative modification (126).

## STATINS AND CVD

Administration of statins significantly reduces primary and secondary fatal and nonfatal cardiovascular events (127). Potential mechanisms for these effects may involve modulation of anti-inflammatory and antithrombotic action, cholesterol metabolism, and endothelial function as well as plaque stabilization (16). Statins also increase myocardial perfusion and reduce recurrent angina episodes after coronary events (128). It has been shown in clinical trials using angiography that there is very little change in the lumen, which is difficult to explain on the basis of simple plaque regression (129).

*Inflammation*. The results of a number of investigations indicate that statins decrease CRP levels, i.e., are anti-inflammatory, and that this action is independent of its cholesterol-lowering effect (130). After 12 wk of treatment, Albert *et al.* (131) found that patients who had received pravastatin for either primary or secondary prevention showed a decrease in CRP levels, and after 24 wk the decrease was significant. The mechanism for this anti-inflammatory effect may be related to the drug's ability to decrease monocyte production and prevent monocyte chemotaxis. Recently, it has been shown that MCP-1 plays an important role in monocyte recruitment and the pathogenesis of atherosclerosis. MCP-1 is produced by a variety of cells including endothelial cells, subendothelial macrophages, and monocytes. The ability of statins such as lovastatin and pravastatin to reduce the production of MCP-1 *in vitro* and *in vivo* was suggested by Romano *et al.* (132), and is consistent with earlier data (133).

*Cholesterol/lipoproteins/TG*. There are currently five statin drugs on the market in the United States: lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin. The major effect

of the statins is to lower LDL cholesterol levels through inhibition of HMG-CoA reductase, an enzyme in the pathway of cholesterol biosynthesis. Numerous investigations including the Scandinavian Simvastin Survival Study (134), The West of Scotland Coronary Prevention Study (135), the Cholesterol and Recurrent Events (CARE) trial (136), and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) (137) have shown that decreasing the levels of LDL causes a reduction of CHD. Moreover, cholesterol-reducing drugs cause a reduction in risk for cerebral ischemia. Sacks and Ridker (127) compared pravastatin and placebo in patients who had experienced an MI and had average cholesterol concentrations that were <240 mg/dL (baseline mean 209 mg/dL) and LDL levels of 115–174 mg/dL. According to their results, pravastatin reduced coronary death or recurrent MI by 24%. A followup study showed a decline of LDL concentration from 174 to ~125 mg/ dL, but no further decline in coronary events was observed in subjects who had LDL values in the range of 71–125 mg /dL. According to these authors, CRP and serum amyloid A were significantly higher among the post-MI patients who were treated with a placebo and who subsequently developed recurrent coronary events; however, this association was not shown in patients treated with pravastatin.

*Endothelial function*. Nitric oxide preserves arterial health by affecting endothelial-leukocyte cell interaction and smooth cell proliferation. Fluvastatin and simvastatin improve nitric oxide bioavailability by both posttranscriptional up-regulation of the mRNA for the enzyme that produces NO, endothelial nitrogen oxide synthase, and by decreasing superoxide anion production in vascular endothelial cells (138,139). There is increased expression of adhesion molecules in atherosclerotic endothelium relative to normal endothelium. Fluvastatin, but not simvastatin, diminishes the level of adhesion molecules in hypercholesterolemic patients (140,141).

*Plaque stability*. Most acute coronary events occur because of the disruption of atherosclerotic plaques, which are filled with lipids and excess activated inflammatory cells (16). Macrophages release matrix metalloproteinases that degrade plaque matrix connective tissue, thereby weakening the fibrous cap and rendering them susceptible to rupture (16). Statins have been shown to decrease the levels of metalloproteinase expression and to decrease expression of tissue factor, a protein in subendothelial tissue, platelets, and leukocytes that is necessary for initiation of thrombin formation (16). Though there was a significant reduction of matrix metalloproteinases expression, pravastatin or simvastatin effected no change in macrophage numbers *in vivo*. Statins increase the collagen content in the plaque, thereby increasing plaque stability (142). Statins are also thought to reduce the size of plaques and prevent new plaques by reducing the production of cholesterol.

*Thrombosis*. Different statins have varying effects on prothrombotic factors, such as tissue factor, tissue factor pathway inhibitor (an anticoagulant protein that inhibits Factor Xa), platelet aggregation, blood and plasma viscosity, fibrinogen, PAI-1, and lipoprotein (143). Cellular expression of tissue factor in human macrophages is suppressed by lipophilic statins such as fluvastatin and simvastatin. Elevated PAI-1 levels are associated with prothrombotic states, and statins reduce the levels of the prothrombotic factor PAI-1 (144).

## INTERACTIONS BETWEEN FISH OIL, ALCOHOL/WINE, ASPIRIN, AND STATIN DRUGS

Currently many Americans who either are worried about developing CHD or are trying to prevent further development of their CHD are taking some combination of fish oil, aspirin, and alcohol/wine. Twenty million Americans are also presently receiving statin drugs. Although each of these compounds/foods has been shown to improve mortality, more work needs to be done to determine how these compounds/foods interact with each other. Some research has been done to establish whether fish oil enhances the impact that statin drugs have on cardiovascular health.

Nordøy *et al.* (145) investigated the effects of simvastatin and ω-3 FA on lipids, lipoproteins, and antioxidant capacity in a heterogeneous group of patients with combined or mixed hyperlipidemia. The combined treatment efficiently reduced serum LDL and VLDL cholesterol and TG and increased HDL cholesterol. These authors also confirm that untreated patients have modified hemostatic variables that increase their tendencies to originate thrombotic events. They also evaluated the effect of simvastation and ω-3 FA on the hemostatic risk profile associated with combined hyperlipidemia (146). Tissue Factor is an antigen that is expressed on the surface of plaques to promote coagulation. They found that ω-3 FA and simvastatin treatment in patients with combined hyperlipidemia reduced the free tissue factor pathway inhibitor fraction in the fasting state and inhibited the activation of factor VII occurring during postprandial lipemia, thereby establishing a potentially beneficial effect on the hemostatic risk profile in the patient group.

More recently, the first large-scale prospective, randomized trial of a statin and an ω-3 FA (EPA) derived from fish oil was completed. A total of 18,645 men and women were recruited for the study. Men were between 40 and 75 yr of age and women were postmenopausal. Subjects received either 10 mg/d of pravastatin or 5 mg/d of simvastatin or the same statin doses with 1,888 mg/d of EPA. The main purpose of this study was to examine the clinical effectiveness of EPA when it was given as an additional treatment with statin drugs. Whereas all treatments lowered LDL cholesterol by the same amount, the combined treatment of statin and EPA produced a greater reduction in major coronary events than did treatment with statins alone, suggesting that fish oil provides a benefit that is independent of lipid lowering. These data unfortunately do not include a control population that received only the fish oil. It is possible that the combined effect is solely due to intake of the ω-3 FA (EPA).

Another interesting study regarding statin interaction with FA metabolism was conducted by Harris *et al.* (147), who analyzed the effects of statin on the serum w-6 and ω-3 FA in hypercholesterolemic patients. Subjects in this study were 106 healthy individuals who were assigned to take 40 mg of simvastatin or placebo for 24 wk. Over the 24-wk study period,

total cholesterol and TG content in the placebo group remained unchanged, whereas the simvastatin group showed a decline of cholesterol by 30% and of TG content by 22%. In treated subjects, serum total FA concentration went down by 22%. With respect to long-chain PUFA, the ratio of AA to EPA and of AA to DHA was elevated. The physiological and clinical implications of such changes in serum long-chain PUFA remain to be explored.

It is crucial that major clinical trials be conducted to establish whether commonly used mortality-improving treatments are synergistic and to see which combinations of treatments are most cost effective. It appears that all four of the compounds studied contribute to the prevention of CHD and CHD-related deaths in some similar ways and also in some unique ways; therefore, they could work together to improve both the quality and length of life. All four of the compounds reviewed play major roles in decreasing inflammation and have a favorable impact on hemopoesis/platelet aggregation. Combined treatments may promote distinct beneficial effects on the one hand, such as the ability of both red wine and aspirin to contribute antioxidant effects. Moreover, undesirable effects associated with one treatment might be balanced by an opposing effect by another treatment. For example, alcohol and ω-3 FA offer distinct benefits, but alcohol raises TG levels, whereas ω-3 FA decrease TG levels. At this time it appears that clinical trails that focus on interaction between these four compounds could provide sound information for government health planners when they try to establish cost-effective ways to advise the American public.

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[Received June 5, 2006; accepted September 13, 2006]