Slippery Slope of Triglycerides
They Are Associated With Risk, But in the Statin Era, Does Targeting Them Confer Benefit?

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For years, the scientific and medical communities have pondered the role of triglycerides in cardiovascular disease (CVD) and mortality risk. Although several studies have shown a relationship between elevated triglyceride levels and CVD, the degree to which triglycerides are independently associated and whether triglycerides directly cause CVD has been hotly debated. This is in contrast to the role of low-density lipoprotein cholesterol (LDL-c) where the direct relationship between LDL-c and CVD is clear. During the years, several pieces of evidence have suggested an independent association between elevated serum triglycerides and CVD; however, the firmness of this conclusion has been seen as tenuous. In fact, a recent large study (>300,000 participants) did not find triglycerides to be an independent risk factor for CAD when adjusted for high-density lipoprotein cholesterol and non–high-density lipoprotein cholesterol. Most likely, the confusion comes because it can be difficult to know whether the triglycerides themselves are the cause of the increased risk or merely a marker of increased risk. High triglycerides usually occur in conjunction with a host of other abnormalities, such as insulin resistance, diabetes mellitus, low-density lipoprotein cholesterol obesity, and hypertension, thus it is difficult to disentangle which is the true causal factor.

In this issue of Circulation: Cardiovascular Quality and Outcomes, the article by Klempfner et al adds further support for a role of triglycerides in promoting mortality, likely via an increase in CVD mortality. The article “Elevated Triglyceride Level Is Independently Associated With Increased All-Cause Mortality in Patients With Established Coronary Heart Disease: A 22-Year Follow-Up of the BIP Study and Registry” reported long-term mortality data on 15,355 patients who were screened for the Bezafibrate Infarction Prevention (BIP) trial. The BIP study was a randomized, placebo-controlled secondary prevention trial designed to assess the efficacy of bezafibrate in reducing cardiovascular events. The parent trial found a 9.4% reduction in the primary end point (fatal and nonfatal myocardial infarction plus sudden death) with bezafibrate, but this was not statistically significant. In this study, the investigators report 22-year mortality data on 15,355 patients screened for the BIP trial (whether they were enrolled) and found that successively higher fasting triglyceride levels led to successively higher age- and sex-adjusted mortality rates. When triglyceride levels were plotted against mortality, the investigators clearly showed an increase in mortality with increasing triglyceride levels and in multivariate analysis (controlling for multiple potential confounders) each unit of natural logarithm triglycerides elevation was associated with a 26% increase in all-cause mortality. In this study, even high normal triglyceride levels (100–149 mg/dL) were associated with increased mortality when compared with low normal triglyceride levels (<100 mg/dL). The 22-year survival rate for patients with the highest triglyceride levels (>500 mg/dL) was only 25%, whereas the survival rate for those with low normal triglyceride levels (<100 mg/dL) was significantly higher at 41%. It is important to note that mortality data for this study were obtained from the official National population registry. The authors excluded participants who developed incidental cancers during follow-up (as determined from the National Cancer registry), thus most of the deaths were presumed to be cardiovascular. This seems to be a valid assumption, but it is an assumption nonetheless and is one of the limitations of the study. Other limitations of this study which temper enthusiasm are the lack of adjudication of deaths, the lack of follow-up lipid values, lack of follow-up ascertainment of important comorbidities, such as diabetes mellitus, and lack of follow-up medication use. These limitations notwithstanding, this work adds to our scientific knowledge about the potential role of elevated triglycerides in cardiovascular risk, especially given the large numbers of individuals studied and the long follow-up.

Furthermore, this research takes on special importance given that elevations in triglycerides are increasingly common in current day society. National Health and Nutrition Examination Survey (NHANES) has collected data on cardiovascular risk factors during the 3 decades, and these data reveal that the average triglyceride levels are increasing in the US population. During the period 1988 to 2010, 47% of the US population had triglyceride levels >150 mg/dL. Although extremely high triglycerides are less common, NHANES did find that 1% of the US population had triglyceride levels >500 mg/dL. In comparison, cholesterol levels have been declining during this time period, which is likely the result of more awareness, better screening, and improved therapies.
But How Should We Incorporate These Findings into Our Practice?

Putting this study into the context of present day clinical care, it is important to remember that this trial was conducted at a time when standard of care lipid management was considerably different from current practices. The authors point out that >90% of the patients in the BIP trial did not receive any lipid modifying medication at the time of enrollment. This is not surprising since at the time that BIP was enrolling, there were no clear guidelines for this population and suboptimal awareness and acceptance of the benefit of lipid-lowering therapy. Lovastatin and simvastatin, Food and Drug Administration approved in 1987 and 1991, respectively, had only recently entered the US market, and trials on their benefits were ongoing.

Currently, statins are the most widely used class of lipid altering medications and also reveal the most robust clinical event reduction. In addition to efficacy in LDL-c lowering, statins have moderate efficacy in triglycerides lowering; however, we still see increased cardiovascular risk in patients with elevated triglycerides, despite statin therapy. Subgroup analysis of the statin secondary prevention trial, PROVE-IT TIMI 22, revealed that in patients with recent acute coronary syndromes treated with statin therapy to an LDL-c <70 mg/dL, there was still a higher risk for recurrent coronary events if triglycerides were elevated >150 mg/dL. Thus, we clearly see evidence that patients with elevated triglycerides are at increased cardiovascular risk, even with statin therapy. Because statins are the mainstay of current lipid management, an important question is what, if any, additional lipid modifying agents on top of statins should be used to target elevated triglycerides. Unfortunately, the largest trials that evaluated this question, The Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial, and the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-2 THRIVE) study did not show benefit of adding additional agents (that primarily target triglycerides lowering) on top of statins. In addition, there are potential harms seen with the medication combinations studied. The results of these outcome trials fail to support the hypothesis that a triglyceride-lowering drug reduces the risk for cardiovascular events among statin-treated patients—or at least the drugs that were studied in those trials. The Food and Drug Administration has publicly stated that it no longer considers a change in serum triglyceride levels sufficient to establish the effectiveness of a drug intended to reduce cardiovascular risk in subjects with serum triglyceride levels <500 mg/dL. Also, current US cholesterol guidelines do not advocate routinely adding triglyceride-lowering medications to statin therapy in patients with elevated triglycerides. The 2013 American College of Cardiology/American Heart Association cholesterol guidelines rightly focus on LDL-c reduction to reduce cardiovascular risk. These guidelines say “As of yet, there are no data to show that adding a nonstatin drug(s) to high-intensity statin therapy will provide incremental ASCVD risk reduction benefit with an acceptable margin of safety.”

So, if moderately elevated triglycerides increase cardiovascular risk, but intervention trials fail to show benefit of adding agents that reduce triglycerides, are we simply lacking the right agents to lower triglycerides safely and effectively or is the hypothesis flawed? Triglyceride-rich lipoproteins, mainly chylomicrons and very low-density lipoprotein, contain a small glycoprotein apolipoprotein C-III, which has been shown to induce proinflammatory processes which are known to cause vascular inflammation, a key step in the formation of atherosclerosis. Two recent Mendelian randomization studies discovered a loss of function mutation in apolipoprotein C-III, resulting in low-triglyceride levels and dramatic reduction in overall cardiovascular risk. This started the development of a new target and a class of therapeutic agents, antisense inhibitors of apolipoprotein C-III. In early clinical trials, these agents have been shown to be effective and safe in lowering triglycerides. Whether these agents will be able to improve cardiovascular outcomes remains to be seen. Currently, lifestyle interventions remain an effective way in lowering triglycerides. In the Diabetes Prevention Program, 3234 nondiabetic persons with pre–diabetes mellitus were randomly assigned to placebo, metformin, or a lifestyle-modification program with the goals of at least a 7% weight loss and at least 150 minutes of physical activity per week. The lifestyle intervention was found to be most successful at preventing progression to diabetes mellitus, and in addition after 10 years of follow-up there was a sustained 12% reduction in triglycerides with lifestyle.

Although we search for the true significance of elevated triglycerides in cardiovascular risk and potentially the optimal method to lower triglycerides, we congratulate Klempfner et al on an important study, which provides support for the idea that triglycerides should be considered more seriously as a future target to improve our patients’ outcomes. Be reminded, however, that we currently do not know if triglyceride elevations will hold similar predictive value in patients whose LDL-c is optimally controlled. And we must always remember that simply because something may or may not be a cardiovascular risk factor, altering it pharmacologically does not always mean that we will lower risk.

Disclosures

None.

References


Key Words: Editorials ◆ cholesterol ◆ risk factor ◆ survival rate ◆ triglycerides
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*Circ Cardiovasc Qual Outcomes*. 2016;9:97-99; originally published online March 8, 2016; doi: 10.1161/CIRCOUTCOMES.116.002675

*Circulation: Cardiovascular Quality and Outcomes* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7705. Online ISSN: 1941-7713

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