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Expert's Opinion

Triglyceride: Current Status in Cardiovascular Disease

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Introduction

In the process of developing treatment for dyslipidaemia, low-density lipoprotein cholesterol (LDL-C) has been the prime target, and the impressive potency of statins in reducing LDL-C made the therapy relatively straight forward. High-density lipoprotein cholesterol (HDL-C) was the next target, but all the trials failed to show clinical benefit though successfully elevating HDL-C level. Triglyceride (TG) remained out of focus, partly because its contribution to cardiovascular disease (CVD) was not clear.

Today, it is generally agreed that TG level of 2 to 10 mmol/L (1 mmol/L=88.57 mg/dL) confers increased CVD risk, and level above 10 mmol/L increases chance of acute pancreatitis. However, statin remains the mainstay of treatment even for elevated TG level. Life style management plays a more crucial role in controlling TG than LDL-C. Also, secondary causes of high TG are important and must be excluded before initiating targeted pharmacotherapy.

Available options are fibrates, niacin, fish oil and saroglitazar and many others targeted and general drugs are being investigated. Except for the recent success with highly purified omega 3 fatty acid, no other TG lowering strategy has shown clear benefit for CVD.

Role of TG in CVD is re-evaluated with the concept of subclasses of LDL-C and HDL-C and the pathogenic role of TG in promoting the harmful sub-particles.

Evidence of Pathogenic Role of Triglycerides

The focus of investigation was always to reduce LDL-C, primarily with statin, and to find out the associated CVD benefit. But most of the major trials excluded patients with high TG at baseline and so role of TG in CVD could not be explored. In the Scandinavian Simvastatin Survival Study (4S) TG >227 mg/dL, in the Cholesterol and Recurrent Events (CARE) trial TG >350 mg/dL and in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial TG >455 mg/dL were exclusion criteria.

TG level, as opposed to LDL-C or HDL-C levels, varies with the prandial state. Meta-analyses of TG trials confirm that high levels of both fasting and nonfasting levels of TG are correlated with increased risk of CVD even after adjustment for HDL-C. However, the post prandial TG level is not standardized both in terms of methodology and normal values.

In a meta-analysis of 17 studies (>55,000 patients), it was found that for every increase in TG level of 89 mg/dL, CVD risk increased by 32% in men and 76% in women.[1]

Data was collected from 594,701 workers (428,334 males and 166,367 females) from all Spanish geographical areas and a cardiovascular risk assessment was performed. The risk of CVD tended to increase as the level of TGs increased, independently of age, sex, smoking, hypertension, diabetes, non-HDL-cholesterol and HDL-cholesterol.[2]

In the combined data derived from the Copenhagen City Heart Study and the Copenhagen General Population Study, increased risks for nonfasting TG of 6.6 mmol/L versus 0.8 mmol/L, after age and sex adjustment, were 5.1 (95% confidence interval, 3.5-7.2) for myocardial infarction (MI), 3.2 (2.5-4.1) for ischaemic heart disease (IHD), 3.2 (2.2-4.7) for ischemic stroke and 2.2 (1.8-2.7) for all-cause mortality.[3,4]

In a recent analysis, TG-rich lipoprotein cholesterol (TRL-C) and small dense LDL-C (sdLDL-C) were measured in baseline samples of 976 subjects. Risk of association was evaluated for total CVD including MI, ischemic stroke, peripheral

vascular disease (PVD) and CVD death, and individual components. The risk of both composite outcomes increased across quartile of TRL-C and sdLDL-C. TRL-C was significantly associated with MI and peripheral artery disease (PAD) while sdLDL-C was associated with MI only. Both markers were a weak association with ischemic stroke. Findings from this analysis suggest that the cholesterol content of TRL and sdLDL influence atherogenesis independently of LDL-C levels and they have potentially different effects on different vascular beds.[5]

Genetic studies also support the role of elevated TG with CVD risk. A Mendelian randomization study of genetic variants which affect the levels of remnant cholesterol or HDL-C, showed that an increase of 1 mmol/L in remnant cholesterol increased the risk of IHD by 2.8-times independent of HDL-C level.

Many pharmaco-intervention studies looked into this issue.

In the Helsinki Heart Study (1987), 4081 men in primary prevention set up were given gemfibrozil versus placebo. In 5 years, the primary end points of MI/CV death were reduced by 34% ($p<0.02$) with gemfibrozil.[6]

In the Veterans Affairs HDL Intervention Study (VAHIT) in 1999, 2531 men with coronary heart disease (CHD) were given gemfibrozil versus placebo. In 5.1 years follow up, primary endpoints of non-fatal MI and fatal coronary heart disease (CHD) were reduced by 20% ($p<0.0006$) with treatment. Unfortunately, because of hepatic toxicity, gemfibrozil did not get popularity and soon was replaced by fenofibrate.[7]

In 2004, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9795 statin-naïve diabetic patients received fenofibrate or placebo. The primary end points of CHD were similar. But there was a 14% reduction of CHD ($p=0.02$) when base line HDL-C was low (<40 mg/dL for men and <50 mg/dL for women).[8]

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial, 5518 diabetic patients on simvastatin were given fenofibrate versus placebo. In 4.7 years follow up, primary end points of CV death/non-fatal MI/non-fatal stroke were similar. Again, there was signal of benefit when baseline TG was above 204 mg/dL and HDL-C was below 34 mg/dL ($p=0.057$).[9]

In the Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial (REDUCE-IT) published in 2018, 8179 patients with either established cardiovascular, cerebrovascular or PVD (secondary prevention cohort) or with diabetes and one other risk factor for CVD (primary prevention cohort) were randomized to get 2 gm twice daily of icosapent ethyl to reduce TG versus placebo. All patients had fasting TG between 150 to 500 mg/dL (lower limit changed to 135 and 200 mg/dL at some points). All patients had LDLC 40 to 100 mg/dL on statin +/- ezetimibe. Baseline TG was 216 mg/dL in both arms, and after 1 year, 175 mg/dL in treatment arm and 221 mg/dL in placebo arm. Primary composite endpoint of CV death, MI, stroke, unstable angina and coronary revascularization was reduced by 25% (95% CI, 0.68-0.83) compared to placebo in 5 years in the treatment arm with a number needed to treat (NNT) of 21 and p value of 0.00000001. All the components also were significantly lower. No significant difference was observed in any other lipoprotein component except TG. However, there were more gastrointestinal side effects and atrial fibrillation in the treatment arm.[10]

The STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia (STRENGTH) trial aspired to look into safety and efficacy of fish oil (a mixture of eicosapentaenoic acid and decosahexaenoic acid) versus placebo in reducing CV events in 13086 patients of mixed dyslipidemia (TG=175-499 mg/dL and low HDL-C) on optimum statin therapy. But the trial was discontinued prematurely in January 2020 due to low chance of getting a beneficial result.[11]

Atherogenic Diabetic Dyslipidaemia

Atherogenic diabetic dyslipidaemia (ADD) describes a pattern of dyslipidaemia commonly associated with diabetes and characterized by high TG, low HDL-C, high TGL-C, high remnant lipoprotein, high lipoprotein/Lp(a) and relatively normal LDL-C. It is postulated that this pattern of dyslipidaemia is highly atherogenic due to the higher level of sdLDL-C particles which easily enter the vascular subendothelial layer via the intercellular gaps in the endothelium, thus initiating the inflammatory macrophage reaction which acts as the nidus of atherosclerosis.

In the United Kingdom Prospective Diabetes Study (UKPDS), in T2DM patients, all the three parameters, i.e., high LDL-C and TG and low HDL-C, have been shown to be equally significantly associated with CV events.[12]

As India is the global capital of diabetes, ADD plays an important role in the premature and rampant atherosclerotic cardiovascular disease (ASCVD) which characterizes IHD in India. It has been found that 85.5% of Indian males and 97.8%

Indian women with type 2 diabetes (T2DM) had dyslipidaemia. In the ICMR-INDIAB study which covered population of four states, of the subjects studied, 13.9% had hypercholesterolemia, 29.5% had hypertriglyceridemia, 72.3% had low HDL-C, 11.8% had high LDL-C levels and 79% had abnormalities in one of the lipid parameters.[13]

Management of Hypertriglyceridaemia

In India it is recommended to measure the fasting TG level as post prandial values are not standardized. Usually fasting levels are 27 mg/dL lower than the 2 hour post prandial value after a standard meal. But it is recognized that it may be difficult to get patients in fasting state in Indian clinical set up.

Unless the baseline TG is above 500 mg/dL, and especially above 850 mg/dL, which increases risk of acute pancreatitis, pharmacotherapy to lower TG should wait till the secondary causes of hypertriglyceridaemia are excluded.

In diabetic patients, glycaemic control is very important. Other important causes include hypothyroidism, nephritic syndrome, chronic liver disease, alcoholism and some drugs like estrogen, thiazides, beta blockers, etc.

Dietary modification can have a big impact on serum TG level as opposed to other lipoprotein fractions. Refined carbohydrates, especially fructose, increase TG level as also alcohol. Total calorie restriction and control of obesity are also important. Thirty to sixty minutes of moderate to heavy exercise at least 5 days a week is also recommended.

Statins variably reduces TG and is the first line of therapy for any type of dyslipidaemia. However, when optimum level of LDL-C is achieved with statin, there is no benefit of increasing statin dose to address the TG issue. If TG is still in the treatable range, i.e., above 150 mg/dl, the available options are to add fibrate or omega 3 fatty acid or saroglitazar, along with continuing statin +/- ezetimibe. Proprotein convertase subtilisin/kexin type-9 inhibitors may reduce TG by 12% only.

In the American College of Cardiology/American Heart Association 2019 lipid guidelines, TG above 175 mg/dL has been positioned as an ASCVD risk enhancer in the primary prevention set up.

The European Atherosclerosis Society/European Society of Cardiology 2019 lipid guidelines recommend icosapent ethyl treatment as class IIa for high risk patients with TG 135 to 499 mg/dL despite statin therapy. In primary prevention set up, fenofibrate or bezafibrate may be given with statin as a class IIb recommendation for TG above 200 mg/dL. However, when fibrate is given with statin, chances of muscle, kidney and liver damages are increased and require close monitoring. Fixed dose combination is to be avoided and the dose of fibrate needs to be kept to the minimum. Fibrates and niacin reduce fasting TG levels by 40-50%. The latter was never used widely due to its unacceptable side effect profile.[14]

Saroglitazar is a novel chemical entity from India which was approved by Drugs Controller General of India for treatment of diabetic dyslipidaemia in 2013. This has minimal side effects and is very compatible with statin. Additionally, it has got recent approval for treating non-alcoholic fatty liver disease or non-alcoholic steatohepatitis which is also commonly associated with ADD.[15]

Future Directions

In the future, several new drugs are being developed specifically aimed at reducing triglycerides. These drugs include apolipoprotein C3 inhibitors and lipoprotein lipase gene replacement therapy. Other new drugs in development have triglyceride-lowering properties among their multiple functions. This group includes microsomal triglyceride protein inhibitors, apolipoprotein B antisense therapies, cholesteryl ester transfer protein inhibitors, diacylglycerol O-acyltransferase-1 inhibitors and peroxisome proliferator-activated receptor agonists.[16]

Conclusion

Hypertriglyceridaemia is established as a CVD risk factor. But LDL-C remains as the primary target for therapeutic intervention. However, different international guidelines are gradually accepting high TG as a target for pharmacotherapy. In India, high TG is even more relevant as a focus of treatment due to very high prevalence of ADD. Most of the available TG specific medicines lack robust evidence of CVD outcome benefit. Some recent breakthrough in this field and future treatment options keep the area pulsating.

Declaration of Conflicting Interest

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