Lipid Management for Patients with Statin Intolerance

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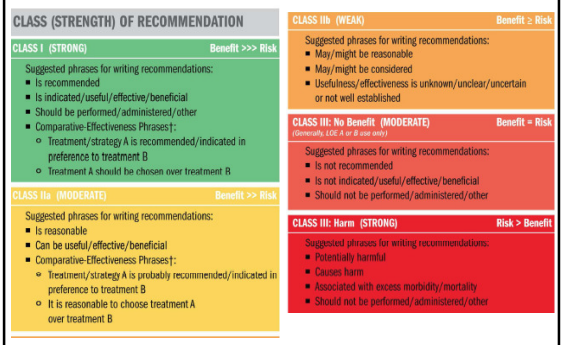
1

OBJECTIVES

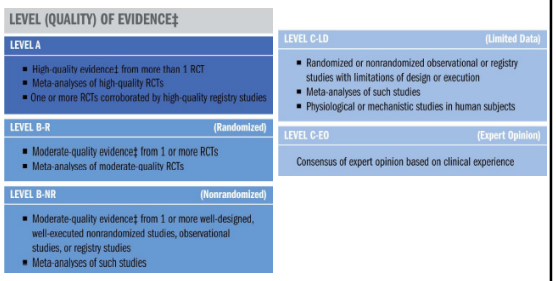
- Review current guidelines of lipid management for dyslipidemia
- Define and identify patients who are statin intolerant.
- Discuss the use of non-statin lipid lowering therapies in those who are statin intolerant or cannot achieve desired lipid levels.

2



AHA/ACC Applying Class of Recommendation

3



AHA/ACC Applying Level of Evidence

4

- 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic CV Risk in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines
  - http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a
- 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol
  - Circulation. 2018;000:e000–e000. DOI: 10.1161/CIR.0000000000000625

5

- 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

6

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?

7

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

8

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

9

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)

10

- 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?

11

- 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

12

- c/o myopathy with pravastatin & reluctant to restart a statin. OPTIONS?
  - Education on importance of lowering CV risk with LDL lowering regardless of his baseline LDL
  - Start very low dose, even qod
  - Atorvastatin 5mg, Rosuvastatin 5 mg
- If he tolerates the statin which statins 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%

13

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

14

LDL Cholesterol

- Remains the cornerstone of therapy
- Increased cholesterol carried by circulating apolipoprotein (apo) B–containing lipoproteins (non-HDL-C and LDL-C, termed atherogenic cholesterol)
  - A root cause of atherosclerosis
  - Key underlying process contributing to most clinical ASCVD events

NLA Guidelines 2015

15

REDUCING ASCVD RISK

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

Lancet 15;385:1397-1405 Curr Opin Lipidol 17;28:291-9
Role of Non-Statins. JACC 17:70:1785-822

16

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

17

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

	6 mon	2 yrs
High-intensity & high adherence (≥ 80% of days)	59%	42%
↓ to low/mod intensity	9%	13%
Low adherence (<80% of days)	17%	19%
Discontinued statin	12%	19%

JAMA Cardiol 17;2:890-95

18

Relative LDL-lowering Efficacy of Statin and Statin-based Therapies – FDA

Atorva	Fluva	Pitava	Lova	Prava	Rosuva	Vytorin *	Simva	%↓ LDL-C
-----	40 mg	1 mg	20 mg	20 mg	-----	-----	10 mg	< 30%
10 mg	80 mg	2 mg	40 or 80 mg	40 mg	-----	-----	20 mg	38%
20 mg	-----	4 mg	80 mg	80 mg	5 mg	10/10 mg	40 mg	41%
40 mg	-----		-----	-----	10 mg	10/20 mg	80 mg	47%
80 mg	-----		-----	-----	20 mg	10/40 mg	-----	55%
	-----		-----	-----	40 mg	10/80 mg	-----	63%

19

Relative LDL-lowering Efficacy of Statins

High intensity	Moderate intensity	Low intensity
≥ 50%	30-50%	< 30%
• Atorvastatin (40 mg) 80 mg • Rosuvastatin 20-40 mg • Simvastatin 40 mg + Ezetimibe 10 mg	• Atorvastatin 10-20 mg • Rosuvastatin 5-10 mg • Simvastatin 20-40 mg • Pravastatin 40-80 mg • Lovastatin 40-80 mg • Fluvastatin XL 80 mg • Fluvastatin 40 mg BID • Pitavastatin 1-4 mg	• Simvastatin 10 mg • Pravastatin 10-20 mg • Lovastatin 20 mg • Fluvastatin 20-40 mg

FDA

2018 Cholesterol Clinical Practice Guidelines. Circulation. 2018;000:e000–e000. DOI:10.1161/CIR.0000000000000625

20

STATIN MUSCLE COMPLAINTS

- RCTs indicate low rates of myalgia (<5%)

Atherosclerosis. Online 6/12/18. https://www.atherosclerosis-journal.com/article/S0021-9150(18)30309-5/fulltext

- "Real world" data suggest complaints ~30%

Cardiovasc Drugs Ther 05;19:403-14 J Clin Lipidol 12;6:208-15
Ann Intern Med 13;158:526-34

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

Clinical and economic consequences of statin intolerance in the United States: results from an integrated health system. J Clin Lipidol 17;11:70-9

21

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

J Clin Lipidol 16;10:739-47

22

STATIN INTOLERANCE

- Most statin intolerance is subjective due to the 'nocebo' effect

Postgrad Med 17;129:801-10 J Am Coll Cardiol 17;70:1290-301

- Patients previously characterized as 'statin-intolerant'
  - Not aware taking a statin
  - Up to 70% tolerated atorvastatin 20 mg/d

J Clin Lipidol. 2014;8(6):554–561

23

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."

J Am Coll Cardiol 17;70:1290-301

24

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

25

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

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

26

STATIN INTOLERANCE – ACC 2017

- Stop statin until resolution of symptoms
  - Rechallenge to verify recurrence of muscle-related symptoms
- Statin intolerance – no universal definition
  - Unacceptable muscle-related symptoms that resolve with stopping statin and recur with rechallenge
  - After at least 2-3 statins
  - With different metabolic pathways & lipophilicity
  - 1 statin at the lowest approved dose

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

27

STATIN KINETICS

	Lipophilicity	Metabolism	$t_{1/2}$ (h)
Atorvastatin	Yes	CYP3A4	**15-30**
Fluvastatin	Yes	CYP2C9	0.5-2.3
Lovastatin	Yes	CYP3A4	2.9
Pitavastatin	Yes	**Glucur-onidaton**	12
Pravastatin	**No**	**Sulfation, oxidation, -OH**	1.3-2.8
Rosuvastatin	**No**	**Biliary, minor CYP2C9 -19**	**19**
Simvastatin	Yes	CYP3A4	2-3

J Am Coll Cardiol 17;70:1290-301

28

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

Joy TR & Brennan ET. Edit. J Clin Lipid. online 6/25/16 JACC 17;70:1290-301
Cardiol Clin 18;36:225-31 ACC Role of Non-statins. JACC 17;70:1785-822

29

STATIN-ASSOCIATED MUSCLE SYMPTOMS – STRATEGY

- Same-statin 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

Joy TR & Brennan ET. Edit. J Clin Lipid. In Press, online 25 June 2016

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

FDA Safety Announcement 2/28/12. http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm
NLA Panel. J Clin Lipidology 14:8:S72-81

31

HYPERGLYCEMIA RISK

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

ACC Update http://www.acc.org/latest-in-cardiology/articles/2015/08/11/09/16/statin-intolerance-not-a-myth?w_nav=ACCUpdate&w_pub=ACCUpdate150821&WT.mc_ev=EmailOpen

- **"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

32

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**."

Joy TR & Brennan ET. Edit. J Clin Lipid. In Press, online 25 June 2016

33

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

34

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 rehosp, 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

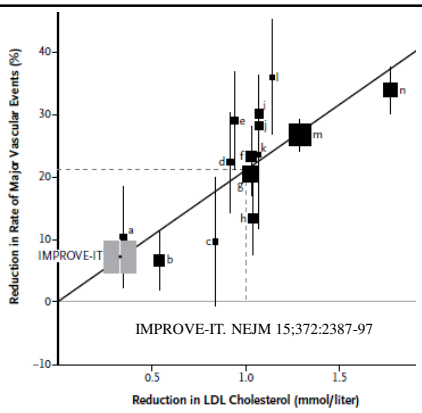
35

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 & Keaney JF. Edit. NEJM 15;372:2448-50

36



IMPROVE-IT. NEJM 15;372:2387-97

37

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

ACC Role of Non-Statins 2017. J Am Coll Cardiol 16;68:92-125

- 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

38

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

ACC Statin Intolerance Guideline 2016. J Am Coll Cardiol 16;68:92-125

  - 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

39

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%

NEJM 15;372:1489-99 Postgrad Med 17;129:801-10 Cardiol Clin 18;36:241-56

40

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!!!**

Pharmacist's Letter/Prescriber's Letter. October 2015 Med Lett Drug Ther 15;57:140-1e

41

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 NTT 29
  - All-cause mortality: LDL >100: ↓ 29% (ARR 1.7%)

ODYSSEY. American College of Cardiology – 67th Scientific Sessions March 10, 2018

42

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. https://www.medscape.com/viewarticle/893754

43

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

44

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

45

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 https://www.medscape.com/viewarticle/903947?nlid=125713_3901&src=wnl_newsalrt_181024_MSCPEDIT&uac=212107EV&impID=1779873&faf=1

46

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

47

ATP III: Updated LDL-C Goals, Treatment Cutpoints

Risk Category	LDL Goal	Initiate TLC	Consider Drug Therapy
High risk: CHD or CHD risk equivalents (10-y risk >20%)	< 100 (optional: < 70)	≥ 100	≥ 100 (< 100: consider drug options)
Moderately high risk: ≥ 2 RFs (10-y risk 10–20%)	< 130 (optional: < 100	≥ 130	≥130 (100-129: consider drug options)

48

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

49

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  - 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

50

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;28:291-9

51

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

Latest in Cardiology. Expert Analysis. Orringer CE. 4/16/18. http://www.acc.org/latest-in-cardiology/articles/2018/04/16/14/51/risk-stratification-and-treatment-implications-for-patients-with-atherosclerotic-cvd

52

Risk Stratification and Treatment Implications for Patients with ASCVD

- After clinician patient discussion the decision is to use non-statins
  - Importance of continuing statin
  - Consider expected LDL lowering efficacy of the agent to be added
    - Ezetimibe ~ 20%; PCSK9 inhibitors ≥50%
  - Consider and carefully discuss with patient the expected benefits, side effects and cost of therapy

J Am Coll Cardiol 2017;70:1785-1822

Latest in Cardiology. Expert Analysis. Orringer CE. 4/16/18. http://www.acc.org/latest-in-cardiology/articles/2018/04/16/14/51/risk-stratification-and-treatment-implications-for-patients-with-atherosclerotic-cvd

53

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

54

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-statins. JACC 17;70:1785-822

55

Grundy SM, et al.
2018 Cholesterol Clinical Practice Guidelines

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

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56

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"

57

ASSESSING CV RISK

- Genetic and acquired risk factors may account for differences to individual CV risk
  - If present helps confirm a higher risk state
- Intermediate CV risk use risk-enhancing factors to individualize decision making
  - The greater risk may support a decision to start meds

58

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)

59

Very High Risk*

- Major ASCVD events
  - ACS within 12 mo
  - h/o MI (other than recent ACS listed above)
  - History of ischemic stroke
  - Symptomatic PAD
- High-risk conditions
  - ≥65 y
  - Heterozygous familial hyperchol
  - 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

*Very high risk h/o multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions

60

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)

61

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)

62

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)

63

Risk-Enhancing Factors

- Lipid/biomarkers
  - Primary hypertriglyceridemia (≥175)
  - hsCRP ≥2.0
  - Lp(a) ≥50
  - apoB ≥130
    - Corresponds to LDL >160
  - ABI <0.9
-

64

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 (ClassI)
  - Risk assessment to consider high-intensity with multiple risk factors (Class IIa)

65

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)

66

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)

67

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

68

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)

69

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)

70

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)

71

AACE 2017 Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE

Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors[a]/10-year risk[b]	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10-20% – Diabetes or CKD 3/4 with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Framingham risk scoring is applied to determine 10-year risk

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

72

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;366:1267-78 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;372:2387-97

73

DYSLIPIDEMIA KEY POINTS

- High or very high CV risk may benefit from large decrease in LDL
  - > LDL lowering the > benefit in reducing CV risk
- **Many do not reach LDL goal with initial med**
  - **Statin adverse effects with intolerance**
  - **Do not reach target with maximal tolerated doses**
- May need statin add-on therapy or statin substitution therapy if statin intolerance

Cardiol Clin 18;36:241-56

74

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"
- "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

75

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?**

76

- 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?

77