When Should You Start Statin Therapy and/or Consider Other Lipid Lowering Medications?

Marc-Andre Cornier, M.D.
Professor of Medicine
Division of Endocrinology, Metabolism & Diabetes
Anschutz Health & Wellness Center
University of Colorado School of Medicine
UC Health Lipid Clinic and Lipoprotein Apheresis Program
marc.cornier@ucdenver.edu

University of Colorado
Anschutz Medical Campus

uchealth

Disclosures

None

Objectives

- Using the “new” *2018 Guideline on the Management of Blood Cholesterol*:
  - Identify higher risk patients who can benefit from LDL-cholesterol lowering with statins
  - Review the recommendations on risk assessment and treatment in primary prevention of ASCVD.
  - Discuss the management of the secondary prevention patient.
  - Describe the role of non-statin therapies in the management of elevated cholesterol

Case 1:

64 y/o woman presents for routine care. Besides being a little overweight and fairly sedentary she is otherwise healthy. She does not take any medications. She went through menopause at age 50 and was on HRT for jus a year or two. She is concerned about her family history of early CVD. She tries to eat a healthy diet, but she does not exercise much. She is former remote smoker. She drinks wine occasionally. Her ROS is otherwise essentially negative.

Exam: BP 134/80 Wt-188 BMI 27 WC 36”
otherwise normal exam

Should we screen her for hyperlipidemia?

If so, what test(s) should we order?

Determine Lipoprotein Levels

- Adults 20 y/o and older should have lipid panel done at least every 4-6 years
- Obtain *complete lipid profile* after 8-12 hr fast (if possible)
  - Can be done non-fasting if no high fat intake within 8 hours
  - Repeat in fasted state if TG's are elevated (esp if >400 mg/dl)
- LDL is still the primary lipoprotein of "interest"
- Newer "Modified Calculation" is more accurate
- Direct LDL-C can be considered when the LDL is very low or with hypertriglyceridemia
- Caveats:
  - Biologic and seasonal variation 4-12%
  - Lab variability 5 – 7%

Case 1:

64 y/o woman presents for routine care. Besides being a little overweight and fairly sedentary she is otherwise healthy. She does not take any medications. She went through menopause at age 50 and was on HRT for jus a year or two. She is concerned about her family history of early CVD. She tries to eat a healthy diet, but she does not exercise much. She is former remote smoker. She drinks wine occasionally. Her ROS is otherwise essentially negative.

Exam: BP 134/80 Wt-188 BMI 27 WC 36”
otherwise normal exam

Labs: Tchol 221 TG 238 HDL 39 LDL 134
Glu-102 A1c 5.9% AST-12 ALT-16

What now, start a statin?

“Pre-2013”: NCEP ATP III

Risk Category	LDL-C Goal (mg/dL)
≤1 RF	<160
≥2 RFs (CAD risk ≤20%)	<130 optional: <100
CAD or CAD risk equivalent (CAD risk >20%)	<100 optional: <70* *consider in “very high-risk” patients

Grundy et al. *Circulation*. 110:227, 2004

2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults

4 Major Statin Benefit Groups:

1. Individuals with known clinical ASCVD
2. Individuals with LDL ≥ 190 mg/dl
3. Individuals with diabetes (>40 yo and LDL>70)
4. Individuals (>40 yo, LDL>70) without ASCVD or diabetes who have an estimated 10-year ASCVD risk ≥ 7.5%

Stone et al. *Circulation* 2013

2018 ACC/AHA Guideline on the Management of Blood Cholesterol

Statin Benefit Groups:

1. known clinical ASCVD
2. Individuals with LDL ≥ 190 mg/dl
3. Individuals with diabetes (>40 yo and LD
4. Individuals (>40 yo, LDL>70) without AS who 0-year ASCVD risk ≥ 7.5%

Consider those at "very high risk" and LDL ≥70 mg/dl for more aggressive therapy

Assess 10-yr ASCVD risk if LDL>70

Consider different levels of risk from low to high

Special populations:
Younger (<40)
Older (>75)
Women
Ethnicity/Race

Expanded list of "Risk Enhancing" Factors

Grundy et al. *Circulation* 2018

Primary Prevention of ASCVD

2018 ACC/AHA Guideline on the Management of Blood Cholesterol

4 Major Statin Benefit Groups:

1. Individuals with known clinical ASCVD
2. **Individuals with LDL ≥ 190 mg/dl**
3. **Individuals with diabetes (>40 yo)**
4. **Individuals (>40 yo, LDL>70) without ASCVD or diabetes who have an elevated 10-year ASCVD risk**

Grundy et al. *Circulation* 2018

Severe Hypercholesterolemia

- Guideline recommendations for patients 20-75 yrs with an LDL ≥190:
  - High-Intensity (maximally-tolerated) statin therapy
  - If achieve less than a 50% reduction in LDL and/or LDL ≥100, consider adding:
    - Ezetimibe
    - Bile Acid Sequestrant (if TGs <300)
    - PCSK9 inhibitor
    - Bempedoic acid
- Screen family members
- Screen for elevated Lipoprotein(a)

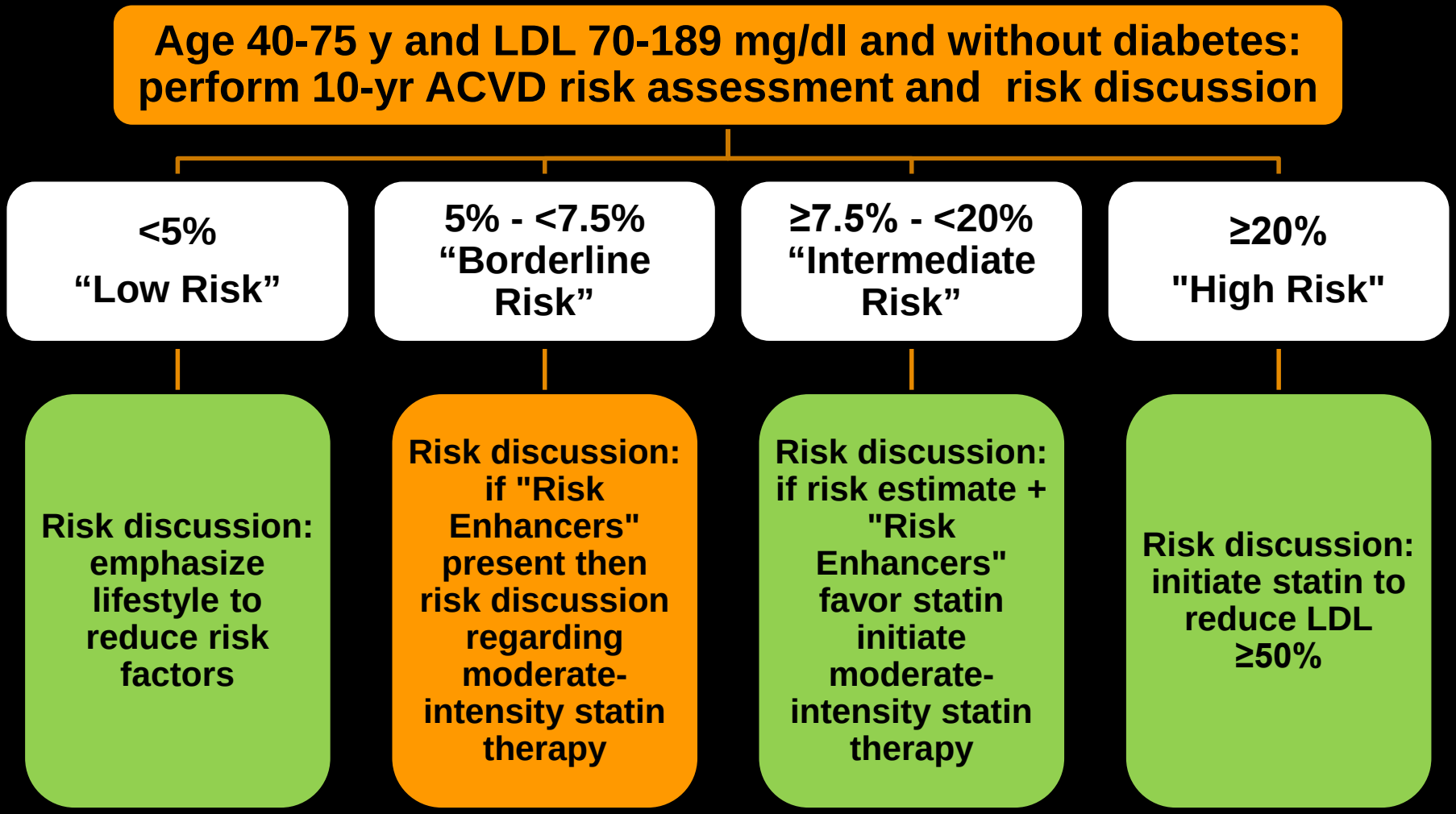
Recommendations for Patients with Diabetes Mellitus (aged ≥ 40)

- Consider moderate-intensity statin therapy regardless of 10-year ASCVD risk
- If LDL ≥70, assess 10-year ASCVD risk and consider high-intensity statin therapy if elevated and/or multiple ASCVD risk factors present
- If 10-year ASCVD risk ≥20% and if achieve less than a 50% reduction in LDL with maximally tolerated statin, then consider adding ezetimibe
- Reasonable to initiate statin therapy in those <40 yo and with diabetes of long duration (T2D ≥10 yrs, T1D ≥20 yrs) and/or microvascular disease

Risk Calculator: Pooled Cohort Equations for ASCVD

- Risk factors used in calculation
  - Sex
  - Age
  - Race (White, African American, other)
  - Total Cholesterol (untreated)
  - HDL
  - Systolic BP (current)
  - Treatment for HTN (Y/N)
  - Diabetes (Y/N)
  - Smoker (Y/N)

Primary Prevention: Assess ASCVD Risk and Emphasize Adherence to Healthy Lifestyle



Grundy et al. *Circulation* 2018

“Risk Enhancing Factors”

Historical Factors

- Family history of premature ASCVD
- Metabolic syndrome
- CKD (no dialysis or transplant)
- Chronic inflammatory disorders (RA, SLE, HIV,...)
- History of premature menopause or pregnancy-related conditions (eclampsia)
- High-risk race/ethnicities (e.g., South Asian ancestry)

Grundy et al. *Circulation* 2018

“Risk Enhancing Factors”

Biomarkers

- Primary hypercholesterolemia: LDL >160
- Hype
- Elev
- Elev
- Elev
- Ankl
- Corc
  - CAC score is ≥100 or ≥75th percentile
  - CAC score is 1-99 in patients ≥55 y
  - Reasonable to withhold statin therapy if CAC is zero

If it potentially changes your management then consider further risk assessments?

Most useful in “moderate risk” patients

Grundy et al. *Circulation* 2018

Case 1: Assessment and Plan

1. Mixed Hyperlipidemia: with moderately elevated TG, low HDL, and a “normalish” LDL
   - Assess 10-yr ASCVD Risk
     - 9.8% = Intermediate Risk
   - Assess for Risk Enhancers:
     - Family history of premature ASCVD
     - Metabolic Syndrome
     - Hypertriglyceridemia
   - Should we consider checking an apo B level in light of her hypertriglyceridemia?
   - Should we consider checking an Lp(a) level especially in light of her family history of premature ASCVD?

*2018 ACC/AHA Guideline on the **Management** of Blood Cholesterol*

Lifestyle modification

- Heart Healthy Dietary Pattern
  - Mediterranean or DASH Diet patterns
  - Emphasize fresh vegetables/fruits, whole grains, low-fat dairy, poultry, fish, legumes, nuts, vegetable oils
- Regular exercise
- Avoidance of tobacco
- Maintenance of a healthy weight

Grundy et al. *Circulation* 2018

*2018 ACC/AHA Guideline on the **Management** of Blood Cholesterol*

Statin Therapy by Intensity

*High-Intensity Statin Therapy	*Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C on average by ≥ 50%	Daily dose lowers LDL-C on average by 30-50%	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 40 mg BID Pitavastatin* 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin* 1 mg

Grundy et al. *Circulation* 2018

Case 1: Assessment and Plan

1. Mixed Hyperlipidemia:
   - "intermediate risk" + multiple "Risk Enhancing Factors"
   - Check Apo B and Lp(a)
   - r/o secondary causes of dyslipidemia: TSH, UA, CMP
   - Recommend healthy lifestyle and weight loss
   - Recommend starting "moderate-intensity" statin
     - In light of family history and multiple risk enhancing factors, I would consider high-intensity statin
     - Discuss potential side/adverse effects
     - Don't start a new exercise regimen at the same time!

Case 2:

- 66 y/o woman with h/o of ASCVD (NSTEMI with stent at age 64, TIA at age 65) and hypertension. Doing well.
- Medications: atorvastatin 80 mg, lisinopril, aspirin, levothryoxine, omeprazole
- Family Hx: no clear premature ASCVD
- Social: heart healthy diet, walks 45 min/d, non-smoker

Exam: BP 130/80 BMI 26 otherwise normal exam

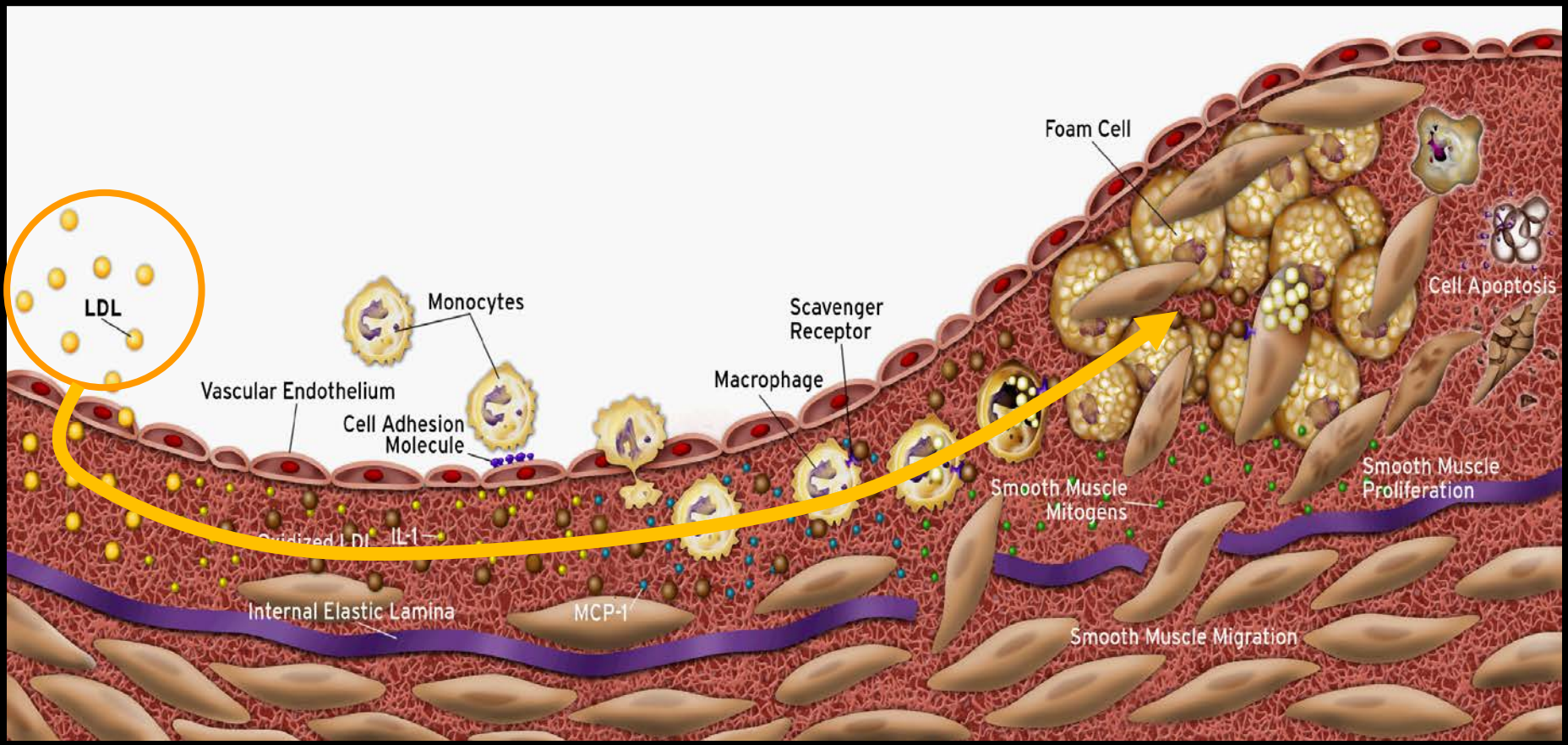
Labs: TChol 171 TG 125 HDL 48 LDL 98

Is this adequate?

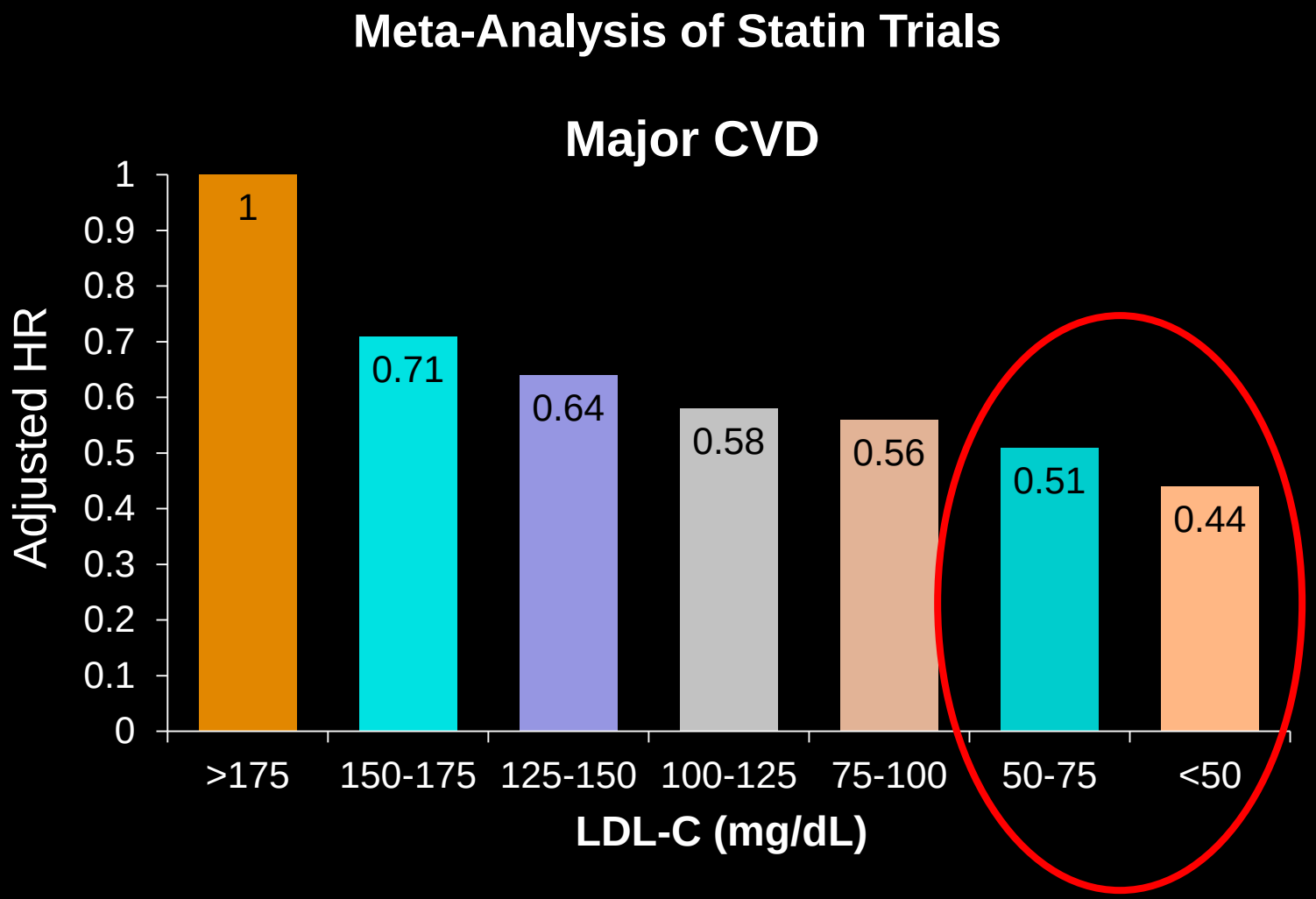
Is “goal therapy” ever indicated?

What do the guidelines recommend?

Atherosclerosis and Plaque Pathogenesis



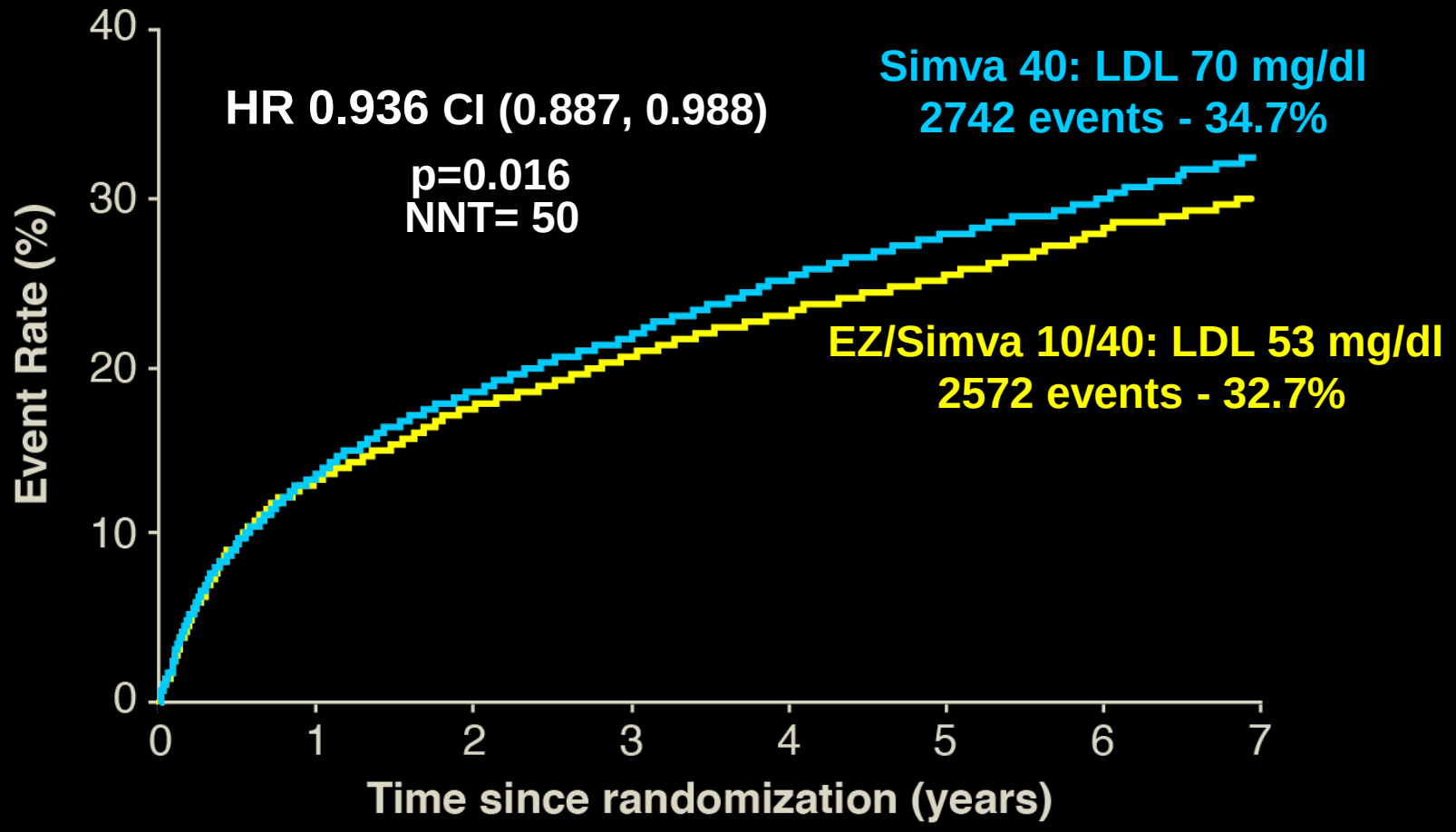
Relationship Between On-Treatment LDL-C and Risk for CV Events: Meta-Analysis



Boekholdt et al. *J Am Coll Cardiol* 64:485-494, 2014

IMPROVE-IT: Primary Endpoint

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

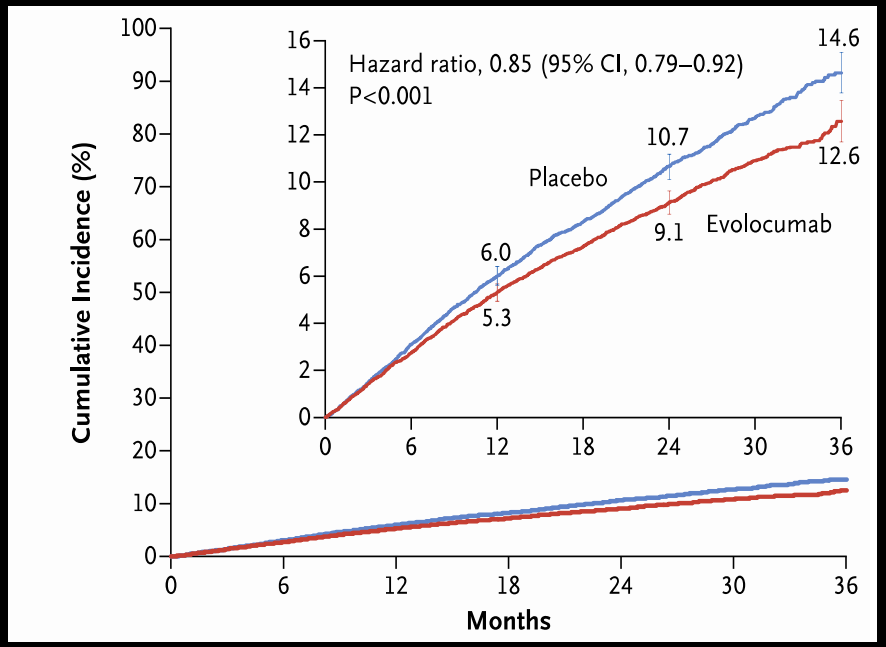


Cannon CP, et. al. *NEJM* 372:2387, 2015

PCSK9 Inhibitors – CV Outcome Trials

FOURIER:

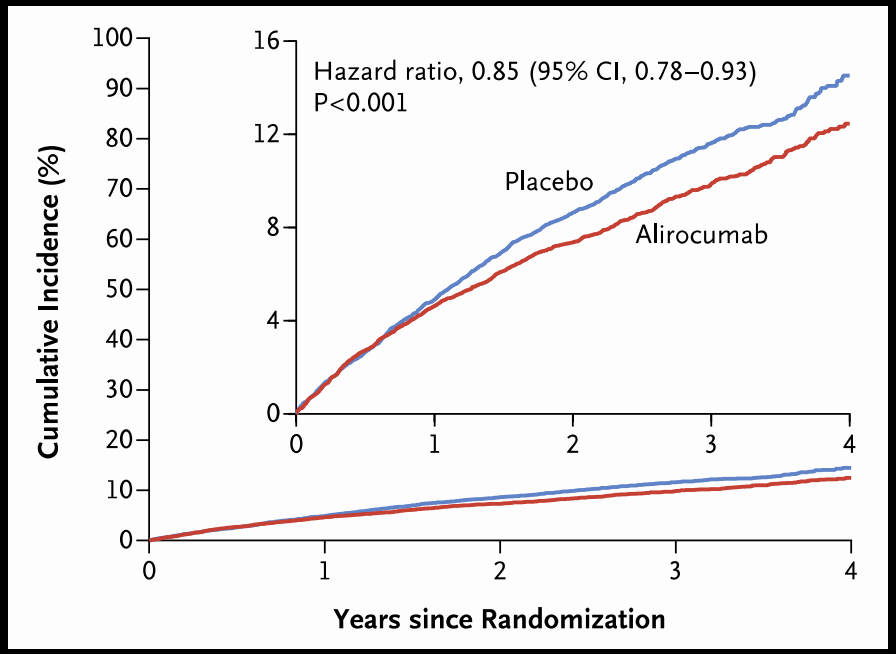
- 27,564 patients with h/o ASCVD and LDL-C ≥70
- LDL-C 92 vs 30 mg/dl with Evolocumab



Sabatine et al. *NEJM*, 2017.

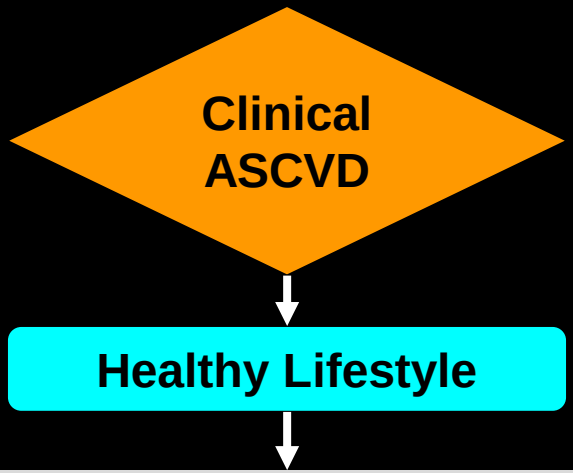
ODYSSEY OUTCOME:

- 18,924 patients with h/o ACS and LDL-C ≥70
- LDL-C 103 vs 66 mg/dl with Alirocumab



Schwartz et al. *NEJM*, 2018.

Secondary Prevention in Patients with Clinical ASCVD



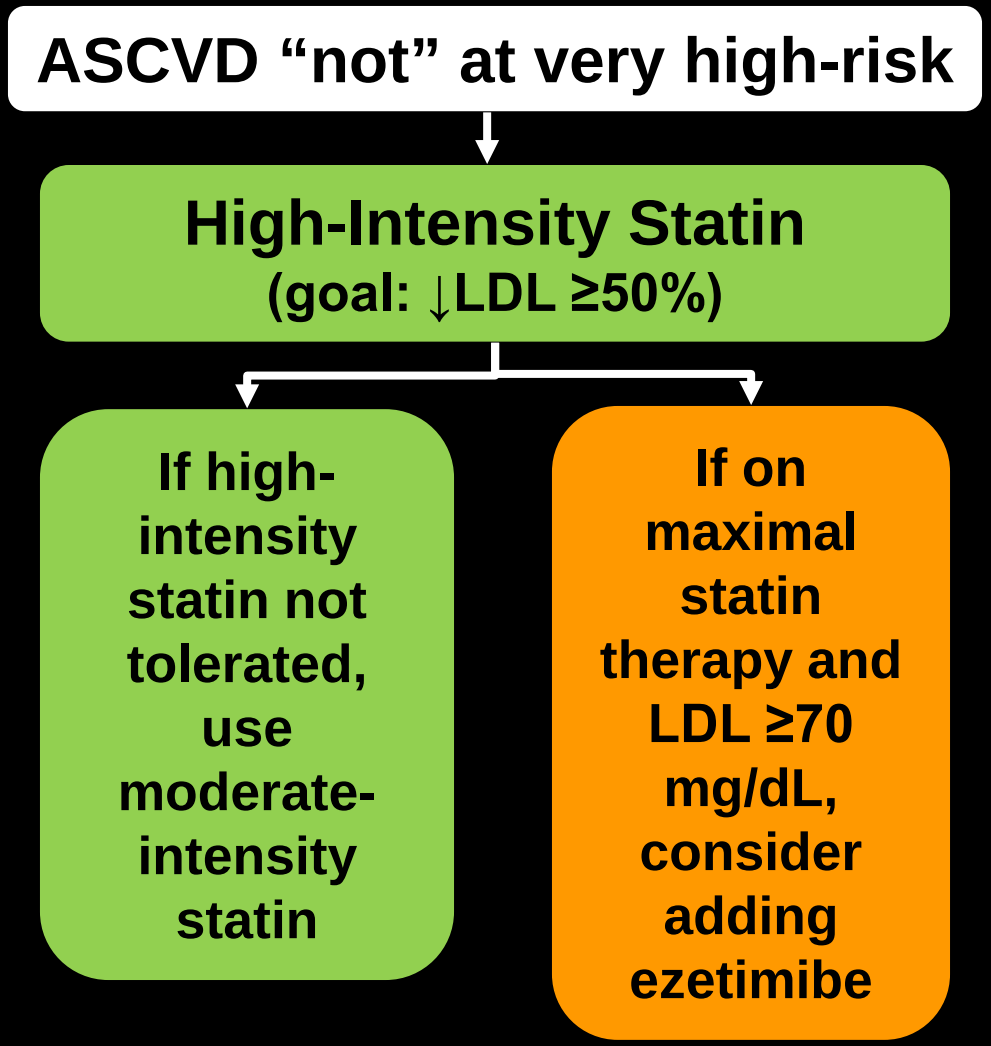
Assess for "Very High-Risk":

- **History of multiple major ASCVD events**

  or

- **Multiple high-risk conditions:**
  - **Age ≥65y**
  - **History of CABG or coronary interventions**
  - **Diabetes**
  - **Hypertension**
  - **CKD**
  - **Smoking**
  - **CHF**
  - **Persistently elevated LDL (≥100 mg/dL)**

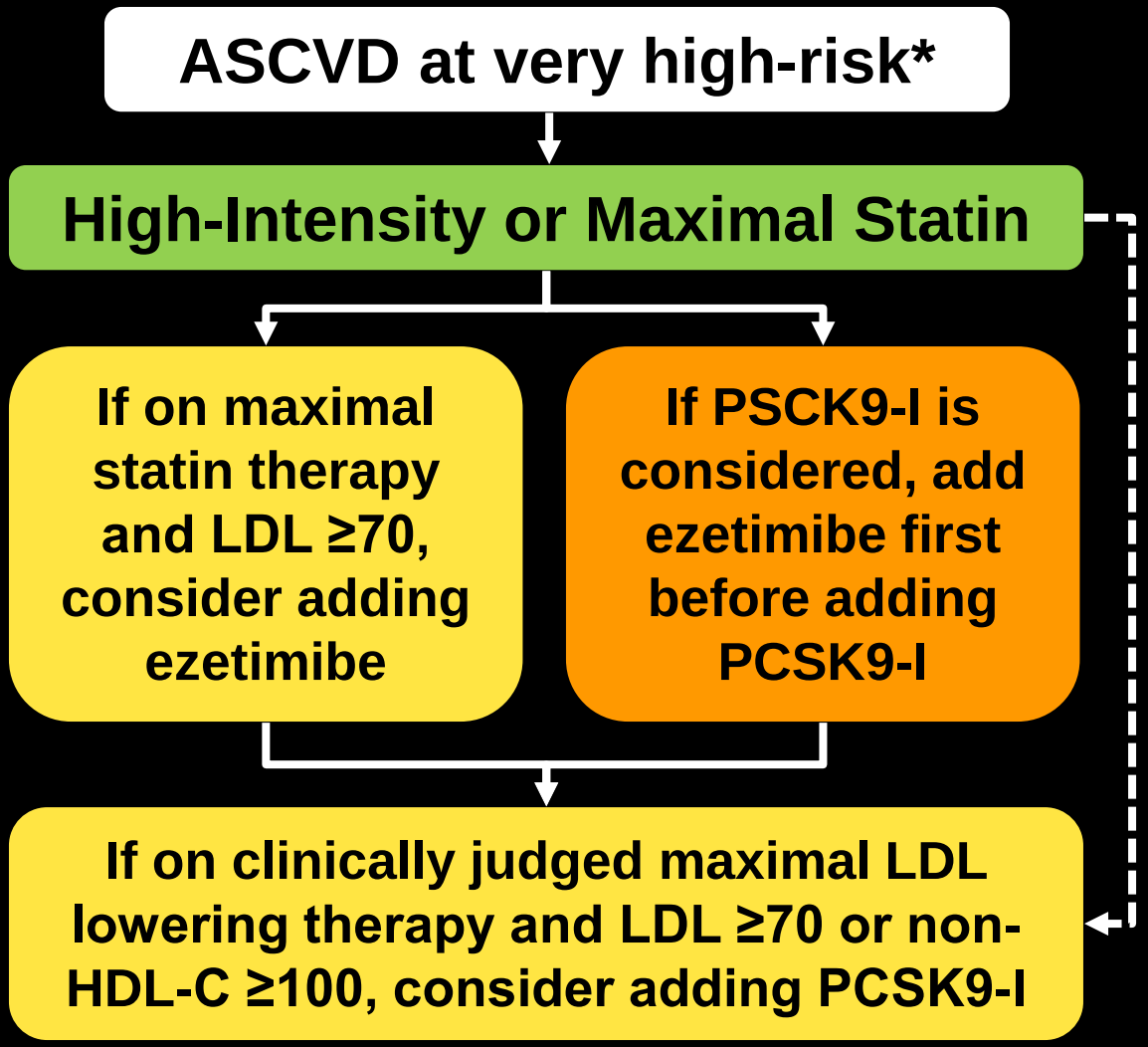
Secondary Prevention in Patients with Clinical ASCVD



*Age >75 y: initiation and/or continuation of statin is reasonable

Grundy et al. *Circulation* 2018

Secondary Prevention in Patients with Clinical ASCVD



Grundy et al. *Circulation* 2018

PCSK9 Inhibitors: Where do they fit in?

- Increase LDL-C clearance by upregulating LDL-Receptors
- ↓ LDL-C by 50-70%
- Reduce ASCVD events
- Well tolerated and safe even with very low LDL-C levels
- Indicated when “more” LDL-C lowering is needed despite maximally tolerated statin therapy in patients with:
  - “known” clinical ASCVD (high risk patients)
  - “Primary” or Familial Hypercholesterolemia
  - Elevated Lp(a)?
- Dosing:
  - Alirocumab (*Praluent*): 75-150 mg SC every 2 weeks
300 mg SC every 4 weeks
  - Evolocumab (*Repatha*): 140 mg SC every 2 weeks
420 mg SC every 4 weeks

Case 2:

- ASCVD and Hypercholesterolemia:
  - Why did she have premature and recurrent ASCVD?
    - Consider checking an Lp(a)
  - Per the new guidelines she is at “very high risk”:
    - multiple major ASCVD events and multiple high risk conditions
  - While she is on high intensity statin therapy, her LDL is >70 so consider more aggressive therapy.
  - Options include:
    - Intensify statin therapy: switch to rosuvastatin 40mg
    - Consider adding ezetimibe first and then consider adding a PCSK9 inhibitor if LDL still >70
    - Go straight to adding a PCSK9 inhibitor
  - Guidelines are meant to be exactly that: “guidelines”

Summary

- Assess ASCVD risk and start appropriate statin dose in high risk patients
- Start with high-intensity statin therapy in the highest risk patients and those with ASCVD
- If cannot tolerate higher dose statins go to maximally tolerated dose
- Consider non-statin lipid lowering therapies in those not at goal on maximally tolerated statin

Thank You!