Lipid Management for Patients with Statin Intolerance

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OBJECTIVES

• Review current guidelines of lipid management for dyslipidemia
• Define and identify patients who are statin intolerant.
• Discuss the use of non-statin lipid lowering therapies in those who are statin intolerant or cannot achieve desired lipid levels.

AHA/ACC Applying Class of Recommendation

AHA/ACC Applying Level of Evidence

  – http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a
  – Circulation. 2018;000:e000-e000. DOI: 10.1161/CIR.000000000000625

• AACE and ACE Guidelines For Management of Dyslipidemia and Prevention of CVD 2017
  – Endocrine Practice 17;23(suppl 2):1-87
• NLA Recommendations for Patient-Centered Management of Dyslipidemia. 2015
  – J Clin Lipidology In press. Released on line 9/18/15
  – https://www.lipid.org/recommendations
CASE

• 57 y/o male presents with acute MI
• BP 150/85, Smoker, Obesity
• HDL 40, TC 200, LDL 109, TG 210
• Therapy? Yes or No?
• No ASCVD?
• DM?
• ASCVD?

AHA CV Statistics 2018

• ~720,000 will have first coronary event
  – Average age 65 y for men
  – Average age 72 y for women
  – Those ≥45 y/o median survival
    • 8.4 y white males; 5.6 y white females; 7 black males; 5.5 black females
• ~335,000/y will have a recurrent coronary event
• CHD mortality dropped 34.4% from 2005-2015
  AHA CV Statistics. Circulation 18;137:e67-e492

AHA CV Statistics 2018

• 56 million (48.6%) ≥40 y/o eligible for statins based on 2013 ACC/AHA guidelines
  – Increase from 43.2 million (37.5%) from old guideline
  – Most of increase statin use in 60-75 y/o without CVD with 10-y ASCVD risk ≥7.5% – primary prevention
• Statin use and LDL levels have not changed since release of 2013 guideline
  AHA CV Statistics. Circulation 18;137:e67-e492

68-y/o Male

• Chest pain
  – Recent chest pressure episodes with minimal exertion
  – Retrosternal with radiation to L shoulder
  – No SOB, diaphoresis
  – Relieved with rest, has SL NTG but has not used
• PMH: GERD, CAD (stable ischemic heart disease with know effort-induced angina)

• Angiogram 14 y prior
  – Occluded obtuse marginal with collaterals
• Medical treatment for 14 y
  – Isosorbide mononitrate CR 30 mg/d
    • Recently stopped due to c/o headache, dizziness
  – ASA 81 mg/d
  – Metoprolol tartrate 50 mg 2xd
  – NTG SL 0.4 mg prn
• WHAT MED IS MISSING?

• TC 166; TG 298; HDL 30; LDL 76
• CAD with possible unstable angina
  – Refuses stress test or angiogram
  – Wants to continue medical therapy
• Any benefit to raising HDL? No
• LDL 76 so it is < 100. Is there any benefit to lowering LDL in this patient?
  – Further lowering of LDL regardless of baseline LDL further reduces CV events
  – Statins are preferred initial therapy with many studies demonstrating efficacy
PREVALENCE OF HIGH TOTAL CHOLESTEROL

- In 2013-14 ~28.5 million (11.9%) have TC > 240 mg/dL
  - Decrease from 18.3% in 1999-2000
- Due to cholesterol-lowering meds rather than changes in diet
  AHA CV Statistics. Circulation 18;137:e67-e492

REDDUCING ASCVD RISK

- Decreasing elevated levels of cholesterol lowers ASCVD risk
  - More LDL lowering leads to greater CV benefit
- Cholesterol lowering options
  - Lifestyle changes
  - Drugs – Statins & non-statins

HMG-CoA Reductase Inhibitors (STATINS)

- Most potent oral LDL-lowering agents
  - Amount of effect varies with agent
- Most studied of lipid-lowering drugs
  - Many positive outcomes studies for primary and secondary prevention
- Recommended as the primary pharmacologic agent to achieve target LDL goals
- Main issue is adherence due to real or perceived muscle adverse effects – statin intolerance

Adherence to Statins Following a MI Among Medicare Beneficiaries

- Retrospective cohort study 2007-2012
  - Those who filled Rx for Atorvastatin 40-80 mg or Rosuvastatin 20-40 mg within 30d of discharge

<table>
<thead>
<tr>
<th></th>
<th>6 mon</th>
<th>2 yrs</th>
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<tbody>
<tr>
<td>High-intensity &amp; high adherence (≥ 80% of days)</td>
<td>59%</td>
<td>42%</td>
</tr>
<tr>
<td>↓ to low/mod intensity</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>Low adherence (&lt;80% of days)</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td>Discontinued statin</td>
<td>12%</td>
<td>19%</td>
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</table>

JAMA Cardiol 17;2:800-95
### Relative LDL-lowering Efficacy of Statin and Statin-based Therapies – FDA

<table>
<thead>
<tr>
<th>Statin</th>
<th>Fluvastatin XL 80 mg</th>
<th>Fluvastatin 40 mg</th>
<th>Pitavastatin 1-4 mg</th>
<th>Lovastatin 40-80 mg</th>
<th>Pravastatin 10-40 mg</th>
<th>Simvastatin 10-20 mg</th>
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</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>80 mg 2 mg 4 mg 80 mg</td>
<td>5 mg 10/10 mg 40 mg</td>
<td>4 mg 80 mg 40 mg</td>
<td>20 mg 38%</td>
<td>40 mg 41%</td>
<td>10 mg 10/20 mg</td>
</tr>
<tr>
<td>20 mg</td>
<td>4 mg 80 mg 80 mg</td>
<td>10 mg 10/20 mg 80 mg</td>
<td>20 mg 38%</td>
<td>40 mg 41%</td>
<td>40 mg 41%</td>
<td>10 mg 10/20 mg</td>
</tr>
<tr>
<td>40 mg</td>
<td>80 mg 80 mg 40 mg</td>
<td>20 mg 10/40 mg 80 mg</td>
<td>55%</td>
<td>63%</td>
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<td>63%</td>
</tr>
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</table>

**Relative LDL-lowering Efficacy of Statins**

<table>
<thead>
<tr>
<th>Intensity</th>
<th>High intensity</th>
<th>Moderate intensity</th>
<th>Low intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50%</td>
<td>Atorvastatin (40 mg)</td>
<td>Atorvastatin 10-20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 40 mg + Ezetimibe 10 mg</td>
<td>Simvastatin 20-40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td>Fluvastatin 40 mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg</td>
<td>Fluvastatin 40 mg</td>
<td>Fluvastatin 40 mg</td>
</tr>
</tbody>
</table>

**STATIN MUSCLE COMPLAINTS**

- RCTs indicate low rates of myalgia (<5%)
- "Real world" data suggest complaints ~30%

**Consequences**
- < likely to achieve LDL goals
- Increased risk for CV events
- Higher healthcare costs

**NOCEBO EFFECT**

- Inverse of placebo effect
- Expectations of harm, usually subjective, from: informed consent in trials, warnings adverse effects, information in media about dangers, etc.
- An explanation for high rate of [statin] muscle symptoms … in clinical practice?
  - Similar symptoms statin vs. placebo in most RCTs

**STATIN INTOLERANCE**

- Most statin intolerance is subjective due to the ‘nocebo’ effect
- Patients previously characterized as ‘statin-intolerant’
  - Not aware taking a statin
  - Up to 70% tolerated atorvastatin 20 mg/d

**NOCEBO EFFECT**

- "Reports of statin adverse events in the news and on the Internet … expectations of harm, or the “nocebo” effect that complicate efforts to reintroduce the same or alternative statin.”
STATIN INTOLERANCE

• “true … intolerance is uncommon”
• Assess with use of a systematic approach
• http://www.acc.org/StatinIntoleranceApp
  – Comprehensive evaluation/management of potential side effects
  – Facilitates the clinician-patient discussion
  – Questions to evaluate symptoms with step-by-step guidance
  – Statin comparison tool for statin characteristics

ACC Role of Non-Statins. JACC 17:70:1785-822

STATIN INTOLERANCE – ACC 2017

• Complete history
  – Are symptoms consistent with statins
  – Myalgias or weakness large proximal muscle groups
• Other causes must be ruled out
  – e.g., hypothyroidism, vit D deficiency, recent exercise and drug interactions
• Increased risk
  – Women, Asian descent, and elderly
  – May be able to tolerate a lower statin intensity, an alternative statin, or alternative dosing strategies

ACC Role of Non-Statins. JACC 17:70:1785-822

STATIN KINETICS

<table>
<thead>
<tr>
<th>Lipophilicity</th>
<th>Metabolism</th>
<th>( t_{1/2} ) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Yes</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Yes</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Yes</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Yes</td>
<td>Glucuronidation</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No</td>
<td>Sulfation, oxidation, -OH</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>No</td>
<td>Biliary, minor CYP2C9-19</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Yes</td>
<td>CYP3A4</td>
</tr>
</tbody>
</table>

Fig. 2. Lipophilicity and half-life of various statins.

J Am Coll Cardiol 17;70:1290-301


STATIN-ASSOCIATED MUSCLE SYMPTOMS – STRATEGY

• No RCTs on management strategies
  – Rechallenge with same statin (lower dose)
  – Statin switch
  – Nondaily dosing with long half-life statins (atorvastatin, rosuvastatin) dosed 3 times/wk or once/wk (no CV outcome studies)
  – Nonstatin therapy only if “statin intolerance has been systematically & rigorously evaluated & documented” or add-on to tolerated dose of statin


J Cardiol Clin 18;36:225-31

ACC Role of Non-Statins. JACC 17:70:1785-822

STATIN-ASSOCIATED MUSCLE SYMPTOMS – STRATEGY

• Same-statn rechallenge
  – Up to 70-80% tolerable and 50% effective
• Switching statin
  – About 30-50% may tolerate & achieve LDL goal
• Tolerability/efficacy of nondaily dosing
  – eg, qod, once weekly
  – 80-100% tolerability with average LDL efficacy
  – CV benefit is unknown


25 26 27 28 29 30
COGNITIVE COMPLAINTS

• Rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion)
  – Frequency is unknown
  – Generally not serious & no evidence for progression or permanent impairment
  – Onset 1 day – years
  – Objective documentation is lacking

NLA Panel. J Clin Lipidology 14:8:S72-81

HYPERGLYCEMIA RISK

• Increased DM risk 10-12%
  – 9-27% observational


• “Mild elevations in blood glucose and/or an increased risk of new onset T2DM … do not outweigh the benefits of statin therapy for ASCVD risk reduction”

AACE/ACE Guidelines 2017 Endocr Pract 17;23 (Suppl 2):1-87

STATIN-ASSOCIATED MUSCLE SYMPTOMS – STRATEGY

• “our clinic, the tolerability and efficacy rates of same-statin rechallenge and statin switch have been similar … same-statin rechallenge can be a useful strategy to try in willing patients.”


STATIN INTOLERANCE – ACC 2017

• Non-statins are not an alternative to evidence-based statin therapy unless statin intolerance has been systematically and rigorously evaluated and documented

Ezetimibe Added to Statin Therapy after ACS, IMPROVE-IT

• 18,144 with ACS within 10d
  – LDL 50-100 if on meds OR 50-125 if not – 93.8
  – Simvastatin 40-80 mg/d ± Ezetimibe 10mg/d
• LDL with combination 54 vs. monotherapy 70
• CV death, nonfatal MI or CVA, UA with rehospr, coronary revasc over 7 years
  – 32.7% vs. 34.7% (HR 0.936; P=0.016) NNT 50
• No benefit seen in all-cause or CV mortality

NEJM 15;372:2387-97

PROOF THAT LOWER IS BETTER – LDL AND IMPROVE-IT

• LDL hypothesis – excess LDL as causal factor for ASCVD
  – Assumes ↓ LDL ↓ CV events – regardless of agent
  – ↓ LDL by ~40 leads to 23% decrease in major CV events over 5 y (CTT. Lancet 05;366:1267-78
• Statin hypothesis – LDL-lowering alone does not account for the CV benefits
  – Statins have unique benefits contributing to efficacy

Jarcho JA & Kearney IP. Edit. NEJM 15;372:2448-50
EZETIMIBE

• "statistically significant but clinically modest”
  JAAC 2016 on line. doi:10.1016/j.jacc.2016.03.519
• First non-statin that should be considered when added to moderate-dose statin
  – Consider as monotherapy in statin-intolerance
  – Combination with statins to further reduce LDL
  AACE/ACE Guidelines 2017 Endocr Pract 17;23 (Suppl 2):1-87

NEW LIPID LOWERING AGENTS
PCSK9 INHIBITORS

• Evolocumab (Repatha)
• Alirocumab (Praluent)
• Monoclonal Ab that inhibits PCSK9
• SQ dosing q2wks
• ~ $13,000-14,000/y – Will come back to this!!!

PCSK9 INHIBITOR STUDIES

• Evolocumab in ASCVD & LDL > 70 on statins
  – Major adverse CV events
    • ↓ 15% (ARR 1.5%) NNT 74 for 2 y
  – No difference in CV or all-cause mortality
    FOURIER NEJM 17;376:1713-22
• Alirocumab in ACS & LDL >70 on statins
  – Major adverse CV events
    • ↓ 15% (ARR 1.6%) at 2.8 y with NNT 64
    • Base line LDL > 100; ↓ 24% (ARR 3.4%) with NNT 29
  – All-cause mortality: LDL >100; ↓ 29% (ARR 1.7%)
    ODYSSEY. American College of Cardiology – 67th Scientific Sessions March 10, 2018

Proprotein Convertase Subtilisin Jexin type 9 (PCSK9) Inhibitors

• LDL binds to hepatic LDL-receptors
  – Transports LDL into liver cells & ↓ plasma LDL
    • More hepatic LDL-receptors – more LDL removed
    – PCSK9 degrades LDL receptor – ↓ receptors
    • ↓ removal of circulating LDL – ↑ plasma LDL
• Anti-PCSK9 human monoclonal antibodies
  – Prevents PCSK9 binding to LDL receptors on liver
  – Increases hepatic LDL receptors
  – Decreases LDL up to 60-65%

EZETIMIBE

• IMPROVE-IT “… suggest that all reductions in LDL …are of equivalent benefit.”
  Jarcho JA & Keaney JF. Edit. NEJM 15;372:2448-50
• First non-statin that should be considered when added to moderate-dose statin
• May consider for monotherapy especially in statin-intolerant
• Can be used in combination with statins to further reduce both LDL and ASCVD risk
  AACE/ACE Guidelines 2017 Endocr Pract 17;23 (Suppl 2):1-87
USE OF PCSK9 INHIBITORS

• “CV benefit may be accrued even when LDL-C levels are reduced at levels well below those recommended by the current guidelines”
  Cardiol Clin 18;36:241-56

• “evidence to date, evolocumab should used in stable atherosclerotic patients with CVD and alirocumab in the ACS setting until a class effect can be confirmed.”
  Sabatine MS. FOURIER lead investigator interview. Medscape 3/10/18.

Cost-effectiveness Analysis of PCSK9 Inhib Based on the FOURIER Trial

• Annual cost of exetimibe ~$3818 vs. PCSK9 inhib ~$14,542 added to statin
• Adding PCSK9 inhibitors to statins estimated to prevent more cardiac events than adding ezetimibe
• NNT for 5 y to prevent 1 cardiac event
  – Ezetimibe 41 vs. PCSK9 37
• Cost-effectiveness per life-year gained
  – Ezetimibe $182,000 vs. PCSK9 $411,000
  JAMA 17;8:748-50

CHALLENGES WITH PCSK9 INHIBITORS

• Because of cost most insurers require prior authorization
• Data from 45,029 new Rx claims
  – 79-85% initial rejection
  – 52.8% rejected after appeal
  – Patients did not fill 34.7%
• Better approval rate by specialists and good documentation of reasons for use
  Postgrad Med 17;129:801-10

Amgen Cuts Repatha’s (Evolucumab) Price 60% as Scrutiny of Drug Costs Heats Up

• Decreased from ~$14,000/y to $5850/y
• Designed to lower out-of-pocket costs esp. for Medicare patients
  Medscape News. 10/24/18

Praluent Price to Drop for Insurers That Ease Rx Restrictions

• “offer payers that agree to reduce burdensome access barriers for high-risk patients a further reduced net price for Praluent (alirocumab).”
• No specific price but at projected cost-effectiveness $4,500-8,000/y in higher-risk with LDL ≥100 despite intensive statin therapy
  https://www.medpagetoday.com/meetingcoverage/acc/71691

ATP III: Updated LDL-C Goals, Treatment Cutpoints

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: CHD or CHD risk equivalents (10-y risk ≥20%)</td>
<td>&lt; 100 (optional: &lt; 70)</td>
<td>≥ 100</td>
<td>≥ 100 (&lt; 100: consider drug options)</td>
</tr>
<tr>
<td>Moderately high risk: ≥ 2 RFs (10-y risk 10-20%)</td>
<td>&lt; 130 (optional: &lt; 100)</td>
<td>≥ 130</td>
<td>≥130 (100-129: consider drug options)</td>
</tr>
</tbody>
</table>
**STATIN BENEFIT GROUPS**

- ASCVD risk reduction benefit clearly exceeds potential for adverse effects in adults
  - ASCVD – high-intensity
  - LDL ≥190 mg/dL – high intensity
  - 40-75 y with DM (no ASCVD) with LDL 70-189
    - Moderate to high intensity (if risk ≥ 7.5%)
  - No ASCVD or DM who are 40-75 y with LDL 70-189 & estimated 10-y ASCVD risk
    - 5-7.5% risk – moderate intensity
    - ≥ 7.5% risk – moderate or high intensity

ACC/AHA Guidelines. Circulation 14;129:S1-S45

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**AHA CV STATISTICS 2018**

- 56 million (48.6%) ≥40 y/o eligible for statins based on 2013 ACC/AHA guidelines
  - Increase from 43.2 million (37.5%) from old guideline
    - Most of increase statin use in 60-75 y/o without CVD with 10-y ASCVD risk > 7.5% – primary prevention
  - Statin use and LDL levels have not changed since release of 2013 guideline

AHA CV Statistics. Circulation 18;137:e67-e492

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**EVIDENCE FOR MORE INTENSIVE CHOLESTEROL LOWERING**

- IMPROVE-IT “… suggest that all reductions in LDL …are of equivalent benefit.”
  - Jarcho JA & Keaney JF. Edit. NEJM 15;372:2448-50
- “CVD risk diminishes … [with]decrease in LDL-C … no evidence that the benefit tails off”
- “LDL-C goals with statins, PCSK9 inhibitors and ezetimibe produces similar reductions in CVD incidence”

Curr Opin Lipidol 17:26-29:1-9

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**Risk Stratification and Treatment Implications for Patients with ASCVD**

- Consider non-statins
  - Less-than-anticipated reductions in LDL despite max tolerated statin (<50%)
  - Achievement of anticipated LDL reduction (eg, >50%) but still elevated LDL (absolute level)
  - Use as monotherapy only if statin-intolerant


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**Stable ASCVD With Comorbidities on Statin**

- Does NOT ↓ LDL ≥ 50% on max tolerated statin (consider LDL < 70 or non-HDL-C < 100)
- Clinician-patient discussion factors to consider
  - Potential further ASCVD risk reduction from adding non-statins
  - Potential for adverse events or drug interactions
  - Patient preferences

ACC Role of Non-statins. JACC 17:70;1785-822
Stable ASCVD With Comorbidities on Statin

• Optional non-statins to consider
• Consider Ezetimibe or PCSK9 inhibitor
• If requires >25% LDL ↓ a PCSK9 inhibitor may be preferred as initial non-statin
  – Consider only if on max tolerated statin with < 50% LDL ↓ (consider LDL ≥70 or non-HDL-C >100)
  – Strongly consider if fully statin intolerant & ezetimibe or bile acid binder with < 50% LDL ↓ (consider LDL ≥70 or non-HDL-C >100)

ACC Role of Non-statin. JACC 17;70:1785-822

ASSESSING CV RISK

• Pooled cohort equations
  – “single most robust tool for estimating 10-year risk in U.S. adults 40 to 75 years of age”
  – Strength – inclusion of major risk factors
  – Limitation – age dominates individual risk scoring with increasing age
  • Population risk factor but “does not necessarily reflect individual risk”

CLINICAL ASCVD

Not at Very High-Risk

• ≤ 75 y
  – High-intensity statin: Goal LDL ≥ 50% (Class I)
    • If not tolerated use moderate-intensity (Class I)
  – If max statin & LDL ≥ 70 adding ezetimibe may be reasonable (Class IIb)

• > 75 y
  – Initiate moderate or high-intensity statin is reasonable (Class IIa)
  – Continue high-intensity is reasonable (Class IIa)

Very High Risk*

• Major ASCVD events
  – ACS within 12 mo
  – I/o MI (other than recent ACS listed above)
  – History of ischemic stroke
  – Symptomatic PAD

• High-risk conditions
  – ≥ 65 y
  – Heterozygous familial hypercholesterolemia
  – Prior CABG or PCI outside of ASCVD event(s)
  – Diabetes mellitus
  – Hypertension
  – CKD (eGFR 15-59)
  – Current smoking
  – LDL ≥100 despite maximally tolerated statin and ezetimibe
  – History of congestive HF
**CLINICAL ASCVD**

**Very High-Risk**

- High-intensity or maximal statin (Class I)
- If on max statin & LDL ≥ 70 adding ezetimibe is reasonable (Class IIa)
- If PCSK9-I is considered add ezetimibe to statin before adding (Class I)
- If on clinically judged maximal LDL therapy & LDL ≥ 70 adding PCSK9-I is reasonable (Class IIa)

**Risk-Enhancing Factors**

- FHx premature ASCVD (males, age <55 y; females, age <65 y)
- Primary hypercholesterolemia (LDL ≥ 160-189; non–HDL-C ≥ 190-219)
- Metabolic syndrome
- CKD (eGFR 15-59 with or without albuminuria)

**Risk-Enhancing Factors**

- Chronic inflammatory conditions (psoriasis, RA, or HIV/AIDS)
- Premature menopause (<40 y) and pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia
- High-risk race/ethnicities (e.g., South Asian ancestry)

**PRIMARY PREVENTION**

- 20-39 y
  - Consider statin if FHx of premature ASCVD & LDL ≥ 160
- LDL ≥ 190: high-intensity statin (Class I)
- DM & 40-75 y: moderate-intensity statin regardless of risk (Class I)
- Risk assessment to consider high-intensity with multiple risk factors (Class IIa)

**DM**

- 10-y ASCVD risk ≥ 20%
  - Reasonable to add ezetimibe to statin to ↓ LDL ≥ 50% (IIb. C-LD)
- > 75 y, reasonable for statin after clinician-patient discussion of benefits/risks (IIb. C-LD)
- 20-39 y with T2DM ≥ 10 y or T1DM ≥ 20 y, albuminuria, eGFR < 60, retinopathy, neuropathy, or ABI <0.9, statin reasonable (IIb. C-LD)
**PRIMARY PREVENTION**

- 40-75 & LDL < 190 without DM
  - < 5% risk: Low Risk
    - Lifestyle (Class I)
  - 5% to < 7.5%: Borderline Risk
    - If risk enhancers then discussion on mod-intensity statin (Class IIb)
  - ≥7.5% to < 20%: Intermediate Risk
    - If risk enhancers favor statin, start mod-intensity (Class I)
  - ≥ 20%: High Risk
    - Start high-intensity statin (Class I)

**Primary Prevention >75 y**

- LDL 70-189 mg/dL initiating a moderate-intensity statin may be reasonable (IIb. B-R)
- May be reasonable to stop statin when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits
- 76-80 y with LDL 70-189 may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy

**STATIN ADVERSE EFFECTS**

- Side effects that are not severe
  - Reassess and to rechallenge to achieve maximal LDL lowering by modified dosing regimen, an alternate statin or in combination with nonstatin therapy (I. B-R)
- Increased DM risk or new-onset DM
  - Continue statin, with added emphasis on adherence, net clinical benefit, and the core non-pharmacologic principles (I. B-R)

**STATIN ADVERSE EFFECTS**

- If increased ASCVD risk with severe muscle symptoms or recurrent muscle symptoms despite appropriate statin rechallenge, reasonable to use RCT proven nonstatin therapy (IIa. B-R)

**STATIN ADVERSE EFFECTS**

- Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS (III: No Benefit B-R)
- Routine CK and transaminases are not useful (III: No Benefit. C-LD)

Framingham risk scoring is applied to determine 10-year risk

*Endocr Pract 17;23:207-38 in AACE/AACE Guidelines 2017
*Endocr Pract 17;23 (Suppl 2):1-87*
**DYSLIPIDEMIA KEY POINTS**

- **LDL** is a major risk factor for CV disease
  
  Cardiol Clin 18;36:241-56

- CV risk is reduced when LDL is decreased
  
  - For each 40 ↓ in LDL ASCVD events ↓ by ~20% after 1 y with statins
    
    CTT. Lancet 05;366:1252-78  
    Curr Opin Lipidol 17;28:291-9
  
  - Statin therapy > placebo
    
    JAMA 01;285:1711-8
  
  - High-intensity > moderate-intensity statin
    
    NEJM 04;350:1495-504
  
  - Ezetimibe > placebo added to a statin
    
    NEJM 15;372:2567-97

**Evidence for More Intensive Cholesterol Lowering**

- “there is no attenuation of … that CVD risk diminishes by about 1/5 for each 40 decrease in LDL-C. … no evidence that the benefit tails off”
  
  Curr Opin Lipidol 17;28:291-9

- “attainment of therapeutic LDL-C goals with statins, PCSK9 inhibitors and ezetimibe produces similar reductions in CVD incidence”
  
  Curr Opin Lipidol 17;28:291-9

**68-y/o Male**

- **c/c:** chest pressure with minimal exertion

- PMH: SIHD with effort-induced angina

- Angiogram 14 y prior
  
  – Occluded obtuse marginal with collaterals
  
  – Patient opted for medical tx
  
  – ASA 81 mg/d; Isosorbide mononitrate
  
  – Metoprolol tartrate 50 mg 2xd

- TC 166; TG 298; HDL 30; LDL 76

- **What Med Is Missing?**

- h/o myopathy with pravastatin & reluctant to restart a statin. Options?
  
  – Educate importance of lowering CV risk with LDL lowering regardless of his baseline LDL
  
  – Start very low dose, even qod

- If tolerates statin which are recommended and what is the goal of therapy?
  
  – Atorvastatin or Rosuvastatin
  
  – Adjust dose upward as he tolerates
  
  – High intensity dose to decrease LDL > 50%
  
  – Absolute LDL <70?