4Q2.5. TG

A high TG to HDL-C ratio (≥2.4) is a strong indicator of the insulin resistance syndrome (10 [EL 4; NE]; 15 [EL 4; NE]; 77 [EL 3; CSS]). Insulin resistance is more common when a family history of ASCVD or T2DM is present (15 [EL 4; NE]). Evidence indicates that when TG levels exceed 140 mg/dL, there is a substantial increase in the production of small, dense LDL-C (156 [EL 3; CSS]); therefore, the presence of hypertriglyceridemia and low HDL-C in an individual should also prompt clinical suspicion for the presence of the small, dense LDL pattern, as well as elevated postprandial TG (15 [EL 4; NE]). TG, which are present in 5 times the amount of cholesterol, are the more important lipid component of VLDL particles. VLDL-C is only important in that it is calculated in a lipid profile to determine the more important LDL-C.

When fasting TG levels are marginally elevated (140 to 200 mg/dL), 2 additional lipid evaluations may be warranted.

- Direct assessment of the LDL-C pattern B phenotype (small, dense LDL) by ultracentrifugation, nuclear magnetic resonance, or gradient gel electrophoresis may be useful because elevated TG and reduced HDL-C are elements of the dyslipidemic triad (10 [EL 4; NE]). This is particularly relevant because many individuals with the small, dense LDL pattern will have optimal or near-optimal LDL-C levels (<130 mg/dL) (10 [EL 4; NE]).
- Evaluation of postprandial TG levels may be useful because evidence indicates that the small TG-rich lipoproteins produced postprandially are particularly atherogenic and may be indicative of insulin resistance and/or diabetes (173 [EL 4; NE]; 305 [EL 3; CSS]; 306 [EL 4; NE]; 307 [EL 4; NE]; 308 [EL 3; CSS]; 309 [EL 3; CSS] 310 [EL 3; CSS]). Although neither an assessment for postprandial TG levels nor a reference range has been standardized, several studies indicate that nonfasting or random TG exceeding usual fasting cutpoints (≥150 mg/dL) is independently associated with increased ASCVD risk (174 [EL 2; PCS]; 175 [EL 2; PCS]; 311 [EL 4; NE]). Others suggest that lack of standardization of postprandial measurement of TG precludes its current use as a screening test (311 [EL 4; NE]).

Thus, elevated TG in a nonfasting state can no longer be ignored as indicative of no increased ASCVD risk. The treatment of hypertriglyceridemia, however, demands they be measured in a standard fasting state to assess the effect of therapy. Fasting TG measurements represent the lowest 24-hour value because daytime TG levels are postprandial and influenced by dietary fat load and TG clearance efficiency.

4Q2.6. Apolipoproteins

A high plasma apo B level (>130 mg/dL) combined with an LDL-C concentration less than 160 mg/dL, with or without hypertriglyceridemia, identifies hyperapobetalipoproteinemia, which is a cause of premature ASCVD (80 [EL 4; NE]).

Evidence from a series of large studies, including the Apolipoprotein-Related Mortality Risk (AMORIS) and Nurses' studies, suggests that apo B provides a uniquely powerful assessment of total atherogenic particle burden that may be equivalent or superior to LDL-C, non-HDL-C, or other cholesterol ratios in predicting risk. It has also been suggested that apo B is more closely associated with the insulin resistance syndrome than LDL-C or non-HDL-C (31 [EL 4; NE]; 312 [EL 2; PCS]; 313 [EL 2; RCCS]). Additionally, an analysis of the Insulin Resistance Atherosclerosis Study (IRAS) revealed that apo B was more closely associated than non-HDL-C with markers such as central adiposity, insulin resistance, thrombosis, and inflammation (314 [EL 3; SS]). There are clinical circumstances where apo B and non-HDL-C are highly correlated but only moderately concordant because of differences in cholesterol enrichment of LDL-C particles, leaving many high-risk individuals whose non-HDL-C is satisfactory with apo B high enough to warrant more intensive therapy (315 [EL 4; NE]). A 2008 post hoc analysis of combined data from 2 major statin trials (pooled N = 18,018) found that both increased apo B and non-HDL-C demonstrated an equivalent or slightly stronger association with major cardiovascular event risk (HR, 1.19; $P<.001$ for both) than increased LDL-C (HR, 1.15; $P<.001$) (21 [EL 1; MRCT]). Among individuals who achieved the ATP III LDL-C goal of 100 mg/dL or less while on statins, LDL-C ceased to be significantly associated with cardiovascular risk, while apo B and non-HDL-C maintained a significant relationship (21 [EL 1; MRCT]). In addition, the apo B to apo AI ratio was a stronger predictor of risk (HR 1.24, $P<.001$) than either the LDL-C to HDL-C ratio (HR 1.20, $P<.001$) or the total cholesterol to HDL-C ratio (HR 1.21, $P<.001$) (21 [EL 1; MRCT]). Similarly, the INTERHEART study found that the apo B to apo AI ratio was among the most significant risk factors for MI, with an odds ratio of 4.73 (99% CI, 3.93-5.69) for the highest versus lowest decile (18 [EL 2; PCS]).

Based on these findings, when the TG concentration is greater than 150 mg/dL or the HDL-C concentration is less than 40 mg/dL, the apo B or the apo B to apo AI ratio may be particularly useful in assessing residual risk in individuals at risk for ASCVD (even when LDL-C levels are controlled); this includes individuals with established ASCVD, T2DM, or the insulin resistance syndrome who are at high risk for ASCVD.