# Identification and Treatment of Hypertriglyceridemia as a Risk Factor for Coronary Heart Disease

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**Current Cardiology Reports** 1999, **1:**233–237
Current Science Inc. ISSN 1523–3782


Recent publications, including new population-based studies and a meta-analysis of prospective, population-based studies, provide strong evidence for an elevated triglyceride level as an independent risk factor for coronary heart disease. Pathophysiologic relationships between elevated triglyceride levels and both reduced high-density lipoprotein levels and an increase in the proportion of low density lipoproteins that are small and dense support the epidemiologic data, and suggest that an elevated triglyceride level should constitute a target for lipid-lowering therapy. There are no clear recommendations for management of patients with hypertriglyceridemia available in the current treatment guidelines. Treatment options include life-style measures and, if drug therapy is required, nicotinic acid, fibrates, more potent 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), or combination therapy with statin plus fibrate or nicotinic acid.

## Introduction

It had long been observed that although hypertriglyceridemia is associated with increased risk for coronary heart disease (CHD) in univariate analyses of cohort studies, the predictive power of triglyceride levels is lost when multivariate analyses, particularly those using high-density lipoprotein (HDL) cholesterol as a covariate, are undertaken. Rather than meaning that triglycerides are not involved in the atherogenic process, those analyses indicate that the role of triglycerides is complex. Indeed, recent epidemiologic studies and analyses have made it clear that plasma triglyceride levels are independent predictors of CHD risk. Moreover, better understanding of the pathophysiology of both dyslipidemia and atherogenesis have provided clear insights into the many roles that hypertriglyceridemia can play in this process, and have also provided a rationale for aggressive therapeutic approaches in patients with dyslipidemia. In this paper, we review the epidemiologic evidence and pathophysiologic rationale for hypertriglyceridemia as a risk factor for CHD. We also review recent data relative to the treatment of patients with this disorder.

## Recent Epidemiologic Evidence

Elevated triglyceride levels have long been recognized as univariate predictors of increased risk for CHD. However, in nearly all studies, when multivariate analyses of data from cohort studies were performed, the predictive power of triglyceride levels was reduced or lost, particularly when HDL cholesterol, serum total cholesterol, or diabetes mellitus, were taken into account [1,2]. Recent findings, however, have provided strong evidence of the independent association of elevated triglycerides and major coronary events. These include a meta-analysis documenting an independent incremental risk of such events with triglyceride elevation [3,4].

The prospective, population-based Münster Heart Study (Prospective Cardiovascular Münster Study [PROCAM]) [5] followed nearly 5000 men, aged 40 to 65 years and free of myocardial infarction (MI) at entry, for 8 years, and showed that risk for MI or sudden cardiac death increased markedly as triglyceride levels increased from less than 200 mg/dL to 799 mg/dL. The association of triglyceride levels with major coronary events remained significant after adjustment for low-density lipoprotein (LDL) and HDL cholesterol levels and after accounting for other important coronary risk factors, including age, smoking, and systolic blood pressure. The association of hypertriglyceridemia (>200 mg/dL) with risk of coronary events was particularly strong in individuals with a high ratio of LDL to HDL cholesterol (>5). This finding was similar to results from the Helsinki Heart Study [6], in which the highest risk for CHD in the placebo group was among those with an LDL/HDL cholesterol ratio greater than 5 and triglyceride level greater than 204 mg/dL (RR, 3.8).

A recent case-control study reported similar findings regarding the effect of triglyceride levels on the risk of MI in men enrolled in the Physicians' Health Study [7]. In that study, men who experienced an MI had significantly smaller LDL particle diameter and significantly higher triglyceride levels than did control subjects. However, after

adjustment for lipid levels and other coronary risk factors, the significant association of LDL particle diameter with CHD risk disappeared, whereas that with elevated triglycerides remained (RR, 1.40 per 100 mg/dL increase) [7]. As in the PROCAM study [5], the triglyceride/total cholesterol interaction was significant, with the highest risk for MI observed in patients with triglyceride levels and total/HDL cholesterol ratios in the highest tertiles [7]. Other recent studies have shown a significant association between LDL particle size and CHD risk (with some data showing it to be an independent risk factor) [8–10], and there is a clear physiologic basis for a link between triglyceride elevation and reduced LDL particle size.

Very recently, an 8-year follow-up of men in Copenhagen, Denmark [11••] showed that an elevated level of fasting triglyceride was a strong and independent risk factor for incident CHD. In 2906 white men initially free of overt cardiovascular disease, increasing triglyceride levels were significantly associated with ischemic heart disease, with the cumulative incidence rates of disease being 4.6% in the lowest triglyceride tertile (0.44–1.09 mmol/L), 7.7% for the middle tertile, and 11.5% for the highest tertile (> 1.60 mmol/L, mean 2.45 mmol/L). Of note, this significant predictive effect remained after adjustment for LDL and HDL cholesterol and other cardiovascular risk factors, with the relative risks of disease being 1.5 and 2.2 for the middle and highest triglyceride tertiles, respectively.

Finally, Hokanson and Austin [3] and Austin *et al.* [4] reported the results of a very large meta-analysis that definitively demonstrates that hypertriglyceridemia is an independent risk factor for cardiovascular disease. The analysis included data on both fatal and nonfatal cardiovascular events, and included only white subjects, because data on other ethnic groups are comparatively limited. A total of 17 studies were included. In the 16 studies including male subjects, there were 2445 cardiovascular events among 46,413 men followed for an average of 8.4 years. Univariate analysis revealed RR estimates associated with a 1 mmol/L (88 mg/dL) increase in triglyceride level to range from 1.07 to 1.98, with a summary RR of 1.32 (95% CI: 1.26-1.39). This indicated a 32% increased risk of disease with a 1 mmol/L elevation in triglyceride level. In the five studies including female subjects, there were 439 events among 10,864 women followed for an average of 11.4 years. Among the women, the univariate RR estimates for events associated with a 1 mmol/L increase in triglyceride level ranged from 1.69 to 2.05 with a summary RR of 1.76 (95% CI: 1.50-2.07). Thus, the women had a 76% increase in risk for disease with a 1 mmol/L increase in triglyceride level.

Although the effect of triglyceride level in predicting cardiovascular disease was attenuated after adjustment for HDL cholesterol in meta-analysis of the six studies containing this measure, it remained statistically significant. All six of the studies included male subjects, with the analysis including a total of 22,293; two of the studies included a total of 6345 female subjects. In men, the multivariate RR estimates for disease associated with a 1 mmol/L increase in triglycerides were 0.98 to 1.39, with the summary RR of 1.14 (95% CI: 1.05-1.28) indicating a 14% increase in risk with the triglyceride increase in risk with a 1 mmol/L increase in triglyceride level ($P<0.05$). For women, the summary multivariate RR estimate was 1.37 (95% CI: 1.13-1.66), indicating a 37% increase in risk with a 1 mmol/L increase in triglyceride level ($P<0.05$).

## Hypertriglyceridemia as an Atherogenic State

Hypertriglyceridemia can contribute to CHD risk via a number of pathways and mechanism. First, chylomicrons and very low-density lipoprotein (VLDL) particles or their remnants could be directly atherogenic [12]. Triglyceride-rich lipoprotein particles bind to the arterial endothelium concomitant with their hydrolysis by local lipoprotein lipase. The product of this interaction is a smaller remnant lipoprotein, and investigations in animal models have shown that particle size determines the rate of particle entry into the artery and contributes to lesion formation. The release of fatty acids during this process may cause endothelial damage that could facilitate movement of the remnant particles into the sub-endothelial space. Support for a direct atherogenic role for triglyceride-rich lipoproteins derives from several studies which have indicated that d<1.006 lipoproteins can be found in atherosclerotic coronary arteries and that postprandial lipemia is an independent predictor of coronary artery [13] and carotid artery [14] disease.

Hypertriglyceridemia is associated with a spectrum of other lipid abnormalities which have atherogenic potential of their own. The so-called atherogenic lipoprotein profile or atherogenic dyslipidemia consists of elevated triglycerides, predominance of small, dense LDL particles, and low HDL cholesterol. Small dense LDL particles, generated by lipase-mediated hydrolysis of triglyceride-enriched LDL, have increased susceptibility to oxidation in vitro, and enhanced potential for retention in the arterial wall. Reduced HDL levels may limit a number of anti-atherogenic functions of this class of lipoproteins, including reverse cholesterol transport. Additionally, this dyslipidemia is associated with increased postprandial lipemia.

Hypertriglyceridemia, small dense LDL, and decreased HDL cholesterol are also associated with insulin resistance and hyperinsulinemia [15,16]. Elevated fasting insulin levels have been associated with an increased risk for ischemic heart disease in a number of studies—including the recent Quebec Cardiovascular Study [17], in which hyperinsulinemia was an independent predictor of risk. Of particular note in this study was the finding that insulin levels interacted dramatically with apolipoprotein B (apoB) levels; subjects with higher plasma concentrations of both insulin and apoB had a 10-fold increase in risk for CHD. Individuals with the atherogenic lipoprotein profile described earlier share many of the metabolic characteris-

tics of patients with Type 2 (non–insulin-dependent) diabetes mellitus, and the predominance of small, dense LDL, as well as hypertriglyceridemia and low HDL cholesterol, has been reported as a risk factor for the development of Type 2 diabetes mellitus [18]. The physiologic basis of the association of small dense LDL with insulin resistance appears to be the concomitant hypertriglyceridemia. Elevated triglycerides may also contribute to atherogenesis through an effect on coagulation [19].

## Treatment of Hypertriglyceridemia

Because hypertriglyceridemia is a central component of a complex array of metabolic abnormalities, the treatment is not a simple as it might be for purely elevated LDL cholesterol levels [20]. First, because patients with elevated triglyceride levels are at higher risk for insulin resistance and its concomitant disorders, hypertension and diabetes mellitus, those problems must be identified and treated. Because triglyceride levels are sensitive to energy balance, the central components of any treatment plan must be diet, weight loss, and exercise. These approaches benefit not only the hypertriglyceridemia, but also the associated hypertension and insulin resistance. After maximal lifestyle changes have been achieved, treatment with pharmacologic agents may be needed. However, the Adult Treatment Panel guidelines published by the National Cholesterol Education Program (NCEP) do not give clear goals or levels for initiation of treatment in terms of triglyceride levels. Thus, in the most recent NCEP guidelines [21], the indications for drug therapy in patients with hypertriglyceridemia include the presence of combined hyperlipidemia; established CHD; family history of premature CHD; concomitant high cholesterol (>240 mg/dL); and genetic forms of hypertriglyceridemia associated with increased risk for CHD, such as familial combined hyperlipidemia or familial dysbetalipoproteinemia. The guidelines do not provide a clear, direct algorithm for triglycerides as they do for LDL cholesterol.

The NCEP guidelines recommend nicotinic acid as the drug of choice in patients with elevated triglycerides; this agent reduces LDL and VLDL levels, and increases HDL levels, and may be particularly valuable for patients with familial combined hyperlipidemia. Niacin can lower triglyceride levels by 30% to 45%, raise HDL cholesterol levels by 15% to 25%, and reduce LDL cholesterol by 15% to 20%. However, nicotinic acid is often poorly tolerated, can exacerbate diabetes mellitus, and should be used only with caution in persons with glucose intolerance. Niaspan (KOS Pharmaceuticals, Miami, FL), a recently approved intermediate/long acting niacin preparation, appears to be as effective as regular niacin in terms of lipid-altering effects, and may allow for better compliance, but more long-term data on safety are still needed. Additionally, it is possible that Niaspan will have effects on glucose tolerance similar to those seen with regular niacin, thereby limiting its use in patients with diabetes mellitus. Studies in this population are underway presently.

Another option for treating hypertriglyceridemia is fibric acid derivatives (*eg*, gemfibrozil and fenofibrate), which lower triglyceride levels and are well tolerated. Both gemfibrozil and fenofibrate can reduce plasma triglyceride concentrations by 35% to 50% and raise HDL levels by 10% to 20%. Fibric acid derivatives may increase LDL in hypertriglyceridemic patients. However, reduction of CHD events in the Helsinki Heart Study [6] was greatest among gemfibrozil recipients who had the combination of elevated triglycerides and an elevated LDL/HDL ratio, and did not appear to correlate with changes in LDL cholesterol. In the recently completed, yet unpublished Veteran's Administration HDL Intervention Trial (VA HIT), presented at the American Heart Association meeting (Dallas, TX, November 5–10, 1998), men with pre-existing coronary artery disease and a mean LDL cholesterol of 111 mg/dL were randomized to gemfibrozil or placebo for five years. In the gemfibrozil-treated group, a 25% reduction in triglycerides and a 7% increase in HDL cholesterol were associated with a 22% reduction in recurrent events compared to the placebo-treated group. This significant benefit occurred despite the lack of any change in LDL cholesterol levels. Using a fibrate in combination with a bile acid-sequestering resin (cholestyramine or colestipol) may reverse any increase in LDL cholesterol associated with fibrate treatment alone.

If lowering LDL cholesterol levels is central to reducing risk, even in patients with hypertriglyceridemia [22], then triglyceride-lowering effects could allow expanded use of statin monotherapy to patients with hypertriglyceridemia and combined hyperlipidemia. Although the less potent statins generally produce only mild reductions in triglycerides, newer and more potent statins at the top doses can produce clinically significant reductions in triglycerides. Thus, triglyceride reductions of 19% to 37% were observed with atorvastatin 10 to 80 mg in a study of patients with severe hypertriglyceridemia (baseline levels >600 mg/dL) [23]. In another study, reductions of 21% and 23% were reported with simvastatin 40 mg and 80 mg, respectively, in a study of patients with moderate levels of triglycerides (baseline mean level of 175 mg/dL) [24].

Recently, Stein *et al*. [25••] reviewed the effects of statins on hypertriglyceridemia using results from many of the large FDA-monitored trials. Their analysis indicated that the percent triglyceride-lowering effects of statins depended on 1) the baseline triglyceride level of the patients, and 2) the percent LDL cholesterol lowering achieved. Thus in patients with baseline triglyceride levels less than 150 mg/dL, the percent reduction in triglycerides was only modest: about 20% of the percent reduction in LDL cholesterol. On the other hand, in patients with baseline triglycerides between 150 and 250 mg/dL, triglyceride lowering was about 50% to 60% of LDL cholesterol lowering, whereas in patients with baseline triglycerides higher

than 250 mg/dL, the percent triglyceride lowering was about equal to the percent LDL cholesterol lowering. Although Stein *et al*. [25••] did not find differences amongst the statins when the data were analyzed in this manner, it should be clear that the more potent statins, when used at their higher doses, will lower triglycerides more than less potent statins because they will be able to lower LDL cholesterol more.

Overall, these recent studies and analyses suggest a potential role for statins as a sole treatment for some patients with combined hyperlipidemia who have predominantly elevated cholesterol. A recent 24-week study [26•] in patients with combined hyperlipidemia compared atorvastatin, 10 mg for 12 weeks and 20 mg for an additional 12 weeks, with fenofibrate 100 mg three times daily for 24 weeks. At both doses, atorvastatin was associated with significantly greater reductions in LDL cholesterol (30% and 38% at weeks 12 and 24 vs 7% and 6% for fenofibrate at those time points) compared with fenofibrate. In contrast, triglyceride levels were reduced only by 25% in atorvastatin patients by the end of the 10 mg dosing period and by 28% at week 24, compared with respective reductions of 47% and 40% in fenofibrate patients. Similar results have been obtained with other statins when compared to fibrates alone. In a study of patients with type 2 diabetes mellitus and combined hyperlipidemia, simvastatin at 40 mg per day decreased LDL cholesterol level by 45% and triglycerides by 25%, whereas gemfibrozil did not lowered LDL cholesterol levels. However, gemfibrozil reduced triglyceride concentrations by about 50% [27].

It is clear from these studies that statins can be considered as first-line agent for many patients with combined hyperlipidemia who require significant lowering of both LDL cholesterol and triglycerides, and may be useful as well in some patients with hypertriglyceridemia who have normal LDL levels that are still well above the NCEP goal. However, it must be remembered that triglyceride lowering will parallel LDL lowering; if a 40% to 50% reduction in is desired in a significantly hypertriglyceridemic subject (>250 mg/dL), only the highest doses of the potent statins will, while concomitantly lowering LDL cholesterol 40% to 50%, achieve that goal. Combination therapy with either gemfibrozil or fenofibrate and a statin, or with nicotinic acid and a statin, has also been effective in familial combined hyperlipidemia [28,29,30•], and may be necessary to reach optimal levels of triglycerides and both HDL and LDL cholesterol in very high risk patients. These combinations are, however, associated with an increased risk of myositis.

## Conclusions

What should the clinician do when faced with the not uncommon middle-aged patient who has hypertriglyceridemia? Although the VA HIT results, when published in full, may change our approach to patients with hypertriglyceridemia and low LDL cholesterol levels at baseline, a reasonable approach based on available evidence would be to use the NCEP guidelines, focusing particularly on the presence of risk factors commonly associated with hypertriglyceridemia (hypertension, diabetes, low HDL cholesterol) to guide the intensity of therapy focused on LDL cholesterol. If a man over 45 years of age or a post-menopausal woman presents with significant hypertriglyceridemia, it is very likely that he or she will have one or more of the risk factors listed by the NCEP guidelines, and would require an LDL-cholesterol level of less than 130 mg/dL. If the patient has clinical atherosclerotic cardiovascular disease, an LDL-cholesterol level of less than 100 mg/dL would be the goal.

When a patient with hypertriglyceridemia without clinical atherosclerotic cardiovascular disease has an LDL cholesterol less than 130 mg/dL, however, the NCEP guidelines do not provide clear direction for therapy regardless of the number of additional risk factors. Here, use of the LDL/HDL ratio might be useful, as both PROCAM [5] and the Helsinki Heart Study [6] indicated that patients with ratios greater than 5.0 and triglyceride levels greater than 200 mg/dL had markedly increased risk. It must be understood, however, that there are no data to support the value of further lowering LDL levels that are already less than 130 mg/dL in patients without clinical atherosclerotic cardiovascular disease.

A therapeutic program for patients with hypertriglyceridemia should obviously include diet, exercise, and weight loss programs; these are even more important in this group than in persons with isolated hypercholesterolemia. When drug therapy is required, the approach outlined above, with statins as the first-line agent, can be followed to reach goal-LDL cholesterol levels. Finally, when LDL-cholesterol goals are met but triglyceride levels remain high (and HDL levels are low), the patient's lipid profile and overall risk for CHD should be reassessed. A goal triglyceride level of less than 200 mg/dL and HDL as close as possible to 40 mg/dL for men and 50 mg/dL for women seems reasonable for high-risk patients. If further therapy is required to optimize triglyceride and HDL cholesterol levels, gemfibrozil or fenofibrate in combination with a statin can be very effective. Niacin in combination with a statin is an alternative. As noted earlier, a high dose of a potent statin alone, that lowers triglycerides significantly, may be adequate in some patients with combined hyperlipidemia, particularly when significant reductions in LDL cholesterol (>35%) are required to meet NCEP goals.

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