4Q2.7. Secondary Causes of Dyslipidemia

Secondary causes of dyslipidemia (Table 11) must be excluded with a thorough medical and dietary history, as well as laboratory testing for glucose and thyroid, liver, and renal function levels (10 [EL 4; NE]; 316 [EL 4; NE]; 317 [EL 2; RCCS]). Treating an underlying contributing disease may alleviate the lipid abnormality (10 [EL 4; NE]); however, dyslipidemia in individuals with serious conditions such as diabetes is a sometimes-overlooked indication for aggressive lipid-lowering therapy.

In addition to excluding secondary causes of dyslipidemia, the physician should perform a thorough family history and physical evaluation to identify additional risk factors, including genetic factors, that could cause or contribute to dyslipidemia.

4Q2.8. Additional Tests

Evidence suggests that hsCRP may be helpful in predicting coronary events (318 [EL 1; RCT]). Although studies suggest that hsCRP may be of limited value as a broadly applied screening tool, it may be helpful in stratifying cardiovascular risk in individuals with a standard risk assessment that is borderline (319 [EL 3; SS]) or in those with an LDL-C level less than 130 mg/dL (319 [EL 3; SS]; 320 [EL 1; RCT]). Normal values of hsCRP are classified as being less than 1.0 mg/L, the intermediate range is 1.0 to 3.0 mg/L, and high risk is greater than 3.0 mg/L (319 [EL 3; SS]). However, in the JUPITER trial, a simpler stratification (<2.0 vs. ≥2 mg/L) was strongly suggested (320 [EL 1; RCT]).

Lp-PLA_2, similar to hsCRP, may also be helpful in predicting ASCVD risk. As previously discussed, elevated Lp-PLA_2 (≥200 ng/mL) has been independently linked with coronary events (223 [EL 2; PCS]). Moreover, Lp-PLA_2 may act synergistically with CRP, further increasing risk when both are elevated (217 [EL 2; PCS]; 218 [EL 2; PCS]). Measurement of Lp-PLA_2, which appears to be more specific than hsCRP, may be helpful when it is necessary to further stratify an individual's risk for ASCVD, especially in the presence of systemic CRP elevations.

A normal apo A1 level in an individual with low HDL-C suggests the existence of an adequate number of HDL-C particles that contain less cholesterol and is an indication of lower risk (8 [EL 4; NE). Therefore, an assessment of apo A1 may be useful in certain cases (80 [EL 4; NE]).

Homocysteine has also emerged as a potential independent risk factor for ASCVD. Homocysteine levels greater than 15 μmol/L are associated with increased ASCVD risk. Goal levels have been less than 10 μmol/L in the U.S. and less than 12 μmol/L in Europe. However, lowering homocysteine to these levels has not been shown to reduce ASCVD risk (238 [EL 4; NE].

CAC and ultrasound measurement of CIMT are noninvasive measures of atherosclerosis that have emerged as adjuncts to standard ASCVD risk factors (321 [EL 3; CSS]; 322 [EL 2; MNRCT]). Noninvasive imaging of carotid arteries is a potential tool for assessing the results of lipid-lowering therapy and has been used in clinical trials of drug efficacy (Table 14) (323 [EL 1; RCT]; 324 [EL 1; RCT]; 325 [EL 1; RCT]; 326 [EL 1; RCT]; 327 [EL 1; RCT]; 328 [EL 1; RCT]; 329 [EL 2; PCS]; 330 [EL 1; RCT]; 331 [EL 1; RCT]; 332 [EL 1; RCT]; 333 [EL 1; RCT]; 334 [EL 1; RCT]). CIMT, along with coronary calcium scoring, is recognized by the AHA as a surrogate marker for coronary artery disease (335 [EL 4; NE]). However, CIMT should not be performed routinely but may be used in certain clinical situations to refine risk stratification and the need for more aggressive preventive strategies (321 [EL 3; CSS]; 322 [EL 2; MNRCT]).

On the other hand, the presence of CAC correlates strongly with coronary atherosclerosis. CAC is an important predictor of ASCVD risk, based on data from MESA, a multicenter, long-term study of subclinical atherosclerosis and its progression and relationship to clinical ASCVD (336 [EL 4; NE]. Multiple analyses of MESA findings show that CAC scores can be a strong marker for ASCVD among individuals with a family history of ASCVD (337 [EL 2; PCS]; 338 [EL 3; SS]), a high risk factor burden (339 [EL 2; PCS]), and even a low lifetime ASCVD risk (340 [EL 2; PCS]). More specifically, a CAC score of 0 (healthy aging) is a strong predictor of low ASCVD risk (341 [EL 2; PCS]). Based on these MESA findings, an algorithm was developed that accurately predicts 10-year ASCVD risk using CAC and traditional risk factors (36 [EL 3; SS]). The MESA algorithm was validated against 2 independent longitudinal cohort studies: Heinz Nixdorf Foundation (HNR) and the Dallas Heart Study (DHS) (36 [EL 3; SS]). The MESA algorithm had an area under the survival receiver-operator characteristic (ROC) curve of 0.81, indicating excellent discrimination between events and nonevents. This compared with a curve of 0.76 without CAC inclusion and provides further evidence of improved prediction with CAC (36 [EL 3; SS]).

Genetic testing to search for mutations in the LDL receptor, apolipoprotein B 100 (ApoB100), or PCSK9 is available to diagnose FH (342 [EL 4; NE]). However, criteria other than genetic testing, such as LDL cholesterol concentrations, physical findings, and family history of early elevated total cholesterol and/or early MI, are most commonly used to diagnose FH (66 [EL 4; NE]; 67 [EL 4; NE]).

Special Considerations: Women

Both the Framingham Heart Study and Lipid Research Clinics Follow-Up Study demonstrated that high total cholesterol, LDL-C, and TG, as well as low HDL-C are ASCVD risk factors in women. Risk assessment tools developed from these and other studies may assist in determining ASCVD risk for women (Table 8).