Should We Worry About Raised Triglycerides?

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David Preiss, PhD, University of Glasgow, Glasgow, United Kingdom, discussed elevated triglycerides (TGs) and whether they pose a concern.

The question becomes relevant when treating, for example, a type 2 diabetic patient at high risk of cardiovascular disease (CVD) with elevated TGs and low high-density lipoprotein (HDL) cholesterol. Lifestyle modifications including exercise, weight loss, diet, altered consumption of alcohol, and judicious and relevant medication use are sound. But the focus of treatment (CVD risk and/or pancreatitis risk and/or microvascular risk) is more problematic and contentious.

Challenges associated with TGs include marked variation within a person (typically 10% to 15%), the difference between fasting and random levels, relationships with other lipids including HDL and small dense low-density lipoprotein, and genetic conditions that elevate TGs and which may or may not elevate CVD risk. Reflecting these challenges, current guidelines are mixed concerning the TG cutoff value of concern and the actions that should be taken (Table 1).

Table 1. Guidelines Concerning Markedly Elevated TGs

Guideline	Triglycerides (mmol/L)	Advice
National Cholesterol Education Program Adult Treatment Panel III[1]	>5.6	• Priority: pancreatitis • Weight and lifestyle changes • If needed: fibrate/niacin/ polyunsaturated fatty acid (PUFA; omega-3)
National Institute for Health and Care Excellence for Diabetes[2]	>4.5	• Pancreatitis may be suspected • Lifestyle, attention to secondary causes • Fibrate as first-line drug therapy
Endocrine Society[3]	>11.4	• Lifestyle • Fibrate as first-line drug therapy
American Heart Association[4]	>5.6	• Lifestyle including weight loss and dietary • Medication if levels remain >500 mg/dL • No specific agent recommended
European Society of Cardiology[5]	>10.0	• Lifestyle • Fibrate as first-line drug therapy • PUFA/niacin as needed

[1]Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults. JAMA, 2001.[2]National Institute for Health and Care Excellence. Type 2 diabetes: National clinical guideline for management in primary and secondary care. Available at http://guidance.nice.org.uk/CG66/Guidance/pdf/English.[3]Berglund L et al. *J Clin Endocrinol Metab* 2012. [4]Miller M et al. *Circulation* 2011. [5]Reiner Z et al. *Eur Heart J* 2011.

Several studies, especially the Emerging Risk Factor Collaboration study involving >302,000 patients [Sarwar DE et al. *JAMA* 2009], have provided convincing evidence that TG measurement is not instructive for prediction of CVD risk, if levels of HDL-cholesterol and cholesterol are already known. Drawing a causal relationship between triglyceride level and CVD (specifically coronary heart disease; CHD) is hindered by involvement of other lipids. Nonetheless, an analysis of 101 studies of the -1131T>C polymorphism of the apolipoprotein A5 gene supported a causal association between triglyceride-mediated pathways and CHD [Sarwar DE et al. *Lancet* 2010].

Several randomized controlled trials have provided data concerning the effect of TG-lowering strategies and CVD. Caveats to the data are that most of the trials excluded individuals with a high TG level (>4.5 mmol/L) and the fact that all tested agents that variably affect all lipoproteins (Table 2).

Table 2. Randomized Controlled Trials: TG Lowering and CVD

Agent	Major Results	Trials
Fibrate	Mixed	FIELD, ACCORD-Lipid, Coronary Drug Project
Niacin (IR/ER)	Failure	AIM-HIGH, HPS2-THRIVE, Coronary Drug Project
Omega-3	Mixed	JELIS, GISSI-Prevenzione and GISSI HF suggested some benefit, other trials negative
Statin	Success	Cholesterol Treatment Trialist Collaboration

An association of TG level with microvascular disease has been reported [Hadjadj S et al. *Diabetes Metab* 2004]. However, a causal relationship is less robust [Rutledge JC et al. *Nature Rev Nephrol* 2010]. Reduced laser treatment for retinopathy has been reported following treatment with fenofibrate [Keech AC et al. *Lancet* 2007] or fenofibrate plus statin [ACCORD and ACCORD Eye Study groups. *N Engl J Med* 2010]. This is of great interest though recent work suggests that beneficial retinal effects are probably due to local ocular effects and not due to any change in lipids.

An association between elevated TGs and pancreatitis exists but is difficult to quantify. While a genetic relationship between severely elevated TGs due to genetic variations (in lipoprotein lipase and related genes) and pancreatitis is established, examinations of the role of elevated triglycerides have suffered from poor study design. One recently reported exception looking at all-cause pancreatitis hospitalization or amylase >300 U/L with TG data acquired from 1993 to 2007 from >67,000 subjects reported increasing hazard ratios depending on TG level [Murphy MJ et al. *JAMA Int Med* 2013]. While fibrates are commonly recommended as first-line therapy to reduce markedly elevated TGs and thereby pancreatitis, analyses of large trials suggest that statins may be a better first-line option as they are the only lipid-modifying agents that have been shown to reduce pancreatitis [Preiss DJ et al. *JAMA* 2012].