Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association

Michael Miller, Neil J. Stone, Christie Ballantyne, Vera Bittner, Michael H. Criqui, Henry N. Ginsberg, Anne Carol Goldberg, William James Howard, Marc S. Jacobson, Penny M. Kris-Etherton, Terry A. Lennie, Moshe Levi, Theodore Mazzone, Subramanian Pennathur and on behalf of the 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 N

Circulation published online Apr 18, 2011;
DOI: 10.1161/CIR.0b013e3182160726
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

AHA Scientific Statement

Triglycerides and Cardiovascular Disease

A Scientific Statement From the American Heart Association

Michael Miller, MD, FAHA, Chair; Neil J. Stone, MD, FAHA, Vice Chair; Christie Ballantyne, MD, FAHA; Vera Bittner, MD, FAHA; Michael H. Criqui, MD, MPH, FAHA; Henry N. Ginsberg, MD, FAHA; Anne Carol Goldberg, MD, FAHA; William James Howard, MD; Marc S. Jacobson, MD, FAHA; Penny M. Kris-Etherton, PhD, RD, FAHA; Terry A. Lennie, PhD, RN, FAHA; Moshe Levi, MD, FAHA; Theodore Mazzone, MD, FAHA; Subramanian Pennathur, MD, FAHA; on behalf of the 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, and Council on the Kidney in Cardiovascular Disease

Table of Contents

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on January 25, 2011. A copy of the statement is available at http://my.americanheart.org/statements by selecting either the "By Topic" link or the "By Publication Date" link. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The American Heart Association requests that this document be cited as follows: 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; on behalf of the 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, and Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation.* 2011;123:●●●–●●●.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit http://my.americanheart.org/statements and click on "Policies and Development."

(*Circulation*. 2011;123:00-00.)

***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIR.0b013e3182160726**

1. Introduction

A long-standing association exists between elevated triglyceride levels and cardiovascular disease* (CVD).[1,2] However, the extent to which triglycerides directly promote CVD or represent a biomarker of risk has been debated for 3 decades.[3] To this end, 2 National Institutes of Health consensus conferences evaluated the evidentiary role of triglycerides in cardiovascular risk assessment and provided therapeutic recommendations for hypertriglyceridemic states.[4,5] Since 1993, additional insights have been made vis-à-vis the atherogenicity of triglyceride-rich lipoproteins (TRLs; ie, chylomicrons and very low-density lipoproteins), genetic and metabolic regulators of triglyceride metabolism, and classification and treatment of hypertriglyceridemia. It is especially disconcerting that in the United States, mean triglyceride levels have risen since 1976, in concert with the growing epidemic of obesity, insulin resistance (IR), and type 2 diabetes mellitus (T2DM).[6,7] In contrast, mean low-density lipoprotein cholesterol (LDL-C) levels have receded.[7] Therefore, the purpose of this scientific statement is to update clinicians on the increasingly crucial role of triglycerides in the evaluation and management of CVD risk and highlight approaches aimed at minimizing the adverse public health–related consequences associated with hypertriglyceridemic states. This statement will complement recent American Heart Association scientific statements on childhood and adolescent obesity[8] and dietary sugar intake[9] by emphasizing effective lifestyle strategies designed to lower triglyceride levels and improve overall cardiometabolic health. It is not intended to serve as a specific guideline but will be of value to the Adult Treatment Panel IV (ATP IV) of the National Cholesterol Education Program, from which evidence-based guidelines will ensue. Topics to be addressed include epidemiology and CVD risk, ethnic and racial differences, metabolic determinants, genetic and family determinants, risk factor correlates, and effects related to nutrition, physical activity, and lipid medications.

2. Scope of the Problem: Prevalence of Hypertriglyceridemia in the United States

In the United States, the National Health and Nutrition Examination Survey (NHANES) has monitored biomarkers of CVD risk for >3 decades. Accordingly, increases in fasting serum triglyceride levels observed between surveys conducted in 1976–1980 and 1999–2002[6] coincided with adjustments in the classification of hypertriglyceridemia[4,10] (Table 1). Current designations are as follows: 150 to 199 mg/dL, borderline high; 200 to 499 mg/dL, high; and ≥500 mg/dL, very high. The prevalence of hypertriglyceridemia by ethnicity in NHANES 1988–1994 and 1999–2008 according to these cut points is shown in Figure 1. Overall, 31% of the adult US population has a triglyceride level ≥150 mg/dL, with no appreciable change between NHANES 1988–1994 and 1999–2008. Among ethnicities, Mexican Americans have the highest rates (34.9%), followed by non-Hispanic whites (33%) and blacks (15.6%) in NHANES 1999–2008 (Table 2). High (≥200 mg/dL) and very high (≥500 mg/dL)

*For the purpose of this statement, CVD is inclusive of coronary heart disease and coronary artery disease.

Table 1. Triglyceride Classification Revisions Between 1984 and 2001

TG Designate	1984 NIH Consensus Panel	1993 NCEP Guidelines	2001 NCEP Guidelines
Desirable	<250	<200	<150
Borderline-high	250–499	200–399	150–199
High	500–999	400–999	200–499
Very high	>1000	>1000	≥500

TG indicates triglyceride; NIH, National Institutes of Health; and NCEP, National Cholesterol Education Program.

Values are milligrams per deciliter.

fasting triglyceride levels were observed in 16.2% and 1.1% of adults, respectively, with Mexican Americans being overrepresented at both cut points (19.5% and 1.4%, respectively). Figure 2 illustrates the sex- and age-related prevalence of triglyceride levels ≥150 mg/dL in NHANES 1999–2008. Within each group, the highest prevalence rates were observed in Mexican American men (50 to 59 years old, 58.8%) and Mexican American women (≥70 years old, 50.5%), followed by non-Hispanic white men and women (60 to 69 years old, 43.6% and 42.2%, respectively) and non-Hispanic black men (40 to 49 years old, 30.4%) and women (60 to 69 years old, 25.3%). The prevalence of triglyceride levels ≥200 mg/dL was also highest in Mexican American men (≥30 years old) and women (≥40 years old; 21% to 36%), followed by non-Hispanic white men (30 to 69 years old, 20% to 25%). Although the prevalence of triglyceride levels ≥500 mg/dL was relatively low (1% to 2%), Mexican American men 50 to 59 years of age exhibited the highest rate (9%) in NHANES 1999–2008.

Serum triglyceride levels by selected percentiles and geometric means are shown in Table 3. Because triglyceride levels are not normally distributed in the population (Section 3.1), the geometric mean, as derived by log transformation, is favored over the arithmetic mean to reduce the potential impact of outliers that might otherwise overestimate triglyceride levels.[11] Over the past 20 years, there were small increases in median triglyceride levels in both men (122 versus 119 mg/dL) and women (106 versus 101 mg/dL). However, the increases in triglycerides primarily were observed in younger age groups (20 to 49 years old), and overall, triglyceride levels continue to be higher than in less industrialized societies (Section 12.1). We now address the epidemiological and putative pathophysiological consequences of high triglyceride levels.

3. Epidemiology of Triglycerides in CVD Risk Assessment

The independent relationship of triglycerides to the risk of future CVD events has long been controversial. An article published in *The New England Journal of Medicine* in 1980 concluded that the evidence for an independent effect of triglycerides was "meager,"[3] yet despite several decades of additional research, the controversy persists. This may in part reflect conflicting results in the quality of studies performed in the general population and in clinical samples. Second, in studies demon-

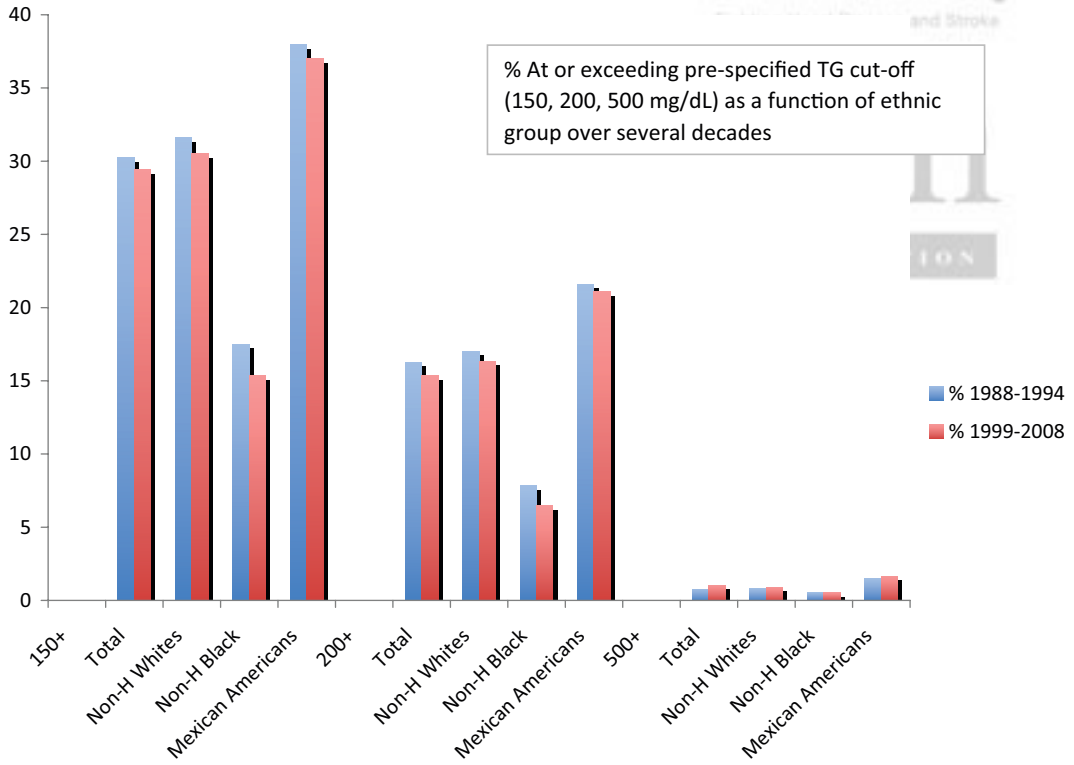

Figure 1. Prevalence of fasting triglyceride levels (≥150, 200, and 500 mg/dL) in males and (non-pregnant) females ≥18 years of age by ethnicity in the National Health and Nutrition Examination Survey (1988–1994 and 1999–2008). TG indicates triglycerides; Non-H, non-Hispanic.

Table 2. Overall Prevalence (%) of Hypertriglyceridemia Based on 150, 200, and 500 mg/dL Cut Points by Age, Sex, and Ethnicity in US Adults, NHANES 1999–2008

	Triglyceride Cut Points, mg/dL		
Demographic	≥150	≥200	≥500
Overall (age ≥20 y)	31.0	16.2	1.1
Age, y			
20–29	20.7	9.5	0.8
30–39	25.8	14.1	0.7
40–49	32.8	16.7	1.6
50–59	36.7	20.1	1.8
60–69	41.6	22.6	1.0
≥70	34.5	17.2	0.5
Sex			
Men	35.4	19.8	1.8
Women*	26.8	12.7	0.5
Ethnicity			
Mexican American	34.9	19.5	1.4
Non-Hispanic, black	15.6	7.6	0.4
Non-Hispanic, white	33.0	17.6	1.1

NHANES indicates National Health and Nutrition Examination Survey.

Data provided by the Epidemiology Branch, National Heart, Lung, and Blood Institute.

*Excludes pregnant women.

Source: NHANES 1999–2008.

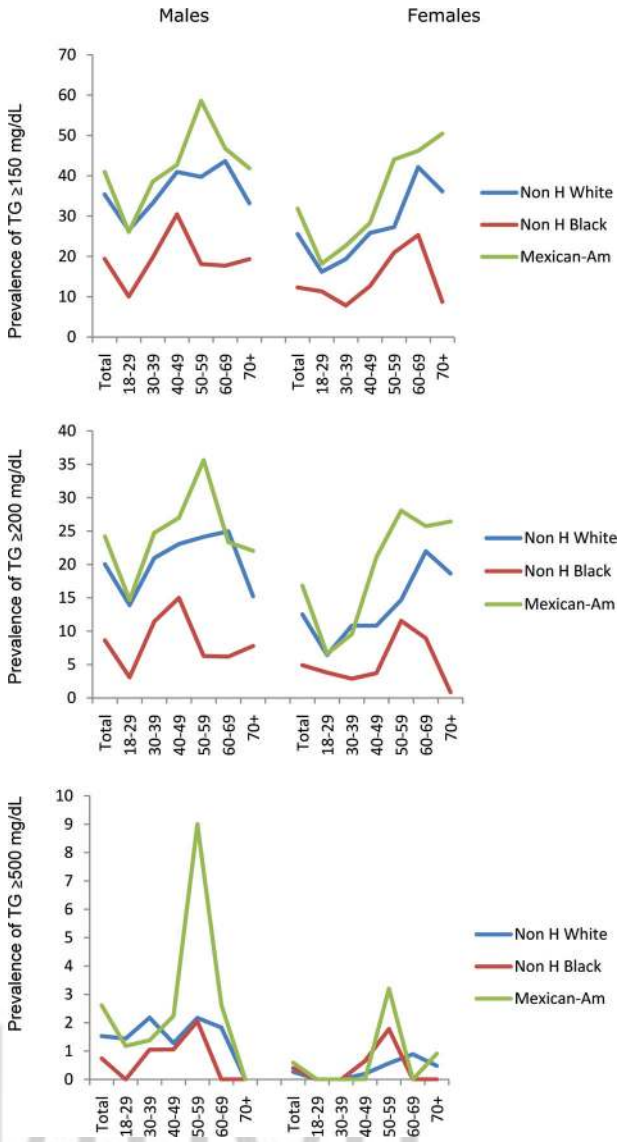

Figure 2. Prevalence of hypertriglyceridemia in males and nonpregnant females ≥18 years of age in NHANES 1999–2008. NHANES indicates National Health and Nutrition Examination Survey; TG, triglycerides; Non H, non-Hispanic; Mexican-Am, Mexican-American.

strating a significant independent relationship of triglycerides to CVD events, the effect size has typically been modest compared with standard CVD risk factors, including other lipid and lipoprotein parameters. Summarized below are methodological considerations and results from representative studies that evaluated triglycerides in CVD risk assessment.

3.1. Methodological Considerations and Effect Modification

Triglyceride has long been the most problematic lipid measure in the evaluation of cardiovascular risk. First, the distribution is markedly skewed, which necessitates categorical definitions or log transformations. Second, variability is high (Section 10) and increases with the level of triglyceride.[12] Third, the strong inverse association with high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (apo) AI, suggests an intricate biological relationship that may not be most suitably represented by the results of multivariate analysis. Finally, evidence from prospective studies of the triglyceride association supports a stronger link with CVD risk in people with lower levels of HDL-C[13,14] and LDL-C[13,14] and with T2DM.[15,16] Such an effect modification could obscure a modest but significant effect, as demonstrated recently.[17]

In addition to the inverse association with HDL-C, triglyceride levels are closely aligned with T2DM, even though T2DM is not always examined as a confounding factor, and when it is, the diagnosis is commonly based on history. Yet at least 25% of subjects with T2DM are undiagnosed,[18] and they are often concentrated within a hypertriglyceridemic population. Similarly, many subjects with high triglyceride levels and impaired fasting glucose who subsequently develop T2DM are not adjusted for in multivariate analysis. Hence, these limitations restrict conclusions that support triglyceride level as an independent CVD risk factor. Compounding the aforementioned problem is the argument that an elevated triglyceride level is simply an epiphenomenon (ie, a by-product) of IR or the metabolic syndrome (MetS). However, analysis of NHANES data evaluating the association of all 5 MetS components with cardiovascular risk found the strongest association with triglycerides.[19]

A pivotal consideration is how triglycerides may directly impact the atherosclerotic process in view of epidemiological studies that have failed to demonstrate a strong relationship between very high triglyceride levels and increased CVD death.[13,20] As will be described in Section 4, hydrolysis of TRLs (eg, chylomicrons, very low-density lipoproteins [VLDL]) re-

Table 3. Serum Triglyceride Levels of US Adults ≥20 Years of Age, 1988–1994 and 1999–2008

	1988–1994							1999–2008						
	Geometric Mean		Selected Percentile					Geometric Mean		Selected Percentile				
	Age-Specific	Age-Adjusted	5th	25th	50th	75th	95th	Age-Specific	Age-Adjusted	5th	25th	50th	75th	95th
Men														
≥20 y		127.9	53	83	119	176	321		128.3	52	85	122	182	361
20–29	95.1		45	65	88	126	237	106.2		45	70	100	150	305
30–39	118.8		52	79	113	169	298	122.1		50	80	119	175	324
40–49	138.4		58	91	133	190	349	143.8		57	94	134	201	473
50–59	146.6		61	95	137	223	394	140.6		61	93	133	197	388
60–69	146.7		64	101	140	200	378	138.2		59	96	133	196	372
≥70	134.3		64	95	131	179	306	121.5		54	87	120	168	266
Women*														
≥20 y		109.7	47	72	101	150	274		110.0	48	74	106	155	270
20–29	83.8		42	60	84	111	182	88.7		39	63	83	123	205
30–39	91.3		43	62	83	121	267	95.8		42	64	91	138	243
40–49	103.0		48	70	102	139	251	105.5		49	73	102	146	249
50–59	129.2		55	84	126	186	325	124.7		55	84	120	176	305
60–69	143.9		61	97	137	203	380	135.9		63	96	137	192	299
≥70	137.2		70	97	134	182	284	133.0		63	95	129	180	293
Race/ethnicity														
Mexican-American														
Men		138.6	53	83	120	185	387		140.8	53	89	126	196	392
Women		131.8	55	85	118	167	291		126.6	48	81	113	164	277
Non-Hispanic black														
Men		102.5	44	65	92	140	259		99.7	44	67	94	129	248
Women		88.8	40	58	79	115	208		88.1	38	62	83	116	209
Non-Hispanic white														
Men		131.3	55	85	123	182	323		130.3	53	87	126	188	368
Women		110.9	48	74	102	154	276		112.1	50	77	109	161	275

Percentile and geometric mean distribution of serum triglyceride (mg/dL).
*Excludes pregnant women.
Data provided by the Epidemiology Branch, National Heart, Lung, and Blood Institute.
Source: National Health and Nutrition Examination Survey III (1988–1994) and Concurrent National Health and Nutrition Examination Survey (1999–2008).

sults in atherogenic cholesterol-enriched remnant lipoprotein particles (RLPs). Accordingly, recent evidence suggests that nonfasting triglyceride is strongly correlated with RLPs,[21] and in 2 recent studies, nonfasting triglyceride was a superior predictor of incident CVD compared with fasting levels.[21,22]

3.2. Case-Control Studies, Including Angiographic Studies

Triglyceride has routinely been identified as a "risk factor" in case-control and angiographic studies, even after adjustment for total cholesterol (TC) or LDL-C[23–34] and HDL-C.[24,27–29,33,34] In another case-control study, case subjects were 3-fold more likely to exhibit small, dense low-density lipoprotein (LDL) particles, referred to as the "pattern B" phenotype.[35] However, the triglyceride level explained most of the risk of the pattern B phenotype and was a stronger covariate than LDL-C, intermediate-density lipoprotein (IDL) cholesterol, or HDL-C. Overall, data from case-control studies have supported triglyceride level as an independent CVD risk factor.

3.3. Prospective Population-Based Cohort Studies

Although many early cohort studies found a univariate association of triglycerides with CVD, this association often became nonsignificant after adjustment for either TC or LDL-C. Most of these earlier studies did not measure HDL-C. Two meta-analyses of the triglycerides-CVD question drew similar conclusions. The first, published in 1996, considered 16 studies in men, 6 from the United States, 6 from Scandinavia, and 4 from elsewhere in Europe.[36] In univariate analysis, the relative risk per 1 mmol/L (88.5 mg/dL) of triglyceride for CVD in men was 1.32 (95% confidence interval 1.26 to 1.39) and 1.14 (95% confidence interval 1.05 to 1.28) after adjustment for HDL-C. In women, the association was more robust in both univariate analysis (relative risk 1.76 per mmol/L) and after adjustment for HDL-C (relative risk 1.37, 95% confidence interval 1.13 to 1.66). The second meta-analysis evaluated 262 000 subjects and found a higher relative risk (1.4) at the upper compared with the lower triglyceride tertile; this estimate improved to

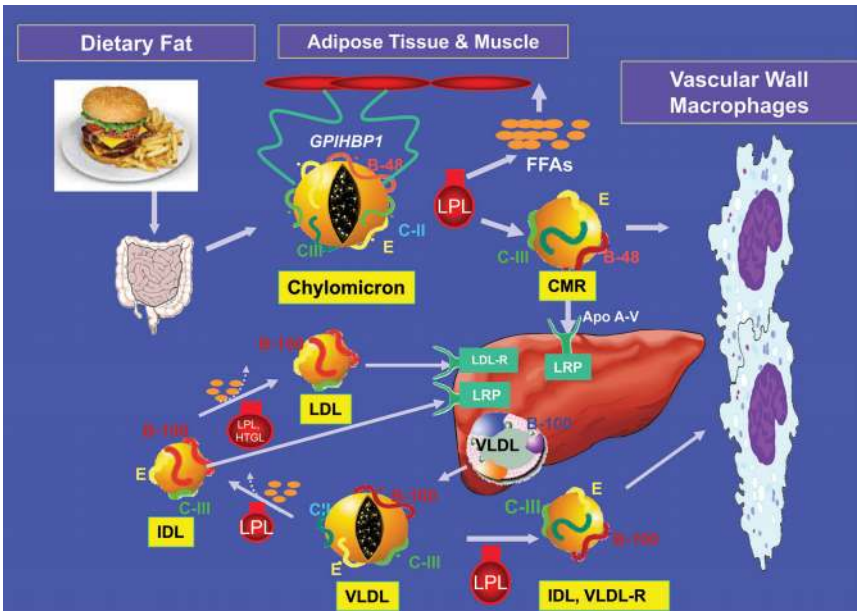

Figure 3. Overview of triglyceride metabolism. Apo A-V indicates apolipoprotein A-V; CMR, chylomicron remnant; FFAs, free fatty acids; HTGL, hepatic triglyceride lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; LPL, lipoprotein lipase; LRP, LDL receptor–related protein; VLDL, very low-density lipoprotein; and VLDL-R, very low-density lipoprotein receptor.

1.72 with correction for "regression dilution bias" (intraindividual triglyceride variation).[2]

A recent meta-analysis from the Emerging Risk Factors Collaboration evaluated 302 430 people free of known vascular disease at baseline in 68 prospective studies.[17] With adjustment for age and sex, triglycerides showed a strong, stepwise association with both CVD and ischemic stroke; however, after adjustment for standard risk factors and for HDL-C and non–HDL-C, the associations for both CVD and stroke were no longer significant. The attenuation was primarily from the adjustment for HDL-C and non–HDL-C, which led to the conclusion 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)."[17]

Additional data from studies involving young men have provided new insight into the triglyceride risk status question.[37] In 13 953 men 26 to 45 years old who were followed up for 10.5 years, there were significant correlations between adoption of a favorable lifestyle (eg, weight loss, physical activity) and a decrease in triglyceride levels. At baseline, triglyceride levels in the top quintile were associated with a 4-fold increased risk of CVD compared with the lowest triglyceride quintile, even after adjustment for other risk factors, including HDL-C. Evaluation of the change in triglyceride levels over the first 5 years and incident CVD in the next 5 years found a direct correlation between increases in triglyceride levels and CVD risk. These observations add a dynamic element of triglyceride to CVD risk assessment based on lifestyle intervention that will be elaborated on later in this statement.

3.4. Insights From Clinical Trials

A related question is the ability of triglyceride levels to predict clinical benefit from lipid therapy in outcome trials. In many of these studies, subjects with elevated triglyceride levels exhibited improvement in CVD risk, irrespective of drug class or targeted lipid fraction,[38–40] primarily because elevated triglyceride level at baseline was commonly accompanied by high LDL-C and low HDL-C, and this combination (ie, the atherogenic dyslipidemic triad) was associated with the highest CVD risk. Taken together, the independence of triglyceride level as a causal factor in promoting CVD remains debatable. Rather, triglyceride levels appear to provide unique information as a biomarker of risk, especially when combined with low HDL-C and elevated LDL-C.

4. Pathophysiology of Hypertriglyceridemia

4.1. Normal Metabolism of TRLs

4.1.1. Lipoprotein Composition

Lipoproteins are macromolecular complexes that carry various lipids and proteins in plasma.[41] Several major classes of lipoproteins have been defined by their physical and chemical characteristics, particularly by their flotation characteristics during ultracentrifugation. However, lipoprotein particles form a continuum, varying in composition, size, density, and function. The lipids are mainly free and esterified cholesterol, triglycerides, and phospholipids. The hydrophobic triglyceride and cholesteryl esters (CEs) compose the core of the lipoproteins, which is covered by a unilamellar surface that contains mainly the amphipathic (both hydrophobic and hydrophilic) phospholipids and smaller amounts of free cholesterol and proteins. Hundreds to thousands of triglyceride and CE molecules are carried in the core of different lipoproteins.

Apolipoproteins are the proteins on the surface of the lipoproteins. They not only participate in solubilizing core lipids but also play critical roles in the regulation of plasma lipid and lipoprotein transport. Apo B_{100} is required for the secretion of hepatic-derived VLDL, IDL, and LDL. Apo B_{48} is a truncated form of apo B_{100} that is required for secretion of chylomicrons from the small intestine.

4.2. Transport of Dietary Lipids on Apo B_{48}–Containing Lipoproteins

Figure 3 provides an overview of triglyceride metabolism. After ingestion of a meal, dietary fat and cholesterol are absorbed into the cells of the small intestine and are incorporated into the core of nascent chylomicrons. Newly formed chylomicrons, representing 80% to 95% triglyceride as a percentage of composition of lipids,[41] are secreted into the lymphatic system and then enter the circulation at the junction of the internal jugular and subclavian veins. In the lymph and blood, chylomicrons acquire apo CII, apo CIII, and apo E. In the capillary beds of adipose tissue and muscle, they bind to glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1),[42] and core triglyceride is hydrolyzed by the enzyme lipoprotein lipase (LPL) after activation by apo CII.[43] The lipolytic products, free fatty acids (FFAs), can be taken up by fat cells and reincorporated into triglyceride or into muscle cells, where they can be used for energy. In addition to apo CII, other activators of LPL include apo AIV,[44] apo AV,[45] and lipase maturation factor 1 (LMF1),[46] whereas apo CIII[47] and angiopoietin-like (ANGPTL) proteins 3 and 4[48] inhibit LPL. Human mutations in *LPL*, *APOC2*, *GPIHBP1*, *ANGPTL3*, *ANGPTL4*, and *APOA5* have all been implicated in chylomicronemia (Section 5).

The consequence of triglyceride hydrolysis in chylomicrons is a relatively CE- and apo E–enriched chylomicron remnant (CMR). Under physiological conditions, essentially all CMRs are removed by the liver by binding to the LDL receptor, the LDL receptor–related protein, hepatic triglyceride lipase (HTGL), and cell-surface proteoglycans.[49–51] Apo AV facilitates hepatic clearance of CMRs through direct interaction with SorLA.[52] HTGL also plays a role in remnant removal,[49] and HTGL deficiency is associated with reduced RLP clearance. However, studies[53] have indicated that HTGL is elevated in T2DM (Section 6) and may be an important contributor to low HDL-C levels in this disease.

4.3. Transport of Endogenous Lipids on Apo B_{100}–Containing Lipoproteins

4.3.1. Very Low-Density Lipoproteins

VLDL is assembled in the endoplasmic reticulum of hepatocytes. VLDL triglyceride derives from the combination of glycerol with fatty acids that have been taken up from plasma (either as albumin-bound fatty acids or as triglyceride–fatty acids in RLPs as they return to the liver) or newly synthesized in the liver. VLDL cholesterol is either synthesized in the liver from acetate or delivered to the liver by lipoproteins, mainly CMRs. Apo B_{100} and phospholipids form the surface of VLDL. Although apos CI, CII, CIII, and E are present on nascent VLDL particles as they are secreted from the hepatocyte, the majority of these molecules are probably added to VLDL after their entry into plasma. Regulation of the assembly and secretion of VLDL by the liver is complex; substrates, hormones, and neural signals all play a role. Studies in cultured liver cells[51,54] indicate that a significant proportion of newly synthesized apo B_{100} may be degraded before secretion and that this degradation is inhibited when hepatic lipids are abundant.[54]

Once in the plasma, VLDL triglyceride is hydrolyzed by LPL, generating smaller and denser VLDL and subsequently IDL. IDL particles are physiologically similar to CMRs, but unlike CMRs, not all are removed by the liver. IDL particles can also undergo further catabolism to become LDL. Some LPL activity appears necessary for normal functioning of the metabolic cascade from VLDL to IDL to LDL. It also appears that apo E, HTGL, and LDL receptors play important roles in this process. Apo B_{100} is essentially the sole protein on the surface of LDL, and the lifetime of LDL in plasma appears to be determined mainly by the availability of LDL receptors. Overall, ≈70% to 80% of LDL catabolism from plasma occurs via the LDL receptor pathway, whereas the remaining tissue uptake occurs by nonreceptor or alternative-receptor pathways.[41,53]

4.4. Metabolic Consequences of Hypertriglyceridemia

Hypertriglyceridemia that results from either increased production or decreased catabolism of TRL directly influences LDL and HDL composition and metabolism. For example, the hypertriglyceridemia of IR is a consequence of adipocyte lipolysis that results in FFA flux to the liver and increased VLDL secretion. Higher VLDL triglyceride output activates cholesteryl ester transfer protein, which results in triglyceride enrichment of LDL and HDL (Figure 4). The triglyceride content within these particles is hydrolyzed by HTGL, which results in small, dense LDL and HDL particles. Experimental studies suggest that hypertriglyceridemic HDL may be dysfunctional,[55,56] that small, dense LDL particles may be more susceptible to oxidative modification,[57,58] and that an increased number of atherogenic particles may adversely influence CVD risk[59]; however, no clinical outcome trials to date have determined whether normalization of particle composition or reduction of particle number optimizes CVD risk reduction beyond that achieved through LDL-C lowering.

An additional complication in hypertriglyceridemic states is accurate quantification of atherogenic particles in the circulation. That is, a high concentration of circulating atherogenic particles is not reliably assessed simply by measurement of TC and/or LDL-C. Moreover, as triglyceride levels increase, the proportion of triglyceride/CE in VLDL increases (ie, >5:1), which results in an underestimation of LDL-C based on the Friedewald formula.[60] Although this scientific statement will address other variables to consider in the hypertriglyceridemic patient (eg, apo B levels), it supports the quantification of non–HDL-C.[60,61]

4.5. Atherogenicity of TRLs

In human observational studies, TRLs have been associated with measures of coronary atherosclerosis.[62] To provide a pathophysiological underpinning for observations that relate specific lipoprotein particles to human atherosclerosis or CVD, experimental models have been developed to investigate the impact of specific lipoprotein fractions on isolated vessel wall cells. For example, in macrophage-based studies, lipoprotein particles that increase sterol delivery or reduce sterol efflux or that promote an inflammatory response are considered atherogenic. In endothelial cell models, lipopro-

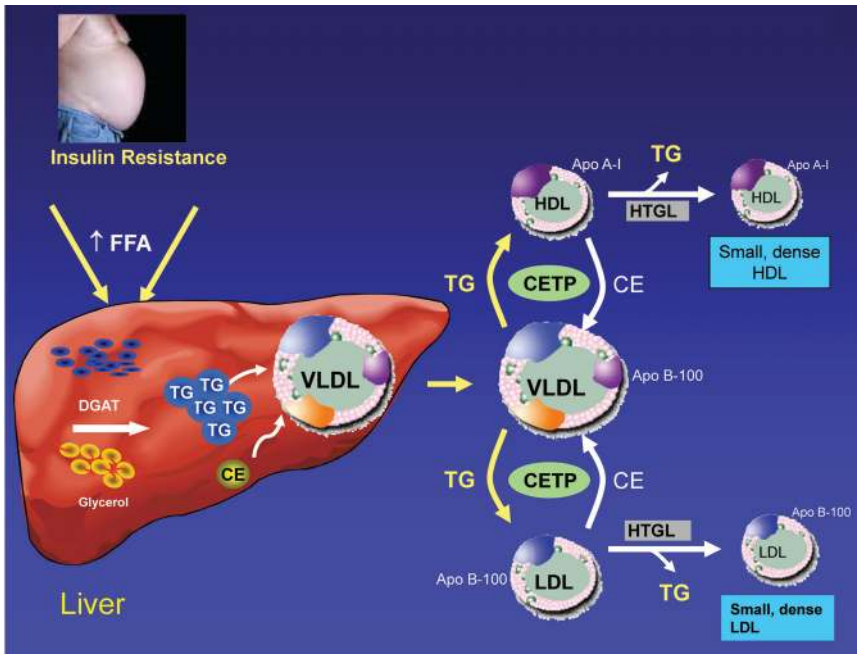

Figure 4. Metabolic consequences of hypertriglyceridemia. Apo A-I indicates apolipoprotein A-I; Apo B-100, apolipoprotein B-100; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; DGAT, diacylglycerol acyltransferase; FFA, free fatty acid; HDL, high-density lipoprotein; HTGL, hepatic triglyceride lipase; LDL, low-density lipoprotein; TG, triglyceride; and VLDL, very low-density lipoprotein.

tein particles that promote inflammation, increase the expression of coagulation factors or leukocyte adhesion molecules, or impair responses that produce vasodilation are also considered atherogenic. These experimental systems have been used to understand the mechanisms by which modified LDL particles are associated with atherosclerosis in humans and in animals.

When one evaluates the usefulness of these systems, it is important to recognize that triglyceride overload is not a classic pathological feature of human atherosclerotic lesions, because the end product, FFA, serves as an active energy source for myocytes or as an inactive fuel reserve in adipocytes. However, the by-product of TRLs (ie, RLPs) may lead to foam cell formation[63] in a manner analogous to modified LDL. In addition, TRLs share a number of constituents with classic atherogenic LDL particles. They include the presence of apo B and CE. Although TRLs contain much less CE than LDL particles on a per particle basis, there are pathophysiological states (eg, poorly controlled diabetes mellitus [DM]) in which CEs can become enriched in this fraction. TRLs also possess unique constituents that may contribute to atherogenicity. For example, the action of LPL on the triglycerides contained in these particles releases fatty acid, which in microcapillary beds could be associated with pathophysiological responses in macrophages and endothelial cells. Apo CIII contained in TRLs has also been shown to promote proatherogenic responses in macrophages and endothelial cells. In the following paragraphs, we will consider selected aspects of the atherogenicity of TRL using in vitro macrophage and endothelial cell models and associated in vivo correlates.

4.5.1. Remnant Lipoprotein Particles

A number of experimental systems have demonstrated that TRLs can produce proatherogenic responses in isolated endothelial cells. RLPs are a by-product of TRL that can be isolated from the postprandial plasma of hypertriglyceridemic subjects; they are intestinal (ie, CMRs) or liver-derived (eg, VLDL remnants) TRLs that have undergone partial hydrolysis by LPL. Liu et al[64] have shown that these particles can accelerate senescence and interfere with the function of endothelial progenitor cells; these cells play an important role in the organismal reparative response to in vivo vessel wall injury. Postprandial TRL (ppTG) has also been shown to increase the expression of proinflammatory genes (eg, interleukin-6, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and monocyte chemotactic protein-1),[65] induce apoptosis,[66] and accentuate the inflammatory response of cultured endothelial cells to tumor necrosis factor-α.[67] After a high-fat meal, ppTG may increase the level of circulating endothelial cell microparticles, a measure of endothelial cell dysfunction in vivo.[68] That is, a high-fat diet increases the level of these particles more effectively than a low-fat diet and is correlated with ppTG levels. Moreover, Rutledge and colleagues have shown that fatty acids released by lipolysis of TRL elicit proinflammatory responses in endothelial cells.[69] TRL may also act to suppress the atheroprotective and antiinflammatory effects of HDL.[70–72] Finally, fatty acid–binding proteins play a role in the intracellular transport of long-chain fatty acids. Recent data support a role for adipocyte- and macrophage-derived fatty acid–binding proteins in systemic inflammatory responses[73] that are likely amplified by high triglyceride loads provided by RLPs to the arterial macrophages.

4.5.2. Apo CIII

Apo CIII is a 79-amino acid glycoprotein that is a major component of circulating TRL and is correlated with triglyceride levels.[74] Recently, a mutation in *APOC3* was identified in association with low triglyceride levels, reduced coronary artery calcification, and suggestion of familial longevity.[75] Emerging evidence from a number of in vitro studies has shown that apo CIII, alone or as an integral component of

TRL, can produce proatherogenic responses in cultured endothelial and monocytic cells.[74,76] These include activation of adhesion and proinflammatory molecule expression and impairment of endothelial nitric oxide production and insulin signaling pathways.[74,76–80]

4.5.3. Macrophage LPL

Macrophages are a rich source of LPL in the vessel wall,[81] and expression of LPL by macrophages could play a role in accelerating atherogenesis by a mechanism that depends on interaction with circulating TRL.[82] For example, direct incubation of mouse peritoneal macrophages with TRL increases macrophage cell triglyceride and fatty acid content; more importantly, this incubation increases expression of macrophage inflammatory proteins, including tumor necrosis factor-α, interleukin-1β, monocyte chemotactic protein-1, intercellular adhesion molecule-1, and matrix metalloproteinase-3.[83,84] Lipolytic products of TRL have also been shown to produce cytotoxicity and apoptosis in isolated macrophages.[85] Macrophage apoptosis is considered an important event that impacts the in vivo atherogenic process.[86]

In summary, in vitro experimental models examining the response of isolated endothelial cells or monocytes and macrophages to TRL have produced results consistent with atherogenicity of this class of particles. These particles, or their lipolytic degradation products, can increase the expression of inflammatory proteins, adhesion molecules, and coagulation factors in endothelial cells or monocytes and macrophages. TRLs may interfere with the ability of HDL to suppress inflammatory responses in cultured endothelial cells and the capacity of apo AI or HDL to promote sterol efflux from monocytes or macrophages. TRLs also impair endothelial cell–dependent vasodilation, enhance the recruitment and attachment of monocytes to endothelium, may be directly cytotoxic, and produce apoptosis in isolated vessel wall cells. However, although the results from in vitro studies provide important pathophysiological context and proof of concept, final conclusions about atherogenicity and clinical significance of lowering triglyceride levels as a surrogate of TRL particles must be based on in vivo studies that use appropriate models of human dyslipidemia in randomized controlled trials (RCTs), as will be elaborated on in Section 15.

5. Causes of Hypertriglyceridemia

5.1. Familial Disorders With High Triglyceride Levels

Familial syndromes with triglyceride levels above the 95th percentile by age and sex may be associated with an increased risk of premature CVD, as in familial combined hyperlipidemia (FCHL).[87–90] Alternatively, when triglyceride elevation is very severe (ie, >1000 mg/dL), fasting chylomicronemia may be the consequence of rare but recognizable single gene mutations.[91–93] The persistence of fasting chylomicronemia leads to a syndrome characterized by eruptive xanthomas, lipemia retinalis, and hepatosplenomegaly and is associated, although not invariably, with acute pancreatitis.[94,95] Because the latter can lead to chronic pancreatitis or death, effective treatment is of paramount importance. Nonetheless, there can be no question that prevention of the markedly elevated triglyceride levels seen in those with genetic syndromes of triglyceride metabolism is an important therapeutic goal.

To understand these disorders, one must focus on LPL regulation, because LPL is needed for the hydrolysis of plasma triglyceride to FFA.[96] The generation of FFA by LPL is regulated by cofactors such as insulin and thyroid hormone. Factors that reduce VLDL clearance can raise triglyceride concentrations in those with high baseline levels (eg, usually >500 mg/dL, because of the competition of VLDL and chylomicrons for a common saturable removal mechanism).[97]

Table 4 lists syndromes of genetic hypertriglyceridemia. The rare but monogenic disorders that cause a marked impairment of LPL activity have clinical expression in childhood. These young patients present with the chylomicronemia syndrome and an increased risk for pancreatitis and may be homozygous for either LPL deficiency, apo CII deficiency, or the more recently described *APOA5* and *GPIHBP1* loss-of-function mutations.[91–93,102,103] In some populations, such as French Canadians, as many as 70% of cases can be traced to a single founder.[104]

For those with less severe genetic disorders of triglyceride metabolism, complex interactions between genetic and environmental factors may lead to the type V phenotype (fasting chylomicronemia and increased VLDL). In these cases, triglyceride concentrations exceed 1000 mg/dL, and when exacerbated by weight gain, certain medications (Table 5) or metabolic perturbations can lead to the chylomicronemia syndrome and increased risk of pancreatitis. Patients with heterozygous LPL deficiency present with elevated triglyceride levels and low HDL-C, but in association with excess alcohol, steroids, estrogens, poorly controlled DM, hypothyroidism, renal disease, or the third trimester of pregnancy, triglyceride levels can rapidly exceed 2000 mg/dL and produce the clinical sequelae of the chylomicronemia syndrome. Although there is no single threshold of triglyceride concentration above which pancreatitis may occur, increased risk is defined arbitrarily by levels exceeding 1000 mg/L. Overall, alcohol abuse and gallstone disease account for at least 80% of all cases of acute pancreatitis, with hypertriglyceridemia contributing ≈10% of cases.[105,134] A history of 2 predisposing factors in the same individual may cause confusion about the proper diagnosis. If elevated triglyceride level persists after the removal of exacerbating causes through diet modification, discontinuation of drugs (Table 5), and/or provision of insulin therapy for patients with poorly treated DM,[135] one must consider rare disorders that are resistant to traditional therapies, such as autoantibodies against LPL.[136]

Additional genetic syndromes in the differential diagnosis of hypertriglyceridemia include mixed or familial combined hyperlipidemia (FCHL), type III dysbetalipoproteinemia, and familial hypertriglyceridemia (FHTG). FCHL is characterized by multiple lipoprotein abnormalities due to hepatic overproduction of apo B–containing VLDL, IDL, and LDL, whereby apo B levels exceed the 90th percentile.[87,88] It is observed in affected relatives in successive generations, and the diagnosis is made when in the face of increased levels of cholesterol, triglyceride, or apo B, at least 2 of the lipid abnormalities identified in the patient also segregate among the patient's first-degree relatives.[137] The variable clinical

Table 4. Familial Forms of High Triglycerides

	Inheritance/Population Frequency	Pathogenesis	Typical Lipid/Lipoprotein Profiles	Comments
Rare genetic syndromes presenting as chylomicronemia syndrome				
LPL deficiency (also known as familial type I)	Autosomal recessive; rare (1 in 10^6)	Increased chylomicrons due to very low or undetectable levels of LPL; circulating inhibitor to LPL has been reported	Homozygotes: TG-to-cholesterol ratio 10:1; TG >1000 mg/dL; increased chylomicrons	Homozygous mutations cause lipemia retinalis, hepatosplenomegaly, eruptive xanthomas accompanying very high TG. CAD believed uncommon, but cases reported
Apo CII deficiency	Autosomal recessive; rare	Increased chylomicrons due to absence of needed cofactor, Apo CII	Homozygotes TG-to-cholesterol ratio 10:1; TG >1000 mg/dL; increased chylomicrons Obligate heterozygotes with normal TG despite apo CII levels ≈30% to 50% of normal	Attacks of pancreatitis in homozygotes can be reversed by plasmapheresis; xanthomas and hepatomegaly much less common than in LPL deficiency
Apo AV homozygosity	Rare	Mutations in the *APOA5* gene, which lead to truncated apo AV devoid of lipid-binding domains located in the carboxy-terminal end of the protein	Homozygotes: TG-to-cholesterol ratio 10:1; TG >1000 mg/dL; increased chylomicrons	Apo A5 disorders can form familial hyperchylomicronemia with vertical transmission, late onset, incomplete penetrance, and an unusual resistance to conventional treatment
GPIHBP1	Rare; expressed in childhood	Mutations in *GPIHBP1* may reduce binding to LPL and hydrolysis of chylomicron triglycerides	TG-to-cholesterol ratio 7:1; TG >500 mg/dL; increased chylomicrons partially responsive to low-fat diet	May have lipemia retinalis and pancreatitis; eruptive xanthomas not reported
Other genetic syndromes with hypertriglyceridemia*				
Heterozygous apo AV	Rare	A heterozygous loss-of-function mutation in 1 of several genes encoding proteins involved in TG metabolism. More than half of type V patients carried 1 of the 2 apo A5 variants compared with only 1 in 6 normolipidemic controls[98]	TG 200-1000 mg/dL until secondary trigger occurs; then TG can exceed 1000 mg/dL; increased VLDL and chylomicrons	The promoter polymorphism −1131T>C is associated with increased TG and CVD risk[98]
Heterozygous LPL deficiency	Rare, but carrier frequency higher in areas with founder effect (eg, Quebec)	Decrease in LPL	TG 200-1000 mg/dL until secondary trigger occurs; then TG can exceed 1000 mg/dL; increased VLDL and chylomicrons	Premature atherosclerosis can be seen[99] (or increased atherosclerosis risk in familial hypercholesterolemia heterozygotes with elevated TG, low HDL[100]
Familial hypertriglyceridemia	Common; ≈5% to 10%; likely polygenic, often not expressed until adulthood because of environmental factors, obesity, stress	VLDL overproduction and reduced VLDL catabolism result in saturation of LPL; secondary causes exacerbate the hypertriglyceridemia	TG 200-1000 mg/dL; apo B levels are not elevated as in FCHL	Usually not associated with CHD unless MetS features are seen or baseline TG levels are high (eg, >200 mg/dL)[101]; then increased CHD may be present
FCHL	Genetically complex disorder; common (1% to 2% in white populations)	Increased production of apo B lipoproteins; FCHL diagnosed with combinations of increased cholesterol, TG, and/or apo B levels in patients and their first-degree relatives. See interaction of multiple genes and environmental factors such as adiposity and the degree of exercise	Elevated cholesterol, TG, or both; elevated apo B; small dense LDL is seen	Obesity as indicated by increased waist-to-hip ratio can greatly increase apo B production in these patients; usually onset is in adulthood, but pediatric obesity may allow for earlier diagnosis
Dysbetalipoproteinemia (also known as familial type III)	Autosomal recessive; rare; requires an acquired second "hit" for clinical expression	Defective apo E (usually apo EII/EII phenotype); commonest mutation Apo EII, Arg158Cys, causes chylomicrons and VLDL remnants to build up in plasma	TG and cholesterol levels elevated and approximately similar should raise clinical suspicion; non–HDL-C is a better risk target than apo B levels, which are low because these are cholesterol-rich VLDL; see increased intermediate-density particles with ratio of directly measured VLDL-C to plasma TG of >0.3	Acquired second "hits" include exogenous estrogen, alcohol, obesity, insulin resistance, hypothyroidism, renal disease, or aging; may be very carbohydrate sensitive

LPL indicates lipoprotein lipase; TG, triglyceride; CAD, coronary artery disease; apo, apolipoprotein; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1; VLDL, very low-density lipoprotein; CVD, cardiovascular disease; HDL, high-density lipoprotein; CHD, coronary heart disease; MetS, metabolic syndrome; FCHL, familial combined hyperlipidemia; LDL, low-density lipoprotein; HDL-C, HDL cholesterol; and VLDL-C, VLDL cholesterol.

*Genetic syndromes that usually require an acquired cause to raise TG to high levels and present with either the type IV (increased VLDL) or type V (increased VLDL and fasting chylomicronemia) phenotypes.

Table 5. Causes of Very High Triglycerides That May Be Associated With Pancreatitis

Genetic[91–95,105–107]
Lipoprotein lipase deficiency
Apolipoprotein CII deficiency
Apolipoprotein AV deficiency
GPIHBP1 deficiency
Marinesco-Sjögren syndrome
Chylomicron retention (Anderson) disease
Familial hypertriglyceridemia (in combination with acquired causes)
Acquired disorders of metabolism*
Hypothyroidism[108]
Pregnancy, especially in the third trimester†[109–111]
Poorly controlled insulinopenic diabetes[112,113]
Drugs (medications)*
α-Interferon[114]
Antipsychotics (atypical)[115]
β-blockers such as atenolol‡[116]
Bile acid resins§[117]
L-Asparaginase[118]
Estrogens‖ (oral, not transcutaneous)[119]
Protease inhibitors[120]
Raloxifene¶[121]
Retinoic acid drugs[122]
Sirolimus[123]
Steroids[108]
Tamoxifen[124]
Thiazides[125]
Diet*
Alcohol excess, especially with a high saturated–fat diet[126,127]
Diseases*
Autoimmune chylomicronemia (eg, antibodies to LPL,[128] SLE[129])
Chronic idiopathic urticaria[130]
Renal disease[131]

GPIHBP1 indicates glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1; LPL, lipoprotein lipase; and SLE, systemic lupus erythematosus.

*These factors are especially concerning in the patient with preexisting known hypertriglyceridemia, often on a genetic basis.

†Triglyceride increase with each trimester, but invariably, it is the third trimester when hypertriglyceridemia in susceptible patients becomes symptomatic.

‡Carvedilol is preferred in diabetic patients and those with hypertriglyceridemia who are receiving β-blockers.[132]

§Bile acid resins should not be used with preexisting hypertriglyceridemia.

‖Estrogens in oral contraceptives or in postmenopausal hormone therapy; hypertriglyceridemia can occur when the progestin component is stopped.[133]

¶In women who experienced hypertriglyceridemia with estrogen therapy.

expression of the lipid phenotypes makes identification difficult, and the combination of both family screening and upper 10th percentile apo B levels is often needed for diagnostic confirmation. A nomogram is available to calculate the probability that a patient is likely to be affected by FCHL.[138] In the absence of age- and sex-adjusted values for a population, it has been further suggested that FCHL may be present if hypertriglyceridemia (>133 mg/dL) and hyperapo B (>120 mg/dL) are present.[58] The important role of weight gain in the clinical expression of the phenotype is underscored by the observation that as adiposity (assessed by an elevated waist-to-hip ratio) increases, FCHL subjects express higher plasma apo B concentrations than matched control subjects. Genetic studies that used ultrasound findings and alanine aminotransferase as surrogates for fatty liver have shown that fatty liver is a hereditable aspect of FCHL.[139] The molecular basis underlying FCHL is largely unknown; genetic variants in the APOA1/C3/A4/A5 cluster and the upstream stimulatory factor 1 (*USF1*) gene may play a role.[140–142] Importantly, FCHL is strongly represented in studies of survivors of myocardial infarction,[87] especially those survivors <40 years of age.[143]

The increased frequency with which FCHL is seen may relate in part to the observation[144] that in addition to multiple genes that upregulate apo B secretion, the worldwide trend of energy excess and associated weight gain exaggerates the baseline abnormalities in apo B secretion. Although the phenotypic expression of FCHL is delayed until young adulthood, as childhood obesity rates increase, the higher adipose tissue mass that drives apo B secretion accelerates the number of cases of FCHL diagnosed in the young adult population.[145]

Familial type III hyperlipoproteinemia or dysbetalipoproteinemia is due to the accumulation of cholesterol-rich VLDL,[146,147] which results in a higher ratio of core CE to triglyceride (>0.3) than in normal VLDL (0.2). The type III phenotype is often characterized by near-equivalent cholesterol and triglyceride values due to impaired receptor-mediated clearance, whereas the hypertriglyceridemia of type III reflects the impaired processing of remnants and increased VLDL hepatic production associated with increased levels of apo E. In this disorder, apo B is not a useful marker of overall atherogenicity, as in FCHL; non–HDL-C would be a more appropriate target.[148] Homozygosity for the rare apo E2 isoform, which displays defective binding to the LDL receptor compared with the most common apo E3 isoform, is necessary for the expression of type III, but it is not sufficient. Rather, additional factors (eg, obesity, T2DM, or hypothyroidism) are generally required for expression of the type III phenotype, which includes the characteristic palmar or tuboeruptive xanthomas and increased cardiovascular and peripheral vascular disease risk. Affected individuals may be extraordinarily responsive to a low-carbohydrate (CHO) diet.[149]

FHTG has a population prevalence of ≈5% to 10% and is defined by the familial occurrence of isolated high VLDL levels with triglyceride values most commonly in the 200 to 500 mg/dL range. It is genetically heterogeneous, and its expression is accentuated by the presence of a secondary factor such as obesity or IR. Initially, it was thought that FHTG was not associated with an increased risk of CVD, as contrasted with FCHL.[87] However, this was reexamined in the National Heart, Lung, and Blood Institute's Family Heart Study, which studied 5381 subjects from 1245 families.[90] FCHL and FHTG were diagnosed in 10.2% and 12.3% of 334 random control families, respectively, and in 16.7% and 20.5% of 293 families with at least 1 case of premature CVD. MetS was identified in 65% of FCHL and 71% of FHTG patients compared with 19% of control subjects without

Table 6. Association Between BMI and Hypertriglyceridemic Status (≥150 mg/dL or ≥200 mg/dL)*

	TG Concentration, mg/dL		TG Concentration, mg/dL	
BMI, kg/m^2	≥150 (n=1744)	<150 (n=3250)	≥200 (n=937)	<200 (n=4057)
<25	20.1	42.7	17.5	39.0
25 to <30	39.9	31.6	39.6	33.3
≥30	39.9	25.6	42.9	27.7

BMI indicates body mass index; TG, triglyceride.

*Values come from National Health and Nutrition Examination Survey 1999–2004. Values are percent of participants within a TG category as a function of BMI status.

FCHL or FHTG. The increased prevalence of the MetS alone could account for the elevated CVD risk associated with both FCHL and FHTG. Thus, the increasing prevalence of both obesity and MetS appears to increase the frequency, onset of expression, and severity of genetic triglyceride syndromes.

Finally, genome-wide association studies have uncovered multiple loci associated with high levels of triglyceride.[150] Specifically, common variants in *APOA5*, glucose kinase regulatory protein (*GCKR*), *LPL*, and *APOB* have been identified, thereby supporting a role for both common and rare variants responsible for hypertriglyceridemia.[151] Efforts are ongoing to identify genetic variants that influence the response to drugs, which may be used to tailor drug selection and dosing to the profile of the individual patient.[152]

5.2. Obesity and Sedentary Lifestyle

Evidence from epidemiological and controlled clinical trials has demonstrated that triglyceride levels are markedly affected by body weight status and body fat distribution. Data from 5610 participants ≥20 years of age from NHANES between 1999 and 2004 reported a relationship between body mass index (BMI) and triglyceride concentration.[153] Approximately 80% of participants classified as overweight (BMI 25 to 30 kg/m^2) and obese (BMI ≥30 kg/m^2) had triglyceride levels ≥150 mg/dL. When the triglyceride cut point was ≥200 mg/dL, ≈83% of participants were classified as overweight or obese (Table 6). Participants with a normal BMI (<25 kg/m^2) were more likely to have triglyceride levels <150 mg/dL (43%) and <200 mg/dL (39%). A similar trend was reported recently for youths in the NHANES Survey 1999–2006[154]; only 5.9% of participants in the normal-weight category had high triglyceride levels (≥150 mg/dL), whereas 13.8% and 24% of overweight or obese individuals had elevated triglyceride levels.[154]

In addition to the association between triglyceride levels and BMI, the Framingham Heart Study[155] reported strong associations of triglyceride levels with both subcutaneous abdominal adipose tissue and visceral adipose tissue in men and women (mean age 50 years). For visceral adipose tissue, the multivariable-adjusted residual effect was approximately twice that for subcutaneous abdominal adipose tissue for both women and men ($P<0.0001$ for both). Thus, although it is clear that excess adiposity is associated with elevated triglyceride levels, visceral adiposity is a greater contributor than subcutaneous adipose tissue.[155,156] Excess visceral fat in patients with IR may further expose the liver to higher levels of FFAs via the portal circulation, and increased flux of FFAs to the liver contributes to increased secretion of VLDL. A consequence of excessive fat combined with impaired clearance or storage of triglycerides in subcutaneous fat is ectopic fat deposition in skeletal muscle, liver, and myocardium, which may result in IR, nonalcoholic fatty liver disease, and pericardial fat.[157,158] A disproportionate amount of visceral versus subcutaneous adipose tissue may also reflect a lack of adipocyte storage capacity, with saturation of the normal sites of fat deposition. Subcutaneous fat may serve as a protective factor with regard to the metabolic consequences of obesity[159]; a relative paucity (ie, lipodystrophy) is associated with hypertriglyceridemia.

5.3. Lipodystrophic Disorders

5.3.1. Genetic Disorders

Lipodystrophy can be inherited or acquired. The inherited lipodystrophies are rare disorders that are characterized by loss of adipose tissue. These disorders may be inherited in either autosomal recessive or dominant patterns. The loss of adipose tissue is selective and variable and may be partial or complete. Some forms manifest at birth, whereas others become evident later in life, with loss of fat beginning in childhood and puberty.[160]

Hypertriglyceridemia is seen in many lipodystrophic disorders, often in association with low HDL-C. The severity of hypertriglyceridemia is related to the extent of the loss of fat,[161] and mechanisms include decreased storage capacity of fat, with delayed clearance of TRLs and increased hepatic lipid synthesis. Fat accumulation in insulin target organs may cause lipotoxicity and IR. One of the most severe forms is congenital generalized lipodystrophy, a rare autosomal recessive disorder that presents at birth with a nearly complete absence of subcutaneous adipose tissue. Affected children may present with metabolic derangements, including severe hypertriglyceridemia, with eruptive xanthomas and pancreatitis.[162] At least 3 molecular variants have been described that involve genes whose products are necessary for the formation and maturation of lipid droplets in adipocytes.[160] Varieties of familial partial lipodystrophy, which are rare autosomal dominant disorders, involve fat loss from the extremities more than the trunk. Hypertriglyceridemia is most severe in the Dunnigan variety, which is caused by a defect in the gene for lamin A and tends to be more severe in women than in men.[162,163]

5.3.2. Acquired Disorders

HIV–associated dyslipidemic lipodystrophy is characterized by increased content of triglycerides in VLDL, LDL, and HDL due to reduced clearance of TRL.[164] The fat distribution abnormalities appear in 1 of 3 prevalent forms: (1) Generalized or localized lipoatrophy, which usually involves the extremities, buttocks, and face; (2) lipohypertrophy with generalized or local fat deposition that involves the abdomen, breasts, dorsocervical region, and supraclavicular area; or (3) a mixed pattern with central adiposity with peripheral lipoatrophy. Factors that influence the development of lipodystrophy include increased duration of HIV infection, high viral load, low CD4 counts before highly active antiretroviral

therapies, and prolonged survival and duration of highly active antiretroviral therapies. Several antiretroviral drugs used to treat HIV infection can cause hypertriglyceridemia, including the protease inhibitors lopinavir and ritonavir.[165]

Other acquired forms of lipodystrophy occur with autoimmune diseases such as juvenile dermatomyositis.[161] Patients with acquired generalized lipodystrophy lose fat from large areas of the body during childhood and adolescence, and this is often accompanied by hepatic steatosis.[162]

6. Diabetes Mellitus

High triglyceride levels that accompany either normal or impaired fasting glucose predict the development of T2DM,[166,167] and therefore, hypertriglyceridemic states should prompt surveillance to rule out T2DM. In addition, ≈35% of T2DM adults have fasting triglyceride levels ≥200 mg/dL[168] associated with decreased HDL-C and small, dense LDL particles.[41,53,112,113,169,170] Patients with poorly controlled type 1 diabetes mellitus (T1DM) may exhibit a similar pattern of dyslipidemia. Causes of hypertriglyceridemia in DM include increased hepatic VLDL production and defective removal of chylomicrons and CMRs, which often reflects poor glycemic control.[171]

6.1. Type 1 Diabetes Mellitus

6.1.1. Chylomicron Metabolism

In general, chylomicron and CMR metabolism can be altered significantly in DM.[49,53] In untreated or poorly controlled T1DM, LPL activity will be low, and ppTG levels will in turn be increased. Insulin therapy rapidly reverses this condition, which results in improved clearance of chylomicron triglyceride from plasma. In chronically treated T1DM, LPL measured in postheparin plasma, as well as adipose tissue LPL, may be normal or increased, and chylomicron triglyceride clearance may also be normal. Other hepatic and intestinally derived proteins that modulate chylomicron production and intestinal lipoprotein secretion (eg, microsomal transfer protein and glucagon-like peptides 1 and 2) have been studied in T1DM-induced rodents, but their clinical relevance vis-à-vis chylomicron metabolism in human T1DM has yet to be established.[172–174]

6.1.2. VLDL Metabolism

Individuals with DM frequently have elevated levels of VLDL triglyceride. In T1DM, triglycerides correlate closely with glycemic control, and marked hyperlipidemia can be found in patients with DM and ketoacidosis. The basis for increased VLDL in subjects with poorly controlled but nonketotic T1DM is usually overproduction of these lipoproteins.[113] Specifically, insulin deficiency results in increased adipocyte lipolysis, with FFA mobilization driving hepatic VLDL apo B secretion. Reduced clearance of VLDL apo B also contributes to triglyceride elevation in severe cases of uncontrolled DM. This results from a reduction of LPL, which returns to normal with adequate insulinization. In fact, plasma triglycerides may be low-normal with intensive insulin treatment in T1DM, with lower than average production rates of VLDL being observed in such instances.

6.2. Type 2 Diabetes Mellitus

6.2.1. Chylomicron Metabolism

In T2DM, metabolism of dietary lipids is complicated by coexistent obesity and the hypertriglyceridemia associated with IR. Defective removal of chylomicrons and CMRs has been observed in T2DM[49]; however, LPL is normal or only slightly reduced in untreated patients.[49,112] Because both fasting hypertriglyceridemia and reduced HDL-C are common in T2DM and are correlated with increased ppTG levels, it is difficult to identify a direct effect of T2DM on chylomicron metabolism. Recently, studies have indicated that IR can result in increased assembly and secretion of chylomicrons.[175] This parallels the central defect of increased hepatic VLDL secretion in IR and T2DM (section 6.2.2) and clearly contributes to increased postprandial lipid levels with T2DM.

6.2.2. VLDL Metabolism

Overproduction of VLDL, with increased secretion of both triglycerides and apo B_{100}, appears to be the central cause of increased plasma VLDL levels in patients with T2DM.[176] Increased assembly and secretion of VLDL is probably a direct result of both IR (with loss of insulin's action to stimulate degradation of newly synthesized apo B) and increases in FFA flux to the liver and de novo hepatic lipogenesis (with increased triglyceride synthesis). LPL levels have been reported to be reduced[112] in T2DM, and this may contribute significantly to elevated triglyceride levels, particularly in severely hyperglycemic patients. Because obesity, IR, and concomitant familial forms of hyperlipidemia are common in T2DM, study of the pathophysiology is difficult. The interaction of these overlapping traits also makes therapy less effective. In contrast to T1DM, in which intensive insulin therapy normalizes (or even "supernormalizes") VLDL levels and metabolism, insulin or oral agents only partly correct VLDL abnormalities in the majority of individuals with T2DM.[113] Therapies such as metformin and the thiazolidinediones can lower plasma triglyceride concentrations 10% to 15% and 15% to 25%, respectively.[177] The thiazolidinediones appear to improve peripheral insulin sensitivity, and this leads to inhibition of lipolysis in adipose tissue. Plasma levels of FFAs fall ≈25% at the highest dose of both of the presently available thiazolidinediones, and such changes should lead to lower hepatic triglyceride synthesis and reduced VLDL secretion. However, pioglitazone lowers triglyceride levels by increasing LPL-mediated lipolysis, whereas VLDL secretion remains unchanged.[178] Rosiglitazone does not affect triglyceride levels, although the basis for this difference is unclear.[179]

6.2.3. Small LDL Particles

LDL particles in patients with DM may be atherogenic even at normal LDL-C concentrations. For example, glycosylated LDL can be taken up by macrophage scavenger receptors in an unregulated manner, thereby contributing to foam cell formation.[180] In addition, hypertriglyceridemia is associated with small, dense, and CE-depleted LDL particles. Thus, individuals with T2DM and mild to moderate hypertriglyceridemia exhibit the pattern B profile of LDL (smaller, denser particles) described by Austin and Krauss[180]; these particles

Table 7. Cardiovascular Risk Components of the Metabolic Syndrome*

Increased waist circumference	>40 inches in men (>35 inches for Asian men); >35 inches in women (>31 inches for Asian women) or population- and country-specific definitions
High triglycerides	≥150 mg/dL, or taking medication for high triglycerides
Low HDL-C (good cholesterol)	<40 mg/dL in men; <50 mg/dL in women, or taking medication for low HDL-C
Elevated blood pressure	≥130 mm Hg systolic ≥85 mm Hg diastolic, or taking antihypertensive medication in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL or taking medication to control blood sugar

HDL-C indicates high-density lipoprotein cholesterol.

*The metabolic syndrome is diagnosed when a person has ≥3 of these risk factors.

Adapted from Huang[182] and NCEP ATP III.[182a]

may be more susceptible to oxidative modification and catabolism via macrophage scavenger receptors than pattern A LDL particles. Overproduction of LDL apo B_{100} may also occur with T2DM even with mild degrees of hyperglycemia, especially if there is concomitant elevation of VLDL, resulting in the atherogenic dyslipidemic triad, mixed hyperlipidemia, or FCHL.

6.2.4. Reduced HDL-C

In T1DM, HDL-C levels are often normal; however, in decompensated T1DM with hypertriglyceridemia, CE transfer protein–mediated exchange will result in low HDL-C concentrations. Similarly, in T2DM, especially in the presence of increased secretion of apo B–containing lipoproteins and concomitant hyperlipidemia, CE transfer protein–mediated transfer of HDL CE to those lipoproteins results in lower levels of HDL-C (and increased HDL triglycerides). Fractional catabolism of apo AI is increased in T2DM with low HDL-C, as it is in nondiabetic subjects with similar lipoprotein profiles. Although apo AI levels are reduced consistently, correction of hypertriglyceridemia does not usually alter apo AI levels.[53,181]

6.2.5. Summary

In summary, T1DM may be associated with elevations of VLDL triglyceride and LDL-C if glycemic control is poor or if the patient is ketotic. In contrast, T2DM is often accompanied by high triglyceride levels, reduced HDL-C, and the presence of smaller CE-depleted LDL particles. Treatment with hypoglycemic agents has a variable drug-dependent effect on plasma lipid levels.

7. Metabolic Syndrome

Elevated triglyceride levels, along with increased waist circumference, elevated fasting glucose, elevated blood pressure, or reduced HDL-C levels, are MetS risk factors, with a tally of 3 needed for the diagnosis (Table 7). The prevalence of MetS in the United States is currently estimated at 35% in both men and women[183] and is higher in CVD patients; in NHANES III, MetS was present in >40% versus 28% of subjects with or without CVD, respectively.[19]

7.1. Prevalence of Elevated Triglyceride in MetS

The prevalence of triglyceride levels ≥150 mg/dL is nearly twice as high in subjects with MetS as in those without MetS.[184,185] Among individual components of MetS, high triglyceride level was the second most common (74%), after elevated blood pressure.[186] A high prevalence of triglyceride levels ≥150 mg/dL (72%) was also observed in patients with MetS and CVD.[187] In contrast, a low prevalence of hypertriglyceridemia was reported in MetS patients with advanced heart failure owing in part to hepatic congestion and cachexia.[188]

7.2. Prognostic Significance of Triglyceride in MetS

Longitudinal and cross-sectional studies have suggested that high triglyceride level may be a predictor of CVD risk. For example, a "hypertriglyceridemic waist," as defined by elevated triglyceride and increased waist circumference, was associated with arteriographic CVD[189]; elevated triglyceride level was also associated with myocardial infarction and stroke risk in NHANES III.[19] Nonetheless, clinical outcome studies have failed to demonstrate the prognostic significance of triglyceride levels in MetS. Rather, other factors (eg, low HDL-C, elevated glucose, or elevated blood pressure) independently predicted CVD and all-cause mortality in RCTs.[184–187] Thus, although elevated triglyceride is highly prevalent in subjects with MetS, it is less predictive of CVD outcomes than other MetS components, thus relegating triglyceride level as an important biomarker rather than a prognosticator of CVD.

8. Chronic Kidney Disease

Dyslipidemia is commonly present in patients with chronic kidney disease (CKD) and occurs at all stages. It occurs in both children and adults,[190] in those with nephrotic syndrome, in patients undergoing dialysis, and after renal transplantation. A triglyceride level >200 mg/dL is present in ≈50% of those with CKD, often in association with low HDL-C. In addition, several risk factors that alter lipoprotein metabolism, such as T2DM, obesity, IR, and MetS, frequently are also found in CKD subjects,[191] which results in qualitative lipoprotein abnormalities that include increased RLPs and small, dense LDL particles. Patients with nephrotic syndrome or undergoing peritoneal dialysis are especially likely to exhibit a proatherogenic lipid profile.[192] In renal transplant recipients, hyperlipidemia is a frequent finding, affecting 80% to 90% of adult recipients despite normal renal function.[193]

The primary abnormality in CKD subjects is reduced catabolism of TRL,[131] which results in elevated levels of RLPs and prolonged ppTG that begins during the early stages of CKD.[194] The diminished clearance of TRL results from reduction in activity of both LPL and HTGL. Alterations in

the composition of circulating triglycerides associated with increases in the LPL inhibitor, apo CIII, and decreases in the LPL activator, apo CII, may exacerbate this defect.[194] Other factors such as increased parathyroid hormone levels,[135] increased calcium accumulation in liver and adipose tissue,[195] and a putative circulating lipase inhibitor (ie, CE-poor pre-β-HDL[196]) have also been shown to downregulate LPL in the plasma of uremic patients. In renal transplant recipients, immunosuppressive agents such as corticosteroids, calcineurin inhibitors, and rapamycin may significantly worsen dyslipidemia. Finally, other factors that accompany CKD, such as DM, MetS, hypothyroidism, obesity, excessive alcohol intake, marked proteinuria, and chronic liver disease, may potentiate hypertriglyceridemia.

Although the beneficial effects of lipid-lowering therapy in both primary and secondary prevention of CVD in the general population are well established, there is a paucity of RCTs addressing the role of treatment of dyslipidemia, particularly hypertriglyceridemia, in the CKD population. In fact, a number of studies have shown a paradoxical effect of low serum cholesterol in CKD and dialysis populations to be an adverse predictor of mortality.[197–200] This might reflect an adverse outcome of chronic inflammation and malnutrition that results in risk reversal. Of 2 clinical outcome trials completed recently, neither demonstrated benefits of LDL-C and lowering triglyceride levels in hemodialysis patients.[201,202] Results from RCTs to date cannot be extrapolated to milder forms of CKD, and therefore, an RCT is warranted in this subgroup. Until then, the benefit of lowering triglyceride levels in CKD remains unproven.

9. Interrelated Measurements and Factors That Affect Triglycerides

9.1. Non–HDL-C, Apo B, and Ratio of Triglycerides to HDL-C

As discussed previously in this statement, TRLs and RLPs in particular are atherogenic. Therefore, when a high-triglyceride profile is assessed, it is important to assess the overall atherogenicity of plasma. Both non–HDL-C (non–HDL-C=TC−HDL-C), which is a summary measure of all the cholesterol carried in apo B–containing particles, and directly measured apo B levels can be used for this purpose.

9.1.1. Non–HDL-C

The value of non–HDL-C in CVD risk assessment was first proposed by Frost and Havel in 1998,[61] and this relationship has now been confirmed in many studies.[203–216] In the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study, an autopsy study of 15- to 34-year-old individuals who died of non-CVD causes, non–HDL-C was correlated with fatty streaks and raised lesions in the right coronary artery.[204] In adults, non–HDL-C correlates with coronary calcification[205,206] and CVD progression.[207] Although the relationship between non–HDL-C and CVD outcomes has been studied less extensively than the relationship between LDL-C, myocardial infarction, and cardiovascular death, there are prospective studies that have demonstrated strong relationships between non–HDL-C levels and CVD events in the absence[208–210] or presence[211,212] of preexisting CVD or acute coronary syndrome. Long-term data from the Lipid Research Clinics Follow-Up Study demonstrated that non–HDL-C levels were strongly predictive of CVD mortality after 19 years of follow-up.[213] In the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study, non–HDL-C predicted 10-year CVD mortality only among those with impaired fasting glucose, not among those with normal fasting glucose.[214] Non–HDL-C levels also predicted ischemic stroke,[215,216] and its predictive value has been further demonstrated in both men and women, across all age and ethnic groups, and with or without CVD or associated risk factors.

Non–HDL-C can be assessed in the nonfasting state[22,217] and is more accurately determined because it does not depend on fasting triglyceride concentrations, as calculated LDL-C does.[61] Data on the distribution of non–HDL-C in the US population are available for children (Bogalusa cohort[218]) and adults (NHANES III[219]), and non–HDL-C levels in childhood strongly predict such levels in adulthood.[219,220] Among adults, age-adjusted non–HDL-C concentrations are lower among women than men, increase with age through age 65 years (to a greater degree in women than in men), and decline in individuals >65 years of age (more so in men than in women).[209] Non-Hispanic black women and men have the lowest non–HDL-C levels, whites are intermediate, and Mexican Americans have the highest level. Among women, non–HDL-C levels were inversely related to education.[219]

The ATP III guidelines recommended that non–HDL-C serve as a secondary treatment target if elevated levels of triglyceride (≥200 mg/dL) persisted after LDL-C target levels had been achieved.[10,221] The non–HDL-C target was set 30 mg/dL higher than LDL-C, based on the fact that a triglyceride level of 150 mg/dL corresponds to a VLDL cholesterol level of 30 mg/dL.[221] A meta-analysis of clinical trial data supports a 1:1 relationship between the percent of non–HDL-C lowering and the percent of cardiovascular reduction.[222] Yet recent data indicate that non–HDL-C remains undertreated in the United States. For example, in the National Cholesterol Education Program Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II survey, the proportion of individuals with triglyceride levels ≥200 mg/dL who had achieved their non–HDL-C goal ranged from 64% with 0 to 1 risk factor to 52% with ≥2 risk factors and only 27% with CVD risk equivalents.[223] Data from NHANES also showed that only a modest proportion (37%) of high-risk individuals were at their non–HDL-C goal.[224] Finally, in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) study of men and women with CVD and DM, the mean non–HDL-C level (131±40 mg/dL) was above the recommended goal of <130 mg/dL.[225]

9.1.2. Apo B

Apo B is contained within all potentially atherogenic lipoproteins, including lipoprotein(a), LDL, IDL, VLDL, and TRL remnants. Moreover, because each of these lipoprotein particles contains 1 apo B molecule, apo B provides a direct measure of the number of atherogenic particles present in the circulation.[58,226] A direct link between apo B and severity of

CVD in patients undergoing diagnostic cardiac catheterization[227] was followed by numerous studies that supported apo B as being highly predictive of CVD and, in some cases, more closely linked to CVD outcomes than LDL-C.[58,228,229] In contrast, findings of studies that compared apo B with non–HDL-C have been more heterogeneous. Although apo B and non–HDL-C are highly correlated, their interrelationship varies depending on the underlying lipid disorder and treatment status.[148,230] As reviewed recently,[231] many epidemiological studies have compared the predictive value of apo B with non–HDL-C for CVD outcomes and have more commonly identified apo B to be either superior or equivalent to non–HDL-C, whereas non–HDL-C has only been more predictive in limited cases.[143] Yet in studies that demonstrated statistically significant differences between apo B and non–HDL-C, the differences in point estimates were often quite small and therefore unlikely to have a major impact in day-to-day clinical practice.[231] Consequently, the ATP III guidelines favored use of non–HDL-C rather than apo B; this was related in part to the limited availability of apo B assays in clinical laboratories, compounded by the relative lack of standardization of the apo B assay and higher cost than for non–HDL-C.[221] Nevertheless, in view of additional data and in the presence of standardization that has accrued since ATP III was released in 2001, a panel of international experts has recommended a revision of this assessment.[229]

9.1.3. Ratio of Triglycerides to HDL-C

The joint occurrence of high triglyceride level and low HDL-C characterizes the dyslipidemia of MetS. It strongly predicts CVD in observational studies, and post hoc analyses of clinical trials suggest that patients who have both adverse markers tend to benefit more from treatment than those who do not.[39,40,232] The ratio of triglycerides to HDL-C serves as a summary measure for either elevated triglyceride level, low HDL-C, or both. It is linked to IR in whites[233,234] (but not in blacks) and to small, dense LDL particles and higher LDL particle numbers.[233,235] The link between IR and the ratio of triglycerides to HDL-C is already apparent in youth.[236] In recent years, case-control and prospective studies have linked the ratio of triglycerides to HDL-C to CVD incidence, outcomes, and all-cause mortality,[237–242] with improved predictive power in some studies compared with LDL-C or non–HDL-C.[238,239,242]

10. Factors That Influence Triglyceride Measurements

Considerable biological and, to a lesser extent, analytic variability exists in the measurement of triglycerides, with a median variation of 23.5% compared with 4.9% for TC, 6.9% for HDL-C, and 6.5% for calculated LDL-C.[243] Although biological variability as a consequence of lifestyle, medications, and metabolic abnormalities accounts for most of the intraindividual variation in triglycerides, other considerations that affect triglyceride measurements include postural effects, phlebotomy-related issues, and fasting versus nonfasting state. These latter considerations become more critical in the design of clinical trials aimed at evaluating the role of triglyceride levels in CVD risk assessment. In this regard, it has been suggested that in addition to the recommendations listed below (ie, posture- and phlebotomy-related issues), an average of 3 fasting serial samples be drawn at least 1 week apart and within a 2-month time frame to provide a more accurate estimate of baseline triglyceride levels.[243]

10.1. Postural Effects

Because TRLs do not readily diffuse between vascular and extravascular compartments, the increase in plasma volume that accompanies movement from a standing to a supine position also results in a temporary decrease in triglyceride concentrations.[244] As a result of these positional changes, triglyceride levels are reduced by ≈12% after 20 to 30 minutes and by 15% to 20% by 40 minutes, with more modest decreases when a person changes from standing to sitting (ie, 8% and 10%, respectively).[245,246] Thus, it is recommended that standardization of blood sampling conditions be instituted on each occasion (eg, 5 minutes in sitting position) to minimize variability in triglyceride measurements.[243]

10.2. Phlebotomy-Related Issues

The 2 relevant phlebotomy-related issues that impact triglyceride levels are the venous occlusion time and differences between serum- and plasma-containing tubes. Because increases of as much as 10% to 15% in triglyceride levels have been reported with prolonged venous occlusion times, the National Cholesterol Education Program Working Group on Lipoprotein Measurement has recommended that a tourniquet not be applied for >1 minute before blood withdrawal.[243] Moreover, plasma tubes contain ethylenediaminetetraacetic acid and reduce triglyceride levels by 3% compared with serum because of the relative dilution of nondiffusible components in plasma.[247] Therefore, reliability in triglyceride measurements will be enhanced when either serum or plasma is used consistently.

10.3. Fasting Versus Nonfasting Levels

Although an overnight fast has been the traditional method for assessment of triglyceride levels, there are several lines of evidence that support a nonfasting measurement to screen for hypertriglyceridemia. First, the fasting state only represents a small proportion of time spent each day and therefore understates levels that are attained in the postprandial state. From a pathophysiological standpoint, a postprandial state enriched in dietary fat (eg, 70 to 100 g) may affect saturation parameters and impede hepatic removal of circulating CMRs,[248] thereby permitting their uptake and incorporation by macrophages.[63,249,250] Supportive observational studies have recently identified nonfasting triglyceride levels to be a superior predictor of CVD risk compared with fasting levels.[21,22]

The relationship between fasting and ppTG levels and factors that influence the response to dietary fat in healthy normolipidemic subjects were reviewed in 39 studies approximating 1500 ppTG measurements.[68,251–288] Although baseline dietary characteristics, fat content, and composition of test meals often varied between studies, a graded association

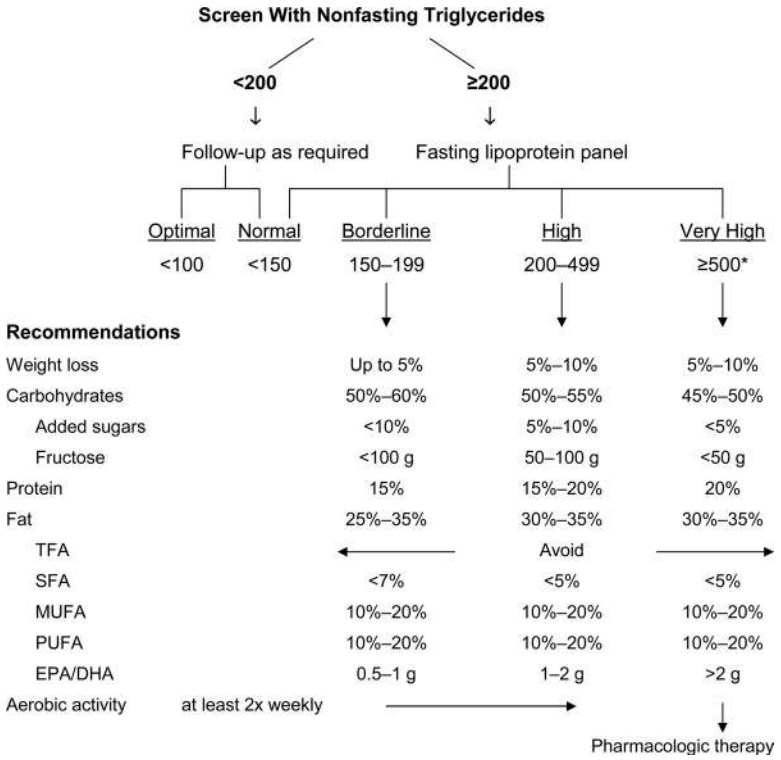

Figure 5. Practical algorithm for screening and management of elevated triglycerides. TFA indicates *trans* fatty acid; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; and EPA/DHA, eicosapentaenoic acid/docosahexaenoic acid.

*When patients present with abdominal pain due to hypertriglyceridemic pancreatitis, removal of all fat from the diet is required (with the possible exception of medium chain triglycerides [MCTs]) until appropriate therapies lower triglyceride levels substantially.

existed between the amount of dietary fat in the test meal and the ppTG response. For example, a meal that contained up to 15 g of fat was associated with minimal (20%) increases in peak ppTG levels,[276] whereas high-fat meals (eg, 50 g), including those served in popular fast-food restaurants, increased triglyceride levels by at least 50% beyond fasting levels.[68,273,275,279] Because median triglyceride levels in US adults range between 106 (women) and 122 (men) mg/dL, measurement of nonfasting triglyceride levels in the absence of a high-fat meal (eg, <15 g) would be expected to eliminate the requirement for a fasting lipid panel in a sizeable proportion of otherwise healthy adults.

A practical algorithm for screening triglyceride measurements is suggested in Figure 5. In normotriglyceridemic subjects (ie, fasting triglyceride levels <150 mg/dL), consumption of a low-fat breakfast (ie, <15 g) before blood sampling would not be expected to raise ppTG levels above 200 mg/dL. In these cases, no further testing for hypertriglyceridemia is indicated, although further discussion of lifestyle measures may be advocated on the basis of that individual's level of risk. However, if nonfasting triglyceride levels equal or exceed 200 mg/dL, a fasting lipid panel is recommended within a reasonable (eg, 2 to 4 weeks) time frame.

11. Special Populations

11.1. Children and Adolescent Obesity

Although the consequences of atherosclerotic CVD are seen only rarely in children, the early pathophysiological changes in arteries begin soon after birth and accelerate during adolescence.[289] The same risk factors associated with disease severity and progression in adults are present in the pediatric population, and the degree to which these risk factors are present in childhood is predictive of their prevalence in adulthood.[290,291] Therefore, it is clear that primary prevention of CVD should begin in childhood, as has been the established policy of the American Heart Association, the American Academy of Pediatrics, and the National Heart, Lung, and Blood Institute.[292,293] The National Heart, Lung, and Blood Institute's Pediatric Cardiovascular Risk Reduction Initiative panel has completed its work, and a full report was anticipated in 2011. Table 8 presents the pediatric cut points for hypertriglyceridemia, although these reference values are based on data from the 1981 Lipid Research Clinics prevalence study.[293] More recent data from NHANES 1999–2006 identified a triglyceride level ≥150 mg/dL in 11.4% of boys and 8.8% of girls 12 to 19 years of age, with the highest rate (16.4%) in the 18- to 19-year-old group.[154]

Table 8. Age- and Sex-Based Reference for Plasma Triglycerides in Children

Triglyceride Percentile	Boys, by Age Group			Girls, by Age Group		
	5–9 y	10–14 y	15–19 y	5–9 y	10–14 y	15–19 y
75th: Acceptable	58	74	88	74	85	85
90th: Borderline	70	94	125	103	104	112
95th: High	85	111	143	120	120	126

Values are milligrams per deciliter.

11.1.1. Risk Factors for Hypertriglyceridemia in Childhood

The genetic abnormalities of triglyceride metabolism (notably, *LPL*, *APOC2*, and, most recently, *APOA5* and *GPIHBP1*) that may be identified in childhood are rare and generally diagnosed soon after birth. More commonly identified are milder triglyceride level elevations (ie, 100 to 500 mg/dL) associated with environmental triggers such as poor diet, lack of exercise, obesity, DM, and MetS.

11.1.2. Obesity and High Triglyceride Levels in Childhood

At least one third of American children and adolescents are overweight, and childhood obesity represents the major cause of pediatric hypertriglyceridemia. Approximately 1 in 5 children with a BMI above the 95th percentile are hypertriglyceridemic, a rate that is 7-fold higher than for nonobese children 6 to 10 years of age.[294,295] Obese children are also more prone to have other CVD risk factors such as IR, high LDL-C, low HDL-C, and hypertension. In 2006, the American Heart Association convened the Childhood Obesity Research Summit to highlight the significance of pediatric obesity in CVD and to set research priorities for prevention and treatment.[295]

11.1.3. IR and T2DM in Childhood

Studies in children, including the Cardiovascular Risk in Young Finns Study[296] and a Pima Indian population study,[297] indicate that IR precedes the development of other risk factors, including obesity, hypertension, and hypertriglyceridemia. There are some impediments to the study of IR in youth, namely, lack of consensus for serum insulin norms and the well-documented physiological IR of puberty. Despite ongoing controversy in this area, 1 recent study identified IR (measured by fasting insulin) as being associated with failure to respond to therapeutic lifestyle change in obese adolescents.[298] In fact, recent data from NHANES III found a 7% prevalence of impaired fasting glucose in US adolescents. However, Mexican Americans and overweight adolescents had the highest rates (13% and 17.8% respectively) of impaired fasting glucose, which was associated with significantly higher fasting insulin, dyslipidemia, and hypertension.[299]

Impaired glucose tolerance is also associated with an increased incidence of hypertriglyceridemia. For example, in the NHANES cohort of 1999–2000, Williams et al[299] found that mean triglyceride levels were 28% higher in adolescents with impaired glucose tolerance than in those with normal fasting glucose concentrations. Triglyceride levels were independently associated with physical activity levels and sugar-sweetened beverage intake in the NHANES 1999–2004 studies of adolescents (n=6967) 12 to 19 years of age. Each additional daily serving of sugar-sweetened beverages was associated with a 2.25-mg/dL increase in triglyceride levels, as well as increases in IR, LDL-C, and systolic blood pressure and a decrease in HDL-C. In boys but not in girls, the combination of a high level of physical activity coupled with low intake of sugar-sweetened beverages was significantly associated with lower triglyceride levels, higher HDL-C, and reduced IR.[300]

11.2. Triglycerides as a Cardiovascular Risk Factor in Women

The Framingham Heart Study was among the first observational studies to recognize elevated triglyceride level as a predictor of CVD in women,[301] and the Lipid Research Clinics Follow-Up Study found a triglyceride level >200 mg/dL to be strongly predictive of cardiovascular death.[302] Triglyceride level is also a significant predictor in older women; in the Cardiovascular Study in the Elderly,[303] a 12-year longitudinal epidemiological study among Italian men and women ≥65 years of age at entry, women in the highest triglyceride quintile had a 2.5- fold greater risk of CVD mortality than women in the lowest quintile, even after adjustment for preexisting CVD, T2DM, obesity, and alcohol consumption. When low HDL-C was also present, risk increased 3.8-fold. Current guidelines for CVD prevention in women encourage fasting triglyceride levels <150 mg/dL and non–HDL-C <130 mg/dL through TLC.[304]

11.2.1. Triglyceride Levels During the Lifespan in Women

Although higher triglyceride levels among female newborns than among male newborns have been reported,[305] triglyceride levels in girls and boys are generally similar during early childhood. In adolescence, girls experience a decrease in triglycerides, whereas boys experience an increase, likely due to a greater degree of IR among males.[306] Population-based data in US adults indicate that compared with men triglyceride levels are lower in young and middle-aged females and among non-Hispanic whites, blacks, and Mexican Americans; in contrast, older women have higher levels than men in all ethnic groups.[6] Mexican American women have the highest triglyceride levels, whereas non-Hispanic white women have intermediate levels, and black women have the lowest levels.[6] Triglyceride levels in the 1999–2002 NHANES survey were higher than those documented in earlier NHANES surveys in 1976–1980 and 1988–1994. This increase occurred despite the fact that the use of lipid-lowering medications among adult women ≥20 years of age increased from 3.5% to 8% between the 1988–1994 and the 1999–2002 surveys.[6]

11.2.2. Prevalence of Hypertriglyceridemia in Women

The prevalence of triglyceride levels ≥150 mg/dL has increased among US women ≥20 years of age from 24.6% in 1988–1994 to 29.9% in 1999–2000,[307] with stabilization at 26.8% (1999–2008; Table 2). Prevalence is highest among Mexican American women, intermediate among non-Hispanic white women, and lowest among black women,[308,309] but data are lacking in other Hispanic and non-Hispanic subgroups (Figure 2). Women who develop DM experience a greater rise in triglyceride levels and have an overall more adverse lipid profile than men who develop DM.[310]

11.2.3. Hormonal Influences

Triglyceride levels in women are significantly impacted by the endogenous hormonal environment and by exogenously administered reproductive hormones. The impact of cyclic hormonal fluctuations on lipoprotein levels during the menstrual cycle in premenopausal women is controversial.[311]

Recent studies have reported no change in basal VLDL triglyceride and apo B_{100} kinetics[312] and triglyceride levels,[313] whereas other studies have shown small changes in triglyceride levels during the cycle but with overall coefficients of variation similar to those of postmenopausal women and men.[314] These findings suggest that screening and risk assessment in premenopausal women can be performed without standardization of lipoprotein measurements to the phase of the menstrual cycle. Women with polycystic ovarian syndrome have higher triglyceride levels than women with normal premenopausal physiology, even after correction for BMI.[315,316] This difference is present in women as young as 18 to 24 years of age and persists thereafter.[315]

Lipid metabolic effects of oral contraceptives vary on the basis of their estrogen and progestin content.[317,318] In the CARDIA study (Coronary Artery Risk Development in Young Adults), which did not distinguish between various formulations, oral contraceptive users had higher triglyceride levels than nonusers, despite their use being associated with lower fasting glucose levels and reduced odds of DM.[319] Higher triglyceride levels among oral contraceptive users were also found in a population-based survey in Canada.[320] Although most studies suggest increases in the 20% to 30% range, triglyceride level increases of as much as 57% (and decreases in LDL particle size) have been reported in some populations.[321]

In pregnancy, women experience a "physiological hyperlipidemia" due to enhanced lipolytic activity in adipose tissue, with >2-fold increases in circulating triglyceride levels during the third trimester.[109,110] As is the case in the nonpregnant state, non-Hispanic black women have lower triglyceride levels during pregnancy than their white counterparts.[322] Although some studies find a hypertriglyceridemia-associated shift toward smaller, denser LDL particle size,[323,324] others have shown a shift toward larger, buoyant LDL particles in late pregnancy.[325] Both IR[326] and hyperestrogenemia[327] represent causative factors for the development or amplification of hypertriglyceridemia during pregnancy and may present a therapeutic challenge, especially if pancreatitis develops.[105] Maternal hypertriglyceridemia in gestational DM also predicts babies that are large for their gestational age.[328] In contrast, endothelial function is not adversely affected as a result of pregnancy-induced hyperlipidemia.[329]

As women transition through menopause in middle age, triglyceride levels increase, but it is not clear how much of this increase is mediated by aging and accompanying lifestyle changes (eg, reduced physical activity) versus a consequence of menopausal hormonal transition.[330–334] In the Study of Women's Health Across the Nation (SWAN), the triglyceride increase peaked during late perimenopause/early postmenopause. The magnitude of change attributable to aging was similar to that associated with the menopausal transition; both were substantially greater than changes directly attributable to decreases in estradiol or increases in follicle stimulating hormone.[335]

Orally administered exogenous estrogens increase triglyceride levels, whereas exogenously administered progestins tend to ameliorate this estrogen-induced hypertriglyceridemia to varying degrees depending on dose and type of progestin.[336,337] Triglyceride levels vary substantially over time in women who are receiving cyclic hormone regimens.[338] It is assumed, but not well documented, that the increase in triglyceride levels induced by oral estrogens is enhanced among women with preexisting hypertriglyceridemia; therefore, hypertriglyceridemia has often been an exclusionary criteria in hormone-based RCTs.[339,340] Triglyceride elevations are not usually observed with transdermally administered estrogens.[337,341,342] Selective estrogen-receptor modulators have less impact on the lipid profile than oral hormone therapy in the absence of hypertriglyceridemia with estrogen therapy.[121] Raloxifene, for example, increased triglyceride levels by 8% in a 3-year study among healthy women but only by 1.5% in the much larger Multiple Outcomes of Raloxifene Evaluation trial, which included women with and without CVD.[343,344] Finally, tamoxifen has been reported to cause marked elevation in triglyceride levels,[124] with rare reports of pancreatitis (Table 5).

11.3. Triglycerides in Ethnic Minorities

Populations from South Asia, including India, Pakistan, Sri Lanka, Bangladesh, and Nepal, have an increased prevalence of MetS and T2DM compared with Europeans.[345] Several factors have been suggested to explain the propensity of South Asians to develop these metabolic risk factors for CVD. For example, South Asians have increased fat compared with muscle tissue, with a more central distribution of body fat, which has been attributed to the "adipose tissue overflow hypothesis."[346] This often occurs without a sufficient increase in waist circumference that meets the criteria of MetS as defined by ATP III, thereby resulting in a lower threshold for abnormal waist circumference for South Asians and several other ethnic groups; a BMI of 23 kg/m^2 in South Asians corresponds to a BMI of 25 kg/m^2 in whites.[347] Other hypotheses include genetic or phenotypic adaptations of the metabolism of South Asians to enable improved survival in the face of inadequate caloric intake.[345,346] In South Asians and other minorities (eg, Mexican Americans, Native Hawaiians, and American Indians), MetS is uniformly accompanied by an increase in atherogenic TRLs, thereby contributing to increased CVD risk in these populations.

Studies in American Indians have provided valuable information with regard to the influence of MetS and T2DM on triglyceride levels. Specifically, the Strong Heart Study, a cross-sectional prospective observational study of 4600 American Indians,[348] found a moderate elevation in triglyceride levels and a significantly increased prevalence of T2DM to have contributed to incident CVD.[349] Additional data from the Strong Heart Study have identified non–HDL-C as an important predictor of CVD in this subgroup.[208]

In contrast to ethnicities who have elevated levels of triglycerides, non-Hispanic blacks often possess lower levels of triglycerides; the mechanism for this inherent difference may be increased LPL activity.[350] A study of 185 blacks in whom IR was documented by the euglycemic-hyperinsulinemic clamp procedure demonstrated mean triglyceride levels (109 mg/dL) below the cut point for elevated triglyceride used in MetS, although they were higher than in the

insulin-sensitive cohort (mean 77 mg/dL).[351] Thus, blacks with MetS or T2DM may not possess high triglyceride levels as commonly as observed in other ethnic groups, thereby attenuating the predictive value of triglycerides or triglycerides-to-HDL ratios in this subgroup to identify IR.[234,350,352]

12. Classification of Hypertriglyceridemia

12.1. Defining Levels of Risk per the National Cholesterol Education Program ATP Guidelines

As described in Section 2: Scope of the Problem, triglyceride levels are classified as normal (<150 mg/dL), borderline high (150 to 199 mg/dL), high (200 to 499 mg/dL), or very high (≥500 mg/dL) based on measurements after a 12-hour fast. The most clinically relevant complication of hypertriglyceridemia is acute pancreatitis, yet only 10% of cases are a direct consequence of triglyceride levels. Because documentation for a specific threshold in triglyceride-induced pancreatitis is lacking, levels associated with increased risk are arbitrarily defined as triglyceride levels ≥1000 mg/dL[105,353]; however, because only 20% of subjects presenting with these extremely high levels develop pancreatitis,[354] it is often difficult to identify a high-risk subject on the basis of triglyceride levels alone. Table 5 lists genetic and secondary causes (disorders of metabolism, diet, drugs, and diseases that cause hypertriglyceridemia-induced pancreatitis[91–95,105–131,355,356]). Even when a secondary cause is identified, family screening to uncover a genetic lipid disorder is also in order.[357] In addition to pancreatitis, other potentially adverse clinical manifestations of chylomicronemia include retinal thrombosis[358] and, in rare cases, blindness. Therefore, very high triglyceride levels often require both therapeutic lifestyle change and pharmacological therapy as outlined in ATP III.[10]

Although borderline-high and high triglyceride levels (150 to 500 mg/dL) are not associated with pancreatitis, they are correlated with atherogenic RLPs and apo CIII–enriched particles.[74] The elevations in triglyceride levels serve as a biomarker for visceral adiposity, IR, DM, and nonalcoholic hepatic steatosis (fatty liver).[156,157,360] It is important to recognize that individuals with values in this range may remain at risk for pancreatitis, especially if they are placed on triglyceride-lowering treatment for very high levels (ie, ≥500 mg/dL) and experience an exacerbation due to secondary factors or interruption of treatment.

A low fasting triglyceride level (ie, <100 mg/dL) is commonly found in underdeveloped societies and countries at low CVD risk (eg, Africa, China, Greece, and Japan),[361–373] as contrasted with the United States, where mean levels are ≈15% to 30% higher.[6] Consistent with a reduced likelihood of abnormal metabolic parameters (eg, IR) are observational studies and clinical trials[3,232,367,374–380] that have consistently demonstrated the lowest risk of incident and recurrent CVD in association with the lowest fasting triglyceride levels. Taken together, these data raise the possibility that an optimal fasting triglyceride level may be <100 mg/dL; similarly, an optimal nonfasting triglyceride level may be <150 mg/dL because of the <50% anticipated increase in ppTG levels after a fat load (Section 10.3., Fasting Versus Nonfasting Levels).

An "optimal" triglyceride cut point is only intended to define one physiological parameter of cardiometabolic health. It does not represent a therapeutic target, because there is insufficient evidence that lowering triglyceride levels improves CVD risk prediction beyond LDL-C and non–HDL-C target goal recommendations. Nevertheless, the ≈25% rise in triglyceride levels in US adults during the past several decades[6] that has coincided with higher caloric intake[9] and higher rates of juvenile obesity and T2DM[8] is of great concern. These developments have provided the impetus for intensification of efforts aimed at therapeutic lifestyle change to halt and potentially reverse an alarming trend that, if not proactively addressed, may eradicate the considerable progress in CVD risk reduction that has been achieved in recent years.[381]

13. Dietary Management of Hypertriglyceridemia

13.1. Dietary and Weight-Losing Strategies

Nutrition measurements that affect triglyceride levels include body weight status; body fat distribution (Section 5.2., Obesity and Sedentary Lifestyle); weight loss; the macronutrient profile of the diet, including type and amount of dietary CHO and fat; and alcohol consumption. Importantly, multiple interventions can yield additive triglyceride-lowering effects that result in significant reductions in triglyceride levels. One intervention is to eliminate dietary *trans* fatty acids, which increase triglycerides and atherogenic lipoproteins (ie, lipoprotein[a], LDL-C)[382] and are linked to increased cardiovascular risk.[383] Although *trans* fatty acid consumption represents a small proportion of total caloric intake, certain food products, such as bakery shortening and stick margarine, contain high *trans* fatty acid concentrations (ie, 30% to 50%), and each 1% replacement of *trans* fatty acids for monounsaturated fat (MUFA) or polyunsaturated fat (PUFA) lowers triglyceride levels by ≈1%.[384]

13.1.1. Weight Status, Body Fat Distribution, and Weight Loss

Weight loss has a beneficial effect on lipids and lipoproteins.[385] A weight loss of 5% to 10% results in a 20% decrease in triglycerides, approximately a 15% reduction in LDL-C, and an 8% to 10% increase in HDL-C.[386] The magnitude of decrease in triglycerides is directly related to the amount of weight loss.[387] Meta-analyses have reported that for every kilogram of weight loss, triglyceride levels decrease ≈1.9%, or 1.5 mg/dL.[388,389]

13.2. Macronutrients

13.2.1. Total Fat, CHO, and Protein

The relationship between percent of total fat intake and change in triglyceride and HDL-C concentrations was reported in a meta-analysis of 19 studies published by the Institute of Medicine.[390] In this analysis comparing low-fat, high-CHO diets versus higher-fat diets, for every 5% decrease in total fat, triglyceride level was predicted to increase by 6% and HDL-C to decrease by 2.2%. In a subsequent meta-analysis of 30 controlled feeding studies in patients with

or without T2DM (n=1213), a moderate-fat diet (32.5% to 50% of calories from fat) versus a lower-fat diet (18% to 30% of calories from fat) resulted in a decrease in triglyceride level of 9.4 mg/dL (range from −6.1 to −12.2 mg/dL, $P<0.00001$) in those without T2DM[391]; however, in those with T2DM, the moderate-fat diet resulted in greater triglyceride reduction (−24.8 mg/dL, $P<0.05$) than seen with the low-fat diet.[391] Lastly, in a large meta-analysis of 60 controlled feeding studies,[392] replacement of any fatty acid class with a mixture of dietary CHOs increased fasting triglyceride levels. Specifically, for each 1% isoenergetic replacement of CHOs, decreases in triglyceride levels resulted with saturated fat (SFA; 1.9 mg/dL), MUFA (1.7 mg/dL), or PUFA (2.3 mg/dL) interchange (all $P<0.001$), which translated into an approximate 1% to 2% decrease in triglyceride levels.

The evidence statement from ATP III relative to dietary CHOs conveyed the following message: "… [V]very high intakes of carbohydrate (>60 percent of total calories) are accompanied by a reduction in HDL cholesterol and a rise in triglyceride …. These latter responses are sometimes reduced when carbohydrate is consumed with viscous fiber …; however, it has not been demonstrated convincingly that viscous fiber can fully negate the triglyceride-raising or HDL-lowering actions of very high intakes of carbohydrates."[221] Accordingly, the recommendation by ATP III for dietary CHO was, "Carbohydrate intakes should be limited to 60 percent of total calories. Lower intakes (eg, 50 percent of calories) should be considered for persons with the metabolic syndrome who have elevated triglycerides or low HDL cholesterol."[221]

As a follow-up to the recommendation from ATP III that high-CHO diets be avoided in individuals with elevated triglyceride levels, Berglund et al[393] evaluated a high-CHO (54% of calories) and low-fat (8% SFA) diet versus a high-MUFA (37% of calories from fat; 22% MUFA, 8% SFA) and average American (37% of calories from fat; 16% SFA) diet in individuals with any combination of HDL-C ≤30th percentile, triglyceride levels ≥70th percentile, or insulin ≥70th percentile. Although triglyceride levels were not affected by the MUFA diet compared with the average American diet, they were higher on the CHO diet than with either the average American diet or the MUFA diet (7.4% and 12%, respectively; $P<0.01$ for both).

Since ATP III, several large clinical trials have reported no increase in triglycerides in response to a reduction in total fat and a concurrent increase in dietary CHOs. In the DASH (Dietary Approaches to Stop Hypertension) trial, the effects of 3 dietary patterns on blood pressure, lipids, and lipoproteins were evaluated.[394,395] DASH emphasizes fruits and vegetables (8 to 10 servings per day) and low-fat dairy products (2 to 3 servings per day), including whole grains, legumes, fish, and poultry, and limits added sugars and fats. The DASH diet is high in dietary fiber (≈30 g/d) and provides 27% of calories from total fat, <7% of total calories from SFA, 150 mg of cholesterol per day, and 18% of calories from protein. In the DASH study, 436 adults with mildly elevated blood pressure (systolic blood pressure <160 mm Hg and diastolic blood pressure 80 to 95mm Hg) were randomized to consume either a Western diet (control diet; 48% CHO, 15% protein, 37% total fat, 16% SFA), a fruits and vegetables diet (which provided more fruits and vegetables and fewer snacks and sweets than the control diet but otherwise had a similar macronutrient distribution), or the DASH diet for 8 weeks. Compared with a Western diet, the DASH diet reduced TC (−9.5%), LDL-C (−9.1%), and HDL-C (−9.2%) but did not adversely affect triglycerides. TC, LDL-C, HDL-C, and triglyceride levels did not change with the fruits and vegetables diet.

In the OmniHeart (Optimal Macronutrient Intake) Trial, the effects of substituting SFA with CHO, protein, or unsaturated fat were evaluated in a 3-period, 6-week crossover feeding study that involved 164 prehypertensive or stage 1 hypertensive subjects.[396] Each diet period emphasized 1 macronutrient: High CHO (58% of total calories), moderate/high protein (25% of total calories, 50% of which were from plant proteins), or high unsaturated fat (37% of total calories, of which 21% came from MUFA and 10% from PUFA). All test diets provided 6% of calories from SFA and were high in dietary fiber (>30 g/d). Compared with baseline levels, triglyceride levels decreased significantly after the high-unsaturated-fat and high-protein diets (−9.3 and −16.4 mg/dL, respectively) but not after the high-CHO diet (increase of 0.1 mg/dL). Another major clinical trial, the Women's Health Initiative (WHI) Dietary Modification Trial of 48 835 postmenopausal women, found no differences in triglyceride levels (142 versus 145 mg/dL) between the low-fat dietary intervention and a higher-fat comparator group after 3 years of follow-up.[397] Thus, although many studies of high-CHO diets have shown increases in triglyceride levels, others (eg, DASH, OmniHeart, and WHI) have shown no effect. This discrepancy may reflect higher fiber intake (≈30 g/d; DASH, OmniHeart), higher protein intake (>15% of energy; DASH, OmniHeart, WHI), or a combined effect. Notably, the dietary patterns in DASH, OmniHeart, and WHI were high in fruits and vegetables, as well as grains (including whole grains). Results also suggest that moderate intake of predominately unsaturated fat (30% to 35% of energy or more) and plant-based proteins (17% to 25% of energy) may produce a triglyceride-lowering effect.

13.2.2. Mediterranean-Style Dietary Pattern

Epidemiological and clinical trial evidence suggests that the Mediterranean-style dietary pattern[398,399] is associated with decreased triglyceride levels. In the Framingham Heart Study Offspring Cohort (n=2730), subjects in the highest quintile for Mediterranean-style dietary pattern score had the lowest triglyceride levels (103 versus 114 mg/dL, $P<0.001$) over a 7-year follow-up.[398] Several clinical trials have reported beneficial effects of a Mediterranean-style diet on triglycerides compared with a lower-fat diet. Esposito et al[400] compared the effects of a Mediterranean-style diet with a control diet over a 2-year period on markers of CVD risk in patients (n=180) with MetS. The Mediterranean-style diet comprised more foods rich in MUFA, PUFA, and dietary fiber. Total fruit, vegetables, nuts, whole grains, and olive oil were higher in the intervention group. The intervention diet provided 28% of calories from total fat, with 8%, 12%, and 8% of calories from SFA, MUFA, and PUFA, respectively. The control diet

provided 30% of calories from total fat, with 14%, 10%, and 7% of calories from SFA, MUFA, and PUFA, respectively. After 2 years, triglyceride levels decreased 12% in the intervention group ($P=0.001$ versus the control diet). In addition, subjects on the intervention diet decreased body weight by 6.2 lb or 2.8 kg ($P<0.001$) and waist circumference by 0.8 inches or 2 cm ($P=0.01$) compared with the control group. Similarly, reduced triglyceride levels were reported in the Mediterranean Diet, Cardiovascular Risks and Gene Polymorphisms (Medi-RIVAGE) Study.[401] Finally, the PREDIMED (Prevención con Dieta Mediterránea) Study evaluated the effects of a Mediterranean diet plus virgin olive oil (1 L per week) and a Mediterranean diet plus mixed nuts (30 g/d; walnuts, hazelnuts, and almonds) versus a low-fat diet (control diet) in subjects (n=1224) at increased risk for CVD.[402] Both Mediterranean-style diets provided higher energy intake from fat than the control diet (41% to 43% versus 38% of calories) and were higher in MUFA content (21% to 22% versus 19.4% of calories). After 1 year, hypertriglyceridemia was less prevalent in both Mediterranean-style diet groups (12.3% and 13.6%) than in those eating the control diet (21.3%). With few exceptions, such as the Lyon Diet Heart Study,[403] which found no significant change in triglyceride levels on a MUFA-enriched versus low-fat, high-n-6 PUFA diet, implementation of a Mediterranean-style diet versus a low-fat diet is more commonly associated with an approximately 10% to 15% lowering of triglycerides and a reduced prevalence of hypertriglyceridemia.

13.3. Type of Dietary CHO

13.3.1. Dietary Fiber

The role of fiber in CVD risk has been reviewed by Erkkila and Lichtenstein,[404] and the evidence specifically for associations or effects on triglycerides is limited, especially in the absence of T2DM. In contrast, data exist related to fiber intake and triglycerides in individuals with or at increased risk for T2DM. The Botnia Dietary Study, a population study of 248 male and 304 female adult nondiabetic relatives of patients with T2DM from West Finland, reported an inverse association between serum triglycerides and total dietary fiber, water-insoluble fiber, and water-soluble fiber.[405] Anderson et al[406] conducted meta-analyses of T2DM to evaluate the lipid, lipoprotein, and glycemic effects of diets low (<10 g/1000 kcal) or high (>20 g/1000 kcal) in dietary fiber and with moderate (30% to 59.9% of energy) or high (>60% of energy) CHO intake. In 7 studies (n=98) that compared moderate CHO and high fiber versus moderate CHO and low fiber, triglyceride levels decreased by 8% in the high-fiber groups. Similarly, in 9 studies (n=119) that compared high CHO and high fiber versus moderate CHO and low fiber, triglyceride levels decreased 13% in the high-fiber group. Therefore, these data support a triglyceride-lowering effect for dietary fiber in individuals with T2DM.

13.3.2. Added Sugars

Consumption of added sugars has increased markedly in the United States from 1977–1978, when it was 10.6% of calories, to the current intake of 15.8% of calories.[407,408] The American Heart Association recommends limiting added sugars to fewer than 100 calories daily (ie, 6 tsp) for women and 150 calories daily (9 tsp) for men (≈5% of total energy).[9] The association of added sugars with increased obesity, T2DM, dental carries, and decreased diet quality is evident, which is part of the evidence base for recommendations made by other organizations to limit added sugars.[409,410] Recently, the association between added sugars and lipid measures was evaluated in a cross-sectional study of US adults (n=6113) that used NHANES 1999–2006 data.[408] The lowest triglyceride levels were observed when added sugar represented <10% of total energy. Conversely, higher triglyceride levels (5% to 10%) were observed when added sugar represented a greater proportion of energy intake.

13.3.3. Glycemic Index/Load

The glycemic index (GI) is defined as the ratio of the blood glucose response to a specific food and the glucose response to a standard food (ie, white bread). By comparison, the glycemic load (GL) of a food is calculated by multiplying the GI by CHO intake (in grams) and dividing by 100. In general, most refined starchy foods in the American diet have a high GI, whereas nonstarchy vegetables, fruit, and legumes typically have a low GI.

The role of GI and GL in CVD risk assessment remains controversial.[411–413] Two epidemiological studies, the Nurses' Health Study and the Women's Health Study, reported a positive association between GL and/or GI and fasting triglyceride levels.[414,415] A positive correlation between GI/GL and triglyceride levels was also reported in a cohort of Japanese women.[416] In terms of race/ethnicity, GL was positively associated with triglyceride levels in whites but not in blacks or Hispanics.[417] In an elderly population, however, there was no association between GI and triglyceride levels.[418] Other studies have reported mixed results. For example, the Insulin Resistance Atherosclerosis Study[419] found GL but not GI to be positively associated with triglycerides, whereas in the Whitehall II Study, GI but not GL correlated with triglyceride levels.[420] A Cochrane review of 15 RCTs from 1982 to 2003 assessing the relationship between low-GI diets and lipids found no evidence that low-GI diets affected plasma triglycerides[421]; however, 2 subsequent studies reported lower triglyceride levels with low-GI diets.[422,423] The relationship between GI/GL and triglycerides also remains unresolved in patients with T2DM, with 1 meta-analysis having identified a 6% reduction in triglyceride level in low- versus high-GI diets[406] but another study finding no appreciable differences in triglyceride levels in 162 subjects with T2DM assigned to a low- or high-GI diet.[424]

13.3.4. Fructose

Americans consume fructose in large quantities (up to 150 g/d). Fructose enhances lipogenesis and triglyceride synthesis. In contrast to glucose metabolism, which is regulated in part by phosphofructokinase, fructose metabolism is relatively unregulated.[425] In the past 4 decades, fructose consumption has increased appreciably because it is used in many beverages and foods sweetened with sucrose or "table sugar," the content of which is 50% fructose, or high-fructose

Table 9. Fructose Content in Selected Foods and Beverages From the USDA Nutrient Database*

Item	Amount, g
Cola with HFCS (12 oz)	22.5
Lemon-lime soda with HFCS (12 oz)	21.7
Ginger ale with HFCS (12 oz)	13.5
Raisins, seedless (1.5-oz box)	13
Power bar (chocolate)	10.9
Agave nectar (tbsp)†	8.9
Honey (tbsp)	8.6
Applesauce, sweetened (3.5 oz)	8
Fruit (apple, pear)	4–10
Molasses (tbsp)	2.6
Table sugar (tsp)	2

USDA indicates US Department of Agriculture; HFCS, high-fructose corn syrup; tbsp, tablespoon; and tsp, teaspoon.

*Available at http://www.nal.usda.gov/fnic/foodcomp/search/ and derived from the Association of Official Analytical Chemists method of analysis (http://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/SR23/sr23_doc.pdf).

†Data obtained from Patzold and Bruckner.[429]

corn syrup, which comprises 42% to 55% fructose.[426] Recent data suggest that dietary supplementation with fructose increases ppTG and CMRs compared with glucose.[427] In an extensive meta-analysis of 60 studies that evaluated the effects of fructose consumption on triglyceride levels, intakes ≤100 g/d had no significant effects on fasting plasma triglycerides. The lack of effect was demonstrated irrespective of whether fructose replaced starch, sucrose, or glucose. In contrast, intakes of fructose that exceeded 100 g/d revealed a dose-related increase in plasma triglycerides.[428] Similarly, in the 12 studies that monitored ppTG, a dose-dependent increase was observed above the 50-g fructose dose.[428] These data support limiting fructose in men and women with borderline or elevated triglyceride levels (Figure 5). A list of fructose-containing products is provided in Table 9.

Mechanistically, high CHO intake triggers pancreatic insulin release in response to increased blood glucose. Insulin, in turn, activates sterol regulatory element–binding protein, (SREBP-1c), a transcription factor that regulates fatty acid and triglyceride synthesis.[430] Recently, 2 additional transcription factors, X-box binding protein 1 (XBP1) and CHO response element–binding protein (ChREBP), have been identified as inducers of hepatic lipogenesis in response to ingested CHOs (eg, fructose and glucose) that is independent of insulin.[431,432] In contrast, unsaturated fatty acids reduce or inhibit SREBP-1c transcription, thereby reducing hepatic fatty acid synthesis[430] and plasma triglycerides.

13.4. Weight Loss and Macronutrient Profile of the Diet

Historically, there has been an interest in evaluating the effect of the macronutrient profile of the diet on weight loss and accompanying effects on lipids and lipoproteins. The Preventing Obesity Using Novel Dietary Strategies (POUNDS LOST) trial evaluated 4 weight loss diets that varied in macronutrient composition.[433] After 2 years, weight loss was similar in participants assigned to low and high protein (15% versus 25%), low and high fat (20% versus 40%), or low and high CHO (65% versus 35%). Irrespective of macronutrient composition, all diets decreased triglyceride levels similarly (12% to 17%).[433] Another popular weight loss alternative is a very low-CHO diet, defined as intake of <35 g of CHO per day.[434] A meta-analysis of RCTs that evaluated low-CHO versus low-fat (<30% of energy) diets found greater reductions in triglyceride levels on the low-CHO diet.[435] Consistent with these findings, Bonow and Eckel[434] concluded that low-CHO diets produced a more robust triglyceride-lowering effect than low-fat diets despite a similar magnitude of weight loss after 1 year.

The effect of a reduced-fat weight loss diet intervention was also evaluated in the Diabetes Prevention Program, a program comparing the effects of intensive therapeutic lifestyle change versus metformin on the development of T2DM in patients with impaired glucose tolerance. After 2.8 years, the intensively treated group lost weight (mean 5.6 kg) in association with a reduction in triglyceride levels (22 mg/dL).[436] Another analysis of the Diabetes Prevention Program that evaluated subjects with MetS reported a downward shift in the prevalence of triglyceride levels ≥150 mg/dL from 73% to 60% in the intensive-lifestyle versus placebo group.[437] Similar results were reported in the Look AHEAD (Action for Health in Diabetes) Trial,[438] in which weight reduction also translated into appreciable triglyceride lowering. The effects of a Mediterranean-style weight loss diet were compared with low-CHO and low-fat energy-restricted diets.[439] After 6 months, triglyceride levels were reduced the most in the low-CHO group (22%), but after 12 months, similar reductions were observed in both the low-CHO and Mediterranean-style groups, with minimal change in the low-fat group. Two additional studies evaluated 4 popular weight loss diets[440,441] in free-living subjects for 1 year. Dansinger et al[440] studied the effects of the Atkins diet, the Zone diet, the Weight Watchers diet, and the very low-fat Ornish diet on weight loss and CVD risk factors. Weight loss was similar after 12 months (4.8 to 7.3 kg) for all 4 diets. Although significant reductions in triglycerides occurred after 2 months on the Atkins and Zone diets, these effects were no longer significant after 12 months. In the study by Gardner et al,[441] which compared the Atkins, Zone, LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition) and Ornish diets, weight loss was greatest on the Atkins diet (4.7 kg) followed by LEARN (2.6 kg), Ornish (2.2 kg), and Zone (1.6 kg), with corresponding reductions in triglyceride levels (3% to 23%). Thus, diets that produce significant and sustained weight loss offer the most favorable reductions in triglyceride levels.

13.5. Alcohol

Prospective studies have demonstrated an inverse relationship between moderate alcohol consumption (ie, up to 1 oz daily) and CVD.[442] In evaluating the relationship between alcohol consumption and triglycerides, some studies have shown no association,[443–445] whereas others found modestly lower triglyceride levels in women who consumed up to 0.6 oz

daily.[446] At higher intakes, triglyceride levels increase,[447,448] and Rimm et al[449] estimated that ingestion of 1 oz/d would correspond to a 5% to 10% higher triglyceride concentration than found in nondrinkers.

In contrast, alcohol abuse may be associated with hypertriglyceridemia; nearly 1 in 5 hospitalized alcoholics have triglyceride levels exceeding 250 mg/dL.[450] An exaggerated rise in triglycerides occurs in the setting of excess alcohol intake combined with a meal high in saturated fat. Ethanol-induced lipemia may be due to inhibition of LPL-mediated hydrolysis of chylomicrons.[126,451,452] Therefore, in subjects with very high triglyceride levels, complete abstinence is strongly recommended in concert with reduced saturated fat intake to reduce the likelihood of pancreatitis.[105]

13.6. Marine-Derived Omega-3 PUFA

The American Heart Association recommends 2 to 4 g of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) per day, provided as capsules under a physician's care, for patients who need to lower their triglyceride level.[453] This recommendation is based on a large body of evidence showing triglyceride-lowering effects of marine-derived omega-3 PUFA. In a comprehensive review of human studies, Harris[454] reported that ≈4 g of marine-derived omega-3 PUFA per day decreased serum triglyceride concentrations by 25% to 30%, with accompanying increases of 5% to 10% in LDL-C and 1% to 3% in HDL-C. A dose-response relationship exists between marine-derived omega-3 PUFA and triglyceride lowering, with an approximate 5% to 10% reduction in triglycerides for every 1 g of EPA/DHA consumed[455]; efficacy is greater in individuals with higher triglyceride levels before treatment.[455–457] Skulas-Ray et al[458] reviewed studies that evaluated baseline triglyceride levels and the response to EPA plus DHA dose and found that the response was curvilinear, with individuals at lower baseline triglyceride levels having less of a triglyceride-lowering effect (≈20% versus 30% for higher triglyceride levels).

Mechanistically, decreased VLDL triglyceride secretion results from preferential shunting of omega-3 PUFA into phospholipid cellular synthesis, reduced expression of SREBP-1, and enhanced peroxisomal β-oxidation. In addition, upregulation of LPL facilitates VLDL triglyceride clearance.[459,460] Individually, EPA or DHA may reduce triglyceride,[461] ppTG,[462] or CMR[463] levels. However, marine-derived dietary sources contain both EPA and DHA in varying proportions. Table 10 lists foods enriched in marine-derived omega-3 PUFA. Because the amount needed for significant triglyceride lowering (2 to 4 g) is difficult to attain through diet alone on a daily basis, supplementation with capsules may be needed. The content of EPA/DHA per capsule is highly variable and ranges from 300 mg to ≈850 mg. Although marine-derived omega-3 PUFA capsules have been shown to be free of contaminants, their clinical efficacy at high doses (2 to 4 g/d) has yet to be established. Therefore, a well-designed RCT will be important to determine the extent to which triglyceride and non–HDL-C lowering through supplementation with marine-derived omega-3 PUFA improves CVD outcomes beyond standard-of-care therapy.

Table 10. EPA/DHA Content in Selected Foods (per 3.5-oz Serving)

Fish	Omega-3 PUFA, g
Anchovy (canned)	2.1
Herring, Atlantic (kippered)	2.1
Salmon, Atlantic (farmed)	2.1
Salmon, Atlantic (wild)	1.8
Herring, Atlantic (pickled)	1.4
Sardines, canned in tomato sauce	1.4
Salmon, coho	1.3
Trout, rainbow (farmed)	1.2
Halibut, Greenland	1.2
Salmon, sockeye	1.2
Salmon, pink or red (canned)	1.1
Sardines, canned in oil	1.0
Trout, rainbow (wild)	1.0
Tuna, white (canned in water)	0.9
Halibut, Atlantic or Pacific	0.5
Crabs	0.5
Lobster	0.5
Salmon, smoked (lox)	0.5
Shrimp	0.5
Tuna, light (canned in water)	0.3
Tuna, white (canned in oil)	0.2

EPA indicates eicosapentaenoic acid; DHA, docosahexaenoic acid; and PUFA, polyunsaturated fatty acid.

13.7. Nonmarine Omega-3 PUFA

Dietary marine-derived omega-3 PUFA intake is very low, at <0.2 g of the ≈1.4 g of total omega-3 PUFA consumed daily in the United States.[464,465] Non–marine-based omega-3 PUFA is derived from α-linolenic acid, a plant-based PUFA found in canola, chia, flaxseed, perilla, rapeseed, soybeans, walnuts, and purslane.[465,466] Yet non–marine-based PUFAs have not demonstrated consistent reductions in triglycerides[467]; this may reflect very low conversion rates of α-linolenic acid and its intermediary, stearidonic acid,[468] to the active triglyceride-lowering omega-3 compounds EPA and DHA.[469] Therefore, if omega 3 PUFAs are used for triglyceride lowering, they should be exclusively marine-derived EPA and/or DHA.

13.8. Dietary Summary

Overall, optimization of nutrition-related practices can result in a marked triglyceride-lowering effect that ranges between 20% and 50%. These practices include weight loss, reducing simple CHO at the expense of increasing dietary fiber, eliminating industrial-produced *trans* fatty acids, restricting fructose and SFA, implementing a Mediterranean-style diet, and consuming marine-derived omega-3 PUFA (Table 11). Dietary practices or factors that are associated with elevated triglyceride levels include excess body weight, especially visceral adiposity; simple CHOs, including added sugars and fructose; a high glycemic load; and alcohol.

14. Physical Activity and Hypertriglyceridemia

The high triglyceride levels observed with sedentary living, high SFA intake, visceral obesity, and IR commonly are

Table 11. Effects of Nutrition Practices on Triglyceride Lowering

Nutrition Practice	TG-Lowering Response, %
Weight loss (5% to 10% of body weight)	20
Implement a Mediterranean-style diet vs a low-fat diet	10–15
Add marine-derived PUFA (EPA/DHA) (per gram)	5–10
Decrease carbohydrates	
1% Energy replacement with MUFA/PUFA	1–2
Eliminate *trans* fats	
1% Energy replacement with MUFA/PUFA	1

TG indicates triglyceride; PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; and MUFA, monounsaturated fatty acid.

accompanied by an increased content of intramyocellular triglyceride that largely reflects ineffective utilization of fat (ie, reduced muscle fatty acid oxidation).[470–472] In contrast, aerobic activity enhances lipid oxidation, thereby facilitating the hydrolysis and utilization of triglycerides in skeletal muscle.[473] The effect of physical activity on triglyceride levels varies depending on baseline triglyceride, level of intensity, caloric expenditure, and duration of activity. For example, an optimal fasting triglyceride level (eg, <100 mg/dL) was associated with minimal (ie, <5%) reductions in postexercise triglyceride levels compared with greater (ie, 15% to 20%) reductions if baseline triglyceride levels exceeded 150 mg/dL.[474] Moreover, in a study of 2906 middle-aged men, moderately intensive activity (ie, jogging 10 miles weekly) versus no activity was associated with a 20% lower fasting triglyceride level; the highest activity level (>20 miles weekly) was also accompanied by the lowest mean fasting triglyceride level (86 mg/dL).[475] Higher baseline triglyceride levels (mean 197 mg/dL) also translated into significant triglyceride reductions (26%) in a 6-month trial of overweight subjects who walked 12 miles weekly at 40% to 55% of peak oxygen consumption.[476] However, other studies evaluating walking duration, frequency, and intensity (30 minutes daily at a maximum 65% to 75% of age-predicted heart rate) in the absence of weight loss did not demonstrate differences in postexercise triglyceride levels.[477] Similarly, increasing energy expenditure through physical activity without changing energy intake did not result in lower triglyceride levels if baseline levels were relatively normal (ie, mean 110 mg/dL). However, a reduction in energy intake (300 kcal/d) resulted in a 23% reduction in fasting triglyceride levels during the 1-year trial.[478] Additional benefits of exercise include reduction in the ppTG response and attenuation of the triglyceride elevations observed after consumption of a low-fat, high-CHO diet.[479] In fact, 60 minutes of aerobic exercise daily abolishes the CHO-induced increases in TRL.[480] Overall, exercise is most effective in lowering triglycerides (eg, 20% to 30%) when baseline levels are elevated (ie, >150 mg/dL), activity is moderate to intensive, and total caloric intake is reduced.[481]

15. Pharmacological Therapy in Patients With Elevated Triglyceride Levels

The association of elevated triglycerides with increased CVD risk and clustered metabolic abnormalities (as discussed in other sections of this scientific statement) has led to research and clinical interest in the potential protective benefit of reducing high levels of triglycerides. Although no published clinical trials have been designed specifically to examine the effect of triglyceride reduction on CVD event rate, secondary analyses from major trials of lipid-regulating therapy have assessed CVD risk in subgroups with high triglyceride levels. Unfortunately, most clinical trials limited entry triglyceride level to <400 mg/dL, and no known triglyceride-specific data from trials of diet and other lifestyle modifications are available. With the noted limitations of the published trial data, we attempt to address the following 3 questions:

1. *Do patients with elevated triglyceride levels at baseline benefit from pharmacological monotherapy?*

Table 12. Effect of Lipid-Lowering Therapies on Triglyceride Reduction[504,480a–480d]

Drug	% Triglyceride Reduction
Fibrates	30–50
Immediate-release niacin	20–50
Omega-3	20–50
Extended-release niacin	10–30
Statins	10–30
Ezetimibe	5–10

The triglyceride-lowering effects of lipid-altering agents are shown in Table 12. As monotherapy, fibrates offer the most triglyceride reduction, followed by immediate-release niacin, omega-3 methyl esters, extended-release niacin, statins, and ezetimibe. In contrast, bile acid resins may raise triglyceride levels (Table 5). A number of trials of statin or fibrate monotherapy have examined the potential role of baseline triglyceride level, categorized by various criteria (eg, cut points, MetS, combined with low HDL-C), on CVD risk. To date, similar analyses are not available for ezetimibe or niacin. In statin trials, subgroups with increased baseline triglyceride levels were reported to have increased CVD risk in the Scandinavian Simvastatin Survival Study (4S),[40,482,483] the Cholesterol and Recurrent Events (CARE) Trial,[484] the West of Scotland Coronary Prevention Study (WOSCOPS),[485] the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),[482] and the Treating to New Targets (TNT) study[486] and to have greater CVD risk reduction with lipid therapy in 4S[482,483] and CARE.[487] However, CVD event reductions were similar across categories of baseline triglycerides in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID),[488] the Heart Protection Study,[489] and WOSCOPS,[490] and CVD event reduction was greater in patients without MetS in the Anglo-Scandinavian Cardiac Outcome Trial.[491] Thus, in patients with hypertriglyceridemia, statin therapy may be beneficial in the setting of an LDL-C level that merits treatment.

Although statins have consistently shown benefit in subgroups with or without high triglyceride levels, fibrates have more commonly been shown to provide greater benefit in subgroups with increased triglyceride levels. These high-cardiovascular-risk subgroups benefited in the Helsinki Heart

Study,[39] the Bezafibrate Infarction Prevention study,[492,493] and the Fenofibrate Intervention and Event Lowering in Diabetes study.[494,495] In the Veterans Affairs HDL Intervention Trial (VA-HIT),[496,497] fibrate therapy reduced cardiovascular risk across all categories of baseline triglycerides. The recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which did not show an overall benefit for fibrate therapy added to statin therapy in T2DM, did show benefit in the subgroup with elevated triglyceride levels (>204 mg/dL) and low HDL-C (<34 mg/dL).[498] In summary, the aggregate data suggest that statin or fibrate monotherapy may be beneficial in patients with high triglyceride levels, low HDL-C, or both.

2. *Is a high triglyceride level in individuals receiving pharmacological monotherapy associated with increased CVD risk?*

Fewer trials have reported the potential effect of on-treatment triglyceride levels on CVD risk, even in secondary analyses. On-treatment triglyceride level was not associated with CVD risk in AFCAPS/TexCAPS[499] and was not predictive of CVD event rate or risk reduction in VA-HIT.[497] However, in LIPID, although baseline triglyceride level was not significantly associated with CVD risk in patients given placebo, each 89-mg/dL decrease in on-treatment triglyceride level in patients given pravastatin significantly decreased CVD risk by 11%, as well as by 14% after adjustment for nonlipid risk factors. However, the lipid-related parameters most strongly associated with CVD risk in LIPID were apo B, LDL-C, and the ratio of TC to HDL-C.[500] In the PROVE IT-TIMI 22 trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction), achievement of an on-treatment triglyceride level <150 mg/dL was associated with a 27% reduction in CVD risk compared with higher levels; each 10-mg/dL decrease in on-treatment triglyceride level was associated with CVD risk reductions of 1.8% in the unadjusted estimate and 1.4% in the fully adjusted model.[378] In a post hoc analysis of combined data from IDEAL (Incremental Decrease in Endpoints through Aggressive Lipid lowering) and TNT, CVD risk was ≈30% higher in patients with on-treatment triglyceride levels >150 mg/dL than in patients with lower on-treatment levels and 63% higher in patients in the top quintile for on-treatment triglyceride than for those in the lowest quintile in age- and sex-adjusted analysis. However, additional adjustment for HDL-C and the ratio of apo B to apo AI decreased the predictive ability of on-treatment triglyceride levels, and further adjustment for baseline glucose, BMI, hypertension, T2DM, and smoking eliminated the association.[501] Thus, high-risk statin-treated patients who continue to have elevated triglyceride levels display an increased risk for CVD, but these patients also have other metabolic abnormalities, and adjustment for measures of these associated abnormalities, such non–HDL-C and apo B, decreases the predictive effect of triglycerides.

3. *Do patients with elevated triglyceride levels while undergoing statin therapy receive additional cardiovascular risk reduction by the addition of a second drug that targets triglycerides or TRL?*

In the Japan EPA Lipid Intervention Study (JELIS), in which patients received a statin plus either EPA or a placebo, CVD risk reduction with combination therapy was not statistically significant in either baseline triglyceride subgroup (<151 or ≥151 mg/dL).[502] However, subgroup analysis of primary prevention patients in JELIS (80% of the study population) indicated that patients with baseline triglyceride levels at or exceeding 150 mg/dL and HDL-C <40 mg/dL had significantly increased CVD risk. Moreover, combination therapy with statin plus EPA in this high-risk subgroup reduced CVD risk by 53% compared with statin monotherapy,[503] even though the dose of EPA (up to 1.8 g/d) translated into minimal triglyceride reduction (5% between groups). Consequently, the cardiovascular benefit in JELIS was not a primary triglyceride-mediated effect.

Trials that used statin plus niacin (or in some cases bile acid resin) combination therapy have shown a reduction in coronary arteriographic progression and regression, as well as regression of carotid artery intima-media thickness.[504,505] Reduction in CVD outcomes were observed in several of these studies, although event rates were low, a statin placebo group was not used, and the studies were neither powered nor prespecified to address CVD events as a primary outcome measure. Nevertheless, they set the stage for the statin-niacin outcome trials listed below.

Unfortunately, there are limited data on the potential benefit of adding a second drug in high-risk patients treated with a statin who continue to have high triglyceride levels. As noted above, the ACCORD trial[498] did not find that fibrate therapy added to statin reduced cardiovascular events in DM patients (median triglyceride level of 162 mg/dL) except in the subgroup in the upper triglyceride tertile and lowest HDL-C tertile ($P=0.06$). Although ongoing clinical trials are not specifically designed to examine this issue, secondary analyses of the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH),[506] Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE),[507] and the ezetimibe-statin trial, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT),[508] may provide useful information.

16. Preventive Strategies Aimed at Reducing High Triglyceride Levels

The rise in triglyceride levels coinciding with the current epidemic of juvenile obesity, IR, and DM[509–511] has created new opportunities for establishing and disseminating CVD health promotion efforts aimed at maximizing primordial prevention. For example, resolutions have now been adopted in all 50 states targeting obesity, including the elimination of high caloric sugared sodas and *trans* fatty acid products from public school vending machines and increasing the number of walking and bicycle paths.[512,513] Initiatives such as reducing access to low-nutrient, energy-dense foods in school cafeterias serve as other adjunctive measures for controlling high triglyceride and obesity rates.[514] Among the most comprehensive national programs has been Healthy People 2010, the

initiative established by the Centers for Disease Control and Prevention in 1998 for health promotion and disease prevention.[515] The principal objectives are to improve the quality of healthy living and eliminate health disparities through interventions aimed at heart disease and stroke prevention.[515,516] In addition to community-based outreach programs, nutrition education beginning in elementary school may yield considerable dividends toward reducing obesity rates, because dietary behaviors are often established in childhood.[517] Prototypical pilot studies demonstrate a greater understanding of healthy food choices, which in turn may also improve academic performance.[518,519] Strategies to attenuate hypertriglyceridemia and its associated metabolic complications include increasing physical activity during school and afterschool sessions,[520,521] incentivizing schools committed to fostering nutrition education,[522] and offering a variety of fresh fruits and vegetables daily to school cafeterias.[523] Overall, identification of the most successful pilot programs for implementation on a national level will require coordinated efforts by clinicians, policymakers, and advocacy groups focused on reducing hypertriglyceridemia, obesity, and IR through a greater emphasis on and implementation of intensive lifestyle interventions.

17. Statement Summary and Recommendations

This scientific statement reviews the pivotal role of triglycerides in lipid metabolism and reaffirms that triglyceride is not directly atherogenic but represents an important biomarker of CVD risk because of its association with atherogenic remnant particles and apo CIII. Although some familial disorders of triglyceride metabolism are associated with increased risk for pancreatitis when fasting triglyceride level exceeds 1000 mg/dL, others are associated with increased atherosclerotic risk. Moreover, IR, obesity, and sedentary lifestyle can all lead to or aggravate metabolic syndrome risk factors, which should urgently prompt clinicians to focus first on improving the patient's lifestyle. Knowledge of the metabolic pathways of triglyceride-rich particles and the consequences of hypertriglyceridemia is crucial in understanding the characteristic lipid alterations in DM, lipodystrophic disorders including those seen with HIV, and chronic renal disease. Measurements of non–HDL-C, apo B, or both may be especially useful in those with prominent triglyceride/HDL abnormalities in which LDL-C measurements may underestimate true atherosclerotic vascular risk.

This statement suggests the following new designations: (1) Optimal fasting triglyceride levels, defined as <100 mg/dL, as a parameter of metabolic health, and (2) nonfasting triglyceride levels, to screen for those with high fasting triglyceride levels. A suggested practical algorithm for screening and management of elevated triglyceride levels is outlined in Figure 5. A nonfasting level of <200 mg/dL is commensurate with a normal (<150 mg/dL) or optimal (<100 mg/dL) fasting triglyceride level and requires no further testing. Fasting samples are used to designate borderline high (150 to 199 mg/dL), high (200 to 499 mg/dL), and very high (≥500 mg/dL) triglyceride levels. Nonfasting triglyceride levels are not used in the definition of MetS and should not be used in the calculation of LDL-C by the Friedewald formula.

Overall, the treatment of elevated triglyceride levels focuses on intensive therapeutic lifestyle change. For example, a 5% to 10% reduction in body weight anticipates a triglyceride-lowering response of 20%. Further offsets in CHO calories by reducing added sugars and fructose while increasing unsaturated fat intake may contribute an additional 10% to 20% reduction in triglyceride levels. Elimination of *trans* fats, restriction of SFA,[524–527] and increasing consumption of marine-based omega-3 products, coupled with aerobic activity, will further optimize triglyceride-lowering efforts. Taken together, reductions of 50% or more in triglyceride levels may be attained through intensive therapeutic lifestyle change.

In subjects with very high triglyceride levels or a history of triglyceride-induced pancreatitis, additional dietary considerations include complete abstinence from alcohol, the nutrition practices listed above, the possible use of MCTs[528] and pharmacological therapies (see also Tables 11 and 12). The subject of medication and triglycerides is still lacking crucial clinical trial evidence. Nonetheless, several points should be made. First, clinicians should rule out medications as a potential cause of an elevated triglyceride value. For example, hormone therapy (Table 5) can greatly influence triglyceride levels; in women of reproductive age who develop hypertriglyceridemia while taking oral contraceptive therapy, lower estrogen-containing preparations or other forms of contraception should be considered. For postmenopausal women with hypertriglyceridemia who require postmenopausal hormone preparations, switching to transdermal preparations may blunt the triglyceride increases observed with oral compounds. Second, utilizing triglyceride-lowering medications to prevent pancreatitis in those with triglyceride levels >500 mg/dL is reasonable in addition to intensive therapeutic lifestyle change. In those with a history of triglyceride-induced pancreatitis, it is especially important to keep triglyceride levels well controlled, and this will require both lifestyle and pharmacological approaches. What remains to be established is whether these modalities favorably influence CVD outcomes beyond proven therapies (eg, statins). Therefore, additional clinical outcome trials are necessary.

Acknowledgments

We are indebted to Drs Michael Wolz (National Institutes of Health; National Heart, Lung, and Blood Institute), Katherine Carroll (Centers for Disease Control and Prevention; Office of Surveillance, Epidemiology, and Laboratory Services; National Center for Health Statistics), and Paul Sorlie (National Institutes of Health; National Heart, Lung, and Blood Institute) for their invaluable statistical assistance.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Michael Miller	University of Maryland	None	None	None	None	None	None	None
Neil J. Stone	Northwestern University/ Northwestern Medical Faculty Foundation	None	None	American Association of Clinical Endocrinologists*; Association of Diabetes Nurse Educators*; Aurora Healthcare*; Eisenhower Hospital Mentoring Program*; Hartford Hospital Cardiology Grand Rounds*; National Lipid Association*; AHA*; Preventive Cardiology Nurses Association*; Unilever (donated to AHA)*	None	None	Abbott*; Merck*; Schering-Plough*; (All ended in May 2008)	None
Christie Ballantyne	Baylor College of Medicine	Abbott†; AstraZeneca†; GlaxoSmithKline†; Merck†; Pfizer†; Sanofi-Synthelabo†; Schering-Plough†; Takeda†	None	Abbott*; AstraZeneca†; Atherogenics*; GlaxoSmithKline†; Merck†; Merck/Schering-Plough*; Pfizer*; Reliant*; Schering-Plough*; Takeda*	None	None	Abbott*; Amylin*; AstraZeneca*; Atherogenics*; Bristol-Myers Squibb*; GlaxoSmithKline*; Kowa*; Merck*; Merck/ Schering-Plough*; Metabasis*; NicOx*; Novartis*; Pfizer*; Reliant*; Resverlogix*; Roche*; Sanofi-Synthelabo*; Schering-Plough*; Takeda*	None
Vera Bittner	University of Alabama at Birmingham	None	None	National Lipid Association*	None	None	Pfizer*	Chair, ACC Prevention Committee*; Immediate Past President, National Lipid Association*; Chair, AHA Exercise, Rehabilitation and Prevention Committee*
Michael H. Criqui	University of California, San Diego	None	None	None	None	None	None	None
Penny M. Kris-Etherton	Pennsylvania State University	Almond Board of California†; California Walnut Commission†; Canola Council of Canada†; General Mills†; GlaxoSmithKline*; Hass Avocado Board†; National Cattleman's Beef Association†; The Peanut Institute†	None	None	None	None	California Walnut Commission*; MonaVie*; Unilever*	None
Henry N. Ginsberg	Columbia University	AstraZeneca†; Isis Pharmaceuticals/ Genzyme†; Merck†; Reliant†; Roche*; Sanofi†; Takeda†	None	Abbott*; AstraZeneca*; Bristol-Myers Squibb*; Merck†; Merck/ Schering-Plough†; Novartis*; Pfizer*; Roche*; Sanofi*; Takeda*	None	None	Abbott*; Archer Daniels Midland†; AstraZeneca*; Bristol-Myers Squibb*; GlaxoSmithKline*; Isis/Genzyme*; Merck†; Merck/Schering-Plough†; Novartis*; Pfizer*; Reliant*; Roche*; Sanofi*; Takeda*	None
Anne Carol Goldberg	Washington University	Abbott†; Aegerion†; Amarin†; AstraZeneca†; GlaxoSmithKline†; Isis†; KOS†; Merck†; Novartis†; Reliant†; Sanofi-Aventis†; Sankyo†; Takeda†	None	Abbott*; Merck/ Schering-Plough*; Sanofi*; Sanofi-Aventis*	None	None	Abbott*; Genzyme-ISIS*; Merck*; Roche*; Sanofi-Aventis*	None
William James Howard	Washington Hospital Center	AstraZeneca*; Pfizer*	None	Abbott*; Merck†; Pfizer*; Sankyo*; Schering-Plough†	None	None	None	None
Marc S. Jacobson	Private practice	Merck (formerly Schering-Plough)†	None	None	None	None	None	None
Terry A. Lennie	University of Kentucky	None	None	None	None	None	None	None
Moshe Levi	University of Colorado	Abbott*; Genzyme*; Intercept Pharmaceuticals*	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Theodore Mazzone	University of Illinois at Chicago	Takeda†	None	Merck*	None	None	Abbott Laboratories*; GlaxoSmithKline*; Merck*	None
Subramanian Pennathur	University of Michigan	None	None	Merck/Schering- Plough*	None	None	None	None
Melissa A. Austin	University of Washington	None	None	None	None	None	None	None
Sergio Fazio	Vanderbilt University	ISIS*	None	None	None	None	Merck*	None
Ron Goldberg	University of Miami	Abbott†	None	GlaxoSmithKline*	None	None	GlaxoSmithKline*	None
William S. Harris	University of South Dakota	None	None	None	None	None	None	None
Peter W.F. Wilson	Emory University School of Medicine	Liposcience† Merck†	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

References

1. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol*. 1998;81:7B–12B.
2. 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;115:450–458.
3. Hulley SB, Rosenman RH, Bawol RD, Brand RJ. Epidemiology as a guide to clinical decisions: the association between triglyceride and coronary heart disease. *N Engl J Med*. 1980;302:1383–1389.
4. Consensus Conference: treatment of hypertriglyceridemia. *JAMA*. 1984;251:1196–1200.
5. NIH Consensus Development Panel on Triglyceride, High-Density Lipoprotein, and Coronary Heart Disease. NIH Consensus Conference: triglyceride, high-density lipoprotein, and coronary heart disease. *JAMA*. 1993;269:505–510.
6. Carroll MD, Lacher DA, Sorlie PD, Cleeman JI, Gordon DJ, Wolz M, Grundy SM, Johnson CL. Trends in serum lipids and lipoproteins of adults, 1960–2002. *JAMA*. 2005;294:1773–1781.
7. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA*. 2002;288:1723–1727.
8. Daniels SR, Arnett DK, Eckel RH, Gidding SS, Hayman LL, Kumanyika S, Robinson TN, Scott BJ, St Jeor S, Williams CL. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. *Circulation*. 2005;111:1999–2012.
9. Johnson RK, Appel LJ, Brands M, Howard BV, Lefevre M, Lustig RH, Sacks F, Steffen LM, Wylie-Rosett J; on behalf of American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Epidemiology and Prevention. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation*. 2009;120:1011–1020.
10. 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;285:2486–2497.
11. 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 [published correction appears in *Am J Cardiol*. 2010;106:1826]. *Am J Cardiol*. 2010;106:969–975.
12. Jacobs DR Jr, Barrett-Connor E. Retest reliability of plasma cholesterol and triglyceride: the Lipid Research Clinics Prevalence Study. *Am J Epidemiol*. 1982;116:878–885.
13. Criqui MH, Heiss G, Cohn R, Cowan LD, Suchindran CM, Bangdiwala S, Kritchevsky S, Jacobs DR Jr, O'Grady HK, Davis CE. Plasma triglyceride level and mortality from coronary heart disease. *N Engl J Med*. 1993;328:1220–1225.
14. Laakso M, Lehto S, Penttilä I, Pyörälä K. Lipids and lipoproteins predicting coronary heart disease mortality and morbidity in patients with non-insulin-dependent diabetes. *Circulation*. 1993;88:1421–1430.
15. West KM, Ahuja MM, Bennett PH, Czyzyk A, De Acosta OM, Fuller JH, Grab B, Grabauskas V, Jarrett RJ, Kosaka K. The role of circulating glucose and triglyceride concentrations and their interactions with other "risk factors" as determinants of arterial disease in nine diabetic population samples from the WHO multinational study. *Diabetes Care*. 1983;6:361–369.
16. Fontbonne A, Eschwège E, Cambien F, Richard JL, Ducimetière P, Thibult N, Warnet JM, Claude JR, Rosselin GE. Hypertriglyceridaemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes: results from the 11-year follow-up of the Paris Prospective Study. *Diabetologia*. 1989;32:300–304.
17. 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;302:1993–2000.
18. American Diabetes Association. Economic costs of diabetes in the U.S. in 2007 [published correction appears in *Diabetes Care*. 2008;31:1271]. *Diabetes Care*. 2008;31:596–615.
19. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. *Circulation*. 2004;109:42–46.
20. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study [published correction appears in *Circulation*. 1998;97:1995]. *Circulation*. 1998;97:1029–1036.
21. 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;298:299–308.
22. 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;298:309–316.
23. Brunner D, Altman S, Loebl K, Schwartz S, Levin S. Serum cholesterol and triglycerides in patients suffering from ischemic heart disease and in healthy subjects. *Atherosclerosis*. 1977;28:197–204.
24. Castelli WP, Doyle JT, Gordon T, Hames CG, Hjortland MC, Hulley SB, Kagan A, Zukel WJ. HDL cholesterol and other lipids in coronary heart

disease: the Cooperative Lipoprotein Phenotyping Study. *Circulation*. 1977; 55:767–772.
25. Wilhelmsen L, Bengtsson C, Elmfeldt D, Vedin A, Wilhelmsson C, Tibblin G, Lindqvist O, Wedel H. Multiple risk prediction of myocardial infarction in women as compared with men. *Br Heart J*. 1977;39: 1179–1185.
26. Scott DW, Gotto AM, Cole JS, Gorry GA. Plasma lipids as collateral risk factors in coronary artery disease: a study of 371 males with chest pain. *J Chronic Dis*. 1978;31:337–345.
27. Fager G, Wiklund O, Olofsson SO, Wilhelmsen L, Bondjers G. Multivariate analyses of serum apolipoproteins and risk factors in relation to acute myocardial infarction. *Arteriosclerosis*. 1981;1:273–279.
28. Kukita H, Imamura Y, Hamada M, Joh T, Kokubu T. Plasma lipids and lipoproteins in Japanese male patients with coronary artery disease and in their relatives. *Atherosclerosis*. 1982;42:21–29.
29. Hamsten A, Walldius G, Dahlén G, Johansson B, De Faire U. Serum lipoproteins and apolipoproteins in young male survivors of myocardial infarction. *Atherosclerosis*. 1986;59:223–235.
30. Gotto AM, Gorry GA, Thompson JR, Cole JS, Trost R, Yeshurun D, DeBakey ME. Relationship between plasma lipid concentrations and coronary artery disease in 496 patients. *Circulation*. 1977;56:875–883.
31. Anderson AJ, Barboriak JJ, Rimm AA. Risk factors and angiographically determined coronary occlusion. *Am J Epidemiol*. 1978; 107:8–14.
32. Cabin HS, Roberts WC. Relation of serum total cholesterol and triglyceride levels to the amount and extent of coronary arterial narrowing by atherosclerotic plaque in coronary heart disease: quantitative analysis of 2,037 five mm segments of 160 major epicardial coronary arteries in 40 necropsy patients. *Am J Med*. 1982;73:227–234.
33. Reardon MF, Nestel PJ, Craig IH, Harper RW. Lipoprotein predictors of the severity of coronary artery disease in men and women. *Circulation*. 1985;71:881–888.
34. Freedman DS, Gruchow HW, Anderson AJ, Rimm AA, Barboriak JJ. Relation of triglyceride levels to coronary artery disease: the Milwaukee Cardiovascular Data Registry. *Am J Epidemiol*. 1988;127:1118–1130.
35. Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM. Low-density lipoprotein subclass patterns and risk of myocardial infarction. *JAMA*. 1988;260:1917–1921.
36. 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;3:213–219.
37. Tirosh A, Rudich A, Shochat T, Tekes-Manova D, Israeli E, Henkin Y, Kochba I, Shai I. Changes in triglyceride levels and risk for coronary heart disease in young men. *Ann Intern Med*. 2007;147:377–385.
38. Carlson LA, Rosenhamer G. Reduction of mortality in the Stockholm Ischaemic Heart Disease Secondary Prevention Study by combined treatment with clofibrate and nicotinic acid. *Acta Med Scand*. 1988;223: 405–418.
39. 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;85:37–45.
40. Ballantyne CM, Olsson AG, Cook TJ, Mercuri MF, Pedersen TR, Kjekshus J. Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. *Circulation*. 2001;104:3046–3051.
41. Ginsberg HN. Lipoprotein physiology. *Endocrinol Metab Clin North Am*. 1998;27:503–519.
42. Young SG, Davies BS, Fong LG, Gin P, Weinstein MM, Bensadoun A, Beigneux AP. GPIHBP1: an endothelial cell molecule important for the lipolytic processing of chylomicrons. *Curr Opin Lipidol*. 2007;18: 389–396.
43. Havel RJ, Shore VG, Shore B, Bier DM. Role of specific glycopeptides of human serum lipoproteins in the activation of lipoprotein lipase. *Circ Res*. 1970;27:595–600.
44. 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;265:4266–4272.
45. Merkel M, Loeffler B, Kluger M, Fabig N, Geppert G, Pennacchio LA, Laatsch A, Heeren J. Apolipoprotein AV accelerates plasma hydrolysis of triglyceride-rich lipoproteins by interaction with proteoglycan-bound lipoprotein lipase. *J Biol Chem*. 2005;280:21553–21560.
46. Dallinga-Thie GM, Franssen R, Mooij HL, Visser ME, Hassing HC, Peelman F, Kastelein JJ, Péterfy M, Nieuwdorp M. The metabolism of triglyceride-rich lipoproteins revisited: new players, new insight. *Atherosclerosis*. 2010;211:1–8.
47. Brown WV, Baginsky ML. Inhibition of lipoprotein lipase by an apoprotein of human very low density lipoprotein. *Biochem Biophys Res Commun*. 1972;46:375–382.
48. Robciuc MR, Tahvanainen E, Jauhiainen M, Ehnholm C. Quantitation of serum angiopoietin-like proteins 3 and 4 in a Finnish population sample. *J Lipid Res*. 2010;51:824–831.
49. Cooper AD. Hepatic uptake of chylomicron remnants. *J Lipid Res*. 1997;38:2173–2192.
50. Bishop JR, Stanford KI, Esko JD. Heparan sulfate proteoglycans and triglyceride-rich lipoprotein metabolism. *Curr Opin Lipidol*. 2008;19: 307–313.
51. Davis RA. Cell and molecular biology of the assembly and secretion of apolipoprotein B-containing lipoproteins by the liver. *Biochim Biophys Acta*. 1999;1440:1–31.
52. Nilsson SK, Lookene A, Beckstead JA, Gliemann J, Ryan RO, Olivecrona G. Apolipoprotein A-V interaction with members of the low density lipoprotein receptor gene family. *Biochemistry*. 2007;46: 3896–3904.
53. Ginsberg HN. Lipoprotein physiology in nondiabetic and diabetic states: relationship to atherogenesis. *Diabetes Care*. 1991;14:839–855.
54. Fisher EA, Ginsberg HN. Complexity in the secretory pathway: the assembly and secretion of apolipoprotein B-containing lipoproteins. *J Biol Chem*. 2002;277:17377–17380.
55. Greene DJ, Skeggs JW, Morton RE. Elevated triglyceride content diminishes the capacity of high density lipoprotein to deliver cholesteryl esters via the scavenger receptor class B type I (SR-BI). *J Biol Chem*. 2001;276:4804–4811.
56. Skeggs JW, Morton RE. LDL and HDL enriched in triglyceride promote abnormal cholesterol transport. *J Lipid Res*. 2002;43:1264–1274.
57. Chait A, Brazg RL, Tribble DL, Krauss RM. Susceptibility of small, dense, low-density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. *Am J Med*. 1993; 94:350–356.
58. Kwiterovich PO Jr. Clinical relevance of the biochemical, metabolic, and genetic factors that influence low-density lipoprotein heterogeneity. *Am J Cardiol*. 2002;90:30i–47i.
59. Ip S, Lichtenstein AH, Chung M, Lau J, Balk EM. Systematic review: association of low-density lipoprotein subfractions with cardiovascular outcomes. *Ann Intern Med*. 2009;150:474–484.
60. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
61. Frost PH, Havel RJ. Rationale for use of non-high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. *Am J Cardiol*. 1998;81:26B–31B.
62. Colhoun HM, Otvos JD, Rubens MB, Taskinen MR, Underwood SR, Fuller JH. Lipoprotein subclasses and particle sizes and their relationship with coronary artery calcification in men and women with and without type 1 diabetes. *Diabetes*. 2002;51:1949–1956.
63. Botham KM, Moore EH, De Pascale C, Bejta F. The induction of macrophage foam cell formation by chylomicron remnants. *Biochem Soc Trans*. 2007;35:454–458.
64. Liu L, Wen T, Zheng XY, Yang DG, Zhao SP, Xu DY, Lu GH. Remnant-like particles accelerate endothelial progenitor cells senescence and induce cellular dysfunction via an oxidative mechanism. *Atherosclerosis*. 2009;202:405–414.
65. Norata GD, Grigore L, Raselli S, Redaelli L, Hamsten A, Maggi F, Eriksson P, Catapano AL. Post-prandial endothelial dysfunction in hypertriglyceridemic subjects: molecular mechanisms and gene expression studies. *Atherosclerosis*. 2007;193:321–327.
66. 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;109:1022–1028.
67. Ting HJ, Stice JP, Schaff UY, Hui DY, Rutledge JC, Knowlton AA, Passerini AG, Simon SI. Triglyceride-rich lipoproteins prime aortic endothelium for an enhanced inflammatory response to tumor necrosis factor-alpha. *Circ Res*. 2007;100:381–390.

68. Ferreira AC, Peter AA, Mendez AJ, Jimenez JJ, Mauro LM, Chirinos JA, Ghany R, Virani S, Garcia S, Horstman LL, Purow J, Jy W, Ahn YS, de Marchena E. Postprandial hypertriglyceridemia increases circulating levels of endothelial cell microparticles. *Circulation*. 2004;110: 3599–3603.
69. Wang L, Gill R, Pedersen TL, Higgins LJ, Newman JW, Rutledge JC. Triglyceride-rich lipoprotein lipolysis releases neutral and oxidized FFAs that induce endothelial cell inflammation. *J Lipid Res*. 2009;50: 204–213.
70. Palmer AM, Murphy N, Graham A. Triglyceride-rich lipoproteins inhibit cholesterol efflux to apolipoprotein (apo) A1 from human macrophage foam cells. *Atherosclerosis*. 2004;173:27–38.
71. Patel S, Puranik R, Nakhla S, Lundman P, Stocker R, Wang XS, Lambert G, Rye KA, Barter PJ, Nicholls SJ, Celermajer DS. Acute hypertriglyceridaemia in humans increases the triglyceride content and decreases the anti-inflammatory capacity of high density lipoproteins. *Atherosclerosis*. 2009;204:424–428.
72. Linsel-Nitschke P, Jansen H, Aherrarhou Z, Belz S, Mayer B, Lieb W, Huber F, Kremer W, Kalbitzer HR, Erdmann J, Schunkert H. Macrophage cholesterol efflux correlates with lipoprotein subclass distribution and risk of obstructive coronary artery disease in patients undergoing coronary angiography. *Lipids Health Dis*. 2009;8:14.
73. Furuhashi M, Fucho R, Görgün CZ, Tuncman G, Cao H, Hotamisligil GS. Adipocyte/macrophage fatty acid-binding proteins contribute to metabolic deterioration through actions in both macrophages and adipocytes in mice. *J Clin Invest*. 2008;118:2640–2650.
74. Ooi EM, Barrett PH, Chan DC, Watts GF. Apolipoprotein C-III: understanding an emerging cardiovascular risk factor. *Clin Sci (Lond)*. 2008; 114:611–624.
75. 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;322:1702–1705.
76. Caron S, Staels B. Apolipoprotein CIII: a link between hypertriglyceridemia and vascular dysfunction? *Circ Res*. 2008;103:1348–1350.
77. Kawakami A, Aikawa M, Alcaide P, Luscinskas FW, Libby P, Sacks FM. Apolipoprotein CIII induces expression of vascular cell adhesion molecule-1 in vascular endothelial cells and increases adhesion of monocytic cells. *Circulation*. 2006;114:681–687.
78. Kawakami A, Aikawa M, Libby P, Alcaide P, Luscinskas FW, Sacks FM. Apolipoprotein CIII in apolipoprotein B lipoproteins enhances the adhesion of human monocytic cells to endothelial cells. *Circulation*. 2006;113:691–700.
79. Kawakami A, Osaka M, Tani M, Azuma H, Sacks FM, Shimokado K, Yoshida M. Apolipoprotein CIII links hyperlipidemia with vascular endothelial cell dysfunction. *Circulation*. 2008;118:731–742.
80. Kawakami A, Osaka M, Aikawa M, Uematsu S, Akira S, Libby P, Shimokado K, Sacks FM, Yoshida M. Toll-like receptor 2 mediates apolipoprotein CIII-induced monocyte activation. *Circ Res*. 2008;103: 1402–1409.
81. Babaev VR, Fazio S, Gleaves LA, Carter KJ, Semenkovich CF, Linton MF. Macrophage lipoprotein lipase promotes foam cell formation and atherosclerosis in vivo. *J Clin Invest*. 1999;103:1697–1705.
82. Goldberg IJ. Lipoprotein lipase and lipolysis: central roles in lipoprotein metabolism and atherogenesis. *J Lipid Res*. 1996;37:693–707.
83. Van Eck M, Zimmermann R, Groot PH, Zechner R, Van Berkel TJ. Role of macrophage-derived lipoprotein lipase in lipoprotein metabolism and atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2000;20:E53–E62.
84. Saraswathi V, Hasty AH. The role of lipolysis in mediating the proinflammatory effects of very low density lipoproteins in mouse peritoneal macrophages. *J Lipid Res*. 2006;47:1406–1415.
85. Wehinger A, Tancevski I, Schgoer W, Eller P, Hochegger K, Morak M, Hermetter A, Ritsch A, Patsch JR, Foeger B. Phospholipid transfer protein augments apoptosis in THP-1-derived macrophages induced by lipolyzed hypertriglyceridemic plasma. *Arterioscler Thromb Vasc Biol*. 2007;27:908–915.
86. Seimon T, Tabas I. Mechanisms and consequences of macrophage apoptosis in atherosclerosis. *J Lipid Res*. 2009;50(suppl):S382–S387.
87. Goldstein JL, Schrott HG, Hazzard WR, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease, II: genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest*. 1973;52:1544–1568.
88. Brunzell JD, Schrott HG, Motulsky AG, Bierman EL. Myocardial infarction in the familial forms of hypertriglyceridemia. *Metabolism*. 1976;25:313–320.
89. Genest JJ Jr, Martin-Munley SS, McNamara JR, Ordovas JM, Jenner J, Myers RH, Silberman SR, Wilson PW, Salem DN, Schaefer EJ. Familial lipoprotein disorders in patients with premature coronary artery disease. *Circulation*. 1992;85:2025–2033.
90. Hopkins PN, Heiss G, Ellison RC, Province MA, Pankow JS, Eckfeldt JH, Hunt SC. Coronary artery disease risk in familial combined hyperlipidemia and familial hypertriglyceridemia: a case-control comparison from the National Heart, Lung, and Blood Institute Family Heart Study. *Circulation*. 2003;108:519–523.
91. Brunzell JD. Familial lipoprotein lipase deficiency and other causes of chylomicronemia syndrome. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Base of Inherited Disease.* New York, NY: McGraw- Hill; 1995:1913–1932.
92. Priore Oliva C, Pisciotta L, Li Volti G, Sambataro MP, Cantafora A, Bellocchio A, Catapano A, Tarugi P, Bertolini S, Calandra S. Inherited apolipoprotein A-V deficiency in severe hypertriglyceridemia. *Arterioscler Thromb Vasc Biol*. 2005;25:411–417.
93. Hegele RA. Monogenic dyslipidemias: window on determinants of plasma lipoprotein metabolism. *Am J Hum Genet*. 2001;69:1161–1177.
94. Leaf DA. Chylomicronemia and the chylomicronemia syndrome: a practical approach to management. *Am J Med*. 2008;121:10–12.
95. Chait A, Brunzell JD. Chylomicronemia syndrome. *Adv Intern Med*. 1992;37:249–273.
96. Goldberg IJ. Hypertriglyceridemia: impact and treatment. *Endocrinol Metab Clin North Am*. 2009;38:137–149.
97. Brunzell JD, Hazzard WR, Porte D Jr, Bierman EL. Evidence for a common, saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man. *J Clin Invest*. 1973;52: 1578–1585.
98. 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-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet*. 2010;375:1634–1639.
99. Benlian P, De Gennes JL, Foubert L, Zhang H, Gagné SE, Hayden M. Premature atherosclerosis in patients with familial chylomicronemia caused by mutations in the lipoprotein lipase gene [published correction appears in *N Engl J Med*. 1997;336:451]. *N Engl J Med*. 1996;335: 848–854.
100. Wittekoek ME, Moll E, Pimstone SN, Trip MD, Lansberg PJ, Defesche JC, van Doormaal JJ, Hayden MR, Kastelein JJ. A frequent mutation in the lipoprotein lipase gene (D9N) deteriorates the biochemical and clinical phenotype of familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 1999;19:2708–2713.
101. Austin MA, McKnight B, Edwards KL, Bradley CM, McNeely MJ, Psaty BM, Brunzell JD, Motulsky AG. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: a 20-year prospective study. *Circulation*. 2000;101:2777–2782.
102. Olivecrona G, Ehrenborg E, Semb H, Makoveichuk E, Lindberg A, Hayden MR, Gin P, Davies BS, Weinstein MM, Fong LG, Beigneux AP, Young SG, Olivecrona T, Hernell O. Mutation of conserved cysteines in the Ly6 domain of GPIHBP1 in familial chylomicronemia. *J Lipid Res*. 2010;51:1535–1545.
103. Beigneux AP, Franssen R, Bensadoun A, Gin P, Melford K, Peter J, Walzem RL, Weinstein MM, Davies BS, Kuivenhoven JA, Kastelein JJ, Fong LG, Dallinga-Thie GM, Young SG. Chylomicronemia with a mutant GPIHBP1 (Q115P) that cannot bind lipoprotein lipase. *Arterioscler Thromb Vasc Biol*. 2009;29:956–962.
104. Ma Y, Henderson HE, Murthy V, Roederer G, Monsalve MV, Clarke LA, Normand T, Julien P, Gagne C, Lambert M, Davignon J, Lupien PJ, Brunzell J, Hayden MR. A mutation in the human lipoprotein lipase gene as the most common cause of familial chylomicronemia in French Canadians. *N Engl J Med*. 1991;324:1761–1766.
105. Ewald N, Hardt PD, Kloer HU. Severe hypertriglyceridemia and pancreatitis: presentation and management. *Curr Opin Lipidol*. 2009;20: 497–504.
106. Okura Y, Hayashi K, Shingu T, Kajiyama G, Nakashima Y, Saku K. Diagnostic evaluation of acute pancreatitis in two patients with hypertriglyceridemia. *World J Gastroenterol*. 2004;10:3691–3695.
107. Miller M. Disorders of hypertriglyceridemia. In: Kwiterovich PO, ed. *The Johns Hopkins Textbook of Dyslipidemia.* Baltimore, MD: Lippincott Williams & Wilkins; 2009:74–88.

108. Stone NJ. Secondary causes of hyperlipidemia. *Med Clin North Am*. 1994;78:117–141.
109. Herrera E, Amusquivar E, López-Soldado I, Ortega H. Maternal lipid metabolism and placental lipid transfer. *Horm Res*. 2006;65(suppl 3):59–64.
110. Mazurkiewicz JC, Watts GF, Warburton FG, Slavin BM, Lowy C, Koukkou E. Serum lipids, lipoproteins and apolipoproteins in pregnant non-diabetic patients. *J Clin Pathol*. 1994;47:728–731.
111. Yoshimura T, Ito M, Sakoda Y, Kobori S, Okamura H. Rare case of autoimmune hyperchylomicronemia during pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 1998;76:49–51.
112. Taskinen MR. Hyperlipidaemia in diabetes. *Baillieres Clin Endocrinol Metab*. 1990;4:743–775.
113. Dunn FL. Hyperlipidemia in diabetes mellitus. *Diabetes Metab Rev*. 1990;6:47–61.
114. Eland IA, Rasch MC, Sturkenboom MJ, Bekkering FC, Brouwer JT, Delwaide J, Belaiche J, Houbiers G, Stricker BH. Acute pancreatitis attributed to the use of interferon alfa-2b. *Gastroenterology*. 2000;119:230–233.
115. Stahl SM, Mignon L, Meyer JM. Which comes first: atypical antipsychotic treatment or cardiometabolic risk? *Acta Psychiatr Scand*. 2009;119:171–179.
116. Haitas B, Disler LJ, Joffe BI, Seftel HC. Massive hypertriglyceridemia associated with atenolol. *Am J Med*. 1988;85:586–587.
117. Crouse JR 3rd. Hypertriglyceridemia: a contraindication to the use of bile acid binding resins. *Am J Med*. 1987;83:243–248.
118. Nakagawa M, Kimura S, Fujimoto K, Atumi H, Imura J, Chikazawa Y, Imamura H, Okuyama H, Yamaya H, Fukushima T, Nakagawa A, Asaka M, Yokoyama H. A case report of an adult with severe hyperlipidemia during acute lymphocytic leukemia induction therapy successfully treated with plasmapheresis. *Ther Apher Dial*. 2008;12:509–513.
119. Parker WA. Estrogen-induced pancreatitis. *Clin Pharm*. 1983;2:75–79.
120. Perry RC, Cushing HE, Deeg MA, Prince MJ. Ritonavir, triglycerides, and pancreatitis. *Clin Infect Dis*. 1999;28:161–162.
121. Carr MC, Knopp RH, Brunzell JD, Wheeler BS, Zhu X, Lakshmanan M, Rosen AS, Anderson PW. Effect of raloxifene on serum triglycerides in women with a history of hypertriglyceridemia while on oral estrogen therapy. *Diabetes Care*. 2005;28:1555–1561.
122. Flynn WJ, Freeman PG, Wickboldt LG. Pancreatitis associated with isotretinoin-induced hypertriglyceridemia. *Ann Intern Med*. 1987;107:63.
123. Fernandez-Bussy S, Akindipe O, Baz M, Gosain P, Rosenberg A, Zumberg M. Sirolimus-induced severe hypertriglyceridemia in a lung transplant recipient. *Transplantation*. 2010;89:481–482.
124. Hozumi Y, Kawano M, Saito T, Miyata M. Effect of tamoxifen on serum lipid metabolism. *J Clin Endocrinol Metab*. 1998;83:1633–1635.
125. Weidmann P, de Courten M, Ferrari P, Böhlen L. Serum lipoproteins during treatment with antihypertensive drugs. *J Cardiovasc Pharmacol*. 1993;22(suppl 6):S98–S105.
126. Pownall HJ, Ballantyne CM, Kimball KT, Simpson SL, Yeshurun D, Gotto AM Jr. Effect of moderate alcohol consumption on hypertriglyceridemia: a study in the fasting state. *Arch Intern Med*. 1999;159:981–987.
127. Barson JR, Karatayev O, Chang GQ, Johnson DF, Bocarsly ME, Hoebel BG, Leibowitz SF. Positive relationship between dietary fat, ethanol intake, triglycerides, and hypothalamic peptides: counteraction by lipid-lowering drugs. *Alcohol*. 2009;43:433–441.
128. Moret M, Pruneta-Deloche V, Sassolas A, Marcais C, Moulin P. Prevalence and function of anti-lipoprotein lipase auto-antibodies in type V hyperchylomicronemia. *Atherosclerosis*. 2010;208:324–327.
129. de Carvalho JF, Bonfá E, Borba EF. Systemic lupus erythematosus and "lupus dyslipoproteinemia." *Autoimmun Rev*. 2008;7:246–250.
130. Garcia-Otin AL, Civeira F, Peinado-Onsurbe J, Gonzalvo C, Llobera M, Pocovi M. Acquired lipoprotein lipase deficiency associated with chronic urticaria: a new etiology for type I hyperlipoproteinemia. *Eur J Endocrinol*. 1999;141:502–505.
131. Vaziri ND. Causes of dysregulation of lipid metabolism in chronic renal failure. *Semin Dial*. 2009;22:644–651.
132. Bell DS, Bakris GL, McGill JB. Comparison of carvedilol and metoprolol on serum lipid concentration in diabetic hypertensive patients. *Diabetes Obes Metab*. 2009;11:234–238.
133. Isley WL, Oki J. Estrogen-induced pancreatitis after discontinuation of concomitant medroxyprogesterone therapy. *Am J Med*. 1997;102:416–417.
134. Banks PA, Conwell DL, Toskes PP. The management of acute and chronic pancreatitis. *Gastroenterol Hepatol (N Y)*. 2010;6(suppl 3):1–16.
135. Stone NJ. Clinical evaluation for genetic and secondary causes of dyslipidemia. In: Ballantyne C, ed. *Clinical Lipidology, A Companion to Braunwald's Heart Disease*. Philadelphia, PA: Saunders; 2009:144–157.
136. Pruneta-Deloche V, Marçais C, Perrot L, Sassolas A, Delay M, Estour B, Lagarde M, Moulin P. Combination of circulating antilipoprotein lipase (Anti-LPL) antibody and heterozygous S172 fsX179 mutation of LPL gene leading to chronic hyperchylomicronemia. *J Clin Endocrinol Metab*. 2005;90:3995–3998.
137. Cantor RM, de Bruin T, Kono N, Napier S, van Nas A, Allayee H, Lusis AJ. Quantitative trait loci for apolipoprotein B, cholesterol, and triglycerides in familial combined hyperlipidemia pedigrees. *Arterioscler Thromb Vasc Biol*. 2004;24:1935–1941.
138. Veerkamp MJ, de Graaf J, Hendriks JC, Demacker PN, Stalenhoef AF. Nomogram to diagnose familial combined hyperlipidemia on the basis of results of a 5-year follow-up study. *Circulation*. 2004;109:2980–2985.
139. Brouwers MC, Cantor RM, Kono N, Yoon JL, van der Kallen CJ, Bilderbeek-Beckers MA, van Greevenbroek MM, Lusis AJ, de Bruin TW. Heritability and genetic loci of fatty liver in familial combined hyperlipidemia. *J Lipid Res*. 2006;47:2799–2807.
140. Eichenbaum-Voline S, Olivier M, Jones EL, Naoumova RP, Jones B, Gau B, Patel HN, Seed M, Betteridge DJ, Galton DJ, Rubin EM, Scott J, Shoulders CC, Pennacchio LA. Linkage and association between distinct variants of the APOA1/C3/A4/A5 gene cluster and familial combined hyperlipidemia. *Arterioscler Thromb Vasc Biol*. 2004;24:167–174.
141. Pajukanta P, Lilja HE, Sinsheimer JS, Cantor RM, Lusis AJ, Gentile M, Duan XJ, Soro-Paavonen A, Naukkarinen J, Saarela J, Laakso M, Ehnholm C, Taskinen MR, Peltonen L. Familial combined hyperlipidemia is associated with upstream transcription factor 1 (USF1). *Nat Genet*. 2004;36:371–376.
142. Lee JC, Weissglas-Volkov D, Kyttälä M, Sinsheimer JS, Jokiaho A, de Bruin TW, Lusis AJ, Brennan ML, van Greevenbroek MM, van der Kallen CJ, Hazen SL, Pajukanta P. USF1 contributes to high serum lipid levels in Dutch FCHL families and U.S. whites with coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2007;27:2222–2227.
143. Wiesbauer F, Blessberger H, Azar D, Goliasch G, Wagner O, Gerhold L, Huber K, Widhalm K, Abdolvahab F, Sodeck G, Maurer G, Schillinger M. Familial-combined hyperlipidaemia in very young myocardial infarction survivors (< or =40 years of age). *Eur Heart J*. 2009;30:1073–1079.
144. Sniderman A, Bailey SD, Engert JC. Familial combined hyperlipidaemia: how can genetic disorders be common, complex and comprehensible? *Clin Sci (Lond)*. 2007;113:365–367.
145. ter Avest E, Sniderman AD, Bredie SJ, Wiegman A, Stalenhoef AF, de Graaf J. Effect of aging and obesity on the expression of dyslipidaemia in children from families with familial combined hyperlipidaemia. *Clin Sci (Lond)*. 2007;112:131–139.
146. Breslow JL. Genetics of lipoprotein abnormalities associated with coronary artery disease susceptibility. *Annu Rev Genet*. 2000;34:233–254.
147. Mahley RW, Huang Y, Rall SC Jr. Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia): questions, quandaries, and paradoxes. *J Lipid Res*. 1999;40:1933–1949.
148. Sniderman AD, Hogue JC, Bergeron J, Gagne C, Couture P. Non-HDL cholesterol and apoB in dyslipidaemia. *Clin Sci (Lond)*. 2008;114:149–155.
149. Retterstøl K, Hennig CB, Iversen PO. Improved plasma lipids and body weight in overweight/obese patients with type III hyperlipoproteinemia after 4 weeks on a low glycemic diet. *Clin Nutr*. 2009;28:213–215.
150. Kathiresan S, Willer CJ, Peloso GM, Demissie S, Musunuru K, Schadt EE, Kaplan L, Bennett D, Li Y, Tanaka T, Voight BF, Bonnycastle LL, Jackson AU, Crawford G, Surti A, Guiducci C, Burtt NP, Parish S, Clarke R, Zelenika D, Kubalanza KA, Morken MA, Scott LJ, Stringham HM, Galan P, Swift AJ, Kuusisto J, Bergman RN, Sundvall J, Laakso M, Ferrucci L, Scheet P, Sanna S, Uda M, Yang Q, Lunetta KL, Dupuis J, de Bakker PI, O'Donnell CJ, Chambers JC, Kooner JS, Hercberg S, Meneton P, Lakatta EG, Scuteri A, Schlessinger D, Tuomilehto J, Collins FS, Groop L, Altshuler D, Collins R, Lathrop GM, Melander O, Salomaa V, Peltonen L, Orho-Melander M, Ordovas JM, Boehnke M,

Abecasis GR, Mohlke KL, Cupples LA. Common variants at 30 loci contribute to polygenic dyslipidemia. *Nat Genet*. 2009;41:56–65.
151. Johansen CT, Wang J, Lanktree MB, Cao H, McIntyre AD, Ban MR, Martins RA, Kennedy BA, Hassell RG, Visser ME, Schwartz SM, Voight BF, Elosua R, Salomaa V, O'Donnell CJ, Dallinga-Thie GM, Anand SS, Yusuf S, Huff MW, Kathiresan S, Hegele RA. Excess of rare variants in genes identified by genome-wide association study of hypertriglyceridemia. *Nat Genet*. 2010;42:684–687.
152. Manolio TA. Genomewide association studies and assessment of the risk of disease. *N Engl J Med*. 2010;363:166–176.
153. Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Hypertriglyceridemia and its pharmacologic treatment among US adults. *Arch Intern Med*. 2009;169:572–578.
154. Centers for Disease Control and Prevention. Prevalence of abnormal lipid levels among youths: United States, 1999–2006 [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2010;59:78]. *MMWR Morb Mortal Wkly Rep*. 2010;59:29–33.
155. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, Vasan RS, Murabito JM, Meigs JB, Cupples LA, D'Agostino RB Sr, O'Donnell CJ. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation*. 2007;116:39–48.
156. Nicklas BJ, Penninx BW, Ryan AS, Berman DM, Lynch NA, Dennis KE. Visceral adipose tissue cutoffs associated with metabolic risk factors for coronary heart disease in women. *Diabetes Care*. 2003;26:1413–1420.
157. Després JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, Rodés-Cabau J, Bertrand OF, Poirier P. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk [published correction appears in *Arterioscler Thromb Vasc Biol*. 2008;28:e151]. *Arterioscler Thromb Vasc Biol*. 2008;28:1039–1049.
158. Rosito GA, Massaro JM, Hoffmann U, Ruberg FL, Mahabadi AA, Vasan RS, O'Donnell CJ, Fox CS. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation*. 2008;117:605–613.
159. Porter SA, Massaro JM, Hoffmann U, Vasan RS, O'Donnel CJ, Fox CS. Abdominal subcutaneous adipose tissue: a protective fat depot? *Diabetes Care*. 2009;32:1068–1075.
160. Simha V, Garg A. Inherited lipodystrophies and hypertriglyceridemia. *Curr Opin Lipidol*. 2009;20:300–308.
161. Simha V, Garg A. Lipodystrophy: lessons in lipid and energy metabolism. *Curr Opin Lipidol*. 2006;17:162–169.
162. Garg A. Acquired and inherited lipodystrophies. *N Engl J Med*. 2004;350:1220–1234.
163. Garg A. Gender differences in the prevalence of metabolic complications in familial partial lipodystrophy (Dunnigan variety). *J Clin Endocrinol Metab*. 2000;85:1776–1782.
164. Balasubramanyam A, Sekhar RV, Jahoor F, Jones PH, Pownall HJ. Pathophysiology of dyslipidemia and increased cardiovascular risk in HIV lipodystrophy: a model of "systemic steatosis." *Curr Opin Lipidol*. 2004;15:59–67.
165. Thompson MA, Aberg JA, Cahn P, Montaner JS, Rizzardini G, Telenti A, Gatell JM, Günthard HF, Hammer SM, Hirsch MS, Jacobsen DM, Reiss P, Richman DD, Volberding PA, Yeni P, Schooley RT. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA Panel. *JAMA*. 2010;304:321–333.
166. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA*. 1990;263:2893–2898.
167. D'Agostino RB Jr, Hamman RF, Karter AJ, Mykkanen L, Wagenknecht LE, Haffner SM; Insulin Resistance Atherosclerosis Study Investigators. Cardiovascular disease risk factors predict the development of type 2 diabetes: the Insulin Resistance Atherosclerosis Study. *Diabetes Care*. 2004;27:2234–2240.
168. Resnick HE, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1999–2002: the National Health and Nutrition Examination Survey. *Diabetes Care*. 2006;29:531–537.
169. Betteridge DJ. Diabetes, lipoprotein metabolism and atherosclerosis. *Br Med Bull*. 1989;45:285–311.
170. Brunzell JD. Clinical practice: hypertriglyceridemia. *N Engl J Med*. 2007;357:1009–1017.
171. Kreisberg RA. Diabetic dyslipidemia. *Am J Cardiol*. 1998;82:67U–73U.
172. Lally S, Owens D, Tomkin GH. Genes that affect cholesterol synthesis, cholesterol absorption, and chylomicron assembly: the relationship between the liver and intestine in control and streptozotosin diabetic rats. *Metabolism*. 2007;56:430–438.
173. Hsieh J, Longuet C, Baker CL, Qin B, Federico LM, Drucker DJ, Adeli K. The glucagon-like peptide 1 receptor is essential for postprandial lipoprotein synthesis and secretion in hamsters and mice. *Diabetologia*. 2010;53:552–561.
174. Hsieh J, Longuet C, Maida A, Bahrami J, Xu E, Baker CL, Brubaker PL, Drucker DJ, Adeli K. Glucagon-like peptide-2 increases intestinal lipid absorption and chylomicron production via CD36. *Gastroenterology*. 2009;137:997–1005, 1005.e1–1005.e4.
175. Hsieh J, Hayashi AA, Webb J, Adeli K. Postprandial dyslipidemia in insulin resistance: mechanisms and role of intestinal insulin sensitivity. *Atheroscler Suppl*. 2008;9:7–13.
176. Kissebah AH, Alfarsi S, Evans DJ, Adams PW. Integrated regulation of very low density lipoprotein triglyceride and apolipoprotein-B kinetics in non-insulin-dependent diabetes mellitus. *Diabetes*. 1982;31:217–225.
177. van Wijk JP, de Koning EJ, Martens EP, Rabelink TJ. Thiazolidinediones and blood lipids in type 2 diabetes. *Arterioscler Thromb Vasc Biol*. 2003;23:1744–1749.
178. Nagashima K, Lopez C, Donovan D, Ngai C, Fontanez N, Bensadoun A, Fruchart-Najib J, Holleran S, Cohn JS, Ramakrishnan R, Ginsberg HN. Effects of the PPARgamma agonist pioglitazone on lipoprotein metabolism in patients with type 2 diabetes mellitus. *J Clin Invest*. 2005;115:1323–1332.
179. Ginsberg H, Plutzky J, Sobel BE. A review of metabolic and cardiovascular effects of oral antidiabetic agents: beyond glucose-level lowering. *J Cardiovasc Risk*. 1999;6:337–346.
180. Austin MA, Krauss RM. LDL density and atherosclerosis. *JAMA*. 1995;273:115.
181. Horowitz BS, Goldberg IJ, Merab J, Vanni TM, Ramakrishnan R, Ginsberg HN. Increased plasma and renal clearance of an exchangeable pool of apolipoprotein A-I in subjects with low levels of high density lipoprotein cholesterol. *J Clin Invest*. 1993;91:1743–1752.
182. Huang PL. A comprehensive definition for metabolic syndrome. *Dis Model Mech*. 2009;2:231–237.
182a. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735–2752.
183. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645.
184. Schwartz GG, Olsson AG, Szarek M, Sasiela WJ. Relation of characteristics of metabolic syndrome to short-term prognosis and effects of intensive statin therapy after acute coronary syndrome: an analysis of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial. *Diabetes Care*. 2005;28:2508–2513.
185. Suzuki T, Katz R, Jenny NS, Zakai NA, LeWinter MM, Barzilay JI, Cushman M. Metabolic syndrome, inflammation, and incident heart failure in the elderly: the Cardiovascular Health Study. *Circ Heart Fail*. 2008;1:242–248.
186. Kasai T, Miyauchi K, Kurata T, Ohta H, Okazaki S, Miyazaki T, Kajimoto K, Kubota N, Daida H. Prognostic value of the metabolic syndrome for long-term outcomes in patients undergoing percutaneous coronary intervention. *Circ J*. 2006;70:1531–1537.
187. Anderson JL, Horne BD, Jones HU, Reyna SP, Carlquist JF, Bair TL, Pearson RR, Lappé DL, Muhlestein JB; Intermountain Heart Collaborative (IHC) Study. Which features of the metabolic syndrome predict the prevalence and clinical outcomes of angiographic coronary artery disease? *Cardiology*. 2004;101:185–193.
188. Karadag MK, Akbulut M. Low HDL levels as the most common metabolic syndrome risk factor in heart failure. *Int Heart J*. 2009;50:571–580.
189. Lemieux I, Pascot A, Couillard C, Lamarche B, Tchernof A, Alméras N, Bergeron J, Gaudet D, Tremblay G, Prud'homme D, Nadeau A, Després JP. Hypertriglyceridemic waist: a marker of the atherogenic metabolic

triad (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men? *Circulation*. 2000;102:179–184.
190. Saland JM, Ginsberg HN. Lipoprotein metabolism in chronic renal insufficiency. *Pediatr Nephrol*. 2007;22:1095–1112.
191. Tsimihodimos V, Dounousi E, Siamopoulos KC. Dyslipidemia in chronic kidney disease: an approach to pathogenesis and treatment. *Am J Nephrol*. 2008;28:958–973.
192. Kasiske BL. Hyperlipidemia in patients with chronic renal disease. *Am J Kidney Dis*. 1998;32(suppl 3):S142–S156.
193. Kasiske B, Cosio FG, Beto J, Bolton K, Chavers BM, Grimm R Jr, Levin A, Masri B, Parekh R, Wanner C, Wheeler DC, Wilson PW. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Transplant*. 2004;4(suppl 7):13–53.
194. Bagdade JD, Porte D Jr, Bierman EL. Hypertriglyceridemia: a metabolic consequence of chronic renal failure. *N Engl J Med*. 1968;279:181–185.
195. Akmal M, Perkins S, Kasim SE, Oh HY, Smogorzewski M, Massry SG. Verapamil prevents chronic renal failure-induced abnormalities in lipid metabolism. *Am J Kidney Dis*. 1993;22:158–163.
196. Cheung AK, Parker CJ, Ren K, Iverius PH. Increased lipase inhibition in uremia: identification of pre-beta-HDL as a major inhibitor in normal and uremic plasma. *Kidney Int*. 1996;49:1360–1371.
197. Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, Tracy RP, Powe NR, Klag MJ. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA*. 2004;291:451–459.
198. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Inverse association between lipid levels and mortality in men with chronic kidney disease who are not yet on dialysis: effects of case mix and the malnutrition-inflammation-cachexia syndrome. *J Am Soc Nephrol*. 2007;18:304–311.
199. Iseki K, Yamazato M, Tozawa M, Takishita S. Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. *Kidney Int*. 2002;61:1887–1893.
200. Harper CR, Jacobson TA. Managing dyslipidemia in chronic kidney disease. *J Am Coll Cardiol*. 2008;51:2375–2384.
201. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis [published correction appears in *N Engl J Med*. 2005;353:1640]. *N Engl J Med*. 2005;353:238–248.
202. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis [published correction appears in *N Engl J Med*. 2010;362:1450]. *N Engl J Med*. 2009;360:1395–1407.
203. Miller M, Ginsberg HN, Schaefer EJ. Relative atherogenicity and predictive value of non-high-density lipoprotein cholesterol for coronary heart disease. *Am J Cardiol*. 2008;101:1003–1008.
204. Rainwater DL, McMahan CA, Malcom GT, Scheer WD, Roheim PS, McGill HC Jr, Strong JP; PDAY Research Group. Lipid and apolipoprotein predictors of atherosclerosis in youth: apolipoprotein concentrations do not materially improve prediction of arterial lesions in PDAY subjects. *Arterioscler Thromb Vasc Biol*. 1999;19:753–761.
205. Martin SS, Qasim AN, Mehta NN, Wolfe M, Terembula K, Schwartz S, Iqbal N, Schutta M, Bagheri R, Reilly MP. Apolipoprotein B but not LDL cholesterol is associated with coronary artery calcification in type 2 diabetic whites. *Diabetes*. 2009;58:1887–1892.
206. Orakzai SH, Nasir K, Blaha M, Blumenthal RS, Raggi P. Non-HDL cholesterol is strongly associated with coronary artery calcification in asymptomatic individuals. *Atherosclerosis*. 2009;202:289–295.
207. Blankenhorn DH, Alaupovic P, Wickham E, Chin HP, Azen SP. Prediction of angiographic change in native human coronary arteries and aortocoronary bypass grafts: lipid and nonlipid factors. *Circulation*. 1990;81:470–476.
208. Lu W, Resnick HE, Jablonski KA, Jones KL, Jain AK, Howard WJ, Robbins DC, Howard BV. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the Strong Heart Study. *Diabetes Care*. 2003;26:16–23.
209. Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. *Am J Cardiol*. 2006;98:1363–1368.
210. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA*. 2005;294:326–333.
211. Bittner V, Hardison R, Kelsey SF, Weiner BH, Jacobs AK, Sopko G; Bypass Angioplasty Revascularization Investigation. Non-high-density lipoprotein cholesterol levels predict five-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation*. 2002;106:2537–2542.
212. Ray KK, Cannon CP, Cairns R, Morrow DA, Ridker PM, Braunwald E. Prognostic utility of apoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22. *Arterioscler Thromb Vasc Biol*. 2009;29:424–430.
213. Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, Bush TL. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med*. 2001;161:1413–1419.
214. Zhang L, Qiao Q, Tuomilehto J, Hammar N, Ruotolo G, Stehouwer CD, Heine RJ, Eliasson M, Zethelius B; DECODE Study Group. The impact of dyslipidaemia on cardiovascular mortality in individuals without a prior history of diabetes in the DECODE Study. *Atherosclerosis*. 2009;206:298–302.
215. Bang OY, Saver JL, Liebeskind DS, Pineda S, Ovbiagele B. Association of serum lipid indices with large artery atherosclerotic stroke. *Neurology*. 2008;70:841–847.
216. Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Relationships between lipoprotein components and risk of ischaemic and haemorrhagic stroke in the Apolipoprotein MOrtality RISk study (AMORIS). *J Intern Med*. 2009;265:275–287.
217. Mora S, Rifai N, Buring JE, Ridker PM. Fasting compared with nonfasting lipids and apolipoproteins for predicting incident cardiovascular events. *Circulation*. 2008;118:993–1001.
218. Srinivasan SR, Myers L, Berenson GS. Distribution and correlates of non-high-density lipoprotein cholesterol in children: the Bogalusa Heart Study. *Pediatrics*. 2002;110:e29.
219. Gardner CD, Winkleby MA, Fortmann SP. Population frequency distribution of non-high-density lipoprotein cholesterol (Third National Health and Nutrition Examination Survey [NHANES III], 1988–1994). *Am J Cardiol*. 2000;86:299–304.
220. Srinivasan SR, Frontini MG, Xu J, Berenson GS. Utility of childhood non-high-density lipoprotein cholesterol levels in predicting adult dyslipidemia and other cardiovascular risks: the Bogalusa Heart Study. *Pediatrics*. 2006;118:201–206.
221. National Cholesterol Education Program (U.S.). Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. *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): Final Report.* Washington, DC: National Institutes of Health, National Heart, Lung, and Blood Institute; 2002. NIH publication No. 02-5215.
222. Robinson JG, Wang S, Smith BJ, Jacobson TA. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. *J Am Coll Cardiol*. 2009;53:316–322.
223. Davidson MH, Maki KC, Pearson TA, Pasternak RC, Deedwania PC, McKenney JM, Fonarow GC, Maron DJ, Ansell BJ, Clark LT, Ballantyne CM. Results of the National Cholesterol Education (NCEP) Program Evaluation ProjecT Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations. *Am J Cardiol*. 2005;96:556–563.
224. Ghandehari H, Kamal-Bahl S, Wong ND. Prevalence and extent of dyslipidemia and recommended lipid levels in US adults with and without cardiovascular comorbidities: the National Health and Nutrition Examination Survey 2003–2004. *Am Heart J*. 2008;156:112–119.
225. Pambianco G, Lombardero M, Bittner V, Forker A, Kennedy F, Krishnaswami A, Mooradian AD, Pop-Busui R, Rana JS, Rodriguez A, Steffes M, Orchard TJ. Control of lipids at baseline in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *Prev Cardiol*. 2009;12:9–18.
226. Kwiterovich PO Jr. Identification and treatment of heterozygous familial hypercholesterolemia in children and adolescents. *Am J Cardiol*. 1993;72:30D–37D.

227. Sedlis SP, Schechtman KB, Ludbrook PA, Sobel BE, Schonfeld G. Plasma apoproteins and the severity of coronary artery disease. *Circulation*. 1986; 73:978–986.
228. Sniderman AD, Furberg CD, Keech A, Roeters van Lennep JE, Frohlich J, Jungner I, Walldius G. Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. *Lancet*. 2003;361: 777–780.
229. Barter PJ, Ballantyne CM, Carmena R, Castro Cabezas M, Chapman MJ, Couture P, de Graaf J, Durrington PN, Faergeman O, Frohlich J, Furberg CD, Gagne C, Haffner SM, Humphries SE, Jungner I, Krauss RM, Kwiterovich P, Marcovina S, Packard CJ, Pearson TA, Reddy KS, Rosenson R, Sarrafzadegan N, Sniderman AD, Stalenhoef AF, Stein E, Talmud PJ, Tonkin AM, Walldius G, Williams KM. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. *J Intern Med*. 2006;259: 247–258.
230. Ballantyne CM, Raichlen JS, Cain VA. Statin therapy alters the relationship between apolipoprotein B and low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol targets in high-risk patients: the MERCURY II (Measuring Effective Reductions in Cholesterol Using Rosuvastatin) trial. *J Am Coll Cardiol*. 2008;52:626–632.
231. de Graaf J, Couture P, Sniderman A. A diagnostic algorithm for the atherogenic apolipoprotein B dyslipoproteinemias. *Nat Clin Pract Endocrinol Metab*. 2008;4:608–618.
232. Assmann G, Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience): Prospective Cardiovascular Münster Study. *Am J Cardiol*. 1992;70:733–737.
233. McLaughlin T, Reaven G, Abbasi F, Lamendola C, Saad M, Waters D, Simon J, Krauss RM. Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? *Am J Cardiol*. 2005;96:399–404.
234. Sumner AE, Finley KB, Genovese DJ, Criqui MH, Boston RC. Fasting triglyceride and the triglyceride-HDL cholesterol ratio are not markers of insulin resistance in African Americans. *Arch Intern Med*. 2005;165: 1395–1400.
235. Hanak V, Munoz J, Teague J, Stanley A Jr, Bittner V. Accuracy of the triglyceride to high-density lipoprotein cholesterol ratio for prediction of the low-density lipoprotein phenotype B. *Am J Cardiol*. 2004;94: 219–222.
236. Hannon TS, Bacha F, Lee SJ, Janosky J, Arslanian SA. Use of markers of dyslipidemia to identify overweight youth with insulin resistance. *Pediatr Diabetes*. 2006;7:260–266.
237. Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE. Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. *Circulation*. 1997;96:2520–2525.
238. Drexel H, Aczel S, Marte T, Benzer W, Langer P, Moll W, Saely CH. Is atherosclerosis in diabetes and impaired fasting glucose driven by elevated LDL cholesterol or by decreased HDL cholesterol? *Diabetes Care*. 2005;28:101–107.
239. Bittner V, Johnson BD, Zineh I, Rogers WJ, Vido D, Marroquin OC, Bairey-Merz CN, Sopko G. The triglyceride/high-density lipoprotein cholesterol ratio predicts all-cause mortality in women with suspected myocardial ischemia: a report from the Women's Ischemia Syndrome Evaluation (WISE). *Am Heart J*. 2009;157:548–555.
240. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Low triglycerides–high high-density lipoprotein cholesterol and risk of ischemic heart disease. *Arch Intern Med*. 2001;161:361–366.
241. Shishehbor MH, Hoogwerf BJ, Lauer MS. Association of triglyceride-to-HDL cholesterol ratio with heart rate recovery. *Diabetes Care*. 2004; 27:936–941.
242. Barzi F, Patel A, Woodward M, Lawes CM, Ohkubo T, Gu D, Lam TH, Ueshima H; Asia Pacific Cohort Studies Collaboration. A comparison of lipid variables as predictors of cardiovascular disease in the Asia Pacific region. *Ann Epidemiol*. 2005;15:405–413.
243. National Cholesterol Education Program (U.S.). Working Group on Lipoprotein Measurement. *Recommendations on Lipoprotein Measurement.* Bethesda, Md.: National Institutes of Health, National Heart, Lung, and Blood Institute; 1995. NIH publication No. 95-3044.
244. Dixon M, Paterson CR. Posture and the composition of plasma. *Clin Chem*. 1978;24:824–826.
245. Miller M, Bachorik PS, Cloey TA. Normal variation of plasma lipoproteins: postural effects on plasma concentrations of lipids, lipoproteins, and apolipoproteins. *Clin Chem*. 1992;38:569–574.
246. Hagan RD, Upton SJ, Avakian EV, Grundy S. Increases in serum lipid and lipoprotein levels with movement from the supine to standing position in adult men and women. *Prev Med*. 1986;15:18–27.
247. Laboratory Methods Committee of the Lipid Research Clinics Program of the National Heart, Lung, and Blood Institute. Cholesterol and triglyceride concentrations in serum/plasma pairs. *Clin Chem*. 1977;23: 60–63.
248. Berr F. Characterization of chylomicron remnant clearance by retinyl palmitate label in normal humans. *J Lipid Res*. 1992;33:915–930.
249. Zilversmit DB. Atherogenesis: a postprandial phenomenon. *Circulation*. 1979;60:473–485.
250. Yu KC, Cooper AD. Postprandial lipoproteins and atherosclerosis. *Front Biosci*. 2001;6:D332–D354.
251. Havel RJ. Early effects of fat ingestion on lipids and lipoproteins of serum in man. *J Clin Invest*. 1957;36:848–854.
252. Patsch JR, Karlin JB, Scott LW, Smith LC, Gotto AM Jr. Inverse relationship between blood levels of high density lipoprotein subfraction 2 and magnitude of postprandial lipemia. *Proc Natl Acad Sci U S A*. 1983;80:1449–1453.
253. Patsch JR, Miesenböck G, Hopferwieser T, Mühlberger V, Knapp E, Dunn JK, Gotto AM Jr, Patsch W. Relation of triglyceride metabolism and coronary artery disease: studies in the postprandial state. *Arterioscler Thromb*. 1992;12:1336–1345.
254. Genest J, Sniderman A, Cianflone K, Teng B, Wacholder S, Marcel Y, Kwiterovich P Jr. Hyperapobetalipoproteinemia: plasma lipoprotein responses to oral fat load. *Arteriosclerosis*. 1986;6:297–304.
255. Weintraub MS, Eisenberg S, Breslow JL. Dietary fat clearance in normal subjects is regulated by genetic variation in apolipoprotein E. *J Clin Invest*. 1987;80:1571–1577.
256. Harris WS, Connor WE, Alam N, Illingworth DR. Reduction of postprandial triglyceridemia in humans by dietary n-3 fatty acids. *J Lipid Res*. 1988;29:1451–1460.
257. Cohen JC, Noakes TD, Benade AJ. Serum triglyceride responses to fatty meals: effects of meal fat content. *Am J Clin Nutr*. 1988;47:825–827.
258. Cohn JS, McNamara JR, Cohn SD, Ordovas JM, Schaefer EJ. Postprandial plasma lipoprotein changes in human subjects of different ages. *J Lipid Res*. 1988;29:469–479.
259. Lewis GF, O'Meara NM, Soltys PA, Blackman JD, Iverius PH, Druetzler AF, Getz GS, Polonsky KS. Postprandial lipoprotein metabolism in normal and obese subjects: comparison after the vitamin A fat-loading test. *J Clin Endocrinol Metab*. 1990;71:1041–1050.
260. Groot PH, van Stiphout WA, Krauss XH, Jansen H, van Tol A, van Ramshorst E, Chin-On S, Hofman A, Cresswell SR, Havekes L. Postprandial lipoprotein metabolism in normolipidemic men with and without coronary artery disease. *Arterioscler Thromb*. 1991;11:653–662.
261. De Bruin TW, Brouwer CB, Gimpel JA, Erkelens DW. Postprandial decrease in HDL cholesterol and HDL apo A-I in normal subjects in relation to triglyceride metabolism. *Am J Physiol*. 1991;260(part 1):E492–E498.
262. Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Gualtieri LJ, Goldin BR, Ordovas JM, Schaefer EJ. Effects of canola, corn, and olive oils on fasting and postprandial plasma lipoproteins in humans as part of a National Cholesterol Education Program Step 2 diet. *Arterioscler Thromb*. 1993;13:1533–1542.
263. Schneeman BO, Kotite L, Todd KM, Havel RJ. Relationships between the responses of triglyceride-rich lipoproteins in blood plasma containing apolipoproteins B-48 and B-100 to a fat-containing meal in normolipidemic humans. *Proc Natl Acad Sci U S A*. 1993;90: 2069–2073.
264. Karpe F, Steiner G, Olivecrona T, Carlson LA, Hamsten A. Metabolism of triglyceride-rich lipoproteins during alimentary lipemia. *J Clin Invest*. 1993;91:748–758.
265. Miller M, Kwiterovich PO Jr, Bachorik PS, Georgopoulos A. Decreased postprandial response to a fat meal in normotriglyceridemic men with hypoalphalipoproteinemia. *Arterioscler Thromb*. 1993;13:385–392.
266. Uiterwaal CS, Grobbee DE, Witteman JC, van Stiphout WA, Krauss XH, Havekes LM, de Bruijn AM, van Tol A, Hofman A. Postprandial triglyceride response in young adult men and familial risk for coronary atherosclerosis. *Ann Intern Med*. 1994;121:576–583.
267. Ryu JE, Craven TE, MacArthur RD, Hinson WH, Bond MG, Hagaman AP, Crouse JR 3rd. Relationship of intraabdominal fat as measured by magnetic resonance imaging to postprandial lipemia in middle-aged subjects. *Am J Clin Nutr*. 1994;60:586–591.
268. Bergeron N, Havel RJ. Influence of diets rich in saturated and omega-6 polyunsaturated fatty acids on the postprandial responses of apolipo-

proteins B-48, B-100, E, and lipids in triglyceride-rich lipoproteins. *Arterioscler Thromb Vasc Biol*. 1995;15:2111–2121.
269. Dubois C, Armand M, Senft M, Portugal H, Pauli AM, Bernard PM, Lafont H, Lairon D. Chronic oat bran intake alters postprandial lipemia and lipoproteins in healthy adults. *Am J Clin Nutr*. 1995;61:325–333.
270. Karpe F, Bell M, Bjorkegren J, Hamsten A. Quantification of postprandial triglyceride-rich lipoproteins in healthy men by retinyl ester labeling and simultaneous measurement of apolipoproteins B-48 and B-100. *Arterioscler Thromb Vasc Biol*. 1995;15:199–207.
271. Ginsberg HN, Jones J, Blaner WS, Thomas A, Karmally W, Fields L, Blood D, Begg MD. Association of postprandial triglyceride and retinyl palmitate responses with newly diagnosed exercise-induced myocardial ischemia in middle-aged men and women. *Arterioscler Thromb Vasc Biol*. 1995;15:1829–1838.
272. Roche HM, Gibney MJ. Postprandial triacylglycerolaemia: the effect of low-fat dietary treatment with and without fish oil supplementation. *Eur J Clin Nutr*. 1996;50:617–624.
273. Vogel RA, Corretti MC, Plotnick GD. Effect of a single high-fat meal on endothelial function in healthy subjects. *Am J Cardiol*. 1997;79:350–354.
274. Tangney CC, Hafner JM, McQuiston BD, Domas AJ, Rosenson RS. Postprandial changes in plasma and serum viscosity and plasma lipids and lipoproteins after an acute test meal. *Am J Clin Nutr*. 1997;65:36–40.
275. Plotnick GD, Corretti MC, Vogel RA. Effect of antioxidant vitamins on the transient impairment of endothelium-dependent brachial artery vasoactivity following a single high-fat meal. *JAMA*. 1997;278:1682–1686.
276. 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;67:31–38.
277. Miller M, Teter B, Dolinar C, Georgopoulos A. An NCEP II diet reduces postprandial triacylglycerol in normocholesterolemic adults. *J Nutr*. 1998;128:582–586.
278. Karpe F, de Faire U, Mercuri M, Bond MG, Hellénius ML, Hamsten A. Magnitude of alimentary lipemia is related to intima-media thickness of the common carotid artery in middle-aged men. *Atherosclerosis*. 1998;141:307–314.
279. Abia R, Perona JS, Pacheco YM, Montero E, Muriana FJ, Ruiz-Gutiérrez V. Postprandial triacylglycerols from dietary virgin olive oil are selectively cleared in humans. *J Nutr*. 1999;129:2184–2191.
280. Mekki N, Christofilis MA, Charbonnier M, Atlan-Gepner C, Defoort C, Juhel C, Borel P, Portugal H, Pauli AM, Vialettes B, Lairon D. Influence of obesity and body fat distribution on postprandial lipemia and triglyceride-rich lipoproteins in adult women. *J Clin Endocrinol Metab*. 1999;84:184–191.
281. Couillard C, Bergeron N, Prud'homme D, Bergeron J, Tremblay A, Bouchard C, Mauriège P, Després JP. Gender difference in postprandial lipemia: importance of visceral adipose tissue accumulation. *Arterioscler Thromb Vasc Biol*. 1999;19:2448–2455.
282. Koutsari C, Malkova D, Hardman AE. Postprandial lipemia after short-term variation in dietary fat and carbohydrate. *Metabolism*. 2000;49:1150–1155.
283. Couillard C, Bergeron N, Bergeron J, Pascot A, Mauriège P, Tremblay A, Prud'homme D, Bouchard C, Després JP. Metabolic heterogeneity underlying postprandial lipemia among men with low fasting high density lipoprotein cholesterol concentrations. *J Clin Endocrinol Metab*. 2000;85:4575–4582.
284. Vogel RA, Corretti MC, Plotnick GD. The postprandial effect of components of the Mediterranean diet on endothelial function. *J Am Coll Cardiol*. 2000;36:1455–1460.
285. Ooi TC, Cousins M, Ooi DS, Steiner G, Uffelman KD, Nakajima K, Simo IE. Postprandial remnant-like lipoproteins in hypertriglyceridemia. *J Clin Endocrinol Metab*. 2001;86:3134–3142.
286. Chung BH, Cho BH, Liang P, Doran S, Osterlund L, Oster RA, Darnell B, Franklin F. Contribution of postprandial lipemia to the dietary fat-mediated changes in endogenous lipoprotein-cholesterol concentrations in humans. *Am J Clin Nutr*. 2004;80:1145–1158.
287. Redgrave TG, Carlson LA. Changes in plasma very low density and low density lipoprotein content, composition, and size after a fatty meal in normo- and hypertriglyceridemic man. *J Lipid Res*. 1979;20:217–229.
288. Volek JS, Sharman MJ, Gomez AL, DiPasquale C, Roti M, Pumerantz A, Kraemer WJ. Comparison of a very low-carbohydrate and low-fat diet on fasting lipids, LDL subclasses, insulin resistance, and postprandial lipemic responses in overweight women. *J Am Coll Nutr*. 2004;23:177–184.
289. McGill HC Jr, McMahan CA, Zieske AW, Sloop GD, Walcott JV, Troxclair DA, Malcom GT, Tracy RE, Oalmann MC, Strong JP; Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. *Arterioscler Thromb Vasc Biol*. 2000;20:1998–2004.
290. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults: the Bogalusa Heart Study. *N Engl J Med*. 1998;338:1650–1656.
291. Lauer RM, Clarke WR. Use of cholesterol measurements in childhood for the prediction of adult hypercholesterolemia: the Muscatine Study. *JAMA*. 1990;264:3034–3038.
292. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. *Circulation*. 2006;114:2710–2738.
293. Daniels SR, Greer FR; Committee on Nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics*. 2008;122:198–208.
294. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics*. 1999;103:1175–1182.
295. Daniels SR, Jacobson MS, McCrindle BW, Eckel RH, Sanner BM. American Heart Association Childhood Obesity Research Summit: executive summary. *Circulation*. 2009;119:2114–2123.
296. Raitakari OT, Porkka KV, Rönnemaa T, Knip M, Uhari M, Akerblom HK, Viikari JS. The role of insulin in clustering of serum lipids and blood pressure in children and adolescents: the Cardiovascular Risk in Young Finns Study. *Diabetologia*. 1995;38:1042–1050.
297. Odeleye OE, de Courten M, Pettitt DJ, Ravussin E. Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. *Diabetes*. 1997;46:1341–1345.
298. Pinhas-Hamiel O, Lerner-Geva L, Copperman N, Jacobson MS. Insulin resistance and parental obesity as predictors to response to therapeutic life style change in obese children and adolescents 10–18 years old. *J Adolesc Health*. 2008;43:437–443.
299. Williams DE, Cadwell BL, Cheng YJ, Cowie CC, Gregg EW, Geiss LS, Engelgau MM, Narayan KM, Imperatore G. Prevalence of impaired fasting glucose and its relationship with cardiovascular disease risk factors in US adolescents, 1999–2000. *Pediatrics*. 2005;116:1122–1126.
300. Bremer AA, Auinger P, Byrd RS. Relationship between insulin resistance-associated metabolic parameters and anthropometric measurements with sugar-sweetened beverage intake and physical activity levels in US adolescents: findings from the 1999–2004 National Health and Nutrition Examination Survey. *Arch Pediatr Adolesc Med*. 2009;163:328–335.
301. Castelli WP. The triglyceride issue: a view from Framingham. *Am Heart J*. 1986;112:432–437.
302. Bass KM, Newschaffer CJ, Klag MJ, Bush TL. Plasma lipoprotein levels as predictors of cardiovascular death in women. *Arch Intern Med*. 1993;153:2209–2216.
303. Mazza A, Tikhonoff V, Schiavon L, Casiglia E. Triglycerides+high-density-lipoprotein-cholesterol dyslipidaemia, a coronary risk factor in elderly women: the CArdiovascular STudy in the ELderly. *Intern Med J*. 2005;35:604–610.
304. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Pina IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Jr, Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *Circulation*. 2011;123:1243–1262.
305. Bansal N, Cruickshank JK, McElduff P, Durrington PN. Cord blood lipoproteins and prenatal influences. *Curr Opin Lipidol*. 2005;16:400–408.

306. Moran A, Jacobs DR Jr, Steinberger J, Steffen LM, Pankow JS, Hong CP, Sinaiko AR. Changes in insulin resistance and cardiovascular risk during adolescence: establishment of differential risk in males and females. *Circulation*. 2008;117:2361–2368.
307. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. adults. *Diabetes Care*. 2004;27:2444–2449.
308. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, Ballantyne CM, Heiss G. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. *Diabetes Care*. 2005;28:385–390.
309. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. *Arch Intern Med*. 2003;163:427–436.
310. Walden CE, Knopp RH, Wahl PW, Beach KW, Strandness E Jr. Sex differences in the effect of diabetes mellitus on lipoprotein triglyceride and cholesterol concentrations. *N Engl J Med*. 1984;311:953–959.
311. Godsland IF, Wynn V, Crook D, Miller NE. Sex, plasma lipoproteins, and atherosclerosis: prevailing assumptions and outstanding questions. *Am Heart J*. 1987;114:1467–1503.
312. Magkos F, Patterson BW, Mittendorfer B. No effect of menstrual cycle phase on basal very-low-density lipoprotein triglyceride and apolipoprotein B-100 kinetics. *Am J Physiol Endocrinol Metab*. 2006;291:E1243–E1249.
313. Barnett JB, Woods MN, Lamon-Fava S, Schaefer EJ, McNamara JR, Spiegelman D, Hertzmark E, Goldin B, Longcope C, Gorbach SL. Plasma lipid and lipoprotein levels during the follicular and luteal phases of the menstrual cycle. *J Clin Endocrinol Metab*. 2004;89:776–782.
314. Reed RG, Kris-Etherton P, Stewart PW, Pearson TA; DELTA (Dietary Effects on Lipoproteins and Thrombogenic Activity) Investigators. Variation of lipids and lipoproteins in premenopausal women compared with men and postmenopausal women. *Metabolism*. 2000;49:1101–1105.
315. Talbott E, Guzick D, Clerici A, Berga S, Detre K, Weimer K, Kuller L. Coronary heart disease risk factors in women with polycystic ovary syndrome. *Arterioscler Thromb Vasc Biol*. 1995;15:821–826.
316. Valkenburg O, Steegers-Theunissen RP, Smedts HP, Dallinga-Thie GM, Fauser BC, Westerveld EH, Laven JS. A more atherogenic serum lipoprotein profile is present in women with polycystic ovary syndrome: a case-control study. *J Clin Endocrinol Metab*. 2008;93:470–476.
317. Greenlund KJ, Webber LS, Srinivasan S, Wattigney W, Johnson C, Berenson GS. Associations of oral contraceptive use with serum lipids and lipoproteins in young women: the Bogalusa Heart Study. *Ann Epidemiol*. 1997;7:561–567.
318. Godsland IF, Crook D, Simpson R, Proudler T, Felton C, Lees B, Anyaoku V, Devenport M, Wynn V. The effects of different formulations of oral contraceptive agents on lipid and carbohydrate metabolism. *N Engl J Med*. 1990;323:1375–1381.
319. Kim C, Siscovick DS, Sidney S, Lewis CE, Kiefe CI, Koepsell TD. Oral contraceptive use and association with glucose, insulin, and diabetes in young adult women: the CARDIA Study: Coronary Artery Risk Development in Young Adults. *Diabetes Care*. 2002;25:1027–1032.
320. Connelly PW, Stachenko S, MacLean DR, Petrasovits A, Little JA; Canadian Heart Health Surveys Research Group. The prevalence of hyperlipidemia in women and its association with use of oral contraceptives, sex hormone replacement therapy and nonlipid coronary artery disease risk factors. *Can J Cardiol*. 1999;15:419–427.
321. Foulon T, Payen N, Laporte F, Bijaoui S, Dupont G, Roland F, Groslambert P. Effects of two low-dose oral contraceptives containing ethinylestradiol and either desogestrel or levonorgestrel on serum lipids and lipoproteins with particular regard to LDL size. *Contraception*. 2001;64:11–16.
322. Koukkou E, Watts GF, Mazurkiewicz J, Lowy C. Ethnic differences in lipid and lipoprotein metabolism in pregnant women of African and Caucasian origin. *J Clin Pathol*. 1994;47:1105–1107.
323. Silliman K, Shore V, Forte TM. Hypertriglyceridemia during late pregnancy is associated with the formation of small dense low-density lipoproteins and the presence of large buoyant high-density lipoproteins. *Metabolism*. 1994;43:1035–1041.
324. Hubel CA, Shakir Y, Gallaher MJ, McLaughlin MK, Roberts JM. Low-density lipoprotein particle size decreases during normal pregnancy in association with triglyceride increases. *J Soc Gynecol Investig*. 1998;5:244–250.
325. Winkler K, Wetzka B, Hoffmann MM, Friedrich I, Kinner M, Baumstark MW, Wieland H, März W, Zahradnik HP. Low density lipoprotein (LDL) subfractions during pregnancy: accumulation of buoyant LDL with advancing gestation. *J Clin Endocrinol Metab*. 2000;85:4543–4550.
326. McIntyre HD, Chang AM, Callaway LK, Cowley DM, Dyer AR, Radaelli T, Farrell KA, Huston-Presley L, Amini SB, Kirwan JP, Catalano PM; Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group. Hormonal and metabolic factors associated with variations in insulin sensitivity in human pregnancy. *Diabetes Care*. 2010;33:356–360.
327. Montelongo A, Lasunción MA, Pallardo LF, Herrera E. Longitudinal study of plasma lipoproteins and hormones during pregnancy in normal and diabetic women. *Diabetes*. 1992;41:1651–1659.
328. Son GH, Kwon JY, Kim YH, Park YW. Maternal serum triglycerides as predictive factors for large-for-gestational age newborns in women with gestational diabetes mellitus. *Acta Obstet Gynecol Scand*. 2010;89:700–704.
329. Saarelainen H, Laitinen T, Raitakari OT, Juonala M, Heiskanen N, Lyyra-Laitinen T, Viikari JS, Vanninen E, Heinonen S. Pregnancy-related hyperlipidemia and endothelial function in healthy women. *Circ J*. 2006;70:768–772.
330. Davis CE, Pajak A, Rywik S, Williams DH, Broda G, Pazucha T, Ephross S. Natural menopause and cardiovascular disease risk factors: the Poland and US Collaborative Study on Cardiovascular Disease Epidemiology. *Ann Epidemiol*. 1994;4:445–448.
331. Lindquist O, Bengtsson C, Lapidus L. Relationships between the menopause and risk factors for ischaemic heart disease. *Acta Obstet Gynecol Scand Suppl*. 1985;130:43–47.
332. Bonithon-Kopp C, Scarabin PY, Darne B, Malmejac A, Guize L. Menopause-related changes in lipoproteins and some other cardiovascular risk factors. *Int J Epidemiol*. 1990;19:42–48.
333. Campos H, McNamara JR, Wilson PW, Ordovas JM, Schaefer EJ. Differences in low density lipoprotein subfractions and apolipoproteins in premenopausal and postmenopausal women. *J Clin Endocrinol Metab*. 1988;67:30–35.
334. Do KA, Green A, Guthrie JR, Dudley EC, Burger HG, Dennerstein L. Longitudinal study of risk factors for coronary heart disease across the menopausal transition. *Am J Epidemiol*. 2000;151:584–593.
335. Derby CA, Crawford SL, Pasternak RC, Sowers M, Sternfeld B, Matthews KA. Lipid changes during the menopause transition in relation to age and weight: the Study of Women's Health Across the Nation. *Am J Epidemiol*. 2009;169:1352–1361.
336. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial [published correction appears in *JAMA*. 1995;274:1676]. *JAMA*. 1995;273:199–208.
337. Godsland IF. Effects of postmenopausal hormone replacement therapy on lipid, lipoprotein, and apolipoprotein (a) concentrations: analysis of studies published from 1974–2000. *Fertil Steril*. 2001;75:898–915.
338. Weintraub MS, Grosskopf I, Charach G, Eckstein N, Ringel Y, Maharshak N, Rotmensch HH, Rubinstein A. Fluctuations of lipid and lipoprotein levels in hyperlipidemic postmenopausal women receiving hormone replacement therapy. *Arch Intern Med*. 1998;158:1803–1806.
339. Grady D, Applegate W, Bush T, Furberg C, Riggs B, Hulley SB. Heart and Estrogen/progestin Replacement Study (HERS): design, methods, and baseline characteristics. *Control Clin Trials*. 1998;19:314–335.
340. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19:61–109.
341. Seed M, Sands RH, McLaren M, Kirk G, Darko D. The effect of hormone replacement therapy and route of administration on selected cardiovascular risk factors in post-menopausal women. *Fam Pract*. 2000;17:497–507.
342. Crook D, Cust MP, Gangar KF, Worthington M, Hillard TC, Stevenson JC, Whitehead MI, Wynn V. Comparison of transdermal and oral estrogen-progestin replacement therapy: effects on serum lipids and lipoproteins. *Am J Obstet Gynecol*. 1992;166:950–955.
343. Reid IR, Eastell R, Fogelman I, Adachi JD, Rosen A, Netelenbos C, Watts NB, Seeman E, Ciaccia AV, Draper MW. A comparison of the effects of raloxifene and conjugated equine estrogen on bone and lipids in healthy postmenopausal women. *Arch Intern Med*. 2004;164:871–879.

344. Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hoszowski K, Rautaharju P, Harper KD; MORE Investigators (Multiple Outcomes of Raloxifene Evaluation). Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA*. 2002;287:847–857.
345. Forouhi NG, Sattar N. CVD risk factors and ethnicity: a homogeneous relationship? *Atheroscler Suppl*. 2006;7:11–19.
346. Bainey KR, Jugdutt BI. Increased burden of coronary artery disease in South-Asians living in North America: need for an aggressive management algorithm. *Atherosclerosis*. 2009;204:1–10.
347. Misra A, Khurana L. The metabolic syndrome in South Asians: epidemiology, determinants, and prevention. *Metab Syndr Relat Disord*. 2009;7:497–514.
348. Howard BV, Lee ET, Cowan LD, Fabsitz RR, Howard WJ, Oopik AJ, Robbins DC, Savage PJ, Yeh JL, Welty TK. Coronary heart disease prevalence and its relation to risk factors in American Indians: the Strong Heart Study. *Am J Epidemiol*. 1995;142:254–268.
349. Howard BV, Lee ET, Cowan LD, Devereux RB, Galloway JM, Go OT, Howard WJ, Rhoades ER, Robbins DC, Sievers ML, Welty TK. Rising tide of cardiovascular disease in American Indians: the Strong Heart Study. *Circulation*. 1999;99:2389–2395.
350. Sumner AE, Cowie CC. Ethnic differences in the ability of triglyceride levels to identify insulin resistance. *Atherosclerosis*. 2008;196:696–703.
351. Stein E, Kushner H, Gidding S, Falkner B. Plasma lipid concentrations in nondiabetic African American adults: associations with insulin resistance and the metabolic syndrome. *Metabolism*. 2007;56:954–960.
352. Sharma MD, Pavlik VN. Dyslipidaemia in African Americans, Hispanics and whites with type 2 diabetes mellitus and hypertension. *Diabetes Obes Metab*. 2001;3:41–45.
353. Fortson MR, Freedman SN, Webster PD 3rd. Clinical assessment of hyperlipidemic pancreatitis. *Am J Gastroenterol*. 1995;90:2134–2139.
354. Lloret Linares C, Pelletier AL, Czernichow S, Vergnaud AC, Bonnefont-Rousselot D, Levy P, Ruszniewski P, Bruckert E. Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. *Pancreas*. 2008;37:13–12.
355. Durrington PN, Twentyman OP, Braganza JM, Miller JP. Hypertriglyceridaemia and abnormalities of triglyceride catabolism persisting after pancreatitis. *Int J Pancreatol*. 1986;1:195–203.
356. Athyros VG, Giouleme OI, Nikolaidis NL, Vasiliadis TV, Bouloukos VI, Kontopoulos AG, Eugenidis NP. Long-term follow-up of patients with acute hypertriglyceridemia-induced pancreatitis. *J Clin Gastroenterol*. 2002;34:472–475.
357. Brunzell JD, Bierman EL. Chylomicronemia syndrome. Interaction of genetic and acquired hypertriglyceridemia. *Med Clin North Am*. 1982;66:455–468.
358. Nagra PK, Ho AC, Dugan JD Jr. Lipemia retinalis associated with branch retinal vein occlusion. *Am J Ophthalmol*. 2003;135:539–542.
359. Imke C, Rodriguez BL, Grove JS, McNamara JR, Waslien C, Katz AR, Willcox B, Yano K, Curb JD. Are remnant-like particles independent predictors of coronary heart disease incidence? The Honolulu Heart study. *Arterioscler Thromb Vasc Biol*. 2005;25:1718–1722.
360. Kashyap SR, Diab DL, Baker AR, Yerian L, Bajaj H, Gray-McGuire C, Schauer PR, Gupta M, Feldstein AE, Hazen SL, Stein CM. Triglyceride levels and not adipokine concentrations are closely related to severity of nonalcoholic fatty liver disease in an obesity surgery cohort. *Obesity (Silver Spring)*. 2009;17:1696–1701.
361. Gebre-Yohannes A, Rahlenbeck SI. Coronary heart disease risk factors among blood donors in northwest Ethiopia. *East Afr Med J*. 1998;75:495–500.
362. Vorster HH, Kruger A, Venter CS, Margetts BM, Macintyre UE. Cardiovascular disease risk factors and socio-economic position of Africans in transition: the THUSA study. *Cardiovasc J Afr*. 2007;18:282–289.
363. Murray MJ, Murray AB, Murray NJ, Murray MB. Serum cholesterol, triglycerides and heart disease of nomadic and sedentary tribesmen consuming isoenergetic diets of high and low fat content. *Br J Nutr*. 1978;39:159–163.
364. El ayachi M, Mziwira M, Vincent S, Defoort C, Portugal H, Lairon D, Belahsen R. Lipoprotein profile and prevalence of cardiovascular risk factors in urban Moroccan women. *Eur J Clin Nutr*. 2005;59:1379–1386.
365. Pauletto P, Puato M, Caroli MG, Casiglia E, Munhambo AE, Cazzolato G, Bittolo Bon G, Angeli MT, Galli C, Pessina AC. Blood pressure and atherogenic lipoprotein profiles of fish-diet and vegetarian villagers in Tanzania: the Lugalawa study. *Lancet*. 1996;348:784–788.
366. Hu FB, Wang B, Chen C, Jin Y, Yang J, Stampfer MJ, Xu X. Body mass index and cardiovascular risk factors in a rural Chinese population. *Am J Epidemiol*. 2000;151:88–97.
367. He Y, Lam TH, Li LS, He SF, Liang BQ. Triglyceride and coronary heart disease mortality in a 24-year follow-up study in Xi'an, China. *Ann Epidemiol*. 2004;14:1–7.
368. Elisaf MS, Siamopoulos KC, Tselegarides TJ, Bairaktari E, Goudevenos JA, Tselepis AD, Tsolas OE, Sideris DA. Lipid abnormalities in Greek patients with coronary artery disease. *Int J Cardiol*. 1997;59:177–184.
369. Nakanishi N, Okamota M, Makino K, Suzuki K, Tatara K. Distribution and cardiovascular risk correlates of serum triglycerides in young Japanese adults. *Ind Health*. 2002;40:28–35.
370. Hodge AM, Dowse GK, Erasmus RT, Spark RA, Nathaniel K, Zimmet PZ, Alpers MP. Serum lipids and modernization in coastal and highland Papua New Guinea. *Am J Epidemiol*. 1996;144:1129–1142.
371. Bovet P, Romain S, Shamlaye C, Mendis S, Darioli R, Riesen W, Tappy L, Paccaud F. Divergent fifteen-year trends in traditional and cardiometabolic risk factors of cardiovascular diseases in the Seychelles. *Cardiovasc Diabetol*. 2009;8:34.
372. Masia R, Pena A, Marrugat J, Sala J, Vila J, Pavesi M, Covas M, Aubo C, Elosua R; REGICOR Investigators. High prevalence of cardiovascular risk factors in Gerona, Spain, a province with low myocardial infarction incidence. *J Epidemiol Community Health*. 1998;52:707–715.
373. Miller M. The epidemiology of triglyceride as a coronary artery disease risk factor. *Clin Cardiol*. 1999;22(suppl):II-1–II-6.
374. Castelli WP. Cholesterol and lipids in the risk of coronary artery disease: the Framingham Heart Study. *Can J Cardiol*. 1988;(suppl A):5A–10A.
375. Menotti A, Scanga M, Morisi G. Serum triglycerides in the prediction of coronary artery disease (an Italian experience). *Am J Cardiol*. 1994;73:29–32.
376. Miller M, Seidler A, Moalemi A, Pearson TA. Normal triglyceride levels and coronary artery disease events: the Baltimore Coronary Observational Long-Term Study. *J Am Coll Cardiol*. 1998;31:1252–1257.
377. Stavenow L, Kjellstrom T. Influence of serum triglyceride levels on the risk for myocardial infarction in 12,510 middle aged males: interaction with serum cholesterol. *Atherosclerosis*. 1999;147:243–247.
378. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E. 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;51:724–730.
379. Morrison JA, Glueck CJ, Horn PS, Yeramaneni S, Wang P. Pediatric triglycerides predict cardiovascular disease events in the fourth to fifth decade of life. *Metabolism*. 2009;58:1277–1284.
380. Onat A, Sari I, Yazici M, Can G, Hergenc G, Avci GS. Plasma triglycerides, an independent predictor of cardiovascular disease in men: a prospective study based on a population with prevalent metabolic syndrome. *Int J Cardiol*. 2006;108:89–95.
381. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med*. 2007;356:2388–2398.
382. Kreisberg RA, Oberman A. Medical management of hyperlipidemia/dyslipidemia. *J Clin Endocrinol Metab*. 2003;88:2445–2461.
383. Mozaffarian D, Stampfer MJ. Removing industrial trans fat from foods. *BMJ*. 2010;340:c1826.
384. Mozaffarian D, Clarke R. Quantitative effects on cardiovascular risk factors and coronary heart disease risk of replacing partially hydrogenated vegetable oils with other fats and oils. *Eur J Clin Nutr*. 2009;63(suppl 2):S22–S33.
385. Pasanisi F, Contaldo F, de Simone G, Mancini M. Benefits of sustained moderate weight loss in obesity. *Nutr Metab Cardiovasc Dis*. 2001;11:401–406.
386. Van Gaal LF, Mertens IL, Ballaux D. What is the relationship between risk factor reduction and degree of weight loss? *Eur Heart J Suppl*. 2005;7(suppl L):L21–L26.
387. Poobalan A, Aucott L, Smith WC, Avenell A, Jung R, Broom J, Grant AM. Effects of weight loss in overweight/obese individuals and long-term lipid outcomes: a systematic review. *Obes Rev*. 2004;5:43–50.
388. Anderson JW, Konz EC. Obesity and disease management: effects of weight loss on comorbid conditions. *Obes Res*. 2001;9(suppl 4):326S–334S.
389. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr*. 1992;56:320–328.

390. Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper References Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academies Press; 2005.
391. Cao YMD, Pelkman CL, Zhao G, Townsend SM, Kris-Etherton PM. Effects of moderate (MF) versus lower fat (LF) diets on lipids and lipoproteins: a meta-analysis of clinical trials in subjects with and without diabetes. *J Clin Lipidol*. 2009;3:19–32.
392. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003;77:1146–1155.
393. Berglund L, Lefevre M, Ginsberg HN, Kris-Etherton PM, Elmer PJ, Stewart PW, Ershow A, Pearson TA, Dennis BH, Roheim PS, Ramakrishnan R, Reed R, Stewart K, Phillips KM; DELTA Investigators. Comparison of monounsaturated fat with carbohydrates as a replacement for saturated fat in subjects with a high metabolic risk profile: studies in the fasting and postprandial states. *Am J Clin Nutr*. 2007;86:1611–1620.
394. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N; DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med*. 1997;336:1117–1124.
395. Obarzanek E, Sacks FM, Vollmer WM, Bray GA, Miller ER 3rd, Lin PH, Karanja NM, Most-Windhauser MM, Moore TJ, Swain JF, Bales CW, Proschan MA; DASH Research Group. Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Clin Nutr*. 2001;74:80–89.
396. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER 3rd, 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;294:2455–2464.
397. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, Lewis CE, Limacher MC, Margolis KL, Mysiw WJ, Ockene JK, Parker LM, Perri MG, Phillips L, Prentice RL, Robbins J, Rossouw JE, Sarto GE, Schatz IJ, Snetselaar LG, Stevens VJ, Tinker LF, Trevisan M, Vitolins MZ, Anderson GL, Assaf AR, Bassford T, Beresford SA, Black HR, Brunner RL, Brzyski RG, Caan B, Chlebowski RT, Gass M, Granek I, Greenland P, Hays J, Heber D, Heiss G, Hendrix SL, Hubbell FA, Johnson KC, Kotchen JM. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:655–666.
398. 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;90:1608–1614.
399. Rumawas ME, Dwyer JT, McKeown NM, Meigs JB, Rogers G, Jacques PF. The development of the Mediterranean-style dietary pattern score and its application to the American diet in the Framingham Offspring Cohort. *J Nutr*. 2009;139:1150–1156.
400. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA*. 2004;292:1440–1446.
401. Vincent-Baudry S, Defoort C, Gerber M, Bernard MC, Verger P, Helal O, Portugal H, Planells R, Grolier P, Amiot-Carlin MJ, Vague P, Lairon D. The Medi-RIVAGE study: reduction of cardiovascular disease risk factors after a 3-mo intervention with a Mediterranean-type diet or a low-fat diet. *Am J Clin Nutr*. 2005;82:964–971.
402. Salas-Salvadó J, Fernández-Ballart J, Ros E, Martínez-González MA, Fitó M, Estruch R, Corella D, Fiol M, Gómez-Gracia E, Arós F, Flores G, Lapetra J, Lamuela-Raventós R, Ruiz-Gutiérrez V, Bulló M, Basora J, Covas MI; PREDIMED Study Investigators. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch Intern Med*. 2008;168:2449–2458.
403. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99:779–785.
404. Erkkila AT, Lichtenstein AH. Fiber and cardiovascular disease risk: how strong is the evidence? *J Cardiovasc Nurs*. 2006;21:3–8.
405. Ylönen K, Saloranta C, Kronberg-Kippilä C, Groop L, Aro A, Virtanen SM; Botnia Dietary Study. Associations of dietary fiber with glucose metabolism in nondiabetic relatives of subjects with type 2 diabetes: the Botnia Dietary Study. *Diabetes Care*. 2003;26:1979–1985.
406. Anderson JW, Randles KM, Kendall CW, Jenkins DJ. Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence. *J Am Coll Nutr*. 2004;23:5–17.
407. Glinsmann WH, Irausquin H, Park YK. Evaluation of health aspects of sugars contained in carbohydrate sweeteners: report of Sugars Task Force, 1986. *J Nutr*. 1986;116(suppl):S1–S216.
408. Welsh JA, Sharma A, Abramson JL, Vaccarino V, Gillespie C, Vos MB. Caloric sweetener consumption and dyslipidemia among US adults. *JAMA*. 2010;303:1490–1497.
409. Dietary Guidelines for Americans. 2005; 6th ed. US Department of Health and Human Services Web site. http://www.healthierus.gov/dietaryguidelines. Accessed September 13, 2010.
410. Nishida C, Uauy R, Kumanyika S, Shetty P. The joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases: process, product and policy implications. *Public Health Nutr*. 2004;7:245–250.
411. Dickinson S, Brand-Miller J. Glycemic index, postprandial glycemia and cardiovascular disease. *Curr Opin Lipidol*. 2005;16:69–75.
412. Franz MJ. Is there a role for the glycemic index in coronary heart disease prevention or treatment? *Curr Atheroscler Rep*. 2008;10:497–502.
413. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med*. 2009;169:659–669.
414. Liu S, Manson JE, Stampfer MJ, Holmes MD, Hu FB, Hankinson SE, Willett WC. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Am J Clin Nutr*. 2001;73:560–566.
415. Levitan EB, Cook NR, Stampfer MJ, Ridker PM, Rexrode KM, Buring JE, Manson JE, Liu S. Dietary glycemic index, dietary glycemic load, blood lipids, and C-reactive protein. *Metabolism*. 2008;57:437–443.
416. Amano Y, Kawakubo K, Lee JS, Tang AC, Sugiyama M, Mori K. Correlation between dietary glycemic index and cardiovascular disease risk factors among Japanese women. *Eur J Clin Nutr*. 2004;58:1472–1478.
417. Shikany JM, Tinker LF, Neuhouser ML, Ma Y, Patterson RE, Phillips LS, Liu S, Redden DT. Association of glycemic load with cardiovascular disease risk factors: the Women's Health Initiative Observational Study. *Nutrition*. 2010;26:641–647.
418. van Dam RM, Visscher AW, Feskens EJ, Verhoef P, Kromhout D. Dietary glycemic index in relation to metabolic risk factors and incidence of coronary heart disease: the Zutphen Elderly Study. *Eur J Clin Nutr*. 2000;54:726–731.
419. Liese AD, Gilliard T, Schulz M, D'Agostino RB Jr, Wolever TM. Carbohydrate nutrition, glycaemic load, and plasma lipids: the Insulin Resistance Atherosclerosis Study. *Eur Heart J*. 2007;28:80–87.
420. Mosdøl A, Witte DR, Frost G, Marmot MG, Brunner EJ. Dietary glycemic index and glycemic load are associated with high-density-lipoprotein cholesterol at baseline but not with increased risk of diabetes in the Whitehall II study. *Am J Clin Nutr*. 2007;86:988–994.
421. Kelly S, Frost G, Whittaker V, Summerbell C. Low glycaemic index diets for coronary heart disease. *Cochrane Database Syst Rev*. 2004;(4):CD004467.
422. Ebbeling CB, Leidig MM, Sinclair KB, Seger-Shippee LG, Feldman HA, Ludwig DS. Effects of an ad libitum low-glycemic load diet on cardiovascular disease risk factors in obese young adults. *Am J Clin Nutr*. 2005;81:976–982.
423. Sichieri R, Moura AS, Genelhu V, Hu F, Willett WC. An 18-mo randomized trial of a low-glycemic-index diet and weight change in Brazilian women. *Am J Clin Nutr*. 2007;86:707–713.
424. Wolever TM, Gibbs AL, Mehling C, Chiasson JL, Connelly PW, Josse RG, Leiter LA, Maheux P, Rabasa-Lhoret R, Rodger NW, Ryan EA. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 dia-

betes: no effect on glycated hemoglobin but reduction in C-reactive protein. *Am J Clin Nutr*. 2008;87:114–125.
425. Stanhope KL, Havel PJ. Endocrine and metabolic effects of consuming beverages sweetened with fructose, glucose, sucrose, or high-fructose corn syrup. *Am J Clin Nutr*. 2008;88:1733S–1737S.
426. Putnam JJ, Allshouse JE. *Food Consumption, Prices, and Expenditures, 1970–97*. Washington, DC: Food and Rural Economics Division, Economic Research Service, US Department of Agriculture; 1999. Statistical Bulletin No. 965.
427. Stanhope KL, Havel PJ. Fructose consumption: recent results and their potential implications. *Ann N Y Acad Sci*. 2010;1190:15–24.
428. Livesey G, Taylor R. Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: meta-analyses and meta-regression models of intervention studies. *Am J Clin Nutr*. 2008; 88:1419–1437.
429. Pätzold R, Brückner H. Mass spectrometric detection and formation of D-amino acids in processed plant saps, syrups, and fruit juice concentrates. *J Agric Food Chem*. 2005;53:9722–9729.
430. Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest*. 2002;109:1125–1131.
431. Glimcher LH, Lee AH. From sugar to fat: how the transcription factor XBP1 regulates hepatic lipogenesis. *Ann N Y Acad Sci*. 2009;1173(suppl 1): E2–E9.
432. Uyeda K, Repa JJ. Carbohydrate response element binding protein, ChREBP, a transcription factor coupling hepatic glucose utilization and lipid synthesis. *Cell Metab*. 2006;4:107–110.
433. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, Leboff MS, Rood JC, de Jonge L, Greenway FL, Loria CM, Obarzanek E, Williamson DA. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med*. 2009;360: 859–873.
434. Bonow RO, Eckel RH. Diet, obesity, and cardiovascular risk. *N Engl J Med*. 2003;348:2057–2058.
435. Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS Jr, Brehm BJ, Bucher HC. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials [published correction appears in *Arch Intern Med*. 2006;166:932]. *Arch Intern Med*. 2006;166:285–293.
436. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
437. Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, Fowler S; Diabetes Prevention Program Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med*. 2005;142:611–619.
438. Wadden TA, West DS, Delahanty L, Jakicic J, Rejeski J, Williamson D, Berkowitz RI, Kelley DE, Tomchee C, Hill JO, Kumanyika S; Look AHEAD Research Group. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it [published correction appears in *Obesity (Silver Spring)*. 2007;15:1339]. *Obesity (Silver Spring)*. 2006;14:737–752.
439. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, Tangi-Rozental O, Zuk-Ramot R, Sarusi B, Brickner D, Schwartz Z, Sheiner E, Marko R, Katorza E, Thiery J, Fiedler GM, Bluher M, Stumvoll M, Stampfer MJ; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet [published correction appears in *N Engl J Med*. 2009;361:2681]. *N Engl J Med*. 2008;359:229–241.
440. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA*. 2005;293:43–53.
441. Gardner CD, Kiazand A, Alhassan S, Kim S, Stafford RS, Balise RR, Kraemer HC, King AC. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. *JAMA*. 2007;297:969–977.
442. Goldberg IJ, Mosca L, Piano MR, Fisher EA; Nutrition Committee, Council on Epidemiology and Prevention, and Council on Cardiovascular Nursing of the American Heart Association. AHA Science Advisory: wine and your heart: a science advisory for healthcare professionals from the Nutrition Committee, Council on Epidemiology and Prevention, and Council on Cardiovascular Nursing of the American Heart Association. *Circulation*. 2001;103:472–475.
443. Marques-Vidal P, Cambou JP, Nicaud V, Luc G, Evans A, Arveiler D, Bingham A, Cambien F. Cardiovascular risk factors and alcohol consumption in France and Northern Ireland. *Atherosclerosis*. 1995;115: 225–232.
444. Nanchahal K, Ashton WD, Wood DA. Alcohol consumption, metabolic cardiovascular risk factors and hypertension in women. *Int J Epidemiol*. 2000;29:57–64.
445. Burger M, Mensink G, Brönstrup A, Thierfelder W, Pietrzik K. Alcohol consumption and its relation to cardiovascular risk factors in Germany. *Eur J Clin Nutr*. 2004;58:605–614.
446. Razay G, Heaton KW, Bolton CH, Hughes AO. Alcohol consumption and its relation to cardiovascular risk factors in British women. *BMJ*. 1992;304:80–83.
447. Chrysohoou C, Panagiotakos DB, Pitsavos C, Skoumas J, Toutouza M, Papaioannou I, Toutouzas PK, Stefanadis C. Effects of chronic alcohol consumption on lipid levels, inflammatory and haemostatic factors in the general population: the "ATTICA" Study. *Eur J Cardiovasc Prev Rehabil*. 2003;10:355–361.
448. Foerster M, Marques-Vidal P, Gmel G, Daeppen JB, Cornuz J, Hayoz D, Pécoud A, Mooser V, Waeber G, Vollenweider P, Paccaud F, Rodondi N. Alcohol drinking and cardiovascular risk in a population with high mean alcohol consumption. *Am J Cardiol*. 2009;103:361–368.
449. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ*. 1999;319:1523–1528.
450. Feinman L, Lieber CS. Ethanol and lipid metabolism. *Am J Clin Nutr*. 1999;70:791–792.
451. Pownall HJ. Dietary ethanol is associated with reduced lipolysis of intestinally derived lipoproteins. *J Lipid Res*. 1994;35:2105–2113.
452. Erkelens DW, Brunzell JD. Effect of controlled alcohol feeding on triglycerides in patients with outpatient "alcohol hypertriglyceridemia." *J Hum Nutr*. 1980;34:370–375.
453. Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease [published correction appears in *Circulation*. 2003;107:512]. *Circulation*. 2002;106:2747–2757.
454. Harris WS. n-3 Fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr*. 1997;65(suppl):1645S–1654S.
455. Balk E, Chung M, Lichtenstein A, Chew P, Kupelnick B, Lawrence A, DeVine D, Lau J. *Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease*. Evidence Report/Technology Assessment No. 93 (prepared by Tufts-New England Medical Center Evidence-Based Practice Center under contract No. 290-02-0022). AHRQ publication No. 04-E010-2. Rockville, MD: Agency for Healthcare Research and Quality; 2004.
456. Lungershausen YK, Abbey M, Nestel PJ, Howe PR. Reduction of blood pressure and plasma triglycerides by omega-3 fatty acids in treated hypertensives. *J Hypertens*. 1994;12:1041–1045.
457. Jacobson TA. Role of n-3 fatty acids in the treatment of hypertriglyceridemia and cardiovascular disease. *Am J Clin Nutr*. 2008;87: 1981S–1990S.
458. Skulas-Ray AC, West SG, Davidson MH, Kris-Etherton PM. Omega-3 fatty acid concentrates in the treatment of moderate hypertriglyceridemia. *Expert Opin Pharmacother*. 2008;9:1237–1248.
459. Harris WS, Miller M, Tighe AP, Davidson MH, Schaefer EJ. Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives. *Atherosclerosis*. 2008;197:12–24.
460. Sampath H, Ntambi JM. Polyunsaturated fatty acid regulation of gene expression. *Nutr Rev*. 2004;62:333–339.
461. Grimsgaard S, Bonaa KH, Hansen JB, Nordøy A. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. *Am J Clin Nutr*. 1997;66:649–659.
462. Hansen JB, Grimsgaard S, Nilsen H, Nordøy A, Bønaa KH. Effects of highly purified eicosapentaenoic acid and docosahexaenoic acid on fatty acid absorption, incorporation into serum phospholipids and postprandial triglyceridemia. *Lipids*. 1998;33:131–138.
463. Kelley DS, Siegel D, Vemuri M, Mackey BE. Docosahexaenoic acid supplementation improves fasting and postprandial lipid profiles in hypertriglyceridemic men. *Am J Clin Nutr*. 2007;86:324–333.

464. Kris-Etherton PM, Harris WS, Appel LJ; Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease [published correction appears in *Arterioscler Thromb Vasc Biol*. 2003; 23:151–152]. *Arterioscler Thromb Vasc Biol*. 2003;23:e20–e30.
465. Adkins Y, Kelley DS. Mechanisms underlying the cardioprotective effects of omega-3 polyunsaturated fatty acids. *J Nutr Biochem*. 2010; 21:781–792.
466. de Lorgeril M, Salen P. Alpha-linolenic acid and coronary heart disease. *Nutr Metab Cardiovasc Dis*. 2004;14:162–169.
467. Prasad K. Flaxseed and cardiovascular health. *J Cardiovasc Pharmacol*. 2009;54:369–377.
468. Whelan J. Dietary stearidonic acid is a long chain (n-3) polyunsaturated fatty acid with potential health benefits. *J Nutr*. 2009;139:5–10.
469. Brenna JT, Salem N Jr, Sinclair AJ, Cunnane SC. alpha-Linolenic acid supplementation and conversion to n-3 long-chain polyunsaturated fatty acids in humans. *Prostaglandins Leukot Essent Fatty Acids*. 2009;80: 85–91.
470. Pan DA, Lillioja S, Kriketos AD, Milner MR, Baur LA, Bogardus C, Jenkins AB, Storlien LH. Skeletal muscle triglyceride levels are inversely related to insulin action. *Diabetes*. 1997;46:983–988.
471. Kelley DE, Goodpaster BH, Storlien L. Muscle triglyceride and insulin resistance. *Annu Rev Nutr*. 2002;22:325–346.
472. Kraegen EW, Cooney GJ, Ye J, Thompson AL. Triglycerides, fatty acids and insulin resistance: hyperinsulinemia. *Exp Clin Endocrinol Diabetes*. 2001;109:S516–S526.
473. Martin WH 3rd. Effects of acute and chronic exercise on fat metabolism. *Exerc Sport Sci Rev*. 1996;24:203–231.
474. Couillard C, Després JP, Lamarche B, Bergeron J, Gagnon J, Leon AS, Rao DC, Skinner JS, Wilmore JH, Bouchard C. Effects of endurance exercise training on plasma HDL cholesterol levels depend on levels of triglycerides: evidence from men of the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study. *Arterioscler Thromb Vasc Biol*. 2001;21:1226–1232.
475. Kokkinos PF, Holland JC, Narayan P, Colleran JA, Dotson CO, Papademetriou V. Miles run per week and high-density lipoprotein cholesterol levels in healthy, middle-aged men: a dose-response relationship. *Arch Intern Med*. 1995;155:415–420.
476. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CW, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med*. 2002;347:1483–1492.
477. Duncan GE, Anton SD, Sydeman SJ, Newton RL Jr, Corsica JA, Durning PE, Ketterson TU, Martin AD, Limacher MC, Perri MG. Prescribing exercise at varied levels of intensity and frequency: a randomized trial. *Arch Intern Med*. 2005;165:2362–2369.
478. Fontana L, Villareal DT, Weiss EP, Racette SB, Steger-May K, Klein S, Holloszy JO; and the Washington University School of Medicine CALERIE Group. Calorie restriction or exercise: effects on coronary heart disease risk factors: a randomized, controlled trial. *Am J Physiol Endocrinol Metab*. 2007;293:E197–E202.
479. Gill JM, Hardman AE. Exercise and postprandial lipid metabolism: an update on potential mechanisms and interactions with high-carbohydrate diets (review). *J Nutr Biochem*. 2003;14:122–132.
480. Koutsari C, Karpe F, Humphreys SM, Frayn KN, Hardman AE. Exercise prevents the accumulation of triglyceride-rich lipoproteins and their remnants seen when changing to a high-carbohydrate diet. *Arterioscler Thromb Vasc Biol*. 2001;21:1520–1525.
480a. Jones PH. Fibrates. In: Ballantyne C, ed. Clinical Lipidology, A Companion to Braunwald's Heart Disease. Philadelphia, PA: Saunders; 2009: 315–325.
480b. Harris WS, Jacobson TA. Omega-3 Fatty Acids. In: Ballantyne C, ed. Clinical Lipidology, A Companion to Braunwald's Heart Disease. Philadelphia, PA: Saunders; 2009:326–338.
480c. McKenney JM, Ganz P, Wiggins BS, Saseen JS. Statins. In: Ballantyne C, ed. Clinical Lipidology, A Companion to Braunwald's Heart Disease. Philadelphia, PA: Saunders; 2009:253–280.
480d. Norata GD, Catapano AL. In: Ballantyne C, ed. Clinical Lipidology, A Companion to Braunwald's Heart Disease. Philadelphia, PA: Saunders; 2009:288–297.
481. Durstine JL, Grandjean PW, Cox CA, Thompson PD. Lipids, lipoproteins, and exercise. *J Cardiopulm Rehabil*. 2002;22:385–398.
482. Girman CJ, Rhodes T, Mercuri M, Pyörälä K, Kjekshus J, Pedersen TR, Beere PA, Gotto AM, Clearfield M; 4S Group and the AFCAPS/TexCAPS Research Group. The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Am J Cardiol*. 2004;93:136–141.
483. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) [published correction appears in *Diabetes Care*. 1997;20:1048]. *Diabetes Care*. 1997;20: 614–620.
484. Sacks FM, Alaupovic P, Moye LA, Cole TG, Sussex B, Stampfer MJ, Pfeffer MA, Braunwald E. VLDL, apolipoproteins B, CIII, and E, and risk of recurrent coronary events in the Cholesterol and Recurrent Events (CARE) trial. *Circulation*. 2000;102:1886–1892.
485. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation*. 2003;108:414–419.
486. Deedwania P, Barter P, Carmena R, Fruchart JC, Grundy SM, Haffner S, Kastelein JJ, LaRosa JC, Schachner H, Shepherd J, Waters DD; Treating to New Targets Investigators. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. *Lancet*. 2006; 368:919–928.
487. Pfeffer MA, Sacks FM, Moyé LA, East C, Goldman S, Nash DT, Rouleau JR, Rouleau JL, Sussex BA, Theroux P, Vanden Belt RJ, Braunwald E. Influence of baseline lipids on effectiveness of pravastatin in the CARE Trial: Cholesterol And Recurrent Events. *J Am Coll Cardiol*. 1999;33:125–130.
488. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
489. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
490. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ; West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301–1307.
491. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003; 361:1149–1158.
492. 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: 21–27.
493. Tenenbaum A, Motro M, Fisman EZ, Tanne D, Boyko V, Behar S. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. *Arch Intern Med*. 2005;165: 1154–1160.
494. 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;366:1849–1861.
495. 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;32:493–498.
496. 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;341:410–418.

497. Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, McNamara JR, Kashyap ML, Hershman JM, Wexler LF, Rubins HB; for the VA-HIT Study Group. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA*. 2001;285:1585–1591.
498. Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, 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 [published correction appears in *N Engl J Med*. 2010;362:1748]. *N Engl J Med*. 2010;362:1563–1574.
499. Gotto AM Jr, Whitney E, Stein EA, Shapiro DR, Clearfield M, Weis S, Jou JY, Langendörfer A, Beere PA, Watson DJ, Downs JR, de Cani JS. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation*. 2000; 101:477–484.
500. Simes RJ, Marschner IC, Hunt D, Colquhoun D, Sullivan D, Stewart RA, Hague W, Keech A, Thompson P, White H, Shaw J, Tonkin A; LIPID Study Investigators. Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? *Circulation*. 2002;105:1162–1169.
501. 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;104:459–463.
502. 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 [published correction appears in *Lancet*. 2007;370:220]. *Lancet*. 2007;369: 1090–1098.
503. 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) [published correction appears in *Atherosclerosis*. 2009;204:233]. *Atherosclerosis*. 2008;200:135–140.
504. Brown B, Canner PL, McGovern ME, Guyton JR, Carlson LA. Nicotinic acid. In: Ballantyne C, ed. *Clinical Lipidology, A Companion to Braunwald's Heart Disease*. Philadelphia, PA: Saunders; 2009:298–314.
505. Taylor AJ, Villines TC, Stanek EJ, Devine PJ, Griffen L, Miller M, Weissman NJ, Turco M. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med*. 2009;361:2113–2122.
506. Brown G, Boden W. Niacin Plus Statin to Prevent Vascular Events. http://clinicaltrials.gov/ct/show/NCT00120289. Accessed July 27, 2010.
507. A Randomized Trial of the Long-Term Clinical Effects of Raising HDL Cholesterol With Extended Release Niacin/Laropiprant. http://clinicaltrials.gov/ct2/show/NCT00461630. Accessed July 27, 2010.
508. Cannon CP, Giugliano RP, Blazing MA, Harrington RA, Peterson JL, Sisk CM, Strony J, Musliner TA, McCabe CH, Veltri E, Braunwald E, Califf RM; IMPROVE-IT Investigators. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. *Am Heart J*. 2008;156:826–832.
509. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999–2000. *JAMA*. 2002;288:1728–1732.
510. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. *Int J Obes Relat Metab Disord*. 1998;22:39–47.
511. Dietz WH. Health consequences of obesity in youth: childhood predictors of adult disease. *Pediatrics*. 1998;101:518–525.
512. Boehmer TK, Brownson RC, Haire-Joshu D, Dreisinger ML. Patterns of childhood obesity prevention legislation in the United States. *Prev Chronic Dis*. 2007;4:A56.
513. Greves HM, Rivara FP. Report card on school snack food policies among the United States' largest school districts in 2004–2005: room for improvement. *Int J Behav Nutr Phys Act*. 2006;3:1.
514. Fox MK, Dodd AH, Wilson A, Gleason PM. Association between school food environment and practices and body mass index of US public school children. *J Am Diet Assoc*. 2009;109(suppl):S108–S117.
515. Labarthe DR. Heart-healthy and stroke-free, 2008. *Prev Chronic Dis*. 2008;5:A32.
516. Veazie MA, Galloway JM, Matson-Koffman D, LaBarthe DR, Brownstein JN, Emr M, Bolton E, Freund E Jr, Fulwood R, Guyton-Krishnan J, Hong Y, Lebowitz M, Ochiai E, Schoeberl M, Robertson RM. Taking the initiative: implementing the American Heart Association Guide for Improving Cardiovascular Health at the Community Level: Healthy People 2010 Heart Disease and Stroke Partnership Community Guideline Implementation and Best Practices Workgroup. *Circulation*. 2005;112:2538–2554.
517. Strauss R. Childhood obesity. *Curr Probl Pediatr*. 1999;29:1–29.
518. DeVault N, Kennedy T, Hermann J, Mwavita M, Rask P, Jaworsky A. It's all about kids: preventing overweight in elementary school children in Tulsa, OK. *J Am Diet Assoc*. 2009;109:680–687.
519. Shilts MK, Lamp C, Horowitz M, Townsend MS. Pilot study: EatFit impacts sixth graders' academic performance on achievement of mathematics and English education standards. *J Nutr Educ Behav*. 2009;41: 127–131.
520. Kelder SH, Springer AS, Barroso CS, Smith CL, Sanchez E, Ranjit N, Hoelscher DM. Implementation of Texas Senate Bill 19 to increase physical activity in elementary schools. *J Public Health Policy*. 2009; 30(suppl 1):S221–S247.
521. Topp R, Jacks DE, Wedig RT, Newman JL, Tobe L, Hollingsworth A. Reducing risk factors for childhood obesity: the Tommie Smith Youth Athletic Initiative. *West J Nurs Res*. 2009;31:715–730.
522. He M, Callaghan C, Evans A, Mandich G. Healthy eating champions award for elementary schools. *Can J Diet Pract Res*. 2009;70:101–104.
523. Davis EM, Cullen KW, Watson KB, Konarik M, Radcliffe J. A Fresh Fruit and Vegetable Program improves high school students' consumption of fresh produce. *J Am Diet Assoc*. 2009;109:1227–1231.
524. Watts GF, Lewis B, Brunt JN, Lewis ES, Coltart DJ, Smith LD, Mann JI, Swan AV. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' Atherosclerosis Regression Study (STARS). *Lancet*. 1992;339:563–569.
525. Miller M. Hold the patty, not the lettuce: processing foods for over a quarter century in the Nurses' Health Study. *Circulation*. 2010;122: 859–860. Letter.
526. Bernstein AM SQ, Hu FB, Stampfer MJ, Manson JE, Willet WC. Major dietary protein sources and risk of coronary heart disease in women. *Circulation*. 2010;122:876–883.
527. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med*. 2010;7:e1000252.
528. Hauenschild A, Bretzel RG, Schnell-Kretschmer H, Kloer HU, Hardt PD, Ewald N. Successful treatment of severe hypertriglyceridemia with a formula diet rich in omega-3 fatty acids and medium-chain triglycerides. *Ann Nutr Metab*. 2010;56:170–175.

KEY WORDS: AHA Scientific Statements ■ triglycerides ■ atherosclerosis ■ diabetes mellitus ■ epidemiology ■ fatty acids ■ hyperlipoproteinemia ■ lipids ■ lipoproteins ■ obesity