# Impact of Triglycerides on Lipid and Lipoprotein Biology in Women

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## ABSTRACT

**Background:** Because atherosclerosis, a leading cause of morbidity and mortality in women, is thought of as a sterol (cholesterol and noncholesterol sterol)-mediated disease, plasma triglyceride (TG) levels (the concentration of all TG trafficked within all of the lipoproteins per dL of plasma), TG biology, and TG pathobiology historically have been ignored or frequently misunderstood in both risk assessment and treatment decisions.

**Objectives:** This review presents information on the importance of TG (chemical name, triacylglycerol) in atherogenesis and the relationship of TG to gender, adiposopathy (the pathophysiological transformation of functional adipose tissue into an organ with pathogenic endocrine and immune responses), insulin resistance, sterol-trafficking lipoproteins, and overall vascular health. In addition, this review seeks to explain the complexities of lipid homeostasis and how it is influenced by lipid-modulating medications, reproductive hormones, and selective estrogen receptor modulators (SERMs).

**Methods:** Using peer-reviewed materials published in English from the extensive libraries of the authors, this narrative review references key epidemiologic, basic science lipid/lipoprotein publications as well as efficacy trials of lipid-modulating, hormonal, and SERM therapies.

**Results:** TG are associated with insulin resistance; the metabolic syndrome; increased atherogenic lipoproteins; and rheologic, inflammatory, and coagulation abnormalities. TG can be influenced by lifestyle and multiple medications used by women, including hormonal therapies. Several studies, but not all, support sex differences in TG.

**Conclusions:** Through effects on sterol-trafficking lipoproteins, TG have a significant influence on atherosclerotic cardiovascular disease risk in menopausal women. TG-rich lipoproteins are affected by lipid-modulating drugs, estrogen therapy, estrogen-progestogen therapy, and SERMs. (*Gend Med.* 2010;7:189–205) © 2010 Excerpta Medica Inc.

**Key words:** triglyceride, lipoprotein, apolipoprotein B, non–HDL-C, LDL-P, LDL size.

## INTRODUCTION

Despite aggressive risk assessment and treatment, primarily centered on cholesterol measurements, atherosclerotic disease outcomes in women continue to lag behind those seen in men.[1,2] Triglycerides (TG)—in which 3 fatty acids, variable as to saturated, monounsaturated, or polyunsaturated, are attached to a glycerol backbone (**Figure 1**[3])—are the means by which energy is trafficked by lipoproteins from the liver or jejunum to cells requiring energy (eg, muscles) or to cells that store energy (eg, adipocytes). Specific increases in serum TG-containing saturated fatty acids and decreases in TG-containing polyunsaturated fatty acids may characterize insulin resistance. Like most hydrophobic lipids, the majority of TG are trafficked within protein-enwrapped, water-soluble particles called *lipoproteins*. The importance of hypertriglyceridemia (HTG) or TG-rich lipoproteins (TGRLPs) in women was addressed in a corresponding journal in 2002.[4] Many of the novel concepts discussed at that time remain intact, but others do not, and much new information exists. It is the authors' intention to provide a current review of normal TG biology, TG pathobiology, the relationship of TG to coronary heart disease (CHD) risk, TG as a goal of therapy, and how TG can be influenced by therapeutic medications such as estrogen therapy (ET), estrogen/progestogen therapy (EPT), and selective estrogen receptor modulators (SERMs).

## METHODS

Using peer-reviewed materials published in English from the extensive libraries of the authors, this narrative review references key epidemiologic, basic science lipid/lipoprotein publications as well as efficacy trials of lipid-modulating, hormonal, and SERM therapies.

## DISCUSSION

### Normal Triglyceride Physiology

Atherogenesis, which results when sterols as core components of lipoproteins are trafficked into the arterial intima, is a lipoprotein-mediated disease.[5] TG influence atherogenesis by affecting both the composition and concentrations of all sterol-trafficking lipoproteins, and also by affecting rheologic, thrombotic, and inflammatory forces. Fatty acid and/or TG homeostasis is dependent on nutrition and physical activity, and is controlled by cellular energy–regulating nuclear transcription factors such as retinoid X receptor, peroxisome proliferator-activated receptors, liver X receptor, farnesoid X receptor, Forkhead box O1



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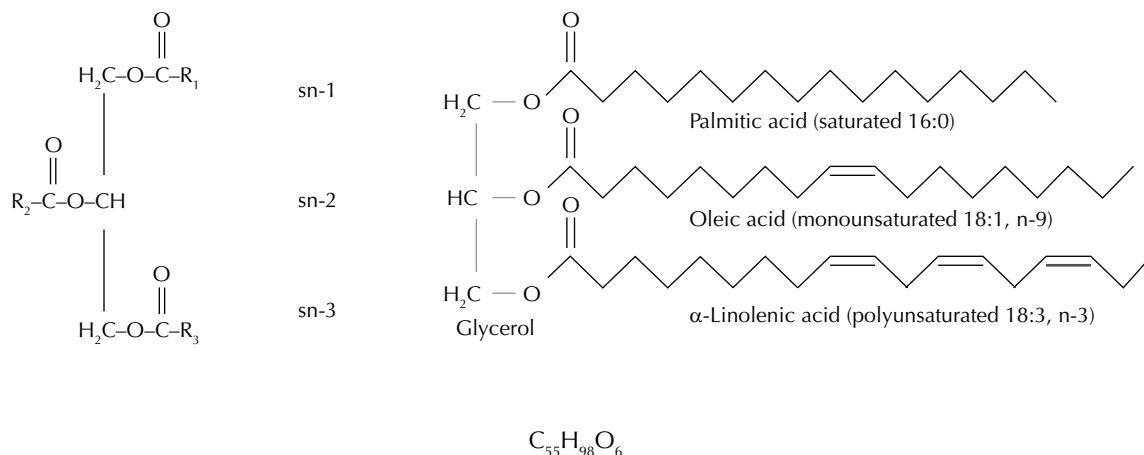
**Figure 1.** Triglycerides (TG) or triacylglycerols are water-insoluble lipids consisting of a mixture of 3 fatty acids (acyl group) esterified to 1 glycerol molecule at distinct positions described as stereospecific numbering (sn). They represent a concentrated source of metabolic energy contributing 9 kcal/g. TG consist of multiple different fatty acids, most with 16, 18, or 20 carbons. The most common saturated fats in TG are lauric and myristic acids (the tropical oils) and palmitic and stearic acids (from meats).[3] R = fatty acid chain.

receptor, short heterodimer partner protein, estrogen receptors, androgen receptors, and others.[6,7]

## Normal Triglyceride Trafficking

Fatty acids are absorbed, synthesized de novo, or derived from the hydrolysis of existing TG by lipases. Enterocytes, hepatocytes, and adipocytes produce the majority of TG in humans in a multistep process whereby, after synthesis or absorption, fatty acids are attached to glycerol, monoacylglycerol, and diacylglycerol.[8] When released from adipocytes or lipoproteins, fatty acids are bound to albumin and trafficked in plasma for use by cells including hepatocytes. In enterocytes or hepatocytes, single molecules of a structural apolipoprotein (apoB-48 and apoB-100, respectively) are lipidated in the endoplasmic reticulum with nonesterified or free cholesterol, cholesteryl ester (CE), TG, and phospholipids, creating primordial apoB-containing lipoproteins.[9,10] The intestinally produced lipoprotein is a chylomicron, and the hepatic-produced lipoprotein is a VLDL. ApoB-48 is the enterocyte-produced structural apolipoprotein that is shorter (truncated) than, and has 48% of the molecular weight of, hepatic-produced apoB-100. ApoB-100, but not apoB-48, also serves as a ligand for the LDL receptor. Several other surface proteins—including apolipoproteins A-V; C-I, -II, and -III; D; and E (also a ligand for the LDL receptor and LDL receptor-related protein)—are acquired by chylomicrons and VLDLs during assembly or on entry into the lymph (chylomicrons) or plasma (chylomicrons and VLDLs) by transfer from existing lipoproteins.[11] The liver secretes TG-richer VLDL in women than in men.[12]

Both chylomicrons and VLDLs are TGRLPs, with a core composition of ≥80% TG and 20% cholesterol (mostly in esterified form), whose function is to traffic energy in the form of TG to muscles and/or adipocytes whose vascular beds are enriched with a TG-hydrolyzing enzyme or triglyceridase termed *lipoprotein lipase*. In fasting states, the vast majority of TG is trafficked within VLDL and postprandially in both chylomicrons and VLDL. Lipolysis refers to the process by which the core TG are hydrolyzed to fatty acids by lipoprotein lipase on interaction with apoC-II, E, and A-V. As the

TGRLPs lose their core TG, their surface crumbles and the particles shrink, resulting in the liberation of phospholipids and some apolipoproteins. These now-smaller apoB-containing lipoproteins, primarily trafficking CE, are termed *chylomicron remnants*, *VLDL remnants*, or *intermediate-density lipoprotein* (IDL). The chylomicrons are usually rapidly cleared by a hepatic LDL receptor–related protein or LDL receptor/apoE interaction, whereas many of the smaller VLDLs and IDLs are cleared by LDL receptors via an apoE or apoB-100 interaction. Before removal, some of the smaller VLDLs and the IDLs undergo further lipolysis by hepatic lipase, an enzyme with both triglyceridase and phospholipase properties creating LDLs. Ultimately, the LDLs are also internalized by cellular LDL receptors (the vast majority of which are hepatic).[13] Because LDLs lack apoE, their clearance takes longer than do apoE-rich remnants, explaining the longer half-life of LDL particles (**Table I**). Although apoB concentrations are a collective sum of chylomicron, VLDL, IDL, and LDL particles, >90% of the circulating apoB particles are LDL because of their much longer plasma residence time. Both apoB (an immunoassay) and the LDL-particle concentration (LDL-P) tests (ultracentrifugation or nuclear magnetic resonance) are readily available from commercial laboratories.[14]

## Triglycerides and High-Density Lipoprotein

TG also influence the non-apoB particles or HDLs, which have 2 to 4 molecules of apoA-I and

**Table I.** Human apolipoprotein-B plasma residence time.

| Particle | Normal Half-Life | HTG States |
|---|---|---|
| Chylomicron | 1–2 Hours | Several hours |
| VLDL | 4–6 Hours | 8–12 Hours or more |
| IDL | 1–2 Hours | Increased |
| LDL | | |
|   Normal sized | 1.5–2 Days | 1.5–2 Days |
|   Small dense | 3–5 Days | 3–5 Days |

HTG = hypertriglyceridemia; IDL = intermediate-density lipoprotein.

no apoB as their main structural protein. HDLs have many biological functions, including trafficking numerous immunomodulatory and other proteins throughout the body as well as cholesterol obtained from liver, intestinal, and peripheral cells, including arterial wall sterol-laden macrophages. Although peripheral cells contribute, the vast majority (>90%) of plasma HDL-C originates in the liver and jejunum. HDLs traffic cholesterol to steroidogenic cells, adipocytes, and ultimately, back to the liver and intestine for reuse or excretion in bile and stool. Enhancing the lipid-trafficking system is the ability of all lipoproteins to share (swap) neutral lipids and apolipoproteins. TG and CE can be exchanged between the apoB and the apoA-I (HDL) particles using a hepatic-produced but HDL-trafficked protein called *apoD* or *cholesteryl ester transfer protein* (CETP). The ability of an HDL to pass its CE to an apoB particle allows the now-delipidated HDLs to acquire additional cellular free cholesterol.[15] In summary, during physiological circumstances, VLDLs, IDLs, and chylomicrons traffic energy (TG) and phospholipids to specific cells and then return the remaining particle core CE and phospholipids to the liver. Some IDLs become LDLs, CE-rich (80%) TG-poor (20%) particles that can serve as a supply of CE to cells needing it. All of the apoB-particles, including LDL, can also acquire CE from HDLs via the CETP process. Ultimately, VLDLs, IDLs, and LDLs return their cholesterol to the liver in a process termed *indirect reverse cholesterol transport*. Normal lipid homeostasis occurs when all lipoproteins lipidate and delipidate properly and efficiently and exist in physiological concentrations, and atherosclerosis cannot occur. Current lipid and lipoprotein nomenclature and concentrations are shown in **Figure 2**, **Table II**, and **Table III**[16].

## Lipoproteins and Atherogenesis

Atherosclerosis occurs when apoB-containing particles <70 nm in diameter (not the larger chylomicrons or VLDL species but rather their remnants) enter the arterial intimal layer, where they are oxidized and then internalized by monocytes turned macrophages, creating sterol-laden macrophages termed *foam cells*.[5,17] The determining

factor regulating apoB-particle arterial entry is particle number, not as previously assumed, particle lipid content or particle size. The major risk related to small dense LDL particles, which because of their size are CE-depleted, is that patients with small LDLs require as many as 70% more particles to traffic a given level of cholesterol than those patients with larger LDLs, resulting in high LDL-P and apoB levels. Likewise, TG-rich CE-poor LDL particles (large or small) would also be cholesterol depleted, necessitating increased LDL-P to traffic the cholesterol.[18,19] Atherosclerotic lesions reveal the presence of chylomicrons, VLDLs, IDLs, and LDLs, with the latter being by far the most numerous. Not surprisingly, in many epidemiologic and clinical trials, apoB and LDL-P are significantly better predictors of CHD risk than are lipid measurements.[20,21] Non–HDL-C (calculated as total cholesterol minus HDL-C, therefore requiring no fasting) is a measure of the cholesterol within all of the apoB particles and serves as a practical surrogate of apoB or LDL-P. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) established non–HDL-C as a better surrogate of total apoB-cholesterol than is LDL-C, and made it a secondary goal of therapy in patients with TG levels >200 mg/dL.[22] Despite this recommendation, although apoB, LDL-P, and non–HDL-C have good correlation in predicting CHD risk, there is still moderate discordance between non–HDL-C and apoB levels in many individual patients.[23] In recent position statements, the American Diabetes Association/American College of Cardiology (ADA/ACC)[24] and the American Association of Clinical Chemists (AACC)[21] advocated particle concentration testing in patients with cardiometabolic risk. A graphic representation of lipid and lipoprotein measurements is shown in **Figure 3**.

## Triglycerides and Insulin Resistance

Person-specific data from the 1998–2004 National Health and Nutrition Examination Survey, an ongoing epidemiologic survey assessing the health and nutrition of adults and children in the United States, revealed that insulin resistance and its associated metabolic abnormalities explain the
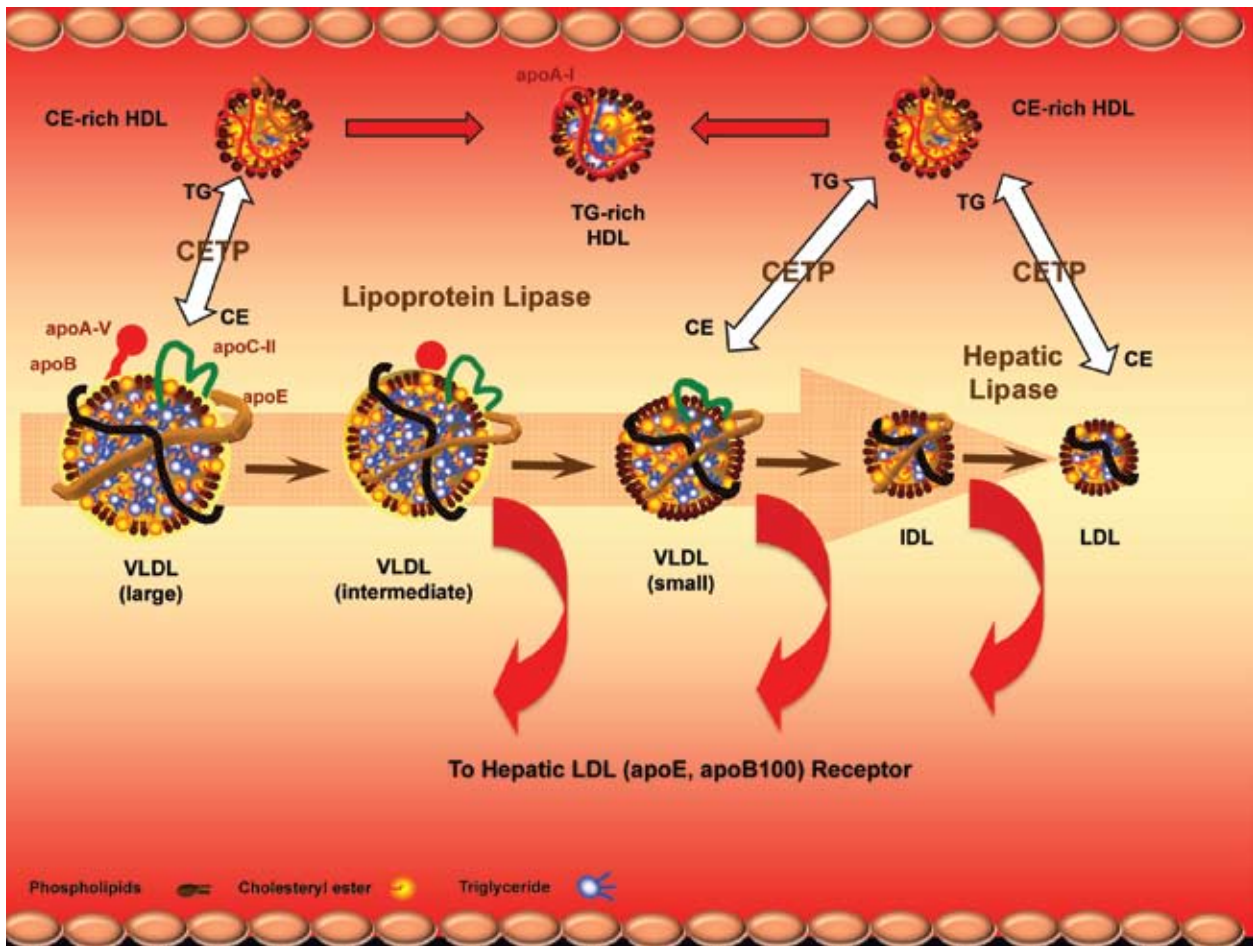
**Figure 2.** Several apolipoproteins (apos) on the hepatic-secreted VLDLs and enteric-secreted chylomicrons interact with lipoprotein lipase and VLDL receptors expressed in muscular and adipocyte vascular beds. Triglyceride (TG) hydrolysis results in release of fatty acids and phospholipids, causing particle size reduction. There is also a cholesteryl ester (CE) transfer protein (CETP)–mediated exchange of CE for TG between the TG-containing apoB particles and the CE-rich HDL particles. Some of the smaller VLDLs and the intermediate-density lipoproteins (IDLs) undergo further lipolysis, creating LDL particles.

majority of cardiovascular events.[25] Compared with noninsulin-resistant patients with respect to lipid measurements, insulin-resistant patients typically manifest what is termed a *TG/HDL axis disorder,* characterized by elevations of TG, high levels of VLDL-C, reduced levels of HDL-C, elevations of non–HDL-C, and variable levels of LDL-C. TG and HDL-C abnormalities, impaired fasting glucose, hypertension, and increased waist size characterize the metabolic syndrome and adiposopathy.[26,27]

During the menopausal transition, as testosterone rises, sex hormone–binding globulin and estrogen levels decrease, and the prevalence of the metabolic syndrome increases. This may be a

pathway by which cardiovascular disease (CVD) develops during menopause.[28] The loss of estrogen at menopause is associated with a fat redistribution from gluteofemoral to central areas.[29] Menopause is also associated with unfavorable changes in the lipoprotein profile, including rising TG and reductions in HDL-C.[30] A 2001 analysis of the Framingham Heart Study data identifies isolated HTG (>200 mg/dL) or TG/HDL axis disorders (elevated TG and decreased HDL-C <50 mg/dL) as the most frequent lipid abnormalities in menopausal women in a primary prevention setting who go on to have clinical coronary events. Two thirds of the women having events had LDL-C

**Table II**. Lipid nomenclatures and definitions and lipo-protein laboratory terms.

| | |
|---|---|
| TC | Cholesterol within all of the lipoproteins per dL of plasma |
| LDL-C | Cholesterol within all of the LDLs per dL of plasma |
| VLDL-C | Cholesterol within VLDL particles: calculated as TG/5 |
| HDL-C | Cholesterol within all of the HDLs per dL of plasma |
| TG | TG within all of the lipoproteins per dL of plasma |
| Non–HDL-C | Cholesterol within all of the apoB particles per dL of plasma |
| ApoB | Concentration of all apoB particles per dL of plasma |
| VLDL-P & LDL-P | No. of VLDL or LDL particles expressed in nmol/L |
| HDL-P | No. of HDL particles expressed in µmol/L |

TC = total cholesterol; TG = triglycerides; apo = apolipoprotein; -P = particle concentration.

levels <140 mg/dL.[31] The TG-associated CHD risk plateaus at levels approaching 200 to 250 mg/dL.[32] Furthermore, a waist size of >35 inches with a fasting TG >128 mg/dL was associated with CHD in a study of 557 Danish menopausal women, and these 2 risk factors were better predictors of CHD mortality than other features of the metabolic syndrome.[33] The HTG so common in these patients is associated with several other CHD risk factors, including lipoprotein abnormalities, increased blood viscosity, decreased endothelial function, hypercoagulation, and inflammation. **Table IV**[22] lists the causes of HTG according to the NCEP ATP-III guidelines. Borderline CHD risk is present with TG >150 mg/dL, high risk with TG >200 mg/dL, and very high risk (as the risk of pancreatitis begins) with TG >500 mg/dL. Persons without the conditions listed in the table rarely have a TG >100 mg/dL. Interestingly, 4 of the causes of HTG are also listed in the NCEP ATP-III table of causes of low HDL-C.[22] Reduced HDL-C in the presence of HTG is often merely a reflection of elevated numbers of atherogenic apoB-containing lipoproteins and reduced numbers of potentially antiatherogenic apoA-I–containing lipoproteins (HDLs).[34,35] Some, but not all, studies have found that TG may be a more important risk factor for women than for men. Analysis of the Women's Health Study revealed HTG and especially postprandial TG elevations to be predictors of risk,[36] and a recent meta-analysis of >250,000 patients showed that fasting or postprandial TG levels

**Table III**. Lipid and lipoprotein laboratory values in women.[16]

| Laboratory Value | Optimal | Elevated Risk | Comments |
|---|---|---|---|
| LDL-C | <100 mg/dL | >100–130 mg/dL | Calculated as TC – (HDL-C + VLDL-C) or direct assay |
| HDL-C | >50 mg/dL | <50 mg/dL | Assay |
| Fasting TG | <100 mg/dL | >130–150 mg/dL | Assay |
| Nonfasting TG | <170 mg/dL | >170–200 mg/dL | Assay |
| VLDL-C | <15–20 mg/dL | >30 mg/dL | Calculated as TG/5 |
| Non–HDL-C | <120 mg/dL | >130 mg/dL | Calculated as TC – HDL-C |
| ApoB | <80 mg/dL | >90 mg/dL | Immunoassay |
| ApoA-I | >160 mg/dL | <140 mg/dL | Assay |
| LDL-P | <1000 nmol/L | >1350 nmol/L | NMR, ultracentrifugation |
| HDL-P | ≥35 µmol/L | <35 µmol/L | NMR |

TC = total cholesterol; TG = triglycerides; apo = apolipoprotein; -P = particle concentration; NMR = nuclear magnetic resonance spectroscopy.
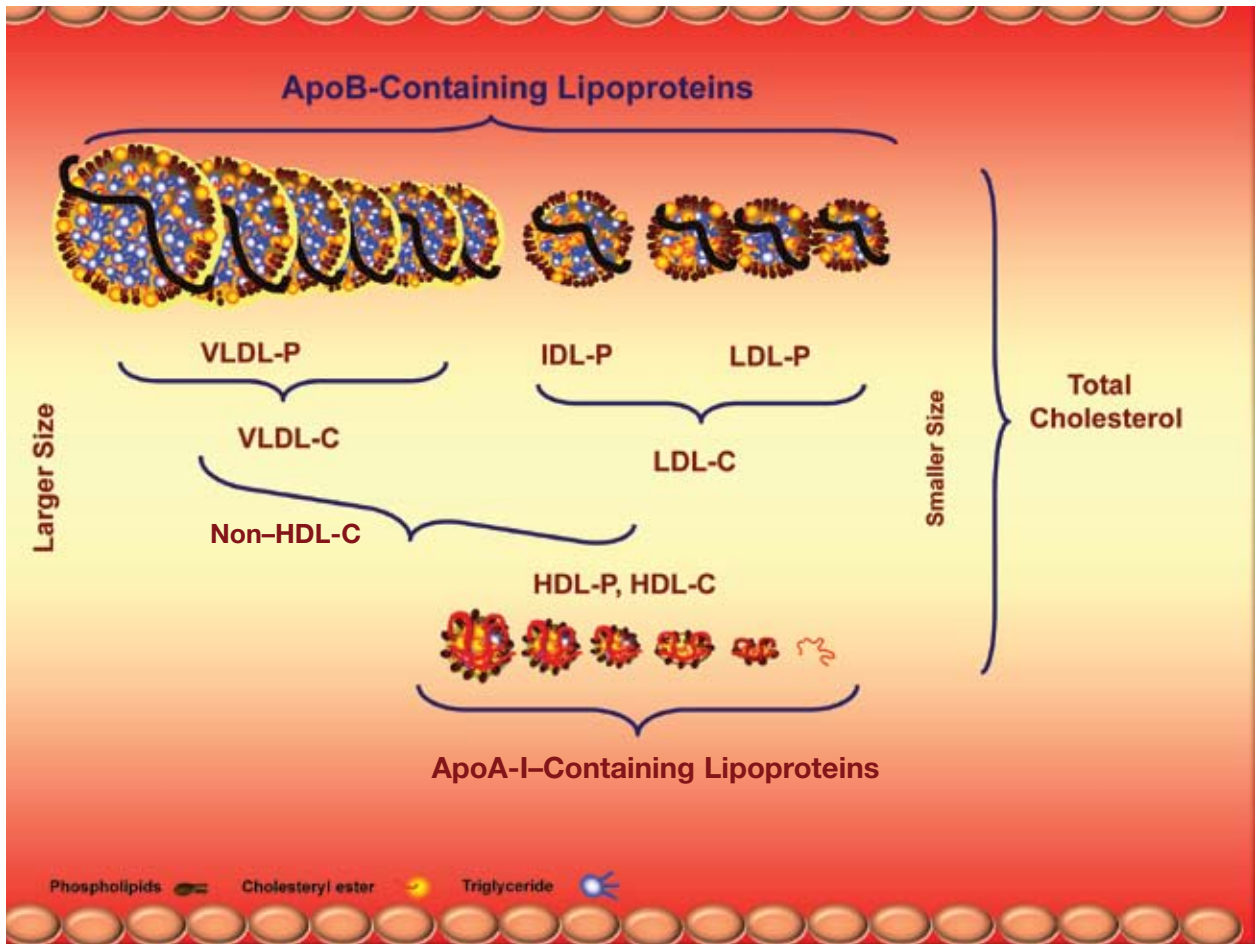
**Figure 3.** The apolipoprotein (apo) B–containing lipoproteins each contain a single molecule of apoB (VLDL-P + IDL-P + LDL-P). Because of their much longer half-life, >90% of apoB particles are LDL particles. Non–HDL-C is the cholesterol carried within the apoB particles (the vast majority of which are LDL particles). The apoA-I–containing HDL particles have 2 to 4 molecules of apoA-I per particle. ApoA-I or total HDL-P can be used to quantify HDL particle concentration. -P = particle concentration; IDL = intermediate-density lipoprotein.

**Table IV**. Most common causes of elevated triglyceride concentrations.[22]

Overweight and obesity; insulin resistance

Physical inactivity

Excessive alcohol intake

High carbohydrate diet (>60% of energy)

Cigarette smoking

Medications (eg, β-blockers, protease inhibitors, corticosteroids, estrogens, retinoids)

Other disease states (eg, diabetes, nephrosis, chronic renal failure, hypothyroidism)

Genetic dyslipidemias

>170 mg/dL, compared with TG levels <110 mg/dL, were a powerful predictor of risk in both sexes.[37,38]

Insulin resistance states are characterized by increased amounts of fatty acids, as a result of exogenous intake, hydrolysis of stored TG, or de novo synthesis. In a 6-year longitudinal study of metabolic changes comparing 35 newly menopausal women with age-matched premenopausal women, menopause was associated with body fat redistribution with an increase in the accumulation of abdominal adipose tissue, more specifically, visceral adiposity.[39] Furthermore, in a study of 108 menopausal women, the combination of abdominal visceral adipose tissue and insulin

resistance best predicted the variance in plasma TG, HDL-C, LDL peak particle size, VLDL particle concentration (VLDL-P), high-sensitivity C-reactive protein, fasting glucose, and 2-hour postprandial glucose.[40] In the liver, fatty acid homeostasis is a delicate balance between lipogenic and oxidative forces. Fatty acid–derived acyl groups esterify glycerol to form monoacyl, diacyl, and ultimately triacylglycerol, which can be stored or exported within VLDL or chylomicron particles. The amount of TG will affect VLDL-P, VLDL size, and/or VLDL core lipid composition. Under physiological conditions, the VLDLs have a 5:1 ratio of TG to cholesterol (thus VLDL-C is calculated as TG/5).[41,42]

## Triglycerides and Lipoprotein Pathology

Patients with elevated TG will usually have an overproduction of TG-rich apoB VLDL particles. Insulin resistance states are characterized by delayed lipolysis of these TG-rich particles, which allows enough time for CETP activity to exchange core TG for CE from CE-rich LDLs and HDLs. VLDL-C increases, but LDL-C and HDL-C decrease. The now TG-rich, CE-poor LDLs and HDLs, upon the action of hepatic lipase, are catabolized to small dense LDLs, which are less efficiently removed by hepatic LDL receptors and small dense HDLs. The latter are subject to further breakup with renal excretion of apoA-I, leading to a reduction of apoA-I and HDL particle concentration (HDL-P). The CE-rich VLDLs still carrying some TG undergo further lipolysis, and become smaller TG-poor, CE-rich particles called *remnants*.[43] Delayed lipolysis also results in both fasting and postprandial lipemia, which is associated with increased blood viscosity, increased markers of coagulation, and reduced flow-mediated dilation, indicative of endothelial dysfunction.[44,45] Therefore, patients with rising TG may have unremarkable or even reduced LDL-C but reduced HDL-C, higher VLDL-C, and non–HDL-C. With respect to lipoproteins, these patients have reduced apoA-I and HDL-P, with a predominance of small HDL and reductions in larger HDL species, as well as elevated apoB (remnants and especially LDL, the majority of which are small). Typically, (high) apoB:apoA-I or LDL-P:HDL-P ratios are present and are powerful predictors of risk.[46] The TG:HDL-C ratio at levels >3.8 is not only a predictor of the presence of small LDL, but in the Women's Ischemia Syndrome Evaluation study, it was also a predictor of total and cardiovascular mortality.[47,48] In the Estrogen Replacement and Atherosclerosis trial, an angiographic study of 309 women with existing coronary artery disease who were randomized to receive oral EPT or placebo, the degree of angiographic coronary atherosclerosis in postmenopausal women was linked to abnormal TG:HDL metabolism.[49] Subpopulations of TG-rich remnants ($P = 0.05$), as measured by remnant-cholesterol and HDL (small, preβ1) particles ($P = 0.03$), were better predictors of disease than were TG and HDL-C concentrations.

In simple terms, TG induce the formation of too many atherogenic apoB particles (VLDL, IDL, and chylomicron remnants, and especially small LDL). It is important to note that >90% of these apoB particles entering the artery are LDLs. Data from 4019 persons in the Framingham Offspring study, including 1626 women in the fourth examination cycle, showed that, in women, adding VLDL-P to LDL-P did not strengthen the CVD association (hazard ratio [HR] = 1.33; 95% CI, 1.17–1.51) compared with LDL-P alone (HR = 1.33; 95% CI, 1.17–1.50).[50] Increasing lipolysis of TG-rich HDLs expedites catabolism and elimination of the potentially antiatherogenic apoA-I particles. It is important for clinicians to recognize that LDL-C values are a poor correlate of remnants and small LDLs (apoB, LDL-P). Although the use of non–HDL-C as advised by the NCEP ATP-III and the 2004 and 2007 American Heart Association's women's guidelines is a step in the right direction in better estimating and treating CHD risk,[51,52] ultimately (and the time is now), transitioning to lipoprotein concentrations as per ADA/ACC and AACC statements should significantly improve care of patients. The use of non–HDL-C, apoB, and LDL-P will make it easier to identify lipoprotein-related risk in women with unremarkable LDL-C. As TG rise, VLDL-C (TG/5) rises, HDL-C drops, LDL-C is variable but often drops, and most importantly, non–HDL-C (apoB, LDL-P surrogate) increases.

## Triglyceride-Modulating Drugs

Therapeutic lifestyle changes and lipid-modulating therapies that reduce CVD risk do so by reducing production and/or enhancing removal of atherogenic lipoproteins, making particle composition less atherogenic and facilitating HDL-mediated delipidation of plaque (macrophage reverse cholesterol transport). Drugs typically used to reduce TG and TGRLP are statins, fibrates, niacin, N-3 fatty acids, orlistat, and ezetimibe.[53–55] Statins or statin/ezetimibe or statin/bile acid sequestrant combinations, by upregulating hepatic LDL receptors, enhance the clearance of apoB-containing TGRLP (statins by inhibiting hepatic cholesterol synthesis; ezetimibe by blocking intestinal absorption and hepatic reabsorption of cholesterol from the gut and bile, respectively; orlistat by inhibiting intestinal lipases and reducing absorption of fatty acids; and bile acid sequestrants by sequestering bile acids in the intestine, forcing the liver to utilize hepatic free cholesterol to make new bile acids). However, by reducing hepatic bile acids, colesevelam and other bile acid sequestrants downregulate the farnesoid X receptor, which can lead to an increase in TG synthesis, and thus, clinicians must be wary of using bile acid sequestrant monotherapy when baseline TG levels exceed 200 mg/dL.[56] Fibrates, niacin, and N-3 fatty acids decrease de novo hepatic fatty acid synthesis; increase hepatic β-oxidation of fatty acids, thereby reducing TG substrate; inhibit TG assembly enzymes; reduce VLDL-TG and VLDL size; and reduce CETP activity, thereby increasing LDL particle size, which promotes clearance of the more readily cleared large LDL particles. Collectively, this reduces not only VLDL-C and non–HDL-C but also apoB and plasma viscosity, and improves endothelial function and coagulation factors.[57–59] Despite beneficial modulation of lipids in women, there are no level I evidence clinical trial data, other than for statins,[60] that attest to the efficacy of these therapies in reducing clinical events in women.

## Estrogen and Triglycerides

An understanding of lipoprotein metabolism allows the clinician to better understand the varying lipid effects of different hormone therapies and SERMs (**Table V**[22]). Varying in intensity by preparation and dose, oral estrogens may significantly increase TG and HDL-C as well as significantly lower LDL-C, compared with baseline values. For years, investigators have spoken of the lipid-modulating benefits of estrogen, yet raising TG is unlikely to be beneficial and, indeed, estrogen has little effect on improving apoB and LDL-P. This has been suggested as a reason estrogen use has not been found to be beneficial in cardiovascular outcome trials. In a dose-dependent fashion, oral estrogens increase hepatic TG production and the synthesis of TG-rich, cholesterol-poor, apoB-containing VLDL particles. Although not well understood, estrogen downregulates the farnesoid X receptor, which is associated with downregulation of the short heterodimer partner protein and upregulation of liver X receptor, and in turn, upregulation of sterol element regulatory binding protein 1c, which activates fatty acid and TG synthesis enzymes.[61,62] Other estrogen-induced metabolic changes that might be explained by modulation of these and other nuclear transcription factors are increased production of apoA-I and bile acids (perhaps explaining estrogen-related cholelithiasis) and improved insulin sensitivity.[63,64]

Oral estrogen upregulates hepatic LDL receptors, which should facilitate removal of apoB-containing particles and reduce apoB and LDL-P concentrations.[65] However, the oral estrogen–induced TG increase (in a metabolic ward study of 6 menopausal women, after 28 days of oral estrogen, TG levels were elevated 67% with a mean [SD] increase of 56 [20] mg/dL, $P < 0.01$, compared with baseline) results in increased production of TG-rich VLDL particles,[66,67] which via CETP activity and hepatic lipase action are catabolized to CE-poor LDL particles (either TG-rich, CE-poor LDLs or smaller TG, CE-poor LDLs). Smaller LDLs tend to accumulate, owing to their less-efficient binding to hepatic LDL receptors. As little as a 15-mg/dL estrogen-induced increase in TG can shift LDL particle size downward in 25% of patients. Due to the reduction in LDL particle size or the incorporation of TG into the core of the LDL particle, the LDL particles are cholesterol

**Table V**. Effect of medications ([±] no or minimal effect; [+] raises; [-] lowers) on lipid parameters.[22*†]

| Agent | TC | LDL-C | TG | Non–HDL-C | ApoB/LDL-P |
|---|---|---|---|---|---|
| Statins | ---- | ----- | -- | ---- | ----- |
| Fibrates | -- | -- | ---- | -- | -- |
| Niacin | -- | -- | --- | -- | -- |
| Ezetimibe | -- | -- | - | -- | -- |
| Colesevelam | -- | -- | ± | -- | -- |
| N-3 Fatty acids at 4 g | - | + | ---- | -- | - |
| Estradiol | -- | -- | + | ± | ± |
| CEE | -- | -- | ++ | ± | ± |
| Estropipate | ± | ± | ± | ± | ? |
| CEE/MPA | -- | -- | + | ± | ± |
| CEE/MP | -- | -- | +++ | ± | ? |
| Estradiol 1 mg + norgestimate | ± | ± | + | ± | ? |
| Estradiol 1 mg/NETA 0.5 mg | -- | -- | - | - | - |
| Ethinyl estradiol 5 µg/NETA 1 mg | -- | -- | ++ | ? | ? |
| Estradiol 1 mg/drospirenone 0.5 mg | -- | -- | - | - | - |
| Transdermal (matrix) estradiol | - | - | ± | ± | ± |
| Transdermal estradiol/NETA | - | - | - | ± | ? |
| Estrogen gel† | - | - | - | - | ± |
| Raloxifene | -- | -- | - | -- | -- |
| Tamoxifen | -- | -- | + | -- | -- |

TC = total cholesterol; TG = triglycerides; apo = apolipoprotein; LDL-P = LDL particle concentration; CEE = conjugated equine estrogen; MPA = medroxyprogesterone acetate; MP = micronized progesterone; NETA = norethindrone acetate.
*Lipid data were not available on the following products: levonorgestrel, synthetic conjugated estrogens, and transdermal (reservoir, spray) and vaginal estradiol.
†No studies at the US-approved dose of 1.25 mg/d. European studies have used 1.5 to 3 mg/d.

depleted and LDL-C falls by 10% to 15%.[68,69] The TG-altered LDL particle creates the paradox of seemingly beneficial LDL-C reduction with no change in the more important atherogenic particle number (apoB or LDL-P).

A nested case–control study of 354 women with early coronary events and matched controls from the Women's Health Initiative provides the strongest evidence to date for the concept of estrogen's paradoxical lipid and lipoprotein effects. Among women assigned to ET or EPT (oral conjugated equine estrogen [CEE] 0.625 mg or oral CEE 0.625 mg plus medroxyprogesterone acetate 2.5 mg), LDL-C compared with placebo decreased by 16% among women assigned to EPT and 12% among those assigned to ET (both, $P < 0.001$). In contrast, neither LDL-P nor LDL-P + VLDL-P was reduced by ET or EPT; in fact, ET increased LDL-P by 5% versus 3% for EPT. Baseline LDL-C and LDL-P (both, $P < 0.001$), VLDL-P ($P < 0.005$), and TG ($P < 0.001$) were positively associated with CHD. On treatment (both ET and EPT arms), LDL-C was not associated with CHD, whereas the association of LDL-P with CHD persisted, but was weakened. Thus, in the face of no reductions in atherogenic particle numbers, we can now better understand the lack of a cardioprotective effect from these agents in the face of seemingly favorable lipid changes (+HDL-C, –LDL-C).[61] The accompanying editorial stated that "this trial provides important

new evidence that LDL-P predicts risk better than LDL-C, and confirms that not all therapies lowering LDL-C will lower LDL-P."[70] Lower dosages of oral estrogen (ie, less than the equivalent of 0.625 mg of CEE per day) and transdermal estrogens do not increase TG nor create CE-depleted LDL.[71] Transdermal estrogen, by avoiding hepatic metabolism, does not raise TG but has little ability to upregulate LDL receptors and lower apoB and LDL-P. Lipid information is lacking on the newer transdermal estrogen products or other skin-applied estrogen creams, but there is no reason to think that their lipid and lipoprotein effects would differ significantly from the original transdermal patch studies. Likewise, there are few published data on the lipid/lipoprotein effects of the many vaginal estrogen preparations.

## Progestogens and Triglycerides

The choice of progestogen has a significant influence on estrogen-induced HTG.[72] Progesterone itself has little effect on TG. Norgestimate (0.09 mg in an available combination product with estradiol 1 mg) partially negates (9.4%) the estrogen-induced rise in TG concentration (29%).[73] The addition of norethindrone acetate (NETA) 0.5 mg, which has androgenic properties, inhibited estradiol-induced HTG in a prospective, randomized lipid trial, producing an actual reduction in TG, and was not associated with the formation of small dense LDL particles, a unique effect among moderate dose combined-continuous EPT preparations.[74] In fact, unlike most EPT combinations, apoB, compared with estradiol, was significantly reduced by 9% by the estradiol 1 mg/NETA 0.5 mg preparation ($P < 0.01$).[75] Although potentially favorable, the clinical significance of this preparation's apoB reduction remains unknown. A relatively new combined preparation of estradiol 1 mg/drospirenone 0.5 mg appears to have similar lipid/lipoprotein effects compared with baseline, lowering apoB by 7.1% ($P \leq 0.01$) and TG by 9.7% ($P = NS$).[76]

ET and EPT also have many complex effects on HDL biology and HDL lipid parameters, some of which are related to product-specific estrogen/progestogen effects on TG. Oral estrogen increases HDL-C by multiple mechanisms, many mediated by influencing nuclear transcription factors including farnesoid X receptor antagonist effects on short heterodimer partner protein and agonist effects on liver X receptor, specifically, decreased hepatic lipase activity (reducing HDL lipolysis and thereby increasing HDL size), and by decreasing HDL catabolism through hepatic scavenger receptor B-1 receptor downregulation.[77] Testosterone and androgenic progestins such as NETA suppress production of apoA-1 and increase hepatic lipase. All of these effects are dose dependent, as illustrated by the reduction of HDL-C in the Continuous Hormones as Replacement Therapy study, a 2-year, double-blind, placebo-controlled, parallel-group clinical trial of 1265 women aged ≥40 years, where ethinyl estradiol 5 μg significantly raised TG by 25% and HDL-C by 5% ($P < 0.05$), but when combined with NETA 1 mg, negated the TG rise and reduced the mean change in HDL-C by 6.7% ($P < 0.05$).[78] However, in a trial using estradiol 1 mg with NETA 0.5 mg, there was a TG reduction not accompanied by a reduction in HDL-C.[75] As discussed previously, TG raising via a CETP-mediated effect is associated with reduced HDL-C, and TG lowering with increased HDL-C. Transdermal estradiol has little HDL-C effect, but the addition of an androgenic progestin such as NETA in a combination hormone therapy patch is associated with a significant reduction in HDL-C.[79] The clinical meaning of these HDL-C changes is unknown, as the antiatherogenicity of HDL has little to do with its cholesterol content.[80] There is evidence that oral but not transdermal estrogens may adversely affect HDL functionality. If estrogen-induced amyloid is present on the HDL, the particle loses other potentially beneficial surface apolipoproteins, which may adversely affect HDL functionality.[81]

## Selective Estrogen Receptor Modulators, Aromatase Inhibitors, and Triglycerides

SERMs have varying effects on lipids and lipoproteins, with raloxifene and tamoxifen being the most studied agents. Unlike oral estrogen, raloxifene does not increase TG and there is no TG-enrichment of VLDL.[82] Similar to oral estrogen, raloxifene upregulates hepatic LDL receptors,

which when combined with the lack of VLDL overproduction, leads to an overall reduction of apoB-containing lipoproteins. In most studies, raloxifene has little effect on apoA-1 production or HDL-C, although similar to estrogen, via hepatic lipase inhibition, raloxifene shifts HDL size upwards. Post hoc analysis of lipids and lipoproteins in women from a substudy of the Multiple Outcomes of Raloxifene Evaluation trial revealed that in women with both high and low TG, raloxifene significantly improved LDL-C, total cholesterol, non–HDL-C, HDL-C, apoB, and apoA-I compared with placebo (all, $P < 0.05$).[83] Mean levels of LDL-C and apoB were reduced by 16.5% and 15.8%, respectively, in women with high TG, and by 12.7% and 11.3% in women with normal TG, compared with baseline ($P < 0.01$ between raloxifene and placebo). The subgroup of women with HTG, who would be expected to have elevated cardiovascular risk, appeared to derive at least equal, if not greater, overall effect on lipid and lipoprotein below baseline values with raloxifene. Reductions in apoB lipoproteins would be expected to reduce cardiovascular risk, yet in the Raloxifene Use for The Heart trial, there was no reduction in CVD events, and raloxifene use had no effect on overall stroke incidence but was associated with an increased risk (HR = 1.49; 95% CI, 1.00–2.24; $P = 0.05$) of fatal stroke (absolute risk increase, 0.7 per 1000 woman-years).[84] The use of cardioprotective medications (lipid-lowering medications, antihypertensive agents, and antiplatelet agents) was encouraged in the trial, perhaps accounting for the lower-than-expected rate of coronary events and perhaps overwhelming the beneficial apoB-lowering effects of raloxifene. Tamoxifen treatment has been found to reverse the effects of chemotherapy-induced ovarian failure on serum lipids by lowering LDL-C, although HDL-C did not change and TG increased.[85] Data from the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial indicated that when used for breast cancer prevention in women with or without heart disease, tamoxifen was not associated with beneficial or adverse cardiovascular event rate effects, despite reductions in LDL-C and apoA-1 and increases in TG

similar to that with CEE.[86] Newer SERMs, such as droloxifene and toremifene, are structurally related to tamoxifen, and at doses of 60 mg daily, reduce LDL-C but do not affect HDL-C or TG.[87,88] Aromatase inhibitors have come into increasing use, and clinical trials have thus far not demonstrated any significant impact on lipid profiles, including TG, in menopausal patients with breast cancer, or any significant increase in ischemic cardiovascular events compared with tamoxifen.[89] Other aromatase inhibitors have variable effects on lipid levels, and the correlation of these effects with cardiovascular events is currently unknown.[90]

## CONCLUSIONS

Owing to the epidemic of obesity, adiposopathy, and aging of the population, insulin resistance is on the rise. This is compounded in women with the loss of estrogen, and its desirable insulin-sensitizing and fat-redistribution properties. Because insulin resistance is associated with TG/HDL axis abnormalities, it should not be surprising that many women have elevated TG contributing to their CHD risk. Overproduction of TGRLPs, with their longer plasma residence associated with increased fasting and postprandial TG levels, leads to increased numbers of atherogenic lipoproteins (apoB, LDL-P), adverse compositional changes in HDLs and LDLs, and other vascular disturbances, all of which are associated with risk. Therapeutic lifestyle change is the cornerstone of treatment of TGRLP, but clinicians must be aware of pharmacologic TG-modulating therapies and of the complex changes that may occur with various ET and EPT strategies. For those clinicians not routinely performing apoB or LDL-P testing, it becomes crucial to realize that the NCEP ATP-III goal of therapy for patients with HTG or high TG with low HDL-C is not TG per se, but rather non–HDL-C, a free, easily calculated (total cholesterol minus HDL-C), practical surrogate for apoB.[21] Although non–HDL-C is a better alternative goal than LDL-C, the apoB level and the number of nuclear magnetic resonance–measured LDL particles (LDL-P) are the most powerful lipid and lipoprotein measures, and should be ordered with discretion by physicians seeking to use them to improve lipid-altering therapies.[91]

## ACKNOWLEDGMENTS

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