Deep Dive into Contemporary Cholesterol Management

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7 October 2016

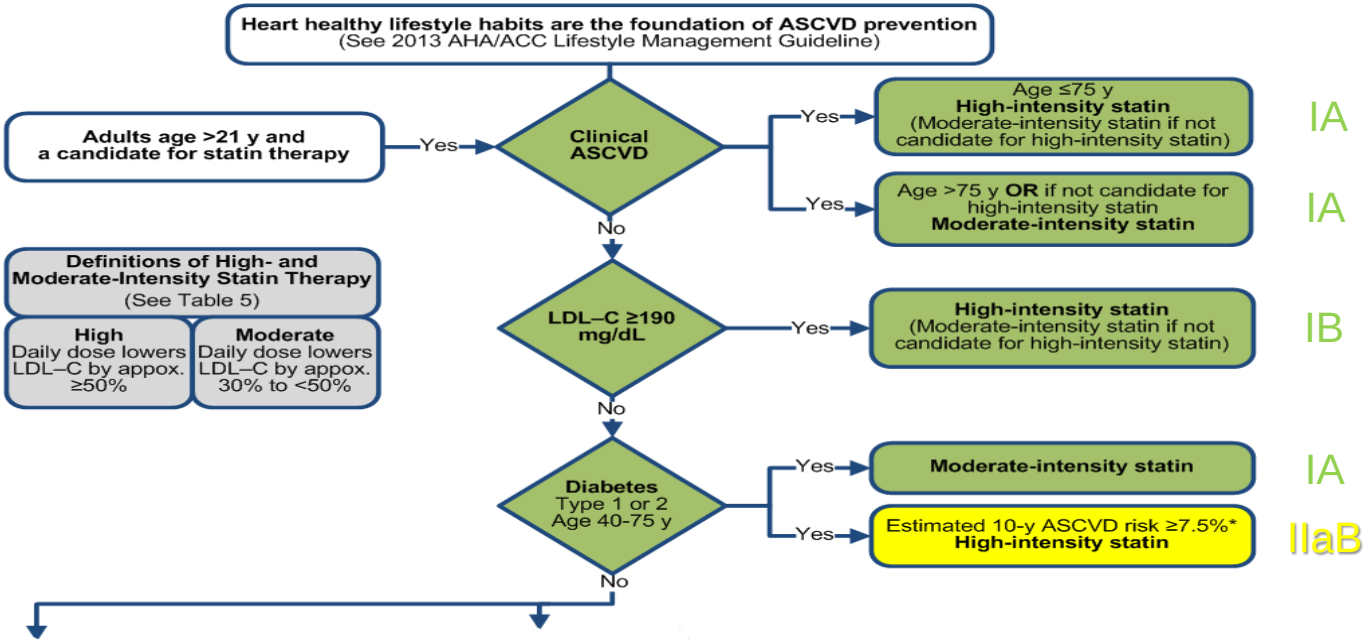
Mexico City

ACC Latin America Conference 2016

Introduction: Pamela B. Morris, MD, FACC

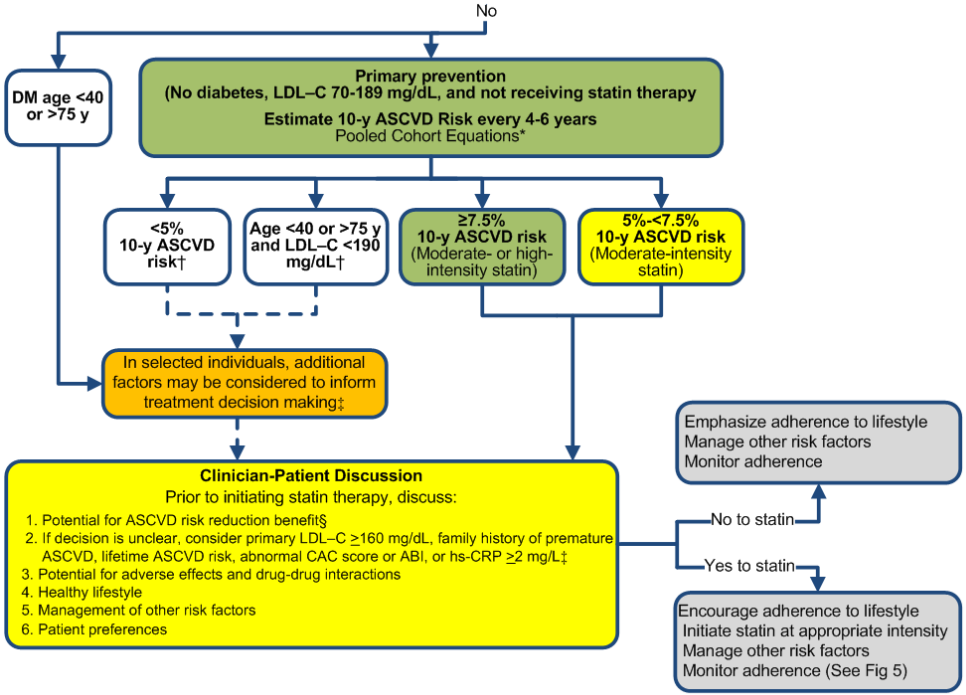
COMING TO CONSENSUS IN A NEW ERA: THE ROLE OF NON-STATIN THERAPIES

2013 Cholesterol Guidelines: Recommendations for Initiating Statin Therapy



J Am Coll Cardiol 2013;2889-934.

2013 Cholesterol Guidelines:
Recommendations for Initiating Statin Therapy - 2



J Am Coll Cardiol 2013;2889-934.

2013 ACC/AHA Cholesterol Guidelines Recommendations on Use of Non-Statins

- "Clinicians treating high risk patients who have a ***less than anticipated response to statins***, who are ***unable to tolerate a less than recommended intensity of a statin*** or who are ***completely statin intolerant***, may consider the addition of non-statin cholesterol lowering therapy…"

- "In this situation, this guideline recommends clinicians *preferentially prescribe* ***drugs that have been shown in RCTs to provide ASCVD risk-reduction benefits*** that outweigh the potential for *adverse effects* and *drug-drug interactions* and consider *patient preferences*."

J Am Coll Cardiol 2013;2889-934.

2016 Expert Consensus Decision Pathway

Background

- September 2015: 2nd "LDL: Address the Risk Think Tank"
  - Multi-stakeholder quality initiative to improve patient outcomes by driving awareness of gaps in lipid management
  - Expert clinicians, patient advocacy groups, health plans, pharmacy benefit managers, drug manufacturers, EHR vendors, and health systems

  - **Identified need for expert consensus guidance regarding incorporation of non-statin therapies into treatment strategies for higher-risk patients**

J Am Coll Cardiol. 2016;():. doi:10.1016/j.jacc.2016.03.519

2016 Expert Consensus Decision Pathway

Rationale

- Provide more specific guidance on the adequacy of statin therapy and whether or when to use non-statin therapies if response to statins is deemed inadequate or less than anticipated
- Extend beyond 2013 evidence base to incorporate recent trial data and address current gaps in care for LDL-C lowering to reduce ASCVD risk
  - HPS2-THRIVE (niacin/laropiprant)
  - IMPROVE-IT (ezetimibe+simvastatin)
- Consider use of drugs FDA-approved after publication of 2013 guideline (alirocumab, evolocumab)

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 68, NO. 1, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.03.519

EXPERT CONSENSUS DECISION PATHWAY

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 Clinical Expert Consensus Documents

Endorsed by the National Lipid Association

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2016 Expert Consensus Decision Pathway

Questions Addressed

1. In what ***patient populations*** should non-statin therapies be considered?

2. In what ***situations*** should non-statin therapies be considered?
   - When is the *amount of LDL-C lowering* less than anticipated, less than desired, or inadequate, and which treatment options should be considered in patients who are truly statin intolerant?

3. If non-statin therapies are to be added, ***which agents*** or therapies should be considered and in ***what order***?

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2016 Expert Consensus Decision Pathway

Assumptions and Definitions

- **Thresholds for consideration of net benefit**
  - Maximally-tolerated statin therapy
  - ***Percent*** LDL-C reduction: Achieve ≥50% LDL-C reduction on high-intensity statin, or ≥30% to <50% reduction for moderate-intensity statin
  - May consider ***absolute*** LDL-C levels (or non-HDL-C in patients with DM) as factors
    - WG emphasizes that these are not firm triggers (not "goals") for adding medication but factors that may be considered within the broader context of an individual patient's clinical situation

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2016 Expert Consensus Decision Pathway

Non-Statin Therapies Considered

- Ezetimibe
- Bile-acid sequestrants (BAS)
- PCSK9 inhibitors
  - Alirocumab, evolocumab
- Mipomersen
- Lomitapide
- LDL apheresis

} For selected pts with HoFH under care of a lipid specialist

- Niacin NOT routinely recommended

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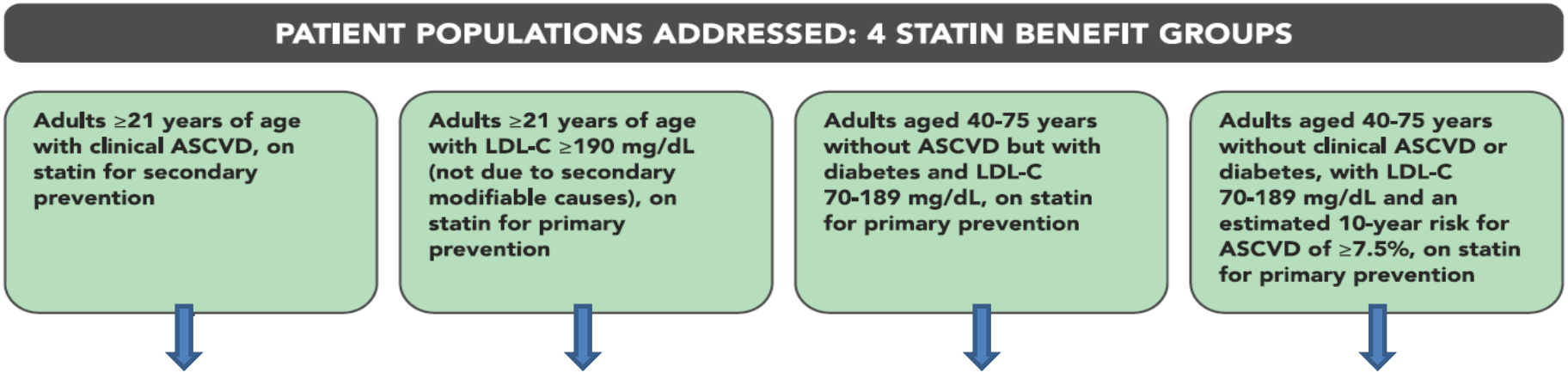
2016 Expert Consensus Decision Pathway

Patient Populations Addressed



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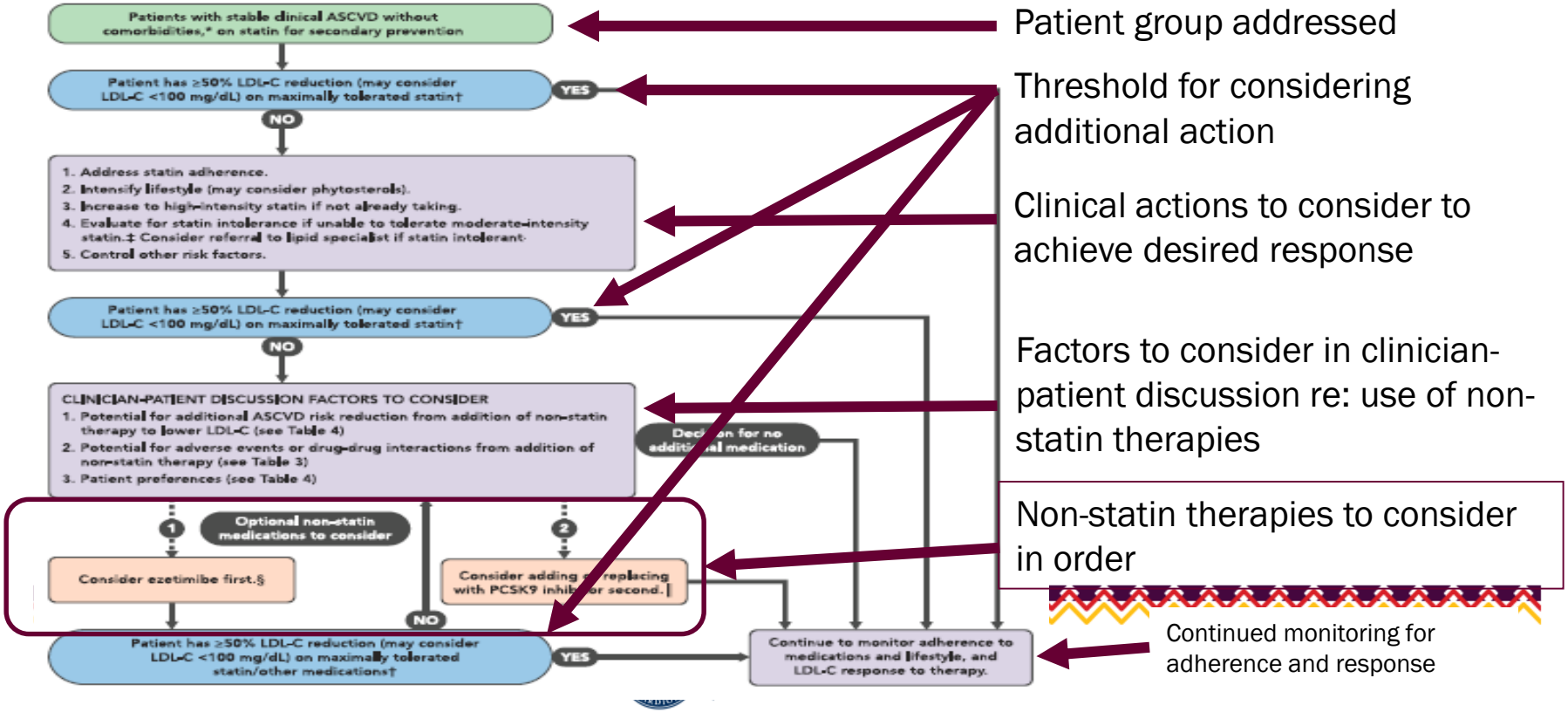
Decision Pathway Algorithms

General



Patient group addressed

Threshold for considering additional action

Clinical actions to consider to achieve desired response

Factors to consider in clinician-patient discussion re: use of non-statin therapies

Non-statin therapies to consider in order

Continued monitoring for adherence and response

2016 Expert Consensus Decision Pathway

Summary: Patient Populations Addressed

PATIENT POPULATIONS ADDRESSED: 4 STATIN BENEFIT GROUPS

Adults ≥21 years of age with clinical ASCVD, on statin for secondary prevention	Adults ≥21 years of age with LDL-C ≥190 mg/dL (not due to secondary modifiable causes), on statin for primary prevention	Adults aged 40-75 years without ASCVD but with diabetes and LDL-C 70-189 mg/dL, on statin for primary prevention	Adults aged 40-75 years without clinical ASCVD or diabetes, with LDL-C 70-189 mg/dL and an estimated 10-year risk for ASCVD of ≥7.5%, on statin for primary prevention
• Ezetimibe first • PCSK9i may then be added or replace ezetimibe • LDL-C ≥190 mg/dl *either* agent first	• Ezetimibe OR PCSK9i may be considered first	• Ezetimibe may be considered • PCSK9i not recommended in primary prevention patients with DM	• Ezetimibe may be considered • PCSK9i are not recommended

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2016 ESC/EAS Guidelines for Management of Dyslipidemias:

Table 11
Recommendations for treatment goals for low-density lipoprotein-cholesterol

Recommendations	Class [a]	Level [b]	Ref [c]
In patients at VERY HIGH CV risk[d], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B	61, 62, 65, 68, 69, 128
In patients at HIGH CV risk[d], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B	65, 129
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	-

European Heart Journal. 2016; doi:10.1093/eurheartj/ehw272

2016 ESC/EAS Guidelines for Management of Dyslipidemias:

Recommendations for lipid-lowering therapy in patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention

Recommendations	Class [a]	Level [b]	Ref [c]
It is recommended to initiate or continue high dose statins early after admission in all ACS patients without contra-indication or history of intolerance, regardless of initial LDL-C values.	I	A	64, 358–360
If the LDL-C target is not reached with the highest tolerable statin dose, ezetimibe should be considered in combination with statins in post-ACS patients.	IIa	B	63
If the LDL-C target is not reached with the highest tolerable statin dose and/or ezetimibe, PCSK9 inhibitors may be considered on top of lipid-lowering therapy; or alone or in combination with ezetimibe in statin intolerant patients or in whom a statin is contra-indicated.	IIb	C	115, 116
Lipids should be re-evaluated 4–6 weeks after ACS to determine whether target levels of LDL-C <1.8 mmol/L (<70 mg/dL) or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) have been reached and whether there are any safety issues. The therapy dose should then be adapted accordingly.	IIa	C	
Routine short pretreatment or loading (on the background of chronic therapy) with high-dose statins before PCI should be considered in elective PCI or in NSTE-ACS.	IIa	A	363–365

European Heart Journal. 2016; doi:10.1093/eurheartj/ehw272

Clinical ASCVD and baseline LDL-C ≥190 mg/dL

Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia

Recommendations	Class [a]	Level [b]
FH patients are recommended to be treated with intense-dose statin, often in combination with ezetimibe.	I	C
Treatment should be considered to aim at reaching an LDL-C <2.6 mmol/L (100 mg/dL) or in the presence of CVD <1.8 mmol/L (70 mg/dL). If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations.	IIa	C
Treatment with a PCSK9 antibody should be considered in FH patients with CVD or with other factors putting them at very high-risk for CHD, such as other CV risk factors, family history, high Lp(a) or statin intolerance.	IIa	C
Children with FH should be educated to adopt a proper diet and treated with statin from 8–10 years of age. Targets for treatment should be LDL-C <3.5 mmol/L (135 mg/dL) at >10 years of age.	IIa	C

European Heart Journal. 2016; doi:10.1093/eurheartj/ehw272

2016 Expert Consensus Decision Pathway

Take-Home Points

- Follow evidence-based 2013 ACC/AHA Cholesterol Guidelines for use of lipid-lowering therapies to reduce ASCVD risk
- Engage in shared decision making to consider potential benefits and harms of non-statin therapies
- Consider specific non-statin therapies only in higher-risk pts who have inadequate response to statin or statin intolerance
- Individualize care for other patient groups

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Case Presentations

Case Presentation #1

Case Presentation #1:

ASCVD and LDL-C ≥190 mg/dl

- A 61 yo female presents with STEMI and undergoes PCI of proximal LAD lesion.
  - Mild hypokinesia of anterior wall, preserved LV ejection fraction
  - Baseline LDL-C is 208 mg/dL (5.4 mmol/L).
  - She is discharged on atorvastatin 80 mg daily.

Case Presentation #1:

ASCVD and LDL-C ≥190 mg/dl

- Post STEMI/PCI follow-up in 8 weeks
  - Reports adherence to medications and lifestyle recommendations, in cardiac rehabilitation program.
  - Repeat fasting lipid panel shows:
    - Total cholesterol 218 mg/dL (5.6 mmol/L)
    - HDL-C 44 mg/dL (1.14 mmol/L)
    - LDL-C 142 mg/dl (3.67 mmol/L)
    - Triglycerides 160 mg/dL (1.81 mmol/L)
    - LDL-C reduction 32%

ARS: Has this patient achieved anticipated LDL-C lowering with high-intensity statin therapy?

- 1. Yes
- 2. No

ARS: Which ONE of the following non-statin therapies would you consider adding as first agent to achieve additional LDL-C lowering?

- 1. Colesevelam
- 2. Nicotinic acid
- 3. Ezetimibe
- 4. PCSK9 inhibitor
- 5. None

Case Presentation #1:

ASCVD and LDL-C ≥190 mg/dl

- Following clinician-patient discussion ezetimibe 10 mg is added.
  - Follow-up lipid panel in 8 weeks demonstrates:
    - Total cholesterol 187 mg/dL (4.84 mmol/L)
    - HDL-C 42 mg/dL (1.09 mmol/L)
    - LDL-C 114 mg/dL (2.95 mmol/L)
    - Non-HDL-C 145 mg/dL
    - Triglycerides 155 mg/dL (1.75 mmol/L)
    - Total LDL-C reduction on combination therapy = 45%

ARS: Has this patient achieved anticipated LDL-C lowering with high-intensity statin therapy?

- 1. Yes
- 2. No

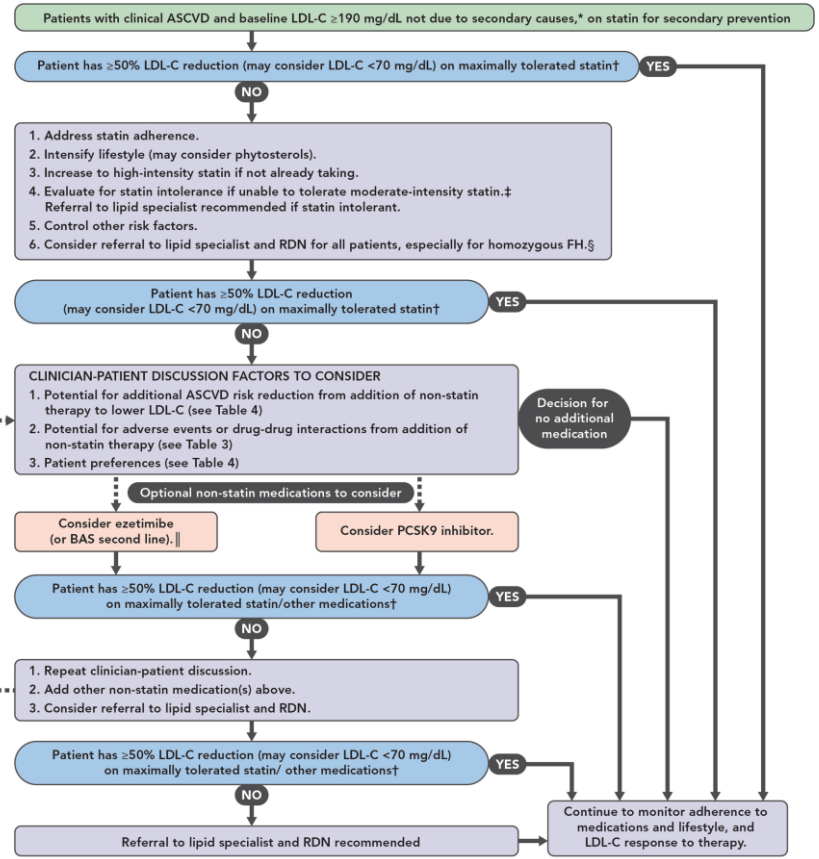
ARS: Which ONE of the following non-statin therapies would you consider adding to achieve additional LDL-C lowering?

- 1. Colesevelam
- 2. Nicotinic acid
- 3. Ezetimibe
- 4. PCSK9 inhibitor
- 5. None

Discussion

- Has this patient achieved anticipated reduction in atherogenic lipoproteins?
- Is the degree of lowering of atherogenic lipoproteins acceptable?
- Would you consider additional modifications to the patient's regimen?
- What factors would you consider in the decision to further modify the patients medical regimen?

Clinical ASCVD and baseline LDL-C ≥190 mg/dL



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Case Presentation #2

Case Presentation #2:

Recurrent ASCVD event on maximally-tolerated statin therapy

- 41 yo male who is an ex-smoker with symptomatic peripheral arterial disease and prior NSTEMI with PCI to LAD and OM1.
  - Baseline fasting lipid panel:
    - Total cholesterol 283 mg/dL (7.32 mmol/L)
    - HDL-C 38 mg/dL (0.98 mmol/L)
    - LDL-C 217 mg/dL (5.61 mmol/L)
    - Triglycerides 142 mg/dL (1.60 mmol/L)

Case Presentation #2:

Recurrent ASCVD event on maximally-tolerated statin therapy

- Patient now presents with recurrent NSTEMI/ACS.
- He undergoes PCI to RCA without complications.
- On admission he reports excellent adherence to therapy with rosuvastatin 40 mg and lifestyle modifications.
  - 41% reduction in LDL-C on high-intensity statin therapy
  - Absolute level LDL-C 128 mg/dL (3.31 mmol/L)

ARS: Has this patient achieved anticipated LDL-C lowering with high-intensity statin therapy?

- 1. Yes
- 2. No

ARS: Which ONE of the following non-statin therapies would you consider adding as first agent to achieve additional LDL-C lowering?

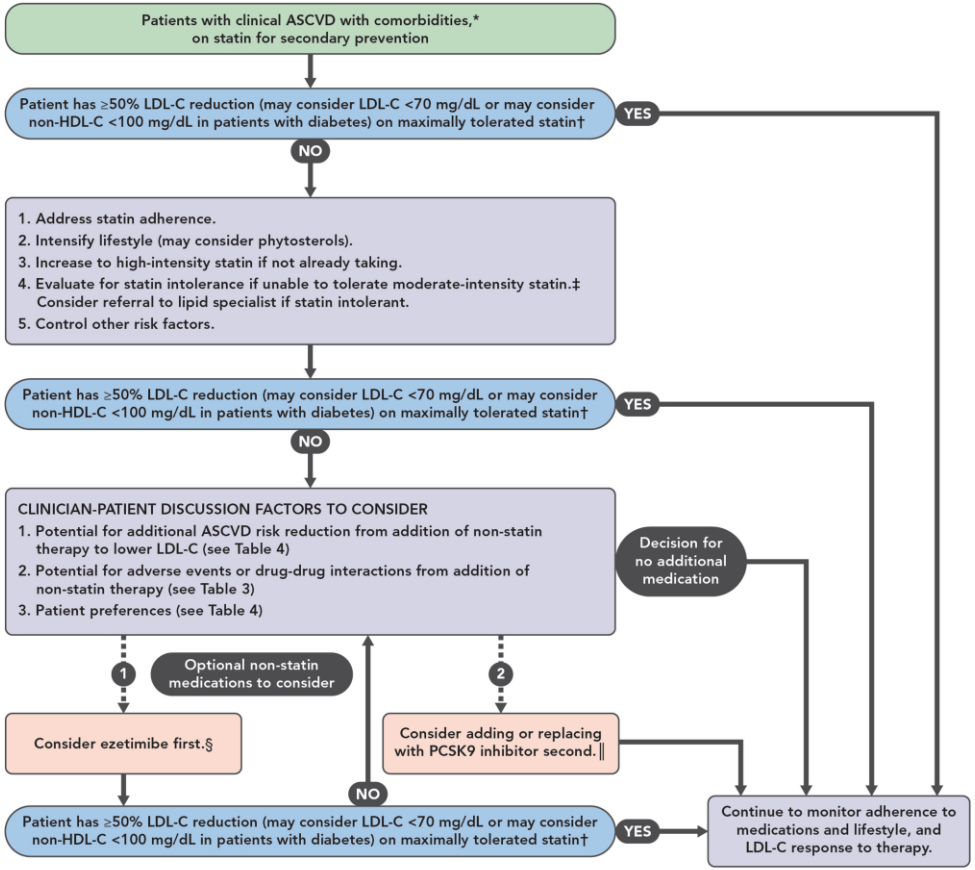
- 1. Colesevelam
- 2. Nicotinic acid
- 3. Ezetimibe
- 4. PCSK9 inhibitor
- 5. None

Discussion

- Has this patient achieved anticipated reduction in atherogenic lipoproteins?
- Is the degree of lowering of atherogenic lipoproteins acceptable?
- Would you consider additional modifications to the patient's regimen?
- What factors would you consider in the decision to further modify the patients medical regimen?

Clinical ASCVD with comorbidities

(DM, recent acute ASCVD event, ASCVD event while on statin, baseline LDL-C ≥190 mg/dl, uncontrolled major RFs, elevated Lp(a), CKD)



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