Dyslipidemia Clinical Practice Guidelines

Definition

Dyslipidemia, refers to an abnormality within the lipid profile, encompassing a variety of disorders relating to elevations in total cholesterol, LDL, or TG, or conversely, lower levels of HDL. It may present as a single disorder affecting only one lipoprotein parameter, or may represent a combination of lipoprotein abnormalities, such as elevated TG and low HDL.

A dyslipidemia may be the result of over-production or lack of clearance of the lipoprotein particles, or related to other defects in the apolipoproteins or enzyme deficiencies.

Assessment (History and Examination)

Dyslipidemia itself usually causes no symptoms but can lead to symptomatic vascular disease, including coronary artery disease, stroke, and peripheral artery disease.

High levels of triglycerides (> 500 mg/dL [> 5.65 mmol/L]) can cause acute pancreatitis. Very high triglyceride levels can also cause hepatosplenomegaly, paresthesia, dyspnea, and confusion.

High levels of LDL can cause arcus cornea and tendinous xanthomas at the Achilles, elbow, and knee tendons and over metacarpophalangeal joints. Other clinical findings that occur in patients with high LDL (eg, in familial hypercholesterolemia) include xanthelasma (lipid rich yellow plaques on the medial eyelids). Xanthelasma can also occur in patients with primary biliary cirrhosis and normal lipid levels.

Patients with the homozygous form of familial hypercholesterolemia may have arcus cornea, tendinous xanthomas and xanthelasma plus planar or tuberous xanthomas. Planar xanthomas are flat or slightly raised yellowish patches. Tuberous xanthomas are painless, firm nodules typically located over extensor surfaces of joints.

Patients with severe elevations of TGs can have eruptive xanthomas over the trunk, back, elbows, buttocks, knees, hands, and feet.

Patients with the rare dysbetalipoproteinemia can have palmar and tuberous xanthomas.

Severe hypertriglyceridemia (> 2000 mg/dL [> 22.6 mmol/L]) can give retinal arteries and veins a creamy white appearance (lipemia retinalis). Extremely high lipid levels also give a lactescent (milky) appearance to blood plasma. Symptoms can include paresthesia, dyspnea, and confusion.

Management

Initial management for dyslipidemia involves lifestyle modifications. This approach should include a diet with an emphasis on the intake of vegetables, fruits, and whole grains within an appropriate calorie requirement. Also, adults should participate in moderate to vigorous aerobic physical activity 3 to 4 times a week for at least 40 minutes. First-line treatment for dyslipidemia is statins that inhibit 3-hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) reductase.

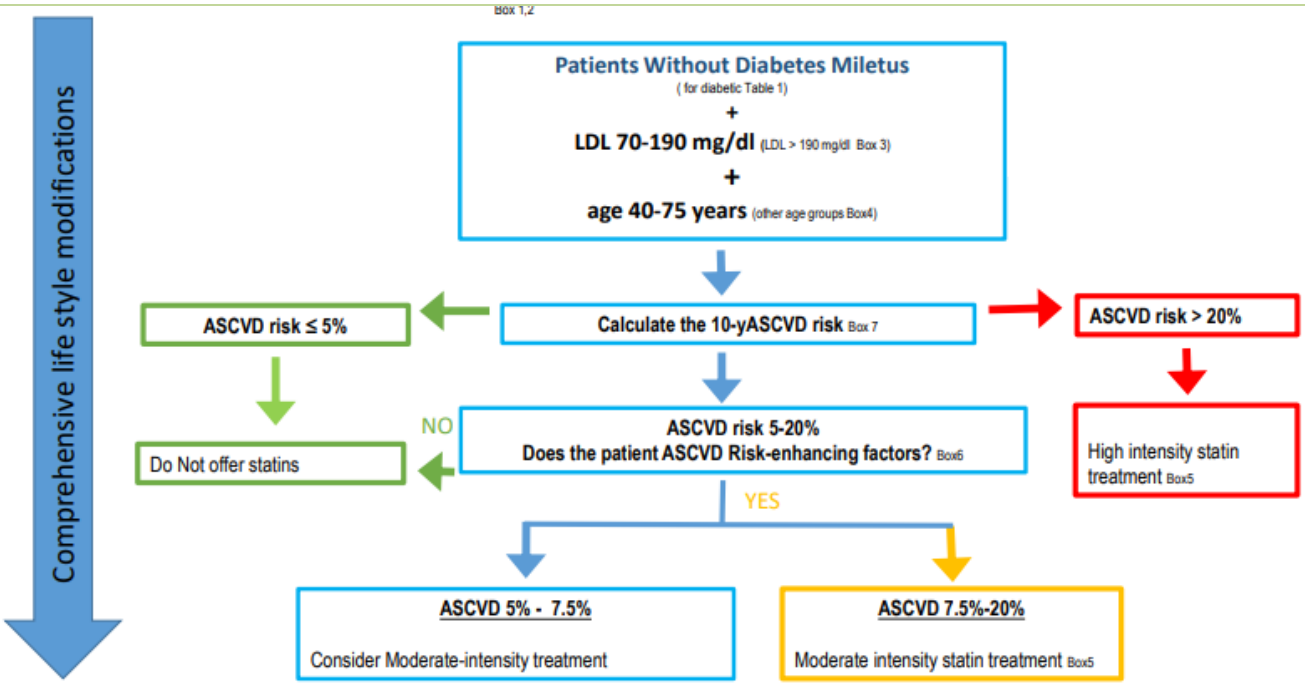


Table 1: ADA recommendation for statin therapy in diabetics

Age	ASCVD or 10-year ASCVD risk >20%	Statin Therapy
<40 years	No	No treatment
	Yes	High intensity
≥40 years	No	Moderate intensity
	Yes	High intensity

Box1: Cardiovascular disease prevention
- This guideline concerns primary CVD prevention.
- Patients with established ASCVD should be on high intensity statin treatment .

Box 2: measuring blood cholesterol
- Fasting or non-fasting plasma lipid levels is effective in estimating ASCVD risk
- If initial non-fasting lipid profile reveals a triglyceride ≥ 400 mg/dl a repeat fasting lipid profile should be obtained
- Fasting lipid measurement should be repeated 4 to 12 weeks after starting or changing statin therapy to assess: adherence, response to medications and lifestyle changes.
- Afterwards; lipid measurement should be repeated every 3 to 12 months as needed

Box 3: LDL > 190 mg/dl
- **High intensity statin if LDL > 190 mg/dl regardless of age**

Box4 : other age groups
- Age < 20 y: start statin if Familial Hypercholesterolemia
- Age 20-39 y: consider statin if family history, premature ASCVD & LDL > 160 mg/dl
- > 75yrs: consider lower intensity statin based on risk assessment & discussion

Box 5: statin dose & treatment targets Boxes 8,9 ,10

Moderate-intensity therapy
- Atorvastatin 10-20 mg
- Rosuvastatin 5-10 mg
- Simvastatin 20-40 mg

Target: 30-50% LDL-C reduction.

High-intensity therapy
- Atorvastatin 40-80 mg
- Rosuvastatin 20 mg

Target: >50% LDL-C reduction

Box 6: ASCVD Risk-enhancing factors:
- Family history of premature ASCVD
- Persistently elevated LDL-C > 160 mg/ dl
- Metabolic syndrome
- Chronic kidney disease
- History of preeclampsia or premature menopause (younger than 40 years)
- Chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, chronic HIV infection)
- High-risk ethnic groups (e.g., south Asian descent)
- Persistent triglyceride levels of >175/dl

Reference:
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease
A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.

Box 7: Atherosclerotic cardiovascular Disease (ASCVD) Risk Estimator

- **Intended for patients with LDL-C < 190 mg/dl, No ASCVD, not on LDL-C lowering therapy**
- **Components include : sex, age, race, Total cholesterol , HDL-C, systolic blood pressure, diabetes, smoking, treatment for hypertension.**
- **http://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calulate/estimator/**

Box 8 : Statins

Common agents: Simvastatin 10-80 mg , Atorvastatin 10-80 mg, Rosuvastatin 5-20 mg.
Dose titration : increase dose gradually at intervals of at least 4 weeks.
Cautions: history of liver disease , at risk of muscle toxicity (muscle disease , high alcohol intake), untreated hypothyroidism
Interaction: Clopidogril (reduce dose of Rosuvastatin), Clarithromycin (stop Simvastatin ,Atorvastatin for the duration of treatment), Amlodipine (reduce dose of Simvastatin).
Side effects: Common: lack of energy , constipation, diarrhea, nausea, dizziness, headache , myalgia thrombocytopenia, sleep disorders.
Uncommon: alopecia, memory loss, pancreatitis, paresthesia, sexual dysfunction, hepatic disorder.
Rarely: myopathy, peripheral neuropathy, tendinopathy,.
Frequency unknown : depression , diabetes mellitus , interstitial lung disease
Simvastatin: rarely acute kidney injury , frequency unknown: cognitive impairment
Atorvastatin: epistaxis, hyperglycemia, hypersensitivity, laryngeal pain, nasopharyngitis
Rosuvastatin: rarely gynecomastia, hematuria
Muscle effect: The risk of myositis, myopathy and rhabdomyolysis is rare although myalgia is common among statin users.
If statin is suspected to cause myopathy and Creatine kinase is markedly elevated stop statins and monitor symptoms, once CK concentration return to normal re introduce statin at lower dose and monitor patient.
Monitoring:
Prior to starting treatment: all patients should have their TSH, Liver function, and Renal panel checked.
NICE guidelines suggest checking liver function before treatment and at 3 and 12 months.
If ALT/AST are elevated but less than 3 times upper limit of reference statin therapy should not be stopped routinely.
Creatine kinase should be measured in patients with persistent generalized unexplained muscle pain prior to treatment.
Statin can be started if the level is elevated less than 5 times upper limit on 2 repeated sample 1 week apart.
Diabetes: patients at risk should have HbA1c before starting and repeated 3 months after starting statin treatment .
Renal impairment: eGFR <30 (avoid Rosuvastatin, reduce simvastatin to 10 mg , atorvastatin reduce to 20 mg).
Pregnancy: discontinue 3 months before attempting to conceive
Breast feeding: Avoid
Hepatic Impairment: avoid

Box 9 : other lipid lowering agents

Ezetimibe (Ezetrole)

Indications: Adjunct to dietary measures and Statins treatment in primary hypercholesterolemia, familial hypercholesterolemia, and in adults in whom initial statin therapy is contraindicated or can not be tolerated.
Dose: 10 mg daily.
Caution: increases the risk of rhabdomyolysis when given with Atorvastatin.
Side effects: fatigue, diarrhea; gastrointestinal discomfort; arthralgia , chest pain, hypertension, hot flushes.
Hepatic impairment: avoid in moderate to severe impairment.
Pregnancy: no information available .

Fenofibrate

Indications: severe Hypertriglyceridemia (TG >500 mg/dl), if statin is contraindicated or not tolerated, adjunct to statin if triglycerides inadequately controlled in patients at high cardiovascular risk.
Dose: 145 mg daily
Contraindications: Gall bladder disease; pancreatitis (unless due to severe hypertriglyceridemia); photosensitivity.
Caution: Correct hypothyroidism before initiating treatment, may increase risk of hypoglycemia if the patient is on insulin sulfonylurea. Increase the anticoagulant effect of warfarin. May cause myopathy/rhabdomyolysis when used with statins. **Side effects**: Abdominal pain; diarrhea; flatulence; nausea; vomiting, sexual dysfunction, skin reaction, embolism and thrombosis, headache, cholelithiasis, pancreatitis.
Pregnancy, **Breast feeding & Hepatic impairment :** avoid
Renal Impairment: avoid if eGFR <30 (max. dose 67 mg daily if eGFR 30–59).

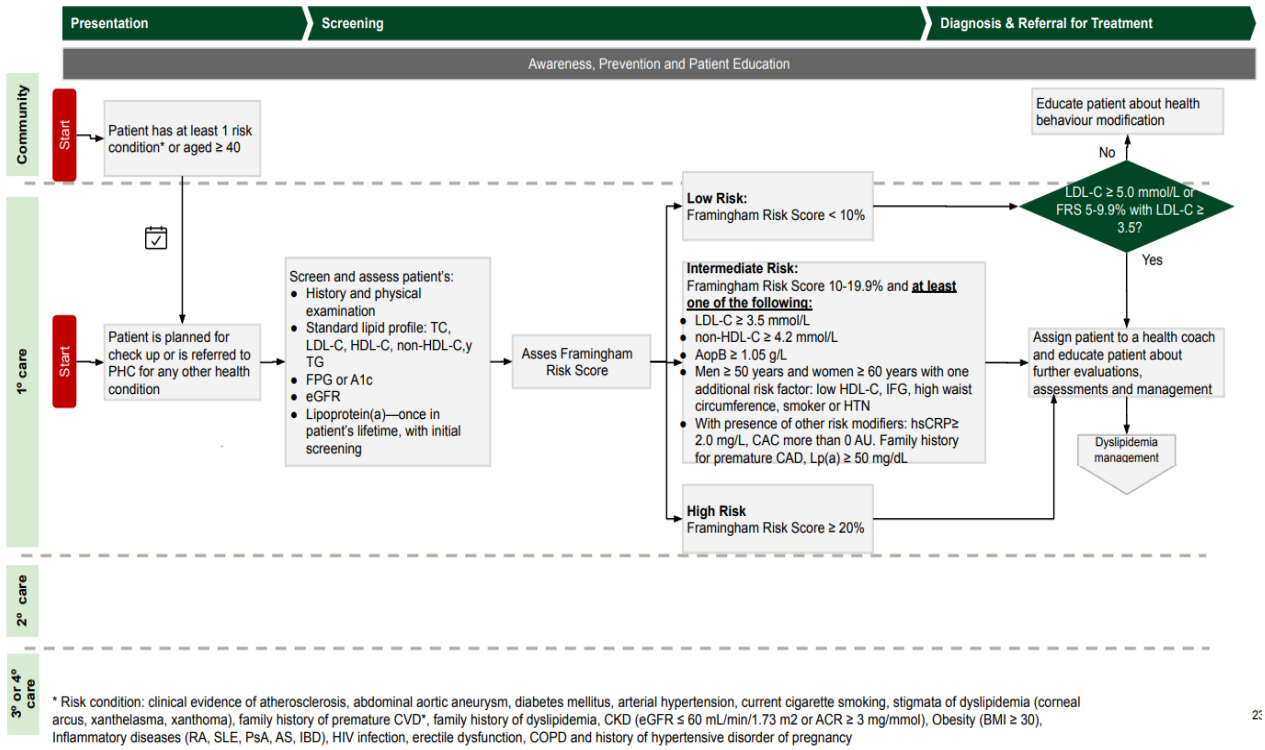
Box 10: When to refer to secondary care :

- Suspected Familial Hypercholesterolemia
- Family history of Premature Heart Disease
- Cholesterol > 290 mg/dl in the absence of Family history
- Triglycerides level > 885 Box11.
- Intolerance to Statins

Box 11: Hypertriglyceridemia

- Rule out Secondary causes : Alcohol, hypothyroidism, obesity, Diabetes, Drug Induced.
- Aim of Treatment is to prevent Pancreatitis and lower the risk Cardiovascular risk.
- Refer Triglycerides higher than > 885mg/dl.
- In Isolated Hypertriglyceridemia treat with Omega 3 or fibrates to a target less then 500mg/dl.
- If the patient is already on Statin and triglyceride is persistently above 500mg/dl then add omega 3 or refer to secondary care.
- If the patient has an indication to start statin and triglyceride is above 500mg/dl then the first line will be statin and they do reduce triglyceride.

R3 DLP Pathway:



* Risk condition: clinical evidence of atherosclerosis, abdominal aortic aneurysm, diabetes mellitus, arterial hypertension, current cigarette smoking, stigmata of dyslipidemia (corneal arcus, xanthelasma, xanthoma), family history of premature CVD*, family history of dyslipidemia, CKD (eGFR ≤ 60 mL/min/1.73 m2 or ACR ≥ 3 mg/mmol), Obesity (BMI ≥ 30), Inflammatory diseases (RA, SLE, PsA, AS, IBD), HIV infection, erectile dysfunction, COPD and history of hypertensive disorder of pregnancy

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Adopted from:

-AHA/ACC lipid guidelines; personalized care to prevent CVD 2020- Cleveland clinic journal of medicine .
-Latest AHA/ACC Guidelines dated 2019 .
-USPSTF guidelines) statin use for the primary prevention of CVD.