The Forgotten Lipids: Triglycerides, Remnant Cholesterol, and Atherosclerotic Cardiovascular Disease Risk

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ABSTRACT Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death worldwide. Low-density lipoprotein cholesterol (LDL-C) is a well-established mediator of atherosclerosis and a key target for intervention for the primary and secondary prevention of ASCVD. However, despite substantial reduction in LDL-C, patients continue to have recurrent ASCVD events. Hypertriglyceridemia may be an important contributor of this residual risk. Observational and genetic epidemiological data strongly support a causal role of triglycerides (TGs) and the cholesterol content within triglyceride-rich lipoproteins (TGRLs) and/or remnant cholesterol (RC) in the development of ASCVD. TGRLs are composed of hepatically derived very low-density lipoprotein and intestinally derived chylomicrons. RC is the cholesterol content of all TGRLs and plasma TGs serve as a surrogate measure of TGRLs and RC. Although lifestyle modification remains the cornerstone for management of hypertriglyceridemia, many novel drugs are in development and have shown impressive efficacy in lowering TG levels. Several ongoing, randomized controlled trials are underway to examine the impact of these novel agents on ASCVD outcomes. In this comprehensive review, we provide an overview of the biology, epidemiology, and genetics of TGs and ASCVD; we discuss current and novel TG-lowering therapies under development. ***(Endocrine Reviews 40: 537 – 557, 2019)***

Elevated low-density lipoprotein (LDL) cholesterol (LDL-C) is a well-known risk factor for atherosclerotic cardiovascular disease (ASCVD) and is the primary target of therapy for primary and secondary prevention, according to national and international guidelines (1–3). Observational and genetic epidemiology consistently demonstrate that individuals with low plasma levels of LDL-C over the life course have lower rates of ASCVD compared with those with average or high levels of LDL-C (4–8). Moreover, the introduction of the statins 30 years ago provided the critical evidence linking substantial lowering of LDL-C levels to substantial reductions in ASCVD events (9). However, despite reductions in LDL-C levels with statins and newer lipid-lowering agents, substantial residual risk persists, with the majority of predicted first and recurrent ASCVD events not being averted (10). A growing amount of evidence suggests that triglycerides (TGs) and/or the cholesterol content within triglyceride-rich lipoproteins (TGRLs) may contribute to this residual risk (11). This notion is of particular interest because the burgeoning epidemics of obesity, metabolic syndrome, and diabetes are associated with a dramatic increase in the prevalence of hypertriglyceridemia and its potential intersection with ASCVD (12).

Historically, the relationship between TGs and ASCVD has been controversial. Hypertriglyceridemia is frequently associated with concomitant lipoprotein alterations such as decreased high-density lipoprotein (HDL) cholesterol (HDL-C) levels and elevated levels of non–HDL-C; small, dense and total LDL particles; intermediate-density lipoprotein (IDL); and total apolipoprotein CIII (apoCIII), all of which are associated with increased ASCVD risk (13). All this may confound the causal association between elevated TG levels and ASCVD. In addition, equivocal clinical trial results of TG-lowering therapies have raised the question as to whether TGs represent a surrogate for other causal mechanisms at play for atherosclerotic disease (12, 14–16). Much of the emphasis over the past decade centered on the inverse relationship of

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ESSENTIAL POINTS

- Despite substantial reduction in low-density lipoprotein cholesterol, patients continue to have recurrent atherosclerotic events
- Hypertriglyceridemia maybe an important contributor of this residual risk
- Observational and genetic epidemiological data strongly support a causal role of triglycerides and the cholesterol content within triglyceride-rich lipoproteins and/or remnant cholesterol in the development of atherosclerotic cardiovascular disease
- Although lifestyle modification remains the cornerstone of management of hypertriglyceridemia, many novel drugs are in development and have shown impressive triglyceride-lowering efficacy.
- Several ongoing, randomized controlled trials are under way to examine the impact of these novel agents on atherosclerotic cardiovascular disease outcomes

HDL-C and ASCVD, with large-scale efforts aimed at elucidating the role of HDL in atheroprotection. However, evidence from Mendelian randomization studies and a series of failed randomized controlled cardiovascular (CV) outcomes trials suggests that HDL-C, although a useful biomarker of risk, may not be a causal risk factor for ASCVD (11, 17–22). These findings have led to a renewed interest in the role of TGs and/or remnant cholesterol (RC) in the development of vascular disease. In this review, we discuss the epidemiology, genetics, and biology of TGRLs, RC, and ASCVD, and provide an overview of current and novel TG-lowering therapies under development.

Population Distribution and Causes of Hypertriglyceridemia

Hypertriglyceridemia is commonly defined as a fasting serum TG level ≥150 mg/dL (1.7 mmol/L) (12). TG levels are classified as follows by the Adult Treatment Panel III of the National Cholesterol Education Program (23): borderline high (150 to 199 mg/dL), high (200 to 499 mg/dL), and very high (≥500 mg/dL). In the general population, TG distribution is skewed with a tail toward the highest levels compared with normal distribution of other lipid parameters such as total cholesterol, LDL-C, and HDL-C (24). Data from the National Health and Nutrition Examination Survey demonstrated that approximately 31%, 16.2%, and 1.1% of the adult US population had TG levels ≥150 mg/dL, ≥200 mg/dL ,and ≥500 mg/dL, respectively (12, 25). Mexican Americans have the highest prevalence of hypertriglyceridemia across all categories of TG levels, followed by non-Hispanic whites and non-Hispanic blacks (12, 25). Hypertriglyceridemia is a well-known cause of acute pancreatitis. Typically, the risk of acute pancreatitis increases progressively with fasting TG levels >500 mg/dL, with a substantial increase when TG levels exceed 1000 mg/dL. The lifetime risk of pancreatitis is about 5% and 10% to 20% with fasting TG levels >1000 mg/dL and >2000 mg/dL, respectively (26). At these levels, chylomicrons are usually the main carriers of TG in plasma. Severe hypertriglyceridemia is associated with hyperviscosity in the pancreatic capillaries, which leads to ischemia and release of pancreatic lipases and toxic free fatty acids (FFAs) that cause inflammation and pancreatitis (27, 28).

Hypertriglyceridemia occurs because of increased TG production, altered processing and catabolism of TGRLs, or reduced clearance. Moderately elevated TG concentrations are commonly due to suboptimal lifestyle habits, including diets enriched in simple carbohydrates and/or saturated fats, excess alcohol consumption, obesity, and sedentary behavior. Excess alcohol consumption is associated with increased adipocyte lipolysis and flux of FFAs to the liver, resulting in increased very-low-density lipoprotein (VLDL) production (29). Other secondary causes of hypertriglyceridemia include pregnancy, hypothyroidism, chronic kidney disease, poorly controlled diabetes and/or metabolic syndrome, and medications (11, 30). In pregnancy, plasma TG levels can increase two- to fourfold during the third trimester owing to physiologic hormonal changes and are generally not clinically important (31). Increase in estrogen levels during the third trimester stimulates hepatic VLDL secretion and reduces the clearance of TGs by lipoprotein lipases (LPLs) in the liver and adipose tissues resulting in elevated TG levels (31). Thyroid hormone is an important regulator of LPL activity and elevated TG levels in hypothyroidism are due to decreased LPL activity (32). Patients with chronic kidney disease frequently have elevated TG levels due to diminished activity of LPL, reduced clearance of TGRL, and increased VLDL secretion (12). The attenuation of LPL activity is largely due to increased concentrations of apoCIII, an endogenous inhibitor of LPL, observed in uremic states (33).

Atherogenic dyslipidemia, a combination of moderate hypertriglyceridemia; prevalence of small, dense LDL particles; and low HDL-C, is observed in 35% and 40% of individuals with type 2 diabetes mellitus (T2DM) and metabolic syndrome, respectively (34, 35). Insulin resistance associated with obesity, metabolic syndrome, and T2DM is a key predisposing factor for hypertriglyceridemia. Insulin plays a key role in the regulation of apolipoprotein (apo) B metabolism, in which it stimulates degradation of newly synthesized apoB, limiting VLDL formation (36). However, derangements in the insulin signaling pathway leading to inhibition of apoB degradation is one of the proposed mechanisms for hypertriglyceridemia in insulin-resistant states such as obesity, metabolic syndrome, and T2DM. Furthermore, in the insulin-resistant state, increased adipocyte lipolysis results in increased FFA flux to the liver, which also fuels the lipidation of apoB leading to increased VLDL production and *de novo* hepatic lipogenesis (36). This increased flux of FFA in the circulation also enhances intestinal chylomicron secretion leading to elevated TG levels (12).

In addition to the many secondary causes of increased TG levels, mutations in at least six genes [*i.e.*, *LPL*, apolipoprotein A5 (*APOA5*), *APOC2*, (*LMF1*), glycerol-3-phosphate dehydrogenase 1 (*GPD1*), glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein-1 (*GPIHBP1*)] involved with VLDL/chylomicron clearance can also result in severe hypertriglyceridemia (37). A purely monogenic disorder is rare but should be considered when severe hypertriglyceridemia is present and first diagnosis dates back to early childhood. More commonly, the genetic basis for moderate to severe hypertriglyceridemia is polygenic, which can synergize with environmental factors to profoundly alter TG/VLDL production and clearance (38, 39). Table 1 summarizes the genetic, nongenetic, and drug-related causes of hypertriglyceridemia.

TG Metabolism

Circulating lipoproteins contain both cholesterol and TGs. Although HDL and LDL predominantly transport cholesterol, VLDL, chylomicrons, and their remnants are enriched in TGs. These TGRLs represent a heterogenous group of lipoproteins of varying size, density, protein cargo, and core lipid composition. TGRLs are derived via two routes: an endogenous (hepatic) pathway and an exogenous (intestinal) pathway (Fig. 1) (41).

In the endogenous pathway, VLDL is produced in the endoplasmic reticulum (ER) of hepatocytes by constitutive synthesis of apoB100 with concomitant lipidation via microsomal triglyceride transport protein (MTP). The FFAs for lipidation are derived from the circulation (FFA released from adipocytes and uptake of chylomicron or VLDL remnants) or newly synthesized in the liver (36). Subsequently, a variety of apolipoproteins are added to the surface of the nascent VLDL particle during secretion, including ApoCI, apoCII, apoCIII, and apoE. Once VLDL particles are secreted into the plasma, LPL along the luminal surface of capillaries hydrolyzes the TGs within the core of VLDL particles into FFAs, which can then be taken up by myocytes and adipocytes. As FFAs are liberated from VLDL, these TGRLs are remodeled both physically (become smaller by shedding FFAs and surface phospholipids) and chemically (become relatively cholesterol enriched) to become smaller and denser VLDL and IDL particles (13, 41). These IDL particles can be further catabolized to generate LDL. The constitutive production and regulation of hepatic apoB plays a key role in VLDL synthesis and secretion, and safeguards against hepatic steatosis. On the other hand, genetic or therapeutic antagonism of apoB production can lead to hepatic steatosis through suppression of VLDL secretion (36). Incomplete lipidation of apoB by MTP leads to its proteasomal degradation with subsequent decrease in VLDL production. Studies suggest that there are differential effects of apoB vs MTP inhibition on hepatic steatosis (42). Rodent studies have demonstrated that inhibition of apoB synthesis did not increase hepatic steatosis compared with inhibition of MTP (42, 43). The absence of hepatic steatosis with apoB inhibition is thought to be due to accumulation of lipids in the ER, which stimulates ER autophagy, leading to fatty acid (FA) oxidation and protection from fat accumulation (42). The long-term clinical consequences of hepatic steatosis due to pharmacologic apoB or MTP inhibition in humans remain unclear (44).

In the exogenous pathway, TGs are hydrolyzed to form FAs and 2-monoacylglycerol in the stomach and proximal small intestine (13). The FFAs and monoacylglycerols are then absorbed by enterocytes and incorporated into apoB48 containing chylomicrons. These chylomicrons are then secreted into the lymphatic system and enter the venous circulation via the thoracic duct, where they acquire apoCII, apoCIII, and apoE (13). Once in the circulation, LPL along the luminal surface of capillaries hydrolyzes the TGs within the core of chylomicrons into FFAs, which can then be taken up by myocytes and adipocytes in a manner analogous to that of VLDL particles. The smaller, cholesterol-enriched chylomicron remnants are cleared from the circulation by binding to the LDL receptor or LDL receptor–related protein-1 via apoE and the heparan sulfate proteoglycan pathway in the liver (13, 41).

LPL, the central node in TGRL metabolism, is synthesized by several cells types, including cardiomyocytes, adipocytes, and macrophages, and must be then transported to the capillary lumen by an endothelial protein, GP1HBP1 (45), which also

Table 1. Causes of Hypertriglyceridemia

Cause
Genetic (primary) (12, 37, 40)
Familial hyperchylomicronemia
Autosomal recessive mutations in *LPL, APOC2, APOA5, LMF1, GPIHBP1*, or *GPD1*
Increased TGs/chylomicrons
Familial combined hyperlipidemia
Due to rare variants in genes associated with hypertriglyceridemia
Familial hypertriglyceridemia
Polygenic
Elevated TCs, TGs, apoB
Dysbetalipoproteinemia (familial type III)
Autosomal recessive mutation in APOE
Defective apoE (apo EII/EII phenotype)
Increased TC/TG, VLDL remnants, and chylomicrons
Nongenetic (secondary) (12, 37, 40)
Hypothyroidism
Pregnancy (especially in the third trimester)
Poorly controlled diabetes
Obesity
Alcohol intake
Metabolic syndrome
Renal disease (nephrotic syndrome, glomerulonephritis)
Acute hepatitis
Diet (high saturated fat or high glycemic index)
Systemic lupus erythematosus
HIV
Cushing syndrome
Lipodystrophy
Glycogen storage disease
Drugs (12, 37, 40)
Nonselective β blockers
Corticosteroids
Oral estrogens
Diuretics (thiazides)
Tamoxifen, raloxifene
Androgens
Bile acid sequestrants
Cyclosporine
Atypical antipsychotics
Sirolimus, tacrolimus
L-asparaginase retinoic acid drugs (isotretinoin)
Cyclophosphamide
Protease inhibitors
Interferon

Abbreviation: TC, total cholesterol.

provides a platform for LPL-mediated lipolytic processing along the capillary lumen (46). Maturation of LPL after synthesis is mediated by lipase maturation factor 1 (LMF 1) in the ER of parenchymal cells (*e.g.*, myocytes and adipocytes) (47). LPL plays a critical role in plasma TG clearance; therefore, its enzymatic activity is highly regulated by various proteins, including apoCI, apoCII, apoCIII, apoA5, apoE, and the angiopoietin-like proteins ANGPTL3, ANGPTL 4, and ANGPTL 8 (13, 48). It is important to note that although apoCIII is a potent inhibitor of LPL activation, recent studies have shown that it has a pleiotropic role in the regulation of TGRL metabolism independent of LPL pathways. These include inhibition of hepatic lipase activity and inhibition of hepatic TGRL remnant clearance (49). Table 2 summarizes the action of these proteins on LPL.

Measurement of TGs and RC

As mentioned, TGRLs encompass hepatically secreted (VLDL) and intestinally derived (chylomicrons) particles. The cholesterol content of partially lipolyzed TGRL, also called RC, includes the cholesterol cargo of VLDL and IDL in the fasting state and of chylomicron remnants in the nonfasting state (as well as the altered fasting state in individuals with hypertriglyceridemia) (55). Clinically, plasma TG concentrations serve as a surrogate measure of TGRLs and RC.

Circulating plasma apoB–containing lipoproteins penetrate the endothelial cell lining of the artery wall in susceptible regions and enter the intimal space, where they may be trapped by interaction with subendothelial proteoglycans (56, 57). These retained apoB-containing lipoproteins can then be engulfed by arterial macrophages. Within macrophages, cholesterol cannot be metabolized; thus it accumulates, leading to engorged, dysfunctional foam cells. However, the TGs are catabolized by macrophages and therefore do not accumulate in atherosclerotic plaque.

Thus, the TGs themselves, although possibly potentiating atherogenesis, may not directly lead to plaque formation. This suggests that the cholesterol content in TGRLs (*e.g.*, RC), rather than the TGs, may be more important in atherogenesis, because it accumulates in atherosclerotic plaque and is in the causal pathway of atherosclerosis. Therefore, an estimation of RC may be more important than the TG level itself.

An estimate of RC can be calculated from a standard lipid profile as follows: RC equals total cholesterol minus LDL-C minus HDL-C. The Friedewald equation is generally used to calculate LDL-C. However, this approximation becomes completely unreliable when TG >500 mg/dL (58). The Friedewald equation assumes a fixed ratio of TG to VLDL cholesterol (VLDL-C) of 5:1; however, the actual ratio varies across the range of TG and cholesterol levels

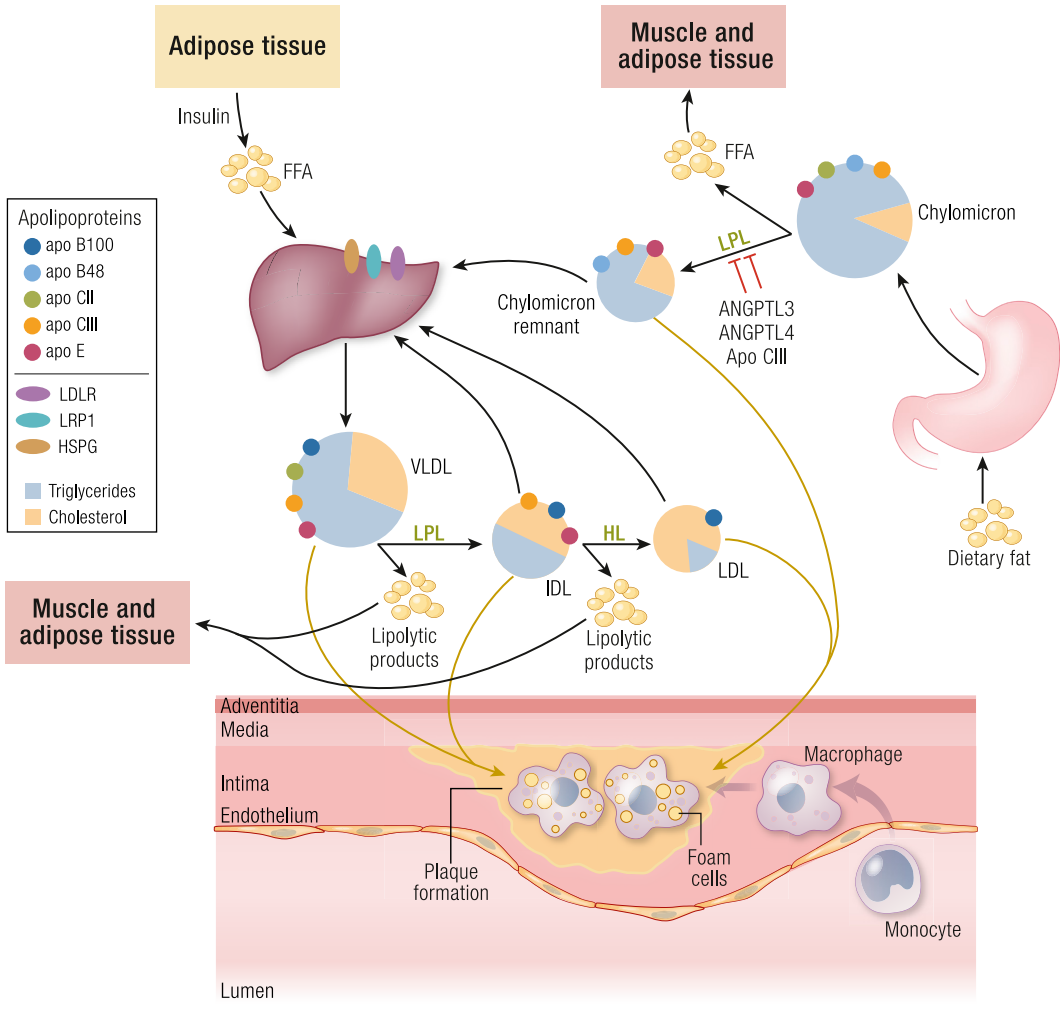

Figure 1. Triglyceride-rich lipoprotein metabolism and mechanism of atherosclerosis. TGRLs are derived from an endogenous pathway through the liver and an exogenous pathway through the small intestine. In the endogenous pathway, VLDL is produced in the hepatocytes from FFAs derived from the circulation or newly synthesized in the liver. A variety of apolipoproteins are added to the surface of the nascent VLDL particle during secretion, including apoB100, apoCII, apoCIII, and apoE. Once VLDL is secreted into the plasma, LPL along the luminal surface of capillaries hydrolyzes the TGs within the core of VLDL into FFAs generating VLDL remnant/IDL particles and lipolytic products. The FFAs are taken up by muscle and adipose tissue. The IDL particles are further catabolized into LDL and lipolytic products by HL. In the exogenous pathway, dietary fats are absorbed by enterocytes and incorporated into apoB48 containing chylomicrons, which are then secreted into the lymphatic system and enter the circulation, where they acquire apoCII, apoCIII, and apoE. In the circulation, LPL along the luminal surface of capillaries hydrolyzes the TGs within the core of chylomicrons into FFAs generating chylomicron remnant particles. The FFAs can be taken up muscle and adipose tissue. Endogenous and exogenous remnants are cleared from the circulation by hepatic uptake via the LDL receptor, LRP1, and HSPG receptor. LPL plays a key role in TGRL metabolism and is highly regulated by various proteins. ANGPTL 3, ANGPTL 4, and apoCIII inhibit LPL activity, whereas apoCII is an important activator of LPL activity. TGRL and their remnants readily penetrate the arterial wall and can be taken up by scavenger receptors on macrophages directly without oxidative modification, leading to formation of foam cells and atherosclerotic plaque development. ANGPTL, angiopoietin-like protein; HL, hepatic lipase; LRP1, LDL receptor related protein-1; HSPG, heparan sulfate proteoglycan.

Table 2. Lipoprotein Lipase–Modulating Proteins

	Effect on LPL Activity	Mechanism	Effect on Plasma TGs
Liver derived			
ApoCI (50)	Inhibits LPL	Displace LPL from TG-rich particles	↑TG
ApoCII (51)	Activates LPL	Unclear	↓TG
ApoCIII (50)	Inhibits LPL	Displace LPL from TG-rich particles	↑TG
ApoA5 (48)	Activates LPL	Unclear	↓TG
ApoE (48)	Inhibits LPL	Unclear	↑TG
Angiopoietin-like proteins			
ANGPTL 3 (52)	Inhibits LPL	Renders LPL more susceptible to proteolytic inactivation by proprotein convertases	↑TG
ANGPTL 4 (53)	Inhibits LPL	Inactivates LPL in the subendothelial space by binding to the LPL *N*-terminus and dissociating its catalytically active homodimers to monodimers	↑TG
ANGPTL 8 (54)	Inhibits LPL	May inhibit LPL activity directly or indirectly by promoting cleavage and activation of ANGPTL3	↑TG

(58). Newer methods estimate LDL-C levels using an adjustable factor for the TG-to-VLDL-C ratio based on TG and non–HDL-C concentrations (59). Alternatively, direct LDL-C measurements can also be used to more accurately calculate RC in the setting of significantly elevated TG levels.

In addition to calculation methods, RC can be directly measured using a variety of analytical methods, including ultracentrifugation, nuclear magnetic resonance spectroscopy, and by a direct automated assay. The automated assay by Denka Seiken measures the cholesterol content in chylomicrons and VLDL remnants using enzymes and surfactants (60). RC can also be measured by immunoseparation assays using antibodies to apoA1 and apoB100 (61, 62). This immunoaffinity mixed gel containing apoA1 and B100 antibodies absorbs almost all lipoproteins with the exception of certain subpopulations of TGRLs (density $<$ 1.006 g/dL), specifically chylomicrons and VLDL remnants, which can then be quantified (61). The automated assay only measures a fraction (approximately 13%) of the calculated RC compared with the immunoseparation assay, which correlates better with the calculated levels (55, 60). The vertical auto profile method measures RC (IDL cholesterol and VLDL-C) after separation of lipoproteins by density-gradient ultracentrifugation (63, 64). The quantification of RC from the exogenous pathway (*i.e.*, chylomicron remnants) can be done via ultracentrifugation or, indirectly, by measuring apoB48 (55, 65, 66). ApoB48 is the truncated gene product created by posttranslational modification of the larger apoB100 and is found exclusively on chylomicrons and their remnants (67). ApoB48 is primarily synthesized in the small intestine and plays a key role in chylomicron assembly. Each chylomicron and chylomicron remnant particle contains a single apoB48 molecule, which can be used as a measure of intestinally derived RC (67). At this time, these direct assays to measure RC have limited clinical applicability because they do not measure all RC in the plasma and are labor intensive and costly. There is an unmet need for the development of automated assays that accurately and reproducibly measure all RC, which may take on increased urgency if RC is ultimately vindicated as an important causal and targetable ASCVD risk factor (11).

Fasting vs nonfasting measurement

Historically, lipid profiles have been measured in the fasting state, following an 8- to 12-hour period without food intake. Fasting provides sufficient time for catabolism of dietary TGs (*e.g.*, chylomicrons). Early epidemiologic studies demonstrated that fasting TG levels independently associated with cardiovascular disease (CVD) and correlated well with nonfasting TG levels (68, 69). The use of the Friedewald equation for LDL-C estimation, which depends on fasting lipoprotein measurements, resulted in early guideline recommendations to use fasting lipid profiles (13, 24, 70). However, because most individuals eat regularly throughout the day and fast only for a few hours in a 24-hour cycle (during sleep), nonfasting lipid levels may be a better indicator of plasma atherogenic lipoprotein concentrations when compared with fasting levels. Moreover, a robust evidence base has accumulated in recent years that also suggests remnant lipoproteins are important contributors to atherosclerosis and

development of CVD (71–78). In fact, postprandial TG concentrations have been shown to be an equal, if not superior, predictor of future CVD events compared with fasting levels (73, 74). These studies accounted for the variability in postprandial TG concentrations through stratification by time since last meal and controlling for factors such as age, body mass index, diabetes, hormone use, menopausal status, and ethnicity. In the postprandial period, both intestinally and hepatically derived lipoproteins can be measured in the circulation, representing a potentially more accurate reflection of the atherogenic lipoprotein burden in a 24-hour period (13, 79). Compared with the fasting state, maximal mean changes in random, nonfasting lipoprotein levels are +26 mg/dL for TG, +8 mg/dL for RC, −8 mg/dL for total cholesterol, −8 mg/dL for LDL-C, and −8 mg/dL for non–HDL-C, whereas HDL-C levels are generally unaffected in the general population (79). These postprandial changes in TGs depend on baseline TG levels, fat load in the meal, and time since the last meal (71, 79, 80). In most individuals, these differences in plasma fasting and nonfasting TG level are small and therefore likely clinically insignificant. In general, consumption of a low-fat breakfast (<15 g of fat) before blood sampling is unlikely to increase postprandial TG levels by >20% or levels >200 mg/dL in individuals with fasting TG levels <150 mg/dL (81, 82). Thus, it may be reasonable to obtain a nonfasting lipid profile for a vast majority of patients in the general population, given its advantages such as convenience and ease of sampling, lack of clinically important difference in lipid levels, and comparable efficacy in assessing and managing ASCVD risk compared with fasting lipid measurements (71). Accordingly, several current recommendations support the use of a random, nonfasting lipid profile in clinical practice for CV risk prediction (2, 12, 71, 83–85), although it is not clear as to how to use nonfasting lipids once treatment is started with lipid-lowering therapy.

TGRLs and Atherosclerosis

If, in fact, TGs are causal in the atherosclerotic pathway, the exact underlying mechanisms by which they facilitate and participate in atherosclerotic plaque formation are unclear. Large TG-rich chylomicrons and VLDL particles cannot penetrate the arterial wall to be retained within the subendothelial space and engulfed by vascular macrophages (86–88). This notion is supported by studies of individuals with familial chylomicronemia syndrome due to LPL deficiency, whose TGs are poorly degraded in plasma. Despite severe hypertriglyceridemia, these individuals do not develop atherosclerosis in the absence of other CV risk factors (89). On the other hand, TGRLs and their remnants are thought to be equally or more atherogenic than LDL. TGRLs can readily penetrate the arterial wall and are susceptible to retention by connective tissue matrix through interaction of the positively charged residues (arginine and lysine) on apoB with the negatively charged sulfate groups of subendothelial proteoglycans, similar to LDL. Once trapped in the subendothelial space, LDL particles must be modified (*e.g.,* oxidative modification) before they can be taken up by scavenger receptors on the surface of macrophages, leading to the formation of foam cells and development of atherosclerotic plaque (Fig. 1) (56, 57). On the other hand, TGRLs can be taken up by arterial wall macrophages directly without oxidative modification (90). Moreover, remnants, due to their larger size, carry more cholesterol per particle than LDL (13).

Endothelial dysfunction often precedes the development of atherosclerosis. TGRL remnants have been linked to impaired coronary vasomotor function, decreased brachial artery flow–mediated dilatation, and increased carotid intima media thickness (91–93). Although the exact underlying mechanisms by which TGRL remnants promote endothelial dysfunction need to be elucidated, there are several proposed theories. TGRL remnants promote endothelial dysfunction through increased production of reactive oxygen species and induce endothelial cell apoptosis by increased secretion of TNF-α and IL-1β (41, 94). Furthermore, impairment of endothelium-dependent vasodilation and increased oxidative stress may also play a role in promoting endothelial dysfunction (95, 96).

TGRL and Inflammation

LPL-mediated hydrolysis of TGRL produces lipolytic products such as oxidized FFAs (41). These FFA and TGRL remnants induce production of cytokines (*i.e.*, TNF-α), interleukins (*i.e.*, IL-1, IL-6, IL-8), and proatherogenic adhesion molecules (*i.e.*, intracellular adhesion molecule-1 and vascular cell adhesion molecule-1) that facilitate migration of leukocytes to the site of inflammation (97). Thus, this TGRL-induced inflammatory response is characterized by monocyte adhesion to the endothelium and neutrophil activation (97, 98). In addition to their proinflammatory effects, TGRLs lead to activation of the coagulation cascade through assembly of the prothrombinase complex and upregulation of the expression of the plasminogen activator inhibitor-1 gene and the plasminogen activator inhibitor-1 antigen (86, 99). Collectively, these processes lead to enhanced platelet aggregation and clot formation (41, 99). It is still a matter of debate whether the cholesterol content of TGRL remnants primarily contributes to the progression of atherosclerosis, rather than the TGs themselves (100). Interestingly, Mendelian randomization suggests a causal association of elevated nonfasting RC

with low-grade inflammation and ischemic heart disease (IHD), whereas elevated LDL-C associates with IHD but not inflammation (101).

Epidemiologic Studies of TGs and Risk of CVD

Numerous epidemiological studies and meta-analyses have demonstrated a positive association of TGs with risk of ASCVD (68, 102–105) (Table 3). In particular, two prospective observational studies, the Copenhagen General Population Study and the Copenhagen City Heart Study, have provided important insights into the association between TGs and ASCVD (74, 78, 106). The Copenhagen City Heart Study enrolled 13,981 participants not taking lipid-lowering therapy and demonstrated that increasing levels of nonfasting TG levels were associated with increased risk of myocardial infarction (MI), IHD, and death in men and women over a 27-year follow-up (74). Nonfasting TG levels >5 mmol/L (440 mg/dL) were associated with a 4.6-fold and 16.8-fold increase in risk of MI for men and women, respectively, compared with TG levels <1 mmol/L (88 mg/dL). Similarly, increased levels of nonfasting TGs were associated with a 3.2-fold and 5.1-fold increase in risk of ischemic stroke for men and women, respectively (78). The higher risk of events in women compared with men has been attributed to confounding from higher levels of alcohol intake in men (11). A subsequent larger study of approximately 100,000 participants from the Copenhagen City Heart Study and the Copenhagen General Population Study demonstrated similar findings. Specifically, 5.1-fold, 3.2-fold, 3.2-fold, and 2.2-fold increases in risk of MI, IHD, ischemic stroke, and all-cause mortality, respectively, were found for individuals with nonfasting TG level >6.6 mmol/L (580 mg/dL) compared with those with TG level <0.8 mmol/L (70 mg/dL) (100). More recently, Varbo *et al.* (106) demonstrated that higher concentrations of nonfasting TGs were associated with a stepwise increase in risk of heart failure with a multivariable hazard ratio of 2.59 (95% confidence interval, 1.48-4.54) for participants with nonfasting TG ≥ 5 mmol/L (440 mg/dL) compared with those with TG concentrations < 1 mmol/L (88 mg/dL).

In the Women's Health Study, a prospective observational cohort of 26,509 healthy US women, nonfasting TG levels were associated with a 1.98-fold increase in risk of CVD events, independent of traditional risk factors, other lipids, and markers of insulin resistance (73). However, fasting TG levels were not significantly associated with CVD events after adjustment for TC, HDL-C, and measures of insulin resistance (p-value=0.90). Interestingly, when stratified by time since last meal, TG measurements 2 to 4 hours postprandially had the strongest association with CVD events (4.48-fold increase in risk).

In an analysis by the Emerging Risk Factors Collaboration, including 302,430 individuals without known vascular disease from 68 long-term prospective studies with 2.79 million person-years of follow up, fasting and nonfasting TG levels were associated with increased risk of coronary heart disease [CHD; hazard ratio (HR), 1.37; 95% CI, 1.31 to 1.42) after adjustment for nonlipid risk factors (72). However, the association was attenuated after adjustment for HDL-C and was nonsignificant after adjustment for non–HDL-C. In addition, TGs were not associated with stroke after adjustment for lipids. In this largest epidemiological study to date, the authors concluded that "for population-wide assessment of vascular risk, triglyceride measurement provides no additional information about vascular risk given knowledge of HDL-C and total cholesterol levels, although there may be separate reasons to measure triglyceride concentration (eg, prevention of pancreatitis)" (72). Although debate continued about the relative importance of the relationship between TGs and ASCVD, the investigative agenda for the next decade largely transitioned from TGs to HDL-C as a potential causal risk factor for ASCVD and a potential target of therapy. Two large randomized controlled trials (RCTs) evaluating the efficacy of extended-release niacin vs placebo on background statin therapy in individuals with established ASCVD did not demonstrate a reduction in vascular events (18, 19). Furthermore, three large RCTs of cholesterol ester transfer protein inhibitors (dalcetrapib, evacetrapib, and torcetrapib) did not improve CV outcomes despite substantial increases in plasma HDL-C levels (20–22).

In an attempt to clarify the issue of causality, a number of genetic studies have provided important insights. Genetic studies, and in particular Mendelian randomization studies, provide a robust tool to establish causality because they capture a life-time effect of an exposure. DNA variants can be used to assess if a biological marker (*e.g.*, TG) that has an epidemiological association for risk of disease (*e.g.*, CHD) is likely causal for the disease. Therefore, if a DNA variant is known to have a direct influence on the biomarker level or activity of a protein that influences the biomarker level and that biomarker is causal for disease, then the DNA variant should be associated with the disease risk without the possibility of reverse causality (110). The biomarker is likely not causal for the disease if similar association between the DNA variant and disease risk as seen in observational studies is not apparent (110). As such, Mendelian randomization studies are an effective way to understand the causal role of TGRLs and CVD. Mendelian randomization is essentially an RCT that has been performed by nature, because there is a random allocation of alleles to offspring at the time of conception that is unaffected by reverse causation and independent of environmental and genetic confounders (110). Consistent

with these RCTs, Mendelian randomization studies further support the notion that HDL-C may not be causally related to CHD risk (110, 111).

Given the failed HDL-C drug trials and new insights from the Mendelian randomization studies, it is now generally accepted that HDL-C, although associated with ASCVD, is not in the causal pathway. Thus, the pendulum has shifted back once again to a focus on TGRLs and RC as potentially etiologic in atherosclerosis.

Several studies have also examined the relationship between RC (both calculated and measured) and ASCVD (60, 64, 76, 101, 112–114). Varbo *et al.* (76) demonstrated that each 1 mmol/L (39 mg/dL) increase in nonfasting RC (calculated as total cholesterol minus HDL-C minus LDL-C) associated with a 2.8-fold increase in risk of IHD independent of low HDL-C. In another study of 97,962 participants from the Copenhagen City Heart Study and the Copenhagen General Population Study, nonfasting calculated RC was associated with a stepwise increase in risk of IHD, MI, and all-cause mortality (112). In the study by Jepsen *et al.* (60), elevated levels of measured and calculated RC were associated with all-cause mortality in patients with IHD. More recently, a nested case-control study of 4662 individuals from the China Kadoorie Biobank demonstrated that RC concentrations (measured by nuclear magnetic resonance spectroscopy) were associated with a 1.27-fold increased risk of MI and 1.20-fold increased risk of ischemic stroke (107). It is important to note that most of these observational epidemiologic studies were done in the prestatin era.

There are a number of studies (mostly *post hoc* analyses) that have looked at the association between on-treatment TG levels and ASCVD risk. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI 22) study, on-treatment TG level <150 mg/dL (<1.7 mmol/L) was independently associated with a lower risk of recurrent CHD events (HR, 0.72; 95% CI, 0.54 to 0.94; $P = 0.017$) in patients with acute coronary syndrome and LDL-C level <70 mg/dL (108). Similarly, a pooled analysis of the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) and Treating to New Targets (TNT) trials demonstrated that increased TG levels were associated with higher risk of CVD events in statin-treated patients, although the risk was attenuated after adjustment for HDL-C and apoB-to-apoA-I ratio (109).

Genetic Studies of TGs and CVD

The aforementioned observational epidemiology linking TGs and RC to ASCVD is largely consistent. However, the possibility of residual confounding limits the ability to draw causal inference from these observational studies. In fact, one study in particular suggested that TGs are not likely directly related to ASCVD after full adjustment with non–HDL-C (72). However, there is now general consensus that adjustment of TGs by non–HDL-C is inappropriate. Specifically, non–HDL-C encompasses all apoB-containing lipoproteins (including VLDL, IDL, chylomicrons and their remnants) and elevated TG levels are closely linked to non–HDL-C with high intercorrelation between the variables.

The method of Mendelian randomization has also been applied in this context in attempts to disentangle the association of TGRLs and ASCVD. However, a well-known limitation of Mendelian randomization analyses is that they are susceptible to genetic pleiotropy. This phenomenon occurs when the gene variant under study affects more than one pathway; thus, the observed association between the variant and disease risk may not be due to the biomarker of interest (110). In particular, Mendelian randomization studies of variants associated with TGs are commonly affected by the pleiotropic effects of single-nucleotide polymorphisms (SNPs) on multiple metabolic pathways affecting plasma lipids, including HDL-C and LDL-C (110, 115). These SNPs are primarily located on six genes associated with plasma TG levels (*APOA5*, *APOC3*, *ANGPTL4*, *LPL*, *APOA4*, and *TRIB1*) and CHD (110). To overcome the effects of pleiotropy, Do *et al.* (116) used multivariable Mendelian randomization to separate the effects of TG from LDL-C and HDL-C on CAD using 185 SNPs associated with blood TGs, LDL-C, or HDL-C levels. They found that the strength of an SNP's effect on TG levels correlated strongly with the magnitude of effect on CAD, after adjustment for the SNP's effects on LDL-C and HDL-C. This finding supported the notion that plasma TG levels are an independent causal risk factor for CAD (116). In another Mendelian randomization analysis of 10,208 individuals from the Copenhagen City Heart Study, genetically lower concentrations of nonfasting plasma TGs were associated with reduced all-cause mortality (117). Using a multiple SNP instrumental variable meta-analysis approach, Holmes *et al.* (6) demonstrated an independent causal association between TGs and CAD.

Furthermore, insights from variants in genes involved in plasma TGRL metabolism, namely *LPL* and those that modulate its function, including *APOA5*, *APOC3*, *ANGPTL 3*, and *ANGPTL 4* are also associated with ASCVD (19, 76, 77, 110, 118–124). Increased RC levels due to mutations in *APOA5*, an activator of LPL, are associated with a 2.2-fold increased risk of MI (77). Loss-of-function (LOF) mutations in *APOC3* are associated with reduction in plasma TGs and in ASCVD risk (19, 120, 121, 125). In one study, LOF *APOC3* mutations were associated with 39% lower TG levels and 40% lower risk of CHD

"...three other classes of drugs are available for the management of hypertriglyceridemia: fibrates, niacin, and omega-3 fatty acids (OM3FAs)."

Table 3. Epidemiologic Studies of TGs and CVD

Study	Study Population	Findings
Reykjavik and the EPIC-Norfolk studies and 27 prospective studies (68)	Nested case-control comparisons of two different prospective, population-based cohorts (n = 44 and n = 237)	In the Reykjavik study, TG concentrations in the highest tertile were associated with increased odds of CHD (OR, 2.04; 95% CI, 1.78 to 2.32) after adjustment for age and sex compared with the lowest tertile. Further adjustment for risk factors and other lipid measures attenuated the risk (OR, 1.43; 95% CI, 1.23 to 1.65). Similar findings were seen in the EPIC-Norfolk cohort.
	Meta-analysis of 29 studies (n = 262,525 participants)	In the meta-analysis of 29 studies, TG concentrations in the highest tertile were associated with increased risk of adverse CV outcomes (OR, 1.72; 95% CI, 1.56 to 1.90) compared with the lowest tertile after multivariable adjustment for age, sex, smoking, lipid concentrations. and blood pressure
	Mean follow-up, 12.1 y	
CCHS (74)	Cross-sectional prospective cohort study of 13,981 participants	Elevated nonfasting TG levels ≥442.5 mg/dL were associated with increased risk of MI (HR, 2.4 for men, 5.4 for women), IHD (HR, 1.5 for men and 2.6 for women) and death (HR, 1.8 for men and 3.3 for women) compared with TG levels <88.5 mg/dL after multivariable adjustment.
	Mean follow-up, 26 y	
CCHS (78)	Cross-sectional prospective cohort study of 13,956 participants	Elevated nonfasting TG levels ≥443 mg/dL were associated with increased risk of ischemic stroke (HR, 2.5 for men and 3.8 for women) compared with TG levels <89 mg/dL after multivariable adjustment.
	Mean follow-up, 26 y	
CGPS and CCHS (106)	Cross-sectional prospective cohort study of 113,554 participants	Elevated nonfasting TG levels ≥440 mg/dL associated with increased risk of heart failure (HR, 2.6 in CGPS and HR 2.3 in CCHS) compared with TG levels <88 mg/dL) after multivariable adjustment
	Mean follow-up, ≤23 y	LDL-C concentrations were not associated with risk of heart failure.
Women's Health Study (73)	Cross-sectional prospective study of 26,509 healthy US women	Elevated nonfasting TG levels (highest tertile) were associated with increased risk of CV events (HR, 1.98) compared with those in the lowest tertile after full adjustment for risk factors, including HDL-C and measures of insulin resistance.
	Median follow-up, 11.4 y	Elevated fasting TG levels were not independently associated with adverse CV events (*P* for trend = 0.90) because the relationship was nonsignificant after adjustment for HDL-C and measures of insulin resistance.
		In secondary analysis stratified by time since last meal, TG levels measured 2–4 hours postprandially had the strongest association with CV events (HR, 4.48) for the highest vs lowest tertiles after full multivariable adjustment
Emerging Risk Factors Collaboration (72)	Meta-analysis of 302,430 individuals without vascular disease from 68 long-term prospective studies	After adjustment for nonlipid factors, TG levels were associated with risk of CHD (HR, 1.37; 95% CI, 1.31 to 1.42).
	Follow-up, 2.79 million person-y	After further adjustment for HDL-C and non-HDL-C, TG levels were not significantly associated with risk of CHD (HR, 0.99; 95% CI, 0.94 to 1.05).
Copenhagen Ischemic Heart Disease Study (60)	5414 patients with IHD	Calculated remnant cholesterol levels in the highest tertile were associated with an increased risk of all-cause mortality (HR, 1.3; 95% CI 1.2 to 1.5) compared with the lowest tertile.
	35,836 person-y of follow-up	Directly measured RC levels in the highest tertile were associated with an increased risk of all-cause mortality (HR, 1.1; 95% CI 1.0 to 1.3) compared with the lowest tertile.

(*Continued*)

Table 3. *Continued*

Study	Study Population	Findings
JHS and FOCS (64)	Observational primary prevention cohorts	In a combined patient-level analysis, measured RLP-C and IDL-C were associated with an increased risk of CHD (HR, 1.23, 95% CI, 1.06 to 1.42; and HR, 1.26, 95% CI, 1.08 to 1.47, respectively)
	4114 US black participants from the JHS with a mean follow-up of 5.6 y	After adjustment for HDL-C and LDL-C, all associations were attenuated.
	818 predominantly white participants from FOCS with a mean follow-up of 7.5 y	
China Kadoorie Biobank (107)	Prospective cohort study of 4662 individuals	NMR spectroscopy–measured RC concentrations were associated with increased risk of MI (OR, 1.27; 95% CI, 1.15 to 1.39 per SD increase) and ischemic stroke (OR, 1.20; 95% CI, 1.09 to 1.32 per SD increase) but not intracerebral hemorrhage (OR, 1.04; 95% CI 0.95 to 1.13 per SD).
PROVE IT-TIMI 22 study (108)	4162 patients hospitalized for ACS and were randomized to atorvastatin 80 mg or pravastatin 40 mg daily.	On-treatment TG levels <150 mg/dL were associated with lower CHD risk compared with higher TG levels (HR, 0.80; 95% CI, 0.66 to 0.97; P = 0.025) after multivariable adjustment.
		For each 10-mg/dL lowering in on-treatment TG level, the incidence of death, MI, and recurrent ACS was lower by 1.6% ($P < 0.001$) or 1.4% (P = 0.01) after adjustment for LDL-C or non–HDL-C respectively.
IDEAL and TNT trials (109)	*Post hoc* analysis of two prospective, randomized, multicenter studies comparing the efficacy of moderate and high-intensity statin therapy for prevention of recurrent cardiovascular events in patients with established CHD	Patients in the highest quintile of TG concentration had a higher risk of CV events compared with the lowest quintile (HR, 1.63; 95% CI, 1.46 to 1.81).
	IDEAL: compared efficacy of atorvastatin 80 mg vs simvastatin 20–40 mg; Median follow-up, 4.8 y; n = 7232	After adjustment for HDL-C and apoB/ApoA-1, the relationship between TG levels and CV events was attenuated (HR, 1.19; 95% CI, 1.06 to 1.35, for fifth vs first quintile).
	TNT: atorvastatin 80 mg vs atorvastatin 10 mg; median follow-up, 4.9 y; n = 8547	After further adjustment for other risk factors (diabetes, body mass index, glucose, hypertension, and smoking) the relationship between TG levels and CV events was nonsignificant (HR, 1.10; 95% CI, 0.97 to 1.24, for fifth vs first quintile).

Abbreviations: ACS, acute coronary syndrome; CCHS, Copenhagen City Heart Study; CGPS, Copenhagen City General Population; EPIC, European Prospective Investigation of Cancer; FOCS, Framingham Offspring Cohort Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; JHS, Jackson Heart Study; NMR, nuclear magnetic resonance; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction; RLP-C, remnant lipoprotein cholesterol; TNT, Treating to New Targets.

(OR, 0.60; 95% CI, 0.47 to 0.75; $P = 4 \times 10^{-6}$) (19). Thus, apoCIII is a promising target for pharmacologic modulation of TGRL metabolism. Currently, there are numerous therapeutic approaches to antagonize its action at various phases of clinical development.

LOF mutations leading to complete deficiency of ANGPTL3 are associated with a familial combined hypolipidemia, characterized by extremely low circulating LDL-C, HDL-C, and TG levels (123, 126). In three wild-type, first-degree relatives with complete ANGPTL3 deficiency, CT angiography showed no evidence of coronary atherosclerotic plaque (123). Heterozygous carriers of *ANGPTL3* LOF mutations had a 17% reduction in circulating TG levels, a 12% reduction in LDL-C levels, and a 34% reduction in odds of CAD (OR, 0.66; 95% CI, 0.44 to 0.98; P = 0.04) (123). As is the case with apoCIII, drugs are being developed to inhibit ANGPTL3 either at the gene or protein level.

LOF variants in *ANGPTL4*, which codes for a protein that inhibits LPL action, are associated with both reduced plasma TG levels and CHD risk (HR, 0.63; 95% CI, 0.45 to 0.89) (122). Similarly, carriers of the E40K variant in *ANGPTL4* had a 19% lower risk of CAD compared with noncarriers (127). To our knowledge, there have been no human trials of pharmacological agents targeting ANGPTL4. LOF mutations in *LPL* are also associated with increased plasma TG levels and risk of ASCVD (128, 129). Conversely, carriers of the gain-of-function *LPL* variant (S447X) have lower TG levels and lower incidence of ASCVD (130).

Overall, these data suggest elevated TG levels, as a surrogate measure of TGRLs, are an independent

causal risk factor for ASCVD. Future therapies directed at enhancing LPL and ApoA5 function or decreasing APOCIII and ANGPTL3 function may have a role in mitigating the risk of ASCVD associated with TGRL.

TG-Lowering Therapies

Lifestyle changes, including dietary modification (reduction of carbohydrate and fat intake), exercise, reduction of alcohol intake, and weight loss, are the mainstay for management of hypertriglyceridemia. Collectively, these interventions can reduce plasma TG levels by up to 60% (38). Several pharmacologic options to lower plasma TG levels are available and can be used as an adjunct to lifestyle interventions. Although statins are the cornerstone for treatment of LDL-C and its attendant ASCVD risk, they are associated with dose-dependent reduction in TGs by 22% to 45% in individuals with baseline hypertriglyceridemia (131). Currently, three other classes of drugs are available for the management of hypertriglyceridemia: fibrates, niacin, and omega-3 fatty acids (OM3FAs). Table 4 summarizes the approximate reduction in TG concentrations that can be achieved with lifestyle and pharmacologic interventions.

Fibrates

Fibrates or fibric acid derivatives exert their lipid-modifying effects by activating the peroxisome proliferator–activated receptor (PPAR)-α, a nuclear receptor that increases expression of LPL, apoAI, and other lipid-related genes (13). In general, treatment with fibrates lower TG levels by 30% to 50%, depending on baseline plasma concentrations (15). Several studies have evaluated the efficacy of fibrates in reducing adverse outcomes; however, results have been variable. In the Helsinki Heart Study, gemfibrozil reduced the risk of incident CHD by 32% without any significant effect on stroke, CV mortality, or all-cause mortality compared with placebo (14). The Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonstrated that gemfibrozil was associated with a 24% reduction in the combined end point of CHD death, nonfatal MI, and stroke, compared with placebo in 2531 men with CHD and HDL-C level $\leq$40 mg/dL (136). Again, there was no significant difference in all-cause mortality. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study with fenofibrate did not demonstrate a reduction in the rate of the composite primary outcome (CHD death and nonfatal MI) compared with placebo but was associated with a reduction in total CV events (24% reduction in nonfatal MI and 21% reduction in revascularization) (137). Similarly, the Bezafibrate Infarction Prevention (BIP) study did not show a clinical benefit of bezafibrate compared with placebo for the primary composite outcome (fatal or nonfatal MI or sudden death) in patients with CHD (138). Although results from these individual fibrate monotherapies have been inconsistent, *post hoc* analyses of subgroups with atherogenic dyslipidemia (low HDL-C and high TGs) suggest benefit in those with overt hypertriglyceridemia (TG level >200 mg/dL) (138–142). Subsequent meta-analyses have also demonstrated similar findings regarding the benefits of fibrates in patients with true dyslipidemia (143–145).

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, addition of fenofibrate to statin therapy did not result in significant beneficial effects on CVD risk (146). However, as seen with the fibrate monotherapy trials, a subgroup of patients with atherogenic dyslipidemia may have derive CV benefit from the combination of fenofibrate and simvastatin (146). It is important to note that most subjects in the large fibrate trials exhibited baseline TG levels <200 mg/dL, and thus the results are not definitive.

Omega-3 fatty acids

OM3FAs also play an essential role in cellular membrane formation and stability, and serve as precursors for inflammatory mediators (*e.g.*, eicosanoids, prostaglandins, protectins, resolvins, leukotrienes) (147). At therapeutic doses of 2 to 4 g/day, marine-derived OM3FAs [*i.e.*, eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) or EPA alone] reduce blood TG concentrations by up to 30% to 50% depending on baseline levels (28). The TG lowering is linear with a dose-dependent effect such that greater absolute reduction is seen in individuals with higher baseline TG levels (148). TG reduction is mediated by multiple mechanisms, including increased FA catabolism by peroxisomal β-oxidation, decreased hepatic lipogenesis, and increased clearance of plasma TGs (149). In addition to their TG lowering effects, OM3FAs improve vascular function, lower inflammation, decrease platelet aggregation, exert antiarrhythmic effects, and reduce hepatic steatosis and insulin resistance (148).

Prescription OM3FA formulations are available as ethyl esters or FFA forms with varying amounts of EPA plus DHA or EPA alone (150). The FFA formulation has greater bioavailability compared with the ethyl esters (151). Both EPA and DHA formulations lower TGs, non–HDL-C, and apoB levels. However, EPA-only formulations do not increase LDL-C levels compared with DHA-containing formulations (149). Similar to the CV outcomes studies with fibrates, studies of OM3FAs have demonstrated inconsistent results. However, it is important to emphasize that these disparate findings may be due to the inclusion of subjects with normal baseline TG levels (<150 mg/dL) and use of different formulations, concentrations, and doses of OM3FAs (149, 152–156). In a subgroup of

Table 4. Reduction in Plasma TG Levels With Lifestyle and Pharmacological Interventions

Intervention	Approximate Reduction in Plasma TG Level
Lifestyle	
Weight loss (38, 132, 133)	0.27 mg/dL per kg weight loss
	5%–10% reduction in initial body weight reduces TG levels by 25%
Dietary modification (38, 134, 135)	0.18 mmol/L (15.7 mg/dL) reduction in plasma TG levels with a plant-based protein and unsaturated fat–enriched diet
	10%–15% reduction in plasma TG levels with Mediterranean diet
Exercise (38)	≤20% reduction in plasma TG levels with moderate to intense aerobic exercise
	~5% reduction in plasma TG levels with resistance training
Pharmacotherapy	
Statins (131)	Dose-dependent reductions in TG of 22%–45% in individuals with baseline TG >250 mg/dL
	Minimal reduction in TG in individuals with baseline TG <150 mg/dL
Fibrates (15)	30%–50%
Niacin (15)	≤30%
OM3FAs (15)	30%–50%

patients with TG levels ≥1.70 mmol/L (≥150 mg/dL), OM3FA supplementation demonstrated beneficial effects on CV outcomes (relative risk, 0.82; 95% CI, 0.74 to 0.91; $P = 0.006$) compared with lower TG levels (156). Furthermore, the Japan EPA Lipid Intervention Study (JELIS), an open-label, blinded study of supplementation with 1.8 g/day EPA with statin (pravastatin 10 mg or simvastatin 5 mg) vs statin alone, demonstrated a statistically significant ($P = 0.01$) 19% reduction in major coronary events (157). In a subanalysis of JELIS evaluating individuals with TG levels ≥150 mg/dL and HDL-C levels <40 mg/dL, EPA treatment led to a 53% reduction in incident CAD (HR, 0.47; 95% CI, 0.23 to 0.98; $P = 0.043$) (159). Compared with the dose of OM3FAs used in the JELIS study (1.8 g/day), the average dose of OM3FAs in other RCTs has generally been 1 g/day, an amount that will not significantly lower TG levels and may explain, therefore, their inconsistent results (151).

Several ongoing CV outcomes trials with different formulations and higher doses of OM3FAs are currently underway (Table 5). Icosapent ethyl (Vascepa; Amarin), a highly purified EPA-only formulation, lowers plasma TG levels by 10% to 33% at doses of 2 to 4 g/day without any substantial increase in LDL-C levels (164). The Reduction of Cardiovascular Events With EPA-Intervention Trial (REDUCE-IT) demonstrated that the addition of icosapent ethyl 2 g twice daily to optimal medical therapy reduced the primary composite outcome (CV death, nonfatal MI, stroke, coronary revascularization, or unstable angina) by 25% compared to placebo (HR 0.75; 95% CI 0.68-0.83; $P < 0.0001$) in patients with known ASCVD or at high risk (diabetes) for developing CVD (165). Importantly, subjects enrolled in the trial were on baseline statin therapy with well controlled LDL-C. Additionally, there was a 26% reduction (HR 0.74; 95% CI 0.65-0.83; $P < 0.001$) in the key secondary end point (composite of CV death, nonfatal MI, or nonfatal stroke). The results of this trial are likely to be practice-changing as they come on the heels of negative findings of several contemporary trials of OM3FA supplementation and demonstrate an unexpectedly robust improvement in cardiovascular outcomes. Epanova (omega-3-carboxylic acids; AstraZeneca), a combination EPA plus DHA formulation, reduces baseline fasting serum TG levels by 25% to 31% and non–HDL-C levels by 7% to 10% and increases LDL-C levels by 19%, compared with placebo, at doses of 2 to 4 g/day (166). The ongoing Statin Residual Risk Reduction With Epanova in High CV-Risk Patients With Hypertriglyceridemia (STRENGTH) trial is evaluating the impact of EPA plus DHA on ASCVD outcomes.

Niacin

Niacin, or nicotinic acid, can reduce TG levels by up to 30%. It inhibits adipose tissue lipolysis, which reduces the flux of FFAs to the liver and, therefore, leads to reduced hepatic VLDL synthesis (167). The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) study was a large RCT that evaluated the efficacy of extended-release niacin in addition to statin therapy for reduction of ASCVD

Table 5. Emerging Therapies for Hypertriglyceridemia

	Mechanism of Action	Trial	Trial Description
SPPARM-α			
Pemafibrate (Kowa Research Institute)	Selective PPAR-α modulator	PROMINENT (NCT03071692) (159)	RCT evaluating the efficacy of Pemafibrate vs placebo in reducing incidence of adverse CV events in ~10,000 participants
			Inclusion criteria: participants with T2DM and fasting TG ≥200 mg/dL and <500 mg/dL and HDL-C ≤40 mg/dL
OM3FAs			
VASCEPA (icosapent ethyl) also known as AMR101 (Amarin Pharma)	Highly purified ethyl ester of EPA	REDUCE-IT (NCT01492361) (159)	RCT evaluating the efficacy of AMR101 vs placebo in reducing incident CV events in ~8000 participants
Treatment dose: 4 g/d			Inclusion criteria: individuals with established CVD or at high risk with hypertriglyceridemia and receiving statin therapy
Epanova (AstraZeneca)	Omega-3 carboxylic acids	STRENGTH (NCT02104817) (160)	RCT evaluating the efficacy of Epanova vs corn oil in reducing MACE in ~13,000 participants
			Inclusion criteria: patients at high risk for future CV events on stable diet and statin therapy with LDL-C <100 mg/dL and TG level ≥180 mg/dL and <500 mg/dL and HDL-C <42 mg/dL for men or HDL-C <47 mg/dL for women
Omacor	Marine OM3FAs (465 mg of EPA and 375 mg of DHA)	VITAL (NCT01169259) (161)	RCT in 25,871 participants evaluating daily dietary supplementation of 2000 units of vitamin D3 or OM3FAs for reducing the risk of developing cancer, heart disease, and stroke
Treatment dose: 1 capsule/d (840 mg of marine OM3FA)			
Icosabutate (162)	Potent, synthetically modified EPA molecule	No phase 3 outcomes trials underway	N/A
ApoCIII inhibitor			
Volanesorsen	Antisense apoCIII inhibitor	COMPASS (NCT02300233) (160)	RCT evaluating the efficacy of volanesorsen vs placebo given for 52 wk in reducing fasting TG levels
			Inclusion criteria: fasting TG level ≥500 mg/dL
	Antisense apoCIII inhibitor	APPROACH (NCT02211209) (161)	RCT evaluating the efficacy of volanesorsen vs placebo in reducing fasting TG levels in patients with FCS
			Inclusion criteria: FCS with fasting TG level ≥750 mg/dL (8.4 mmol/L) at screening
ANGPTL3 inhibition			
Evinacumab (REGN1500; Regeneron) (124)	Human monoclonal antibody against ANGPTL3	No ongoing CV outcomes trials	N/A
IONIS-ANGPTL$_{Rx}$; Ionis Pharmaceuticals (163)	Antisense oligonucleotides targeting hepatic ANGPTL3 mRNA	No ongoing CV outcomes trials	N/A

Abbreviations: ANGPTL, angiopoietin-like proteins; APPROACH, Study of Volanesorsen (formerly IONIS-APOCIII$_{Rx}$) in Patients With Familial Chylomicronemia Syndrome; COMPASS, Apolipoprotein C-III Inhibition With Volanesorsen in Patients With Hypertriglyceridemia; FCS, familial chylomicronemia syndrome; MACE, major adverse cardiac event; N/A, not applicable; PPAR, peroxisome proliferator–activated receptor; PROMINENT, Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Diabetic Patients; REDUCE-IT, Reduction of Cardiovascular Events With EPA–Intervention Trial; STRENGTH, Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia; VITAL, Vitamin D and Omega-3 Trial.

events (18). Despite reduction in TG levels by 28.6%, no incremental benefit in the primary end point was observed from the addition of niacin to statin therapy and thus the trial was terminated early. In the HPS2-THRIVE study, addition of niacin to statin therapy did not reduce the risk of major vascular events despite mean reductions in TG levels of 33 mg/dL compared with placebo (19). Due to the lack of benefit in reducing CV events and high incidence of adverse effects, the use of niacin is limited in clinical practice. It should be pointed out, however, that similarly to fibrate and OM3FA trials, neither of these large niacin trials sought to recruit patients with hypertriglyceridemia. Also similar to the fibrate and OM3FA trials, a *post hoc* analysis of AIM-HIGH evaluated the impact of niacin on a dyslipidemic subgroup (high, TG levels ≥200 mg/dL; low, HDL-C levels <32 mg/dL) and demonstrated a 37% reduction in CV events in the niacin group (HR, 0.64; $P = 0.032$) (168).

Emerging TG-Lowering Therapies

Insights from genetic studies have led to a new, and perhaps more intelligent, approach to therapeutic drug targeting. In particular, antisense oligonucleotide (ASO) and small interfering RNA (siRNA) technologies, which use gene-silencing strategies through specific mRNA degradation, are being pursued as therapeutic approaches to lower TG and RC levels (169). Gene-silencing technologies have been developed around the principle that DNA is transcribed into mRNA, which is then translated into protein. ASO (a single strand of RNA) or siRNA (a double strand of RNA) can be synthesized to bind the mRNA product of a gene that is known to influence levels of plasma lipoproteins (*e.g.*, TG) and prevent their expression through RNA cleavage or inhibition of translation, thereby silencing, or turning off, the gene (168). To improve their targeting and potency, and to reduce the potential for adverse effects, ASO or siRNAs can be attached to *N*-acetylgalactosamine moieties to facilitate selective delivery to and uptake by hepatocytes through the asialoglycoprotein receptor (170).

Volanesorsen (previously known as ISIS-APOC-III_{RX}) is a second-generation ASO developed to inhibit apoCIII. It binds to the *APOC3* messenger RNA and promotes its degradation, thereby inhibiting apoCIII synthesis in the liver (170). After preclinical and phase 1 studies, this was tested in three patients with familial chylomicronemia syndrome, a rare autosomal recessive disorder caused by mutations in *LPL* (or associated cofactors) leading to very severe hypertriglyceridemia, recurrent pancreatitis, and other complications leading to fatal events (49, 171). All three of these patients had essentially no LPL activity (<5% of normal) yet demonstrated robust reductions in plasma apoCIII (70% to 90%) and TG (56% to 86%) levels, in addition to reductions in apoB48, VLDL particle number, apoE, and non–HDL-C levels (49). These findings were surprising to many and challenged the canonical view of apoCIII as primarily an inhibitor of LPL. We now understand apoCIII as a pleiotropic regulator of TGRL metabolism through LPL-dependent and LPL-independent pathways (49). In a subsequent phase 2 study, volanesorsen reduced apoCIII levels by 80%, with a concomitant reduction in TG level by ≤71%, with an associated increase in HDL-C level of 46% in a dose-dependent manner (170). The Apolipoprotein C-III Inhibition With Volanesorsen in Patients With Hypertriglyceridemia (COMPASS) and Study of Volanesorsen (formerly IONIS-$APOCIII_{Rx}$) in Patients With Familial Chylomicronemia Syndrome (APPROACH) studies are currently testing volanesorsen in a phase 3 clinical trial program (Table 5). Volanesorsen is being evaluated by the US Food and Drug Administration as an orphan drug for familial chylomicronemia syndrome.

As reviewed earlier, ANGPTL3 is an endogenous inhibitor of LPL and LOF variants have been associated with decreased TG, LDL-C, and HDL-C levels. Evinacumab (REGN1500; Regeneron), a human monoclonal antibody against ANGPTL3, reduced fasting TG levels by ≤70% and LDL-C levels by ≤23% in an early-phase trial (124). Similarly, a phase 1 randomized, double-blind, placebo-controlled trial of an ASO targeting hepatic ANGPTL3 (IONIS-$ANGPTL_{RX}$; Ionis Pharmaceuticals) mRNA lowered TG levels by ≤63% and LDL-C by ≤33% (163). These studies highlight the potential of these two new therapeutic targets to lower plasma TG levels (Table 5).

Icosabutate, a synthetic OM3FA, is under clinical development and appears to be a promising option for lowering TG levels. In a study of 140 patients stable while taking their statin therapy and with residual elevations in TGs ranging from 200 mg/dL to 500 mg/dL, treatment with icosabutate reduced TG levels by 27%, VLDL-C levels by 32%, and apoCIII levels by 23% compared with placebo. LDL-C levels did not change significantly and HDL-C levels increased by 10% (162).

Another novel agent for lowering TG levels is alipogene tiparvovec (AAV1-LPLS447X). This is a nonreplicating adeno-associated viral vector that delivers copies of the human *LPL* gene to muscle tissue. In clinical trials, intramuscular injection of alipogene tiparvovec was associated with reduction in the incidence of pancreatitis and was well tolerated (172). Remarkably, this therapy was approved in Europe for patients with familial LPL deficiency but was ultimately pulled from the market, given its prohibitive expense and attendant lack of uptake.

Pemafibrate, a selective PPAR-α modulator, is a novel compound currently under investigation for the treatment of hypertriglyceridemia in the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Diabetic Patients (PROMINENT) trial. This

large, randomized, placebo-controlled trial will examine the efficacy of pemafibrate vs placebo on CV outcomes in approximately 10,000 high-risk patients with diabetes with hypertriglyceridemia and low HDL-C levels who are taking concomitant statin therapy (173, 174).

In conclusion, it is established that LDL is the primary causal factor in the development of atherosclerosis. As such, treatment targeting LDL-C remains a cornerstone for primary and secondary prevention of ASCVD. However, despite substantial reduction in atherosclerotic risk with statins and additional LDL-C–lowering therapies, patients continue to be at a substantial residual risk for recurrent events. Findings from observational and genetic epidemiological studies are consistent and strongly support a causal role of TGRL and/or RC as risk factors for ASCVD. These insights have ushered in an exciting new era of precise therapeutic targeting. Many of these novel investigational agents are in late-stage development with proof of impressive TG-lowering efficacy. The results of the ongoing RCTs testing their impact on CV outcomes are eagerly awaited and are poised to answer the question of whether TGRLs drive ASCVD and whether they should be targeted therapeutically.

References

1. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in J Am Coll Cardiol. 2014;63(25 Pt B):3024–3025]. *J Am Coll Cardiol*. 2014;**63**(25 Pt B):2889–2934.
2. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL, Cooney MT; ESC Scientific Document Group. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J*. 2016;**37**(39):2999–3058.
3. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, McKenney JM, Grundy SM, Gill EA, Wild RA, Wilson DP, Brown WV. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1--full report. *J Clin Lipidol*. 2015;**9**(2):129–169.
4. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, Kahn J, Afonso L, Williams KA Sr, Flack JM. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol*. 2012;**60**(25):2631–2639.
5. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006;**354**(12):1264–1272.
6. Holmes MV, Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, Dale CE, Padmanabhan S, Finan C, Swerdlow DI, Tragante V, van Iperen EP, Sivapalaratnam S, Shah S, Elbers CC, Shah T, Engmann J, Giambartolomei C, White J, Zabaneh D, Sofat R, McLachlan S, Doevendans PA, Balmforth AJ, Hall AS, North KE, Almoguera B, Hoogeveen RC, Cushman M, Fornage M, Patel SR, Redline S, Siscovick DS, Tsai MY, Karczewski KJ, Hofker MH, Verschuren WM, Bots ML, van der Schouw YT, Melander O, Dominiczak AF, Morris R, Ben-Shlomo Y, Price J, Kumari M, Baumert J, Peters A, Thorand B, Koenig W, Gaunt TR, Humphries SE, Clarke R, Watkins H, Farrall M, Wilson JG, Rich SS, de Bakker PI, Lange LA, Davey Smith G, Reiner AP, Talmud PJ, Kivimäki M, Lawlor DA, Dudbridge F, Samani NJ, Keating BJ, Hingorani AD, Casas JP; UCLEB consortium. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J*. 2015;**36**(9):539–550.
7. Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, Thompson A, Butterworth AS, Sarwar N, Wormser D, Saleheen D, Ballantyne CM, Psaty BM, Sundström J, Ridker PM, Nagel D, Gillum RF, Ford I, Ducimetiere P, Kiechl S, Koenig W, Dullaart RP, Assmann G, D'Agostino RB Sr, Dagenais GR, Cooper JA, Kromhout D, Onat A, Tipping RW, Gómez-de-la-Cámara A, Rosengren A, Sutherland SE, Gallacher J, Fowkes FG, Casiglia E, Hofman A, Salomaa V, Barrett-Connor E, Clarke R, Brunner E, Jukema JW, Simons LA, Sandhu M, Wareham NJ, Khaw KT, Kauhanen J, Salonen JT, Howard WJ, Nordestgaard BG, Wood AM, Thompson SG, Boekholdt SM, Sattar N, Packard C, Gudnason V, Danesh J; Emerging Risk Factors Collaboration. Lipid-related markers and cardiovascular disease prediction. *JAMA*. 2012;**307**(23):2499–2506.
8. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;**370**(9602):1829–1839.
9. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, Braunwald E, Sabatine MS. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA*. 2016;**316**(12):1289–1297.
10. Sampson UK, Fazio S, Linton MF. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. *Curr Atheroscler Rep*. 2012;**14**(1):1–10.
11. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. *Circ Res*. 2016;**118**(4):547–563.
12. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, Goldberg AC, Howard WJ, Jacobson MS, Kris-Etherton PM, Lennie TA, Levi M, Mazzone T, Pennathur S; American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism Council on Arteriosclerosis, Thrombosis and Vascular Biology Council on Cardiovascular Nursing, Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2011;**123**(20):2292–2333.
13. Rosenson RS, Davidson MH, Hirsh BJ, Kathiresan S, Gaudet D. Genetics and causality of triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease. *J Am Coll Cardiol*. 2014;**64**(23):2525–2540.
14. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Mäenpää H, Mälkönen M, Mänttäri M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjöblom T, Nikkilä EA. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;**317**(20):1237–1245.
15. Shapiro MD, Fazio S. From lipids to inflammation: new approaches to reducing atherosclerotic risk. *Circ Res*. 2016;**118**(4):732–749.
16. Lalloyer F, Staels B. Fibrates, glitazones, and peroxisome proliferator-activated receptors. *Arterioscler Thromb Vasc Biol*. 2010;**30**(5):894–899.
17. Libby P. Triglycerides on the rise: should we swap seats on the seesaw? *Eur Heart J*. 2015;**36**(13):774–776.
18. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W; AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;**365**(24):2255–2267.
19. Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitziel NO, Lange LA, Lu Y, Tang ZZ, Zhang H, Hindy G, Masca N, Stirrups K, Kanoni S, Do R, Jun G, Hu Y, Kang HM, Xue C, Goel A, Farrall M, Duga S, Merlini PA, Asselta R, Girelli D, Olivieri O, Martinelli N, Yin W, Reilly D, Speliotes E, Fox CS, Hveem K, Holmen OL, Nikpay M, Farlow DN, Assimes TL, Franceschini N, Robinson J, North KE, Martin LW, DePristo M, Gupta N, Escher SA, Jansson JH, Van Zuydam N, Palmer CN, Wareham N, Koch W, Meitinger T, Peters A, Lieb W, Erbel R, Konig IR, Kruppa J, Degenhardt F, Gottesman O, Bottinger EP, O'Donnell CJ, Psaty BM, Ballantyne CM, Abecasis G, Ordovas JM, Melander O, Watkins H, Orho-Melander M, Ardissino D, Loos RJ, McPherson R, Willer CJ, Erdmann J, Hall AS, Samani NJ, Deloukas P, Schunkert H, Wilson JG, Kooperberg C, Rich SS,

Tracy RP, Lin DY, Altshuler D, Gabriel S, Nickerson DA, Jarvik GP, Cupples LA, Reiner AP, Boerwinkle E, Kathiresan S; TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med*. 2014;**371**(1):22–31.
20. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;**357**(21):2109–2122.
21. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;**367**(22):2089–2099.
22. Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, Gibson CM, Granger C, Menon V, Montalescot G, Rader D, Tall AR, McErlean E, Wolski K, Ruotolo G, Vangerow B, Weerakkody G, Goodman SG, Conde D, McGuire DK, Nicolau JC, Leiva-Pons JL, Pesant Y, Li W, Kandath D, Kouz S, Tahirkheli N, Mason D, Nissen SE; ACCELERATE Investigators. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. *N Engl J Med*. 2017;**376**(20):1933–1942.
23. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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). *JAMA*. 2001;**285**(19):2486–2497.
24. Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Borén J, Catapano AL, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Nordestgaard BG, Ray KK, Reiner Z, Taskinen MR, Tokgözoglu L, Tybjærg-Hansen A, Watts GF; European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J*. 2011;**32**(11):1345–1361.
25. Cohen JD, Cziraky MJ, Cai Q, Wallace A, Wasser T, Crouse JR, Jacobson TA. 30-year trends in serum lipids among United States adults: results from the National Health and Nutrition Examination Surveys II, III, and 1999-2006. *Am J Cardiol*. 2010;**106**(7):969–975.
26. Scherer J, Singh VP, Pitchumoni CS, Yadav D. Issues in hypertriglyceridemic pancreatitis: an update. *J Clin Gastroenterol*. 2014;**48**(3):195–203.
27. Karalis DG. A review of clinical practice guidelines for the management of hypertriglyceridemia: a focus on high dose omega-3 fatty acids. *Adv Ther*. 2017;**34**(2):300–323.
28. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects and treatment. *CMAJ*. 2007;**176**(8):1113–1120.
29. Klop B, do Rego AT, Cabezas MC. Alcohol and plasma triglycerides. *Curr Opin Lipidol*. 2013;**24**(4):321–326.
30. Tenenbaum A, Klempfner R, Fisman EZ. Hypertriglyceridemia: a too long unfairly neglected major cardiovascular risk factor. *Cardiovasc Diabetol*. 2014;**13**(1):159.
31. Goldberg AS, Hegele RA. Severe hypertriglyceridemia in pregnancy. *J Clin Endocrinol Metab*. 2012;**97**(8):2589–2596.
32. Pearce EN. Hypothyroidism and dyslipidemia: modern concepts and approaches. *Curr Cardiol Rep*. 2004;**6**(6):451–456.
33. Tsimihodimos V, Mitrogianni Z, Elisaf M. Dyslipidemia associated with chronic kidney disease. *Open Cardiovasc Med J*. 2011;**5**(1):41–48.
34. Grundy SM. Small LDL, atherogenic dyslipidemia, and the metabolic syndrome. *Circulation*. 1997;**95**(1):1–4.
35. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. adults. *Diabetes Care*. 2004;**27**(10):2444–2449.
36. Haas ME, Attie AD, Biddinger SB. The regulation of ApoB metabolism by insulin. *Trends Endocrinol Metab*. 2013;**24**(8):391–397.
37. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, Borén J, Bruckert E, Catapano AL, Descamps OS, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Stroes E, Taskinen MR, Tybjærg-Hansen A, Watts GF, Wiklund O; European Atherosclerosis Society Consensus Panel. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol*. 2014;**2**(8):655–666.
38. Watts GF, Ooi EM, Chan DC. Demystifying the management of hypertriglyceridaemia. *Nat Rev Cardiol*. 2013;**10**(11):648–661.
39. Johansen CT, Kathiresan S, Hegele RA. Genetic determinants of plasma triglycerides. *J Lipid Res*. 2011;**52**(2):189–206.
40. Chait A, Subramanian S, Brunzell JD. Genetic Disorders of Triglyceride Metabolism. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, and Vinik A, eds. *Endotext*. South Dartmouth, MA: MDText.com; 2000.
41. Toth PP. Triglyceride-rich lipoproteins as a causal factor for cardiovascular disease. *Vasc Health Risk Manag*. 2016;**12**:171–183.
42. Conlon DM, Thomas T, Fedotova T, Hernandez-Ono A, Di Paolo G, Chan RB, Ruggles K, Gibeley S, Liu J, Ginsberg HN. Inhibition of apolipoprotein B synthesis stimulates endoplasmic reticulum autophagy that prevents steatosis. *J Clin Invest*. 2016;**126**(10):3852–3867.
43. Lee RG, Fu W, Graham MJ, Mullick AE, Sipe D, Gattis D, Bell TA, Booten S, Crooke RM. Comparison of the pharmacological profiles of murine antisense oligonucleotides targeting apolipoprotein B and microsomal triglyceride transfer protein. *J Lipid Res*. 2013;**54**(3):602–614.
44. Cuchel M, Rader DJ. Microsomal transfer protein inhibition in humans. *Curr Opin Lipidol*. 2013;**24**(3):246–250.
45. Davies BS, Beigneux AP, Barnes RH II, Tu Y, Gin P, Weinstein MM, Nobumori C, Nyrén R, Goldberg I, Olivecrona G, Bensadoun A, Young SG, Fong LG. GPIHBP1 is responsible for the entry of lipoprotein lipase into capillaries. *Cell Metab*. 2010;**12**(1):42–52.
46. Young SG, Davies BS, Voss CV, Gin P, Weinstein MM, Tontonoz P, Reue K, Bensadoun A, Fong LG, Beigneux AP. GPIHBP1, an endothelial cell transporter for lipoprotein lipase. *J Lipid Res*. 2011;**52**(11):1869–1884.
47. Péterfy M, Ben-Zeev O, Mao HZ, Weissglas-Volkov D, Aouizerat BE, Pullinger CR, Frost PH, Kane JP, Malloy MJ, Reue K, Pajukanta P, Doolittle MH. Mutations in LMF1 cause combined lipase deficiency and severe hypertriglyceridemia. *Nat Genet*. 2007;**39**(12):1483–1487.
48. Kersten S. Physiological regulation of lipoprotein lipase. *Biochim Biophys Acta* 2014;**1841**:919–933.
49. Gaudet D, Brisson D, Tremblay K, Alexander VJ, Singleton W, Hughes SG, Geary RS, Baker BF, Graham MJ, Crooke RM, Witztum JL. Targeting APOC3 in the familial chylomicronemia syndrome. *N Engl J Med*. 2014;**371**(23):2200–2206.
50. Larsson M, Vorrsjö E, Talmud P, Lookene A, Olivecrona G. Apolipoproteins C-I and C-III inhibit lipoprotein lipase activity by displacement of the enzyme from lipid droplets. *J Biol Chem*. 2013;**288**(47):33997–34008.
51. Goldberg IJ, Scheraldi CA, Yacoub LK, Saxena U, Bisgaier CL. Lipoprotein ApoC-II activation of lipoprotein lipase. Modulation by apolipoprotein A-IV. *J Biol Chem*. 1990;**265**(8):4266–4272.
52. Lupo MG, Ferri N. Angiopoietin-Like 3 (ANGPTL3) and atherosclerosis: lipid and non-lipid related effects. *J Cardiovasc Dev Dis*. 2018;**5**(3):5.
53. Dijk W, Kersten S. Regulation of lipoprotein lipase by Angptl4. *Trends Endocrinol Metab*. 2014;**25**(3):146–155.
54. Haller JF, Mintah IJ, Shihanian LM, Stevis P, Buckler D, Alexa-Braun CA, Kleiner S, Banfi S, Cohen JC, Hobbs HH, Yancopoulos GD, Murphy AJ, Gusarova V, Gromada J. ANGPTL8 requires ANGPTL3 to inhibit lipoprotein lipase and plasma triglyceride clearance. *J Lipid Res*. 2017;**58**(6):1166–1173.
55. Varbo A, Nordestgaard BG. Remnant lipoproteins. *Curr Opin Lipidol*. 2017;**28**(4):300–307.
56. Borén J, Olin K, Lee I, Chait A, Wight TN, Innerarity TL. Identification of the principal proteoglycan-binding site in LDL. A single-point mutation in apo-B100 severely affects proteoglycan interaction without affecting LDL receptor binding. *J Clin Invest*. 1998;**101**(12):2658–2664.
57. Srinivasan SR, Vijayagopal P, Dalferes ER Jr, Abbate B, Radhakrishnamurthy B, Berenson GS. Low density lipoprotein retention by aortic tissue. Contribution of extracellular matrix. *Atherosclerosis*. 1986;**62**(3):201–208.
58. Martin SS, Blaha MJ, Elshazly MB, Brinton EA, Toth PP, McEvoy JW, Joshi PH, Kulkarni KR, Mize PD, Kwiterovich PO, Defilippis AP, Blumenthal RS, Jones SR. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. *J Am Coll Cardiol*. 2013;**62**(8):732–739.
59. Martin SS, Blaha MJ, Elshazly MB, Toth PP, Kwiterovich PO, Blumenthal RS, Jones SR. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *JAMA*. 2013;**310**(19):2061–2068.
60. Jepsen AM, Langsted A, Varbo A, Bang LE, Kamstrup PR, Nordestgaard BG. Increased remnant cholesterol explains part of residual risk of all-cause mortality in 5414 patients with ischemic heart disease. *Clin Chem*. 2016;**62**(4):593–604.
61. Nakajima K, Saito T, Tamura A, Suzuki M, Nakano T, Adachi M, Tanaka A, Tada N, Nakamura H, Campos E, Havel RJ. Cholesterol in remnant-like lipoproteins in human serum using monoclonal anti apo B-100 and anti apo A-I immunoaffinity mixed gels. *Clin Chim Acta*. 1993;**223**(1-2):53–71.
62. Nguyen SV, Nakamura T, Uematsu M, Fujioka D, Watanabe K, Watanabe Y, Obata JE, Nakamura K, Kugiyama K. Remnant lipoproteinemia predicts cardiovascular events in patients with type 2 diabetes and chronic kidney disease. *J Cardiol*. 2017;**69**(3):529–535.
63. Kulkarni KR. Cholesterol profile measurement by vertical auto profile method. *Clin Lab Med*. 2006;**26**(4):787–802.

64. Joshi PH, Khokhar AA, Massaro JM, Lirette ST, Griswold ME, Martin SS, Blaha MJ, Kulkarni KR, Correa A, D'Agostino RB Sr, Jones SR, Toth PP; Lipoprotein Investigators Collaborative (LIC) Study Group. Remnant lipoprotein cholesterol and incident coronary heart disease: the Jackson Heart and Framingham offspring cohort studies. *J Am Heart Assoc*. 2016;**5**(5).
65. Masuda D, Yamashita S. Postprandial hyperlipidemia and remnant lipoproteins. *J Atheroscler Thromb*. 2017;**24**(2):95–109.
66. Irawati D, Mamo JC, Dhaliwal SS, Soares MJ, Slivkoff-Clark KM, James AP. Plasma triglyceride and high density lipoprotein cholesterol are poor surrogate markers of pro-atherogenic chylomicron remnant homeostasis in subjects with the metabolic syndrome. *Lipids Health Dis*. 2016;**15**(1):169.
67. Nakajima K, Nagamine T, Fujita MQ, Ai M, Tanaka A, Schaefer E. Apolipoprotein B-48: a unique marker of chylomicron metabolism. *Adv Clin Chem*. 2014; **64**:117–177.
68. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation*. 2007;**115**(4):450–458.
69. Lee SH, Lee BW, Won HK, Moon JH, Kim KJ, Kang ES, Cha BS, Lee HC. Postprandial triglyceride is associated with fasting triglyceride and HOMA-IR in Korean subjects with type 2 diabetes. *Diabetes Metab J*. 2011;**35**(4):404–410.
70. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, Stalenhoef AF. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;**97**(9):2969–2989.
71. Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum H, Bruckert E, Watts GF, Sypniewska G, Wiklund O, Borén J, Chapman MJ, Cobbaert C, Descamps OS, von Eckardstein A, Kamstrup PR, Pulkki K, Kronenberg F, Remaley AT, Rifai N, Ros E, Langlois M; European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Joint Consensus Initiative. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Eur Heart J*. 2016;**37**(25): 1944–1958.
72. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J; Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;**302**(18):1993–2000.
73. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA*. 2007;**298**(3):309–316.
74. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. 2007;**298**(3): 299–308.
75. Doran B, Guo Y, Xu J, Weintraub H, Mora S, Maron DJ, Bangalore S. Prognostic value of fasting versus nonfasting low-density lipoprotein cholesterol levels on long-term mortality: insight from the National Health and Nutrition Examination Survey III (NHANES-III). *Circulation*. 2014;**130**(7):546–553.
76. Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol*. 2013;**61**(4):427–436.
77. Jørgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjærg-Hansen A. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. *Eur Heart J*. 2013;**34**(24): 1826–1833.
78. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA*. 2008;**300**(18):2142–2152.
79. Nordestgaard BG. A test in context: lipid profile, fasting versus nonfasting. *J Am Coll Cardiol*. 2017; **70**(13):1637–1646.
80. Langsted A, Freiberg JJ, Nordestgaard BG. Fasting and nonfasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. *Circulation*. 2008; **118**(20):2047–2056.
81. Dubois C, Beaumier G, Juhel C, Armand M, Portugal H, Pauli AM, Borel P, Latgé C, Lairon D. Effects of graded amounts (0-50 g) of dietary fat on postprandial lipemia and lipoproteins in normolipidemic adults. *Am J Clin Nutr*. 1998;**67**(1):31–38.
82. Mora S. Nonfasting for routine lipid testing: from evidence to action. *JAMA Intern Med*. 2016;**176**(7): 1005–1006.
83. Anderson TJ, Grégoire J, Pearson GJ, Barry AR, Couture P, Dawes M, Francis GA, Genest J Jr, Grover S, Gupta M, Hegele RA, Lau DC, Leiter LA, Lonn E, Mancini GB, McPherson R, Ngui D, Poirier P, Sievenpiper JL, Stone JA, Thanassoulis G, Ward R. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can J Cardiol*. 2016;**32**(11):1263–1282.
84. Scartezini M, Ferreira CEDS, Izar MCO, Bertoluci M, Vencio S, Campana GA, Sumita NM, Barcelos LF, Faludi AA, Santos RD, Malachias MVB, Aquino JL, Galoro CAO, Sabino C, Gurgel MHC, Turatti LAA, Hohl A, Martinez TLDR. Positioning about the flexibility of fasting for lipid profiling. *Arq Bras Cardiol*. 2017;**108**(3):195–197.
85. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, Pessah-Pollack R, Wyne K, Smith D, Brinton EA, Fazio S, Davidson M. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocr Pract*. 2017;**23**(Suppl 2):1–87.
86. Reiner Ž. Hypertriglyceridaemia and risk of coronary artery disease. *Nat Rev Cardiol*. 2017;**14**(7):401–411.
87. Nordestgaard BG, Stender S, Kjeldsen K. Reduced atherogenesis in cholesterol-fed diabetic rabbits. Giant lipoproteins do not enter the arterial wall. *Arteriosclerosis*. 1988;**8**(4):421–428.
88. Nordestgaard BG, Zilversmit DB. Large lipoproteins are excluded from the arterial wall in diabetic cholesterol-fed rabbits. *J Lipid Res*. 1988;**29**(11): 1491–1500.
89. Teramoto R, Tada H, Kawashiri MA, Nohara A, Nakahashi T, Konno T, Inazu A, Mabuchi H, Yamagishi M, Hayashi K. Molecular and functional characterization of familial chylomicronemia syndrome. *Atherosclerosis*. 2018;**269**:272–278.
90. Miller YI, Choi SH, Fang L, Tsimikas S. Lipoprotein modification and macrophage uptake: role of pathologic cholesterol transport in atherogenesis. *Subcell Biochem*. 2010;**51**:229–251.
91. Vogel RA, Corretti MC, Plotnick GD. Effect of a single high-fat meal on endothelial function in healthy subjects. *Am J Cardiol*. 1997;**79**(3):350–354.
92. Maggi FM, Raselli S, Grigore L, Redaelli L, Fantappiè S, Catapano AL. Lipoprotein remnants and endothelial dysfunction in the postprandial phase. *J Clin Endocrinol Metab*. 2004;**89**(6):2946–2950.
93. Boquist S, Ruotolo G, Tang R, Björkegren J, Bond MG, de Faire U, Karpe F, Hamsten A. Alimentary lipemia, postprandial triglyceride-rich lipoproteins, and common carotid intima-media thickness in healthy, middle-aged men. *Circulation*. 1999;**100**(7): 723–728.
94. Shin HK, Kim YK, Kim KY, Lee JH, Hong KW. Remnant lipoprotein particles induce apoptosis in endothelial cells by NAD(P)H oxidase-mediated production of superoxide and cytokines via lectin-like oxidized low-density lipoprotein receptor-1 activation: prevention by cilostazol. *Circulation*. 2004; **109**(8):1022–1028.
95. Steinberg HO, Tarshoby M, Monestel R, Hook G, Cronin J, Johnson A, Bayazeed B, Baron AD. Elevated circulating free fatty acid levels impair endothelium-dependent vasodilation. *J Clin Invest*. 1997;**100**(5):1230–1239.
96. Anderson RA, Evans ML, Ellis GR, Graham J, Morris K, Jackson SK, Lewis MJ, Rees A, Frenneaux MP. The relationships between post-prandial lipaemia, endothelial function and oxidative stress in healthy individuals and patients with type 2 diabetes. *Atherosclerosis*. 2001;**154**(2):475–483.
97. Doi H, Kugiyama K, Oka H, Sugiyama S, Ogata N, Koide SI, Nakamura SI, Yasue H. Remnant lipoproteins induce proatherothrombogenic molecules in endothelial cells through a redox-sensitive mechanism. *Circulation*. 2000;**102**(6):670–676.
98. Hua S. Targeting sites of inflammation: intercellular adhesion molecule-1 as a target for novel inflammatory therapies. *Front Pharmacol*. 2013;**4**:127.
99. Olufadi R, Byrne CD. Effects of VLDL and remnant particles on platelets. *Pathophysiol Haemost Thromb*. 2006;**35**(3-4):281–291.
100. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet*. 2014;**384**(9943):626–635.
101. Varbo A, Benn M, Tybjærg-Hansen A, Nordestgaard BG. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. *Circulation*. 2013;**128**(12):1298–1309.
102. Stensvold I, Tverdal A, Urdal P, Graff-Iversen S. Non-fasting serum triglyceride concentration and mortality from coronary heart disease and any cause in middle aged Norwegian women. *BMJ*. 1993; **307**(6915):1318–1322.
103. Stavenow L, Kjellström T. Influence of serum triglyceride levels on the risk for myocardial infarction in 12,510 middle aged males: interaction with serum cholesterol. *Atherosclerosis*. 1999;**147**(2):243–247.
104. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. *Circulation*. 1998;**97**(11):1029–1036.
105. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;**3**(2):213–219.
106. Varbo A, Nordestgaard BG. Nonfasting triglycerides, low-density lipoprotein cholesterol, and heart failure risk: two cohort studies of 113 554 individuals. *Arterioscler Thromb Vasc Biol*. 2018;**38**(2):464–472.
107. Holmes MV, Millwood IY, Kartsonaki C, Hill MR, Bennett DA, Boxall R, Guo Y, Xu X, Bian Z, Hu R,

Walters RG, Chen J, Ala-Korpela M, Parish S, Clarke RJ, Peto R, Collins R, Li L, Chen Z; China Kadoorie Biobank Collaborative Group. Lipids, lipoproteins, and metabolites and risk of myocardial infarction and stroke. *J Am Coll Cardiol*. 2018;**71**(6):620–632.

108. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E; PROVE IT-TIMI 22 Investigators. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*. 2008;**51**(7):724–730.
109. Faergeman O, Holme I, Fayyad R, Bhatia S, Grundy SM, Kastelein JJ, LaRosa JC, Larsen ML, Lindahl C, Olsson AG, Tikkanen MJ, Waters DD, Pedersen TR; Steering Committees of IDEAL and TNT Trials. Plasma triglycerides and cardiovascular events in the Treating to New Targets and Incremental Decrease in End-Points through Aggressive Lipid Lowering trials of statins in patients with coronary artery disease. *Am J Cardiol*. 2009;**104**(4):459–463.
110. Musunuru K, Kathiresan S. Surprises from genetic analyses of lipid risk factors for atherosclerosis. *Circ Res*. 2016;**118**(4):579–585.
111. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet*. 2012;**380**(9841):572–580.
112. Varbo A, Freiberg JJ, Nordestgaard BG. Extreme nonfasting remnant cholesterol vs extreme LDL cholesterol as contributors to cardiovascular disease and all-cause mortality in 90000 individuals from the general population. *Clin Chem*. 2015;**61**(3):533–543.
113. Goliasch G, Wiesbauer F, Blessberger H, Demyanets S, Wojta J, Huber K, Maurer G, Schillinger M, Speidl WS. Premature myocardial infarction is strongly associated with increased levels of remnant cholesterol. J Clin Lipidol. 2015;9:801–806.e801.
114. Bittencourt MS, Santos RD, Staniak H, Sharovsky R, Kondapally R, Vallejo-Vaz AJ, Ray KK, Bensenor I, Lotufo P. Relation of fasting triglyceride-rich lipoprotein cholesterol to coronary artery calcium score (from the ELSA-Brasil Study). *Am J Cardiol*. 2017;**119**(9):1352–1358.
115. Ference BA. Causal effect of lipids and lipoproteins on atherosclerosis: lessons from genomic studies. *Cardiol Clin*. 2018;**36**(2):203–211.
116. Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkilä K, Hyppönen E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikäinen LP, Magnusson PK, Mangino M, Mihailov E, Montasser ME, Müller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney AS, Döring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimäki T, Lin SY, Lindström J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Müller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stančáková A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrières J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Järvelin MR, Jula A, Kähönen M, Kaprio J, Kesäniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, März W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njølstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BH, Altshuler D, Ordovas JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Mohlke KL, Ingelsson E, Abecasis GR, Daly MJ, Neale BM, Kathiresan S. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet*. 2013;**45**(11):1345–1352.
117. Thomsen M, Varbo A, Tybjærg-Hansen A, Nordestgaard BG. Low nonfasting triglycerides and reduced all-cause mortality: a mendelian randomization study. *Clin Chem*. 2014;**60**(5):737–746.
118. Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, Boekholdt SM, Ouwehand W, Watkins H, Samani NJ, Saleheen D, Lawlor D, Reilly MP, Hingorani AD, Talmud PJ, Danesh J; Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies [published correction appears in Lancet. 2010;376(9735):90]. *Lancet*. 2010;**375**(9726):1634–1639.
119. Do R, Stitziel NO, Won HH, Jørgensen AB, Duga S, Angelica Merlini P, Kiezun A, Farrall M, Goel A, Zuk O, Guella I, Asselta R, Lange LA, Peloso GM, Auer PL, Girelli D, Martinelli N, Farlow DN, DePristo MA, Roberts R, Stewart AF, Saleheen D, Danesh J, Epstein SE, Sivapalaratnam S, Hovingh GK, Kastelein JJ, Samani NJ, Schunkert H, Erdmann J, Shah SH, Kraus WE, Davies R, Nikpay M, Johansen CT, Wang J, Hegele RA, Hechter E, Marz W, Kleber ME, Huang J, Johnson AD, Li M, Burke GL, Gross M, Liu Y, Assimes TL, Heiss G, Lange EM, Folsom AR, Taylor HA, Olivieri O, Hamsten A, Clarke R, Reilly DF, Yin W, Rivas MA, Donnelly P, Rossouw JE, Psaty BM, Herrington DM, Wilson JG, Rich SS, Bamshad MJ, Tracy RP, Cupples LA, Rader DJ, Reilly MP, Spertus JA, Cresci S, Hartiala J, Tang WH, Hazen SL, Allayee H, Reiner AP, Carlson CS, Kooperberg C, Jackson RD, Boerwinkle E, Lander ES, Schwartz SM, Siscovick DS, McPherson R, Tybjaerg-Hansen A, Abecasis GR, Watkins H, Nickerson DA, Ardissino D, Sunyaev SR, O'Donnell CJ, Altshuler D, Gabriel S, Kathiresan S; NHLBI Exome Sequencing Project. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. *Nature*. 2015;**518**(7537):102–106.
120. Pollin TI, Damcott CM, Shen H, Ott SH, Shelton J, Horenstein RB, Post W, McLenithan JC, Bielak LF, Peyser PA, Mitchell BD, Miller M, O'Connell JR, Shuldiner AR. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. *Science*. 2008;**322**(5908):1702–1705.
121. Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjærg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N Engl J Med*. 2014;**371**(1):32–41.
122. Folsom AR, Peacock JM, Demerath E, Boerwinkle E. Variation in ANGPTL4 and risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. *Metabolism*. 2008;**57**(11):1591–1596.
123. Stitziel NO, Khera AV, Wang X, Bierhals AJ, Vourakis AC, Sperry AE, Natarajan P, Klarin D, Emdin CA, Zekavat SM, Nomura A, Erdmann J, Schunkert H, Samani NJ, Kraus WE, Shah SH, Yu B, Boerwinkle E, Rader DJ, Gupta N, Frossard PM, Rasheed A, Danesh J, Lander ES, Gabriel S, Saleheen D, Musunuru K, Kathiresan S; PROMIS and Myocardial Infarction Genetics Consortium Investigators. ANGPTL3 deficiency and protection against coronary artery disease. *J Am Coll Cardiol*. 2017;**69**(16):2054–2063.
124. Dewey FE, Gusarova V, Dunbar RL, O'Dushlaine C, Schurmann C, Gottesman O, McCarthy S, Van Hout CV, Bruse S, Dansky HM, Leader JB, Murray MF, Ritchie MD, Kirchner HL, Habegger L, Lopez A, Penn J, Zhao A, Shao W, Stahl N, Murphy AJ, Hamon S, Bouzelmat A, Zhang R, Shumel B, Pordy R, Gipe D, Herman GA, Sheu WHH, Lee IT, Liang KW, Guo X, Rotter JI, Chen YI, Kraus WE, Shah SH, Damrauer S, Small A, Rader DJ, Wulff AB, Nordestgaard BG, Tybjærg-Hansen A, van den Hoek AM, Princen HMG, Ledbetter DH, Carey DJ, Overton JD, Reid JG, Sasiela WJ, Banerjee P, Shuldiner AR, Borecki IB, Teslovich TM, Yancopoulos GD, Mellis SJ, Gromada J, Baras A. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N Engl J Med*. 2017;**377**(3):211–221.

125. Cohen JC, Stender S, Hobbs HH. APOC3, coronary disease, and complexities of Mendelian randomization. *Cell Metab*. 2014;**20**(3):387–389.
126. Musunuru K, Pirruccello JP, Do R, Peloso GM, Guiducci C, Sougnez C, Garimella KV, Fisher S, Abreu J, Barry AJ, Fennell T, Banks E, Ambrogio L, Cibulskis K, Kernytsky A, Gonzalez E, Rudzicz N, Engert JC, DePristo MA, Daly MJ, Cohen JC, Hobbs HH, Altshuler D, Schonfeld G, Gabriel SB, Yue P, Kathiresan S. Exome sequencing, ANGPTL3 mutations, and familial combined hypolipidemia. *N Engl J Med*. 2010;**363**(23):2220–2227.
127. Dewey FE, Gusarova V, O'Dushlaine C, Gottesman O, Trejos J, Hunt C, Van Hout CV, Habegger L, Buckler D, Lai KM, Leader JB, Murray MF, Ritchie MD, Kirchner HL, Ledbetter DH, Penn J, Lopez A, Borecki IB, Overton JD, Reid JG, Carey DJ, Murphy AJ, Yancopoulos GD, Baras A, Gromada J, Shuldiner AR. Inactivating variants in ANGPTL4 and risk of coronary artery disease. *N Engl J Med*. 2016;**374**(12):1123–1133.
128. Wittrup HH, Tybjaerg-Hansen A, Nordestgaard BG. Lipoprotein lipase mutations, plasma lipids and lipoproteins, and risk of ischemic heart disease. A meta-analysis. *Circulation*. 1999;**99**(22):2901–2907.
129. Nordestgaard BG, Abildgaard S, Wittrup HH, Steffensen R, Jensen G, Tybjaerg-Hansen A. Heterozygous lipoprotein lipase deficiency: frequency in the general population, effect on plasma lipid levels, and risk of ischemic heart disease. *Circulation*. 1997;**96**(6):1737–1744.
130. Rip J, Nierman MC, Ross CJ, Jukema JW, Hayden MR, Kastelein JJ, Stroes ES, Kuivenhoven JA. Lipoprotein lipase S447X: a naturally occurring gain-of-function mutation. *Arterioscler Thromb Vasc Biol*. 2006;**26**(6):1236–1245.
131. Stein EA, Lane M, Laskarzewski P. Comparison of statins in hypertriglyceridemia. *Am J Cardiol*. 1998;**81**(4A)66B–69B.
132. Van Gaal LF, Wauters MA, De Leeuw IH. The beneficial effects of modest weight loss on cardiovascular risk factors. *Int J Obes Relat Metab Disord*. 1997;**21**(Suppl 1):S5–S9.
134. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr*. 1992;**56**(2):320–328.
135. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER III, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, Charleston J, McCarron P, Bishop LM; OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA*. 2005;**294**(19):2455–2464.
135. Rumawas ME, Meigs JB, Dwyer JT, McKeown NM, Jacques PF. Mediterranean-style dietary pattern, reduced risk of metabolic syndrome traits, and incidence in the Framingham Offspring Cohort. *Am J Clin Nutr*. 2009;**90**(6):1608–1614.
136. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J; Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med*. 1999;**341**(6):410–418.
137. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;**366**(9500):1849–1861.
138. The BIP Study Group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. The Bezafibrate Infarction Prevention (BIP) study. *Circulation*. 2000;**102**(1):21–27.
139. Scott R, O'Brien R, Fulcher G, Pardy C, D'Emden M, Tse D, Taskinen MR, Ehnholm C, Keech A; Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study Investigators. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetes Care*. 2009;**32**(3):493–498.
140. Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, McNamara JR, Kashyap ML, Hershman JM, Wexler LF, Rubins HB; VA-HIT Study Group. Veterans Affairs High-Density Lipoprotein Intervention Trial. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA*. 2001;**285**(12):1585–1591.
141. Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Mänttäri M, Heinonen OP, Frick MH. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation*. 1992;**85**(1):37–45.
142. Sacks FM, Carey VJ, Fruchart JC. Combination lipid therapy in type 2 diabetes. *N Engl J Med*. 2010;**363**(7):692–694.
143. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, Grobbee DE, Cass A, Chalmers J, Perkovic V. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet*. 2010;**375**(9729):1875–1884.
144. Jakob T, Nordmann AJ, Schandelmaier S, Ferreira-González I, Briel M. Fibrates for primary prevention of cardiovascular disease events. *Cochrane Database Syst Rev*. 2016;**11**:CD009753.
145. Wang D, Liu B, Tao W, Hao Z, Liu M. Fibrates for secondary prevention of cardiovascular disease and stroke. *Cochrane Database Syst Rev*. 2015; (10):CD009580.
146. Ginsberg HN, Elam MB, Lovato LC, Crouse JR III, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC Jr, Cushman WC, Simons-Morton DG, Byington RP; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;**362**(17):1563–1574.
147. Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol*. 2018;**72**(3):330–343.
148. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol*. 2011;**58**(20):2047–2067.
149. Jacobson TA, Glickstein SB, Rowe JD, Soni PN. Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: a review. *J Clin Lipidol*. 2012;**6**(1):5–18.
150. Siscovick DS, Barringer TA, Fretts AM, Wu JH, Lichtenstein AH, Costello RB, Kris-Etherton PM, Jacobson TA, Engler MB, Alger HM, Appel LJ, Mozaffarian D; American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association. *Circulation*. 2017;**135**(15):e867–e884.
151. Schuchardt JP, Schneider I, Meyer H, Neubronner J, von Schacky C, Hahn A. Incorporation of EPA and DHA into plasma phospholipids in response to different omega-3 fatty acid formulations--a comparative bioavailability study of fish oil vs. krill oil. *Lipids Health Dis*. 2011;**10**(1):145.
152. Alexander DD, Miller PE, Van Elswyk ME, Kuratko CN, Bylsma LC. A meta-analysis of randomized controlled trials and prospective cohort studies of eicosapentaenoic and docosahexaenoic long-chain omega-3 fatty acids and coronary heart disease risk. *Mayo Clin Proc*. 2017;**92**(1):15–29.
153. Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med*. 2002;**112**(4):298–304.
154. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA*. 2012;**308**(10):1024–1033.
155. Kwak SM, Myung SK, Lee YJ, Seo HG; Korean Meta-analysis Study Group. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. *Arch Intern Med*. 2012;**172**(9):686–694.
156. Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. Omega 3 fatty acids and cardiovascular outcomes: systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2012;**5**(6):808–818.
157. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;**369**(9567):1090–1098.
158. Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; JELIS Investigators, Japan. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis*. 2008;**200**(1):135–140.
159. Brandt TA, Lee RG, Digenio A, Graham MG, Crooke RM, Hughes SG, Singleton W, Witztum JL, Tsimikas S. ISIS-ANGPTL3RX, an antisense inhibitor to angiopoietin-like 3, reduces plasma lipid levels in mouse models and in healthy human volunteers. *Atherosclerosis*. 2015;**241**(1):e30–e31.
160. Khera AV, Everett BM, Caulfield MP, Hantash FM, Wohlgemuth J, Ridker PM, Mora S. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *Circulation*. 2014;**129**(6):635–642.
161. Albers JJ, Slee A, O'Brien KD, Robinson JG, Kashyap ML, Kwiterovich PO Jr, Xu P, Marcovina SM. Relationship of apolipoproteins A-1 and B, and lipoprotein(a) to cardiovascular outcomes: the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes). *J Am Coll Cardiol*. 2013;**62**(17):1575–1579.

162. Kastelein JJ, Hallén J, Vige R, Fraser DA, Zhou R, Hustvedt SO, Orloff DG, Bays HE. Icosabutate, a structurally engineered fatty acid, improves the cardiovascular risk profile in statin-treated patients with residual hypertriglyceridemia. *Cardiology*. 2016;**135**(1):3–12.
163. Graham MJ, Lee RG, Brandt TA, Tai LJ, Fu W, Peralta R, Yu R, Hurh E, Paz E, McEvoy BW, Baker BF, Pham NC, Digenio A, Hughes SG, Geary RS, Witztum JL, Crooke RM, Tsimikas S. Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides. *N Engl J Med*. 2017;**377**(3):222–232.
164. Nelson SD, Munger MA. Icosapent ethyl for treatment of elevated triglyceride levels. *Ann Pharmacother*. 2013;**47**(11):1517–1523.
165. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Jr., Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM, Investigators R-I. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;**380**:11–22.
166. Kastelein JJ, Maki KC, Susekov A, Ezhov M, Nordestgaard BG, Machielse BN, Kling D, Davidson MH. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa fOr Lowering Very high triglycerideS (EVOLVE) trial. *J Clin Lipidol*. 2014;**8**(1):94–106.
167. Qin W, Sundaram M, Wang Y, Zhou H, Zhong S, Chang CC, Manhas S, Yao EF, Parks RJ, McFie PJ, Stone SJ, Jiang ZG, Wang C, Figeys D, Jia W, Yao Z. Missense mutation in APOC3 within the C-terminal lipid binding domain of human ApoC-III results in impaired assembly and secretion of triacylglycerol-rich very low density lipoproteins: evidence that ApoC-III plays a major role in the formation of lipid precursors within the microsomal lumen. *J Biol Chem*. 2011;**286**(31):27769–27780.
168. Guyton JR, Slee AE, Anderson T, Fleg JL, Goldberg RB, Kashyap ML, Marcovina SM, Nash SD, O'Brien KD, Weintraub WS, Xu P, Zhao XQ, Boden WE. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). *J Am Coll Cardiol*. 2013;**62**(17):1580–1584.
169. Nordestgaard BG, Nicholls SJ, Langsted A, Ray KK, Tybjærg-Hansen A. Advances in lipid-lowering therapy through gene-silencing technologies. *Nat Rev Cardiol*. 2018;**15**(5):261–272.
170. Gaudet D, Alexander VJ, Baker BF, Brisson D, Tremblay K, Singleton W, Geary RS, Hughes SG, Viney NJ, Graham MJ, Crooke RM, Witztum JL, Brunzell JD, Kastelein JJ. Antisense inhibition of apolipoprotein C-III in patients with hypertriglyceridemia. *N Engl J Med*. 2015;**373**(5):438–447.
171. Graham MJ, Lee RG, Bell TA III, Fu W, Mullick AE, Alexander VJ, Singleton W, Viney N, Geary R, Su J, Baker BF, Burkey J, Crooke ST, Crooke RM. Antisense oligonucleotide inhibition of apolipoprotein C-III reduces plasma triglycerides in rodents, nonhuman primates, and humans. *Circ Res*. 2013;**112**(11):1479–1490.
172. Gaudet D, Méthot J, Kastelein J. Gene therapy for lipoprotein lipase deficiency. *Curr Opin Lipidol*. 2012;**23**(4):310–320.
173. Ferri N, Corsini A, Sirtori C, Ruscica M. PPAR-α agonists are still on the rise: an update on clinical and experimental findings. *Expert Opin Investig Drugs*. 2017;**26**(5):593–602.
174. Ishibashi S, Yamashita S, Arai H, Araki E, Yokote K, Suganami H, Fruchart JC, Kodama T; K-877-04 Study Group. Effects of K-877, a novel selective PPARα modulator (SPPARMα), in dyslipidaemic patients: a randomized, double blind, active- and placebo-controlled, phase 2 trial. *Atherosclerosis*. 2016;**249**:36–43.

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Abbreviations

Apo, apolipoprotein; *APOA5*, apolipoprotein A5; apoCIII, apolipoprotein C-III; ASCVD, atherosclerotic cardiovascular disease; ASO, antisense oligonucleotide; CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ER, endoplasmic reticulum; FA, fatty acid; FFA, free fatty acid; *GPD1*, glycerol-3-phosphate dehydrogenase 1; *GPIHBP1*, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein-1; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; IDL, intermediate-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LOF, loss of function; LPL, lipoprotein lipase; MI, myocardial infarction; MTP, microsomal triglyceride transport protein; OM3FA, omega-3 fatty acid; RC, remnant cholesterol; RCT, randomized controlled trial; siRNA, small interfering RNA; SNP, single-nucleotide polymorphism; T2DM, type 2 diabetes mellitus; TG, triglyceride; TGRL, triglyceride-rich lipoprotein; VLDL, very-low-density lipoprotein; VLDL-C, very-low-density lipoprotein cholesterol.