Unblurring the Lines of Statin Use in Primary and Secondary Prevention of Cardiovascular Disease

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Disclosures

- Teryn J. Bibb reports she has no actual or potential conflict of interest in relation to this presentation
- Off-label use of medication will be discussed during this presentation

Pharmacist Learning Objectives

- Describe current literature available guiding statin therapy for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD)
- Identify patient specific factors that increase the risk of ASCVD
- Evaluate appropriateness of statin therapy based on patient specific characteristics
- Determine if a patient is truly statin intolerant
- Apply current literature for the primary or secondary prevention of ASCVD to patient cases

Pharmacy Technician Learning Objectives

- Define the four statin benefit groups
- Describe the different treatment approaches to guiding statin therapy
- Learn patient specific risk factors associated with ASCVD
- Identify a patient that fits the definition of statin intolerance

2013 ACC/AHA CHOLESTEROL GUIDELINES TO REDUCE ASCVD RISK

Statin Benefit Groups

Group 1
- Clinical ASCVD
  - Age 21-75: **High-intensity statin**
  - Age >75: **Moderate-intensity statin**

Group 2
- LDL-C ≥190 mg/dL: **High-intensity statin**

Group 3
- Type 1 or 2 diabetes with LDL-C 70-189 mg/dL
- Age 40-75
  - **Moderate-intensity statin**
- Estimated 10-y ASCVD risk ≥7.5%
  - **High-intensity statin**

Group 4
- Estimated 10-y ASCVD risk ≥7.5%
- Age 40-75
  - **Moderate- to High-intensity statin**

ASCVD Risk Calculator

- Estimates 10-year primary risk of ASCVD in patients age 40-79 years
- Validated among African American and Caucasian men and women
- Evaluates the following:
  - Age
  - Gender
  - Ethnicity
  - Total cholesterol
  - HDL cholesterol
  - Systolic blood pressure
  - Treatment for HTN
  - Diabetes
  - Smoker status

	Rosuvastatin	Atorvastatin	Simvastatin	Pravastatin	Lovastatin	Fluvastatin	Pitavastatin
High-Intensity Statin	40 mg	80 mg		***LDL-C reduced by ≥50%***			
	20 mg	40 mg					
Moderate-Intensity Statin	10 mg	20 mg	40 mg	80 mg	***LDL-C reduced by 30-50%***		
	5 mg	10 mg	20 mg	40 mg	40 mg	40 mg (bid)	4 mg
			10 mg	20 mg	20 mg	40 mg	2 mg
Low-Intensity Statin	***LDL-C reduced by <30%***			10 mg		20 mg	1 mg

Patient-Centered Decision Making

- Patients with 10-y ASCVD risk 5-7.5% with:
  - LDL-C ≥160 mg/dL or genetic hyperlipidemias
  - Family history of premature ASCVD
  - hs-CRP ≥2 mg/L
  - CAC score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity
  - ABI <0.9
  - High lifetime risk of ASCVD
- Risks verses benefits
- Patient preference

NATIONAL LIPID ASSOCIATION PATIENT-CENTERED MANAGEMENT OF DYSLIPIDEMIA

Major Risk Factors for ASCVD

1. Age
   a) Male ≥45 years of age
   b) Female ≥55 years of age
2. Family history of early CHD
   a) <55 years of age in a male first-degree relative
   b) <65 years of age in a female first-degree relative
3. Current cigarette smoking
4. High blood pressure (≥ 140/≥90 mm Hg or on blood pressure medication)
5. Low HDL-C
   1) Male <40 mg/dL
   2) Female <50 mg/dL

Risk Categories

Risk Category	Criteria	Consider Drug Therapy *Non-HDL-C (mg/dL)* *LDL-C (mg/dL)*
Low	• 0-1 major ASCVD risk factors	≥190 ≥160
Moderate	• 2 major ASCVD risk factors • Consider risk scoring	≥160 ≥130

High	• ≥3 major ASCVD risk factors
	• Type 1 or 2 diabetes
	  • 0–1 other major ASCVD risk factors
	  • No evidence of end organ damage
	• Chronic kidney disease stage 3B or 4
	• LDL-C ≥190 mg/dL
	• 10-y ASCVD risk ≥15%
		≥130
		≥100

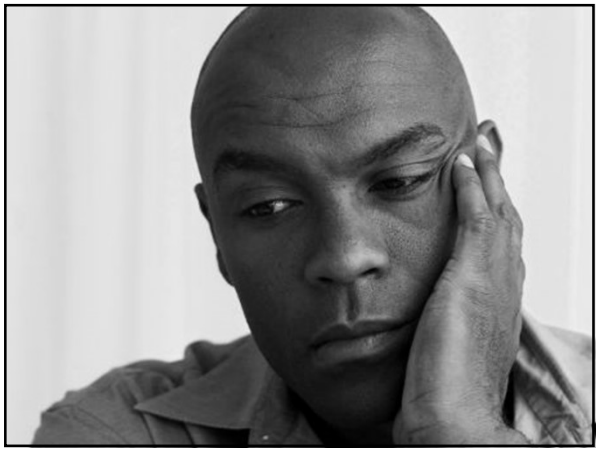
Very High	• ASCVD
	• Type 1 or 2 diabetes
	  • ≥ 2 other major ASCVD risk factors
	  • Evidence of end organ damage
		≥100
		≥70

Treatment Considerations

1. Identify patient's highest risk category
2. Initial intervention
   a) If **low or moderate risk**: attempt lifestyle interventions
   b) If **high or very high risk**: initiate moderate-high intensity statins
3. If treatment goal not achieved:
   a) If **low or moderate risk**: add statin medication
   b) If **high or very high risk**: intensify statin
4. If treatment goal not achieved, may continue intensification or refer to specialist

Treatment Goals

Risk Category	Non-HDL-C (mg/dL)	LDL-C (mg/dL)	Apo-B *(optional)* (mg/dL)
Low	<130	<100	<90
Moderate	<130	<100	<90
High	<130	<100	<90
Very High	<100	<70	<80



The Concerned Family Member

HA is an African American male who recently turned 40 years old. He is presenting to his primary care clinic for his annual physical and expresses concern for his heart health given the loss of his father at a young age due to a heart attack. He has heard a lot about statin medications and wonders if he should start one today.

Patient Information

- PMH: noncontributory
- FH:
  - Father (deceased) – MI at 48 years of age
- SH: nonsmoker
- Medications:
  - Acetaminophen 500 mg as needed
  - Multivitamin daily
- Labs:
  - TC 150
  - HDL 50
  - LDL 78
- BP 119/73
- 10-y ASCVD risk = 2.5%

Based on his concerns today, should HA receive statin therapy?

a) Absolutely! Statins should be in the water.

b) Not at all! He has led a seemingly healthy lifestyle.

c) Maybe. A discussion with the patient about the statins is warranted.

d) I'm not sure.

Guideline Recommendations

ACC/AHA Guidelines	NLA Guidelines
When a risk-based decision is unclear, **family history of premature ASCVD** could be considered. • Patient-centered discussion • Consider risks vs. benefits • Lifestyle interventions • Management of other risk factors • **Consider patient preference**	Patient with **strong family history of premature CHD**, consider increasing risk category • Patient-centered discussion • Consider risks vs. benefits • **Consider patient preference**

Things to Consider…

- Statin therapy?
  - Guidelines do not provide firm recommendations based on this individual risk factor
  - Evidence does not support family history of premature events to elevate the risk factor independently
- Family history considerations
  - Very significant premature event
- Patient preference
  - May provide peace of mind for a patient concerned about something similar occurring in himself

The Older Adult

RP is a 79 year old white female presenting for a 4-week follow-up visit for her hypertension. At her last clinic appointment a 24-hour ambulatory blood pressure monitor revealed hypertension (avg: 156/92). She was then started on hydrochlorothiazide.

Today she had labs to monitor her kidney function and potassium which were WNL. Her physician also decided it would be good to consider her whole heart health and obtained lipids as well, as there was no record of lipids in her medical record.

Patient Information

- PMH:
  - Hypertension
  - Osteoarthritis
  - GERD
- SH: nonsmoker
- Labs:
  - TC 180
  - HDL 40
  - LDL 98
- BP 148/78
- 10-y ASCVD risk = 37.8%
- Medications:
  - Acetaminophen 650 mg as needed
  - Citracal + D3 4 tablets daily
  - Hydrochlorothiazide 12.5 mg daily
  - Zinc sulfate 1 capsule daily
  - Cranberry supplement 1 capsule three times daily
  - Ranitidine 140 mg twice daily
  - Milk of magnesia daily as needed
  - Melatonin 5 mg at bedtime as needed

Based on the information provided, should the physician recommend a statin fro RP?

a) Absolutely! Her risk score is through the roof!

b) Not at all! She probably doesn't want another medication anyways.

c) Maybe. Consideration of the evidence, pros, and cons should occur.

d) I'm not sure.

Guideline Recommendations

ACC/AHA Guidelines	NLA Guidelines

Primary Prevention
Age >75 years
• Consideration of the following:
  • Increasing comorbidities
  • Safety
  • Priorities of care
• Discussion of risks vs. benefits
	Primary Prevention
	Age 65 to 79 years
	• Management based on risk categories
	Age ≥80 years
	• Consider moderate intensity statin
	• Consideration of the following:
	  • Risks vs. benefits
	  • Safety
	  • Polypharmacy
	  • Comorbid conditions (frailty)
	  • Cost
	  • Patient Preference

Guideline Recommendations

ACC/AHA Guidelines	NLA Guidelines

Secondary Prevention
Patients >75 years of age
• Continue statin if already taking and tolerating therapy
• Clinical ASCVD: moderate-intensity statins
	Secondary Prevention / Very High Risk
	Age 65 to 80 years
	• Consider moderate or high intensity statin
	Age ≥80 years
	• Consider moderate intensity statin
	• Consideration of the following:
	  • Risks vs. benefits
	  • Safety
	  • Polypharmacy
	  • Comorbid conditions (frailty)
	  • Cost
	  • Patient preference

	PROSPER	JUPITER	ALLHAT-LLT Elderly
Inclusion criteria	Adults age 70-82 With clinical vascular disease or at risk due to diabetes, smoking, or hypertension	Men ≥50 years Women ≥60 years No clinical ASCVD or diabetes LDL-C <130 mg/dL	Subgroup analysis of adults ≥65 years Stage 1 or 2 HTN PLUS 1 other CHD risk factor No known ASCVD
Primary outcome	Occurrence of coronary event	Occurrence of first major CV event	All-cause mortality
Treatment	40 mg pravastatin Placebo	20 mg rosuvastatin Matching placebo	40 mg pravastatin Usual care
Study population	Median age: 75 years 48% male	Median age: 74 years 51% female 70% white	Mean age: 78.5 years 56-57% female 39% white
Results	Placebo: 473/2913 Prava.: 408/2891 **p=0.014 (HR 0.85, 0.74-0.97)** Subgroup analysis in primary prevention: **p=0.19**	Placebo: 119/2817 Rosuva.: 75/2878 **p<0.001 (HR 0.61, 0.46-0.82)**	Usual care: 65/351 Prava: 92/375 **p=0.07 (HR 1.34, 0.98-1.84)**
Conclusion	Statin therapy significantly reduced the occurrence of a coronary event May not have an effect for primary prevention	Statin therapy significantly reduced the occurrence of the initial cardiovascular events	Statins did not have a significant impact on survival in the elderly

Things to Consider…

- Statin therapy?
  - Guidelines do not provide firm recommendations based on this individual risk factor
  - Evidence does not support family history of premature events to elevate the risk factor independently
- Risk assessment tools
  - Age will increase ASCVD risk single-handedly
- Age related factors
  - Increase risk of side effects
  - Additional comorbid conditions
- Shared decision making

The Statin Intolerant Patient

LT is a 63 year old African American female establishing care with a new internist. She comes to you stating that her former physician told her she was allergic to statins since she had muscle pain about 6 months after starting simvastatin. In her initial interview, she expresses willingness to optimize her medications.

Patient Information

- PMH:
  - Type 2 diabetes
  - Hypertension
  - Dyslipidemia
- SH: nonsmoker
- Medications:
  - Aspirin 81 mg daily
  - Chlorthalidone 25 mg daily
  - Ezetimibe 10 mg daily
  - Insulin glargine 37 units daily
  - Lisinopril 20 mg daily
  - Metformin 1000 mg twice daily
- Labs:
  - TC 203
  - HDL 37
  - LDL 82
- BP 135/74
- Allergies:
  - Statins (muscle aches)
- 10-y ASCVD risk = 24.2%

Based on the information provided, should LT restart statin therapy today?

a) Absolutely! She is a prime candidate based on guidelines.

b) Not at all! "Statins" are on her allergy list.

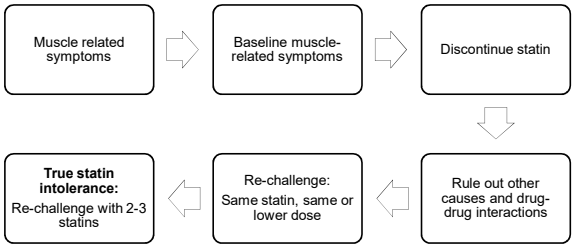
c) Maybe. More information may be needed to determine if her allergy is truly an allergy.

d) I'm not sure.

Guideline Recommendations

ACC/AHA Guidelines	NLA Guidelines
Unexplained severe muscle symptoms • Discontinue statin • Evaluate for rhabdomyolysis **Mild to moderate** muscle symptoms • Discontinue statin until further evaluation	• Consider switching statins • Consider lower doses of statins • Alternative dosing strategies (1-2x per week) • Pursue nonstatin therapy of elevated LDL-C

Determining Statin Intolerance



Patients at high risk for statin-related muscle symptoms:
- **Women**
- **Individuals of Asian descent**
- **elderly**

Statin Pharmacokinetics

	Rosuvastatin	Atorvastatin	Simvastatin	Pravastatin	Lovastatin	Fluvastatin	Pitavastatin
Elimination half-life	19 hours	14 hours	2 hours	2 hours	3 hours	1.5 hours	11 hours
Lipophilicity	Hydrophilic	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Lipophilic	Lipophilic
CYP450 metabolism	Limited	3A4	3A4	None	3A4	2C9	Limited

Things to Consider…

- Statin therapy?
  - Retrial with low-dose simvastatin would be appropriate
  - Consideration of low dose of other statin at a moderate dose and titrate up to target intensity
- Risk factors
  - Female
  - Progressing age
- Shared decision making
  - Re-challenging statins should be decision made by both the patient and clinician
  - If the patient is unwilling to re-challenge, consider other lipid-lowering therapies if indicated

ALTERNATIVE THERAPIES

2017 ACC Decision Pathway for Non-statin Therapies

When LDL-C percent reduction is not met for the following statin benefit groups, may add non-statin therapies to provide increased LDL-C reduction

Clinical ASCVD with comorbidities	LDL-C ≥190 mg/dL	Diabetes	10-y ASCVD risk ≥7.5%
⇩	⇩	⇩	⇩
Ezetimibe	Ezetimibe	Ezetimibe	Ezetimibe
⇩	⇩		
PCSK9 inhibitors	PCSK9 inhibitors		

2017 NLA Update on Use of PCSK9 Inhibitors

- Consider PSCK9 inhibitors in patients on maximally tolerated statins with or without ezetimibe AND:
  - With ASCVD and LDL-C ≥100 mg/dL
  - Heterozygous hypercholesterolemia and LDL-C ≥130 mg/dL
- May consider PSCK9 inhibitors in various high risk patients with ASCVD:
  - Statin intolerance
  - Certain high-risk patients

	IMPROVE-IT	FOURIER	SPIRE-1 and -2
Inclusion criteria	Adults age ≥50 years Hospitalized within 10 days for acute coronary syndrome LDL-C 50-125 mg/dL	Adults age 40-85 years With clinical ASCVD plus: 1 major risk factor 2 minor risk factors LDL-C <130 mg/dL	Clinical ASCVD, diabetes, CKD, or PVD with additional CV risk conditions or familial hypercholesterolemia **LDL≥70 – SPIRE-1** **LDL≥100 – SPIRE-2**
Primary outcome	Occurrence of first major CV event from time of randomization	Occurrence of first major CV event from time of randomization	Composite of cardiovascular events
Treatment	40 mg simvastatin + 10 mg ezetimibe 40 mg Simvastatin + placebo	140 mg evolocumab every 2 weeks Matching placebo	150 mg bococizumab every 2 weeks Matching placebo
Results	Placebo: 2742/9077 Ezetimibe: 2572/9067 **p=0.016 (HR 0.94, 0.89-0.99)**	Placebo: 1563/13780 Rosuva.: 1344/13784 **p<0.001 (HR 0.85, 0.79-0.92)**	*Combined* **p=0.08 (HR 0.88, 0.76-1.02)** *SPIRE-2* Placebo: 224/5309 Bocociz.: 179/5312 **p=0.02 (HR 0.79, 0.65-0.97)**
Conclusion	In the setting of a recent ACS event, the addition of ezetimibe to statin therapy may result in a reduction of cardiovascular morbidity and mortality	Evolocumab significantly reduces major cardiovascular events	Bococizumab combined groups did not significantly impact composite CV events It did provide some benefit in patients with elevated LDL initially

SO WHAT?

Key Take Aways

- **Patients should always be involved in the decision making process to start or stop statin therapy**
- Most statin-related decisions without clear guidance from national organizations will be patient specific and based on needs and preferences
- Statins have been shown to reduce risk of ASCVD in high risk groups, but may also be of benefit to patients at low-moderate risk for ASCVD

Key Take Aways

- Safety and tolerability considerations should be made prior to initiating statin therapy in the less clear patient populations
- Providing education on statin intolerance may provide ASCVD risk-lowering benefit for patients seemingly intolerant
- If a patient cannot utilize statins or has maximized their potential benefit, other options are available that will help reduce ASCVD risk
- Patient-preference should always be considered regardless of risk factors and potential statin benefit

References

- Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *J Am Coll Cardiol.* 2014;63(25 Pt B): 2889–2934.
- Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – full report. *J Clin Lipidol.* 2015;9:129–169.
- Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association Recommendations for the Patient-Centered Management of Dyslipidemia: Part 2. *J Clin Lipidol.* 2015;9:S1–S122.
- Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for Primary Prevention in Older Persons With Elevated C-Reactive Protein and Low to Average Low-Density Lipoprotein Cholesterol Levels: Exploratory Analysis of a Randomized Trial. *Ann Intern Med.* 2010;152(8):488-96, W174.
- Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet.* 2002;360(9346):1623-30.
- Han BH, Sutin D, Williamson JD, et al. Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults The ALLHAT-LLT Randomized Clinical Trial. *JAMA Intern Med.* 2017 ;177(7):955-965.
- Guyton JR, Bays HE, Grundy SM, Jacobson TA. An assessment by the Statin Intolerance Panel: 2014 update. *J Clin Lipidol.* 2014;8:S72-S81.
- Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol.* 2005 Feb;19(1):117-25.
- Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol,* 2017;70(14):1785-1822.
- Orringer CE, Jacobson TA, Saseen JJ, et al. Update on the use of PCSK9 inhibitors in adults: Recommendations from an Expert Panel of the National Lipid Association. *J Clin Lipidol.* 2017;11:880-890.
- Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med.* 2015;372:2387–97.
- Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med.* 2017;376:1713–22.
- Ridker PM, Revkin J, Amarenco P, et al. Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. *N Engl J Med.* 2017;376:1527-1539.

QUESTIONS?

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