Summary of Hyperlipidemia Care Model in Adults

Hyperlipidemia: Introduction

Hyperlipidemia or dyslipidemia can be defined as TC, LDL-C or TG above the 90th percentile or HDL-C below the 10th percentile.

Causes:

- Primary: genetic abnormality in lipid metabolism or transport; multiple defects have been identified.
- Secondary: includes diet, uncontrolled DM, cigarette smoking, excess ETOH, obesity, hypothyroidism, CKD, nephrotic syndrome, cholestatic liver disease, drugs (including thiazide diuretics, beta blockers, cyclosporine, glucocorticoids, amiodorone, protease inhibitors, estrogens, atypical anti-psychotics).

Heart disease is the number 1 cause of death in the US in both men and women; people with elevated cholesterol have twice the risk of heart disease than those with lower levels. 30% of American adults have elevated LDL-C. (CDC)

Hyperlipidemia is one risk factor of ASCVD. It is important to manage all risks.

ABCDE

-Aspirin

-Blood pressure control

-Cholesterol control / Cigarette cessation

-Diet / DM

-Exercise

The goal of treatment of hyperlipidemia is to reduce the risk of ASCVD, including coronary heart disease (ACS, MI, stable or unstable angina, arterial revascularization), ischemic stroke or TIA, or peripheral arterial disease.

Hyperlipidemia: Screening

Dyslipidemia is a predictor of CHD and is generally asymptomatic.

Screening should be based on overall ASCVD risk, including age, gender, smoking status, HTN, DM, obesity and family history of early CHD (CHD in 1st degree male <55 YO or 1st degree female < 65 YO). DM may be considered a CHD equivalent.

- 2013 ACC/AHA: Reasonable to assess ASCVD risk factors every 4 - 6 years for adults 20 - 79 who are free from CHD: ASCVD risk factors include smoking, HTN, DM, TC and HDL-C.
- USPSTF recommendations:

Population	Recommendation	Grade
Men ≥ 35	Screen	A
Men 20 - 35	Screen if increased risk ASCVD	B
Women ≥ 45	Screen if increased risk ASCVD	A
Women 20 - 45	Screen if increased risk ASCVD	B
Men 20 – 35; Women not at increased risk	No recommendation for or against screening	C

Repeat every 5 years; every 1-2 years if near threshold for treatment.

Elderly: there is no upper age limit for testing, and it is appropriate to initially screen at any age. If screening has been normal, may stop at 65 (lipid levels tend to remain flat).

- 2012 AACE recommends more frequent screening all adults > 20 every 5 years; then change to every year or other year men > 45 and women > 55.

Hyperlipidemia: Screening continued

There is considerable intra-individual variation in lipids, with 5 - 10% variation in TC and up to 20% variation in TG. May be related to diet, physical activity, stress, and season (higher in winter). Abnormal screening should be repeated.

LDL-C alone is a poor predictor of CHD risk. Most risk prediction tools use TC and HDL-C. Non-HDL-C (TC - HDL-C) or the ratio of TC/HDL-C are better predictors of CHD risk than LDL-C alone.

Non-HDL-C is favored over apo(b) by National Lipid Association. The American Association Clinical Endocrinologists recommends apo(B) or LDL particle numbers in addition to full fasting lipid panel.

Fasting is not required for TC, HDL-C or LDL-C (measured). Fasting (8 - 12 hours) is required for TG and LDL-C (calculated).

The relationship between CVD risk and lipids is log linear and continuous: there is no threshold below which there is no risk.

Management of hyperlipidemia is based on risk calculation. Use calculator in patients 40 - 75 YO, without CVD, not receiving lipid-lowering therapy. Patient with known ASCVD is considered high risk.

- 2013 AHA/ACC Risk Calculator: calculates **10-yr ASCVD risk**. 9 questions. Same 7 as in Framingham Risk Calculator plus race (Caucasian, African American, other) and DM. Can be found at: http://tools.cardiosource.org/ASCVD-Risk-Estimator/
- Framingham Risk Calculator: calculates **10-yr CHD risk**. 7 questions: age, gender, TC, HDL-C, smoker, systolic BP, medication for HTN. Can be found at: http://cvdrisk.nhlbi.nih.gov/

Hyperlipidemia: Prevention and Management

The 2013 ACC/AHA guidelines have shifted focus from LDL-C target goals (neither recommending for or against a specific goal) to intensity of statin treatment based on risk of ASCVD.

Non-statins are not routinely recommended as add-on therapy, by the 2013 AHA/ACC guidelines, to achieve a specific LDL-C target.

Primary prevention: results in 20% - 30% relative risk reduction of CHD, regardless of baseline LDL-C.

Secondary prevention: significantly reduces the incidence of major vascular events and all-cause mortality. High intensity statin reduces ASCVD events more than lower intensity statin.

The foundation of management of ASCVD risk is lifestyle modification including increasing physical activity (at least 30 minutes activity 4 - 6 times/week), medical nutritional therapy (heart-healthy diet, such as DASH, with low in saturated and trans fats, low in added sugars and high in soluble fiber(fruits, vegetables, whole grains), weigh loss if overweight (3 - 5% can have meaningful impact), smoking cessation, and alcohol moderation. A trial of life style modifications should not delay statin therapy in secondary prevention.

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Page 4: Treatment algorithm based on 2013 ACA/ACC Guidelines

http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/lipid-disorders-in-adults-cholesterol-dyslipidemia-screening

CDC. Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol. United States, 1999–2002 and 2005–2008. MMWR. 2011;60(4):109–14.

Hyperlipidemia: Statins

2013 ACC/AHA Guidelines

Group (40 – 75 YO^)	Statin Dose
Known ASCVD (2°)*	High
LDL-C ≥ 190 mg/dl (1°)**	High
DM, 40 – 75 YO, LDL-C 70 – 189 mg/dl (1°)	Mod; High if risk ≥ 7.5%
No DM, 40 – 75 YO, LDL-C 70 – 189 mg/dl ≥ 7.5% 10-yr ASCVD risk (1°)	Mod to High
As above, 10-yr ASCVD risk 5 – 7.5% (1°)	Consider moderate

^May consider moderate dosage if ↑risk and > 75 YO (shared decision making) *No recommendation for patients with NYHA class II-IV HF or receiving dialysis. **Evaluate for secondary causes. Often familial (screen family).
1°, 2°: primary, secondary prevention

In individuals with 10-yr risk < 7.5%, may consider additional risks including:

- Family HO premature ASCVD
- LDL-C > 160 mg/dL
- HS CRP ≥ 2 mg/dL
- CAC score ≥ 300 Å
- ABI < 0.9

ADA adds for DM < 40 with additional risk, consider mod to high intensity statin.

Uncertain value in risk calculation: Apo(B), CKD, albuminuria, CV fitness. Not recommended: carotid intima-media thickness.

Statin Intensity

- High intensity statin: reduces LDL-C > 50%.
- Moderate intensity statin: reduces LDL 30% - < 50%.
- [Low intensity statin: reduces LDL < 30% - not recommended by guidelines].

Hyperlipidemia: Statins continued

Initiating therapy:

- Shared decision making key.
- Some sources advocate starting statin at target dose (especially if patient has ACS). Others suggest titrating dose to improve tolerance.
- Check ALT at baseline. If OK, repeat only if symptoms or taking other hepatotoxic medications.
- Document pre-existing muscular symptoms to establish baseline.

Monitoring:

- Repeat lipid panel 4 - 12 weeks after target dosage reached. This is checking for adherence, not goal LDL-C.
- Assess adherence to drug and lifestyle q 3 - 12 months.
- Consider statin dose reduction if LDL-C < 40 mg/dL on 2 occasions.

Side effects:

- Muscle effects: range from myalgia (soreness, tenderness with normal CK) to myositis (pain and tenderness with increased CK) to rhabdomyolysis. If CK levels 3 - 5x ULN (& no other explanation), lower or D/C statin. May rechallenge or try a different statin.
- Liver effects: patients with ALT > 3x ULN, lower dose or change statin.
- DM: increased risk of new-onset DM. 0.1 / 100 pt/yr moderate intensity and 0.3 / 100 pt/yr high intensity statin (ADA notes protection against ASCVD events >> risk developing DM).
- Other: GI disturbance, HA, rash, fatigue, ??cognitive decline.

Hyperlipidemia: Statins continued

Cautions:

- Do not use statins in pregnancy.
- Avoid combination of statin and gemfibrozil due to higher risk of rhabdomyolysis.
- Dose adjustments recommended for patients with eGFR < 60 ml/min (except atorvastatin).
- Rosuvastatin drug levels 2-fold higher in patients of Asian descent.
- Strong CYP3A4 inhibitors can increase atorva-, lova-, and simvastatin. Examples include: itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, verapamil, diltiazem, amlodipine, amiodorone.

Management Statin Intolerance

- Discontinue statin. If concern for rhabdomyolysis, check CK, creatinine and consider UA for myoglobinuria.
- Consider other conditions (hypothyroidism, rheumatologic disease, steroid myopathy, etc.) or drug interactions.
- Consider lower dose retrial same drug, alternative drug titration or intermittent statin dosing (QOD of long-acting statin). If unable to tolerate high dose, attempt to use moderate dose statin.
- May consider non-statin, if unable to tolerate alternate statin/dosing.
- Consider referral to lipid specialist.

Treatment Goals (Other)

- 2013 ACC/AHA recommends treat based on risk, others still use lipid treatment goals based on LDL-C, non-HDL-C, or apo(B) targets. (see table 2).

Hyperlipidemia: Other Considerations

PSCK9 Inhibitors

High dose statin often inadequate to treat familial hyperlipidemia. Additional agents may be required. PCSK9 inhibitors now indicated as adjunct in familial hyperlipidemia and in secondary prevention of ASCVD in those who require additional LDL-C lowering. Not indicated for general use in statin-intolerant individuals. Short term trials appear to indicate decrease in CV events and mortality.

HDL-C

- Evidence that raising HDL-C to reduce CV events is not established. 2013 ACC/AHA do not recommend adding drug therapy to ↑ HDL-C in patient on statin. Exercise, weight loss (in overweight or obese individual), smoking cessation, ↓ of saturated fats in diet can raise HDL-C.

Triglycerides

- No evidence for primary prevention of ASCVD.
- Trig/HDL-C ≥ 2.4 strong indicator of insulin resistance.
- ≥ 500 gm/dL treat due to risk for pancreatitis. Fibrates and fish oils can be used (recall gemfibrozil cannot be used with statins, fenofibrate can be used with moderate intensity statin.)

Guidelines are not a substitute for clinical judgment; shared decision making is important for each unique patient.

American Diabetes Association. Cardiovascular Disease and Risk Management. Sec 8 in Standard of Medical Care in Diabetes – 2015. *Diabetes Care 2015;* 38(suppl 1) S49-S57.
American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. *Endocrine Practice* 2012; 18 (suppl 1) S1-S78.

Table 1: Statins

High Intensity Statin Lowers LDL-C ≈ ≥50%	Moderate Intensity Statin Lowers LDL-C ≈ 30% - <50%	Low Intensity Statin Lowers LDL-C ≈ <30%
Atorvastatin (40 –)‡ 80 mg**	Atorvastatin 10 – 20 mg**	Pravastatin 10 – 20 mg#
Rosuvastatin 20 – 40 mg#	Rosuvastatin 5 – 10 mg#	Lovastatin 20 mg*
	Simvastatin 20 – 40 mg*	Pitavastatin 1 mg#†
	Pravastatin 40 – 80 mg#	Simvastatin 10 mg*†
	Lovastatin 40 – 80 mg*	Fluvastatin 20 – 40 mg^†
	Lovastatin extended release 60 mg*	
	Fluvastatin 40 mg BID^	
	Fluvastatin XL 80 mg^†	
	Pitavastatin 2 – 4 mg#†	

HMG-CoA reductase inhibitors (statins) inhibit cholesterol synthesis in the liver. This reduction in synthesis leads to an increased expression of LDL receptors which leads to increased uptake and clearance of LDL-C from the blood. Statins also decrease triglycerides and VLDL and modestly increase HDL-C.

Other effects include: improved endothelial function, reduced inflammation, and decreased platelet aggregation. These latter effects may be clinically evident prior to plaque regression.

‡Atorvastatin 40 mg only used in 1 trial if non-tolerant of 80 mg dose. †No clinical outcomes trials for dosage or formulation *Simvastatin and lovastatin: prodrugs, extensive first pass metabolism by CYP3A4. **Atorvastatin less first pass metabolism by CYP3A4 ^Fluvastatin metabolized primarily by CYP2CY.

Rosuvastatin, pravastatin and pitavastatin are not significantly metabolized by cytochrome P450 enzymes.

Table 2: Prior Treatment Guidelines using Framingham Risk Calculator

Risk	Risk Factors / 10-yr CHD risk	LDL-C, non HDL-C, apo(B)
Very high	Established coronary, carotid or peripheral vascular disease or DM + ≥ 1 RF	< 70, < 100 < 80
High	≥ 2 RF and 10-yr risk > 20% or CHD equivalents, including DM, with no other RF	< 100, < 130 < 80
Mod high	≥ 2 RF and 10-yr risk 10% - 20%	< 130, < 160 < 90
Mod	≥ 2 RF and 10-yr risk < 10%	< 130, < 160 < 90
Low	≥ 1 RF	< 160, <190 < 90

Major Risk Factors: advanced age, ↑ TC, ↑non-HDL-C, ↑ LDL-C, ↓ HDL-C, DM, HTN, cigarette smoking, family HO early CHD.
Additional Risk Factors: Obesity, FH hyper-lipidemia, small, dense LFL-C, ↑ apo (B), ↑LDL-P number, ↑ TG, polycystic ovary syndrome

Table 4: Non-Statin Therapy

Cholesterol absorption inhibitor	Ezetimibe reduces LDL-C ≈ 18%. Moderately reduces CV events, but not mortality. SE: diarrhea, arthralgia, rhabdomyolysis, pancreatitis, thrombocytopenia. May increase anticoagulant effect of warfarin
Fibric Acid Derivatives	Gemfibrozil, fenofibrate and fenofribic acid. SE: GI disturbance, cholelithiasis, hepatitis, myositis. Fenofibrate can increase creatinine. May potentiate effects of oral anticoagulants and hypoglycemics. Gemfibrozil increases serum concentration of statins
Niacin	Increases HDL-C 15% - 35%, decreases TG by 10% - 50% and decreases LDL-C by 5% - 25%. Has been shown in trials to reduce coronary events. SE: flushing, pruritus, GI disturbance, fatigue, glucose intolerance, blurred vision, hyperuricemia, hepatic toxicity
Bile Acid Sequesterant	Cholestyramine, colestipol and colesevelam. Can lower LDL-C by up to 20% and increase HDL-C, but may also raise TG in people with hypertriglyceridemia. SE: constipation, heartburn, nausea, and bloating. Can interfere with absorption other drugs, including statins; colesevelam does not appear to interfere with statin
Fish Oil	Results of recent studies: no convincing evidence for primary or secondary prevention. May be useful in treatment elevated triglycerides. Can be used with statin. SE: Eructation, dyspepsia, aftertaste. Large doses associated with worsening glycemic control and inhibition of bleeding time.
PCSK9 Inhibitors	Alirocumab and Evolocumab. Sub-Q injection q 2 wks. Reduces LDL-C ≈50%. Long term efficiency and safety unknown, $$$. SE local injection reaction.

Table 3: Secondary Causes Dyslipidemia (from 2013 ACC/AHA guidelines)

Secondary Cause	↑ LDL-C	↑ Triglyceride
Diet	Saturated or trans fats, weight gain	Weight gain, high intake refined CHO, excess ETOH
Drugs	Diuretics, cyclosporine, glucocorticoids, amiodorone	Estrogen, SERMs, thiazides, beta-blockers (not carvedilol), glucocorticoids, anabolic steroids, bile acid sequesterants, protease inhibitors, retinoic acid, sirolimus
Diseases	Biliary obstruction, nephrotic syndrome	Nephrotic syndrome, CKJ, lipodystrophy, Cushing's syndrome
Altered States Metabolism	Hypothyroid, obesity, pregnancy	DM (poor control), hypothyroid, obesity, inactivity, pregnancy

Shared Decision Making Discussion Points

- Individual benefit vs. risk
- Patient preference
- Life expectancy
- Cost / insurance
- Age (less clear > 75 YO)
- Comorbidities
- Quality of life
- Clinical judgment
- Tolerability of medication

Treatment Algorithm

Screen adults 20 – 79 for ASCVD risk factors including TC, HDL-C, DM, HTN, smoking every 2 - 5 years; Calculate 10-year ASCVD risk

Risk > 5%

No

Yes

Promote healthy lifestyles (increased exercise, heart-healthy diet, weight loss, tobacco avoidance, moderate ETOH); Manage co-morbidities and other ASCVD risk factors (e.g. DM and HTN, aspirin in appropriate patient); Evaluate for secondary causes (poorly controlled DM, excess ETOH, hypothyroidism, nephrotic syndrome, medications); Consider familial hyperlipidemia, especially with very elevated LDL-C

Clinical ASCVD

Yes

≤ 75 YO: high intensity statin
> 75 YO* or not a candidate for high intensity: moderate intensity statin

No

LDL-C > 190 mg/dl

Yes

≤ 75 YO: high intensity statin
> 75 YO* or not a candidate for high intensity: moderate intensity statin
Addition of non-statin therapy to high intensity may be considered. May need referral to lipid specialist and family screening.

No

DM
LDL-C 70 - 189
40 – 75 YO

Yes

Moderate intensity statin
Consider high intensity statin if estimated 10-yr ASCVD risk ≥ 7.5%

No

No DM
Risk > 5%
LDL-C 70 – 189
40 – 75 YO

Yes

Estimate 10-yr ASCVD risk. If ≥ 7.5% moderate or high intensity statin
If 5 – 7.5%, consider moderate intensity statin

No

Consider statin, in select individuals based on individual risk and preference, with shared decision making

>75 YO* individualize preferences and risk to determine intensity of statin. 2013 ACC.AHA guideline excludes pt with NYHA HF II – IV, ESRD on dialysis and life expectancy < 5 yr. Recommend shared decision making.

Promote healthy lifestyles; manage other risk factors. Involve the patient in shared decision making with evaluation of the potential for ASCVD risk-reduction benefits, adverse effects, and drug-drug interactions. If patient on statin, monitor for adherence and for side effects.
2013 ACC/AHA makes no recommendations for or against specific LDL-C or non-HDL-C goals for primary or secondary prevention of ASCVD.

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. *Circulation 2014;* 129: S1-S45.
National Lipid Association Annual Summary of Clinical Lipidology 2015. *J Clinical Lipidology 2014*; 8: S1 – S36.