About the Guideline

- Developed by the American Association of Clinical Endocrinologists (AACE) in response to a mandate by the AACE and American College of Endocrinology (ACE) board of directors to develop and publish standardized clinical practice guidelines (CPG).

- The purpose of this CPG is to provide a reference for health care professionals, health related organizations and regulatory bodies offering guidance for screening, risk assessment and treatment for individuals with lipid disorders to, in turn, be used as a tool to reduce risk and adverse consequences of dyslipidemia and prevention of cardiovascular disease.
About the Guideline (cont'd.)

- Included in this CPG are specific recommendations for women, children and adolescents, and diabetics with lipid disorders.

- The format of the guideline is organized in four, key, specific clinical questions from which 87 recommendations were derived. Each question is listed below with a summary of relevant recommendations.
Key Clinical Considerations
Question 1

How should individuals be screened for the detection of dyslipidemia (Jellinger et al., 2017)?

Recommendations 1-8 are relevant to global risk assessment.

Based on the literature reviewed for this CPG, the following risk factor categories for ASCVD were surmised...
Major Risk Factors

- Advancing age (men > 45 years of age and women > 55 years of age)
- Increased total serum cholesterol
- Decreased non-high-density lipoprotein cholesterol (non-HDL-C)
- Increased low-density lipoprotein cholesterol (LDL-C)
- Diabetes Mellitus (DM)
- Hypertension
- Chronic kidney disease (CKD)
- Cigarette smoking
- Family history of atherosclerotic cardiovascular disease (ASCVD)
Additional Risk Factors

- Obesity, abdominal obesity

- Family history of hyperlipidemia

- Increased small, dense LDL cholesterol (referred to LDL pattern b)
  - Found in 50% of men with ASCVD; associated with high triglycerides (TG) and low HDL-C

- Increased Apolipoproteins (Apo-B)

- Increased LDL particle concentration

- Fasting/post-prandial hypertriglyceridemia

- Polycystic Ovary Syndrome (PCOS)

- Dyslipidemic triad (high TG, low HDL-C, high small, dense LDL-C)
Nontraditional Risk Factors

- Increased lipoprotein (a)
- Increased clotting factors (plasminogen activator inhibitor 1, increased fibrinogen)
- Increased inflammation markers (hsCRP, Lp-PLA2)
- Increased homocysteine levels
- Apo E4 isoform
- Increased uric acid
- Increased triglyceride remnants
5 Risk Categories Recognized by the AACE/ACE CPGs (Jellinger et al., 2017)

- **Extreme risk**
  - Those with progressive ASCVD and/or unstable angina at goal LDL-C
  - Clinical cardiovascular disease in patients with DM, CKD (stage 3 or 4), or heterozygous familial hypercholesterolemia (HeFH)

- **Very high risk**
  - Recent ACS event, coronary, carotid or peripheral vascular disease, or 10-year calculated risk for ASCVD > 20%
  - DM or CKD (stage 3 or 4) with 1 or more risk factors

- **High risk**
  - ≥ 2 risk factors and 10-year risk 10-20% for ASCVD
  - DM or CKD 3 or 4 with no risk factors

- **Moderate risk**
  - ≥ 2 risk factors and 10-year risk < 10%

- **Low risk**
  - 0 risk factors
Recommendations

Based in the above risk factors and risk categories, the following recommendations were made:

- Identify risk factors for dyslipidemia to allow for identification of lipid disorders to implement personalized and optimal treatment strategies.

- Individuals with type 2 DM should be considered very high risk for the development of atherosclerotic cardiovascular disease (ASCVD).

- Individuals with type 1 DM for more than 15 years or in type 1 diabetics with 2 or more major cardiovascular risk factors, poorly controlled DM, or insulin resistance with metabolic syndrome should be considered very high risk.

- The 10-year risk for coronary events should be assessed using one or more of the following validated assessment tools:
  - Framingham Risk assessment tool (D'Agostino et al., 2006).
  - Multi-Ethnic Study of Atherosclerosis (MESA) 10-year ASCVD Risk with Coronary Artery Calcification Calculator (McClelland et al., 2015).
  - Reynolds Risk Score (Ricker et al., 2007).
  - United Kingdom Prospective Diabetes Study (UKPDS) risk engine to calculate ASCVD risk in individuals with type 2 diabetes (Stevens et al., 2001).

- Special attention should be given to screen women for 10-year risk for ASCVD; the recommended screening tools are either the Reynolds Risk Score or Framingham Risk assessment tool.

- Children and adolescents should be diagnosed and treated as early as possible to reduce risk factors in adulthood.

- Those with HDL-C levels > 60 mg/dL should have 1 risk factor equivalent subtracted from their risk profile.

- Elevated triglycerides should be included in risk assessment and treatment decisions.
Recommendations 9-18 relate to screening specific populations for lipid disorders and include the following key groups (Jellinger et al., 2017):

- Screen for **familial hypercholesterolemia (FH)** in those with family history of premature ASCVD or elevated cholesterol.

- Screen **adults with diabetes** annually (those > 20 years of age).
  - Screen **young men (age 20-45)** and **young women (age 20-55)** every 5 years.
  - Screen **middle-aged men (age 45-65)** and **middle-aged women (age 55-65)** at least every 1-2 years and more frequently when there are risk factors for ASCVD or as judged clinically appropriate.
  - Screen **adults older than 65** years annually.

- Screen **children at risk for FH** beginning at age 3, again between ages 9 – 11, and again at age 18.

- Screen **adolescents (older than 16)** every 5 years and more frequently in those who are obese or overweight, have risk factors for ASCVD, have insulin resistance syndrome, or a family history of premature ASCVD.
Question 2

Which screening tests are recommended for the detection of cardiovascular risk (Jellinger et al., 2017)?

Recommendations 19-34 refer specifically to serum markers and alternate testing for cardiovascular risk and are summarized by test type with specific recommendations:
Fasting Lipid Profile

- Considered the most accurate evaluation of lipids

- Ideally performed fasting (9 - 12 hours) but non-fasting acceptable if fasting not possible

- Includes measurement or calculation of the following:
  - Total cholesterol
  - Low density lipoprotein cholesterol (LDL-C)
    - Can be measured directly or calculated
    - \( \text{LDL-C} = (\text{total cholesterol} - \text{HDL-C}) - (\text{TG}/5) \)
    - Calculation most accurate during fasting state and when TG < 200 mg/dL

- Triglycerides (TG)
  - Elevated TG to HDL-C ratio is a strong predictor of insulin resistance (a risk factor for ASCVD and type 2 diabetes)
  - If marginally elevated consider measuring for LDL type B (small, dense LDL)

- High-density lipoprotein cholesterol (HDL-C)
  - Include in screening test for dyslipidemia
Non-high-density Lipoprotein Cholesterol (Non-HDL-C)

- Non-HDL-C = Total cholesterol – HDL-C
  - the sum of LDL-C and very low-density lipoprotein cholesterol (VLDL-C)
  - Important to evaluate in those with elevated triglycerides, diabetes or known ASCVD and if insulin resistance is suspected
Apolipoproteins (Apo-B)

- An elevated level associated with risk for early ASCVD

- May be more closely associated with insulin resistance, central adiposity, thrombosis and inflammation (Sattar et al. 2004)

- Apo-B > 130mg/dL with LDL-C < 160mg/dL with or without elevated TG considered risk for premature ASCVD
Secondary Causes

In evaluating lipid disorders, exclude secondary causes of dyslipidemia.
Secondary causes of elevated total cholesterol and LDL-C (Jellinger et al., 2017):

- Hypothyroidism
- Nephrosis
- Dysgammaglobulinemia (systemic lupus erythematosus, multiple myeloma)
- Progestin or anabolic steroid treatment
- Cholostatic disease of the liver (i.e. primary biliary cirrhosis)
- Protease inhibitor use in the treatment of HIV
Secondary causes of elevated TGs and VLDL-C (Jellinger et al., 2017):

- Chronic renal failure
- Type 2 DM
- Obesity
- Excessive alcohol intake
- Hypothyroidism
- Anti-hypertensive medications (thiazide diuretics, certain beta-blockers)
- Corticosteroid use or severe stressors inducing endogenous steroid release
- Oral estrogens/progesterone therapies, pregnancy
- Protease inhibitor used in the treatment of HIV
Additional tests endorsed by the AACE/ACE CPG (Jellinger et al., 2017):

- High-sensitivity C-reactive protein (hs-CRP) measurement is recommended in those with borderline standard risk to further stratify risk.

- Lipoprotein-associated phospholipase A2 (Lp-PLA2) elevation is linked to ASCVD risk and may act synergistically with hs-CRP when both elevated; measure to further stratify risk.

- Lp-PLA2 (≥200 ng/mL) has been independently linked with coronary events (Packard et al., 2000).

- Coronary artery calcification measurement is endorsed for additional risk stratification.

- Carotid intima medial thickness (CIMT) is endorsed for additional risk stratification and treatment decisions.
Question 3

What are the treatment recommendations in individuals with dyslipidemia and ASCVD risk (Jellinger et al., 2017)?

Recommendations 34-80 refer to both pharmacologic and nonpharmacological treatment strategies and treatment goals.
Treatment Goals

Treatment goals should be based on risk for ASCVD (based on the 5 risk categories described above and serum markers goals described below).
Low Risk

• LDL-C < 130 mg/dL
• Total cholesterol < 200 mg/dL
• Non-LDL-C 30 mg/dL above LDL goal
• TG < 150 mg/dL
Moderate Risk

- LDL-C < 100 mg/dL
- Total cholesterol < 200 mg/dL
- Non-LDL-C 30 mg/dL above LDL goal
- TG < 150 mg/dL
High Risk

- LDL-C < 100mg/dL
- Total cholesterol < 200mg/dL
- Non-LDL-C 30 above LDL goal
- TG < 150mg/dL
- Apo B < 90 mg/dL
Very High Risk

- LDL-C < 70 mg/dL
- Total cholesterol < 200 mg/dL
- Non-LDL-C 30 mg/dL above LDL goal
- TG < 150 mg/dL
- Apo B < 80 mg/dL
Extreme Risk

- LDL-C < 55 mg/dL
- Total cholesterol < 200 mg/dL
- Non-LDL-C 25 mg/dL above LDL goal
- TG < 150 mg/dL
- Apo B < 90 mg/dL
Children and Adolescents

- LDL-C < 100 mg/dL
- Total cholesterol < 200 mg/dL
- TG < 150 mg/dL
Treatment Recommendations

(Jellinger et al., 2017)
Lifestyle Modifications

- Physical activity
  - 30 minutes of moderate activity 4-6 times a week
  - May be accomplished in single session or multiple sessions throughout day (i.e. 3, 10-minute sessions)
  - Muscle strengthening 2 days/week

- Medical nutrition therapy
  - Low calorie diet with ≥ 5 servings fruit/vegetables daily and consisting of whole grains, fish, lean meats.
  - Limited intake of saturated fats, trans fats, and cholesterol and increased plant stanols/sterols (~2gm/day) and soluble fiber (10-25gm/day) which are known to reduce LDL-C.

- Smoking cessation should be encouraged and facilitated in all patients.
Pharmacologic Treatment

- Statins
  - Recommended as 1st line treatment to achieve LDL-C goals
  - Treat to risk-related LDL-C goals as described above.

- Fibrates
  - First line agents in treatment of TG > 500 mg/dL

- Omega-3 Fish Oil
  - Prescription omega-3 oil (but not dietary supplements/ over the counter) agents are recommended as dose of 2 to 4 grams daily to treat TG > 500 mg/dL

- Niacin
  - Recommended as adjunct agent for treating hypertriglyceridemia

- Bile Acid Sequestrants
  - Consider as adjunct in reducing LDL-C and Apo B and increasing HDL-C
  - May increase TG level
Pharmacologic Treatment (cont'd.)

- Cholesterol absorption agents
  - May be considered in statin intolerant individuals for reduction of LDL-C and Apo-B
  - May be used in combination or as monotherapy to reduce LDL-C and ASCVD risk

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors
  - Recommended in combination with statin to reduce LDL-C in those with familial hypercholesterolemia.
  - Add to statin therapy to achieve LDL-C/non-HDL-C goals with maximal tolerated statin dose
  - Rarely used as monotherapy
Children and Adolescents

- Lifestyle modifications
- Consider pharmacologic therapy in the following circumstances:
  - > 10 years of age AND
    - LDL-C $\geq$ 190mg/dL
    - LDL-C $\geq$ 160 mg/dL with 2 or more ASCVD risk factors
    - Family history of premature ASCVD
    - Obesity, overweight or insulin resistance syndrome
Follow-up and Monitoring

- Repeat lipid panel 6 weeks after initiation of therapy then every 6 to 12 months once treatment goals are reached on chronic pharmacotherapy.

- Evaluate more frequently if clinically indicated (i.e. uncontrolled diabetes, new ASCVD event).

- Measure liver transaminase levels prior to initiation and 3 months after initiation of niacin or fibrate therapy; if normal, check every 6 or 12 months.

- If any subjective complaints of myalgias or muscle weakness on statin therapy, discontinue and check creatinine kinase level.
Question 4

Is treatment of dyslipidemia and prevention of atherosclerotic cardiovascular disease cost-effective (Jellinger et al., 2017)?

Recommendations
81-87
**Recommendations 81-87** refer to the cost-effectiveness of treatment and prevention of ASCVD.

- The **most** cost-effective measures to prevent ASCVD are smoking cessation and dietary management.

- The following pharmacologic measures are considered cost-effective in moderate to high risk individuals (Jellinger et al., 2017):
  - Statin therapy is cost-effective in primary and secondary prevention of ASCVD events for those at moderate or high risk and those at low risk with LDL-C > 190 mg/dL.
  - Fibrates care cost-effective as monotherapy and as combination agent in lowering TG and raising HDL-C but not in reducing ASCVD events with exception of those with TG > 200 mg/dL and HDL-C < 40 mg/dL.
  - Bile acid sequestrants are not a cost-effective alternative to statins as their ability to lower LDL is not as good.
  - Ezetimibe has not been evaluated effectively to make a recommendation.
References


References (cont'd.)


