Hypertriglyceridemia: rationale, design and implementation of the AUSTRIG Registry

Jing Pang¹, Stephen C.H. Li², Dick C. Chan¹, David R. Sullivan³, Ann Marie Woodward⁴, Gerald F. Watts¹,⁴

¹School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Australia
²Core Pathology & Clinical Chemistry, Pathology West, Westmead Hospital, NSW Health Pathology, Westmead
³Department of Chemical Pathology, Royal Prince Alfred Hospital, NSW Health Pathology, Camperdown;
⁴Lipid Disorders Clinic, Departments of Cardiology and Internal Medicine, Royal Perth Hospital, Perth, Australia

Address for correspondence
Winthrop Professor Gerald F Watts, School of Medicine, University of Western Australia, Royal Perth Hospital, GPO Box X2213, Perth, WA 6847, Australia.
Tel: +61-8-9224-0245; E-mail: gerald.watts@uwa.edu.au
ABSTRACT

Purpose of review
Hypertriglyceridemia (HTG) is a risk factor for atherosclerotic cardiovascular disease (ASCVD), aortic stenosis, hepatic steatosis and pancreatitis. We briefly review the aetiology and treatment of HTG and familial chylomicronemia syndrome (FCS), as well as the implementation of a clinical quality registry for improving care, the Australian Hypertriglyceridemia (AUSTRIG) Registry.

Recent findings
There is a need to improve the detection of individuals with severe HTG and FCS, who could benefit from more intense and novel treatments to prevent end-organ damage. Patient registries provide valuable data for advancing care of individuals with severe HTG at high risk of acute pancreatitis, steatohepatitis and ASCVD. However, there is a paucity of registries of such patients. We outline the design and implementation of the AUSTRIG Registry.

Summary
Clinical registries can be employed in many ways for improving outcomes for patients with HTG, through the collation and analysis of data for enabling health service planning, clinical trials and audits, and for better informing and empowering registrants.

Keywords
hypertriglyceridemia, design, implementation, registries
KEY POINTS

- Hypertriglyceridemia (HTG) is an under-recognised and under-treated condition, characterised by significantly elevated plasma concentration of triglyceride-rich lipoproteins.

- HTG is a risk factor for atherosclerotic cardiovascular disease (ASCVD), hepatic steatosis and pancreatitis.

- There is a need to improve the detection of individuals with severe HTG who would benefit from more intense and precise treatment to prevent end-organ damage and ASCVD.

- Patient registries are critical for providing valuable data that will help advance care of individuals with severe HTG.

- Data from contemporary HTG registries can inform clinical service planning, clinical trials, clinical audits and best clinical practices for the condition.
INTRODUCTION
Epidemiological and Mendelian randomisation studies suggest that elevated plasma triglyceride concentration, particularly due to accumulation of triglyceride-rich lipoproteins (TRLs) and their remnants, is a causal risk factor for atherosclerotic cardiovascular disease (ASCVD) [1, 2]. However, the significance of hypertriglyceridemia (HTG) is under-recognised, partly owing to overemphasis on low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol. HTG patients are not only at increased risk of ASCVD, but also at risk of aortic stenosis, hepatic steatosis and pancreatitis [2-5]. Hence, early detection and treatment is important to prevent such complications and improve quality of life.

We review contemporary knowledge of the aetiology and management of HTG, with a primary focus on the rationale, design and implementation of the Australian Hypertriglyceridemia (AUSTRIG) Registry.

DEFINITIONS, ASSESSMENTS, AND CAUSES OF HYPERTRIGLYCERIDEMIA
HTG generally refers to a fasting plasma triglyceride concentration above the 95th percentile for age and gender in a population, but clinical definitions for HTG among guidelines [2, 6-8]. Hegele et al simplified the diagnosis into two groups depending on the degree of triglyceride elevation: mild-to-moderate (plasma triglycerides between 2-10 mmol/L, i.e. 175-880 mg/dL) and severe (plasma triglycerides >10 mmol/L, i.e >880 mg/dL) [6]. The most recent guideline from the American College of Cardiology (ACC) provides definition for persistent HTG: mild-to-moderate HTG (fasting triglycerides ≥ 1.7 mmol/L, i.e. ≥ 150 mg/dL, or nonfasting triglycerides between 2.0-
5.6 mmol/L, i.e. 175-500 mg/dL) and severe (fasting triglycerides ≥5.6 mmol/L, i.e. ≥500 mg/dL) [7].

Measurement of the standard lipid profile requires a 9-12 hr fast. This improves the precision of the estimation of triglycerides and calculated LDL-cholesterol by the Friedewald formula. A non-fasting sample may be the best screening test for HTG, however. Non-fasting triglyceride concentrations are reflective of the postprandial state and superior to fasting triglyceride in predicting risk of ASCVD [5]. There is growing consensus that non-fasting samples may be used for screening for dyslipidemias, including HTG [8, 9]. A standardised oral fat meal test is also recommended by expert guideline as a measure used to assess postprandial triglyceride levels [10]. However, the procedure is time consuming and currently most suitable for research studies alone. Non-HDL-cholesterol (i.e. total cholesterol minus HDL-cholesterol) provides a simple index of all the atherogenic, apolipoprotein (apo) B-containing lipoproteins—very-low density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL and lipoprotein(a) [Lp(a)] (Figure 1). Measurement of apoB reflects the total number of atherogenic TRLs and LDL particles. However, apoB measurement does not adequately reflect chylomicron remnants. Direct quantification of remnant cholesterol, apoC-III and apoB-48 can provide valuable information to reflect TRLs, but these assays are not established clinically.

Severe HTG results from chylomicronemia and is considered to have both monogenic and polygenic determinants [1, 6, 11-15]. A subset of these are a rare form (1 to 10 per million) of monogenic HTG called familial chylomicronemia syndrome (FCS) due to mutations in one of at least 6 genes (LPL, APOC2, LMF1, GOPHBP1, APOA5,
G3PDH1). Homozygous or compound heterozygous mutations in these genes drastically impair chylomicrons clearance, leading to severe HTG than can manifest in youth as eruptive xanthomata, lipaemia retinalis and acute pancreatitis [11].

The majority of people in clinics with elevated HTG have multifactorial (or polygenic) HTG [1, 6, 11, 12, 15, 16]. Multifactorial chylomicronemia syndrome (MCS) is much more frequent than FCS, with a prevalence of 1 in 600 of the population, resulting from a combination of a heterozygous variant in the 6 FCS genes and/or accumulated common small-effect triglyceride-raising polymorphisms identified in genome-wide association studies (GWAS), such as APOA1-C3-A4-A5, TRIB1, LPL, MLXIPL, GCKR, FADS1-2-3, NCAN, APOB, PLTP, ANGPTL3. Homozygosity for the APOE2 allele is a necessary cause of type III dysbetalipoproteinemia (1 in 10,000); this condition causes premature atherosclerosis due to accumulation of TRL remnants that are not cleared efficiently by the liver [1, 6]. Environmental and clinical factors (such as overnutrition, lack of exercise, obesity, insulin resistance, diabetes, chronic kidney disease, alcohol excess, glucocorticoids, and oral contraceptives containing oestrogen and pregnancy) also interact with polygenic factors and contributes to HTG [15, 16]. Even in individuals with persistent mild-to-moderate HTG, the most prevalent contributor is an accumulation of polygenic single nucleotide polymorphisms (SNPs) [16]. These are frequent gene variants that alone have a small effect size on triglyceride metabolism, but when stacked together can lead to marked HTG, depending on secondary factors. Figure 2 summarizes the genetic and secondary causes of hypertriglyceridemia.
Clinical characteristics of patients can be used to differentiate FCS from severe HTG or MCS [17, 18]; a diagnostic criteria (FCS score) have also been proposed [18]. However, genetic testing is the gold standard of establishing the diagnosis for FCS.

**HYPERTRIGLYCERIDEMIA, ATHEROSCLEROSIS CARDIOVASCULAR DISEASE AND ACUTE PANCREATITIS**

The role of HTG as an independent causal factor for ASCVD has been controversial. Earlier epidemiological studies and meta-analyses failed to show an independent association between HTG and ASCVD [19, 20]. A reason for this may relate to co-existence of a wide spectrum of traditional risk factors. Also, the much greater day-to-day variability in plasma triglyceride levels than LDL-cholesterol is also likely to weaken the statistical power to identify causality in epidemiological studies. More recently, several Mendelian randomisation studies of variants in genes involved in TRL metabolism have consistently demonstrated that genetically increased remnant cholesterol and apoB-containing TRLs, particularly involving variation in the APOA5 and LPL genes, increase risk of ASCVD events [21-23]. Additionally, recent analyses of real-world clinical data have also shown an association between elevation in plasma triglyceride level and increased risk of all-cause mortality and ASCVD events [24, 25]. An observational analysis from the Copenhagen General Population Study and the Copenhagen City Heart Study has demonstrated that non-fasting plasma triglycerides (≥ 5 mmol/L, i.e. 440 mg/dL) or remnant cholesterol (>2.3 mmol/L, i.e. 89 mg/dL) increases risk for aortic stenosis, ischaemic stroke and myocardial infarction by 1.5 fold, 3-fold and 5-fold, respectively [3, 5, 26]. More importantly, elevated plasma triglyceride has also be shown to predict ASCVD events against background statin therapy [27, 28]. In a meta-regression analysis of randomized controlled statin and
non-statin trials, triglyceride lowering (per 1 mmol/L reduction) is associated with 16% lower risk of major vascular events after adjusting for LDL-cholesterol [29]. The analyses from the Canadian cohort has demonstrated that approximately 25% patients with ASCVD had HTG and LDL-cholesterol in the general population [25].

While the exact mechanism linking HTG to ASCVD is still elusive, there is good evidence that small TRL remnants readily infiltrate the subendothelial space, where they are retained by connective tissue matrix and rapidly phagocytized by arterial wall macrophages, which are then transformed into “foam cells” Furthermore, TRL remnants impair endothelial function, inhibit fibrinolysis, enhance coagulation, and activate monocytes and inflammation. TRL lipolysis also releases toxic products, such as oxidized fatty acids and lyssolecithin, that induce endothelial cell inflammation and coagulation. The atherogenicity of TRLs in HTG is compounded by other qualitative and quantitative changes in lipoprotein metabolism, including accumulation of smaller, denser LDL and HDL particles [2, 16].

Severe HTG is known to increase risk of acute pancreatitis, which accounts for 1-10% of episodes of acute pancreatitis. Mild-to-moderate HTG (non-fasting plasma triglyceride levels ≥5 mmol/L) is associated with 10-fold increase in risk of acute pancreatitis [4]. The mechanism how HTG contributes to the development of acute pancreatitis is unclear, but may principally involve lipotoxicity and low-grade inflammation [4, 30].
THERAPIES FOR HYPERTRIGLYCERIDEMIA AND TREATMENT GAPS

While there are modest differences in the triglyceride cutpoints, the ACC and European Society Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines are aligned in giving strong recommendations for correcting secondary causes of HTG [7, 8]. The first-line of treatment to lower plasma triglyceride is lifestyle modifications including a low-fat diet, avoidance of refined carbohydrates and alcohol, weight loss and increased habitual physical activity. Statins should be the first-line choice of therapy, followed by fibrates and icosapent ethyl (or omega-3 acid ethyl esters). Optimal treatment aims to reduce the risk of pancreatitis and ASCVD [7]. An update to the 2018 American Heart Association (AHA)/ACC multisociety guideline has recently been provided aimed at the management of ASCVD risk in hypertriglyceridemic subjects (plasma triglycerides 150-499 mg/dL), with ASCVD, diabetes without ASCVD, adults without ASCVD or diabetes, and adults with severe HTG ≥5.6 mmol/L (i.e. ≥500 mg/dL) [7]. The first three basic principle is implementing lifestyle measures and LDL-cholesterol lowering therapies, in particular statins, to achieve target LDL-cholesterol, followed by omega-3 fatty acids (icosapent ethyl or omega-3 acid ethyl esters) to reduce risk of pancreatitis. For the group without ASCVD and diabetes, statin therapy is only recommended in those with high absolute risk of ASCVD.

The management of severe HTG is summarized in Figure 3. In adults with persistent fasting plasma triglycerides between 5.6-11.3 mmol/L (i.e. 500-999 mg/dL) (Figure 3A), the initiate approach is to implement low-fat diets followed by fibrate therapy or prescription of omega-3 fatty acids. Among patients aged 40-75 years with 10-year ASCVD risk >5%, ASCVD or diabetes, initiation or intensification of statin therapy is
recommended. In adults with plasma triglycerides \(\geq 11.3\) mmol/L (i.e. \(\geq 1000\) mg/dL) (Figure 3B), the initial step is to implement a very-low fat diet (<5% of total calories as fat) to achieve triglyceride levels \(\leq 11.3\) mmol/L (i.e. \(\leq 1000\) mg/dL), with optimization of lifestyle factors (e.g. exercise) and correction of insulin resistance and dysglycemia, as indicated. Fibrate and omega-3-fatty acids should be considered to reduce risk of pancreatitis. Statin initiation or intensification in appropriate patient management groups are also recommend. A particular difference with the EAS guidelines is that in patients on statin therapy with residual HTG, fibrates should also be considered [8].

Recent GWAS and Mendelian randomization studies have demonstrated a causal role of apoC-III and angiopoietin-like protein 3 (ANGPTL3) in the development of HTG and ASCVD [31]. These proteins may be targeted with RNA-based therapeutics, such as antisense oligonucleotides (ASOs) and small interfering RNA (siRNA), or with monoclonal antibody (mAb) [32, 33]. For example, ligand-conjugated ASOs (e.g. volanesorsen) and siRNA (e.g. ARO-ANG3) therapies work by inhibiting the mRNA transcripts of ANGPTL3, halting its translation and resulting in mRNA degradation [34, 35]. By contrast, evinacumab is a fully human IgG4 mAb that specifically inhibits ANGPTL3 in the circulation [36]. Both can lower plasma triglyceride concentrations by more than 70% [34-36]. However, data on long-term efficacy, safety, and cost-effectiveness of these potent and selective treatments in mitigating multiple health risks of HTG is required in future large clinical trials.

Although highly prevalent [37], the health impact of elevated triglyceride is overshadowed by LDL-cholesterol, and awareness of the condition is low [38]. A recent population-based study showed that control of plasma triglyceride levels is sub-
optimal in the majority of patients not attaining the treatment targets [38]. This under-recognition and under-treatment predisposes many people to the sequelae of HTG, underscoring a need for implementation of better care.

**CLINICAL REGISTRIES FOR DYSLIPIDEMIA: FH PARADIGM**

Clinical quality registries are essential components for models of care for high impact dyslipidemias [39]. Registries capture relevant clinical and molecular patient data that are rich sources of information essential for the integration of research into clinical practice. Several patient registries of genetic lipid disorders, classically FH registries, have been developed [40-42]. The general aims of these registries are to characterize the at risk patient population and monitor their progress throughout the continuum of care. Registries also function to provide valuable information regarding the prevalence and geographical distribution of major lipid disorders over time. This type of information helps to promote and disseminate new knowledge to inform best clinical practice, and to guide healthcare planning. Such registries are highly pertinent to a condition like HTG, particularly in patients with severe and mild-to-moderate forms of the condition, such as FCS and MCS.

**CLINICAL REGISTRIES FOR HYPERTRIGLYCERIDEMIA**

A literature search revealed the existence of three registries specifically for HTG. In the HTG registry of the Spanish Atherosclerosis Society (SEA), patients with HTG (plasma triglycerides ≥2.3 mmol/L on at least two separate occasions, regardless of their cholesterol levels) of both genders and any age, referred to the Lipid Units of SEA for the screening and treatment of HTG are registered [43, 44]. The Spanish registry has demonstrated that HTG is associated with a high prevalence of the
metabolic syndrome and diabetes [43], as well as ASCVD [44], compared with their general population. The purpose of the National Lipid Association (NLA) patient registry for patients with severe HTG is to assist researchers in the planning of clinical trials for assessing the efficacy of new therapies. Patients with FCS, familial lipoprotein lipase (LPL) deficiency and Type I hyperlipoproteinemia are eligible for registration [45]. There is also a global prospective registry called GENIALL in LPL deficiency which collects physician and patient generated data on the natural course of LPL deficiency, as well as long-term outcomes of gene therapy [46].

PURPOSE, DESIGN AND IMPLEMENTATION OF THE AUSTRIG REGISTRY

Purpose

The AUSTRIG Registry provides a high-level blueprint for other centres to develop and implement their own HTG registry. We intend this registry to ultimately improve the care (i.e. detection and treatment) of patients with HTG. The specific aims of this HTG registry are, 1) to enrol patients with persistently elevated triglycerides who are at risk of acute pancreatitis, hepatic steatosis and ASCVD; 2) to utilise the data to improve service planning by analyses and collection of data on prevalence, genetic variants, clinical features, clinical management and patient outcomes; 3) to employ the data to validate a clinical scoring system for the diagnosis of FCS in an Australian population; and 4) to enable recruitment of patients for clinical trials of new treatments for HTG. Such a clinical registry serves as an attention directing tool for increasing awareness, improving documentation and enhancing the care of at risk patients.

The development of a HTG registry should ideally involve a coalition between clinic networks, research groups, healthcare organizations and patients [47, 48]. Browser-
based, modular architecture and in-built security features are the key technical components required to meet the demands of effectively deploying a registry.

**Design and construction**

REDCap (Research Electronic Data Capture) was chosen as the registry application. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources [47, 48]. The registry structure was designed based on discussions held with practising clinicians and researchers, and the database was subsequently constructed within REDCap. **Table 1** provides a list of the data elements included in the HTG registry. These include demographic, anthropometric, biochemical and lifestyle parameters, as well as information on current medications, cardiometabolic risk factors and genetic testing for lipid disorders. This information is important for evaluation of the prevalence, genetic characteristics, ASCVD risk factors and clinical management of patients.

**Patient recruitment**

Participation in the HTG registry is voluntary with prospective consent obtained at the time of registration. Patients with persistent HTG diagnosed (fasting plasma triglycerides >1.7 mmol/L (i.e. >150 mg/dL) on at least two separate occasions) and managed through the Lipid Disorders Clinic at Royal Perth Hospital (RPH) in Western Australia are invited to join the registry. The selection of fasting triglyceride levels >1.7
mmol/L (>150 mg/dL) is based on recent expert consensus that ASCVD risk becomes clinically relevant [7]. The establishment of the registry was approved by the RPH Human Research Ethics Committee (RGS 4624) and there are no costs to participants to join the registry.

**Data capture and management**

Data are collected and managed using the REDCap electronic data capture tool hosted by the Government of Western Australia, Department of Health [47, 48]. A coordinator oversees the development, management, modifications and implementation of the registry. Currently, more than 90 patients have been registered through REDCap.

**Future directions**

The registry does not currently include children. Although most HTG disorders present in adulthood, some can manifest earlier secondary to genetic predisposition and cardiometabolic factors, such as obesity and insulin resistance [49]. Recruitment of patients to the registry is principally co-ordinated by the lipid disorders clinic. Collaboration with the diabetic clinic and gastrointestinal surgery and intensive care units (for patients with acute pancreatitis) is also recommended to enhance identification of cases with more severe HTG.

**Considerations for implementation**

We are at the stage of developing a full set of implementation strategies not only for the AUSTRIG Registry, but also for the care of HTG. Implementation science practice currently provides the cornerstone for addressing gaps in delivery of health care and
enhances the utilization of clinical recommendations made in best practice guidelines [50]. Management of HTG may be improved by several implementation strategies directed at community, policy, healthcare practitioner and patient level. A taxonomy of implementation strategies may be adopted [51]: these include training and educating stakeholders, engaging consumers and patient advocates, adapting care to existing infrastructure, developing and fostering stakeholder relationships, using evaluative and iterative strategies, and providing technical support for clinicians and allied health staff. The AUSTRIG Registry clearly fulfills an implementation role that will improve the care of patients with HTG. Equally, specific strategies are required to develop the implementation of the registry itself. These include the training of users, obtaining support of consumers and patient advocates, developing the interoperability of the registry platform, providing local technical assistance and information technology support, and securing ongoing finance for the maintenance of the registry platform and employment of core staff. The development of strong stakeholder interrelationships should enable maximal use of the registry data for clinical audits and discussion at multidisciplinary team meetings. A strong governance structure, employing a skilled registry board is essential. The ultimate aim of implementation practice is behaviour change. If the AUST RIG Registry can be employed to achieve this by motivating capable staff to better manage patients with HTG, the worth of such an initiative will be confirmed.

CONCLUSION

There is a need to improve detection and management of individuals with HTG. This applies particularly those with FCS and severe HTG who would benefit from more intense and precise treatment. The design and development of the AUST RIG registry
encompasses key features that should be considered when choosing a system for building a secure and compendious registry. This registry can be readily expanded into a national and global registry for HTG that allows harmonization of data collection across different states and countries, or adapted to include other lipid disorders with high clinical impact, such as familial combined hyperlipidemia and elevated Lp(a).
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**LEGENDS**

**Table 1.** Data elements for AUSTRIG Registry

**Figure 1.** Assessment of lipoproteins associated with hypertriglyceridemia. Remnant-cholesterol in plasma is the sum of cholesterol in triglyceride-rich lipoproteins (chylomicrons, chylomicron remnants, very-low-density lipoproteins and intermediate-density lipoproteins). Non-HDL-cholesterol concentration in plasma is the sum of cholesterol in triglyceride-rich lipoproteins and low-density lipoproteins (including lipoprotein(a) particles).

**Figure 2.** Genetic and secondary causes of hypertriglyceridemia

**Figure 3.** Expert consensus decision pathway for management of severe hypertriglyceridemia in adults aged >20 years with plasma triglyceride between 5.6-11.3 mmol/L (A) and ≥11.3 mmol/L (B), from the American College of Cardiology [7].
REFERENCES

Papers of particular interest, published within the annual period of review, have been highlighted as:

▪ of special interest
▪▪ of outstanding interest


▪ A recent review on the role of pathophysiological and clinical aspects of triglyceride-rich lipoproteins in the development and management of atherosclerotic cardiovascular disease.


- A pragmatic consensus statement from the American College Cardiology (ACC) providing up-to-date guidance on the management of patients with at risk atherosclerotic cardiovascular disease and pancreatitis.


• An excellent review on the genetic causes of hypertriglyceridemia, with a focus on its polygenic aetiology.


   - Real-world data demonstrating a significant association between moderate-to-severe elevation of plasma triglyceride levels and increased risk of all-cause mortality and ASCVD events in a large Italian population.

   - Real-world clinical data showing that 25% of individuals with atherosclerotic cardiovascular disease have hypertriglyceridemia despite controlled LDL-cholesterol.


• An up-to-date review on the use of novel therapies for correcting hypertriglyceridemia through targeting apoC-III and ANGPTL3; registry patients are a good source of participants for new trials.


- Important trial showing that inhibition of hepatic apolipoprotein C-III synthesis with volanesorsen significantly reduced triglyceride concentrations in patients with multifactorial chylomicronemia leading to reduction in the risk of acute pancreatitis.


- An up-to-date review on the use of RNA-based therapeutics targeting ANGPTL3 for dyslipidemias.


- Population-based study showing that primary isolated hypertriglyceridemia is relatively prevalent (0.8%), but only 46% of cases are on lipid-lowering medication, with only 26% attaining desirable triglyceride levels, underscoring underdiagnosis and undertreatment of hypertriglyceridemia.

Good review of the gap between lipid guidelines and lipid management in clinical practice, with a focus on recent studies employing lipid registries and carried out in real-world clinical settings.


