Who Should Manage My Patient's Atherosclerotic Risk Factors?

Should a PCP Refer to a Specialist for Medical Therapy?

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Should a PCP Refer to a Specialist for Medical Therapy?

NO

- Easy to follow guidelines

YES

- Situations when to refer

Learning Objectives

- Relationship between LDL reduction and atherosclerotic events
- What makes a patient very high risk for recurrent ASCVD
- Guideline directed management of LDL and Non-HDL cholesterol
- Addressing statin related side effects
- When to use non-statin therapies
- When to refer to specialist

Cholesterol and Atherosclerotic Cardiovascular Disease

- LDL is the dominant form of atherogenic cholesterol
- Non-fasting samples can be used for risk assessment
  - LDL values vary minimally with time after normal food intake
  - Fasting and non-fasting total cholesterol and HDL provide similar prognostic value
- Patients with prior ASCVD events benefit from statins to reduce major ASCVD events
  - Also for patients with stroke or PAD
- Significant reduction in major vascular events in >75yrs with moderate intensity

Cholesterol and Atherosclerotic Cardiovascular Disease

- Percent LDL reduction is reliable indicator of statin efficacy

- Moderate intensity statins to produce 30%-49% LDL reduction
- High intensity statins to produce ≥50% LDL reduction
  - Additional 15% risk reduction in major vascular events compared to moderate intensity

TABLE 3 High-, Moderate-, and Low-Intensity Statin Therapy*

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Statins	**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 BID** Pitavastatin 1–4 mg	**Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

General Recommendations to Reduce Risk of ASCVD

- Emphasize heart-healthy lifestyle across life span
- Clinical ASCVD or LDL ≥190mg/dL → High-intensity or maximal tolerated statin
- Discussion:
  - Potential benefits and harms
  - Prescribing considerations
  - Patient preferences
- Assess response 4-12 weeks after starting or changing dose
  - Repeat every 3-12 months

Approach to Statin Associated Side Effects

- Muscle symptoms affect 5-20% of patients
- Myalgia most common
  - Bilateral proximal muscles
  - Resolves with discontinuation
  - CK and transaminase should not be routinely measured
- Myopathy, myositis, rhabodmyolysis are rare
  - Require prompt cessation
  - Severe muscle weakness → measure CK
- In large RCTs statin intolerance was low
- SAMSON trial showed most symptoms due to nocebo effect
- Majority of patients can be re-challenged
  - Except for Rhabdo and Statin Associated Autoimunne Myopathy
- Statins not contraindicated in stable liver disease

J Am Coll Cardiol. 2021 Sep 21; 78(12): 1210–1222
2022 ECDP on Role of Nonstatin Therapies for LDL-C Lowering

Approach to Statin Associated Side Effects

- Rule out other causes
  - Hypothyroidism, Vit D deficiency, recent exercise
  - Drug-drug interaction that increase statin exposure
  - Specific populations: Asian decent, women, elderly
- For those with strong guideline recommendations
  - Avoid discontinuing → Keep on max tolerated dose
- Majority of patients with SASEs tolerate re-challenge
  - Alternative dosing
    - Switching dose every other day
    - Lower daily dose of same statin
  - Alternative agent
- Statin intolerance
  - Muscle related symptoms
  - Resolve with discontinuation
  - Recur with re-challenge on at least 2 different statins
    - Preferably 3
    - Tried both
      - Lipophilic (simvastatin, fluvastatin, pitavastatin, lovastatin, atorvastatin)
      - Hydrophilic (rosuvastatin, pravastatin)
    - One at the lowest approved dose
- Refer to lipid specialist

Inadequate Response

- ASCVD patients who did not achieve
  - LDL reduction of ≥ 50%
  - LDL <70
  - LDL <55 in very high risk patients
- Non ASCVD patient who did not achieve
  - LDL reduction of ≥30-49%
  - LDL <100

- Address statin adherence
- Address lifestyle modification

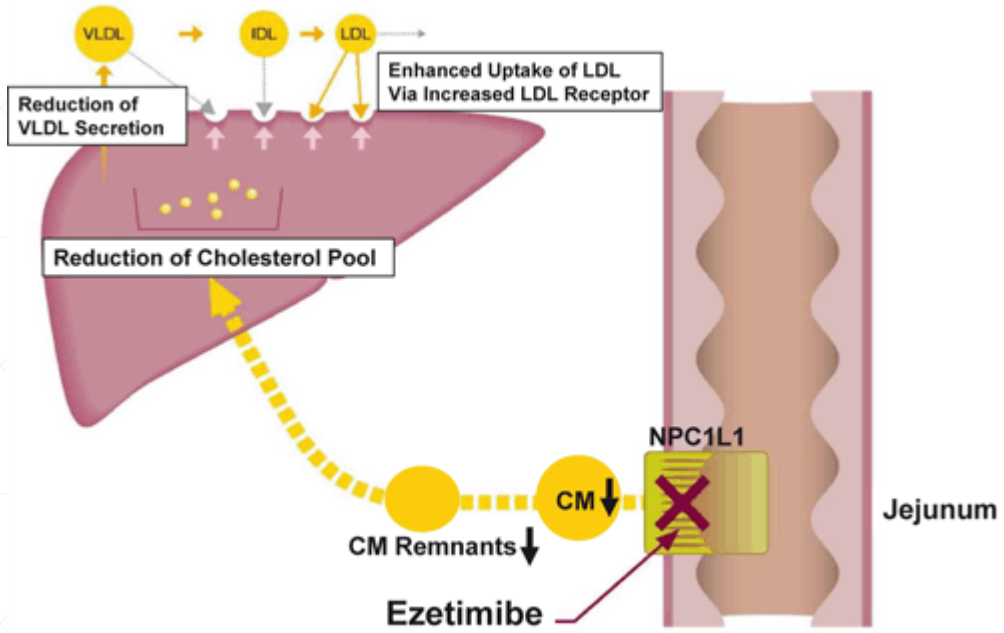
- Address other risk factors
  - Tobacco, DM, BP, Obesity
- Discuss adding non-statin therapy
  - How much additional LDL lowering is needed
    - Sequential addition or two medications at once

Non-Statin Medications

- Ezetimibe
- PCSK9 inhibitors
  - Monoclonal antibodies
- Bempedoic acid

- What patient population
- What situation
- Which to consider and what order

Ezetimibe



- Reduces intestinal cholesterol absorption
  - Targets NPC1L1 protein
- IMPROVE-IT
  - ACS patients with LDL ≥ 50
  - Ezetimibe + moderate intensity statin VS placebo + moderate intensity statin
  - Significant ASCVD risk reduction
  - Ezetimibe + moderate intensity statin ≈ high intensity
    - Consider using this combo in patients with LDL ≥ 70 who can't tolerate high intensity
- Addition of Ezetimibe further reduces LDL by 13-25%
  - Monotherapy reduces LDL by ~15%

https://doi.org/10.1007/978-1-60761-424-1_28
N Engl J Med 2015;372:2387-97.
J Am Coll Cardiol. 2017;69:911–921.
2018 ACC/AHA Cholesterol Clinical Practice Guideline

Proprotein Convertase Subtilisin-Kexin Type 9 (PCSK9) Inhibitors

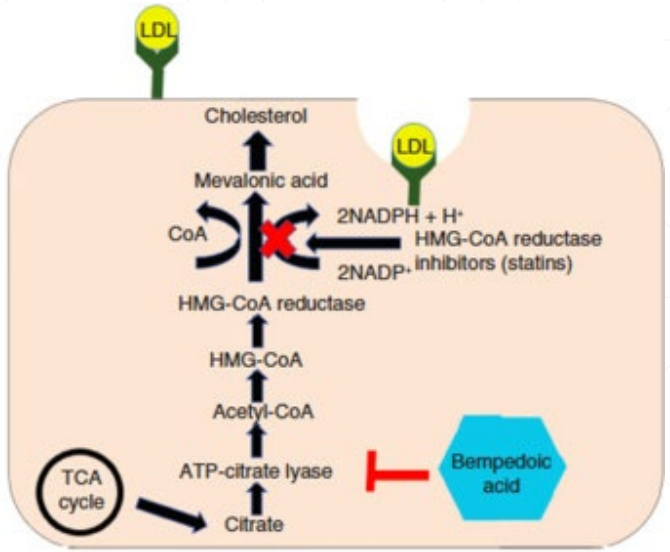
- Monoclonal antibody
  - Decrease LDL receptor degradation
  - Increased LDL uptake from circulation
- FOURIER Trial – evolocumab VS placebo
  - Patients with ASCVD with LDL ≥ 70
    - Max tolerated statin ± ezetimibe
  - Significant reduction in composite endpoint
- ODYSSEY Trial – alirocumab VS placebo
  - Patients with recent ACS with LDL ≥70
    - Max tolerated statin ± ezetimibe
  - Significant reduction in composite endpoint

Table 3. Adverse Events and Laboratory Abnormalities.

Variable	Alirocumab (N=9451)	Placebo (N=9443)
Adverse events — no. (%)		
Any adverse event	7165 (75.8)	7282 (77.1)
Serious adverse event	2202 (23.3)	2350 (24.9)
Adverse event that led to death	181 (1.9)	222 (2.4)
Adverse event that led to discontinuation of the trial regimen	343 (3.6)	324 (3.4)
Local injection-site reaction	360 (3.8)	203 (2.1)
General allergic reaction	748 (7.9)	736 (7.8)
Diabetes worsening or diabetic complication among patients with diabetes at baseline — no./total no. (%)	506/2688 (18.8)	583/2747 (21.2)
New-onset diabetes among patients without diabetes at baseline — no./total no. (%)*	648/6763 (9.6)	676/6696 (10.1)
Neurocognitive disorder	143 (1.5)	167 (1.8)
Hepatic disorder	500 (5.3)	534 (5.7)
Cataracts	120 (1.3)	134 (1.4)
Hemorrhagic stroke, adjudicated	9 (<0.1)	16 (0.2)
Laboratory abnormalities at any time — no./total no. (%)		
Alanine aminotransferase >3 times upper limit of normal range	212/9369 (2.3)	228/9341 (2.4)
Aspartate aminotransferase >3 times upper limit of normal range	160/9367 (1.7)	166/9338 (1.8)
Total bilirubin >2 times upper limit of normal range	61/9368 (0.7)	78/9341 (0.8)
Creatine kinase >10 times upper limit of normal range	46/9369 (0.5)	48/9338 (0.5)
Antidrug antibodies†	67/9091 (0.7)	32/9097 (0.4)
Neutralizing antidrug antibodies	43/9091 (0.5)	6/9097 (<0.1)

N Engl J Med 2017; 376:1713-1722
N Engl J Med 2018; 379:2097-2107
Davidson, M. PCSK9 antibodies: a dividend of the genomics revolution. *Nat Rev Cardiol* **10**, 618–619

Bempedoic Acid



- Similar action to statins
- Inhibitor of ATP citrate lyase
  - Acts upstream of HMG-CoA reductase
- Prodrug activated by liver enzyme
  - Not found in skeletal muscle
- Additional 17-21% LDL reduction
- Significant reduction in rates of
  - Death from CVD
  - Nonfatal MI
  - Nonfatal stroke
- Use with caution in those with gout or tendon rupture history

2022 ECDP on Role of Nonstatin Therapies for LDL-C Lowering
N Engl J Med. 2019;380:1022–1032.
N Engl J Med. 2023 Apr 13;388(15):1353-1364
https://doi.org/10.1016/j.arteri.2021.02.012

ASCVD + Very High Risk

- Very High Risk: Consider as initial non-sta
  - Multiple major ASCVD events
  - 1 major ASCVD event + high risk factors
    - Age ≥ 75
    - ACS within 3 months
    - DM
    - Stroke
    - CABG
    - PAD
    - CKD
    - Smoking
- Primary treatment consideration
  - ≥50% LDL reduction
  - LDL<55
  - non-HDL cholesterol <85
- Make sure patient is on max tolerated statin

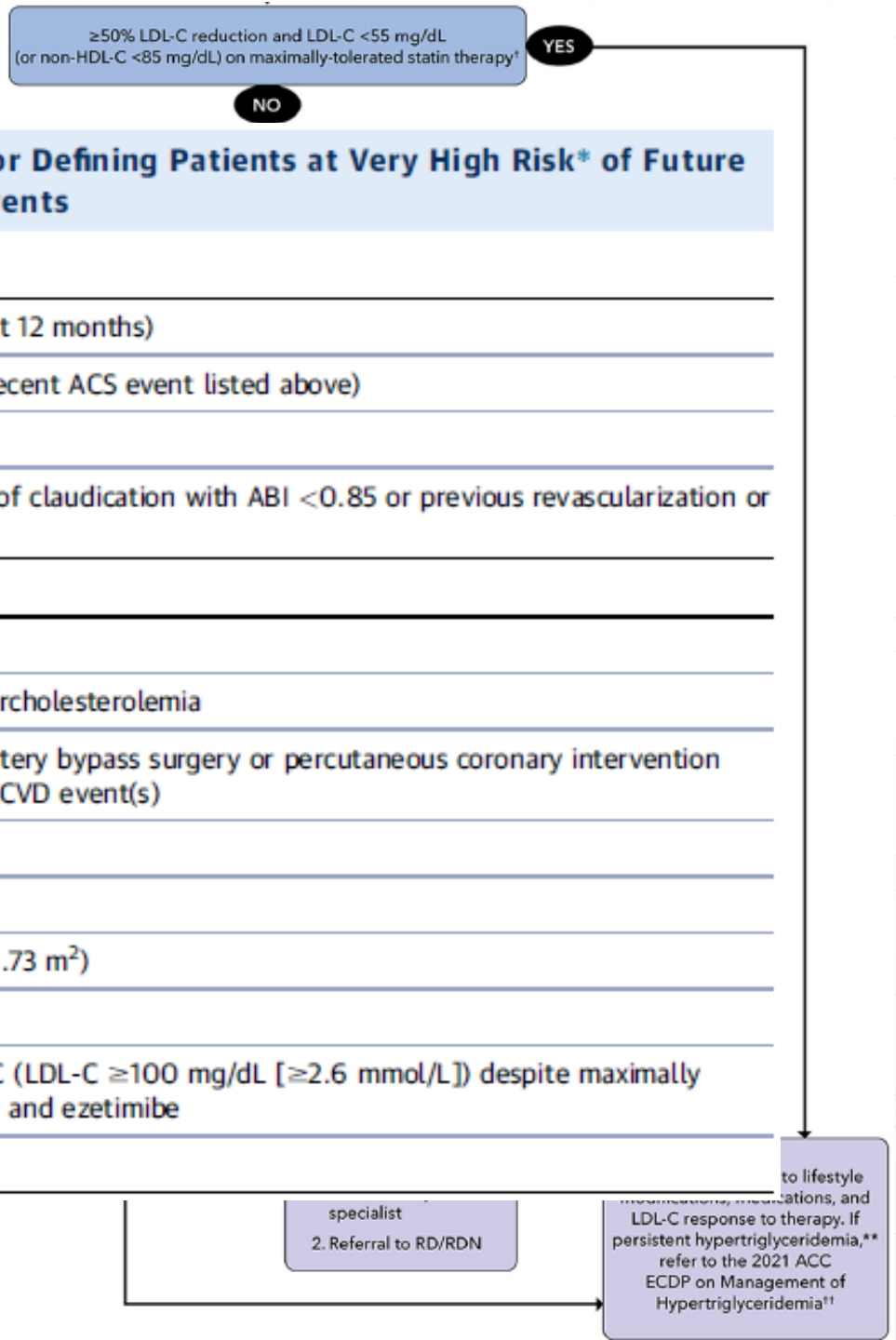


TABLE 1 Criteria for Defining Patients at Very High Risk* of Future ASCVD Events

Major ASCVD Events
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 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

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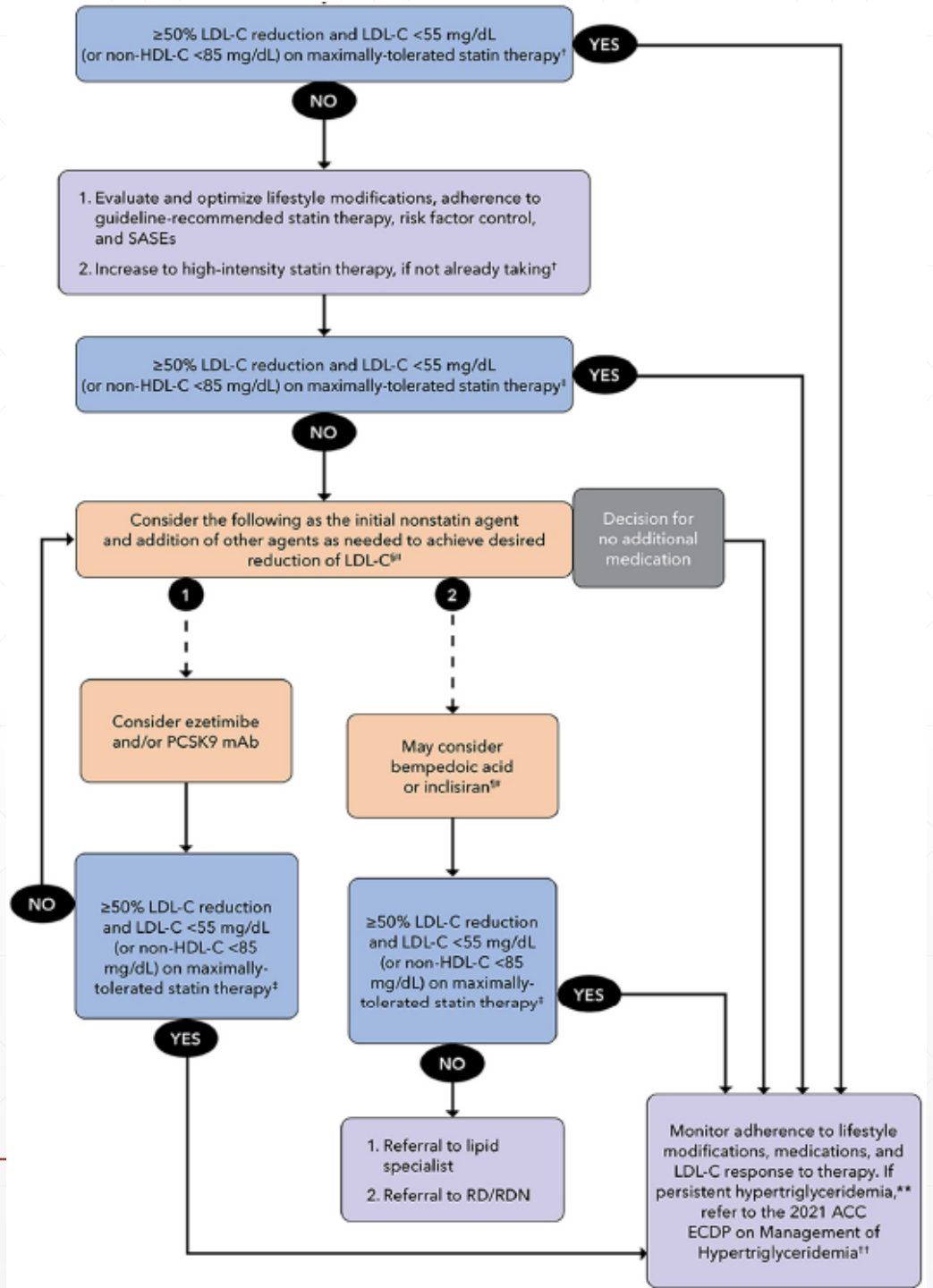
J Am Coll Cardiol. 2017;69:911–921.

ASCVD + Very High Risk

- Consider alicrocumab or evolucumab when
  - Require >25% additional LDL lowering
  - Did not achieve LDL reduction with ezetimibe

- Factors influencing decision
  - 14 day vs monthly dosing
  - Requires refrigeration for storage
  - Cost

- Improved willingness of insurers to pay
  - Decreasing cost
  - CVD risk reduction
  - Patient tolerability



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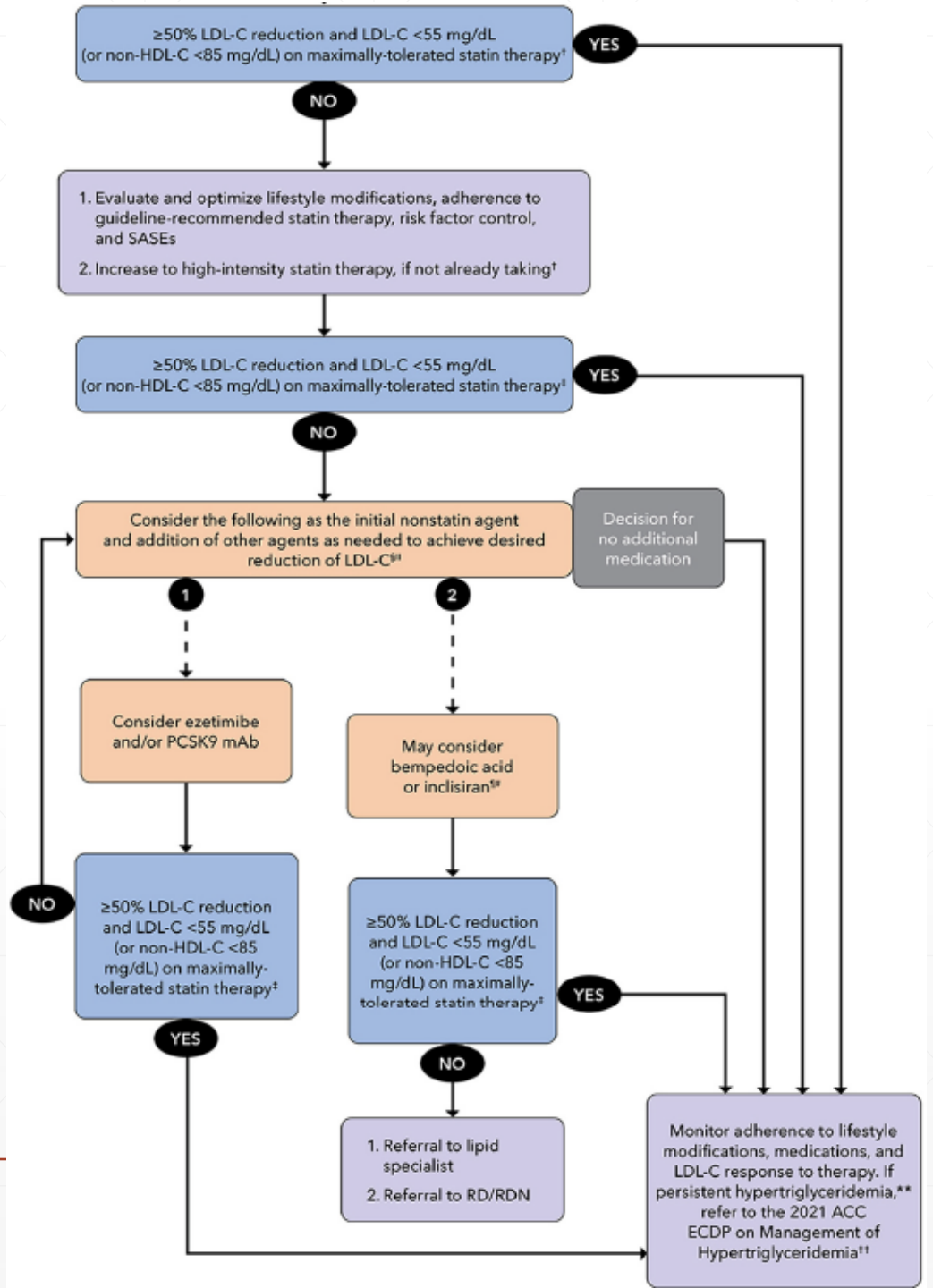
ASCVD + Very High Risk

- Consider bempedoic acid when
  - Max tolerated statin + ezetimibe + PCSK9i

- Factors favoring use of bempedoic acid
  - Other agents contraindicated or not tolerated
  - Statin intolerance
  - Avoidance of injectable medications
  - Cost

- **Consider instead of PCSK9i**

- Use caution with history of gout or tendon rupture



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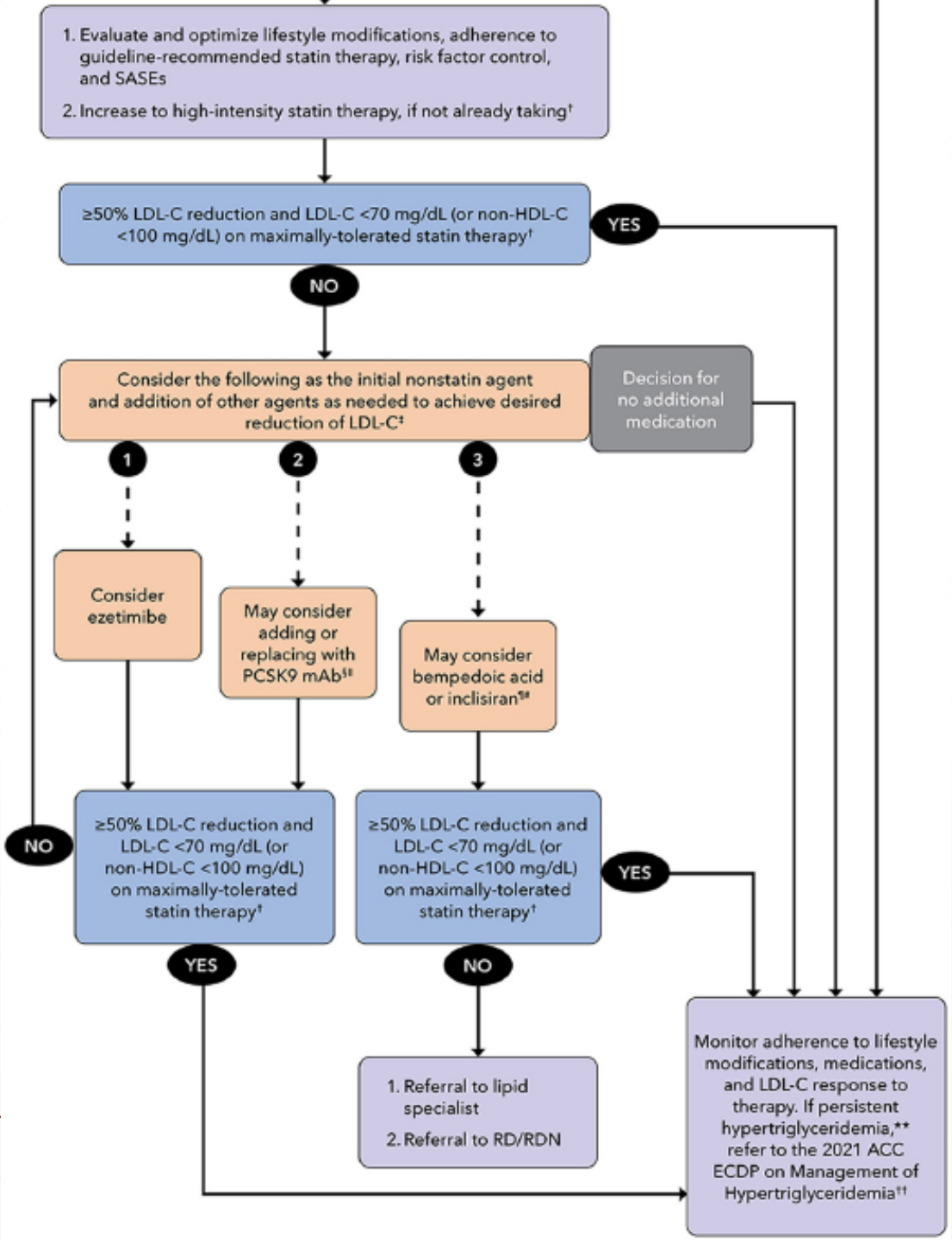
ASCVD and NOT Very High Risk

- Consider ezetimibe or PCSK9 mAb in addition to any statin therapy
  - ≥50% LDL reduction
  - LDL ≥70
  - Age ≤75
  - No ACS within 3 months
- Make sure patient is on max tolerated statin
  - Cost
  - Stroke
  - Ease of use
  - CABG
  - PAD
  - Patient preference
  - CKD
  - Smoking



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ASCVD and NOT Very High Risk

- Consider adding/switching to alirocumab or evolocumab
  - If LDL reduction not achieved with ezetimibe
  - Continue maximum tolerated statin

- Factors influencing decision
  - 14 day vs monthly dosing
  - Requires refrigeration for storage
  - Cost

- Improved willingness of insurers to pay
  - Decreasing cost
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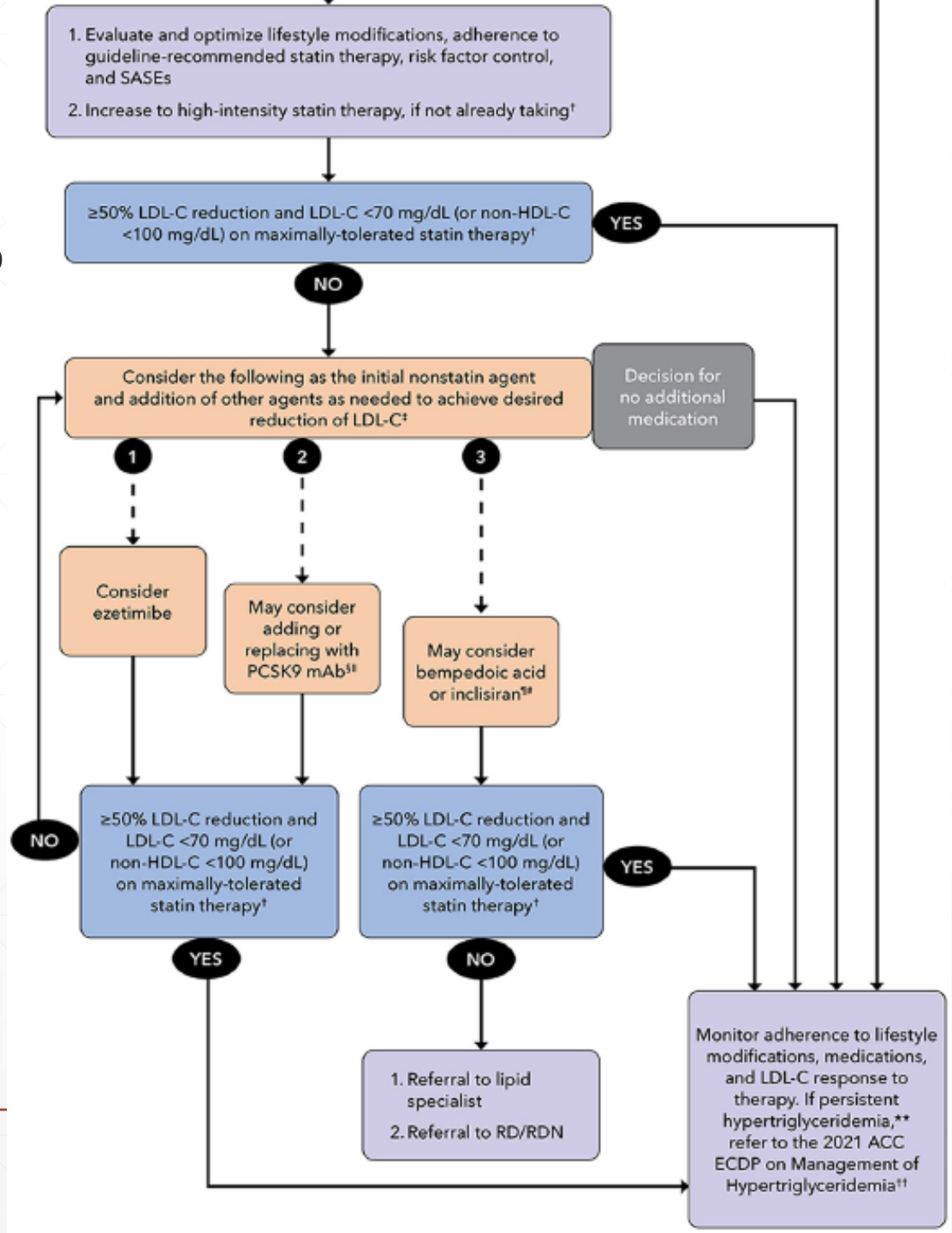
  - Patient tolerability



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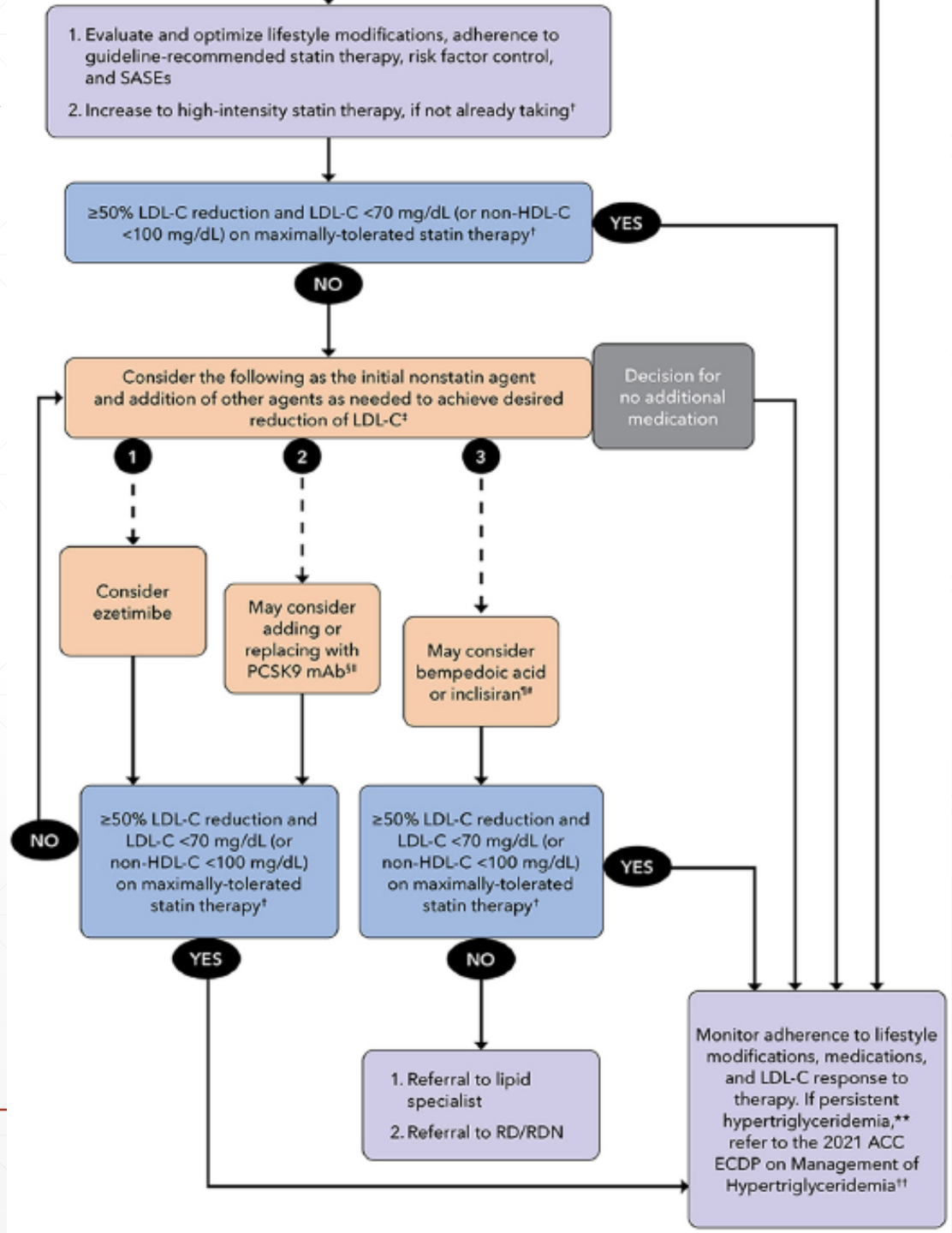

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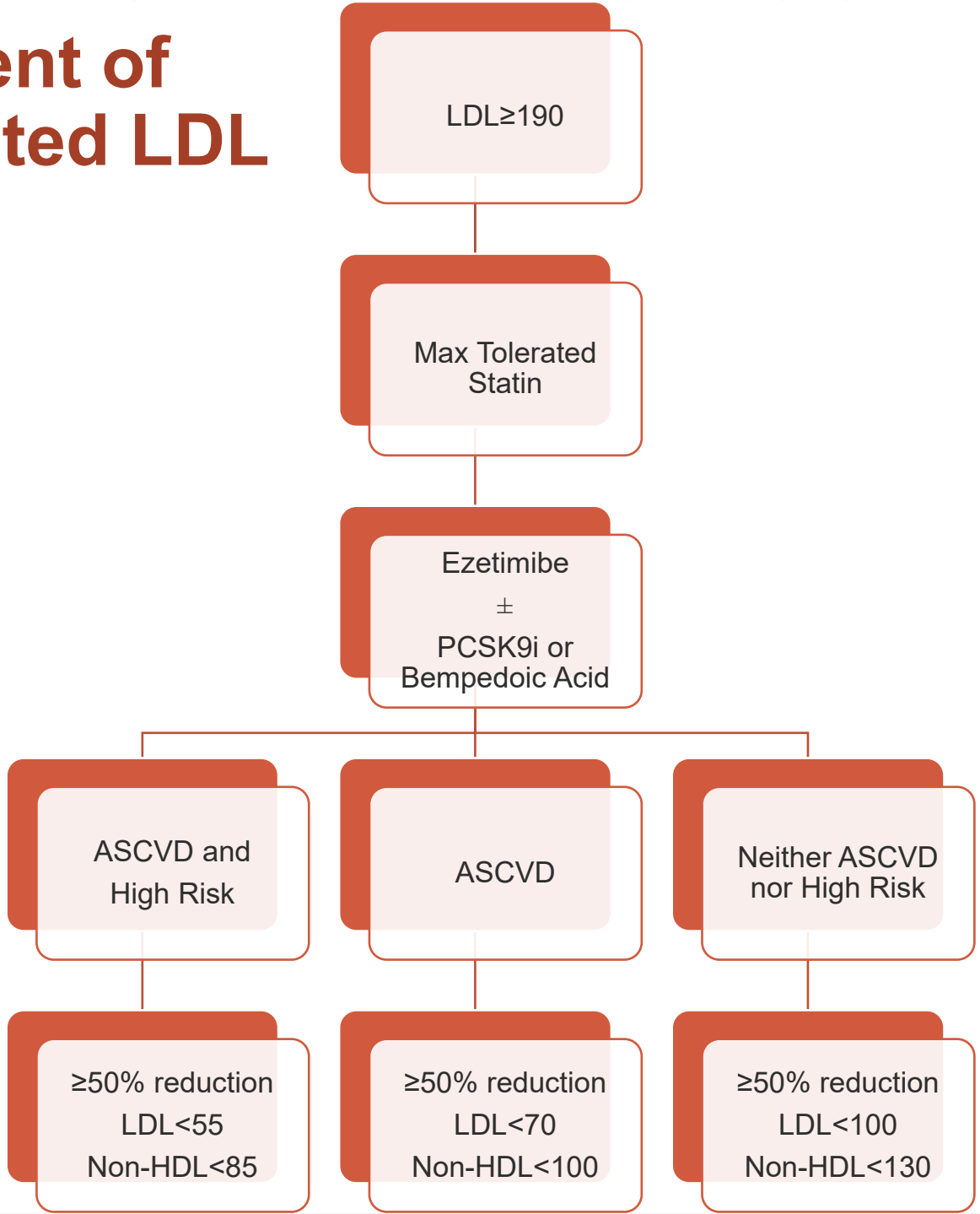
Management of Very Elevated LDL

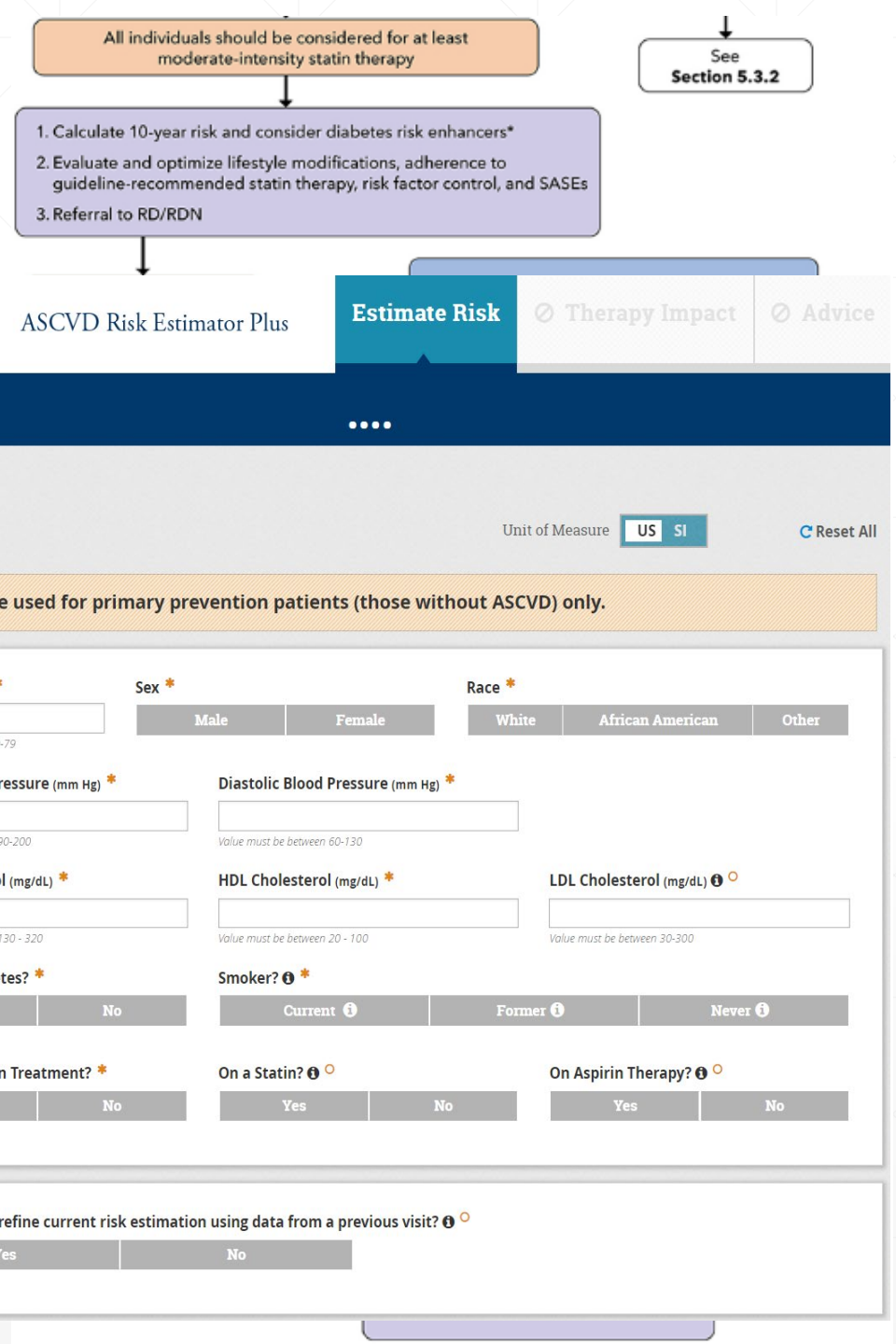


40-75yo with Diabetes and no ASCVD

- All diabetics considered for at least moderate intensity statin
  - ≥30-49% LDL reduction, LDL<100, non-HDL <130
- ASCVD risk ≥7.5% → High intensity statin
  - ≥30-49% LDL reduction, LDL<100, non-HDL <130
  - https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate
- DM specific risk enhancers → High intensity statin
  - ≥30-49% LDL reduction, LDL<100, non-HDL <130
- With A
  - ≥50%

Risk Enhancers

- Long duration (≥10 years for type 2 diabetes mellitus (S4.3-20) or ≥20 years for type 1 diabetes mellitus (S4.3-6))
- Albuminuria ≥30 mcg of albumin/mg creatinine (S4.3-25)
- eGFR <60 mL/min/1.73 m^2 (S4.3-25)
- Retinopathy (S4.3-19)
- Neuropathy (S4.3-16)
- ABI <0.9 (S4.3-22, S4.3-24)



J Am Coll Cardiol. 2019;73: e285–e350
2022 ECDP on Role of Nonstatin Therapies for LDL-C Lowering

Primary Prevention Showdown

2018 ACC Recommendations

- Ages 40-75
- Without ASCVD
- All diabetics

2022 USPTF Recommendations

- Ages 40-75
- Without ASCVD
- ≥ 1 risk factor
  - Diabetes, dyslipidemia, HTN, smoking
- 10 year risk ≥ 10%

Based on data from the NHANES 2017-2020

- 49.7 million treated with ACC/AHA recommendations
- 33.7 million treated with USPTF recommendations – 63%

J Am Coll Cardiol. 2019;73: e285–e350
JAMA. 2022;328(8):746-753.
2022 ECDP on Role of Nonstatin Therapies for LDL-C Lowering

When to Refer to Specialist

- LDL ≥ 190 with or without ASCVD
- Baseline LDL ≥ 190 and ASCVD
  - Max tolerated statin and non statin therapy
  - Did not achieve
    - LDL reduction ≥ 50%
    - LDL < 70
- Clinical ASCVD (± Very High Risk)
  - Max tolerated statin and non statin therapy
  - Did not achieve
  - LDL reduction ≥50%
  - LDL <70 or LDL<55
- Intolerance to ≥ 2 statins
  - 1 at the lowest FDA approved dose
  - Trial of alternative regimen
  - Preferably have tried 3
- Also refer to registered dietician

SUMMARY

- ASCVD + Very High Risk ± LDL ≥190
  - High intensity statin
  - ≥ 50% LDL reduction, LDL <55
- ASCVD (not very high risk) ± LDL ≥190
  - High intensity statin
  - ≥ 50% LDL reduction, LDL <70
- LDL ≥ 190
  - High intensity statin
  - ≥50% LDL reduction, LDL <100
- Diabetics age 40-75
  - Moderate intensity statin
  - ≥30-49% LDL reduction, LDL <100
- If not at goal then sequentially add
  - Ezetimibe – additional 13-25% reduction
  - PCSK9i – additional 40-63% reduction
    - Can add simultaneously with ezetimibe
  - Bempedoic acid – additional 17-20% reduction
    - Use if intolerant to statin or other non-statin therapies
    - Use instead of PCSK9i
    - CLEAR ACS trial: ezetimibe + bempedoic acid with recent ACS
- Refer to lipid specialist and dietician
  - Unable to achieve LDL target with non-statin therapies
  - Statin intolerant patients
  - Intolerant to multiple non-statin therapies
  - LDL ≥190