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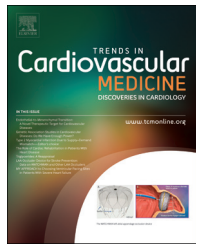

Triglycerides: A reappraisal

*Philipp Wiesner, MD, and Karol E. Watson, MD, PhD, FACC**

UCLA Program in Preventive Cardiology, UCLA Barbra Streisand Women's Heart Health Program, Division of Cardiology, David Geffen School of Medicine at UCLA, Los Angeles, CA

Elevated cholesterol levels are clearly independently associated with adverse cardiovascular events. Another class of lipid particles, triglycerides, is also abundant in the human body and has been found in atherosclerotic plaques. Recent observational studies have demonstrated an association between elevated triglyceride levels and increased risk for future cardiovascular events. With this knowledge and the discovery of effective agents to lower triglyceride levels, the management of triglycerides is currently undergoing a renaissance. Unfortunately, no randomized, controlled clinical trials have been completed to date, proving that lowering triglycerides will reduce cardiovascular events. In this review we highlight some of the evidence that led to this stage and discuss the current data on pharmacologic intervention of triglyceride levels and the effect on clinical outcomes. Lastly, we want to give the reader insight on what the most recent lipid guidelines state about clinical triglyceride management, mention new pharmacological agents, and highlight the clinical evidence for safe and effective lowering of triglycerides levels with life style modification.

Key words: Triglycerides, Cardiovascular disease.

Often decades, even centuries, lie between scientific observations that cause a shift in clinical practice. An example of this is the discovery of the effect of cholesterol, in particular on cardiovascular health. While it is now widely accepted that low-density lipoprotein cholesterol (LDL-c) is the causal agent in atherosclerosis, it took many years and the careers of many scientists to obtain the necessary scientific evidence. Early observations in animal models started as early as 1913, when the Russian scientist Anitschkow discovered the vascular changes leading to atherogenesis in animal models solely fed with a high-cholesterol diet [1]. Many decades passed until it was accepted that the same patterns held true in humans, and even longer before effective therapies were discovered that ultimately led to the reduction of cardiovascular mortality [2]. For the interested reader we highly recommend the excellent review series by Dr. Daniel Steinberg, which precisely documents every important step in this journey [3].

While low-density lipoprotein cholesterol (LDL-c) has been the main focus of our clinical attention in relation to atherosclerosis, triglycerides have begun to gain more attention in recent years. Several observational studies have found an association between elevated triglyceride (TG) levels and increased risk for cardiovascular disease morbidity and mortality. In the 1990s, the lipid research clinics follow-up study [4], the physicians' health study [5], and a meta-analysis of 17 population-based prospective studies going back to as early as 1959 [6] were published. All of these studies show an association between elevated TG levels and CVD mortality or cardiovascular events. Of note, this effect lost statistical significance in some studies after adjusting for common confounders such as high density lipoprotein cholesterol (HDL-c) levels or glucose. However, there continues to be interest in the idea that elevated TG are at least a marker of atherosclerotic risk or in fact may be a causal risk factor for atherosclerosis. In recent years, evidence has also determined that there is a genetic predisposition to elevated TG levels. In 2000, Melissa Austin and colleagues published results suggesting this. These investigators reported results from a 20-year observational study of first degree relatives of

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* *Corresponding author*. Tel.: +310 825 6301; fax: +310 206 9133.
E-mail address: KWatson@mednet.ucla.edu (K.E. Watson).

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patient's with familial hypertriglyceridemia and showed an almost 70% increased risk of CVD mortality in first degree family member of these patients compared to their spouses [7]. Two more recent conflicting large analyses have sparked further debate regarding whether triglycerides are independently associated with CVD. One study of over 300,000 participants did not find an independent association between TG levels and CVD after adjustment for confounders, while another trial with more than 15,000 patients from the Bezafibrate Infarction Prevention (BIP) trial showed a clear correlation between elevated fasting triglyceride levels and higher all-cause mortality rates, even when the data were adjusted for known risk factors and confounders [8,9]. These diverging studies add confusion to the field. We are left to ask the question: Are elevated TG a direct cause of increased cardiovascular risk or do they merely represent a marker for said risk?

Most triglycerides in the bloodstream do not move freely as fatty acids, but rather are carried by large macromolecular structures, mainly very low–density lipoproteins (VLDL) and chylomicrons. These lipoproteins not only have important transport functions, but they also interact with a variety of receptors and enzymes which tightly regulate transport and metabolism [10,11]. The two main sources of plasma triglycerides in the body come from hepatic production and intestinal uptake. Those that come from hepatic production are secreted by the liver into the blood stream as VLDL particles that contain apo-B 100. Dietary triglycerides are absorbed from the gut and packaged into apo-B48 containing chylomicrons and then secreted into the bloodstream via the lymphatic system. Of note, current laboratory assays for the measurement of triglyceride levels are unable to distinguish between the two different forms and always measures total triglyceride content.

The current thinking is that triglycerides do not directly affect the formation of atherosclerosis due to the large size of VLDL particles and chylomicrons, thus limiting their inability to penetrate the arterial wall and cause foam cell formation [12]. However, there is in vitro evidence that triglyceride rich lipoproteins (TRL) can accumulate in the artery wall due to impaired clearance, mediated by associated proteins, for example, apo C-III. Accumulation of TRLs and their remnants also has been shown to induce cytokine mediated, pro-atherogenic responses in the vascular wall, a key step in the formation of atherosclerosis [12–14].

Another important aspect to mention is that triglyceride levels are closely tied to the fasting state. While cholesterol levels only show modest postprandial variations, triglycerides show significant post-prandial elevations depending on dietary contents [15–17]. This is interesting, as the levels of post-prandial triglycerides may have an effect on cardiovascular disease. In clinical practice, triglyceride levels are usually measured in a fasting state, and most trials have used this as a standard. Several studies have looked at the value of non-fasting triglyceride levels. In 2007, Bansal et al. published data from 26,509 healthy US women from the Women's health study. In this review, the association between fasting and non-fasting lipid levels and cardiovascular events was studied. Interestingly, while non-fasting triglyceride levels showed a weak independent relationship with cardiovascular events after adjusting for traditional risk factors including cholesterol and insulin resistance, non-fasting triglyceride levels showed a strong independent relationship with cardiovascular events, even after adjusting for confounding risk factors [18]. Similarly, another large cohort study looked at non-fasting triglyceride levels of 7587 women and 6394 men from Copenhagen, Denmark between 1976 and 2004. The data also show that elevated non-fasting triglyceride levels are associated with increased risk for myocardial infarction, ischemic heart disease, and even death [19]. This suggests that both an individual's response of triglyceride levels to dietary intake and fasting levels likely give us important additional information on the patient's future risk for cardiovascular events.

With the knowledge of increased risk with elevated triglyceride levels, how should this affect our current practice? This topic is of particular importance in our current western society as elevated triglyceride levels, along with factors such as insulin resistance, diabetes, low HDL-c, obesity, and hypertension are on the rise. Between 1988 and 2010, National Health and Nutrition Examination Survey (NHANES) not only showed a clear trend toward increasing TG levels, but also revealed that 47% of the US population had TG levels >150 mg/dl, with only a small number of individuals ($<1\%$) had TG levels >500 mg/dl. This is in sharp contrast to average cholesterol levels. The latter have been declining during the same time, likely as a consequence of increased awareness, better screening, effective therapies, and clear guidelines [20–22].

Statins are the most important lipid-altering agents at present and have been shown in large trials to be highly effective in reducing cardiovascular events [23,24]. The recently published 20-year follow-up data of the West of Scotland Coronary Prevention Study (WOSCOPS) emphasized this finding and also proved that statins are very safe for long term use [25]. Based on this large body of evidence, statins are currently recommended by the guidelines as the first choice of agents for patients at high risk for cardiovascular events, regardless of the cholesterol level. While statins do decrease cholesterol substantially, they may also achieve a modest reduction of triglycerides. In a subgroup analysis of the Prove-It TIMI 22 trial, a statin secondary prevention trial, atorvastatin at a dose of 80 mg daily was shown to achieve a 22.8% reduction in triglyceride levels. While the primary outcome of this trial showed a reduction in recurrent CVD events in patients treated to a LDL-c <70 mg/dl, the subgroup of patients who continued to have TG level >150 mg/dl had an increased risk for future cardiac events, despite achieving low LDL-c levels [26]. Since elevated triglyceride levels seem to be associated with increased risk, even in patients on optimal treatment with statin therapy, it only makes sense that trials are performed that target TG lowering on top of statin therapy.

Besides statins, there are currently 3 agents used for TG lowering. In no particular order, there are fibrates; for example, fenofibrate and bezafibrate; nicotinic acid (Niacin) containing agents, and n-3 polyunsaturated fatty acids. Unfortunately, clinical trials that evaluated the use of these agents in addition to optimal statin therapy for cardiovascular event reduction failed to show additional benefit.