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HYPERLIPIDEMIA-STRATEGIES BEYOND STATINS

GOALS AND THERAPIES TO MANAGE HYPERLIPIDEMIA IN AT-RISK POPULATIONS

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All relevant financial relationships have been mitigated.

QUESTION 1

A 66 yo hx of CABG 10 years ago, hypercholesterolemia and hypertension presented with acute myocardial infarction and stenting to the proximal LAD. The patient is doing well, participates in cardiac rehab, and has been compliant with his medications. His blood pressure is well controlled. He has been on Rosuvastatin 20mg daily His lipids are as follows TC 132, HDL 40, LDL 66, TG 130. Select the best option regarding his lipid management goals

A. A He is at goal, no change is necessary
B. B He is not at goal, and you would recommend increasing Rosuvastatin to 40mg
C. C He is not at goal, and you would recommend Adding Evolocumab 150mg SQ twice a month
D. D He is not at goal, and you would recommend Adding Ezetimibe 10mg daily

QUESTION 2

The current LDL and Non-HDL threshold for ASCVD patients at very high risk is

A. LDL<40 and non-HDL<100
B. LDL<70 and Non-HDL<100
C. LDL<55 and Non-HDL<85
D. LDL<50 and non-HDL<100

QUESTION 3

The following is not an FDA indication for a PCSK9 inhibitor prescription

A. 63 yo with ASCVD not at very high-risk status post CABG 3 yrs. ago LDL 76mg/dL on Atorvastatin 80mg and Zetia 10mg daily
B. 59 yo with familial hypercholesterolemia, hypertension with an LDL of 123mg/dL on Rosuvastatin 5mg 3 times a week (max tolerance) and Zetia 10mg daily
C. 58 yo with a CAC (coronary calcium score) of 500 and an LDL 160 intolerant to 2 statins with one attempt at the lowest dose
D. All of the above

LEARNING OBJECTIVES

- Identify Newer FDA approved non-statin therapies, indications, and % LDL reduction
- Describe treatment options for the truly statin-intolerant pt
- Determine to whom and when non-statins should be considered based on the percentage of LDL reduction or LDL range desired for the level of risk
- Choose which ones to consider and in what order

NONSTATIN THERAPIES FOR CHOLESTEROL LOWERING

- Ezetimibe
- PCSK9 inhibitors
  - Evolocumab
  - Alirocumab
- Bempedoic acid
- Inclisiran
- Angiopoietin-like protein 3 (ANGPTL3) inhibitor
  - Evinacumab (for HoFH)

BEMPEDOIC ACID

- Inhibits an enzyme in the cholesterol synthesis by the liver upstream of HMG CoA reductase
- Administered as an oral prodrug. Requires coenzyme A activation, only expressed in the liver
- No effect on peripheral muscles
- FDA approved for LDL reduction in adults with ASCVD or heterozygous familial hypercholesterolemia as an adjunct to diet and max tolerated statin therapy
- LDL reduction 18%, Combined with Ezetimibe 38%
- May increase uric acid. Need to monitor the uric acid level
- May be associated with tendon rupture
- Outcome trial (CLEAR outcomes - ASCVD or ASCVD risk Statin intolerant and LDL>100) positive benefit. Released at ACC 2023

INCLISIRAN

- siRNA (small interfering RNA) targeting PCSK9 production in the liver by inhibiting hepatic translation of the PCSK9 protein, thereby upregulating LDL receptors
- Administered SQ q6months after the second dose. Requires clinic administration
- FDA approved for LDL reduction in adults with ASCVD or heterozygous familial hypercholesterolemia as an adjunct to diet and max tolerated statin therapy
- LDL reduction of 50%
- Outcome trials in progress (ORION 4 – preexisting ASCVD and LDL>100) and VICTORION-2P – ASCVD on a max statin and LDL>70)

EVINACUMAB

- Inhibits ANGPTL3, a liver-secreted protein that inhibits LPL (lipoprotein lipase), an enzyme involved in lipoprotein metabolism. ANGPTL3 increases the levels of triglycerides and other lipids.
- Loss of function mutation of ANGPTL3 is associated with very low levels of LDL and triglycerides.
- EVINACUMAB inhibits ANGPTL3 and promotes VLDL clearance upstream of LDL formation, therefore reducing triglycerides and LDL independently of the LDL receptor.
- LDL reduction of 47%
- FDA approved for Homozygous Familial Hypercholesterolemia
- No outcome trials

CURRENT THERAPIES FOR LDL REDUCTION

LDL lipid Rx	% LDL reduction	Cost
Statins	60%	+
Ezetimibe	15%	+
PCSK9i	60%	+++
Bempedoic acid	15%	+++
Bempedoic acid + Ezetimibe	38%	+++
Inclisiran	50%	+++
Evinacumab	50%	+++

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EXPERT CONSENSUS DECISION PATHWAY

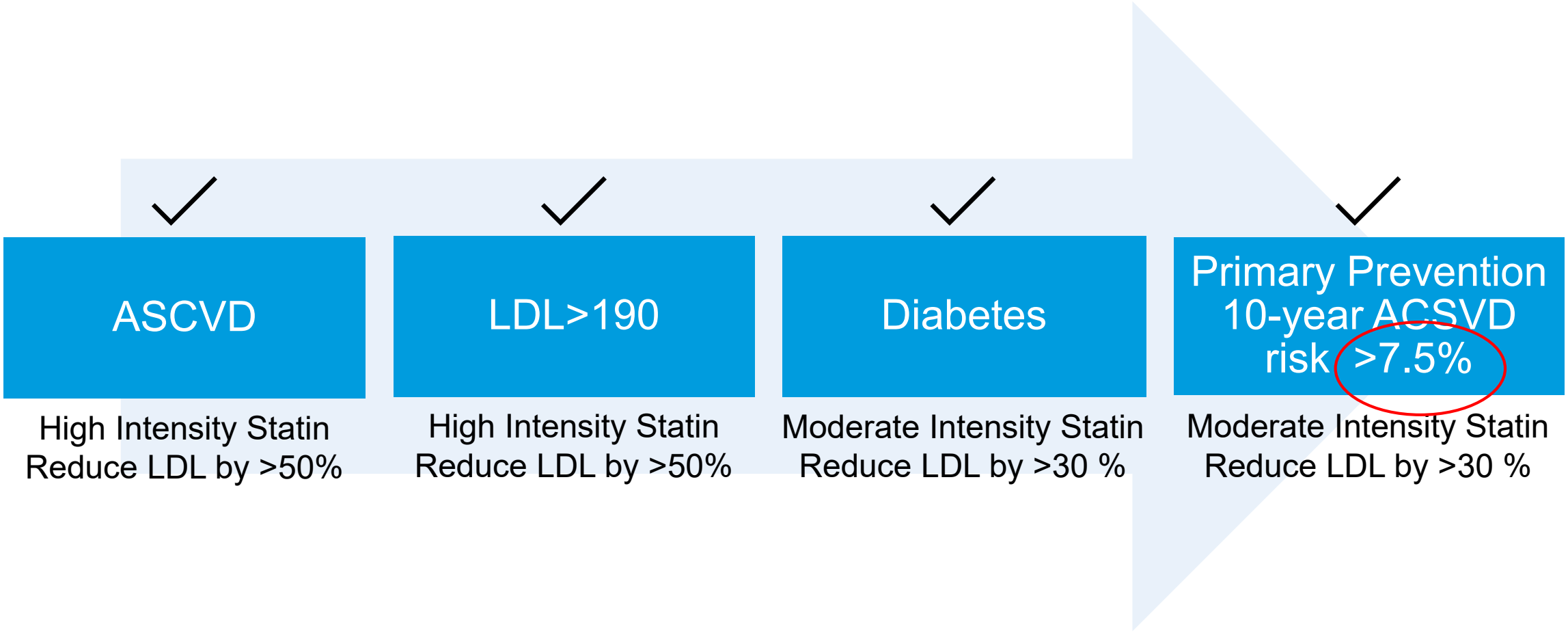
2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the National Lipid Association

2022 American College of Cardiology Foundation. J Am Coll Cardiol 2022; 80:1366-1418

REVIEW OF THE 2018 ACC/AHA CHOLESTEROL GUIDELINE STATIN BENEFIT GROUPS



2018 AHA/ACC Cholesterol Clinical Practice Guidelines

PATIENT MANAGEMENT GROUPS

SECONDARY PREVENTION

A. Clinical ASCVD and very high risk

B. Clinical ASCVD not at very high risk

C. Clinical ASCVD and LDL>190mg/dL without FH

D. Clinical ASCVD and LDL>190mg/dL with FH

PATIENT MANAGEMENT GROUPS

PRIMARY PREVENTION

A. LDL >190 without clinical ASCVD

B. Diabetes with LDL <190 without clinical ASCVD

C. LDL 70-189 without clinical ASCVD or diabetes

CRITERIA FOR DEFINING PATIENTS AT VERY HIGH RISK OF FUTURE ASCVD EVENT

Major ASCDV Event
Recent ACS (within the past 12 months) History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic PAD (history of claudication with ABI <0.85 or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes
Hypertension
CKD (eGFR 15-59mL/min/1.73m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100mg/dL [≥2.6mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

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

Redrawn from J Am Coll Cardiol 2022; 80:1366-1418

RISK ENHANCING FACTORS

LIPID/BIOMARKERS

- Hypertriglyceridemia (>175mg/dL)
- Elevated HSCRP (>2mg/dL)
- Elevated Lp(a) (>125nmol/L)
- Elevated ApoB (130mg/dL)
- ABI<0.9

RISK ENHANCING FACTORS

CLINICAL

- Family history of premature ASCVD
- Primary Hypercholesterolemia
- Metabolic Syndrome
- Chronic Kidney Disease
- Chronic Inflammatory Conditions
- History of premature menopause or preeclampsia
- South Asian ancestry

CLINICAL ASCVD AND VERY HIGH RISK

- More than **50% LDL** reduction and LDL <**55mg/dL**
- Non-HDL <85mg/dL
- If on max tolerated statin therapy and diet optimized or intolerant to 2 statins with one attempt at the lowest dose

1) Consider ezetimibe and/or PCSK9i
2) May consider Bempedoic acid and or inclisiran

55 mg/dL is now the LDL-C threshold recommended by ACC for patients with ASCVD at very high risk

CLINICAL ASCVD AND NOT AT VERY HIGH RISK

- More than 50% LDL reduction and LDL <**70mg/dL**
- Non-HDL <100mg/dL
- If on max tolerated statin therapy and diet optimized or intolerant to 2 statins with one attempt at the lowest dose
    1) Consider ezetimibe
    2) May consider adding or replacing with PCSK9i
    3) May consider Bempedoic acid and or inclisiran

CLINICAL ASCVD AND LDL >190 WITHOUT FH

- More than 50% LDL reduction and LDL <**70mg/dL**
- Non-HDL <100mg/dL
- If on max tolerated statin therapy and diet optimized or intolerant to 2 statins with one attempt at the lowest dose
    1) Consider ezetimibe and or PCSK9i
    2) May consider Bempedoic acid and inclisiran
    3) May consider LDL apheresis

CLINICAL ASCVD AND LDL>190 WITH FH

- More than 50% LDL reduction and LDL <**70mg/dL**
- Non-HDL <100mg/dL
- If on max tolerated statin therapy and diet optimized or intolerant to 2 statins with one attempt at the lowest dose
    1) Consider ezetimibe and or PCSK9i
    2) May consider Bempedoic acid and inclisiran
    3) May consider Evinacumab, lomitapide, or LDL apheresis

WITHOUT CLINICAL ASCVD AND LDL>190 ON STATIN FOR PRIMARY PREVENTION

- More than **50% LDL** reduction and LDL <**100mg/dL** for patients with high-risk features, otherwise **< 130mg/dL**
- **High-Risk Features:** Family history of premature CAD, smoking, diabetes, CKD, subclinical atherosclerosis, elevated Lpa or HSCR
- If on max tolerated statin therapy and diet optimized or intolerant to 2 statins with one attempt at the lowest dose
    1) Consider ezetimibe and or PCSK9i
    2) May consider Bempedoic acid and inclisiran
    3) May consider Evinacumab, lomitapide, or LDL apheresis

ADDITIONAL APPROACH TO PATIENTS WITH AN LDL>190

- Identifies patients with a high likelihood of familial hypercholesterolemia (FH)
- Heterozygous (LDL > 190) 1:250 Births
  - Autosomal dominant trait which means that the chance of a first-degree relative with the disorder is 50%
  - 80% is polygenic (negative genetic testing)
  - 20% is monogenic (positive genetic testing)
    - LDL receptor gene mutation (most common)
    - ApoB gene mutation
    - PCSK9 gain of function mutation
- Please counsel patients on screening all first-degree relatives and consider referral
- Homozygous (LDL > 400) 1: 300,000 Births
    - 2 parents with heterozygous or autosomal recessive

ADULTS WITH DIABETES WITHOUT ASCVD AND A BASELINE LDL LESS THAN 190

- 10-year risk <7.5%
  - 30-49% LDL reduction and LDL<100 or non-HDL <130 on moderate intensity
  - If not:
    - High-intensity statin (particularly in non-HDL > 130)
- 10-year risk >7.5%
  - High-intensity statin
- 10-year risk >20%
  - LDL <70 or Non-HDL<100
  - If not:
    1) May consider Ezetimibe

ADULTS WITH AN LDL 70-189 WITHOUT CLINICAL ASCVD OR DIABETES

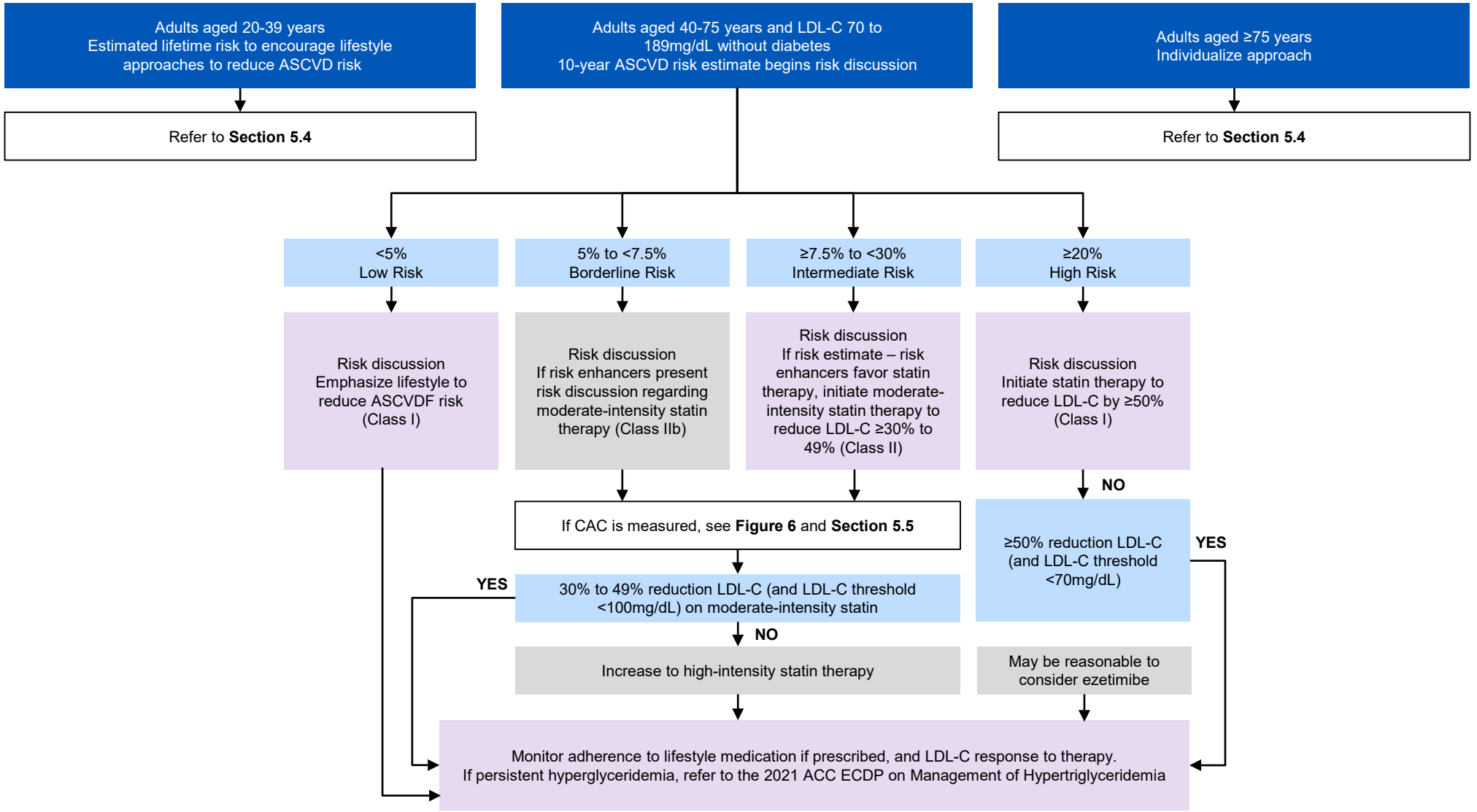
Calculate ASCVD RISK:

- **< 5% (low risk)**
- **5 to <7% (borderline risk)** – may benefit from a moderate-intensity statin. 30-49% LDL reduction and LDL<100 or non-HDL <130
- **>7% (moderate risk) –** benefit from a moderate-intensity statin. 30-49% LDL reduction and LDL<100 or non-HDL <130 (high level of evidence).
- **>20% (high risk) –** benefit from a high-intensity statin. > 50% LDL reduction and LDL <70mg/dL
- If not:
    1) May consider Ezetimibe

ADDITIONAL APPROACH FOR ADULTS WITH AN LDL 70-189 WITHOUT CLINICAL ASCVD OR DIABETES

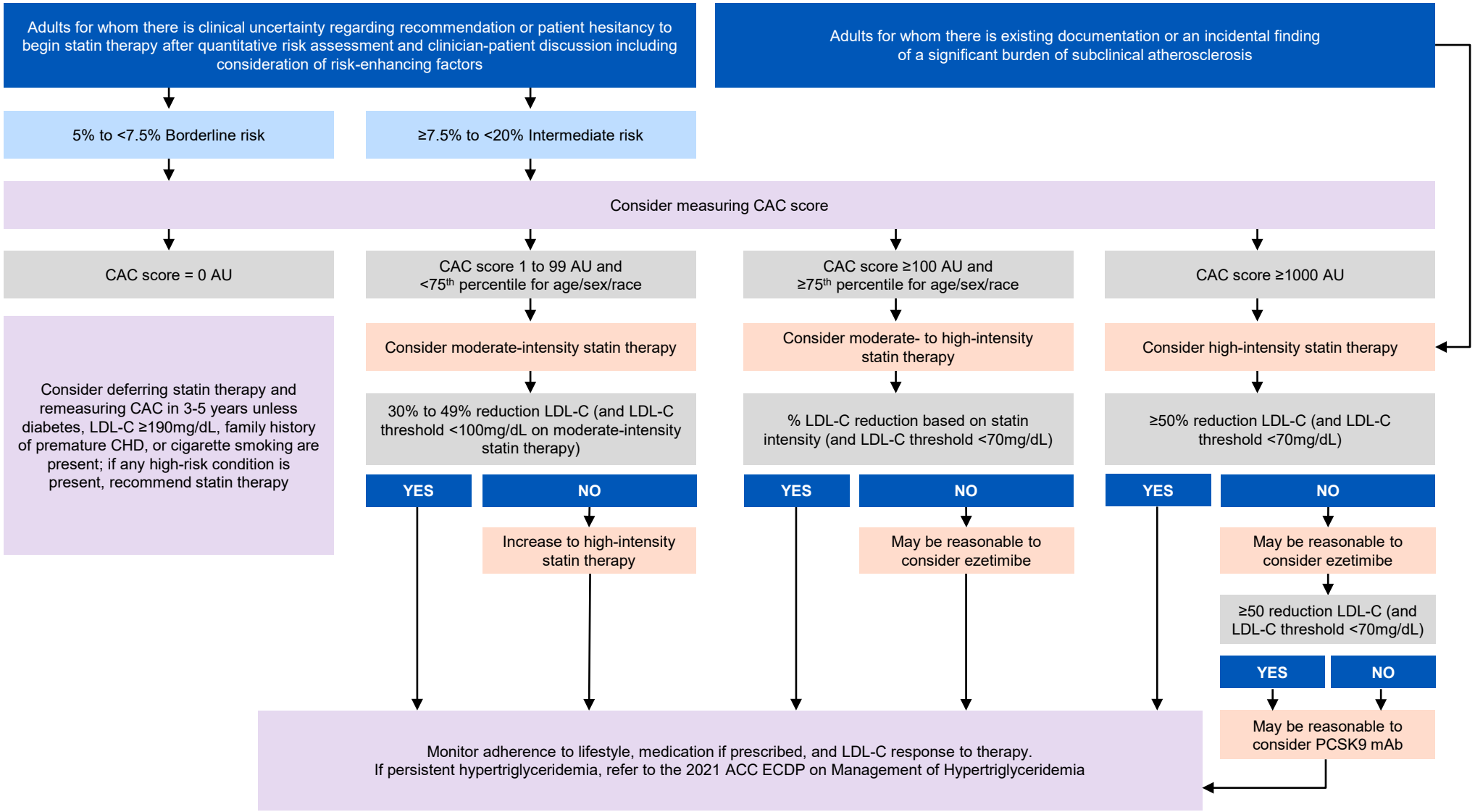
- Use risk enhancers to help with decision
- Measure Lpa (lipoprotein a) in patients with a family history
- Patients younger than 40
  - Don’t use the ASCVD risk calculator due to lack of validation. These pts have low short-term risk but high lifetime risk.
  - patients with an LDL >160 and or family hx may benefit from a statin.
- Patients older than 75
  - Limited RTC data to inform decision
  - Consider ASCVD risk, pt goals, competing risks, frailty, risk of side effects, polypharmacy, etc for individual recommendations
- PCSK9i are not endorsed in this population given limited efficacy data and low cost-effectiveness, however for further guidance on the implementation of statin and non-statin consider CAC (coronary calcium score)

Adults without Clinical ASCVD or Diabetes (LDL 70-189 mg/dL)



Redrawn from 2022 American College of Cardiology Foundation. J Am Coll Cardiol 2022; 80:1366-1418

Incorporation of Subclinical Atherosclerosis Imaging Into Risk Assessment and Treatment for Adults without Clinical ASCVD or Diabetes or LDL-C >190mg/dL



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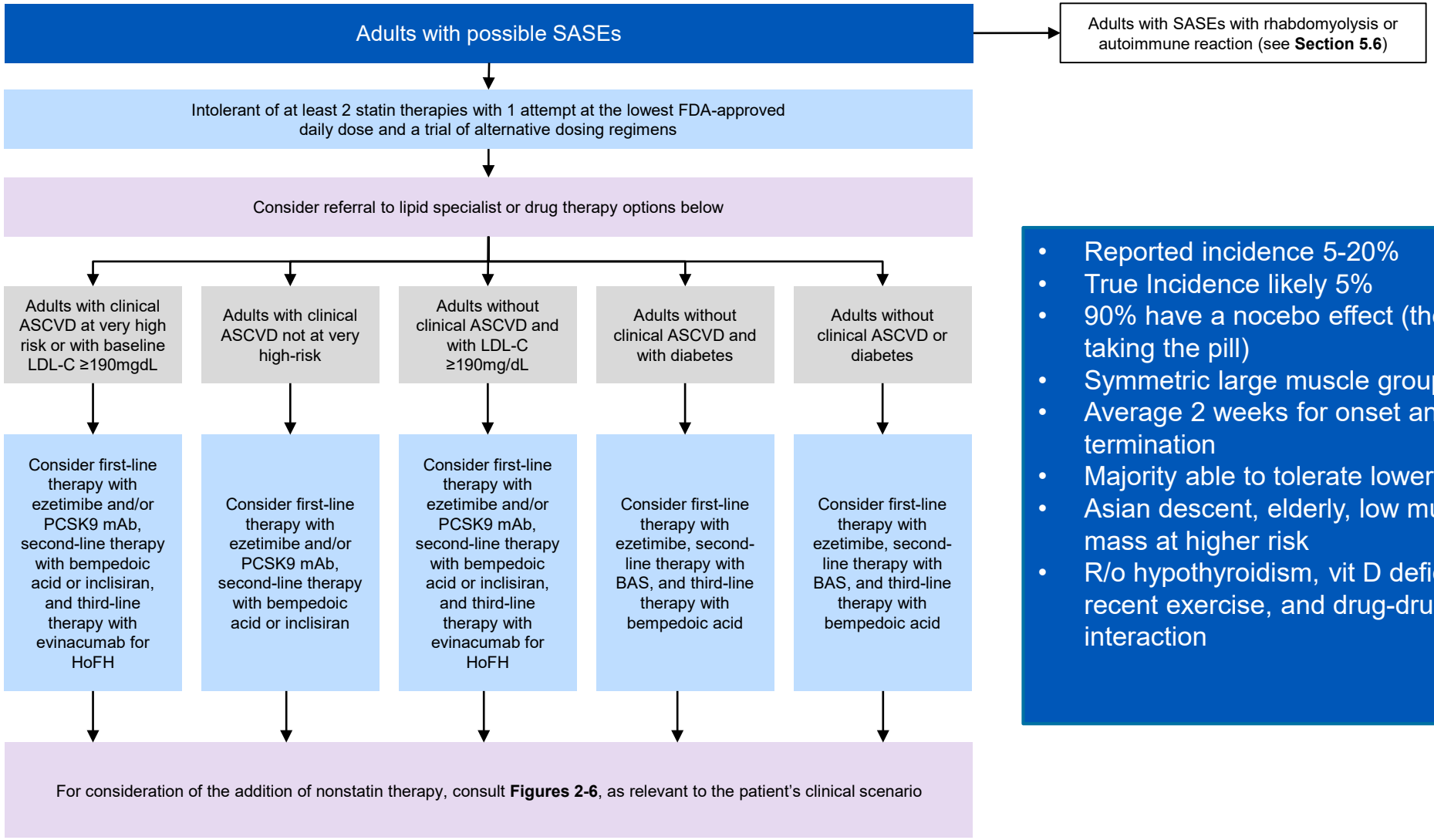
Adults with Possible Statin-Associated Side Effects



- Reported incidence 5-20%
- True Incidence likely 5%
- 90% have a nocebo effect (the act of taking the pill)
- Symmetric large muscle groups
- Average 2 weeks for onset and termination
- Majority able to tolerate lower doses
- Asian descent, elderly, low muscle mass at higher risk
- R/o hypothyroidism, vit D deficiency recent exercise, and drug-drug interaction

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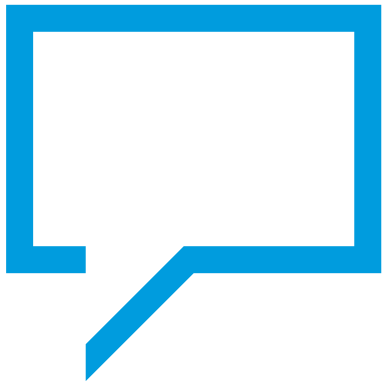
SUMMARY

- Since the 2018 ACC/AHA cholesterol guidelines several new non-statin agents have received FDA approval and are awaiting the results of large-outcome trials
- Additional data in higher risk groups have also allowed for refinement of prior recommendations with current outcome data with Ezetimibe and PCSK9i and efficacy data with Bempedoic acid, Inclisiran and Evinacumab
- Current algorithms discussed included patient management groups
  - Secondary Prevention with ASCVD
  - Primary prevention:
    - LDL>190
    - Diabetes
    - No diabetes

QUESTIONS & DISCUSSION



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