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New HYPErcholesterolemia Guidelines: Are They Worth All the HYPE?

Sunday, December 2, 2018
12:45 PM – 2:15 PM

Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.

Learning Objectives

1. Explain treatment recommendations included in the new American College of Cardiology - American Heart Association (ACC-AHA) hypercholesterolemia guidelines.
2. Apply new guidelines to the management of patients with hypercholesterolemia.
3. Identify clinical controversies regarding the benefits of treating hypercholesterolemia in sub-populations.
4. Evaluate challenges with the application of the updated guidelines when treating hypercholesterolemia.

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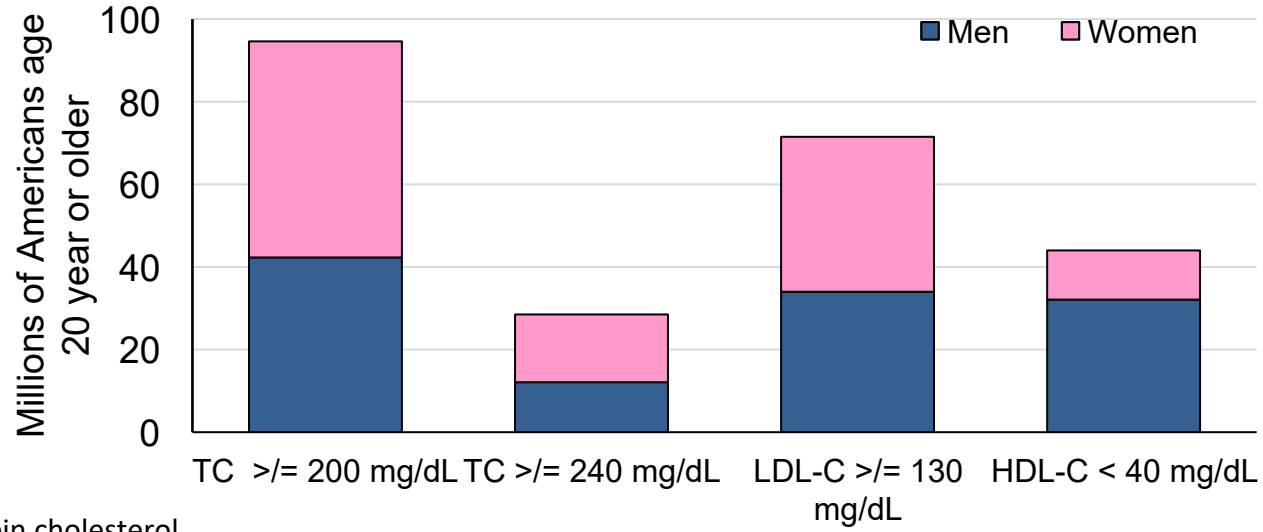
Landscape of Hypercholesterolemia Management

Joel Marrs, Pharm.D.
Associate Professor
University of Colorado

Prevalence of Lipid Abnormalities

AHA Heart Disease and Stroke Statistics 2018

1/3 of US adults have LDL-C ≥ 130 mg/dL



National Health and Nutrition Examination Survey (2011-2014)

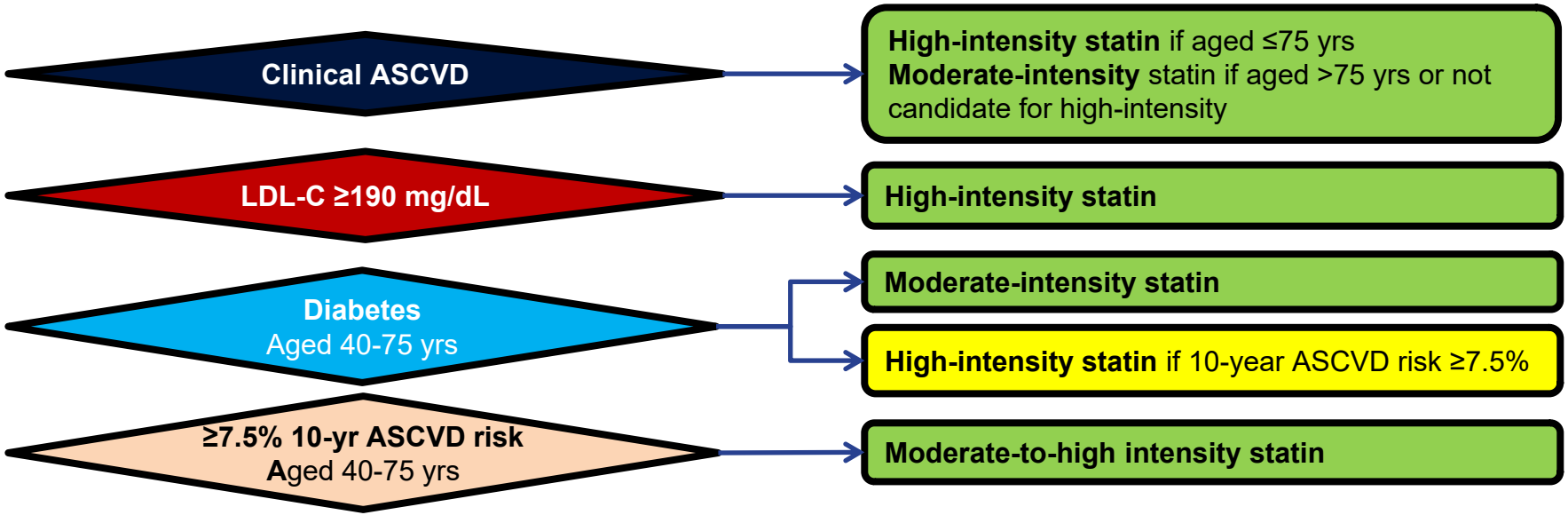
TC = total cholesterol
LDL-C = low-density lipoprotein cholesterol
HDL-C = high-density lipoprotein cholesterol

Benjamin EJ, et al. *Circulation*. 2018;137:e67–e492

Key Hypercholesterolemia Guidelines/Recommendations

- 2013: International Atherosclerosis Society (IAS)Position Paper: Global Recommendations for the Management of Dyslipidemia. (www.athero.org)
- 2013: ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. Circulation. 2013 (online November 12, 2013).
- 2014: National Lipid Association (NLA) Recommendations for Patient-Centered Management of Dyslipidemia: Part 1
- 2015: NLA Recommendations for Patient-Centered Management of Dyslipidemia: Part 2
- 2016: United States Preventative Service Task Force (USPSTF): Recommendations on Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Preventative Medication
- 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
- 2017: American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for the management of dyslipidemia and prevention of cardiovascular disease.
- 2017: Update on the use of PCSK9 inhibitors in adults: Recommendations from an Expert Panel of the National Lipid Association.
- 2017: ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk
- **2018: ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. Circulation. 2018 (online November 10, 2018).**

ACC/AHA 2013 Blood Cholesterol Guideline



Stone NJ et al. *Circulation*. 2014;129(25 suppl 2):S1-S45.

ACC/AHA 2013 Blood Cholesterol Guideline: Statin Intensity

High-Intensity	Moderate-Intensity	Low-Intensity
Daily dose lowers LDL–C on average, by ≥ 50%	Daily dose lowers LDL–C on average, by 30-49%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** (*5*) **10 mg** **Simvastatin 20–40 mg** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 80 mg** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*
Specific statins and doses are noted in **bold** that were evaluated in randomized controlled trials. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in *italics*.		

Stone NJ et al. *Circulation*. 2014;129(25 suppl 2):S1-S45.

NLA Recommendations – Part 1

- Primary Target: Non-HDL-C, and LDL-C
- Secondary Optional Target: Apo B

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

Jacobson T et al. *J Clin Lipidol*. 2014; 8:473-88.

NLA Recommendations – Part 1

Risk Category	Criteria	Non-HDL-C/ LDL-C (mg/dL) Goals
Low	• ≤1 major ASCVD risk factor • Consider other risk factors if known	<130/<100
Moderate	• 2 major ASCVD risk factors • Consider quantitative risk scoring using a 10-yr risk calculator, or others	<130/<100
High	• ≥3 major ASCVD risk factor • Diabetes mellitus (type 1 or 2) with: ○ ≤1 other major ASCVD risk factor, and no evidence of end organ damage • Chronic kidney disease stage 3B or 4 • LDL-C ≥190 mg/dL • Quantitative risk score reaching the high-risk threshold	<130/<100
Very High	• ASCVD • Diabetes mellitus (type 1 or 2) with: ○ ≥2 other major ASCVD risk factors, and evidence of end organ damage	<100/<70

Jacobson T et al. *J Clin Lipidol*. 2014; 8:473-88.

NLA Recommendations – Part 1

- Advocacy for statin based therapy
- Non-HDL-C viewed as better target over LDL-C
- **Primary Prevention:**
  - Non-HDL-C <130 mg/dL and LDL-C <100 mg/dL considered desirable
- **Secondary Prevention:**
  - Non-HDL-C <100 mg/dL and LDL-C <70 mg/dL considered desirable

Jacobson T et al. *J Clin Lipidol*. 2014; 8:473-88.

2016 USPSTF Recommendations: Statin Use for the Primary Prevention of CVD in Adults

	Age 40-75 years ≥ 1 risk factor 7.5-10% 10-yr ASCVD risk	Age 40-75 years ≥ 1 risk factor ≥10% 10-yr ASCVD risk	Age >75 years
Recommendation	Low- to moderate-dose statin (Grade C)	Low- to moderate-dose statin (Grade B)	None (Grade I)
Balance of Benefits and Harms	**SMALL** net benefit	**MODERATE** net benefit	Evidence is insufficient

- Low and moderate dose provide low and moderate intensity LDL-C reductions according to ACC-AHA guidelines
- Risk factors are for CVD, and include: LDL-C >130 mg/dL or HDL-C <40 mg/dL, diabetes, hypertension, and smoking

U.S. Preventive Services Task Force. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016; 316:1997-2007.

AACE/ACE Risk Stratification

Risk Category	Risk Category/10 year Risk
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)
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
High Risk	• ≥2 risk factors and 10-year risk 10-20% • Diabetes or CKD 3/4 with no other risk factors
Moderate Risk	• ≤2 risk factors and 10-year risk <10%
Low Risk	• 0 risk factors

Jellinger PS, et al. Endocr Pract. 2017;23(suppl 2):1-87.

AACE/ACE Guidelines

Lipid Goals for Patients at Risk of ASCVD	
Lipid Parameter	**Goal (mg/dL)**
Total Cholesterol (TC)	< 200
Low Density Lipoprotein Cholesterol (LDL-C)*	< 130 (low risk) <100 (moderate or high risk) <70 (very high risk) < 55 (extreme risk)
Non-High Density Lipoprotein Cholesterol (non-HDL-C)	30 above LDL-C goal [Grade D] 25 above LDL-C goal (extreme risk)*
Triglycerides (TG)	< 150
Apolipoprotein B (Apo B)	< 90 (high risk) < 80 (very high risk with ASCVD or Diabetes plus at least 1 additional RF < 70 (extreme risk)

Jellinger PS, et al. Endocr Pract. 2017;23(suppl 2):1-87. *Grade A; Best Evidence Level (BEL) 1

AACE/ACE Recommendations

- Advocacy for statin based therapy
- Treatment targets for LDL-C, Non-HDL-C, and Apo-B
- **Primary Prevention:**
  - Low Risk patients LDL-C <130 mg/dL and non-HDL-C <160 mg/dL
  - Moderate or High Risk patients LDL-C <100 mg/dL and non-HDL-C <130 mg/dL
- **Secondary Prevention:**
  - Extreme Risk patients LDL-C <55 mg/dL and non-HDL-C <80 mg/dL
  - Very High Risk patients LDL-C <70 mg/dL and non-HDL-C <100 mg/dL

Jellinger PS, et al. Endocr Pract. 2017;23(suppl 2):1-87.

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)

- Randomized, double-blind trial
- 18,144 patients with ACS; age ≥50 yr with high a CV risk feature, LDL -C 50-125 mg/dL
- Randomized to simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg for 4.9 yr
- Primary endpoint:
  - CV death, MI, hospitalization for unstable angina, coronary revascularization, stroke

- Mean LDL-C values (mg/dL)
  - Simvastatin 69.9
  - Ezetimibe/simvastatin 53.2

- 7-yr event rates
  - Simvastatin 34.7%
  - Ezetimibe/simvastatin 32.7%

6% RRR
HR 0.94 (95% CI, 0.89-0.99)
P=0.016

Cannon CP et al. N Engl J Med 2015;372:2387-97.

NLA PCSK9 Inhibitor Recommendations

- **ASCVD**
  - PCSK9 inhibitor therapy **should be considered** with stable ASCVD with additional ASCVD risk factors on max tolerated statin ± ezetimibe and **LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL** (Strength A; Quality High)
  - PCSK9 inhibitor therapy **may be considered** with progressive ASCVD to further reduce LDL-C on max tolerated statin ± ezetimibe and **LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL** (Strength B; Quality Moderate)
- **Very-high-risk/statin intolerance**
  - PCSK9 inhibitor therapy **may be considered** to further reduce LDL-C in selected very-high-risk patients who meet the definition of **statin intolerance** and **require substantial additional atherogenic cholesterol lowering** (Strength C; Quality Low)

Orringer CE, et al. J Clin Lipidol 2017;11:880-90.

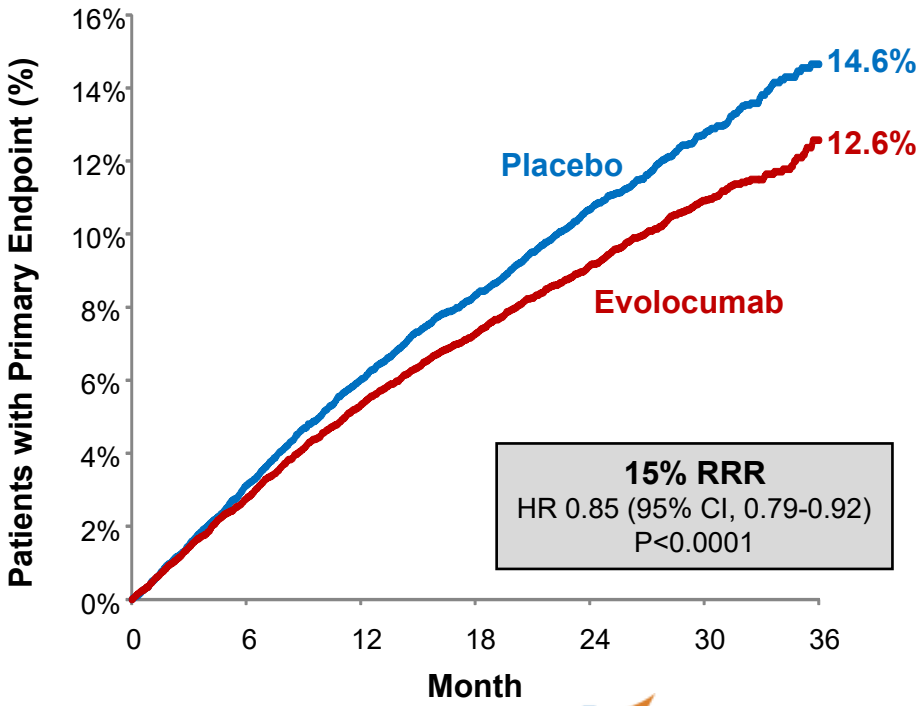
NLA PCSK9 Inhibitor Recommendations

- **LDL-C ≥ 190 mg/dL**
  - PCSK9 inhibitor therapy **may be considered** to further reduce LDL-C with pre-treatment LDL-C ≥ 190 mg/dL, age 40-79 years of age, no uncontrolled ASCVD risk factors and on max tolerated statin ± ezetimibe and **on treatment LDL-C ≥ 100 mg/dL or non-HDL-C ≥ 130 mg/dL** (Strength B; Quality Moderate)
  - PCSK9 inhibitor therapy **may be considered** to further reduce LDL-C with pre-treatment LDL-C ≥ 190 mg/dL, age 40-79 years of age, uncontrolled ASCVD risk factors or high risk markers or genetic FH confirmation and on max tolerated statin ± ezetimibe and on treatment **on treatment LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL** (Strength B; Quality Moderate)
  - PCSK9 inhibitor therapy **may be considered** to further reduce LDL-C with pre-treatment LDL-C ≥ 190 mg/dL, **age 18-39 years of age**, uncontrolled ASCVD risk factors or high risk markers or genetic FH confirmation and on max tolerated statin ± ezetimibe and on treatment on treatment **LDL-C ≥ 100 mg/dL or non-HDL-C ≥ 130 mg/dL** (Strength E; Quality Low)
  - PCSK9 inhibitor therapy **may be considered** to further reduce LDL-C in patients with **homozygous familial hypercholesterolemia**, either of unknown genotype, or those known to be LDL receptor defective and on max tolerated statin ± ezetimibe and **on treatment on treatment LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL** (Strength B; Quality Moderate)

Orringer CE, et al. J Clin Lipidol 2017;11:880-90.

Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)

- Randomized, double-blind trial
- 27,564 patients with ASCVD; age 40-85 yr, and LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL
- On maximal statin therapy
- Randomized to placebo or evolocumab for 2.2 yr
- Primary endpoint:
  - CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization



Sabatine MS et al. N Engl J Med 2017;376:1713-22.

ACC EXPERT CONSENSUS DECISION PATHWAY (ECDP)

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

A Report of the American College of Cardiology Task Force
on Expert Consensus Decision Pathways
Endorsed by the National Lipid Association

Writing Committee, Lloyd-Jones DM, Morris PB et al. *J Am Coll Cardiol.* 2016; 68(1):92-125.
Lloyd-Jones D, Morris PB, Ballantyne CM et al. *J Am Coll Cardiol.* 2017; 70(14):1785-1822.

2016 and 2017 American College of Cardiology (ACC) Expert Consensus Decision Pathway: Nonstatin Therapy

- Nonstatin only after maximally tolerated statin
  - Ezetimibe (or bile acid sequestrant) first followed by PCSK9 inhibitors
  - Niacin not recommended
- PCSK9 inhibitors only in ASCVD and/or baseline LDL-C ≥190 mg/dL
- Actual LDL-C value (or %LDL-C reduction achieved) as the threshold:
  - <70 mg/dL (or 50% reduction) if ASCVD with comorbidities or baseline LDL-C ≥190 mg/dL; otherwise <100 mg/dL

Writing Committee, Lloyd-Jones DM, Morris PB et al. *J Am Coll Cardiol.* 2016; 68(1):92-125.
Lloyd-Jones D, Morris PB, Ballantyne CM et al. *J Am Coll Cardiol.* 2017; 70(14):1785-1822.

2016 and 2017 American College of Cardiology (ACC) Expert Consensus Decision Pathway: Nonstatin Therapy

Statin Benefit Group		LDL-C Threshold: %Reduction or LDL-C value (mg/dL)	Nonstatin Add-On Therapy
Clinical ASCVD	No comorbidities	≥50% or <70	Ezetimibe first, PCSK9i second
	Comorbidities	≥50% or <70	Ezetimibe or PCSK9i
LDL-C ≥190 mg/dL	No clinical ASCVD	≥50% or <100	Ezetimibe or PCSK9i
	Clinical ASCVD	≥50% or <70	
Diabetes Type 1 or 2 Age 40-75 yr	10-yr ASCVD risk <7.5% and no high risk markers	30-49% or <100	Ezetimibe or Bile Acid Sequestrant
	Most patients	≥50% or <100	
≥7.5% estimated 10-yr ASCVD risk and age 40-75 yr	No high risk markers	30-49% or <100	Ezetimibe or Bile Acid Sequestrant
	High risk markers	≥50% or <100	

Lloyd-Jones DM, et al. *J Am Coll Cardiol* 2017;70(14):1785-1822.

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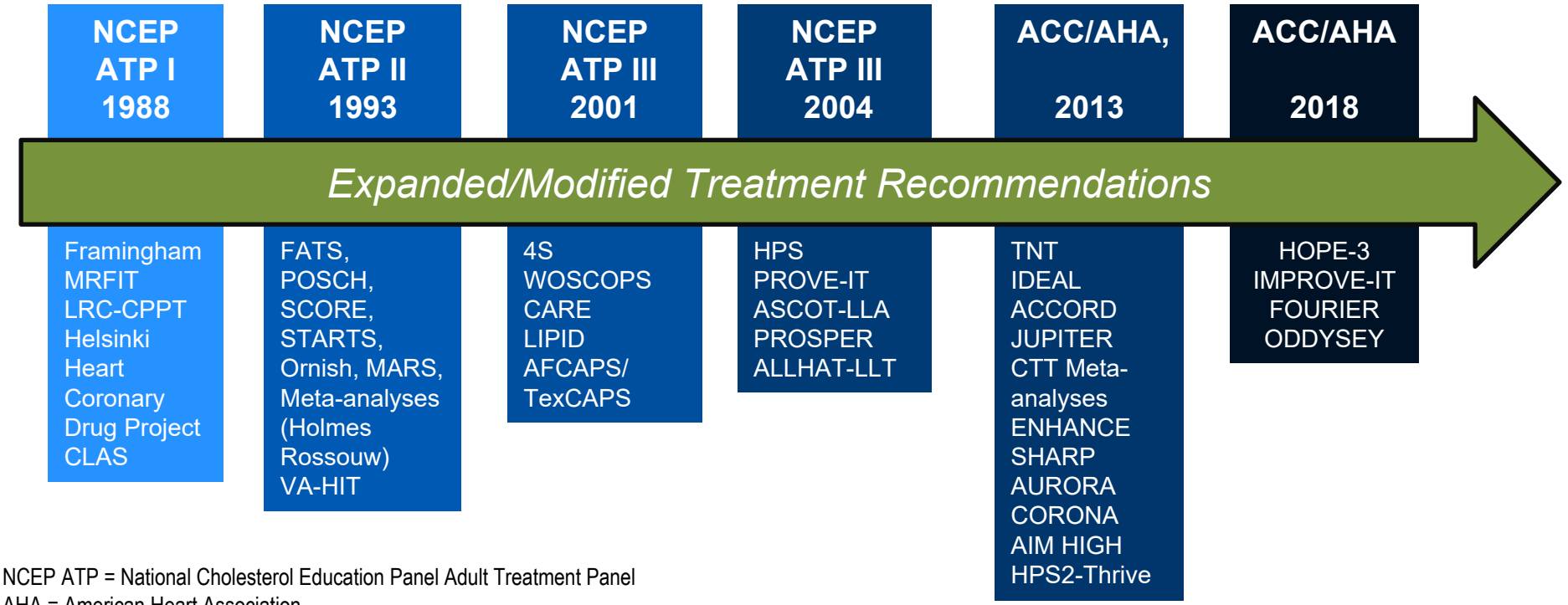
New Hypercholesterolemia Guidelines and Interactive Case Study

Joseph Saseen, Pharm.D.
Professor and Vice Chair of Clinical and Academic Programs
University of Colorado

Evolution of Guidelines and Landmark Trials



NCEP ATP = National Cholesterol Education Panel Adult Treatment Panel
AHA = American Heart Association
ACC = American College of Cardiology

AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

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Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Clinical Scenario...

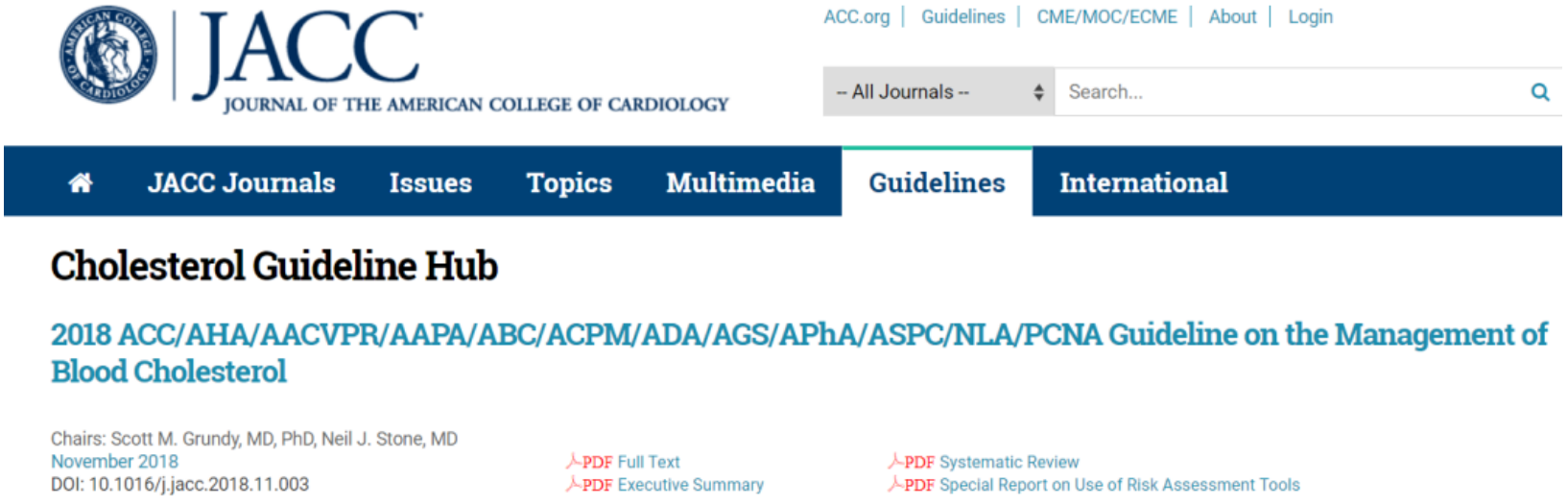
You are required to provide a 20 minute presentation to the clinical pharmacy staff at your health-system on the 2018 ACC-AHA Guideline on the Management of Blood Cholesterol. You had 2 weeks to prepare, but you got behind and your slides are due tomorrow. Which is the most accurate source of information and resources about this new guideline?

a) The chief cardiologist at your health-system
b) Class notes from the PharmD student that is on rotation with you
c) The Blog called *Statin Nation* (http://www.statinnation.net/blog/)
d) Interview of Dr. Oz on YouTube
e) ACC Cholesterol Guideline Hub

AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

ACC Cholesterol Guideline Hub:

- http://www.onlinejacc.org/guidelines/cholesterol



Evidence-Based Recommendations

Class (Strength) of Recommendation

Class I (Strong) — **Benefit >>> Risk**
- Is recommended, is indicated, should be performed

Class IIa (Moderate) — **Benefit >> Risk**
- Is reasonable, can be useful

Class IIb (Weak) — **Benefit ≥ Risk**
- May/might be reasonable/considered, effectiveness unknown

Class III: No Benefit (Moderate) — **Benefit = Risk**
- Is not recommended, is not useful

Class III: Harm (Strong) — **Benefit < Risk**
- Potentially harmful, causes harm

Level (Quality) of Evidence

Level A
- High-quality evidence from > one randomized clinical trial (RCT)
- Meta-analyses of high-quality RCTs

Level B-R (Randomized)
- Moderate-quality evidence from > one RCT
- Meta-analyses of moderate-quality RCTs

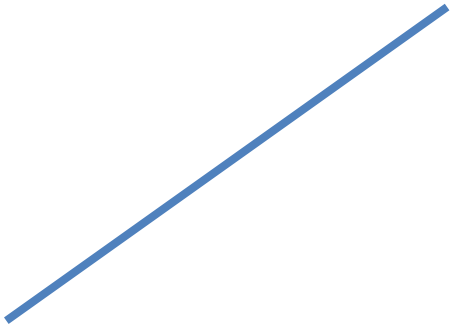
Level B-NR (Nonrandomized)
- Moderate-quality from nonrandomized studies, observational, registry

Level C-D (Limited Data)

Level C-EO (Expert Opinion)

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Prevailing Concept: Lower LDL-C is Better



- Cholesterol Treatment Trialists' Collaboration
  - Meta-analysis of 26 statin trials (n=169,138)
  - 1 mmol/L LDL-C reduction reduced major vascular events 22%
- Cooper Center Longitudinal Study
  - 36,375 low risk (10-yr ASCVD score <7.5%) patients followed for 27 yrs
  - Lower LDL-C associated with lower ASCVD events and death

Top 10 Messages

1. Emphasize a heart-healthy lifestyle across the life course
2. In clinical ASCVD, reduce LDL-C with high-intensity statin therapy or maximally tolerated statin therapy
3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL to consider addition of nonstatins to statin therapy
4. In severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL) without calculating 10-year ASCVD risk, begin high-intensity statin therapy
5. 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL, start moderate-intensity statin therapy without calculating 10-year ASCVD risk
6. 40 to 75 years of age primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Top 10 Messages

7. 40 to 75 years of age without diabetes and LDL-C ≥70 mg/dL, at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy
8. 40 to 75 years of age without diabetes and 10-year risk of 7.5-19.9% (intermediate risk), risk-enhancing factors favor statin therapy
9. 40 to 75 years of age without diabetes and LDL-C 70-189 mg/dL, at a 10-year ASCVD risk of 7.5-19.9%, if a decision about statin therapy is uncertain, consider measuring coronary artery calcium
10. Assess adherence and % LDL-C–lowering response with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

The DEVIL is in the DETAILS...

Clarifying Terminology

Goals…

for LDL-C lowering in response to therapy are defined by percentage responses

Threshold…

a specific value for LDL-C (or non-HDL-C) at or above which clinicians should consider starting or intensifying therapy

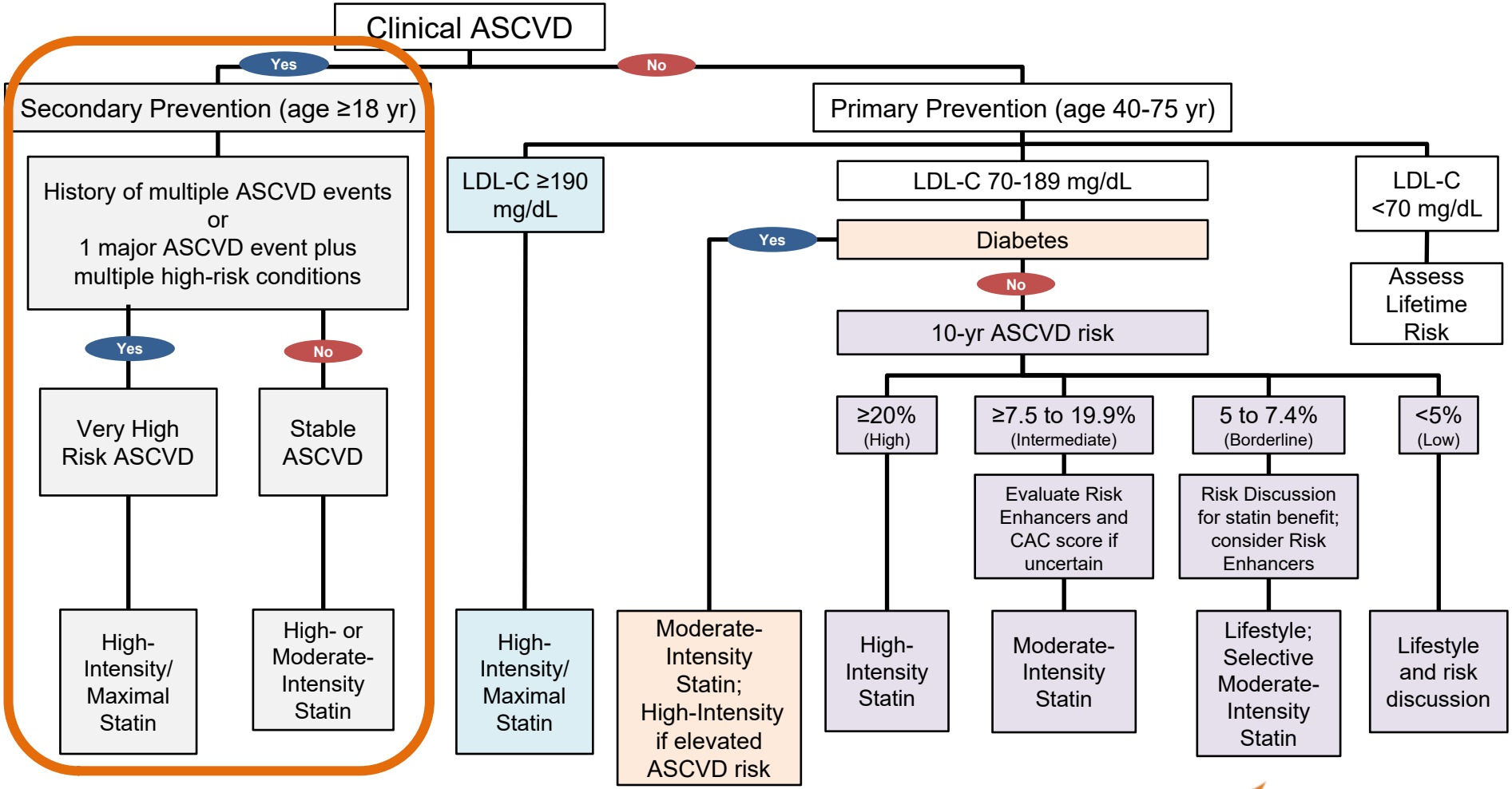
Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

True of False…

The new 2018 ACC-AHA guidelines are similar to the 2013 guidelines in regards to still recommending statin therapy in the previously defined four statin benefit groups?

True

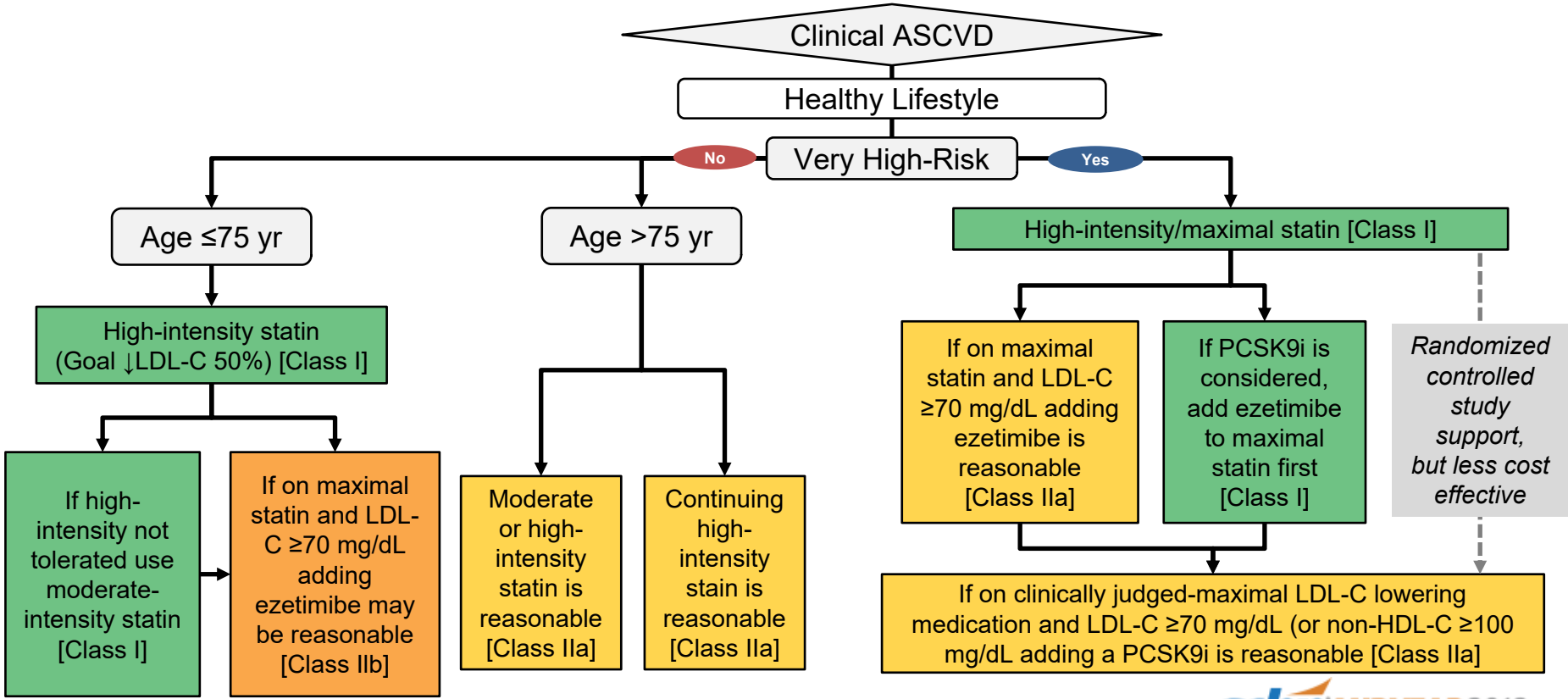
False



ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Secondary Prevention of ASCVD



Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Very High ASCVD

History of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions

Major ASCVD Events
• Recent acute coronary syndrome (past 12 mo) • Prior myocardial infarction (other than recent ACS event listed above) • Prior ischemic stroke • Symptomatic peripheral arterial disease

High-Risk Conditions
• Age ≥65 yr • Heterozygous familial hypercholesterolemia • Prior coronary revascularization outside of the major ASCVD event(s) • Diabetes mellitus • Hypertension • Chronic kidney disease (eGFR 15-59 mL/min/1.73 m^2) • Current smoking • LDL-C ≥100 mg/dL despite maximally tolerated statin and ezetimibe • History of congestive heart failure

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Statin Intensity

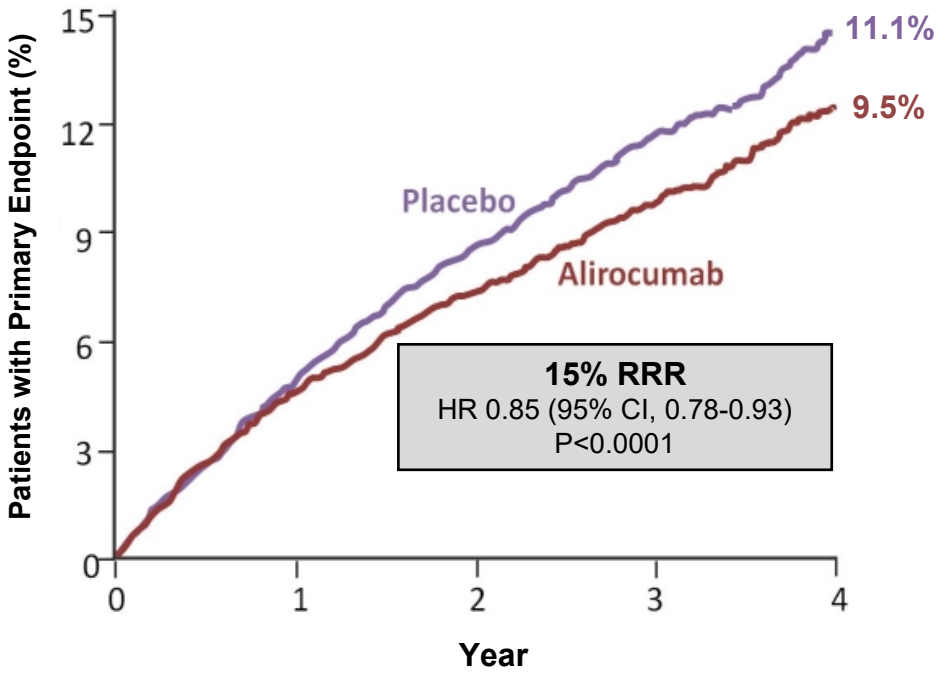
	High Intensity	Moderate Intensity	Low Intensity
LDL-C* Lowering	≥50%	30 to 49%	<30%
	Atorvastatin (40 mg) 80 mg Rosuvastatin 20 mg (40 mg)	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20-40 mg	Simvastatin 10 mg
		Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg twice daily Pitavastatin 1-4 mg	Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

*Reductions with the primary statin medications (atorvastatin, rosuvastatin, simvastatin) estimated using median reduction from the VOYAGER database; for other statin medications (fluvastatin, lovastatin, pitavastatin, pravastatin) identified according to FDA-approved product labeling in adults with hyperlipidemia, primary hypercholesterolemia, and mixed dyslipidemia.

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes)

- Randomized, double-blind trial
- 18,924 patients with recent ACS; age ≥40 yr, and LDL-C ≥70 mg/dL, non-HDL-C ≥100 mg/dL, or ApoB ≥80 mg/dL
- On maximal statin therapy
- Randomized to placebo or alirocumab (titrated) for ≥2 yr
- Primary endpoint:
  - Major Adverse Cardiovascular Events (MACE): CHD death, non-fatal MI, fatal/non-fatal ischemic stroke, or hospitalization for unstable angina



Schwarts GG, et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1801174.

Other Recommendations: Secondary Prevention

COR	LOE	Recommendations
Value Statement: Low Value (LOE: B-NR)		At mid-2018 list prices, PCSK9i have a low cost value (>$150,000 per QALY) compared to good cost value (<$50,000 per QALY)
IIb	**B-R**	HFrEF from ischemic heart disease with reasonable life expectancy (3 to 5 yr) consider initiation of moderate-intensity statin therapy if not on statin

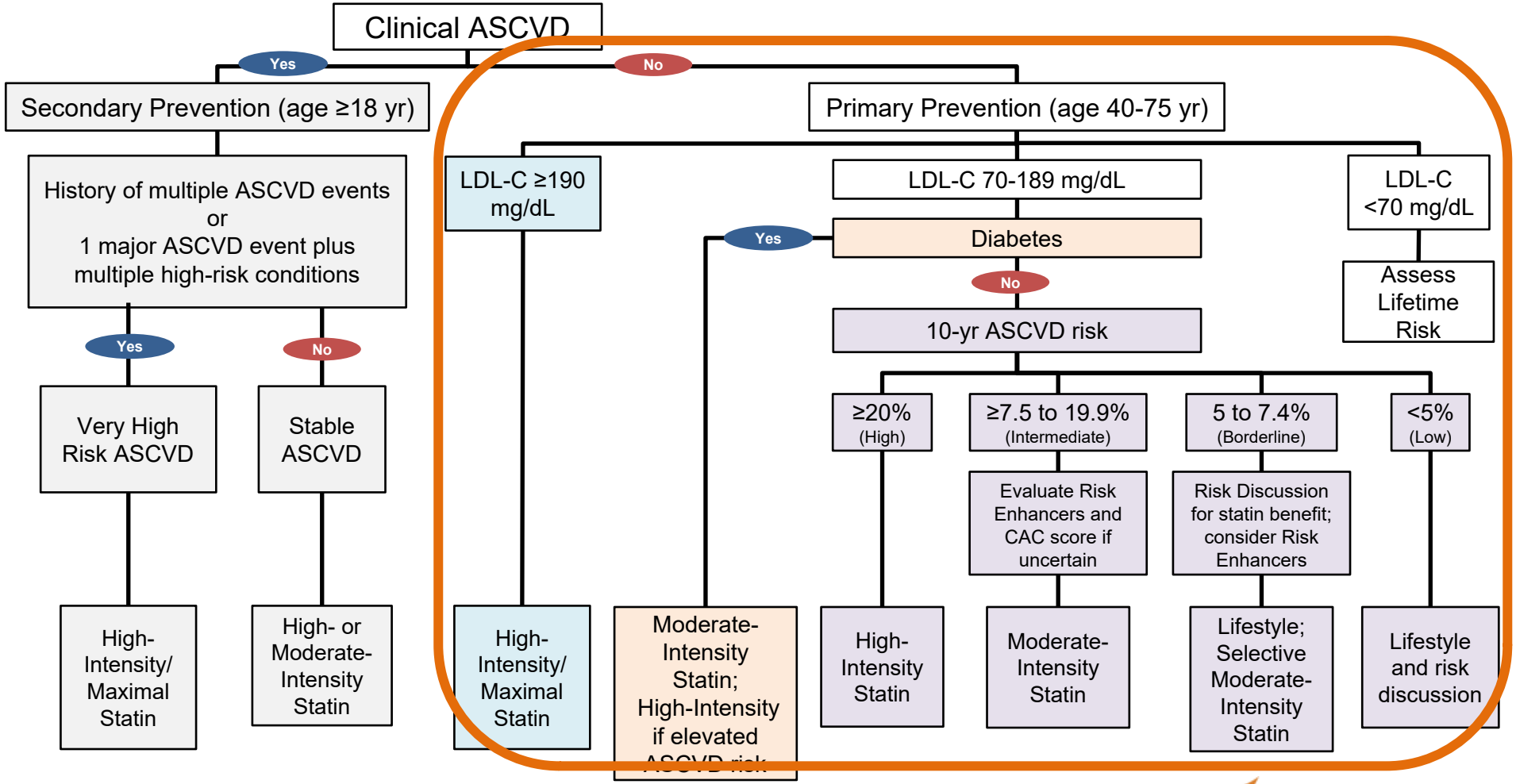
Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Getting LDL-C to <70 mg/dL

- Cohort of 631,855 patients with ASCVD, age 40-85 yr from the VA system meeting FOURIER study criteria
  - 49.9% were on high-intensity statins, 47.5% were on moderate-intensity statins, and 2.6% were on a statin/ezetimibe combination

Predicted percent with LDL-C <70 mg/dL with treatment intensification	
Titration to high-intensity statin therapy alone	18.7%
Addition of ezetimibe therapy alone	50.7%
Titration to high-intensity statin therapy plus ezetimibe use	59.8%

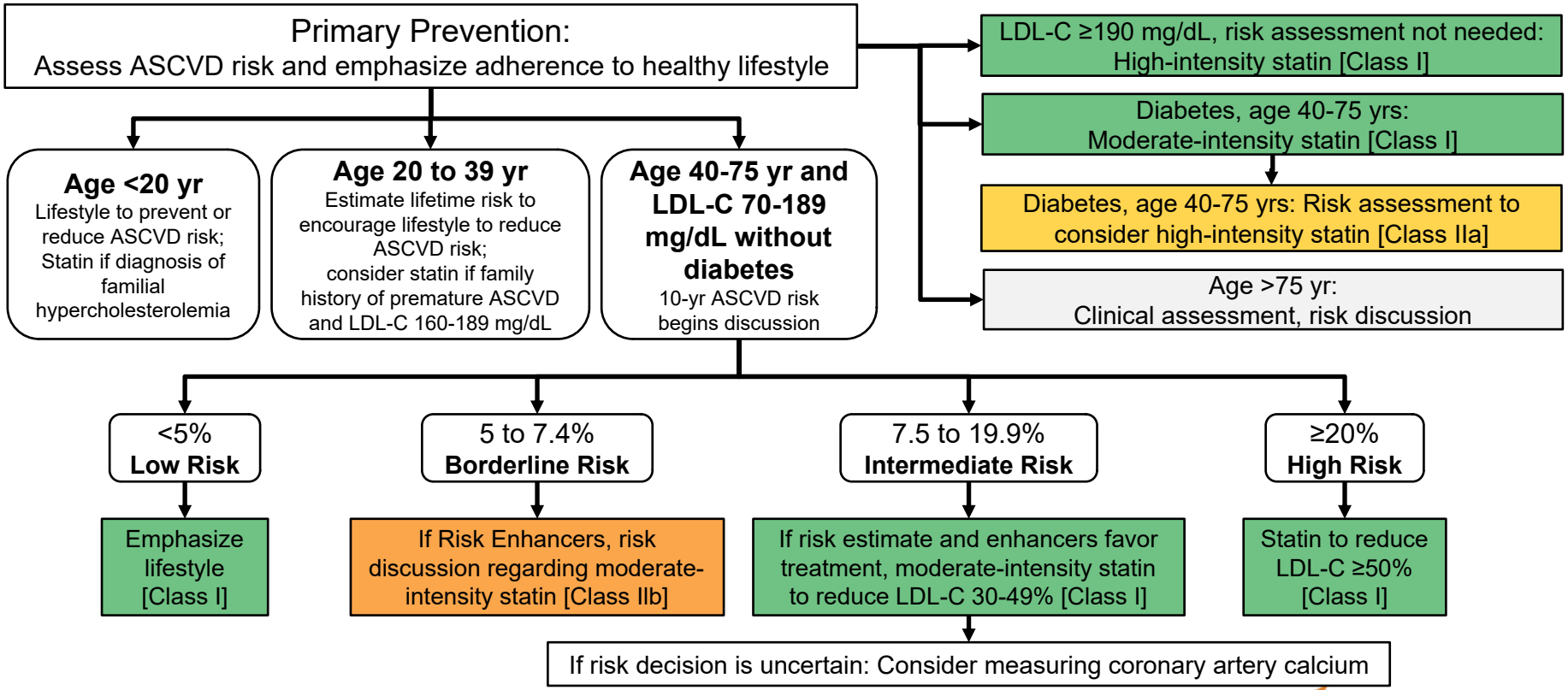
Virani SS et al. Circulation. 2017 20;135(25):2572-2574.



ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Primary Prevention



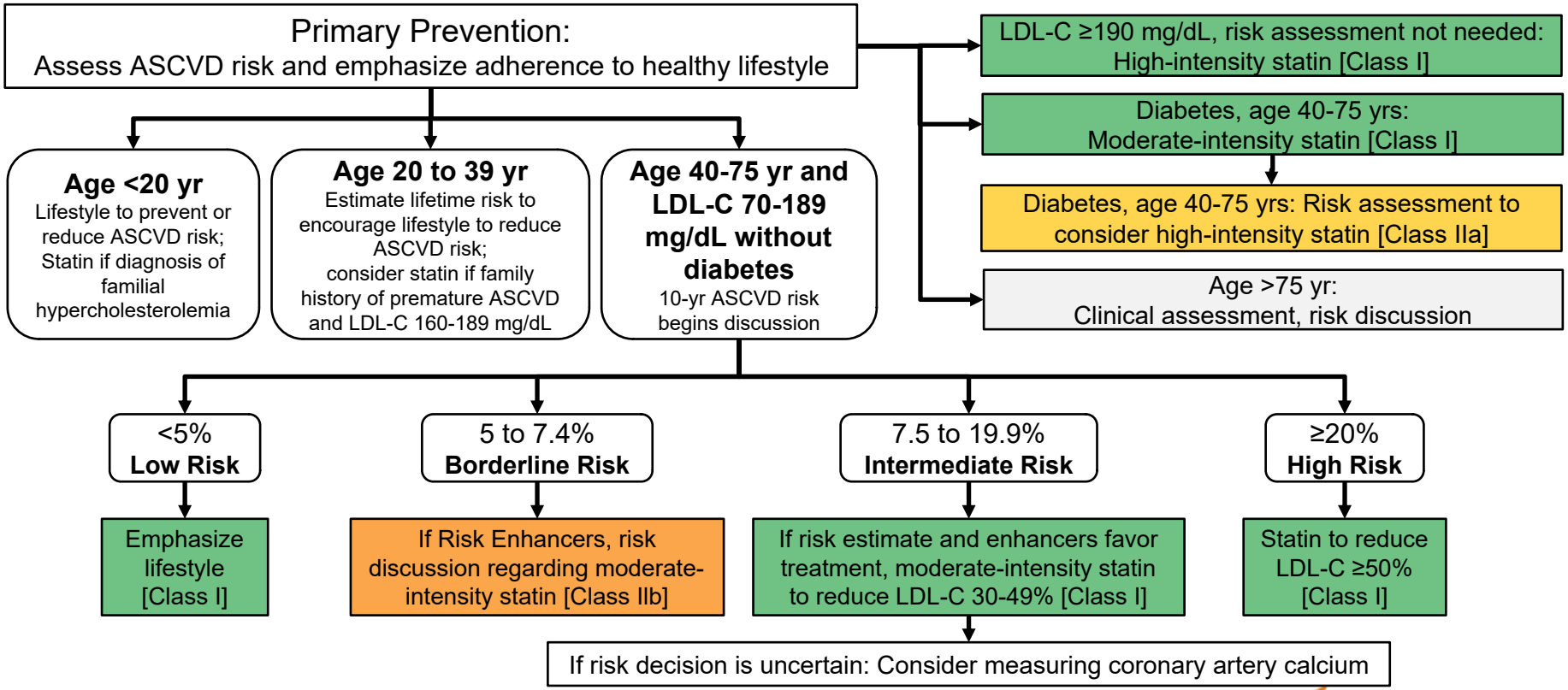
Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Other Recommendations: Primary Prevention Severe Hypercholesterolemia (LDL-C ≥190 mg/dL)

COR	LOE	Recommendations
IIa	B-R	20 to 75 yr, <50% LDL-C reduction with maximally tolerated statin and/or LDL-C level of ≥100 mg/dL, ezetimibe is reasonable
IIb	B-R	20 to 75 yr, <50% LDL-C reduction and fasting triglycerides ≤300 mg/dL with maximally tolerated statin and ezetimibe, consider bile acid sequestrant
IIb	B-R	30 to 75 yr, heterozygous FH and LDL-C ≥100 mg/dL with maximally tolerated statin and ezetimibe therapy, consider PCSK9 inhibitor
IIb	C-LD	40 to 75 yr, baseline LDL-C ≥220 mg/dL and LDL-C ≥130 mg/dL with maximally tolerated statin and ezetimibe, consider a PCSK9 inhibitor
Value Statement: Uncertain Value (B-NR)		FH without clinical ASCVD, with maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at 2018 U.S. list prices

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Primary Prevention



Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Other Recommendations: Primary Prevention and Diabetes

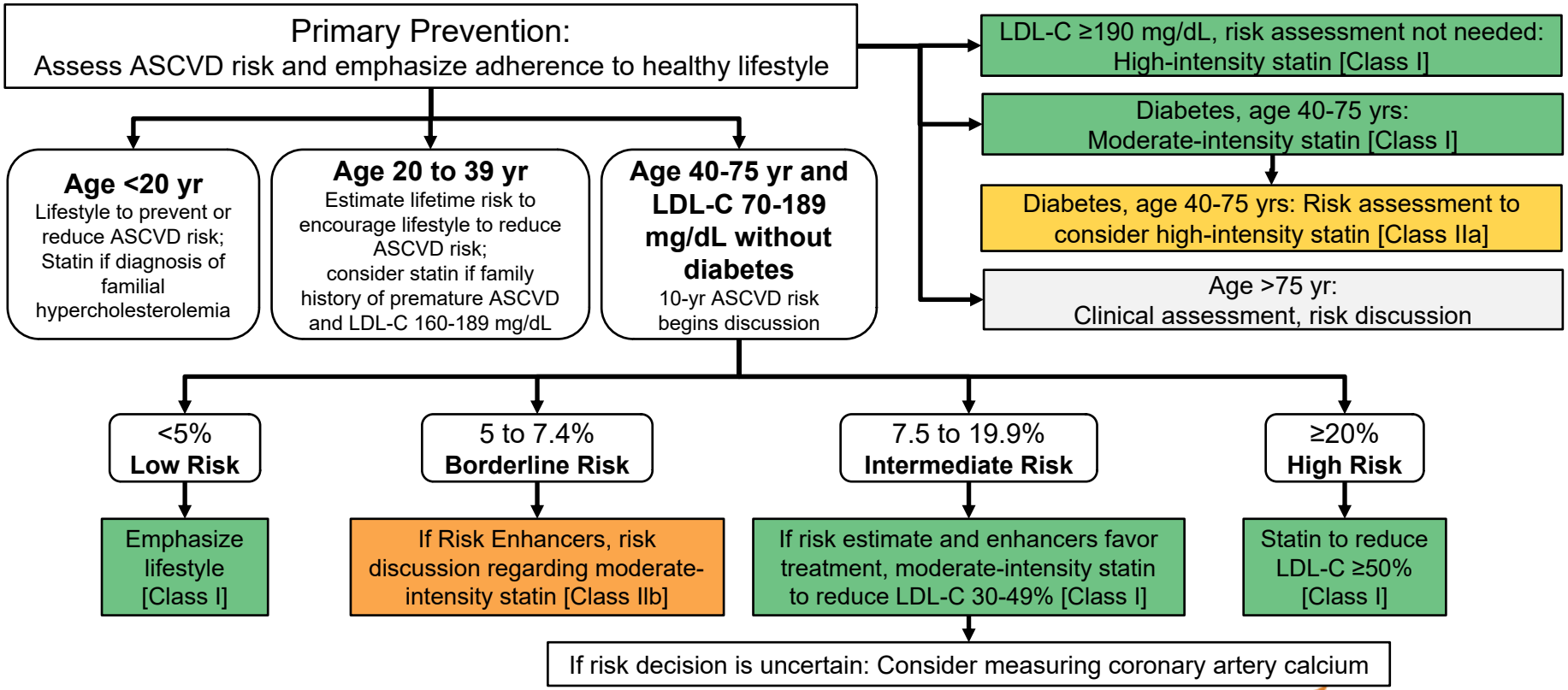
COR	LOE	Recommendations
IIa	B-R	40-75 yr with diabetes and multiple ASCVD risk factors, high-intensity statin therapy is reasonable with the aim to reduce LDL-C ≥50%
IIa	B-NR	>75 yr with diabetes and already on statin therapy, reasonable to continue
IIb	C-LD	40-75 yr with diabetes and 10-year ASCVD risk ≥20%, reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL-C ≥50%

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Other Recommendations: Primary Prevention and Diabetes

COR	LOE	Recommendations
IIb	C-LD	>75 years with diabetes, reasonable to initiate statin therapy after benefit/risk discussion
IIb	C-LD	20 to 39 yr with diabetes reasonable to initiate statin therapy if diabetes-specific risk enhancer present: • long duration (≥10 yr for type 2, ≥20 yr for type 1) • albuminuria (≥30 mcg of albumin/mg creatinine), • eGFR < 60 mL/min/1.73 m^2 • retinopathy • neuropathy • ankle-brachial index <0.9

Primary Prevention



Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Risk Enhancing Factors

- Family history of premature ASCVD
- LDL-C 160–189 mg/dL or non–HDL-C 190–219 mg/dL
- Metabolic syndrome
- CKD
  - eGFR 15–59 mL/min/1.73 m2 with or without albuminuria)
  - not dialysis or kidney transplantation
- Chronic inflammatory conditions (e.g., rheumatoid arthritis, HIV)
- Premature menopause (before age 40 y) and pregnancy-associated conditions that increase later ASCVD risk (e.g., preeclampsia)
- High-risk race/ethnicities (e.g., South Asian ancestry)

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Risk Enhancing Factors, cont.

- Lipid/biomarkers:
  - Persistently elevated, primary hypertriglyceridemia (≥175 mg/dL)

- In select individuals, If measured:
  - High-sensitivity C-reactive protein ≥2.0 mg/L
  - Lp(a) ≥50 mg/dL
  - apoB ≥130 mg/dL
  - Ankle brachial index <0.9

Risk-enhancing factors favor statin therapy in patients at 10-year ASCVD risk of 5 to 7.5% (borderline risk)

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Other Recommendations:
Primary Prevention, without Diabetes, LDL-C 70-189 mg/dL

COR	LOE	Recommendations
IIa	B-NR	**Intermediate-risk or selected borderline-risk in whom a coronary artery calcium (CAC) score is measured:** • Zero: reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher risk conditions are absent (diabetes, family history of premature CHD, cigarette smoking) • 1 to 99: reasonable to initiate statin therapy for patients ≥55 years of age • ≥100*: reasonable to initiate statin therapy

*or ≥ 75th percentile

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Coronary Artery Calcium Measurement

Patients Who Might Benefit from Knowing Their CAC Score Is Zero

- Reluctant to initiate statin therapy and wish to understand their risk/benefit more precisely
- Concerned about need to reinstitute statin after stopping for SAMS
- Older patients (men, 55-80 yr; women, 60-80 yr) with low burden of risk factors who are uncertain
- Middle-aged patients (40-55 yr) with 10-yr ASCVD risk 5 to 7.4% with other factors that increase ASCVD risk

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Other Recommendations:

Primary Prevention, without Diabetes, LDL-C 70-189 mg/dL

COR	LOE	Recommendations
IIb	B-R	>75 yr, moderate-intensity statin may be reasonable
IIb	B-R	>75 yr, reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy
IIb	B-R	76 to 80 yr, reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Other Recommendations: Hypertriglyceridemia

COR	LOE	Recommendations
I	B-NR	≥20 yr with moderate hypertriglyceridemia (triglycerides 175 to 499 mg/dL), address and treat lifestyle factors, secondary factors, and medications that increase triglycerides.
IIa	B-R	40 to 75 yr with moderate or severe hypertriglyceridemia and ASCVD risk ≥7.5%, reevaluate ASCVD risk after lifestyle and secondary factors are addressed; consider persistently elevated triglycerides a factor favoring initiation or intensification of statin therapy.
IIa	B-R	40 to 75 yr with severe hypertriglyceridemia and ASCVD risk of ≥7.5%, address reversible causes and initiate statin therapy.
IIa	B-NR	In severe hypertriglyceridemia, especially fasting triglycerides ≥1000 mg/dL, address other causes; if triglycerides persistently elevated or increasing, implement a very low-fat diet, avoid refined carbohydrates and alcohol, consume omega-3 fatty acids, if necessary to prevent acute pancreatitis, fibrate therapy.

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT)

- Randomized, double-blind trial
- 8179 patients; age ≥45 yr with ASCVD, or age ≥50 yr with diabetes plus CV risk factors; on statin therapy with:
  - Fasting triglyceride 135-499 mg/dL (median 216 mg/dL)
  - LDL-C 41-100 mg/dL (median 75 mg/dL)
- Randomized to icosapent ethyl 4 g/day or placebo for 4.9 yr
- Primary Endpoint: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina

- Results: Primary Endpoint:
  - Placebo 22.0%
  - Icosapent Ethyl 17.2%

25% RRR
HR 0.75 (95% CI, 0.68-0.83)
P<0.0001

Bhatt DL, et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1812792.

Statin Safety

- Statin-associated side effects that are not severe:
  - reassess and rechallenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with nonstatin therapy
- Severe statin-associated muscle symptoms (SAMS):
  - measure creatine kinase
  - measure liver transaminases as well as total bilirubin and alkaline phosphatase if symptoms suggest hepatotoxicity
- If chronic, stable liver disease (including non-alcoholic fatty liver disease) use statins, when indicated, after obtaining baseline measurements and determining a schedule of monitoring and safety checks
- Coenzyme Q10 is not recommended for routine use with statins or for the treatment of SAMS
- Routine creatine kinase and transaminase measurements are not useful

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Noteworthy Additional Elements

- In patients treated with dialysis, it reasonable to continue statin therapy, but do not initiate statin therapy
- Recommendations for certain populations:
  - Women, children and adolescents, racial/ethnic groups, CKD, chronic inflammatory diseases
- Interventions to improve adherence are recommended, including telephone reminders, calendar reminders, integrated multidisciplinary educational activities, and pharmacist-led interventions
- Supplemental tables regarding medications

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Clinical Case...

A 50-year-old primary prevention woman with diabetes has a baseline LDL-C of 90 mg/dL and a 10-year ASCVD risk score of 3%. She does not have any other medical conditions, and all other laboratory tests (serum chemistries, urinalysis) are normal. According to the 2018 ACC-AHA cholesterol guidelines, which therapy is recommended in this patient?

a) Lifestyle modifications alone
b) Lifestyle modifications and moderate-intensity statin therapy
c) Lifestyle modifications and high-intensity statin therapy
d) Lifestyle modifications, high-intensity statin therapy and ezetimibe

Clinical Case...

A 65-year-old woman has a history of ACS 6 months ago, hypertension, is a current smoker, and has peripheral arterial disease. Current lipid-lowering therapy is atorvastatin 80 mg daily. Current fasting lipid panel is:

- TC 125 mg/dL, HDL-C 30 mg/dL, LDL-C 75 mg/dL, triglycerides 125 mg/dL

Which change to her lipid-lowering regimen is recommended?

a) Continue current regimen unchanged
b) Add alirocumab
c) Add ezetimibe
d) Add omega-3 fatty acids

Clinical Case...

A 47-year-old African American with hypertension does not smoke, exercise aerobically 4 times a week, and has no family history of ASCVD. Fasting lipid panel is:

- TC 230 mg/dL, HDL-C 40 mg/dL, LDL-C 150 mg/dL, triglycerides 200 mg/dL
- BP is 128/76 mm Hg, BMI is 27 kg/m^2 and 10-year ASCVD risk score is 8.4%

Both provider and patient are not convinced to start statin therapy.

Which test is recommended to provide additional insight as to whether this patient should start statin therapy?

a) Coronary artery calcium
b) High-sensitivity C-reactive protein
c) Lp(a)
d) apoB

ashp MIDYEAR 2018
Clinical Meeting & Exhibition

Future Directions and Role of Pharmacists in Hypercholesterolemia Management

Joel Marrs, Pharm.D.
Associate Professor
University of Colorado

Guideline Implementation: Pharmacist's Role

COR	LOE	Recommendations
I	A	Interventions focused on **improving adherence** to prescribed therapy are recommended for management of adults with elevated cholesterol levels, including telephone reminders, calendar reminders, **integrated multidisciplinary educational activities, and pharmacist-led interventions**, such as simplification of the drug regimen to once-daily dosing
I	B-R	Clinicians, health systems, and health plans should identify patients who are not receiving guideline-directed medical therapy and **should facilitate the initiation of appropriate guideline-directed medical therapy**, using multifaceted strategies to improve guideline implementation
I	B-R	**Before therapy is prescribed, a patient-clinician discussion** should take place to promote shared decision-making and should include the **potential for ASCVD risk-reduction benefit, adverse effects, drug-drug interactions, and patient preferences**

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

American College of Cardiology Cardiovascular Team and Prevention Councils

Role of the Clinical Pharmacist in the Care of Patients with CVD

- Team-based care, including clinical pharmacists, can efficiently deliver high-quality care
- Substantial effect in a wide variety of settings through:
  - Optimization of drug use
  - Avoidance of adverse drug events
  - Transition of care activities focusing on medication reconciliation and patient education

Dunn SP, et al. *J Am Coll Cardiol* 2015;66(19):2129-2139.

Checklist for Clinician-Patient Shared Decision Making for Initiating Therapy

- ✓ ASCVD Risk Assessment
- ✓ Lifestyle Modifications
- ✓ Potential Net-Clinical Benefit from Pharmacotherapy
- ✓ Cost Considerations
- ✓ Shared Decision Making
  - Have patient verbalize what was heard, ask questions, express preferences
  - Refer patient to trustworthy materials to aid understanding
  - Collaborate with the patient to determine ultimate plan

Grundy SM, et al. J Am Col Cardiol 2018. doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Pharmacists Impact in Managing Dyslipidemia

- Multiple studies have determined that pharmacist-driven dyslipidemia management results in reductions in LDL-C (often greater than usual care)
- RxAct study has demonstrated that pharmacist-driven dyslipidemia management resulted in a 3-fold increase inpatients who achieved target LDL-C goals compared to the standard of care
- RxEACH study was the first large randomized trial of CVD risk reduction (HTN, dyslipidemia, DM) by community pharmacists, demonstrating a significant reduction in risk for CVD events
- A cluster RCT of a pharmacist led collaborative intervention on statin prescribing demonstrated improve statin prescribing and cholesterol target attainment
  - Patients receiving statin outreach support by pharmacists were significantly more likely to have cholesterol at target (69.5% vs 63.5%; OR 1.11, CI 1.00-1.23; p = 0.043)

PLoS One. 2014 Nov 18;9(11):e113370.
Can Pharm J/Rev Pharm Can 2016;149:283–92. Can Pharm J. 2017 Jul 7;150(4):243-250. J Am Coll Cardiol 2016;67:2846-54.
Pharmacotherapy 2000;20:1508–16. Pharmacotherapy 2000;20:410–6. J Manag Care Pharm 2005;11:763–71.

AHA Scientific Statement: Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins

- Specific recommendations for statins with common cardiovascular medications:
  - Other lipid-lowering agents, CCBs, antiarrhythmics, antianginals, anticoagulants, antiplatelets, vasopressin receptor antagonists, calcineurin inhibitors, heart failure medications
- Examples:
  - Doses of lovastatin or simvastatin >20 mg daily when co-administered with amlodipine are not recommended

Wiggins BS, Saseen JJ, et al. *Circulation* 2016:134:e468-e495.

Models where Pharmacists Providing Direct Patient Care for Hypercholesterolemia

- Face-to-face disease state management
  - Ambulatory clinic
  - Community pharmacy
- Collaborative drug therapy management protocols that allow
  - Titration and initiation of medications
  - Laboratory monitoring
  - Adherence assessment
- Inpatient/outpatient Interprofessional models of care
- Telephonic outreach and follow-up
- Prospective population health outreach

Clinical Case...

A 52-year-old Hispanic male with hypertension, gout, and history of MI 2 months ago was started on rosuvastatin 20 mg daily after his MI and he is here today for follow-up. Labs are below:

- (Pre-treatment) TC 207 mg/dL, HDL-C 45 mg/dL, LDL-C 130 mg/dL, triglycerides 160 mg/dL
- (Today) TC 174 mg/dL, HDL-C 44 mg/dL, LDL-C 100 mg/dL, triglycerides 150 mg/dL

Which of the following is the first assessment that is warranted based on this patient's presentation?

a) Thyroid stimulating hormone
b) Medication adherence
c) ASCVD risk score
d) Medication cost

KEY TAKEAWAYS

1) **KEY TAKEAWAY #1**
   Use statin therapy with intensity based on level of ASCVD risk

2) **KEY TAKEAWAY #2**
   Evaluate LDL-C lowering response after implementing therapy to determine if goal % lowering is achieved and if at or above threshold value to intensify therapy or add a nonstatin

3) **KEY TAKEAWAY #3**
   Pharmacists led intervention improve initiation of guideline directed medical therapy and clinical outcomes for patients with hypercholesterolemia