CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will appraise their patients' need for lifestyle changes and drug therapy to control triglyceride levels to currently recommended ranges

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Is triglyceride therapy worth the effort?

ABSTRACT

A scientific statement from the American Heart Association notes that triglyceride levels are an important biomarker of cardiovascular disease risk. Although as yet there is no evidence that lowering elevated triglyceride levels reduces cardiovascular risk, the statement recommends that patients undertake weight loss and dietary changes if fasting levels exceed 150 mg/dL, and that the intensity of these lifestyle measures be increased with higher triglyceride levels. Aerobic activity at least twice a week is also encouraged. Drug therapy is indicated for levels exceeding 500 mg/dL because of an association with pancreatitis.

KEY POINTS

Triglycerides are an excellent marker of coronary heart disease risk and should be treated when fasting levels exceed 150 mg/dL.

The cornerstone of therapy for triglyceride levels up to 500 mg/dL is intensive lifestyle therapy aimed at reducing excess weight through diet and aerobic activity.

Drug therapy with fibrates, niacin, and omega-3 fatty acids is indicated for levels exceeding 500 mg/dL because of concern related to pancreatitis risk.

It remains to be established whether lowering elevated triglyceride levels in patients with coronary heart disease or at risk of it will translate into clinical benefit. However, two studies are under way.

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Triglyceride levels do matter. Not only are they a marker of risk of cardiovascular disease, they may be mechanistically linked to it. Although we still lack evidence that specifically lowering elevated triglyceride levels reduces the risk of cardiovascular disease, the reason is that controlled trials have not yet been done. Such studies are under way to determine whether fish-oil-derived omega-3 preparations added to statin therapy can reduce coronary heart disease risk in high-risk patients with hypertriglyceridemia.

POSSIBLY MECHANISTICALLY LINKED TO CORONARY HEART DISEASE

Hypertriglyceridemia does not cause atherosclerosis directly, but there is evidence that it is mechanistically linked to it.

While lipolysis of triglyceride-rich lipoproteins, chylomicrons, and very-low-density lipoprotein cholesterol serves as a mammalian source of energy, the cholesterol-enriched byproducts are atherogenic.[1] The higher the triglyceride level, the greater the likelihood of accumulation of atherogenic remnant particles.[2] A high-triglyceride state, defined as a fasting level greater than 200 mg/dL, is associated with several atherogenic factors:

- Higher levels of apolipoprotein C3-containing particles, which promote inflammation and insulin resistance[3]
- A higher concentration of atherogenic low-density lipoprotein cholesterol (LDL-C) particles[4]
- Dysfunctional high-density lipoprotein cholesterol (HDL-C) particles.[5]

In general, the risk of death from cardiovascular disease is 25% higher with triglyceride levels above 200 mg/dL than with levels below 150 mg/dL.[6] Hypertriglyceridemic phenotypes, most notably dysbetalipoproteinemia and mixed hyperlipidemia, may be particularly

atherogenic in the presence of other risk factors for cardiovascular disease.[7]

LOW LEVELS ARE BEST

In US adults, the mean age-adjusted triglyceride level is 128 mg/dL in men and 110 mg/dL in women.[1] Currently, a "desirable" fasting level is less than 150 mg/dL, with borderline-high levels between 150 and 199 mg/dL. In its 2011 scientific statement on triglycerides and cardiovascular disease,[1] the American Heart Association defined a fasting triglyceride level of less than 100 mg/dL as "optimal" in order to define a metric of metabolic health.

Supporting the concept that low levels are best, a study of 1,962 middle-aged Norwegian men found that the risk of incident diabetes over a 7-year period was 2.6 times lower in the lowest triglyceride tertile (mean 69 mg/dL) compared with levels in higher tertiles (mean 177 mg/dL).[8]

Moreover, in contrast to the atherogenic phenotype of combined or mixed hyperlipidemia, levels below 100 mg/dL seem to pose a low risk of cardiovascular disease as seen in studies of hunter-gatherer populations.[9] Recent genetic studies have extended these findings: specifically, mutations in the gene encoding apolipoprotein C3 (*APOC3*) have been associated with fasting triglyceride levels less than 100 mg/dL, reduced coronary calcification,[10] and decreased risk of cardiovascular disease.[11,12]

The Baltimore Coronary Observational Long-term Study observed a 50% lower rate of recurrent coronary heart disease events in patients whose baseline triglyceride level was less than 100 mg/dL compared with higher levels.[13] In the Copenhagen Heart Study,[14] levels in the lowest quartile (< 89 mg/dL) were associated with a 41% lower risk of all-cause mortality compared with the highest quartile (> 265 mg/dL).

The Framingham Offspring Study[15] recently reported that an isolated low level of HDL-C—ie, below the median of less than 42 mg/dL in men and less than 54 mg/dL in women—was associated with a very low risk of incident coronary heart disease when accompanied by a triglyceride level below 100 mg/dL and an LDL-C level below 100 mg/dL. However, at higher levels of triglyceride and LDL-C, the risk of myocardial infarction or death from cardiovascular disease was more than twice as high after adjustment for other covariates.[15] This raises the possibility that "isolated" low HDL-C itself is not an atherogenic lipoprotein phenotype, but rather requires other triggers (eg, an increase in triglyceride-rich and LDL-C particles) to drive the process.

Studies discussed in this article

ACCORD—Action to Control Cardiovascular Risk in Diabetes trial and the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes[17,19]

COLTS—Baltimore Coronary Observational Long-term Study[13]

Copenhagen Heart Study[14]

Framingham Offspring Study[15]

PROVE IT-TIMI 22—Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22[22]

REDUCE-IT—Reduction of Cardiovascular Events With EPA Intervention Trial[24]

STRENGTH—Study to Assess Statin Residual Risk Reduction With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia[25]

WHERE DO TRIGLYCERIDES FIT IN THE NEW CHOLESTEROL GUIDELINES?

The 2013 joint guidelines of the American College of Cardiology and the American Heart Association on the treatment of blood cholesterol[16] provide evidenced-based recommendations from randomized clinical trials. While they recommend measuring the fasting triglyceride level if nonfasting levels exceed 500 mg/dL, there are no recommendations for triglyceride-lowering therapies unless fasting levels exceed 500 mg/dL.

This in no way implies that lowering triglyceride levels may not be beneficial when levels are below 500 mg/dL; rather, it stems from a lack of clinical trials designed to address this issue. That is, studies of triglyceride-lowering therapies such as niacin, fibrates, and omega-3 fatty acids from fish oil have focused on patients who did not have hypertriglyceridemia (mean triglyceride levels were less than 200 mg/dL). Yet in subgroup analyses of patients with triglyceride levels greater than 200

The higher the triglyceride level, the more likely that atherogenic remnant particles will accumulate

mg/dL or in the upper tertile (often in association with low levels of HDL-C), either a trend toward or a statistically significant reduced risk of cardiovascular disease was observed.[17–19]

Until results of ongoing randomized controlled trials dictate otherwise, it may be reasonable to consider drug therapy in patients at high risk (eg, those with preexisting cardiovascular disease) whose levels may be insufficiently responsive to lifestyle measures (see discussion below) after the risks of treatment are weighed against the possible benefits.

WHAT HAPPENED TO THE ATP III TARGETS?

In 2002, the Third Adult Treatment Panel recommended that if triglyceride levels were higher than 200 mg/dL, non-HDL cholesterol should become a secondary target of therapy.[20] What happened to this recommendation?

The writing committee of the 2013 American College of Cardiology/American Heart Association cholesterol guidelines based its recommendations on clinical evidence available from randomized controlled trials.[16] Unfortunately, neither LDL-C nor non-HDL-C targets were the primary or secondary variables of interest when the available trials were designed. Still, aggregate data over the past several decades, combined with our knowledge of the pathophysiology of both LDL-C and triglyceride-rich lipoproteins (ie, remnants), indicate that non-HDL-C levels predict the risk of cardiovascular disease.[21]

Intensive lifestyle therapy can reduce triglyceride levels by 30% to 50%, and by more in some cases

Moreover, a post hoc analysis of the PROVE IT-TIMI 22 trial demonstrated residual cardiovascular disease risk in hypertriglyceridemic patients after an acute coronary syndrome event even though the patients were currently on statin therapy at the time.[22]

In addition, the ACCORD study also reported a reduction in cardiovascular disease risk in hypertriglyceridemic patients with low HDL-C assigned to triglyceride-lowering in addition to statin therapy.[17,19]

Finally, data from two large US health care databases of more than 40,000 adults with triglyceride levels above 500 mg/dL at baseline found that patients who had triglyceride levels lower than 200 mg/dL at follow-up had lower rates of pancreatitis and coronary heart disease events.[23]

DOES ADDING TO STATIN THERAPY HAVE LONG-TERM CLINICAL BENEFIT?

Two randomized clinical outcome trials are currently testing whether supplementing statin therapy in order to lower triglyceride levels is superior to statin therapy alone in reducing the risk of cardiovascular events in high-risk patients.

REDUCE-IT

REDUCE-IT[24] is studying whether AMR101 (Vascepa), a purified ethyl ester of eicosapentaenoic acid, reduces risk in patients with hypertriglyceridemia (with a baseline level of 200 to 500 mg/dL) who have cardiovascular disease or are at high risk for it. However, a number of factors in this trial will make it difficult to separate out the clinical benefit directly related to triglyceride-lowering. These factors include associated beneficial effects of the treatment on LDL-C composition, HDL-C remodeling, and remnant accumulation and clearance, as well as other potential benefits on cardiovascular disease risk independent of lipids and lipoproteins, such as inflammation.

Nevertheless, REDUCE-IT should provide valuable insight into whether this therapy may be clinically useful in these high-risk patients. Enrollment of 8,000 patients is nearing completion in this event-driven trial, with an anticipated median treatment and follow-up period of 4 years.[24]

STRENGTH

The STRENGTH study will enroll 13,000 patients with hypertriglyceridemia (200–500 mg/dL) and low HDL-C to receive a fish-oil preparation or placebo. This large 5-year phase 3 outcomes study began enrollment in late 2014.[25]

WHAT IS THE RISK OF PANCREATITIS FROM ELEVATED TRIGLYCERIDES?

The premise of screening for very high triglyceride levels (> 500 mg/dL) in the new cholesterol guidelines and superimposed on the 2011 American Heart Association scientific statement on triglycerides and cardiovascular disease is the concern that very high levels predict pancreatitis. The risk of pancreatitis increases as triglyceride levels exceed 1,000 mg/dL, with an approximate overall risk of 20%.[26]

While there is no absolute proof that treating chylomicronemia reduces the risk of pancreatitis, ample data from case series show that strategies aimed at reducing plasma triglyceride concentrations are also effective in reducing the risk of pancreatitis.[27] Conversely, patients with previous triglyceride-induced pancreatitis unquestionably have recurrent episodes of pancreatitis when they develop severe chylomicronemia. The American Heart Association scientific statement provides a list of other factors, including metabolic conditions and medications, associated with increased risk of pancreatitis.[1]

WHAT ARE THE RECOMMENDATIONS FOR VERY HIGH TRIGLYCERIDES?

Both the American College of Cardiology/American Heart Association cholesterol guidelines[16] and the 2011 American Heart Association statement[1] reserve pharmacologic therapy for very high triglyceride levels, defined as 500 mg/dL or higher.

While lifestyle recommendations are still an important part of therapy (TABLE 1), genetically induced hypertriglyceridemia may not respond as well to diet, exercise, and fish oil. In addition to statin therapy, if there is concomitant cardiovascular disease or diabetes, primary triglyceride-lowering therapies include fibrates (which lower triglycerides 30% to 50%), niacin (20%–50%) and omega-3 fatty acids (10%–40%)[1] with eicosapentaenoic acid alone, docosahexaenoic acid alone, or the two in combination.

The focus of the American Heart Association statement was to intensify lifestyle therapies in patients with triglyceride levels between 200 and 500 mg/dL because weight loss, aerobic activity, and the addition of marine-derived polyunsaturated fatty acids can be very effective. The most important step is aimed at weight loss through combined caloric restriction and energy expenditure, increasing monounsaturated and polyunsaturated fat intake at the expense of less complex carbohydrates, and adding marine-derived omega-3 fatty acids. Intensive lifestyle therapy can reduce triglyceride levels by 30% to 50%, and by more in some cases.

Of note, without weight loss, a Mediterranean high-fat diet can aggravate hypertriglyceridemia, especially in patients with fasting triglyceride concentrations above 500 mg/dL. This is particularly true for patients with genetically induced states (eg, lipoprotein lipase deficiency) or other significant defects in chylomicron clearance because olive oil and nut oils serve as excellent substrates for chylomicron formation.

TABLE 1

Effect of lifestyle practices on triglycerides

Lifestyle practice	Triglyceride-lowering effect
Weight loss (5%–10% of body weight)	≥ 20%
Aerobic activity	≥ 20%
Add fish-oil-derived polyunsaturated fatty acids	≥ 20%
Implement a monounsaturated fatty acid-enriched vs low-fat diet	10%–15%
Decrease carbohydrates (1% energy replacement with mono- and polyunsaturated fatty acids)	1%–2%
Eliminate trans fats	1%

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