Recent Updates in Hyperlipidemia Management

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Faculty Disclosure

- I have no conflicts of interest or financial relationships to disclose.

Educational Need/Practice Gap

- In recent years, there have been several updates in the management of low-density lipoprotein cholesterol (LDL-C) lowering in response to the numerous clinical trials and development of new pharmacologic treatments.

- This educational session will assist clinicians in analyzing the data, prescribing novel cholesterol lowering therapies, and how to implement these recent changes into their current practice.

Objectives

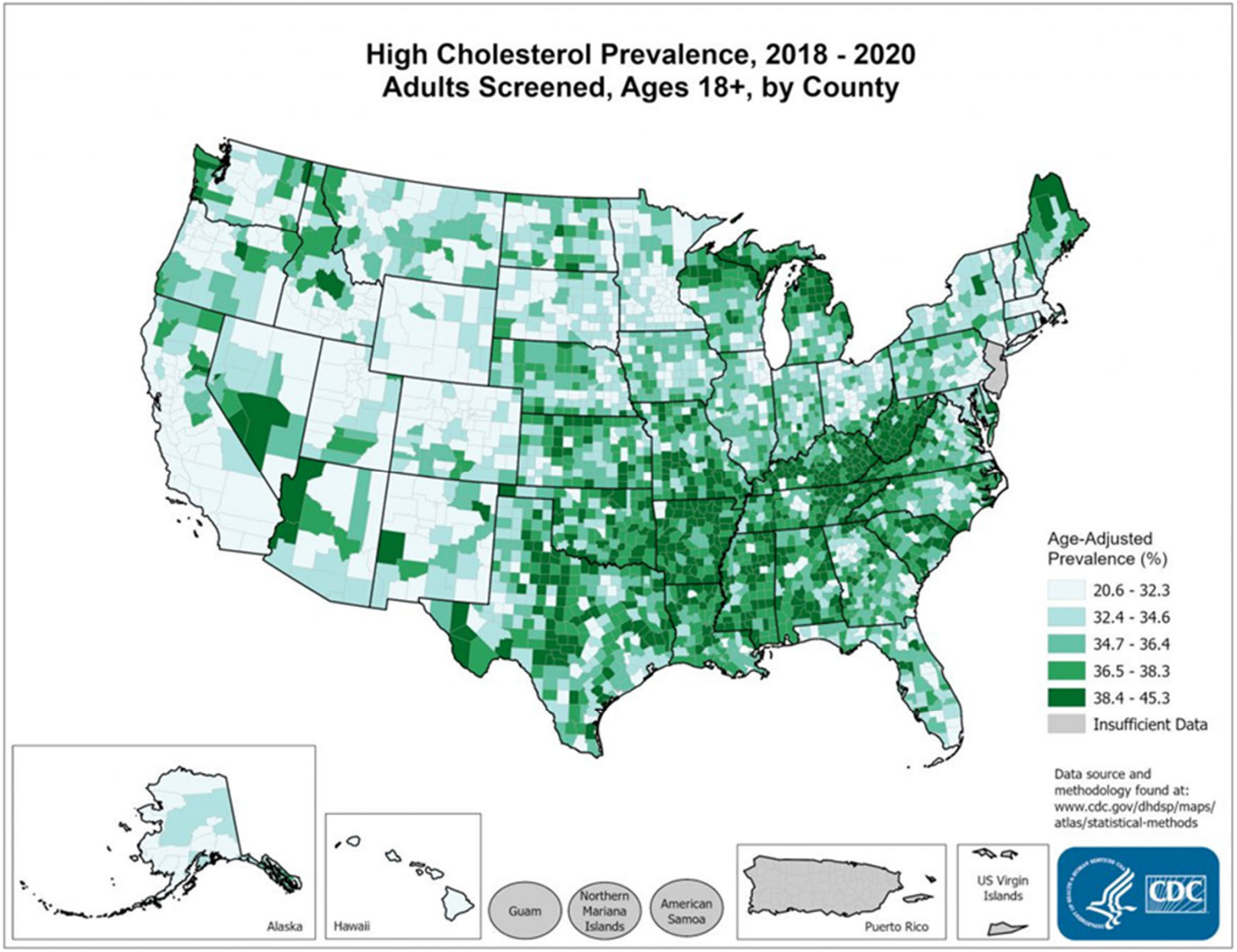
Upon completion of this educational activity, participants will be able to:

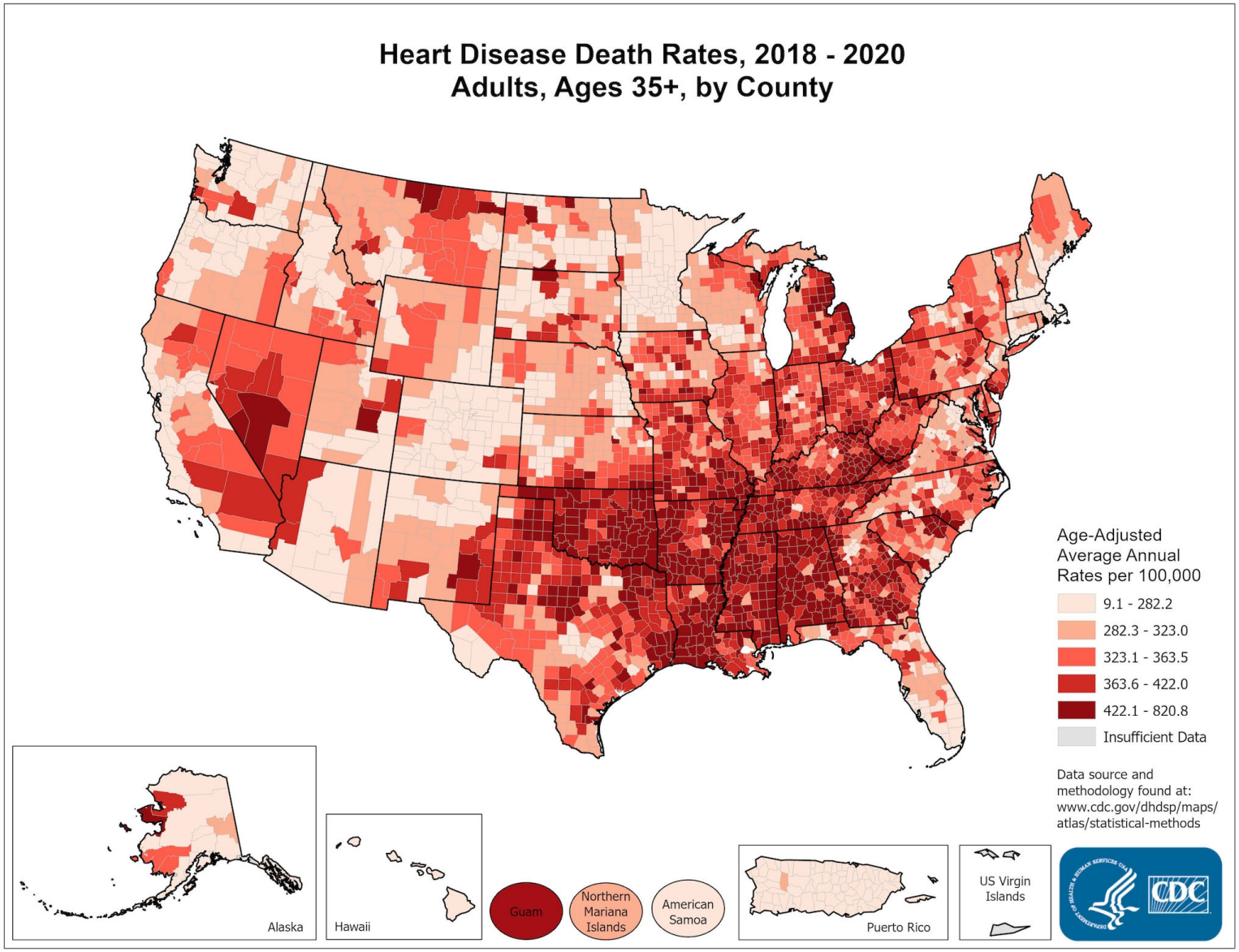
1. Describe the pharmacologic properties of the various drug classes used for the treatment of low-density lipoprotein cholesterol (LDL-C) lowering
2. Summarize the 2018 American College of Cardiology/ American Heart Association (ACC/AHA) Multisociety Hyperlipidemia Guidelines and identify the updates published in the 2022 ACC Expert Consensus Decision Pathway for the Role of Non-Statin Therapies for LDL-C Lowering
3. Discuss the cardiovascular outcomes data for the novel pharmacologic agents used in the treatment of elevated LDL-C and how this data may change our current practices
4. Identify clinician and patient barriers to optimizing LDL-C lowering pharmacotherapies

Expected Outcome

- Increase the comfortability of clinicians to prescribe novel treatments for LDL cholesterol and identification of cholesterol treatment barriers

- To optimize LDL-C lowering and reduce overall atherosclerotic cardiovascular disease (ASCVD) risk for patients


High Cholesterol Prevalence, 2018 - 2020
Adults Screened, Ages 18+, by County
Age-Adjusted Prevalence (%)
20.6 - 32.3
32.4 - 34.6
34.7 - 36.4
36.5 - 38.3
38.4 - 45.3
Insufficient Data
Data source and methodology found at: www.cdc.gov/dhdsp/maps/atlas/statistical-methods
Alaska
Hawaii
Guam
Northern Mariana Islands
American Samoa
Puerto Rico
US Virgin Islands
CDC


Heart Disease Death Rates, 2018 - 2020
Adults, Ages 35+, by County
Age-Adjusted
Average Annual
Rates per 100,000
9.1 - 282.2
282.3 - 323.0
323.1 - 363.5
363.6 - 422.0
422.1 - 820.8
Insufficient Data
Data source and
methodology found at:
www.cdc.gov/dhdsp/maps/
atlas/statistical-methods
Alaska
Hawaii
Guam
Northern
Mariana
Islands
American
Samoa
Puerto Rico
US Virgin
Islands
CDC

Cholesterol Screening Recommendations

Lipid panel is recommended in all adults > 20 years of age

- Recommendations for even earlier screening in patients with known family history of early cardiovascular disease (CVD) or severe hypercholesterolemia

Lipid panel does not need to be fasting in most cases

- If triglyceride (TG) levels > 400 mg/dL, recommended to repeat test while fasting
- In high risk patients with significant family history or suspected familial hypercholesterolemia (FH), fasting sample is recommended.

Goff Jr DC, et al, 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. *Circulation 2014.*

Statins are first line for both primary and secondary prevention

Statin Pharmacology

Low-intensity (lowers LDL-C by ~30%)	Moderate-intensity (lowers LDL-C by ~30-50%)	High-intensity (lowers LDL-C by ≥ 50%)
Fluvastatin 20-40 mg	Fluvastatin 40 mg twice daily (80 mg XL)	
Lovastatin 20 mg	Lovastatin 40 mg	
Pravastatin 10-20 mg	Pravastatin 40-80 mg	
Simvastatin 10 mg	Simvastatin 20-40 mg	
	Atorvastatin 10-20 mg	Atorvastatin 40-80 mg
	Rosuvastatin 5-10 mg	Rosuvastatin 20-40 mg
	Pitavastatin 1-4 mg	

Statin Adverse Effects

Myalgias/ Myopathies	Increased liver function tests (LFTs)	Nausea Vomiting Diarrhea
Fatigue	Cognitive/ Memory Impairment	New onset or worsening diabetes

Statin Associated Muscle Symptoms (SAMS)

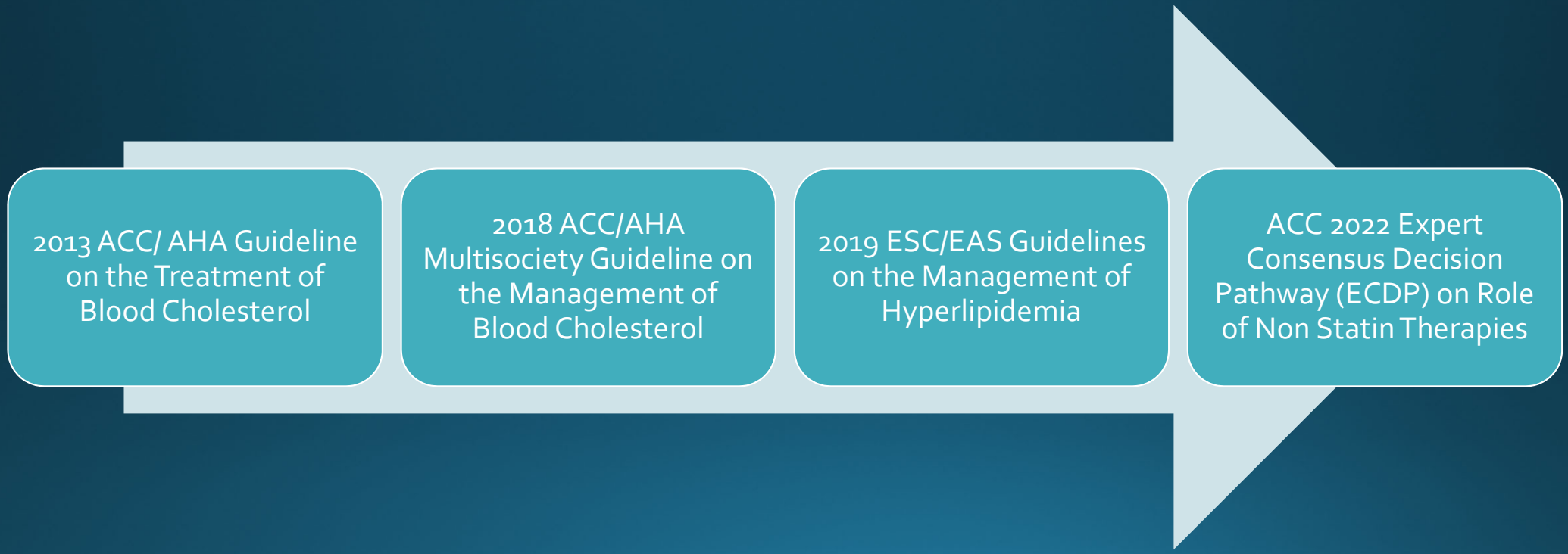
Identify reversible causes

Management of SAMS

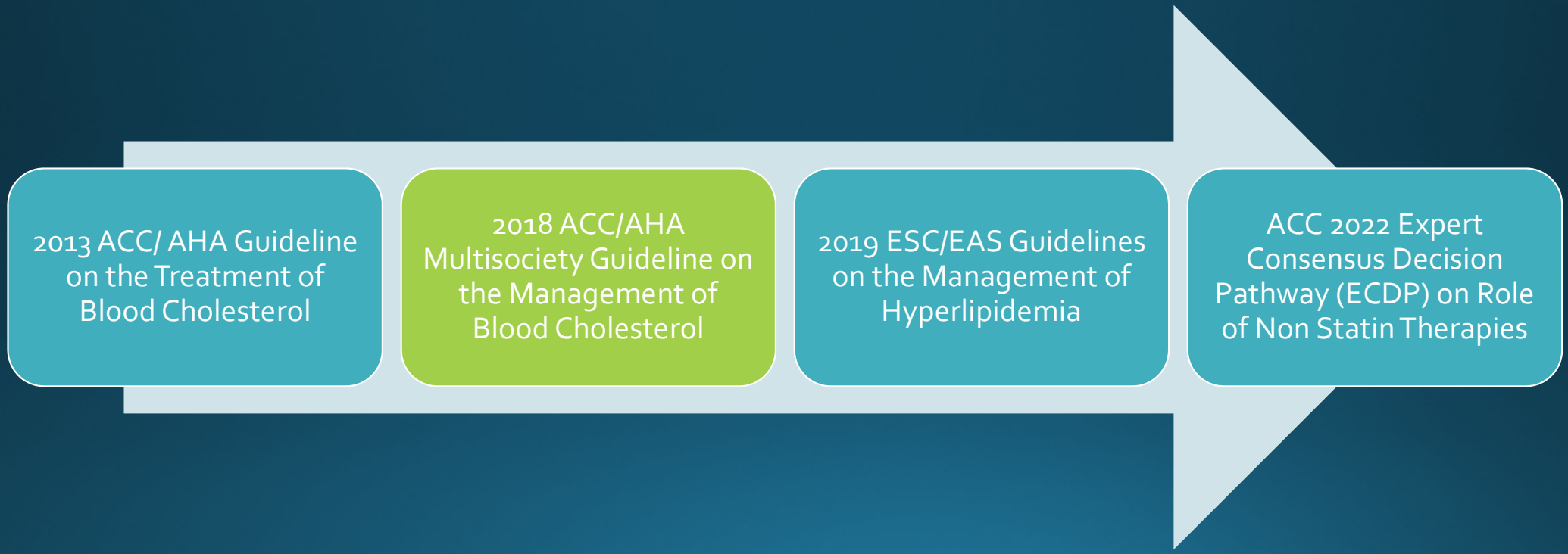
- Temporarily hold statin until resolution of symptoms
- Decrease statin dose
- Change to another statin
  - Lipophilic → hydrophilic
- Alternate Day-Dosing (atorvastatin or rosuvastatin)
- Agent from alternative class

CoQ10 supplementation or CK monitoring are not recommended

Hyperlipidemia Guidance



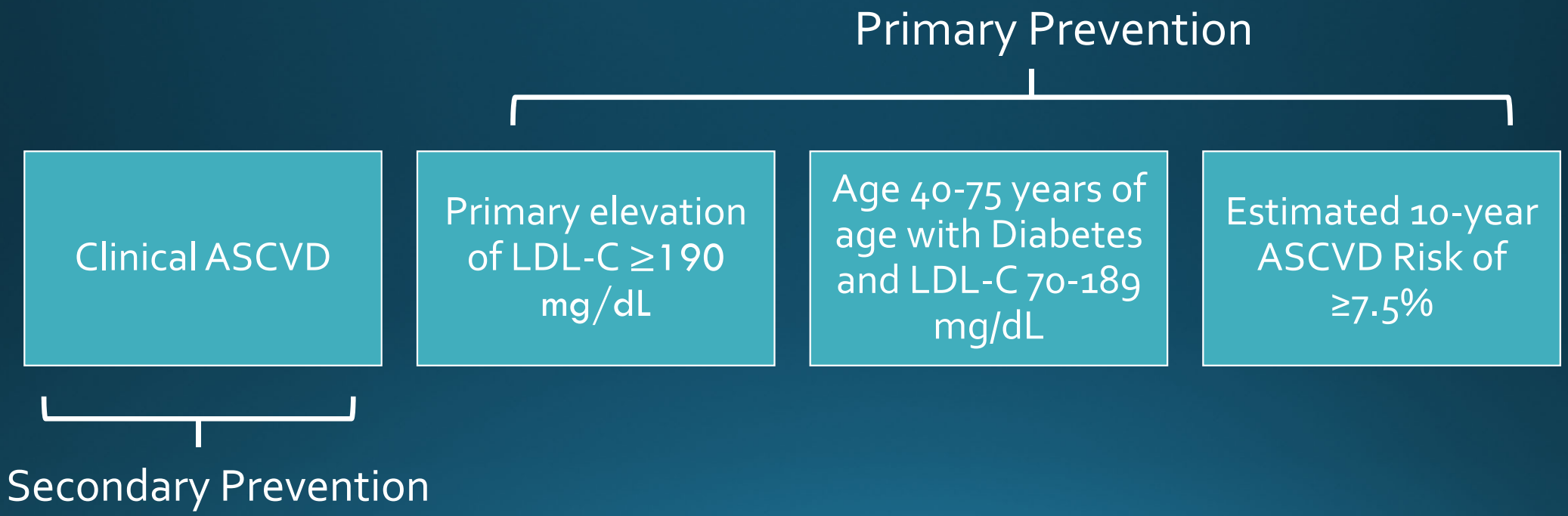
Hyperlipidemia Guidance



Lifestyle Recommendations for ALL

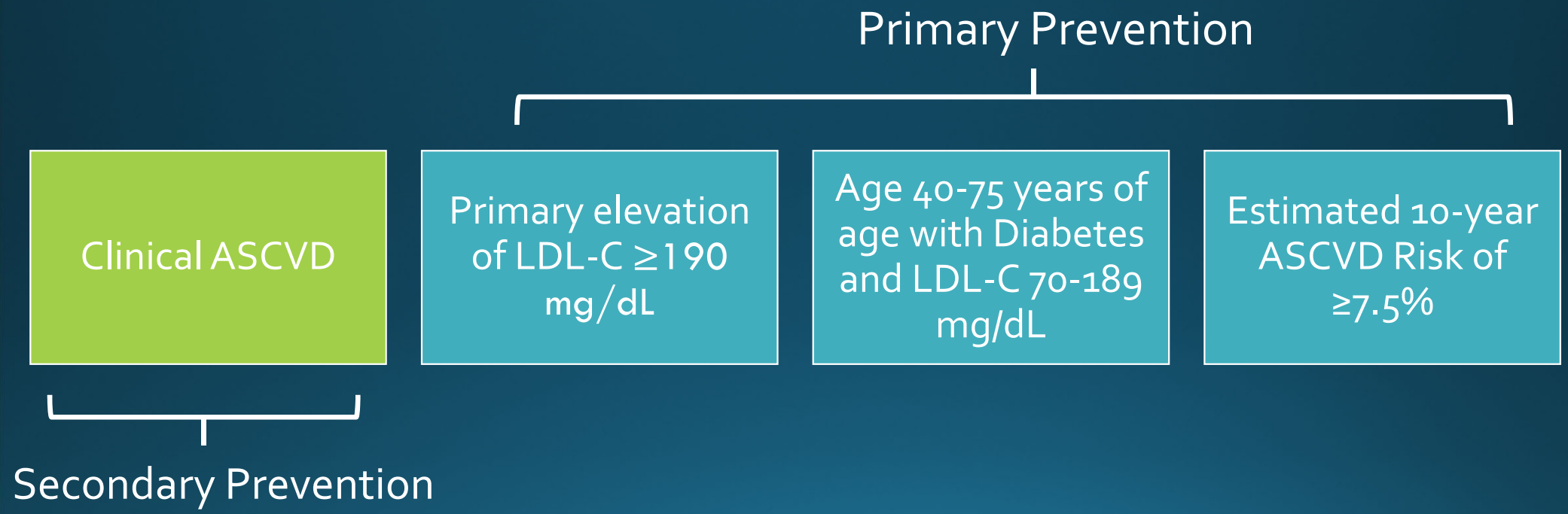
- Diet focused on intake of vegetables, fruit, legumes, whole grains, and lean and low fat protein sources
  - Limit sweets, refined carbohydrates, red meat, and saturated and trans fats
- At least 150 minutes of moderate intensity aerobic exercise
- Tobacco cessation and limiting alcohol use
- Weight loss for patients with elevated body mass index

Statin Benefit Groups



Grundy SM, Stone NJ, Bailey AL, et al. *Circulation.* 2019; 139:e1082-e1143.

Statin Benefit Groups



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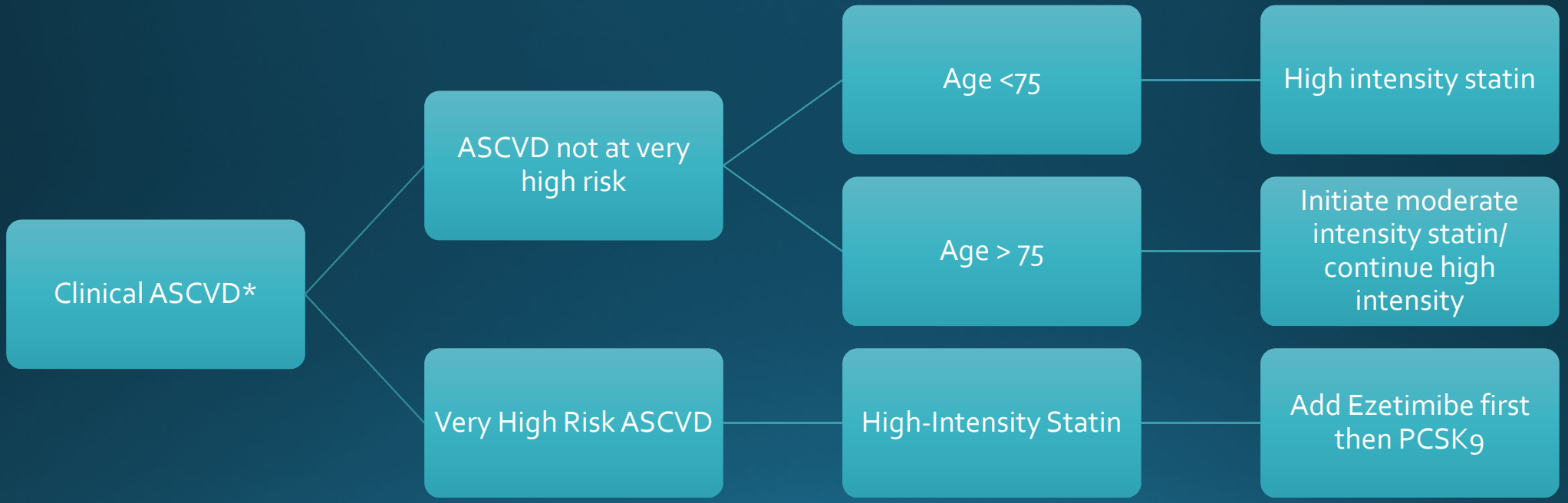
Clinical ASCVD

2018 ACC/ AHA Hyperlipidemia Guidelines



*≥ 18 years of age with history of ACS (MI, stable or UA, revascularization), stroke/TIA, or peripheral arterial disease (including aortic aneurysm)

Grundy SM, Stone NJ, Bailey AL, et al. *Circulation.* 2019; 139:e1082-e1143.

"Very High Risk"

Defined as:
Multiple major ASCVD events
OR
1 major event + multiple high-risk conditions

Major ASCVD Events

- Recent ACS in past 12 months
- History of MI (other than recent ACS listed above)
- History of ischemic stroke
- Symptomatic PAD (intermittent claudication with abnormal ABI, or revascularization or amputation)

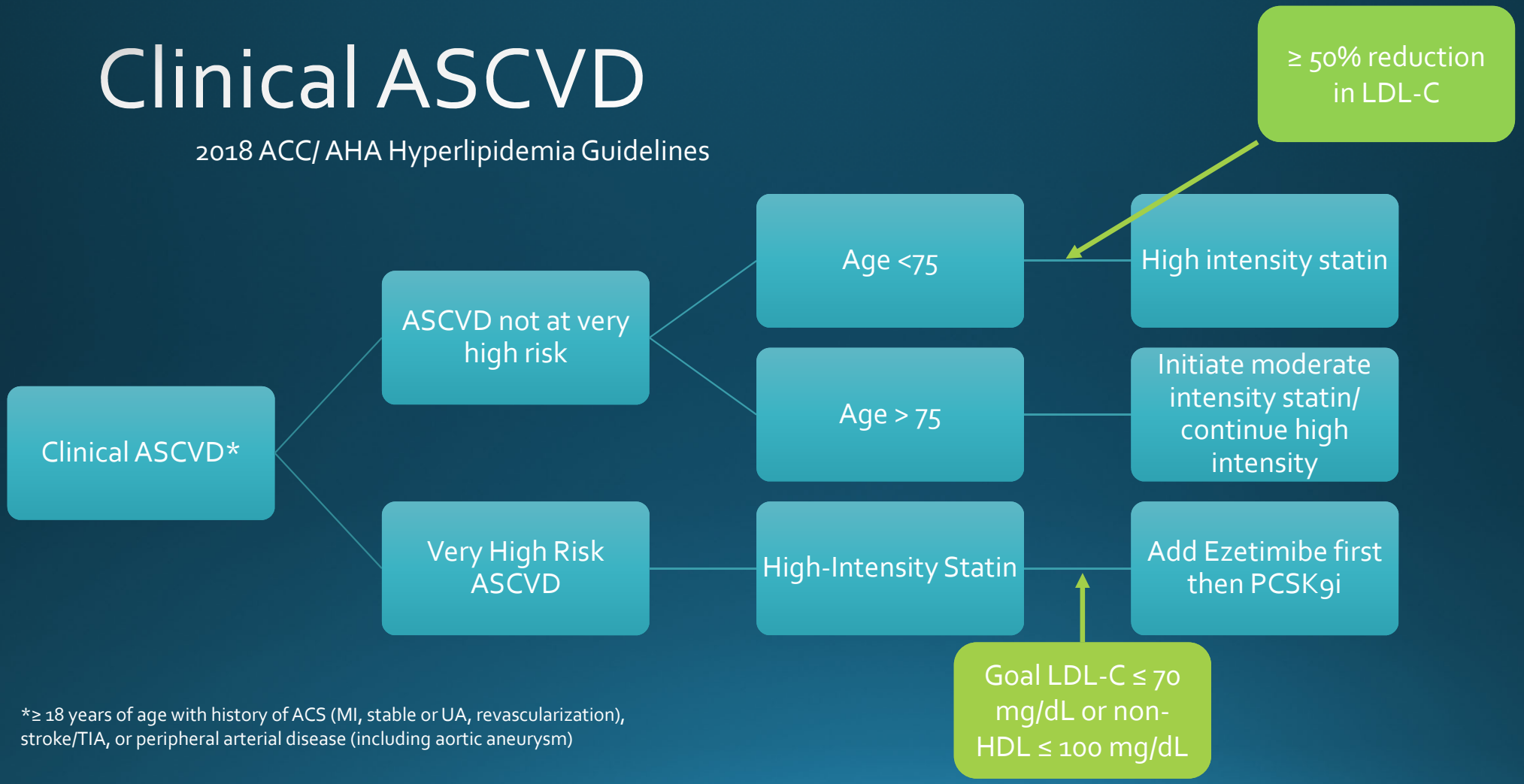
High Risk Conditions

- Age >65 years
- Heterozygous familial hypercholesterolemia
- History CABG or PCI outside major ASCVD event(s)
- Diabetes mellitus
- Hypertension
- CKD
- Current smoking
- Persistent LDL-C >100 mg/dL despite max tolerated statin and ezetimibe
- Congestive heart failure

Grundy SM, Stone NJ, Bailey AL, et al. *Circulation.* 2019; 139:e1082-e1143.

Clinical ASCVD

2018 ACC/ AHA Hyperlipidemia Guidelines



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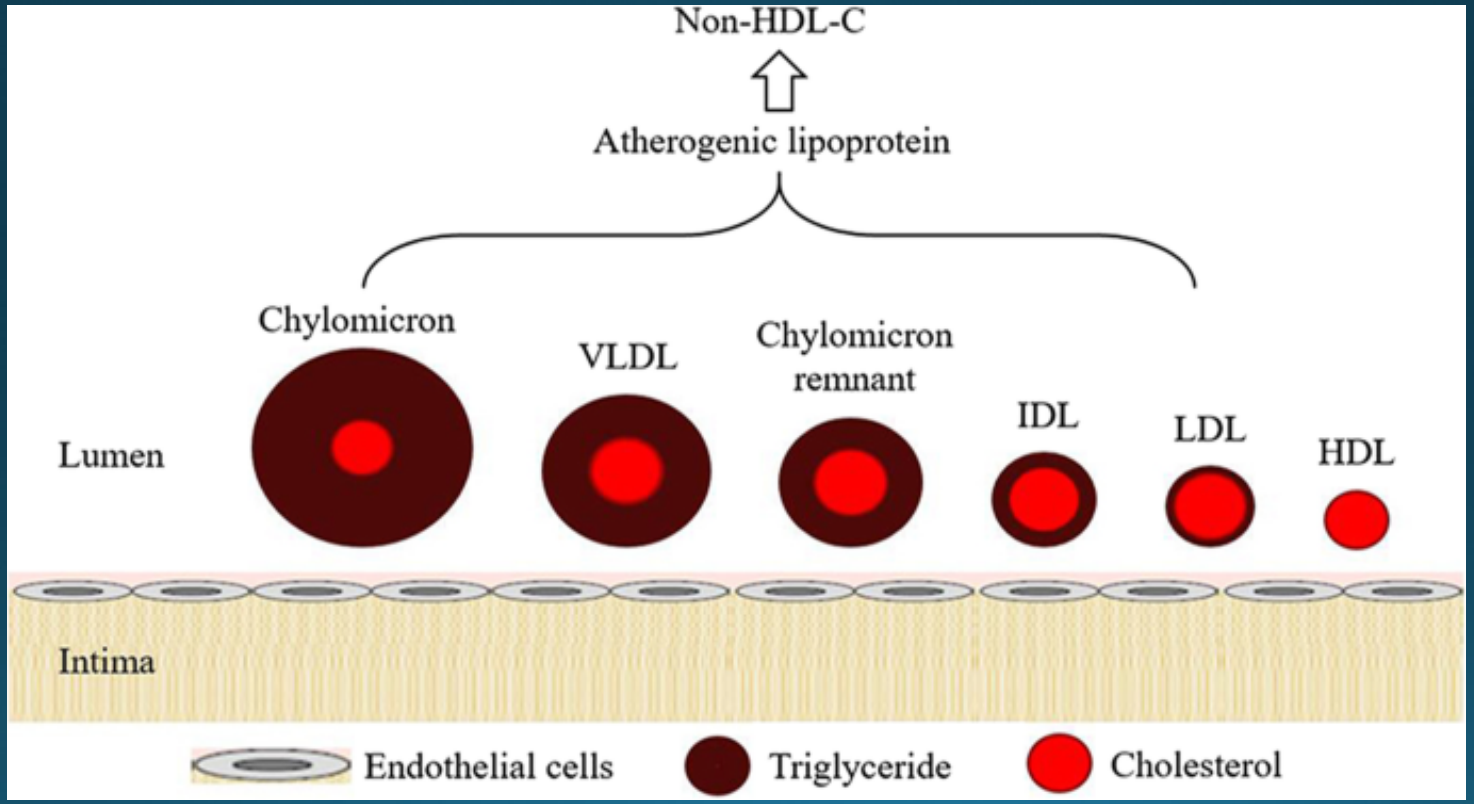
Non-HDL-C


Non-HDL-C
Atherogenic lipoprotein
Chylomicron
VLDL
Chylomicron remnant
IDL
LDL
HDL
Lumen
Intima
Endothelial cells
Triglyceride
Cholesterol

Ezetimibe

Efficacy	
LDL-C	↓ 18-20%
HDL-C	↑ 1-5%
TG	↓ 5-10%

- Mechanism of Action: Inhibits cholesterol absorption from the small intestine
- Side effects:
  - Nausea, diarrhea, bloating
  - Increased LFTs, slightly higher risk when used with statin but still low (1%)
  - Arthralgias
- Also formulated in combination with simvastatin and bempedoic acid

IMPROVE-IT

Design

- Randomized, double-blind, placebo-controlled
- Primary outcome: cardiovascular (CV) mortality, major CV event, or non-fatal stroke

Population

- 18,144 patients > 50 years of age hospitalized within the prior 10 days with acute coronary syndrome (ACS) or high-risk unstable angina

Interventions

- Simvastatin ± ezetimibe 10 mg once daily

Findings

- The addition of ezetimibe to moderate-intensity statin therapy is associated with reduction in adverse CV events over 6 years
  - Composite: 34.7% simvastatin vs. 32.7% simvastatin + ezetimibe (HR 0.94, p=0.016, NNT 50)

PCSK9 Inhibitors

Efficacy	
LDL-C	↓ 50-65%
HDL-C	↑ 2-13%
TG	↓ 15%

- Mechanism of Action: Binds to proprotein convertase subtilisin kexin type 9 (PCSK9) and inhibits its binding to LDL receptors on hepatocytes
- Side effects: injection site reactions, flu-like symptoms, myalgias
- Possibility for antibody development
- Limited drug interactions

Evolocumab (Repatha)

- 140 mg SUBQ every 14 days or 420 mg once monthly

Alirocumab (Praluent)

- 75 mg SUBQ every 14 days or 300 mg monthly
- 150 mg SUBQ every 14 days

ODYSSEY OUTCOMES

Design

- Randomized, double-blind, placebo-controlled
- Primary outcome: death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization

Population

- 18,924 patients ≥ 40 years of age with ACS event within last 12 months on maximally tolerated statin therapy or documented intolerance to statins

Interventions

- Alirocumab vs. placebo

Findings

- The addition of alirocumab to maximally tolerated statin therapy is associated with reduction in major adverse cardiovascular events over median of 2.8 years
  - Composite: 9.5% alirocumab vs 11.1% placebo (HR 0.85, $p<0.001$, NNT 63)

FOURIER

Design

- Randomized, double-blind, placebo-controlled
- Primary outcome: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization

Population

- 24,081 patients ≥ 40 years of age with clinical atherosclerotic disease on moderate or high intensity statin therapy

Interventions

- Evolocumab vs. placebo

Findings

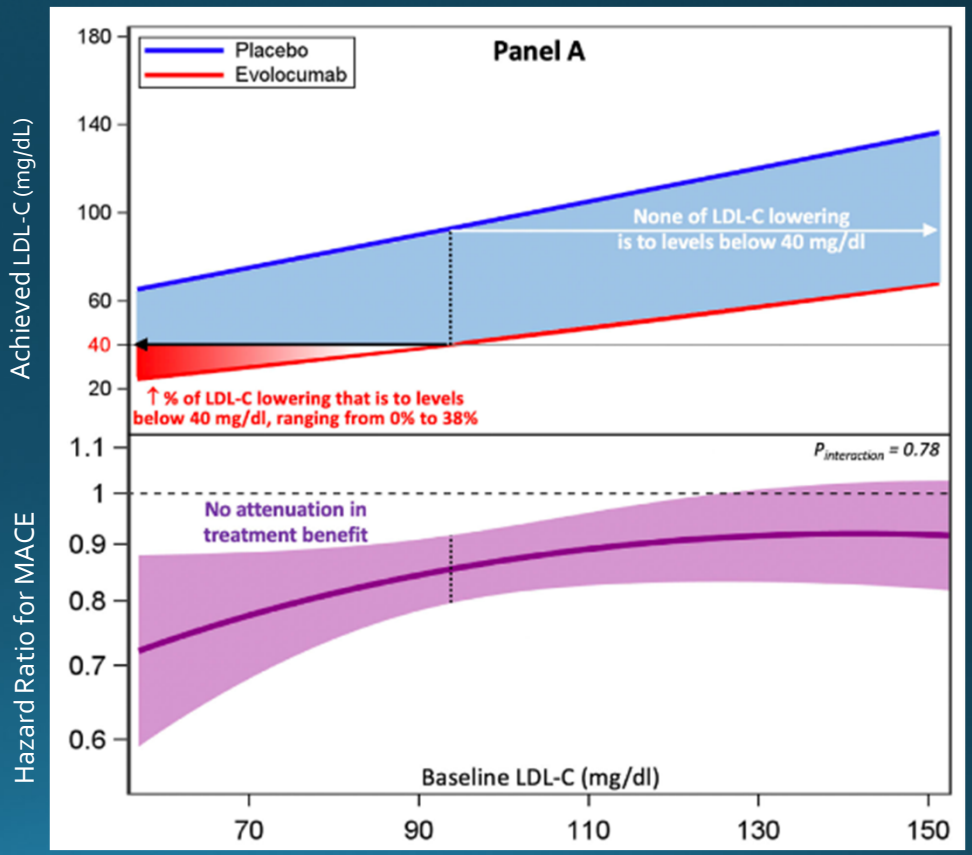
- The addition of evolocumab to statin therapy is associated with reduction in major adverse cardiovascular events over median of 26 months
  - Composite: 9.8% evolocumab vs 11.3% placebo (HR 0.85, p<0.001, NNT 74)

Schwartz et al. *N Engl J Med* 2018; 379:2097-2107.

LDL Targets for Secondary Prevention

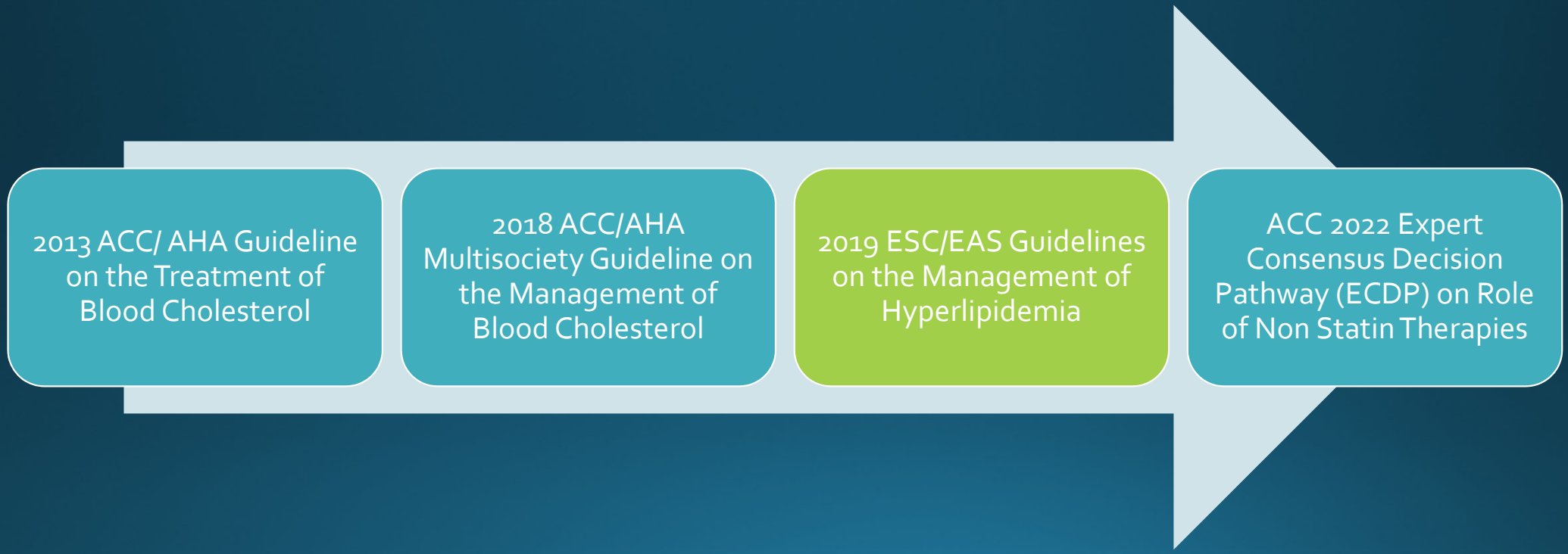
FOURIER trial exploratory analysis

- No evidence of attenuation in treatment effect in LDL-C <40 mg/dL
- No increase in adverse events (new onset diabetes, neurocognitive decline) in patients with LDL-C <40 mg/dL

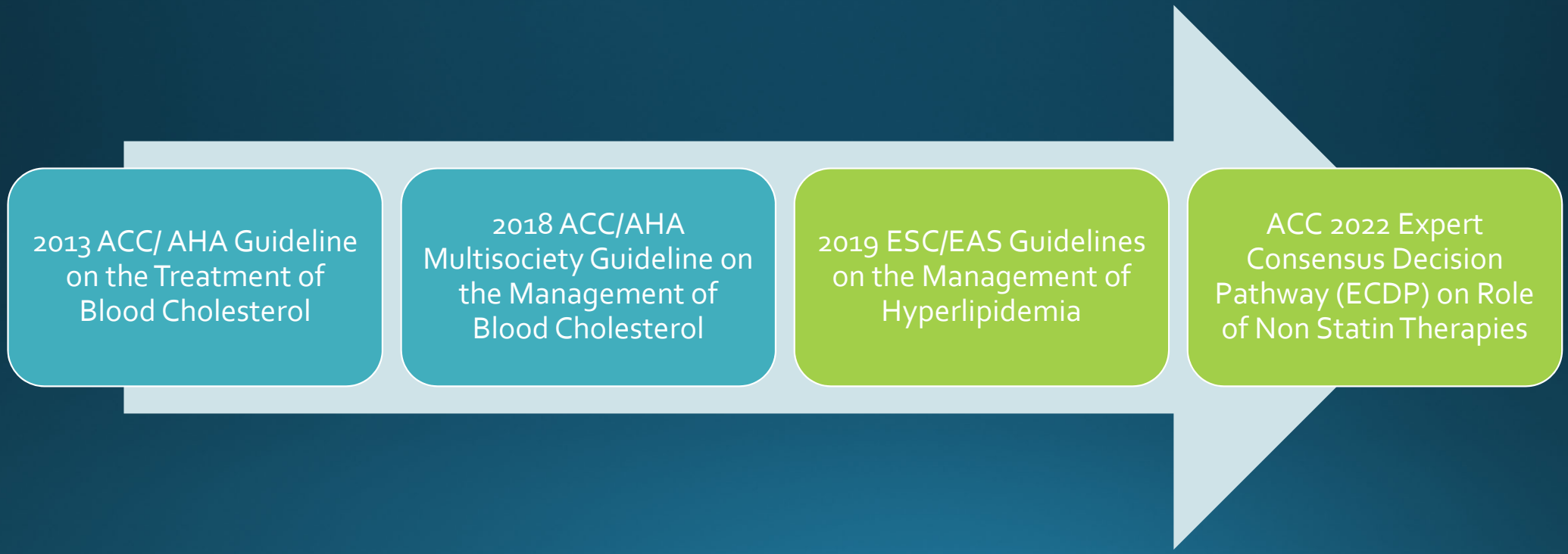


Marston N, et al. *Circulation*. 2021; 144:1732-1734.

Hyperlipidemia Guidance



Hyperlipidemia Guidance



LDL Targets for Secondary Prevention

2019 ESC/EAS Dyslipidemia Guidelines

- Recommend LDL-C goal ≤ 55 mg/dL for patients with very high risk ASCVD
  - Even consider lower goal of ≤ 40 mg/dL in patients with multiple CV events in past 2 years despite optimal statin therapy

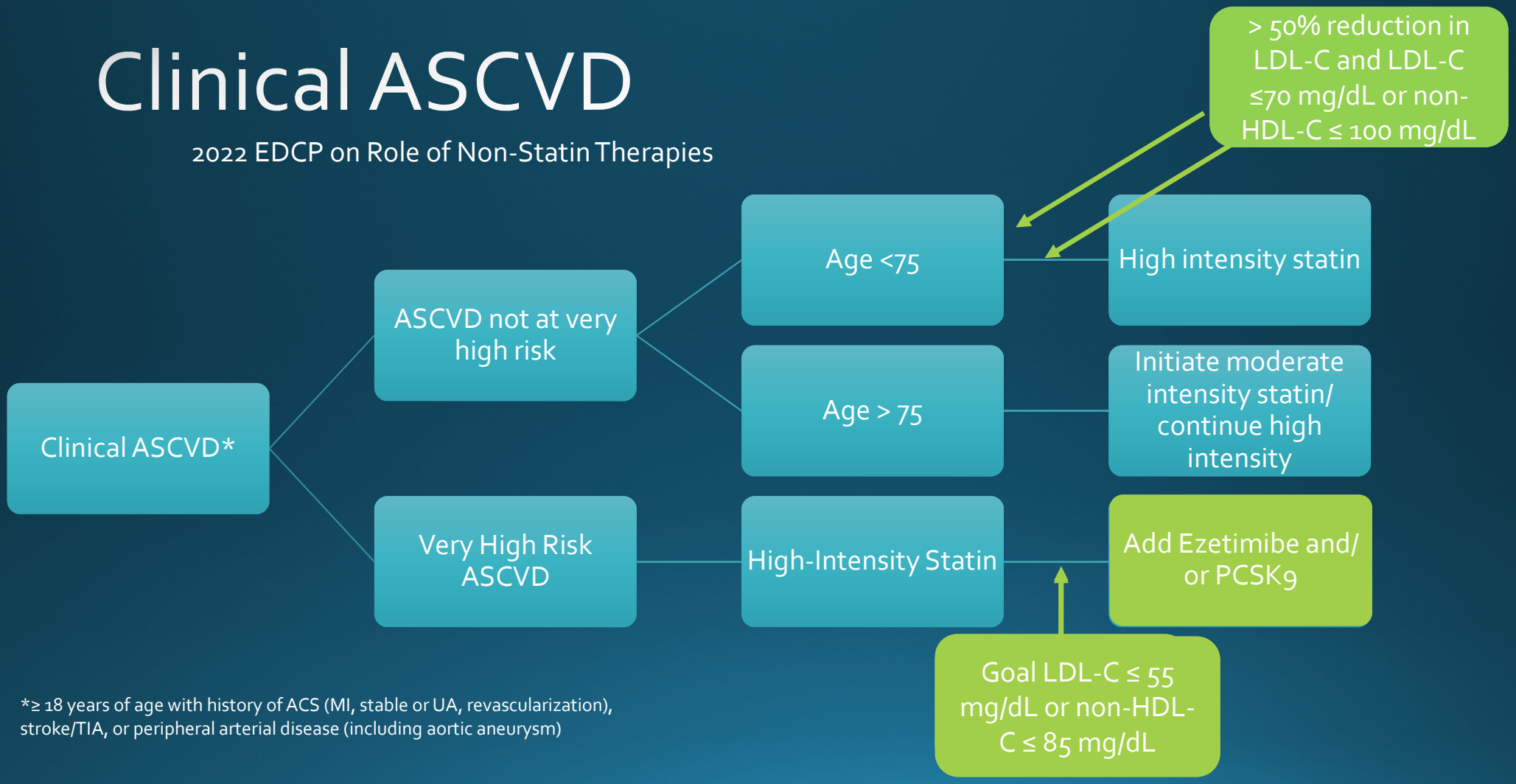
2022 ACC Expert Consensus Decision Pathway on Role of Non-Statin Therapies

- Recommend LDL goal of ≤ 55 mg/dL (or non-HDL ≤ 85 mg/dL) in very high risk patients

Lloyd-Jones D, Morris P, et al. *J Am Coll Cardiol.* 2022 Oct, 80 (14) 1366-1418).

Clinical ASCVD

2022 EDCP on Role of Non-Statin Therapies



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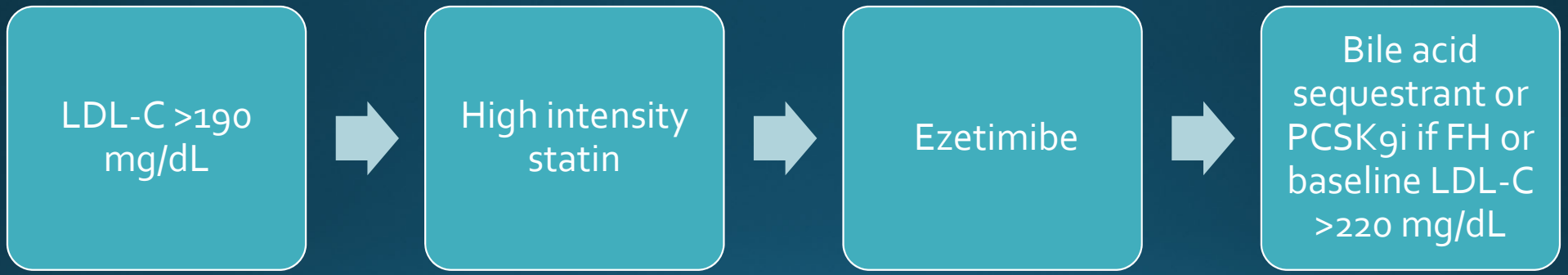
Grundy SM, Stone NJ, Bailey AL, et al. *Circulation.* 2019; 139:e1082-e1143.

Primary Severe Hypercholesterolemia

2018 ACC/ AHA Hyperlipidemia Guidelines



Goal LDL-C reduction of ≥ 50% and LDL-C ≤ 100 mg/dL (or non-HDL-C ≤ 130 mg/dL)

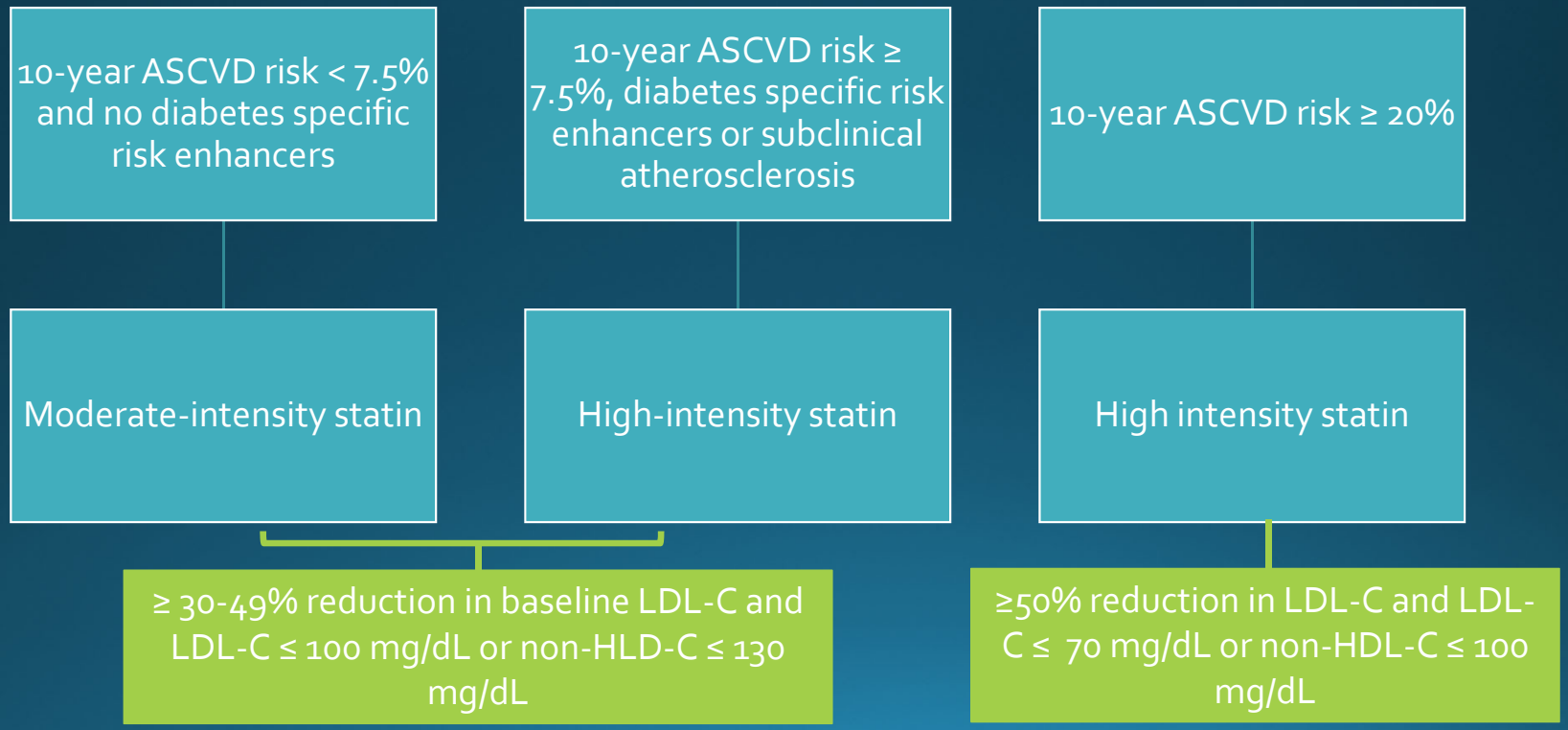
Primary Severe Hypercholesterolemia

2022 EDCP on Role of Non-Statin Therapies

Goal LDL-C reduction of ≥ 50% and LDL-C ≤ 100 mg/dL (or non-HDL-C ≤ 130 mg/dL)

Patient with Diabetes, Age 40-75, and LDL-C 70-189 mg/dL

2022 EDCP on Role of Non-Statin Therapies



Diabetes- Specific Risk Enhancers

Long duration of diabetes (≥10 years for type 2 diabetes or ≥ 20 years for type 1 diabetes)	Albuminuria ≥ 30 mcg albumin/ mg creatinine	eGFR < 60 mL/min/1.73m^2
Retinopathy	Neuropathy	ABI <0.9

Patients 20-39 Years Old with Diabetes

- Low 10-year predicted ASCVD risk but typically have high lifetime predicted risk

- 2018 ACC/AHA/ Multisociety guidelines recommend that for these patients with diabetes-specific risk enhancers, it may be reasonable to initiate statin therapy (IIb)
  - Remember to include family planning in discussion for all women of childbearing age

Adults Without ASCVD, Primary Severe Hypercholesterolemia or Diabetes

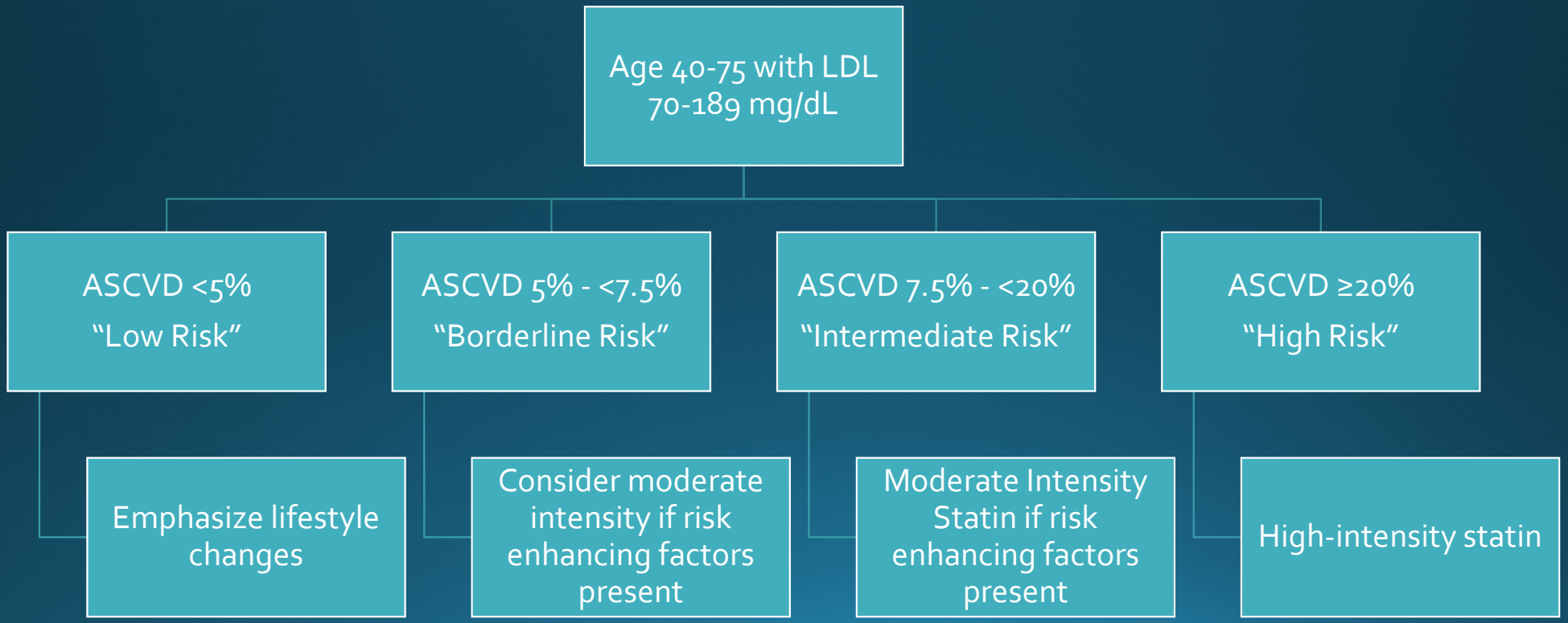
- 10-year ASCVD risk begins the risk discussion

AMERICAN COLLEGE of CARDIOLOGY — ASCVD Risk Estimator Plus

PREVENT™ Online Calculator

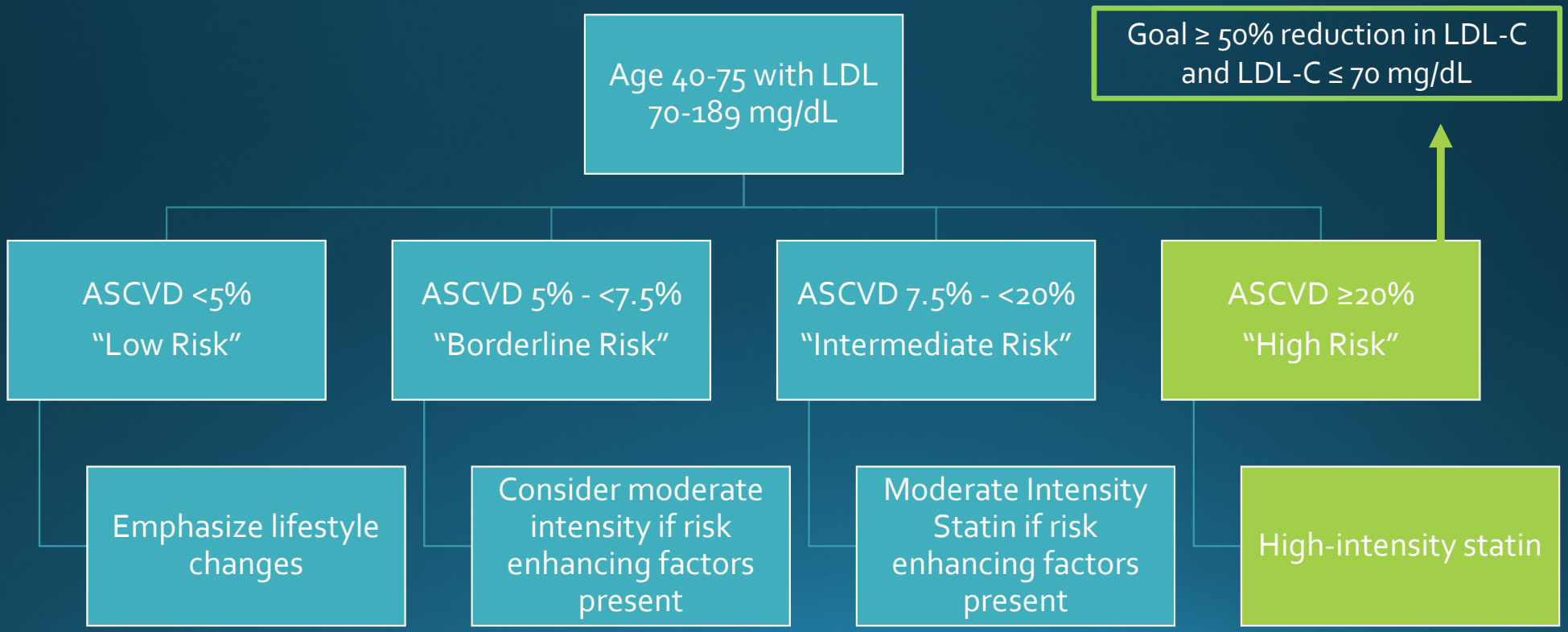
Adults Without ASCVD, Primary Severe Hypercholesterolemia or Diabetes

2022 EDCP on Role of Non-Statin Therapies



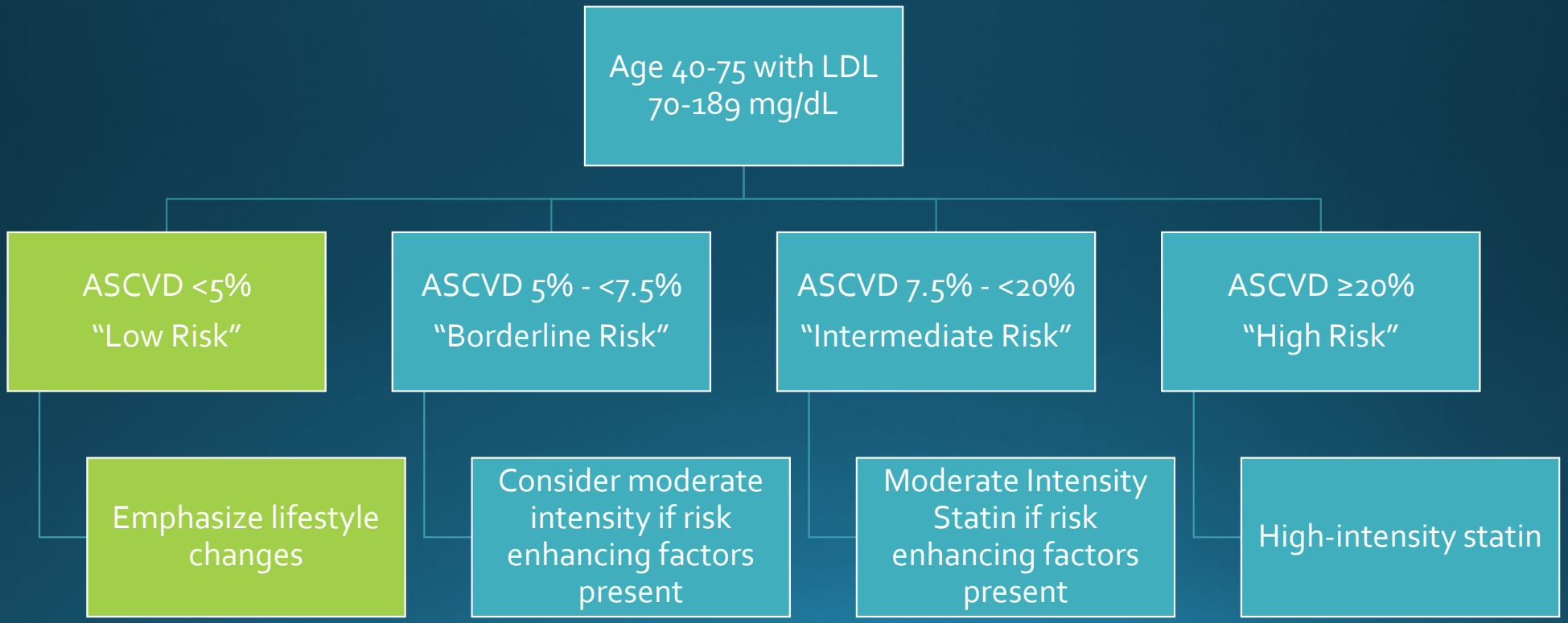
Adults Without ASCVD, Primary Severe Hypercholesterolemia or Diabetes

2022 EDCP on Role of Non-Statin Therapies



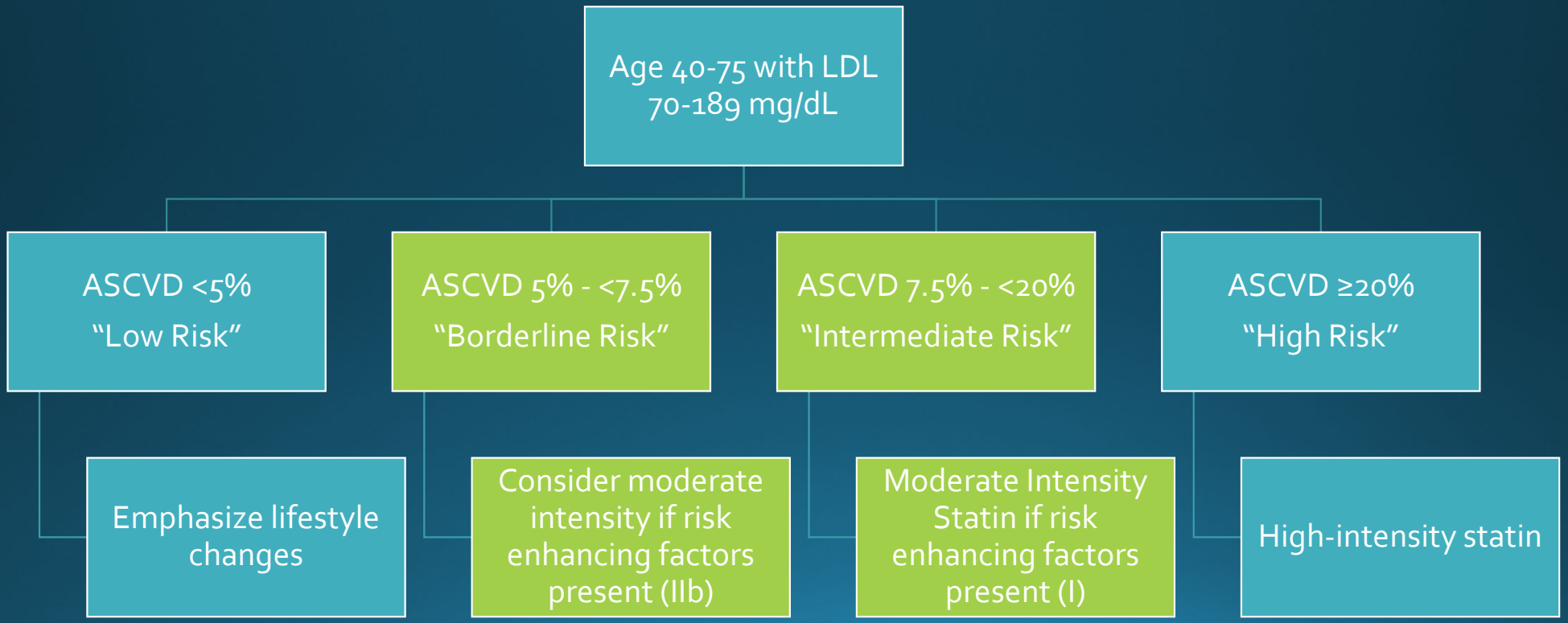
Adults Without ASCVD, Primary Severe Hypercholesterolemia or Diabetes

2022 EDCP on Role of Non-Statin Therapies



Adults Without ASCVD, Primary Severe Hypercholesterolemia or Diabetes

2022 ECDP on Role of Non-Statin Therapies



Clinician Patient Risk Discussion

Clinical Findings	Lipid/Biomarkers
• Family History of premature ASCVD	• Persistently elevated TG (≥175 mg/dL)
• Persistently elevated LDL-C ≥160-189 mg/dL or non-HDL-C 190-219 mg/dL	• and if measured*:
• CKD (eGFR 15-59 mL/min/1.73 m2)	*hs-CRP≥2.0 mg/L
• Metabolic Syndrome	*Lp(a) levels >50 mg/dL
• Preeclampsia, premature menopause (<40, gestational diabetes	*apoB ≥130 mg/dL
• High-risk race/ethnicities (e.g. South Asian ancestry)	*ABI <0.9
• Inflammatory diseases	

Grundy SM, Stone NJ, Bailey AL, et al, 2018 Multisociety Guideline on the Management of Blood Cholesterol. *J Am College Cardiology 2018*

Coronary Artery Calcium (CAC) Score

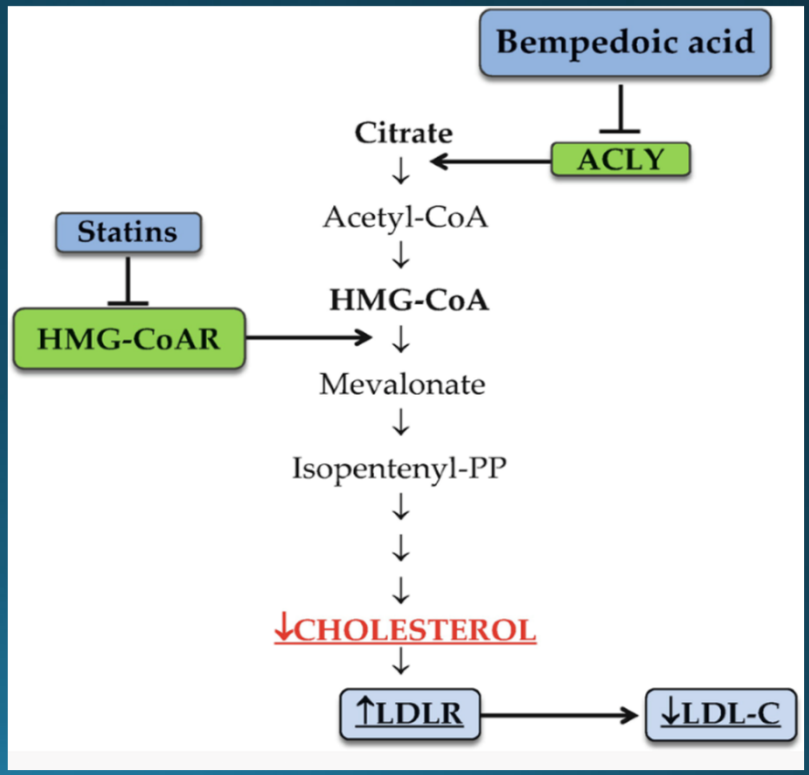
CAC= 0	CAC 1-99	CAC >100
• No statin therapy • Consider remeasuring in 3-5 years	• Statin therapy favored, especially if >55 years old	• Moderate-high intensity statin in any age

Emerging Therapies and Targets

Bempedoic Acid

Efficacy	
LDL-C	↓ 17-28%
HDL-C	↑ 6%
TG	↔

- Dose: 180 mg once daily
  - Comes in combination tablet with ezetimibe
- Significant warnings:
  - Tendon rupture
  - Hyperuricemia/gout
- Other side effects: GI upset, atrial fibrillation
- FDA approved for use in ASCVD and heterozygous familial hypercholesterolemia as adjunct to statin therapy
- Provides ~20% reduction in LDL-C
- Notable lowering of hsCRP (~18 -35%)



CLEAR OUTCOMES

Design

- Randomized, double-blind, placebo-controlled
- Primary outcome: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization

Population

- 13,970 patients ≥ 18 years of age with history of, or high risk for, ASCVD with history of statin intolerance

Interventions

- Bempedoic acid vs. placebo

Findings

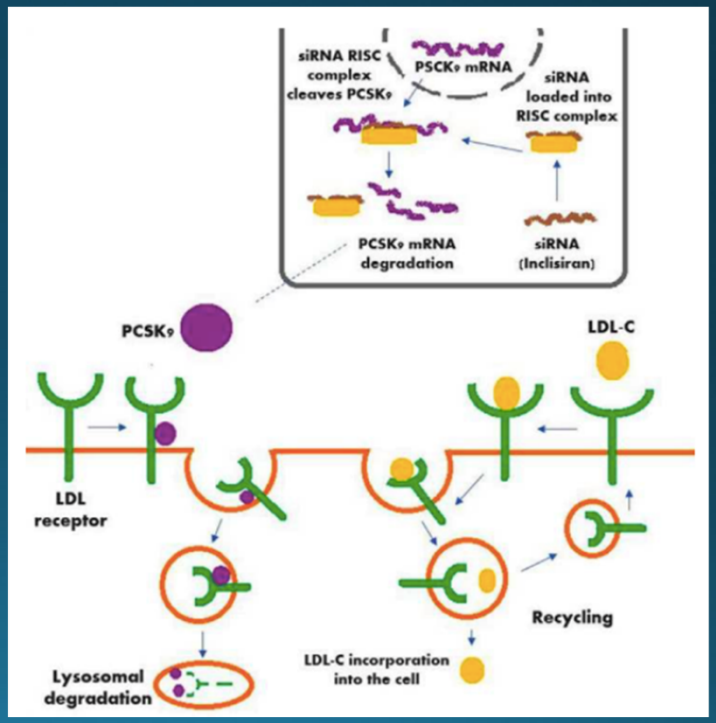
- Bempedoic acid reduced major adverse cardiovascular events over 40 months
  - Composite: 11.7% bempedoic acid vs 13.3% placebo (HR 0.87, p=0.004, NNT 43)

Schwartz et al. *N Engl J Med* 2018; 379:2097-2107.

Inclisiran

Efficacy	
LDL-C	↓ 40-50%
HDL-C	↑ 10%
TG	↓ 10%

- Dose: 300mg subcutaneous injection on day 1, day 90, and every 6 months thereafter
  - Administered by healthcare provider
- Side effects
  - Injection site reactions musculoskeletal pain, nasopharyngitis, diarrhea
- Currently FDA approved for ASCVD and FH



ORION-10

Design

- Randomized, double-blind, placebo-controlled
- Primary outcome: mean percent change in LDL at 510 days

Population

- 1,561 patients ≥ 18 years of age with stable ASCVD on maximally tolerated statin therapy

Interventions

- Inclisiran vs. placebo

Findings

- Inclisiran decreased LDL-C by 56 mg/dL on average at day 510 compared with 1 mg/dL in placebo

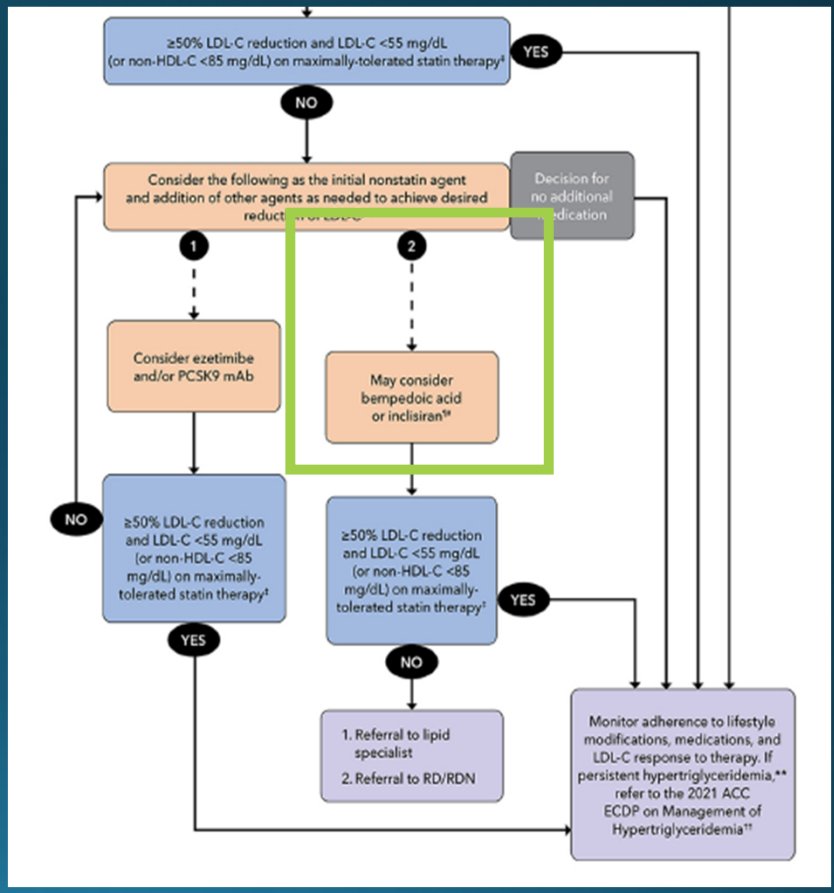
Schwartz et al. *N Engl J Med* 2018; 379:2097-2107.

On the Horizon…

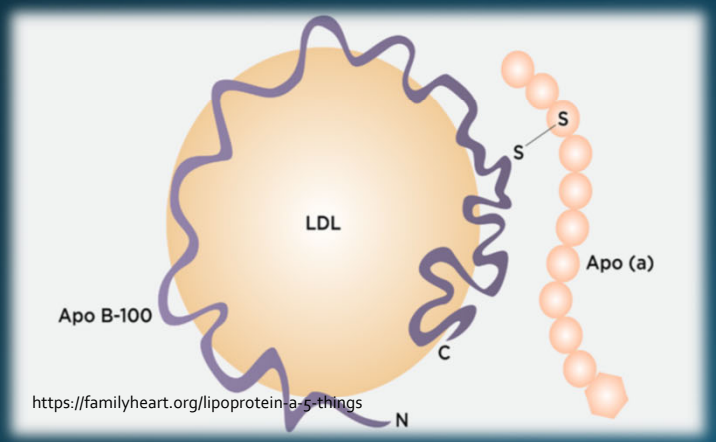
- VICTORIAN 2-PREVENT
  - High intensity statin +/- inclisiran in patients with established ASCVD
    - Primary endpoint: composite of CV death, non-fatal MI, and non-fatal ischemic stroke
- VICTORIAN-1 PREVENT
  - Inclisiran vs placebo for primary prevention in high-risk primary prevention patients
    - Primary endpoint: CV death, non-fatal MI, non-fatal ischemic stroke, and urgent coronary revascularization

2022 EDCP on Role of Non-Statin Therapies

- Bempedoic acid
  - May be useful if additional LDL-C lowering needed, statin-intolerance, or desire to avoid injectable medications
- Inclisiran
  - May be useful if compliance is a concern, unable to self-inject, or if intolerance to statins or PCSK9 inhibitors
- Cost and prior authorization are potential barriers



Lipoprotein (a) (Lp(a))



https://familyheart.org/lipoprotein-a-5-things

- Independently associated with higher risk of ASCVD
- Lp(a) levels remain relatively consistent over one's lifetime
- Elevated levels in 20-25% of the population
- Positive effects of healthy diet and physical activity do not extend to Lp(a) lowering
- Statins do not reduce Lp(a) levels

Lp(a) Testing

Less than 1% of Americans have had their Lp(a) tested

No current consensus on Lp(a) risk thresholds

- ≥50 mg/dL (or ≥125 nmol/L) is an accepted threshold in ACC/AHA guidelines

Becoming more prominent in most guidelines

- Canadian and European guidelines recommend Lp(a) be measured at least once in a persons lifetime as part of initial lipid screening

Lp(a) Treatment

- Currently we do not have any treatments to specifically target Lp(a)
  - PCSK9i- has been shown to reduce Lp(a) by 11-25% in some patients
  - Niacin- modest lowering of Lp(a) but did not reduce major adverse CV outcomes in 3 large randomized controlled trials
- In patients with elevated Lp(a), goals are to:
  - Reduce LDL per guidelines with statins as first line + diet/lifestyle modifications
  - Control other CV risk factors (hypertension, diabetes, obesity, tobacco use)

Alebna et al. *JACC* 2023; Sept 2023.

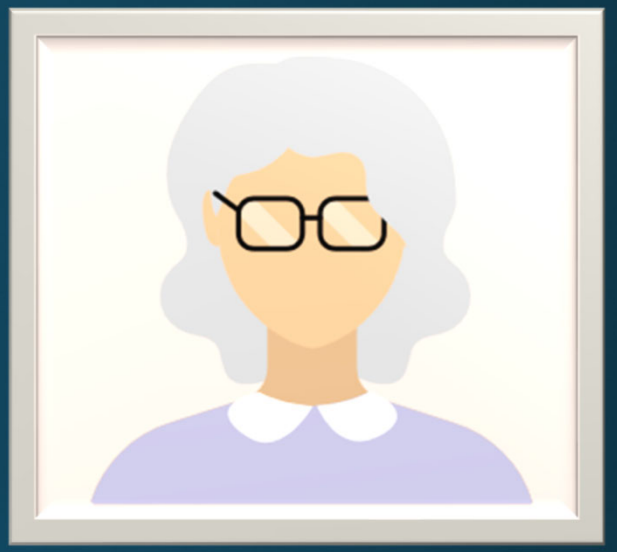
On the Horizon…

- Several phase 2 and 3 trials of novel therapies targeting Lp(a) gene transcription rate using small interfering RNA (siRNA) and gene translation with antisense oligonucelotides (ASOs)

Lp(a) HORIZON *Pelacarsen*	OCEAN(a) DOSE *Olpasiran*
• First CV outcomes study of Lp(a) – projected results in 1-2 years	• Preliminary results- >95% reduction of Lp(a) at week 36

Patient Case

Patient Case: SK



SK is a 67 year old who is being seen in clinic today for follow up after STEMI s/p PCI to LAD ~ 1 year ago

- Other PMH: HTN , T2DM, and hypothyroidism
- Tobacco use (-)
- Insurance: Medicaid
- Medications:
  - Clopidogrel 75 mg daily
  - Rosuvastatin 40 mg once daily
    - Started at 12 months ago at time of STEMI
  - Lisinopril 40 mg once daily
  - Empagliflozin 25 mg once daily
  - Insulin glargine 30 units once daily
  - Levothyroxine 88 mcg once daily

Lipid Panel*	
Total Cholesterol	180 mg/dL
LDL	97 mg/dL
HDL	52 mg/dL
TG	155 mg/dL

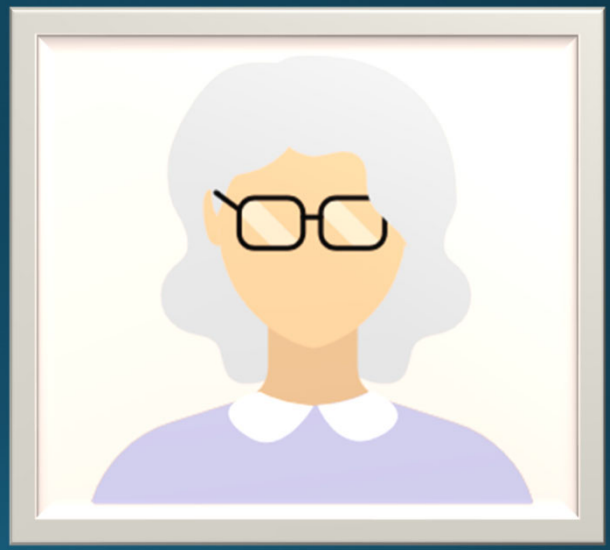
*Obtained prior to clinic appt today

What LDL-C would you target for SK?

A. <55 mg/dL

B. <70 mg/dL

C. <100 mg/Dl



What LDL-C would you target for SK?

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C. <100 mg/Dl

History of STEMI

+

High Risk Conditions

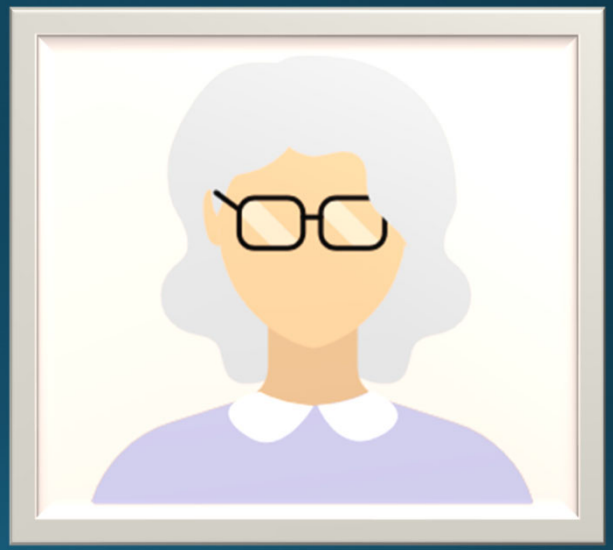
- Age >65 years
- Heterozygous familial hypercholesterolemia
- History CABG or PCI outside major ASCVD event(s)
- Diabetes mellitus
- Hypertension
- CKD
- Current smoking
- Persistent LDL-C >100 mg/dL despite max tolerated statin and ezetimibe
- Congestive heart failure

What change would you make to SK's hyperlipidemia regimen?

A. Change rosuvastatin to atorvastatin 80 mg once daily

B. Add ezetimibe 10 mg once daily

C. Add evolocumab 140 mg every 14 days



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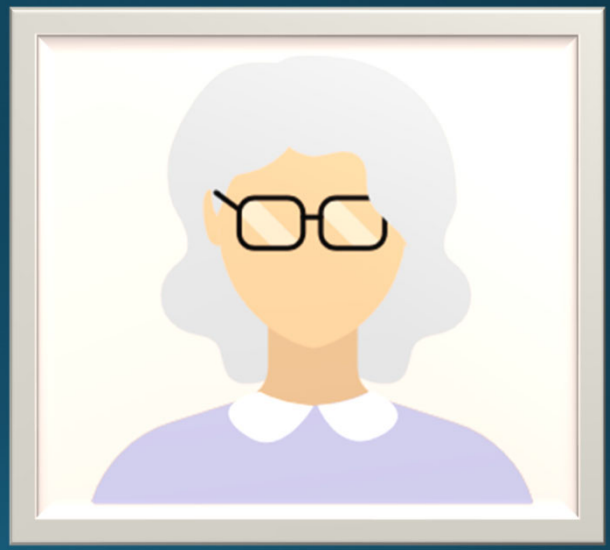

Questions?