as endothelial nitric oxide synthase (eNOS) itself; the latter is crucial in the production of nitric oxide (NO), which is the endogenous endothelial dependent vasodilator. The switch of eNOS from the production of NO to superoxides reduces the production of NO. Superoxides generated by the organic nitrates also inactivate both the nitrate-derived NO as well as the endothelium-derived NO, reducing the bioavailability of NO.

How do organic nitrates induce production of super-oxides? The mechanisms are complex and involve the redox state of thiols in the vascular smooth muscle or platelets. In simplified terms, organic nitrates need to go through reductive denitrification for these drugs to be active. In this reductive process, NADPH and tetrohydro-biopterin are depleted. These are essential cofactors for eNOS, leading eNOS to produce reactive oxygen species instead of NO.

Folic Acid Prevents Nitroglycerin-Induced Nitric Oxide Synthase Dysfunction and Nitrate Tolerance: A Human In Vivo Study

Gori T, Burstein JM, Ahmed S, et al.
Circulation. 2001:104:1119–1123.

In this article, Gori et al showed that folic acid supplementation (10 mg once daily) can prevent nitroglycerin-induced tolerance. Eighteen healthy volunteers were randomized to either folic acid or placebo for 1 week while receiving continuous transdermal nitroglycerin. Three hours after nitroglycerin administration, both groups of subjects manifested a decrease in blood pressure and a rise in

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The observation that this simple intervention with folate improves endothelial function and prevents nitrate tolerance has great clinical implications.

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heart rate. On visit 2 after 6 days of continuous nitrate treatment, systolic blood pressure and heart rate returned back to baseline in the placebo group but not in the folate group. The blood flow responses to acetylcholine in the forearm were significantly blunted in the placebo group (123% vs 583%) as well as to nitroglycerin (93% vs 183%). This suggested chronic nitrate therapy impairs vascular responses to endothelium-dependent and -independent vasodilators and that these responses can be normalized by folate therapy.

The mechanisms of how folate restores endothelial function are not clear. Folic acid possesses antioxidant

properties and can reduce superoxide production from xanthine oxidase. One potential mechanism is also that folate enhances the enzymatic regeneration of tetrahydro-biopterin, thus enhancing the production of NO.

Whatever the precise mechanism, the observation that this simple intervention with folate improves endothelial function and prevents nitrate tolerance has great clinical implications. It implies that patients with angina can enhance the effectiveness of nitrate therapy with folate supplementation. Patients with unstable angina treated with intravenous nitrates can also prevent tachyphylaxis by being given supplementary folates. Whether this is clinically effective in patients with coronary artery disease remains to be determined, but the outlook is certainly promising.

Atherosclerosis

Triglycerides and Coronary Atherosclerosis: Implications for Treatment of Mixed Dyslipidemias

Reviewed by Norman E. Lepor MD, FACC, FAHA
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The goals of medical treatment of patients with mixed dyslipidemias remain controversial. Whether therapy should focus solely on reduction of low-density lipoprotein (LDL-C) or consideration given to raising levels of high-density lipoprotein (HDL-C), reducing triglyceride levels or converting the small dense LDL-C to the less atherogenic large LDL-C particle remains controversial. This issue becomes more important in the context of treating patients with diabetes, a disease whose prevalence is increasing at near epidemic proportions. It is common for the diabetic patient to present with the mixed picture of elevated small dense particle LDL-C, triglycerides, and low HDL-C levels. A review of two selected journal articles will deal with the importance of triglycerides as a risk factor for coronary artery disease and the difference between the effects of the statin atorvastatin and the fibric acid derivative fenofi-

brate in patients with Type 2 diabetes mellitus with mixed hyperlipoproteinemia.

The key message is that interventions using fibric acid derivatives or niacin that have as their major effect the reduction of triglycerides and elevation of HDL-C reduce coronary events. Whether this effect is mediated through the triglyceride or HDL-C effect or combination is not clear. In addition, the fibric acid derivative fenofibrate has positive hemorheologic effects including the reduction of fibrinogen levels and blood viscosity which are in addition to its lipid effects that may explain some of its positive effect on coronary events.

Current Perspectives on the Management of Hypertriglyceridemia

Miller M.
Am Heart J. 2000;140:232–240.

The pathophysiologic consequences of hypertriglyceridemia includes increased synthesis of prothrombotic factors, enhanced uptake of triglyceride-rich lipoproteins (TGRLP) by macrophages and predominance of the atherogenic small, dense LDL-C particle.[1] Even with

Figure 1. *Chylomicron catabolism. Reprinted from Grundy SM.* Cholesterol, Atherosclerosis, & Coronary Heart Disease, *p. 1.10, ©1990, by permission of the publisher, Mosby.*

adjustments for HDL-C, triglycerides have been associated with coronary heart disease.[2] TGLRP's are derived from both dietary (exogenous) and hepatic sources. Dietary fats are packaged as chylomicrons and then hydrolyzed in the circulation by lipoprotein lipase, which resides on the surface of capillary endothelium. During this time surface constituents of the chylomicron including apoproteins, cholesterol esters and phospholipids are transferred to HDL-C leaving a residual remnant molecule. This remnant is highly atherogenic, can be incorporated into the liver or into macrophages where it potentiates foam cell development (Figure 1). Very low-density lipoproteins (VLDL-C) represent the hepatic source of triglyceride and are also hydrolyzed by lipoprotein lipase into VLDL remnants.

The most common hypertriglyceridemic condition associated with coronary artery disease (CAD) is familial combined hyperlipidemia which is present in about 15% of patients with CAD.[3] In addition to genetic and metabolic abnormalities, hypertriglyceridemia can be associated with the use of alcohol, beta-blockers, bile acid sequestrants, oral estrogens, retinoids and steroids.

The impact of hypertriglyceridemia has been evaluated in arteriographic and clinical end point studies. The Monitored Atherosclerosis Regression Study (MARS) evaluated lovastatin versus placebo on coronary and carotid artery atherosclerotic progression. Progression of disease was associated with elevated levels of apolipoprotein C3 a marker for TGRLP.[4] The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) reduced progression coinciding with a 31% reduction of triglycerides and 9% increase in HDL-C, LDL-C was not reduced.[5] In the Lopid Coronary Angiography Trial (LOCAT), gemfibrozil reduced progression of saphenous vein bypass graft lesions with triglyceride reductions of 36% and HDL increases of 21%.[6]

The Coronary Drug Project (CDP) evaluated 8,000 male survivors of myocardial infarctions to one of four regimens including niacin. The niacin treated group had a 27% reduction of CAD events associated with a 26% reduction of triglycerides and 10% reduction of cholesterol.[7] In the Helsinki Heart Study, CAD events were reduced by 34% in patients treated with gemfibrozil over five years associated with a 43% reduction of triglycerides and 10% increase in HDL-C with the biggest in patients impact in patients with triglycerides over 200 mg/dL.[8]

Two recently completed studies have evaluated the impact of fibric acid therapy on coronary events. The Benzafibrate Infarction Prevention Trial (BIP) studied 3122 middle-aged men and women with CAD. In a sub-
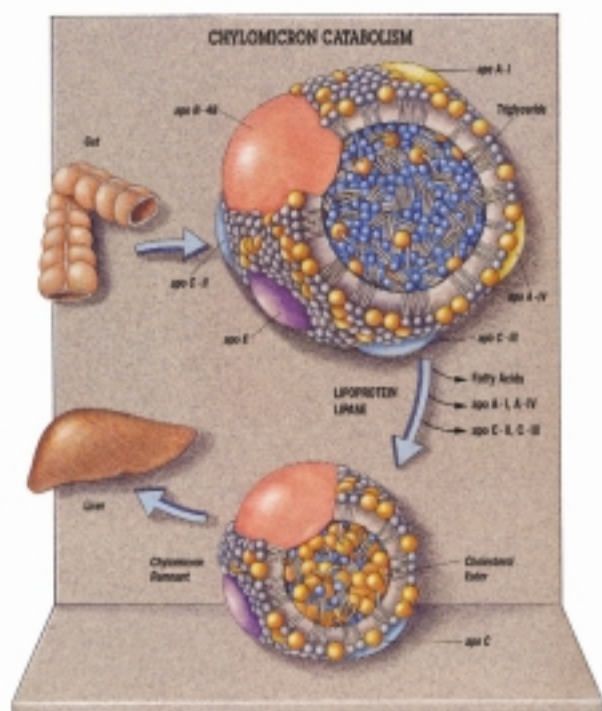
group of patients with triglycerides > 200 mg/dL at baseline, a 40% reduction of the primary end point of death and non-fatal MI in association with a 25% reduction of triglycerides, 10% increase in HDL-C and no significant change in LDL-C.[9] The Veterans Affairs HDL Intervention Trial (VA-HIT) was a 5-year, randomized, double-blind trial of gemfibrozil in patients with underlying CAD. At baseline, LDL-C was 111 mg/dL, triglycerides were 161 mg/dL and HDL-C was 32 mg/dL. A 22% reduction in CAD events occurred in association with a 31% reduction in triglyceride, no change in LDL-C and a 6% increase in HDL-C.[10] The Cholesterol and Recurrant Events (CARE) and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) studies failed to show a benefit of pravastatin in reducing CAD death or non-fatal MI in the subgroup of patients with LDL < 125 mg/dL while proving quite effective in patients with LDL > 130 mg/dL.[11,12] What is not clear at the present time is whether the clinical benefit end point improvement in the fibrate trials was the result of increasing HDL-C or reducing triglycerides. What the VA-HIT trial does indicate that in patients suffering from CAD with low HDL and LDL < 130 may benefit more from the use of a fibrate than from a statin.

For the most part, nicotinic acid and fibrates are the mainstays of triglyceride reduction therapy. Nicotinic acid inhibits the adipose tissue lipases thereby reducing the substrate available for VLDL synthesis by the liver. Higher doses of niacin can lead to triglyceride reductions of 20% to 40%, 15% to 20% reductions of LDL-C, and 15% to 30% elevation of HDL-C. Fibrates are the most potent triglyceride lowering medications with a mean reduction of 20% to 55%. The two most prescribed fibrates are fenofibrate (Tricor) and gemfibrozil (Lopid).

The fibrates act by upregulation of lipoprotein lipase transcription. The VA-HIT trial found no evidence for increased noncardiovascular death. Because these drugs are renally excreted, dose modifications need to be made when serum creatinine is greater than 2.0 mg/dL (see Table 1).

Currently, the desired triglyceride level as defined by the National Cholesterol Education Program (ATP III) is less than 150 mg/dL. With patients having high triglyceride levels (200-499) mg/dL), non-HDL cholesterol becomes a secondary target of therapy. Emphasis is placed on weight reduction, and increased physical activity with drug therapy for patients at high risk to achieve goals.[13]

Effects of Atorvastatin versus Fenofibrate on Lipoprotein Profiles, Low-Density Lipoprotein Subfraction Distribution, and Hemorheologic Parameters in Type 2 Diabetes Mellitus with Mixed Hyperlipoproteinemia

Frost RJ, Carsten O, Geiss HC, Schwandt P, Parhofer KG
Am J Cardio. 2001;87:44–48.

This study was a prospective, randomized, open-label, crossover trial in 13 patients after a 6-week washout period when they were randomized to either 10 mg of atorvastatin or 200 mg of fenofibrate daily for 6 weeks. After another 6-week washout, patients were crossed over to the other arm.

Both atorvastatin and fenofibrate reduced total cholesterol, 24% and 16%, respectively. Though LDL-C reduction was greater with atorvastatin, only fenofibrate reduced triglycerides, VLDL-C, VLDL-triglycerides significantly.

Table 1
Effects of Lipid Lowering Agents on Plasma Lipids*

Agent	TC	LDL-C	HDL-C	TG
Zocor® (simvastatin) 40 mg/day	–25	–29	+13	–28
Tricor® (fenofibrate) 300 mg/day	–16	–6	+15	–45
Niaspan® (niacin) 1500 mg/day	–8	–12	+20	–13
WelChol™ (colesevelam HCl) (3.8 g) 6 tabs/day	–7	–15	+3	+10

* Represents mean percentage change from baseline. Information from package insert.

HDL-C levels increased with both drugs about 10%. Only fenofibrate changed the LDL subtype distribution, decreasing the small, dense LDL fraction (LDL-5).

The hemorheologic parameters measured including fibrinogen levels, blood viscosity and native red cell agglutination were positively affected by fenofibrate with no significant effect with atorvastatin.

Both atorvastatin and fenofibrate improve lipoprotein metabolism in patients with type 2 diabetes. Fenofibrate by reducing triglyceride levels and inducing a shift from small dense LDL particles to the intermediate, less dense, less atherosclerotic particle while atorvastatin exerts its effect by reducing the levels of all forms of LDL-C. Fenofibrate also had the additional positive hemorheologic effects. ∎

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