

## Should We Treat Moderately Elevated Triglycerides?

### Yes: Treatment of Moderately Elevated Triglycerides Is Supported by the Evidence

RADE N. PEJIC, MD, MMM, *Tulane University School of Medicine, New Orleans, Louisiana*

The normal physiologic concentration of triglyceride in human serum is 10 to 70 mg per dL (0.11 to 0.79 mmol per L; mean 30 mg per dL [0.34 mmol per L]).<sup>1</sup> Values greater than 150 mg per dL (1.69 mmol per L) are considered abnormal, and values between 200 and 500 mg per dL (2.26 and 5.65 mmol per L) are considered by the National Cholesterol Education Program (NCEP) to be high.<sup>1</sup> The question for physicians is whether or not patients benefit from treatment of elevated levels.

At values greater than 500 mg per dL, triglycerides may cause pancreatitis. At lower values (200 to 500 mg per dL), especially with normal lipid subfractions, the risk of hypertriglyceridemia is not clear. Patients with familial hypertriglyceridemia (Fredrickson type IV) do not appear to have higher cardiovascular risk. However, patients with abnormal triglyceride values typically have other lipid derangements, such as high levels of low-density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL; e.g., atherogenic dyslipidemia). Additionally, patients with hypertriglyceridemia often have metabolic syndrome (e.g., abdominal obesity, hypertension, insulin resistance, low HDL, high triglycerides), which is a risk factor for developing coronary heart disease (CHD).<sup>2</sup> In this sense, a triglyceride level can be thought of as a lifestyle biomarker identifying patients who are sedentary, have high-carbohydrate diets, and are overweight or obese.

Multiple studies have identified elevated triglyceride levels as an independent risk factor for CHD.<sup>3-5</sup> This risk seems to be greater in women, and in patients with diabetes mellitus or known CHD. Most of this risk



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occurs in patients with low HDL cholesterol and high LDL cholesterol. Although the risk associated with elevated triglyceride levels is largely attenuated by controlling for low HDL levels, residual risk remains.

In the largest study to evaluate risk associated with triglycerides, there was a 14 percent increased risk in men and a 37 percent increased risk in women for every 88 mg per dL (0.99 mmol per L) increase in triglyceride concentration above normal.<sup>6</sup> The most likely reason for this residual risk is that hypertriglyceridemia is a surrogate marker for patients with an excess of atherogenic remnant particles and other proatherogenic conditions. Using conventional lipid testing, a patient's total atherogenic load can be estimated by calculating the non-HDL cholesterol concentration (total cholesterol minus HDL). The NCEP Adult Treatment Panel III (ATP III) guidelines recommend calculating the non-HDL cholesterol value in patients with a triglyceride level greater than 200 mg per dL.<sup>1</sup> Some argue that the non-HDL cholesterol level should be calculated for all patients because it is more closely linked to CHD risk than LDL cholesterol.<sup>7</sup>

Treatment of severe hypertriglyceridemia (greater than 500 mg per dL) should begin immediately to reduce the risk of pancreatitis. Usually, a fibrate is tried first with therapeutic lifestyle changes. Treatment of modest hypertriglyceridemia (200 to 500 mg per dL) should begin with therapeutic lifestyle changes and a search for underlying ►

causes or contributing factors, such as obesity, hypothyroidism, or diabetes. If triglycerides remain elevated, the NCEP-ATP III guidelines recommend treating the LDL cholesterol first, and then the non-HDL cholesterol to reach goals based on the patient's Framingham risk assessment. Drug therapy in these cases should begin with a statin, which should be titrated accordingly. Combination therapy with a fibrate should follow if needed. It is safest to add fenofibrate (Tricor), because there is a chance of rhabdomyolysis with gemfibrozil (Lopid). Omega-3 fish oil (n-3 fatty acid) was recently approved for the treatment of hypertriglyceridemia and can be added to the statin. Niacin is another therapeutic option and is now available in a combination product with simvastatin (Simcor).

There are no specific guidelines from the NCEP-ATP III about treating isolated moderate hypertriglyceridemia. However, if the triglyceride level remains elevated once LDL and non-HDL cholesterol concentrations are normalized, it may be worthwhile to pursue further triglyceride-lowering treatment, especially in high-risk patients with CHD or type 2 diabetes.

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial of patients after acute coronary syndrome, a final triglyceride level less than 150 mg per dL was associated with a 27 percent relative reduction in coronary events.<sup>8</sup> In the Baltimore Coronary Observational Long-Term Study there was an association between increased coronary events and moderate hypertriglyceridemia.<sup>9</sup> Recent findings from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study show a 27 percent relative reduction in CHD and a 38 percent relative reduction in nontraumatic leg amputation in patients with diabetes treated using fenofibrate.<sup>10</sup> The NCEP-ATP III final report states that drugs that modify atherogenic dyslipidemia yield moderate reductions in CHD risk.<sup>1</sup>

Until more refined laboratory techniques become available to clearly identify patients who would benefit from treatment, it seems prudent to aggressively treat high-risk

patients by normalizing their LDL cholesterol, non-HDL cholesterol, and triglyceride levels. Moderate- and low-risk patients should be monitored regularly and given the option for treatment if their lipid levels worsen. All patients with hypertriglyceridemia should be encouraged to stop smoking, exercise regularly, and adhere to their prescribed diet.

Address correspondence to Rade N. Pejic, MD, MMM, at [rpejic@tulane.edu](mailto:rpejic@tulane.edu). Reprints are not available from the author.

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