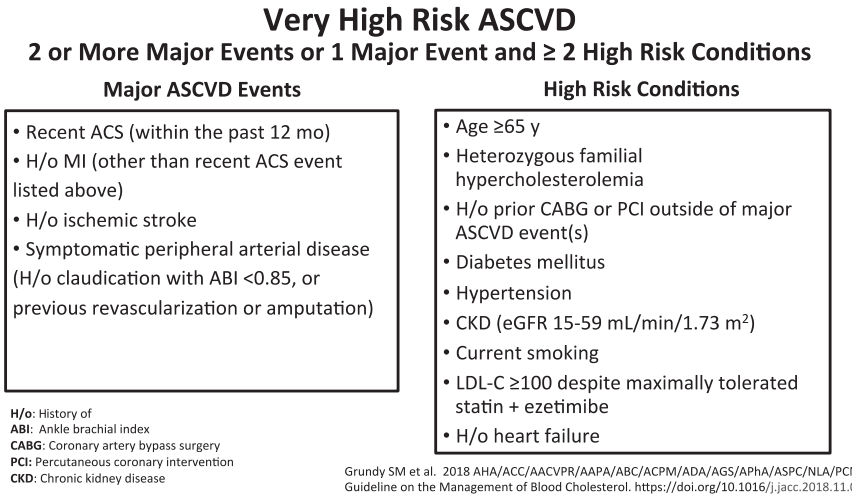

Figure 1 2018 American Heart Association/American College of Cardiology/Multisociety Guideline on Management of Cholesterol: Classification of very high risk atherosclerotic cardiovascular disease (ASCVD)*. *Note: the definitions of high and very high risk for atherosclerotic cardiovascular disease (ASCVD) outlined in the 2018 American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Guideline differ from those used to qualify for entry into the Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial (REDUCE-IT). However, a large majority of subjects in REDUCE-IT had 10-year ASCVD event risk ≥20%, as indicated by a 14.8% incidence of the key secondary end point (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in the placebo group during median follow-up of 4.9 years, which projects to >30% 10-year risk.

heightened risk is associated with increased circulating concentrations of cholesterol carried by partially delipidated TG-rich lipoprotein particles,[22,23] and the often coexistent proinflammatory, prothrombotic, and oxidative milieu[23–25] associated with insulin resistance.[26] The 2018 AHA/ACC/Multisociety Guideline identifies moderate hypertriglyceridemia (TG ≥ 175 mg/dL) as a "risk-enhancing factor" to be considered in the clinician-patient risk discussion, the presence of which favors the initiation or intensification of statin therapy, but does not otherwise make specific recommendations about using TG-lowering drugs to improve cardiovascular outcomes.[16]

NLA's Recommendations for the Patient-Centered Management of Dyslipidemia, published in 2015, outlined the central role of elevated concentrations of cholesterol carried by atherogenic lipoprotein particles (ie, non–HDL-C) as a root cause of atherosclerosis and that reduction in the circulating levels of these lipoproteins would lower ASCVD risk in proportion to the extent that atherogenic cholesterol is reduced.[27,28] Non–HDL-C comprises cholesterol carried by all apolipoprotein B (apo B)–containing lipoproteins, including low-density lipoprotein (LDL), intermediate-density lipoprotein, lipoprotein (a), very-low-density lipoprotein (VLDL), chylomicrons, and chylomicron remnant particles. Throughout this article, the term VLDL-C will be used to denote cholesterol carried by all apo B–containing particles with density lower than LDL, which includes true VLDL-C, as well as chylomicrons and chylomicron remnant particles. Other terms have been used in the literature for this fraction, including remnant cholesterol and TG-rich lipoprotein cholesterol. Elevation in plasma TG is typically accompanied by an elevation in VLDL-C, although the relationship becomes nonlinear at higher levels of TG, particularly above 400 mg/dL, because severe TG elevation is associated with a higher molar ratio of TG to cholesterol in VLDL and other TG-rich lipoprotein particles.[29] Nevertheless, changes in plasma TG concentration induced by pharmaceutical agents such as omega-3 fatty acids, fibrates, niacin, and statins generally correlate strongly with changes in the VLDL-C concentration.[30]

Because of the central role in TG catabolism played by lipoprotein lipase (LPL), identification of mutations in apolipoproteins that alter the activity of this enzyme has been an important focus of studies on the impact of TG and VLDL-C levels on ASCVD risk. apo C3, which resides on the surface of TG-rich lipoproteins, inhibits LPL-mediated lipolysis of these lipoproteins and raises circulating TG levels. Exome sequencing studies of individuals of European or African American descent who have mutations in the gene encoding apo C3 demonstrated that heterozygous carriers of one of four loss-of-function mutations of *APOC3* had circulating TG concentrations that were 39% lower and coronary heart disease (CHD) risk that was 40% lower than noncarriers.[31] Mutations in the *APOA5*, *ANGPTL3*, and *ANGPTL4* genes, as well in the *LPL* gene itself, also result in the altered expression of proteins that affect LPL function, and add further support to the concept that elevated concentrations of TG and TG-rich lipoproteins contribute to ASCVD risk.[32–37]

A series of Mendelian randomization analyses has demonstrated that TG-lowering *LPL* variants and LDL-C-lowering LDL receptor (*LDLR*) variants were associated with similar reductions in risk of CHD per unit difference in LDL-C and VLDL-C, which is estimated with the Friedewald equation as the TG concentration in mg/dL divided