RAISED TRIGLYCERIDES AND RESIDUAL CARDIOVASCULAR RISK

Introduction
A broader view of the clinical entity of hypertriglyceridaemia is essential to developing an understanding of how triglyceride-rich lipoproteins contribute to overall cardiovascular risk. Despite effective lowering of LDL cholesterol, not all cardiovascular events are prevented. This residual risk has once again focused attention on hypertriglyceridaemia and the contribution that triglyceride-rich lipoproteins and their remnants make to atherosclerosis.1

Definition of hypertriglyceridaemia
While there are a number of definitions of hypertriglyceridaemia, a simplified definition provides a convenient basis for clinical action (Table 1).

Table 1. Simplified definition of hypertriglyceridaemia
- Normal: triglyceride concentration <2.0mmol/L
- Mild-to-moderate: 2.0-10.0mmol/L
- Severe: >10.0mmol/L

It is important to understand what the laboratory is actually measuring when they report serum triglycerides. Serum triglyceride levels reflect the sum of the triglyceride content of all lipoproteins. The major contributors to serum triglycerides are chylomicrons (CM - present after meals) and very low density lipoproteins (VLDL). LDL and HDL only contribute a small percentage of the total serum triglyceride content. The triglyceride-rich lipoproteins are therefore CM, VLDL and their remnants.

Understanding the mechanism of hypertriglyceridaemia
It is useful to have a basic understanding of triglyceride-rich lipoprotein (TGRL) metabolism, as illustrated in Figure 1.

Figure 1. Understanding TGRL Mechanism: Metabolic pathway of chylomicrons, VLDL and remnant lipoproteins after fat intake.
Briefly, when a fatty meal is ingested, dietary triglycerides are incorporated into CMs which transport lipids from the intestine to the circulation. In the circulation some of the triglyceride content of CM is hydrolysed by lipoprotein lipase (LPL), leading to the formation of CM remnants. CM remnants are taken up by the liver. The liver exports dietary and endogenously synthesised triglycerides in VLDL particles. VLDL particles undergo LPL-mediated lipolysis in the circulation leading to the formation of VLDL remnants; which can either be further metabolised to LDL particles or be taken up by hepatic receptors.

Multiple mechanisms may lead to hypertriglyceridaemia. One mechanism is overproduction of CMs and/or VLDL. Triglyceride-rich lipoproteins may be overproduced in patients consuming a high fat diet or when medications or alcohol stimulate hepatic VLDL production. Diabetes is also commonly associated with overproduction of VLDL due to high levels of circulating free fatty acids. Impaired clearance is another important mechanism leading to hypertriglyceridaemia and can be seen in conditions such as ageing, hypothyroidism and genetic disorders. A combination of overproduction and impaired clearance is common in most patients with raised triglycerides.

**Genetic basis of hypertriglyceridaemia**

Monogenic hypertriglyceridaemia is rare (one in one million). It usually displays classic autosomal recessive inheritance with high levels of triglycerides (>10mmol/L) from birth and is typically managed within specialist lipid clinics.

Polygenic hypertriglyceridaemia causes moderate to severely elevated triglyceride levels and usually results from an accumulation of deleterious polymorphisms in many genes in the presence of a second factor, such as a metabolic precipitant.

A metabolic precipitant (e.g. becoming diabetic, increased alcohol intake, treatment with steroids or protease inhibitors) may trigger the development of hypertriglyceridaemia (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Secondary causes of hypertriglyceridaemia¹</th>
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<tr>
<td>• Obesity</td>
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<td>• Metabolic syndrome</td>
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<td>• Diet with high positive energy-intake balance; and high fat or high glycaemic index</td>
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<td>• Increased alcohol consumption*</td>
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<td>• Diabetes (mainly type 2 diabetes)</td>
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<td>• Hypothyroidism</td>
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<td>• Renal disease (proteinuria, uraemia, or glomerulonephritis)</td>
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<td>• Pregnancy (particularly in the third trimester)</td>
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<td>• Paraproteinaemia</td>
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<td>• Systemic lupus erythematous</td>
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<td>• Drugs including corticosteroids, oral oestrogen, tamoxifen, thiazides, non-cardioselective β-blockers and bile acid sequestrants, cyclophosphamide, asparaginase, protease inhibitors, and second-generation antipsychotic drugs (e.g. clozapine and olanzapine).</td>
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*Although the range is variable, the clinical risk of hypertriglyceridaemia is generally thought to increase with more than two units daily for men, and more than one unit daily for women.
Complications of severe hypertriglyceridaemia

In patients with triglyceride levels >10-15mmol/L, the focus of care is directed to prevention of acute pancreatitis. Severe hypertriglyceridaemia should be viewed as a medical emergency requiring urgent intervention. In South Africa, alcohol abuse is the major cause of pancreatitis followed by gallstones and then, as a third major cause, severe hypertriglyceridaemia. The advent of pancreatitis is unfortunately poorly predictable; some patients never develop pancreatitis despite very high levels of triglycerides (>50mmol/L). Others may develop acute pancreatitis at much lower triglyceride levels.

Patients with hypertriglyceridaemia are also at increased risk of cardiovascular disease. For example, in the Copenhagen Heart Study...

![Figure 2. Hazard ratios for myocardial infarction, ischaemic heart disease, and total death by increasing levels of non-fasting triglycerides. From the Copenhagen Heart Study2](image-url)
Heart Study, patients were divided into cohorts of non-fasting triglyceride levels. Results clearly show that as triglyceride values increased, the risk of myocardial infarctions and ischaemic heart disease events also increased (Figure 2).

It is important to note that triglycerides are a surrogate marker for remnant cholesterol which is highly atherogenic. The role that TGRL remnants may play in the pathophysiology of atherosclerosis is shown in Figure 3.

**Figure 3. Pathophysiology of atherosclerosis.**

Management of severe hypertriglyceridaemia

The general principle of managing patients with severe hypertriglyceridaemia is to identify and control precipitating secondary causes (Table 2). Treatment includes restriction of all dietary fat intake, exercise and weight loss; with fibrates as the first line of therapy. In South Africa fenofibrate and bezafibrate are the most commonly used fibrates. Statins are generally not effective as primary therapy. Although niacin and high doses (3-4g/day) of omega-3 polyunsaturated fatty acids (fish oils) can reduce triglycerides, they are more effective in treating moderate hypertriglyceridaemia. Additionally, niacin therapy is associated with significant side-effects (especially worsening of glycaemia) and niacin has failed to show a beneficial effect on cardiovascular outcomes. Omega-3 fatty acids are often expensive, and preparations of sufficient purity are not always available.

If there is no clear precipitating cause (e.g. the patient is lean, non-diabetic and not taking any drugs that may precipitate hypertriglyceridaemia), referral to a lipid clinic is advised as this patient may either have a monogenic form of hypertriglyceridaemia or an unusual cause of hypertriglyceridaemia, such as autoantibodies to proteins involved in lipolysis.

Several new therapies are currently being investigated for management of severe hypertriglyceridaemia. Antisense oligonucleotides directed against ApoCIII have entered phase 3 clinical trials.
Management of moderate hypertriglyceridaemia

Patients with triglyceride levels between 2-10 mmol/L are seen much more commonly in general practice. How to treat high cardiovascular risk patients with residual hypertriglyceridaemia despite adequate statin treatment is a clinical question that is not yet fully answered. Several ongoing clinical trials, such as the STRENGTH study and REDUCE-IT, are focusing on high-dose omega-3 fatty acids added to statins, while another trial (PROMINENT) is evaluating addition of a novel fibrate to statin-based therapy. Figure 4 illustrates the potential role that treating high triglycerides (and thus remnant cholesterol) may play in reducing residual risk. Although both patients have identical levels of LDL cholesterol, the second patient has moderate hypertriglyceridaemia and high estimated remnant cholesterol.

52 year old man
Previous ACS with stent to LAD
Atorvastatin 80mg/d

Because both patients are at very high risk (previous ACS with stent), statin therapy must be optimised and high-intensity statin therapy is required (atorvastatin 40-80mg or rosuvastatin 20-40mg daily).

Evidence for adding a fibrate to statin-based therapy is based currently only on a sub-analysis of the ACCORD trial.3 This post hoc sub-analysis evaluated patients with high triglycerides and low HDL at baseline and showed that addition of a fibrate to simvastatin may reduce cardiovascular event rates in this subgroup. Earlier studies of fibrate monotherapy have been re-evaluated by creating similar high triglyceride and low HDL cholesterol subgroups; and have also shown cardiovascular event reduction with fibrate therapy in these specific subgroups.

“Currently however, there is not enough evidence for unequivocal guideline recommendations on how patients with moderate hypertriglyceridaemia on adequate statin therapy should be treated. The current EAS/ESC guideline states that one may consider adding fenofibrate in patients receiving adequate statin therapy who have triglycerides >2.3 mmol/L (Class IIB, Level C). These patients should ideally be referred to a physician/other specialist to evaluate the benefit/risk of added therapy”, Dr Blom concluded. He added that this advice may change in the next few years as further evidence emerges from current trials.
HYPERTRIGLYCERIDAEMIA AND RESIDUAL CARDIOVASCULAR RISK

Summary of major conclusions

What are the ‘known knowns’? Recommended action is summarised in Table 3. This conclusion stresses that LDL cholesterol should be treated aggressively. In severe hypertriglyceridaemia, fibrate therapy is first-line therapy to prevent pancreatitis.

In patients with moderate hypertriglyceridaemia, fibrates can be considered after achieving LDL cholesterol control and lifestyle intervention. Supporting this approach is the recent announcement of top-line results from the double-blind, randomised, placebo-controlled REDUCE-IT trial. This trial showed that treatment for a median duration of 4.9 years with high-dose EPA (4g/day) results in a 25% reduction in MACE in statin treated patients with raised triglycerides (entry criteria 1.7 to 5.63mmol/L; observed median at baseline 2.44mmol/L) and a previous cardiovascular event or diabetes with at least one additional cardiac risk factor. The median LDL cholesterol at baseline was 1.93mmol/L. This is an important trial as it provides new evidence that an additional therapy that is not primarily focused on LDL cholesterol reduction can lower cardiovascular risk further.

Table 3. The known knowns

| • Treat LDLC (or apoB/non-HDLC) aggressively |
| • Lower LDL cholesterol is better |
|   - Statin therapy ± ezetimibe ± PCSK9i |
| • Severe hypertriglyceridaemia (TG >10mmol/L) |
|   - Fibrates to prevent pancreatitis |
| • Normal TG, normal HDLC |
|   - No fibrates for atherosclerosis prevention |

References
