Hyperlipidemia or Dyslipidemia

Diagnosis/Condition:	Hypercholesterolemia, pure Hyperlipidemia, mixed Hypertriglyceridemia Disorder of lipid metabolism, unspecified
Discipline:	ND, LAc
ICD-10 Codes:	E78.0, E78.1, E78.2, E78.9
Origination Date:	2010
Review/Revised Date:	07/2024
Next Review Date:	07/2026

Hyperlipidemia is defined as the increased levels of lipids (fats) in the blood, including cholesterol and triglycerides. This condition can significantly increase the risk of coronary artery disease (CAD) or atherosclerosis. In the U.S., Heart Disease is the #1 cause of death, accounting for 25% of mortalities (~700,000/year).[1] Of the numerous types of Heart Disease, CAD is the most common, accounting for ~50% of Heart Disease deaths (~375,000/yr). Despite being a modifiable risk factor, hyperlipidemia remains one of the most prevalent contributors to CAD.[2,3] U.S. data estimates that ~34% of U.S. adults have elevated low-density lipoprotein (LDL) cholesterol and only ~33% have this condition reduced to a safe level. First lines of defense are lifestyle modifications, e.g., exercise, diet, and smoking cessation. Complementary and Integrative Health providers encounter patients with these risk factors, which are a priority public health issue. These encounters are an important opportunity to promote evidence-based health promotion and chronic disease prevention strategies.[4]

The chart below summarizes lipid levels according to low-very high values for screening.[5] Anything above optimal/desirable should be treated appropriately to reduce cardiovascular risks. Note: High HDL is considered a negative risk factor (removes a risk factor).

	Low mg/dL (mmol/L)	Optimal/Desirable mg/dL (mmol/L)	Borderline High mg/dL (mmol/L)	High mg/dL (mmol/L)	Very High mg/dL (mmol/L)
Total Cholesterol (TC)	N/A	Less than 200 (5.17)	200 to 239 (5.17 to 6.18)	≥240 (6.20)	N/A
Low-density lipoprotein (LDL)	N/A	Less than 100- 129 (2.58 to 3.33)/ If have CHD and risk factors - 70 to 80 (1.81 to 2.07)	130 - 159 (3.36 to 4.11)	160 to 189 (4.13 to 4.88)	≥190 (4.91)

High-density lipoprotein (HDL)	<40 (1.03)	40 to 60 (1.03 to1.55)	N/A	N/A	≥ 60 or 1.55
Triglycerides		Less than 150 (1.69)	150 to 199 (1.69 to 2.25)	200 to 499 mg/dL (2.25 to 5.63)	>500 (5.65)

Total-to-HDL-cholesterol ratio is of greater predictive value than the serum total or LDL-C and should be used to guide treatment options.[6]

Numerous international clinical practice guidelines have been developed for treatment, each with variations of treatment strategies.[7,8,9,10]A recent publication highlights a few key differences between these.[11] For instance, there is no consensus among these guidelines on the risk assessment tool that should be used (e.g., Framingham Risk Score) or the threshold at which to initiate treatment (i.e., statins). Similar to differences among international recommendations, the current U.S. guideline recognizes that algorithms are, at times, inadequate and that individualized care is often needed.

The most current U.S. guideline, developed by the American Heart Association and American College of Cardiology (AHA/ACC), expanded the focus from CHD only, to include atherosclerotic cardiovascular disease (ASCVD); which includes CHD, stroke and peripheral arterial disease.[7] The general approach recommended is to discuss the risks of ASCVD before prescribing statins and to triage patients into one of four risk categories using the AHA/ACC risk calculator. Compared with the previous guideline (2013), the 2019 update suggests more attention on reducing LDL cholesterol as a treatment goal, as well as long-term monitoring of therapeutic efficacy. It is worth noting that the first line of treatment for all individuals is encouragement and recommendation of *"A heart-healthy lifestyle beginning in childhood"* and suggests screening should begin in adolescents to reduce lifetime risk for ASCVD.

Lipid Management and Treatment Goals based on ACC/AHA 2018 Guidelines			
Clinical Scenario	**Statin Treatment Intensity**	**Goals and Follow Up**	*Lifestyle Modifications recommended for all scenarios.
Very High Risk Multiple major ASCVD events or one event and other risk factors	MAX	LDL <70 or non-HDL≥100	
Primary Hypercholesterolemia LDL-C ≥190		LDLC ≥100	
High Risk 10-year ASCVD risk ≥20%	HIGH	High intensity: Aim for reduction of 50% of LDL-C.	
Stable ASCVD Clinical ASCVD without risk factors		Moderate intensity: Aim for reduction of 30-49% of LDL-C.	
Diabetes If multiple risk factors, then higher dose of statin	MODERATE		

Intermediate Risk 10-year ASCVD risk between 7.5-20%. Consider risk enhancers*		Risk Discussion	
Low Borderline Risk 10-year ASCVD risk < 7.5. Consider risk enhancers.	UNKNOWN		

Risk-enhancing Factors

- Family history of premature ASCVD (male < 55 years or female < 65 years).
- Primary hypercholesterolemia with LDL 160-189 mg/dL.
- Metabolic syndrome.
- Chronic kidney disease.
- Chronic inflammatory disorders (e.g., rheumatoid arthritis, HIV/AIDS).
- Premature menopause (< 40 years).
- Pregnancy-associated complications with higher ASCVD risk (e.g., preeclampsia).
- Non-fasting triglycerides > 175 mg/dL on at least 3 occasions.
- Biomarkers: high-sensitivity CRP > 2 mg/dL, Lp(a) > 50 mg/dL, apoB > 130 mg/dL.
- ABI (ankle brachial index) < 0.9.

Deciding Who to Treat[14]

Patients' cardiovascular risk should be calculated using appropriate risk models, such as the Framingham Risk Score for men and women. Patients and their providers can then decide whether a 20 to 30 percent relative risk reduction translates into an absolute risk reduction large enough to be worth the cost, burdens, and potential side effects of medical treatment. The calculator can be found here: http://cvdrisk.nhlbi.nih.gov/calculator.asp

Major Atherosclerotic Cardiovascular Disease (ASCVD) Risk Factors

Major Risk Factors	**Additional Risk Factors**	**Nontraditional Risk Factors**
Advancing age (Age > 65 years)	Obesity, abdominal obesity	⇧ Lipoprotein (a)
Low HDL-C	Family history of (heterozygous) hyperlipidemia	⇧ Clotting factors
Hypertension	⇧ Small, dense LDL-C	⇧ Inflammation markers (hsCRP; Lp-PLA_2)
⇧ Total serum cholesterol level	⇧ Apo B	⇧ Homocysteine levels
⇧ Non–HDL-C	⇧ LDL particle concentration	Apo E4 isoform
⇧ LDL-C above 100 mg/dL despite max statin	Fasting/postprandial hypertriglyceridemia	⇧ Uric acid

therapy		
Diabetes mellitus	Dyslipidemic triad	⇧ TG-rich remnants
Stage 3 or 4 chronic kidney disease	PCOS	
Family History of ASCVD	Hypothyroidism	
Ischemic stroke, Symptomatic peripheral artery disease (claudication with ABI < 0.85, or previous revascularization or amputation)	Prior coronary bypass surgery or PCI outside of the above events	
ACS in last 12 months	Current smoker	
Multiple heart attacks	Congestive heart failure	

Risk categories for ASCVD are based on patient's 10-year ASCVD risk. They are now divided into **Low Risk** (<5%); **Borderline** (5-7.5%); **Intermediate** (7.5%-20%); and **High Risk** (>20%).[7] Treatment goals vary for each Risk Category. Women and children have specific parameters and treatment goals to consider.[7] Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease(ASCVD) risk estimation and those in other age categories should be evaluated based upon risk factors, with younger patients getting assessed more often.[20]

Subjective Findings and History

- CAD or risk factors for CAD include underlying conditions, such as diabetes mellitus types 1 and 2, carotid artery disease, hyperthyroidism, liver disease, kidney disease, peripheral artery disease, and abdominal aortic aneurysm. Other risk factors include cigarette smoking, stress levels, hypertension (BP ≥140/90 or being treated for hypertension), family history of premature CAD in a first-degree relative, male gender, and increased age.
- Several other risk factors for CAD have been suggested by epidemiologic data. These include obesity, physical inactivity, impaired fasting glucose, markers for inflammation, excess calorie consumption, excess alcohol consumption, homocysteine levels, abnormalities of thrombosis, and endothelial dysfunction.
- Use of drugs such as hormones, oral contraceptives, corticosteroids, retinoids, thiazide

diuretics, and possibly antiviral drugs used to treat human immunodeficiency virus (HIV) infection and AIDS can cause triglyceride levels to increase.
- Genetics (familial or hereditary hyperlipidemia, familial dysbetalipoproteinemia or lipoprotein lipase deficiency and apolipoprotein CII deficiency).[21]

Objective Findings

- Generally asymptomatic.
- If presents with other risk factors (as listed above) or CAD, may include chest pain (angina), history of a myocardial infarction (MI), or a stroke.
- High lipid levels can cause fat to be deposited in the skin and tendons and forms bumps called xanthomas.
- Very high triglyceride levels can cause the liver or spleen to enlarge and may increase the risk of developing pancreatitis, which can cause severe abdominal pain and is occasionally fatal.

Assessment

- A lipid profile (LDL-C, HDL-C, Non-HDL-C, Triglycerides) is usually measured in fasting labs (12 hours) and a ten-year risk for developing CAD is determined and based on the Framingham Heart Study.[22]
    - Baseline lipid panel should be done at age 20 and then every 5 years if no other risk factors (family history of high cholesterol or other risk factors, like smoking or diabetes).
    - Highly sensitive C-reactive protein (hsCRP)[23] and apolipoproteins (Lp=PLA2, Apo B and/or an apo B/apo A1 ratio calculation and evaluation).
- Coronary artery calcification measurement (scoring) in:
    1. Patients who are reluctant to start a statin.
    2. Patients who are reluctant to re-start a statin after stopping for statin-associated symptoms.
    3. Older patients (men 50-88 years and women 60-80 years) with low burden of risk factors and question benefit of starting a statin.
    4. Middle-aged adults (40-55 years) who fall in the "borderline" ASCVD risk category and have additional risk factors that increase their ASCVD risk.
- Homocysteine.
- Carotid intima media thickness.
- Cardiovascular exam.
- Peripheral vascular exam.
- Retinal exam.
- Comprehensive physical exam.

Plan

The Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) from the National Cholesterol

Education Program (NCEP) has summarized the current recommendations for the management of high serum cholesterol. [24]

- A 5-year clinical trial (4S) with over 4400 patients with heart disease found that lowering cholesterol led to fewer heart attacks (37%) and reduced death from heart disease (42%) in men and women who already had heart disease and high cholesterol. Another study (CARE) showed that lowering cholesterol (using statins) in patients with heart disease reduced the risk of having another heart attack or dying by 24%. The LIPID study is another study that showed statins with dietary changes had a large effect on cholesterol numbers. It also reduced the overall death rate by 22%, heart attacks by 29%, stroke by 19% and the need for bypass or angioplasty by 20%.[26,27]

    - The Portfolio study took a variety of known cholesterol-lowering foods and compared their effect of this to the use of a statin-drug combined with a low-fat diet. The foods included plant sterols (found in vegetables, nuts (almonds), and seeds and legumes, soy protein, and soluble fiber. After one month, cholesterol reduction was 28%, which was comparable to the statin/low-fat diet group and both these groups were statistically significantly better than control.[45]

Lifestyle and Dietary Modifications:

- Weight loss and increase in physical activity as indicated (30-60 minutes daily or 150 minutes per week).[20,55]
- Regular moderate exercise works in combination with a low-fat diet and has been shown to decrease triglycerides and LDL and increase HDL levels. Being overweight lowers HDL cholesterol and increases risk of heart disease and stroke. Studies in children with familial hypercholesterolemia show that a heart healthy diet implemented with dietary advice can lower total cholesterol levels.[56,57,58]
- Stress reduction (meditation, exercise, tai chi, learning and using coping skills).[59]
- Nicotine cessation.
- Dietary changes[60], including:
    - Mediterranean Diet.[61]
    - DASH Diet. [62]
    - Tibetan diet.[63]
    - Soy protein.
        - A 2019 meta-analysis (46 RCTs) concluded, found a 3-4% reduction in LDL and concluded, *"…data support the advice given to the general public internationally to increase plant protein intake."*[64]
- Plant based diet.
- Decrease "bad fats", such as trans fats and increase polyunsaturated, or monounsaturated fats.
- Decrease dietary cholesterol (this does not include a general limitation on eggs as previously reported)[65]
- Increase the amount of wild heart-healthy fish consumed.

- Alcohol in moderation.
- Increase in soluble fiber (fruits, vegetables, grains, oat bran, oatmeal, beans, peas, rice bran, barley, citrus fruits, strawberries, and apple pulp.[66,67]
- Lifestyle changes in patients with diabetes are crucial.

Herbal Medicine (Western):

- Red yeast rice (RYR) extract. Produced by the fungus *Monascus purpureus* during the fermentation of rice; main component is monacolin K which is structurally identical to Lovastatin.
    - A 2024 meta-analysis (14 RCTs; N=770) as well as an earlier 2022 meta-analysis (15 RCTs, N=1,012) suggests red yeast rice (RYR: 200-4,800mg daily) is a safe and effective treatment.[68,69]
        - 2024 MA(14 RCTs; N=770): RYR was superior to control; MD: 37.43mg/dL (95% CI: -47.08 to 27.79; p<0.001)
        - 2022 MA (9 RCTs; N=613): RYR was superior to control; MD: 35.82 (95% CI: -43.36 to -28.29; p<0.00001)
        - 2022 MA (2 RCTs; N=103): RYR was equivalent to statins; MD: -2.71 (95% CI: -10.59 to 5.17; *p*=0.50)
          **N.B. Research suggests that a reduction of TC by 19.3mg/dL leads to a 9% reduction in all-cause mortality for the average U.S. adult.[70] The average U.S. adult has a TC level of 203 mg/dL.[71]*
- Policosanol (mixed results).[72,73]
- Various herbal medicines and combination supplements.
  Curcuma longa (Curcumin),[74,75]*Irvingia gabonensis,*[76]*Vaccinium macrocarpon* (Cranberry),[77] *Citrullus colocynthis*[78]*, Hibiscus sabdariffa,*[79,80] *Terminalia arjuna,*[184] *Cinnamomum verum or spp.(*Cinnamon),[81,82]*Cynara cardunculus* (Artichoke) leaf extract,[83,84] Berberis spp. Berberine,[85,86] *Achillea millefolium* (Yarrow),[87]*Ocimum tenuiflorum* (Holy basil),[88] Aloe vera,[89] *Salvia miltiorrhiza,*[90] *Pueraria lobata,*[91]*Trigonella foenum-graecum* (Fenugreek) seeds and leaves.[92,93]
- Lycopene.[94]
- Bergamot and RYR appear to be the most effective nutraceuticals in terms of LDL-C and TC reduction.[95]

Herbal Medicine (Traditional East Asian Medicine):

- Chinese Herbal Medicine
    - A 2022 network meta-analysis (47 RCTs; N=4,824) suggests that RYR combined with Chinese herbs, has comparable and in some cases superior effects compared to Simvstatin.[96,97]
        - TC levels: Xuezhikang (*SUCRA: 84.5%); Simvastatin (66.4%) Zhibitai (65.4%).
        - LDL-C: Xuezhikang (SUCRA: 82.6%); Simvastatin (SUCRA: 74.9%); Zhibituo (SUCRA: 52.8%).

- The authors suggest interpreting the results with caution due to low methodological quality. Of note, all trials were published in Chinese, and none were indexed on PubMed.
    - **Surface Under the Cumulative Ranking Curve (SUCRA) is a statistical technique to estimate probability effects as a numeric presentation of ranking, presented as a single number for each treatment.*

Supplements and Nutrients:

- Fish and fish oil (DHA/EPA)[98]
    - There is strong evidence to show that fish oils (EPA plus DHA) can decrease triglycerides and LDL, and increase HDL (2-4 grams/day, 4:1 EPA: DHA) in part by reducing liver production and release of VLDL. Reduction does appear to be dose dependent. If fish oil supplements are to be used, the label should be checked for contaminant testing (heavy metals and pesticides).[99,100,101] Avoid in patients with known hypersensitivity to fish. May prolong bleeding time. Assess coagulation studies as needed.
    - A 2023 network meta-analysis (90 RCTs; N= 72 598) concluded that combined intake of omega-3 fatty acids near linearly lowers triglyceride and non-high-density lipoprotein cholesterol.[102]
- Omega-3 rich oils (walnuts, almonds, avocados, olive oil, and flax seeds are all good sources of these "healthy oils".[103,104,105]
    - Certain nuts (almonds, pecans, macadamias, and walnuts) are high in polyunsaturated or monounsaturated fatty acids and compounds such as plant sterols, and fiber. Consumption has been associated with a decrease in LDL. The American Heart Association (AHA) dietary guidelines suggest using nuts and other sources of unsaturated fatty acids as a replacement for foods containing saturated and trans-fatty acids.[106]
    - Flaxseed (20 - 50 g) is a very healthy fiber food and one benefit is it seems to reduce TC and LDL levels, but further studies are needed to determine its precise role in treating hyperlipidemia.[107]
- Soluble Fiber (oat bran, barley flour, psyllium, legumes (peas and beans), fruits (apples, pears, prunes), some vegetables (yams, Brussels sprouts).[45,108,109]
    - Five to 10 g/day is associated with a 5% reduction in LDL. This can be obtained with a high-fiber diet or with dietary supplementation.[110]
- Almonds[111], pistachios.[112]
- Pomegranate seed oil.[113]
- Garlic (mixed studies) (caution with blood thinners).[114,115,116]
- Plant sterols/stanols (phytosterols).[117, 118, 119]
    - These occur naturally in some fruits, vegetables, nuts, seeds, legumes, vegetable oils, and other plant sources.
- Barley oil extract or fiber.[120,121,,122]
- CoQ10 (may decrease muscle pain associated with "statin" treatment).[123,124]
- L-Arginine.

- Pycnogenol.[125]
- Anthocyanins.[126]
- Probiotics.[127,128]
- Chia seed.[129]
- Rice bran oil.[130,131]
- L-carnitine.[132]
- Green tea.

Pharmaceuticals (Prescription):

There are specific guidelines for drug treatment options based upon the National Cholesterol Education Program (NCEP; Adult Treatment Panel [ATP] III). These include treatment specifics for elevated cholesterol vs. triglycerides or both and focus on atherosclerotic cardiovascular disease (ASCVD) risk reduction. Guidelines for initiation and monitoring can be found in the American College of Cardiology/American Heart Association Guideline[133] which can be found at: http://www.onlinejacc.org/content/accj/63/25_Part_B/2889.full.pdf

There are mixed results on the research of aspirin in the routine primary prevention of cardiovascular disease.

Prescription Medications:

- Lipid-lowering medications (statins) is first line pharmaceutical therapy.
  Statins are the strongest drugs for lowering LDL cholesterol and are the most effective researched drug for prevention of coronary heart disease, heart attack, stroke, and death. Statins may decrease the body's synthesis of cholesterol and can reduce LDL levels by as much as 20 to 60 percent. In addition, statins can lower triglycerides and slightly raise HDL cholesterol levels.[134,135,136,137,138] Side effects of statins include myalgia, elevated liver enzymes and liver damage (LFTS should be measured at baseline and regularly). Rare adverse effects are rhabdomyolysis, digestive problems, rash or flushing, and neurological effects.[139] Patient compliance can be low due to side effects.

The Blood Cholesterol Expert Panel concluded that based on "a large and consistent body of evidence, 4 major statin benefit groups were identified for whom the ASCVD risk reduction clearly outweighs the risk of adverse events. Individuals with: 1) with *clinical* ASCVD; 2) primary elevations of LDL–C >190 mg/dL; 3) diabetes aged 40 to 75 years with LDL– C 70 to 189 mg/dL and without clinical ASCVD, or; 4) without *clinical* ASCVD or diabetes with LDL–C 70 to189 mg/dL and estimated 10-year ASCVD risk >7.5%."

The results of this meta-analysis suggest that the absolute risk reductions of treatment with statins in terms of all-cause mortality, myocardial infarction, and stroke are modest compared with the relative risk reductions, and the presence of significant heterogeneity reduces the certainty of the evidence. A conclusive association between absolute reductions in LDL-C levels and individual clinical outcomes was not established, and these findings underscore the importance of discussing absolute risk reductions when making informed clinical decisions

with individual patients.[140]

Patients who do not tolerate statins, should be started on a non-statin lipid-lowering medication.

- Ezetimibe (cholesterol absorption inhibitors).[141]
- Bile acid sequestrants (should be avoided until triglyceride levels have been normalized).
- PCSK9 Inhibitors (Proprotein convertase subtilisin/kexin type 9).
- Evolocumab (monoclonal antibody).[142]
- Fibrates (gemfibrozil, fenofibrate and fenofibric acid).
- Nicotinic acid (Niacin) – available OTC or as a prescription in higher doses (Nicotinic acid may worsen glucose tolerance in diabetic patients).[143,144,145]
- Inclisiran is a reasonable alternative to, PCSK-9 inhibitors, in patients who struggle with the self-injection.[146]

Treatment of elevated lipid levels in children is controversial.

Soft Tissue Therapies:

- Yoga.[147]
- Tai Chi.[148]

Acupuncture (excluding pharmocoacupture):

- Lifestyle modifications are a component of acupuncture treatments, where time is afforded to weave TCM- based lifestyle advice into the discussion. It is advised to discuss the lifestyle recommendation mentioned above during patient visits. In total, ~70 publications have assessed the effect of acupuncture on lipid levels, however <20 have been published in English. Of note, the majority of research seems to have focused on the effects of a single acupoint, ST-40.[149,150,151,152,153,154,155] Based on the limited amount of evidence no conclusions can be made.
    - A small body of literature indicates that modest benefits may be observed for patients with hyperlipidemia.[156,157,158,159,160,161]
        - Limited RCTs published in English (n=2).
        - Caution is warranted due to low methodological quality.

Length of Treatment

- Lifestyle and diet modification may take 6-12 months to take effect.
- Supplementation or prescription medications may take 6-12 weeks for lab values to change. Labs should be rechecked every 3-6 months until values are optimized. Measuring LDL-C response at 4-12weeks after initiating therapy and every 3-12 months depending on the patient. Thereafter, it may also be helpful in assessing adherence to medication and diet.[272] Liver function tests should be performed prior to therapy and as clinically indicated thereafter.

- The prevention and treatment of high cholesterol and/or triglycerides is a lifelong process.
- Stopping treatment or discontinuing beneficial changes in diet or exercise usually results in an increase in lipid levels.

Referral Criteria

Refer patients who may need a more extensive cardiovascular workup, those with significant personal or family history of cardiovascular disease, who develop concomitant risk factors or disease, or those who do not respond to treatment.

Resources for Clinicians

Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74(10):1376-1414.

Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020; 41:111–188.

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;73(24):e285-e350.

National Heart Lung and Blood Institute. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). https://www.nhlbi.nih.gov/health-topics/blood-cholesterol

Resources for Patients

American Heart Association
http://www.heart.org/HEARTORG/Conditions/Cholesterol/Cholesterol_UCM_001089_SubHomePage.jsp

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