Clinical Focus Session #1: Key Considerations for Treatment of Lipid Disorders

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DISCLOSURES

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  - Genentech

- Medical Advisory Board
  - Clocktree
  - Measure Labs

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  - Amgen (Principal Investigator for FOURIER, FOURIER-OLE, and EBBINGHAUS trials)
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Case Presentation

- **38F who presents after a workplace screening event identified her as having "high cholesterol." She has 2 children (age 12 and 8), denies smoking, diabetes, taking any medications. Her family history is significant for premature CAD in her father who had an MI at age 44.**
- **Exam:**
  - **BP 132/84; HR 72 (sinus); 99% RA; RR 14; BMI 28.2 kg/m²**
  - **Unremarkable cardiovascular exam**
- **Labs:**
  - **Total cholesterol: 343 mg/dL**
  - **LDL-C: 248 mg/dL**
  - **HDL: 50 mg/dL**
  - **TG: 165 mg/dL**
  - **HbA1c: 5.2%**
  - **TSH: normal**

Case Presentation

What is the next best step for primary ASCVD prevention for this patient?

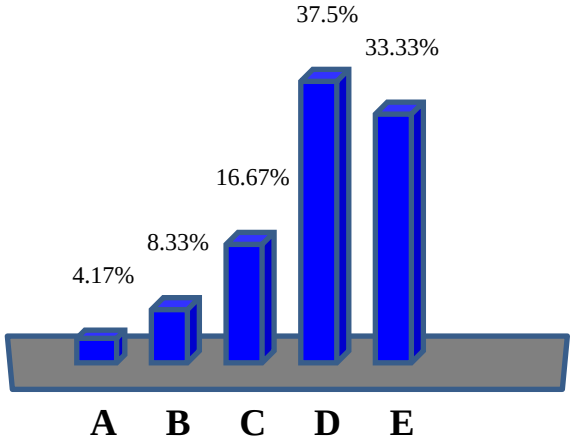
A. Lifestyle modification and repeat lipid panel in 6 months

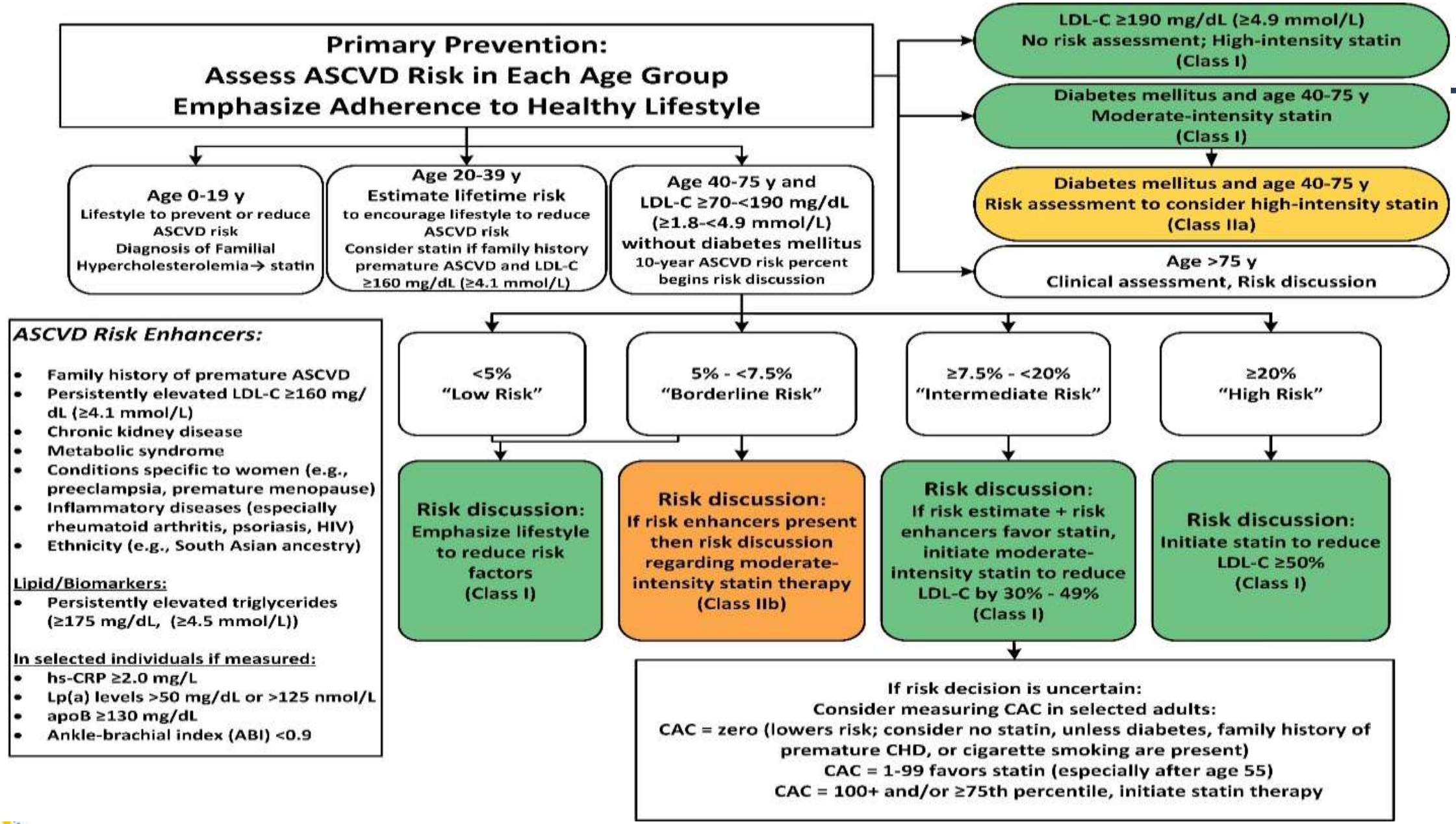
B. Need more information: obtain hsCRP, Lp(a), or CAC score

C. Initiate atorvastatin 10 mg and check LFTs in 4 weeks

D. Initiate atorvastatin 80 mg

E. Calculate a 10-year ASCVD risk score to estimate risk to determine if therapy is needed.




Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin
Age 20-39 y
Estimate lifetime risk
to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and
LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L)
without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
ASCVD Risk Enhancers:
Family history of premature ASCVD
Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity (e.g., South Asian ancestry)
Lipid/Biomarkers:
Persistently elevated triglycerides (≥175 mg/dL, (≥4.5 mmol/L))
In selected individuals if measured:
hs-CRP ≥2.0 mg/L
Lp(a) levels >50 mg/dL or >125 nmol/L
apoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9
<5%
"Low Risk"
5% - <7.5%
"Borderline Risk"
≥7.5% - <20%
"Intermediate Risk"
≥20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

Diagnostic Criteria for FH

Diagnostic Criteria for Familial Hypercholesterolemia

There are currently three accepted resources for FH diagnosis: the Simon Broom Criteria, the MEDPED Criteria, and the FH Dutch Lipid Clinic Criteria.

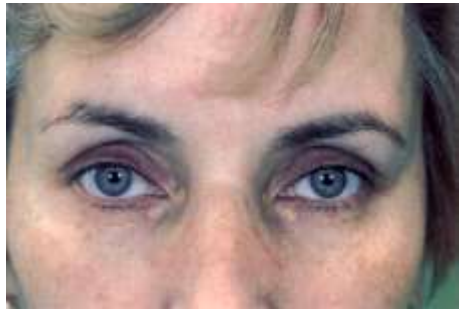
SIMON BROOME DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA[1]	
Point	**Criteria**
1	Total cholesterol levels > 290mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L) in adults. Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L)
2	Tendon xanthomas in the patient or tendon xanthomas in a first or second degree relative.
3	DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.
4	Family history of myocardial infarction before age 50 years in a second degree relative or before age 60 years in a first degree relative.
5	Family history of elevated total cholesterol > 290 mg/dL (7.5 mmol/L) in an adult first or second-degree relative. Family history of elevated totacl cholesterol > 260 mg/dL (6.7 mmol/L) in a child, brother, or sister 16 years or younger.
DIAGNOSIS	
Definite familial hypercholesterolemia = 1+2 or 3 Possible familial hypercholesterolemia = 1+4 or 5	

[1] *Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. American journal of epidemiology. 2004;160:407-420.*

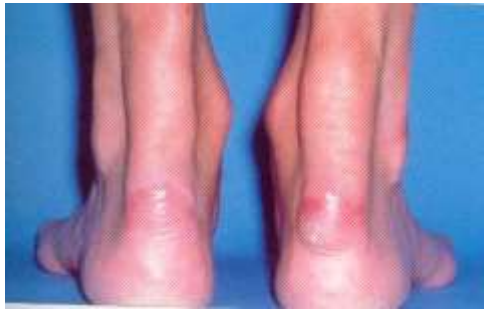
Diagnostic Criteria for FH

A. AHA diagnostic criteria for FH: LDL ≥ 190 md/dL
B. Prevalence of FH is ~1 in 250
C. No risk assessment with PCE is needed
D. All adults with LDL ≥ 190 should get a high-intensity statin unless contraindicated
E. Screen relatives early

Xanthelasma

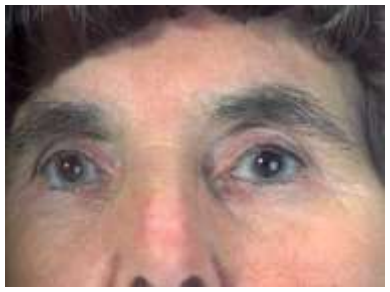


Achilles Tendon Xanthomas

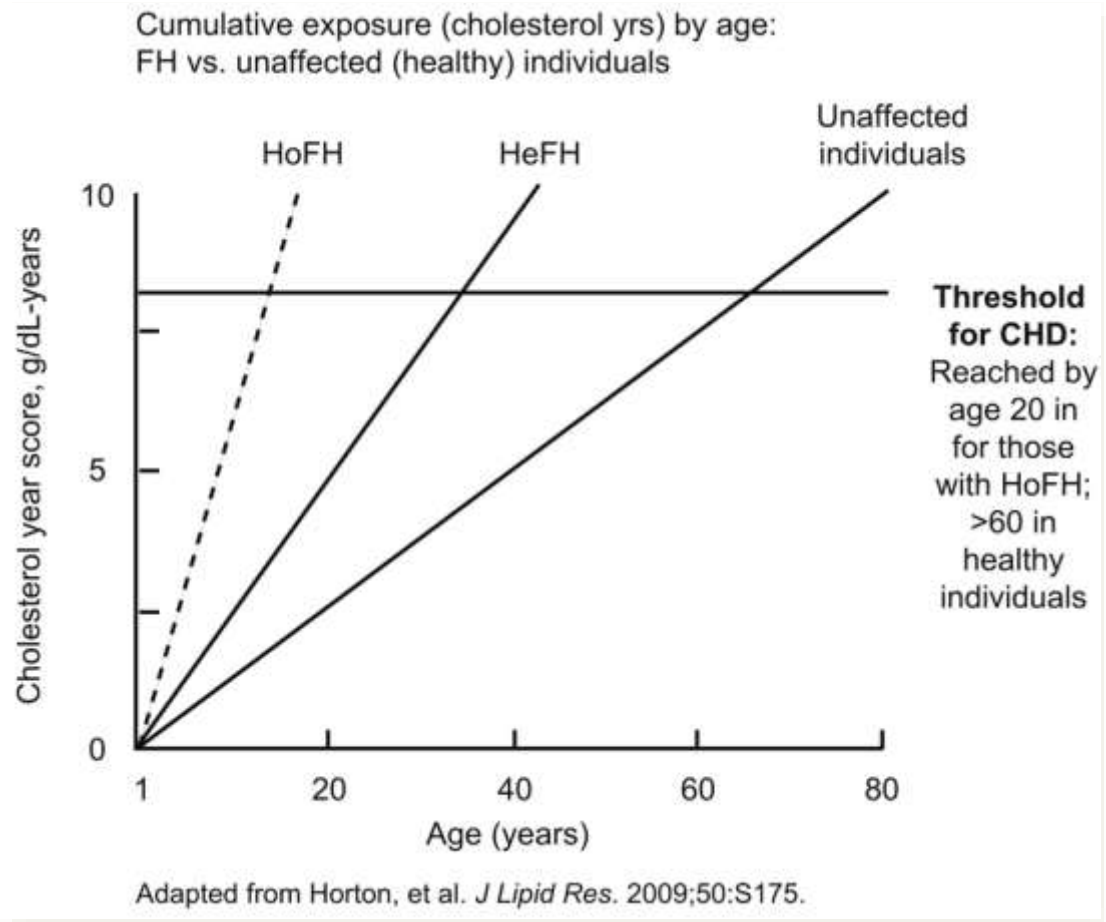


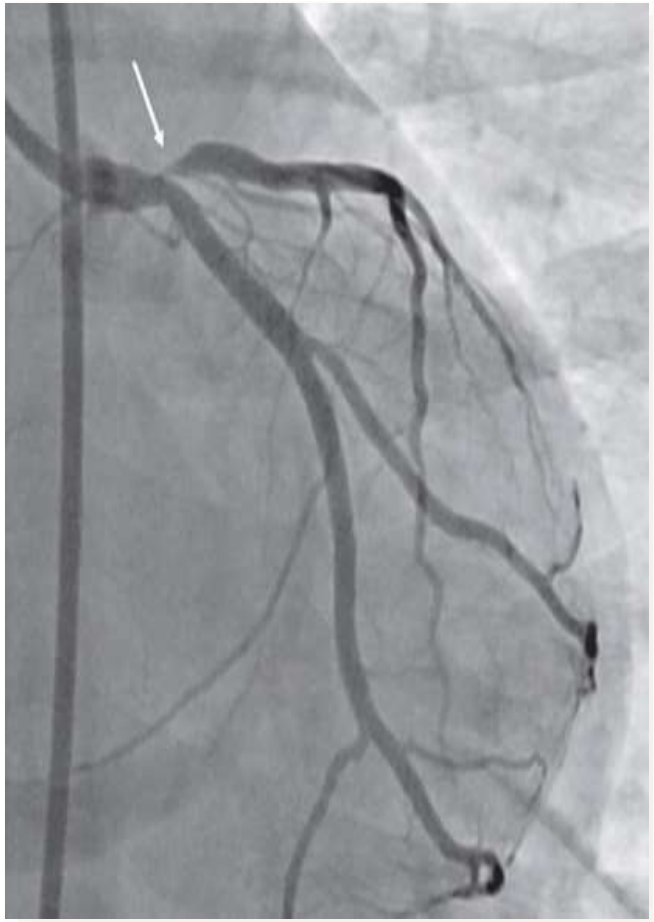
Hand Extensor Tendon Xanthomas

Arcus Corneae



FH Causes Premature CAD



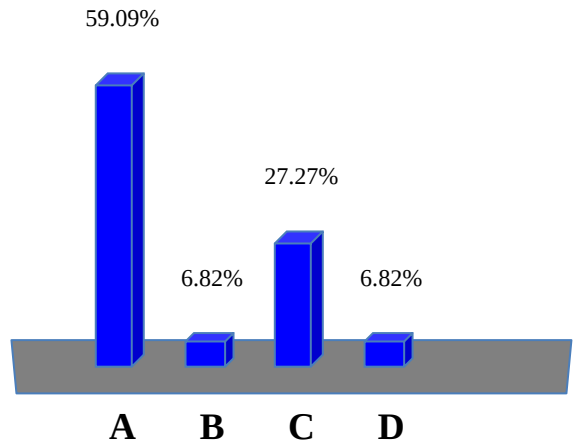


Case Presentation

A 45-year-old man discharged from the hospital 6 weeks ago following an admission for unstable angina during which he undergoes stenting of the right coronary artery presents to the clinic. He reports no history of diabetes, smoking, hypertension, or a family history of premature heart disease. Discharge daily medications include metoprolol succinate 25 mg, aspirin 81 mg, atorvastatin 20 mg, and clopidogrel 75 mg. His body mass index is 27 kg/m2, waist circumference is 42 inches, and blood pressure is 135/85 mm Hg.

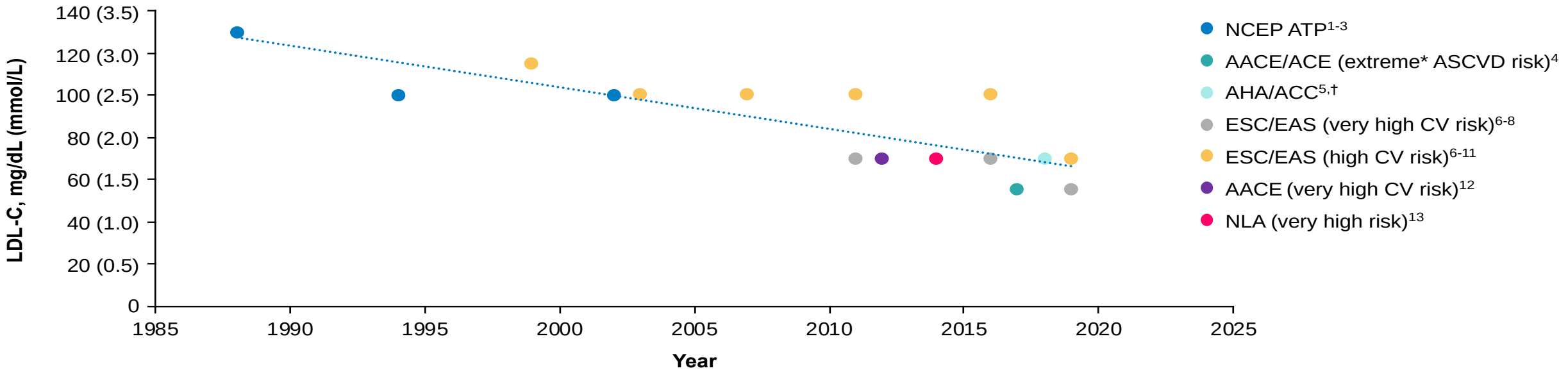
His laboratory results (on admission) were:
-Total cholesterol 230 mg/dl
-Triglycerides 350 mg/dl
-High-density lipoprotein 35 mg/dl
-Low-density lipoprotein 125 mg/dl
-Fasting glucose 99 mg/dl

Which of the following is the most appropriate next step for this patient?
A. Increase atorvastatin to 80 mg.
B. Continue current therapy.
C. Add fenofibrate.
D. Add ezetimibe.



Guidelines Reflect Evolving Evidence of Lowering LDL-C

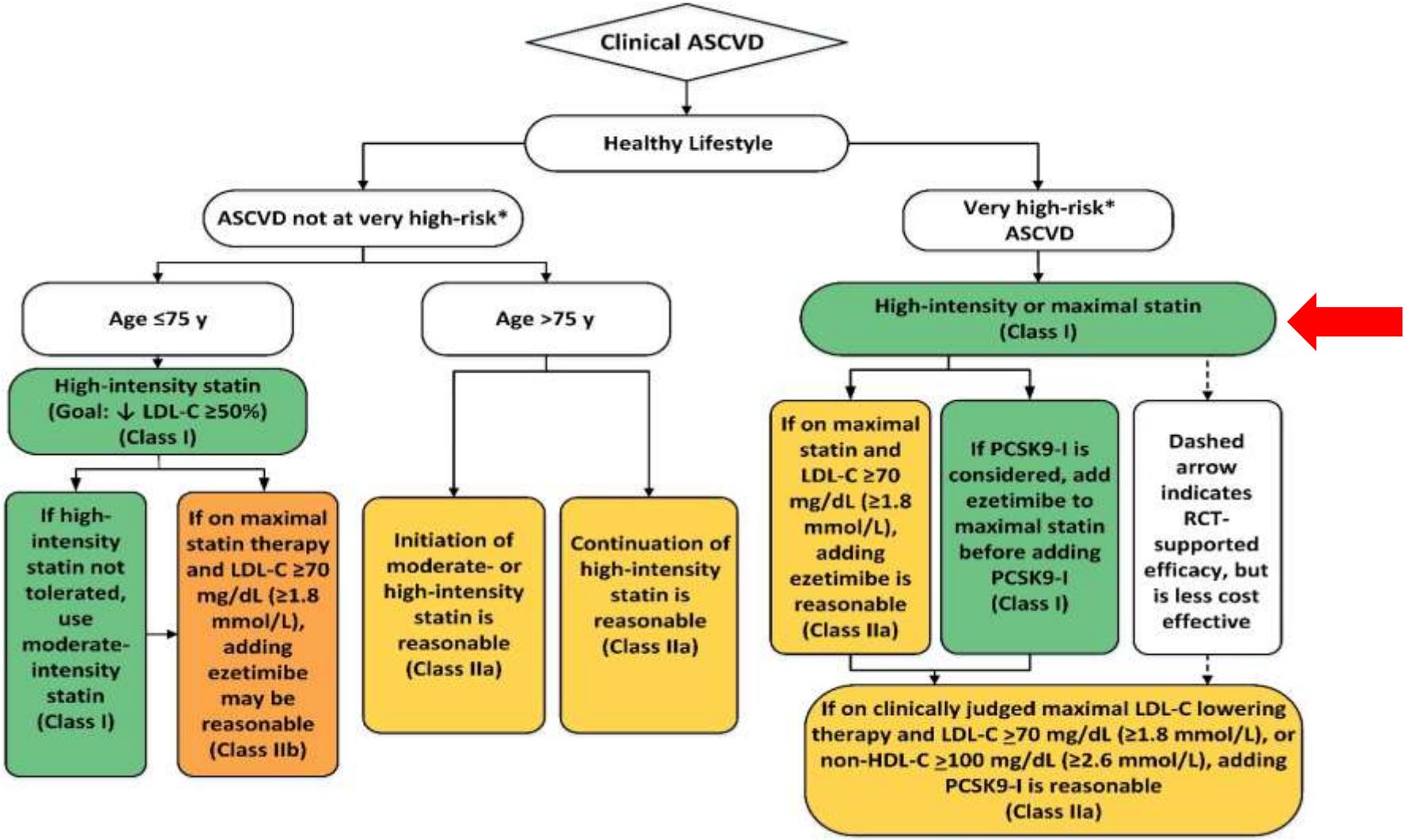
Historical Perspective of LDL-C Targets/Thresholds as Recommended by Globally Recognized Guidelines[1-13]



Progressive ASCVD, including UA that persists after achieving an LDL-C < 70 mg/dL (1.8 mmol/L), or established clinical ASCVD in individuals with diabetes, CKD stage 3 or 4, and/or HeFH, or in individuals with a history of premature ASCVD (< 55 years of age for males or < 65 years of age for females). †In very high risk ASCVD, use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider the addition of nonstatins to statin therapy. A threshold is the point/trigger at which intensification of therapy may be considered. Additional AHA/ACC guidelines were published in 2013 but did not provide a recommendation for target LDL-C levels to reduce the ASCVD risk.[14]

1. Goodman DS, et al. *Arch Intern Med*. 1988;148:36-69. 2. Grundy SM, et al. *JAMA*. 1993;269:3015-3023. 3. NCEP. *Circulation*. 2002;106:3143-3421. 4. Jellinger PS, et al. *Endocr Pract*. 2017;23(suppl 2):1-87. 5. Grundy SM, et al. *J Am College Cardiol*. 2019;73:e285- e350. 6. Reiner Z, et al. *Eur Heart J*. 2011;32:1769-1818. 7. Catapano AL, et al. *Eur Heart J*. 2016;37:2999-3058. 8. Mach F, et al. *Eur Heart J*. 2020;41:111-188. 9. Wood D, et al. *Eur J Gen Pract*. 1999;5:154-161. 10. De Backer G, et al. *Atherosclerosis*. 2004;173:381-391. 11. Graham I, et al. *Eur Heart J*. 2007;28:2375-2414. 12. Jellinger PS, et al. *Endocr Pract*. 2012;18(suppl 1):1-78. 13. Jacobson TA, et al. *J Clin Lipidol*. 2014;8:473-488. 14. Stone NJ, et al. *J Am Coll Cardiol*. 2014;63(25 pt B):2889-2934.

2018 ACC/AHA Guidelines

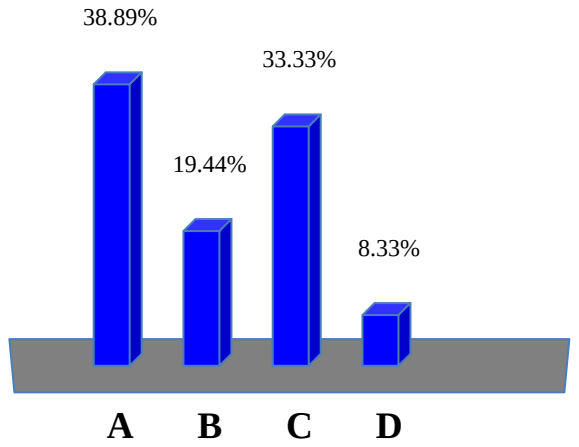


Case Presentation

- Our patient from Case #1 (38F with family history of premature CAD and He-FH) was started on atorvastatin 80 mg daily
- Within a few days, complained of back and lower limb pains and lower limb weakness
- Also complains of insomnia, and poor memory
- Laboratory (on treatment)
  - CK 63 U/L
  - ALT 45 U/L
  - TC 185mg/dL, LDL 105 mg/dL, HDL 45 mg/dL

What is the Next Best Step in Management?

A. Inform patient that symptoms are unlikely related to statin therapy and therefore should continue atorvastatin.
B. Change from atorvastatin 20 mg to rosuvastatin 40 mg daily.
C. Provide reassurance, temporarily discontinue statin therapy and plan for re-challenge in 4-6 weeks.
D. Tell the patient they are no longer a candidate for statin therapy and discuss non-statin options for secondary prevention.



Statin Intolerance

Table 1 Definitions of statin intolerance

Society	Definition of statin intolerance	Year	References
National Lipid Association (NLA)	"Inability to tolerate at least two statins: one statin at the lowest starting daily dose and another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal laboratory determinations, which are temporally related to statin treatment and reversible upon statin discontinuation"	2014	[22]
International Lipid Expert Panel (ILEP)	"Inability to tolerate at least two statins: one statin at the lowest starting daily dose and another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal laboratory determinations, which are temporally related to statin treatment and reversible upon statin discontinuation. The resolution of symptoms or changes in biomarkers or even significant improvement with dose reduction or withdrawal of treatment; symptoms or changes in biomarkers are not attributable to predispositions (drug–drug interactions and recognized conditions), increasing the risk of statin intolerance"	2014	[23]
European Atherosclerosis Society (EAS)	"The assessment of statin-associated muscle symptoms (SAMS) includes the nature of muscle symptoms, increased creatine kinase levels and their temporal association with initiation of therapy with statin, and statin therapy suspension and rechallenge"	2015	[24]
Canadian Consensus Working Group	"A clinical syndrome, not caused by drug interactions or risk factors for untreated intolerance and characterized by significant symptoms and/or biomarker abnormalities that prevent the long-term use and adherence to statins documented by challenge/dechallenge/rechallenge, where appropriate, using at least two statins, including atorvastatin and rosuvastatin, and that leads to failure of maintenance of therapeutic goals, as defined by national guidelines"	2016	[25]

Toth PP et al. Am J Cardiovasc Drugs; 2018: 18:157-173.

Reported Adverse Effects of Statins

- Muscle-related symptoms
- Elevated hepato-cellular enzymes
- Cancer
- New diabetes
- Hemorrhagic stroke
- Fatigue
- Neuro-psychiatric effects and insomnia
- Memory loss, dementia
- Proteinuria / hematuria
- Erectile dysfunction
- Alopecia

Liver Injury Associated with Statin Use

Type of liver injury	Frequency	Comment
Asymptomatic elevations in aminotransferases	0.1%-3.0%	Dose-dependent; class effect; clinically not significant
Clinically significant acute liver injury	Very rare	May be seen in combination with other medications
Fulminant hepatic failure	Extremely rare (isolated case reports)	It was estimated that risk of fulminant liver failure is 2 per million
Autoimmune hepatitis	Case reports	Statins may induce AIH in genetically susceptible individuals

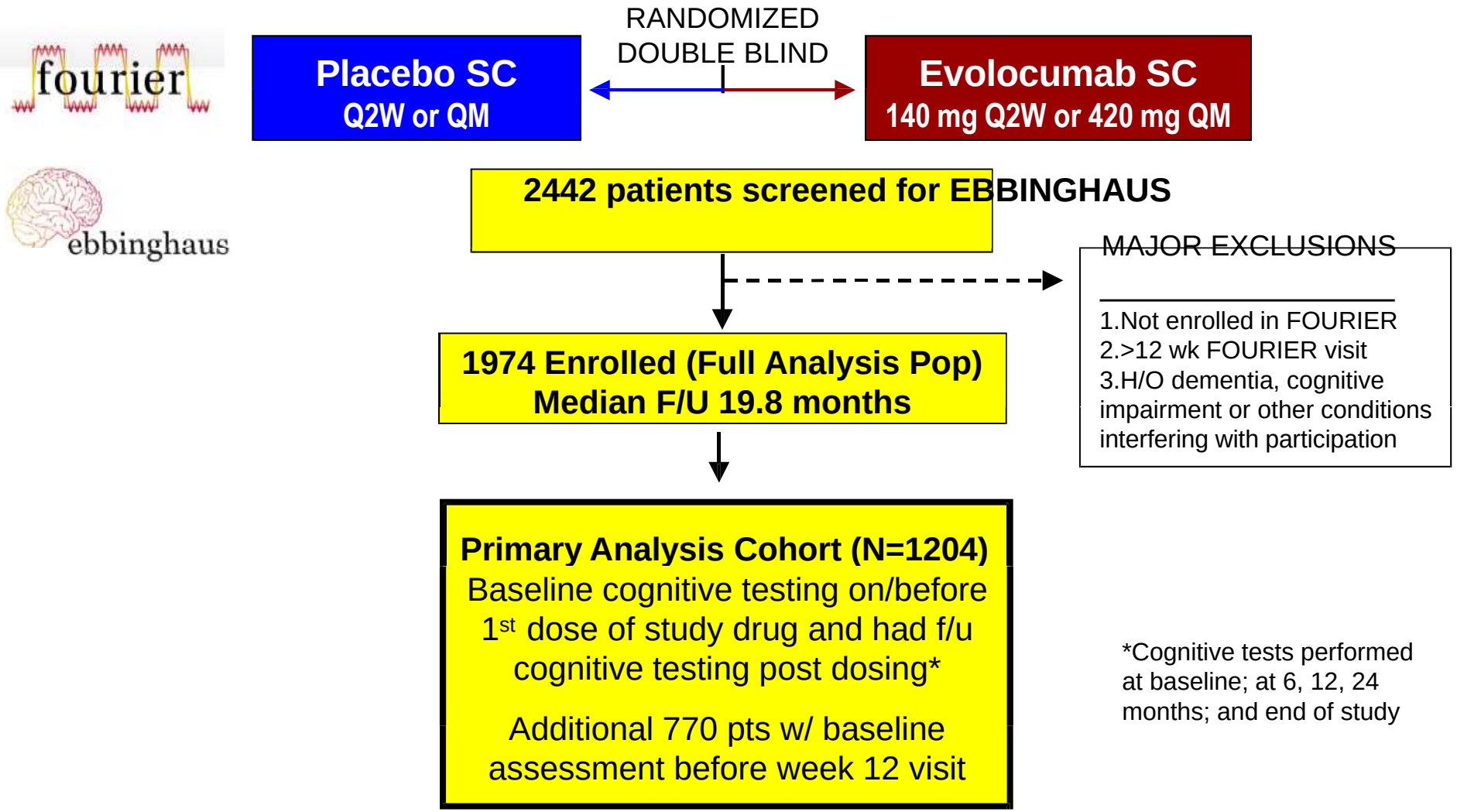
Bhardwaj SS et al. *Clin Liver Dis* 2007; 11:597-613

LDL-C Levels and Neurocognition

- Case series and 2 small, 6-month RCTs with statins raised concern regarding cognitive deficits
- In 2012 FDA added risk of adverse cognitive effects to label of all statins
- However analyses from large scale RCTs do not support these findings and 2014 Statin Cognitive Safety Task Force* concluded that statins are not associated with cognitive side effects.

*The National Lipid Association Rojas-Fernandez CH, et al. *J Clin.Lipidol.* 2014;8(3 Suppl):S5-16.

EBBINGHAUS Trial



*Cognitive tests performed at baseline; at 6, 12, 24 months; and end of study

Giugliano RP et al. *Clin Card* 2017;40:59–65

EBBINGHAUS Trial: Endpoints

1. **Cambridge Neuropsychological Test Automated Battery (CANTAB) Assessments, a standardized, well-validated computer tablet-based testing platform.**
   Assessed at baseline, 6, 12, 24, 48 mos and study end.

– **Primary: Spatial working memory strategy index of executive function**

  – Secondary: Spatial working memory between errors

    Paired associates learning Reaction time

  – Exploratory: Global score (combines above 4 tests)

2. **Patient survey of everyday cognition* at study end**
3. **Investigator report of cognitive AEs**

*Memory and executive function domains.

Giugliano RP et al. *Clin Card* 2017;40:59-65

EBBINGHAUS Trial: Results

All Patients	Placebo	Evolocumab	
	Mean (SD)	Mean (SD)	P-Value
Memory	1.16 (0.39)	1.17 (0.39)	0.81
Executive functioning total score	1.11 (0.32)	1.12 (0.32)	0.28
Planning	1.08 (0.31)	1.10 (0.32)	0.20
Organization	1.09 (0.32)	1.10 (0.33)	0.57
Divided attention	1.15 (0.42)	1.16 (0.41)	0.54
Total Score	**1.13 (0.33)**	**1.14 (0.33)**	**0.42**

Patient self-report at end of study as compared to randomization, graded as

1. *Better or no change*
2. *Questionable / occasionally worse*
3. *Consistently a little worse*
4. *Consistently much worse*

Lower scores represent better cognition

Giugliano RP et al. NEJM 2017;177.

Statins and New-Onset Diabetes

Study	Proportion of patients with new-onset diabetes (%)		RR, statin vs placebo	95% CI
	Statins	Placebo		
WOSCOPS (N=5974)	1.9%	2.8%	0.69	0.49-0.96
HPS (N=14,543)	4.6%	4.0%	1.14	0.98-1.33
ASCOT (N=7773)	3.9%	3.5%	1.14	0.90-1.43
LIPID (N=7937)	4.3%	4.6%	0.95	0.77-1.16
CORONA (N=3534)	5.6%	5.0%	1.13	0.86-1.49
JUPITER (N=17,802)	3.0%	2.4%	1.25	1.05-1.49
Combined all above (N=57,593)	3.8%	3.5%	1.06	0.93-1.22 (*P*=0.38)
Combined all above except WOSCOPS (N=51,619)	4.0%	3.5%	1.13	1.03-1.23 (*P*=0.008)

Absolute risk of developing DM 0.3-0.5%
Note
- Patient reported diabetes
- No formal testing for diabetes

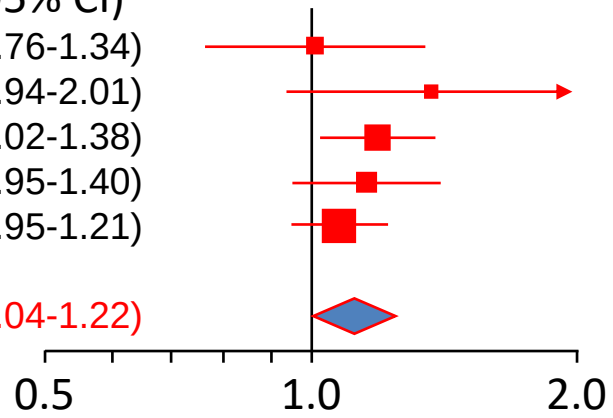
Risk factors for Statin associated DM
- Obesity
- IFG
- Elevated TG / HDL

Sattar N et al. *Lancet* 2010; 375:735-42

Statins and New-Onset Diabetes In Context of Reduction of CV Events:

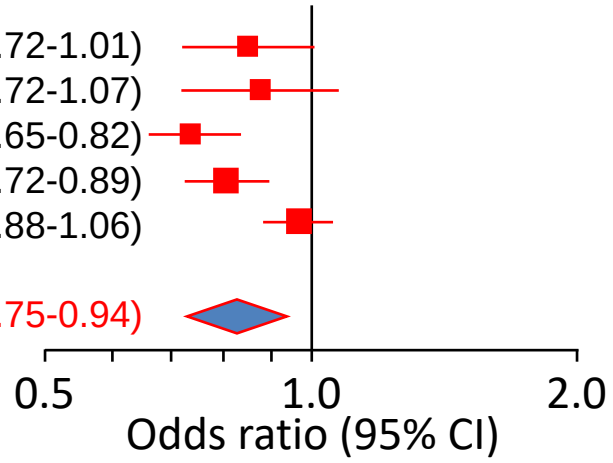
Incident Diabetes

	Intensive dose	Moderate dose	OR (95% CI)
PROVE-IT - TIMI 22, 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z, 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT, 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL, 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH, 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	1449/16,408 (8.8)	1300/16,344 (8.0)	1.12 (1.04-1.22)



Incident CVD

PROVE-IT - TIMI 22, 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z, 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)
TNT, 2005	647/3798 (17.0)	830/3797 (21.9)	0.73 (0.65-0.82)
IDEAL, 2005	776/3737 (20.8)	917/3724 (24.6)	0.80 (0.72-0.89)
SEARCH, 2010	1184/5398 (21.9)	1214/5399 (22.5)	0.97 (0.88-1.06)
Pooled odds ratio	3134/16,408 (19.1)	3550/16,344 (21.7)	0.84 (0.75-0.94)



NNT/yr **155 for CV events**

NNH/yr **498 for new-onset diabetes**

Preiss D et al. *JAMA* 2011; 305:2556-64

Muscle Related Adverse Effects of Statins

- Major symptom limiting the use of statins (up to 30% of patients), compromises quality of life and reduces adherence.
- Myalgia
  - Muscle aches or weakness in absence of CK rise
- Myositis
  - Elevated CK in presence of muscle symptoms
  - No absolute CK cut-off to define elevated
- Rhabdomyolysis
  - Pronounced CK elevation (> 10x ULN) with muscle symptoms
  - May be associated with urine myoglobin and renal dysfunction

Mancini GB et al. *CJC* 2011; 27:635-662
Cohen JD et al. *J Clin Lipid* 2012; 6 (3):208-15

Evaluation/Risk Factors for SAMS

Table 1. Risk factors associated with statin-associated muscle symptoms

Female gender[53]
Advanced age (>75 years). Statins are generally well tolerated in the elderly. In RCTs there were no differences in muscle symptoms among patients treated with statin or placebo and also in study drug discontinuation; however, there are different factors and conditions that can increase adverse events in the elderly (decrease in lean body mass, reduction in albumin levels, decreased glomerular filtration rate, etc[54].
Abdominal obesity and metabolic syndrome[55, 56]
Frailty
Vitamin D deficiency: Low vitamin D levels are associated with myalgia in patients receiving statin therapy; however, there is no evidence of benefit from Vitamin D supplementation, even in patients with insufficient levels to prevent SAMS[27, 57].
Alcohol consumption: There is risk over 30 g/d in men and 20 g/d in women[55]
Excessive physical activity[35]
Not controlled hypothyroidism[58]
Chronic Kidney Disease: Although a meta-analysis showed little or no risks of myalgia (RR0.99, CI 0.94-1.04) and elevated CK levels (RR 1.11, CI 0.80-1.04), precaution is necessary when statins are used in this condition[59].
Liver disease
Metabolic muscle disorders
Family history of statin intolerance and personal history of intolerance to other statins and lipid-lowering therapies
Drugs affecting statin metabolism increasing their plasma levels[60] (inhibitors of CYP3A4: Macrolides, Fluoxetine, Verapamil, Protease inhibitors, grape fruit, etc.), lovastatin; inhibitors CYP2C9: ketoconazole, Fluconazole, Fluoxetine, Amiodarone, etc.; inhibitors of organic anion transporting peptide 1B1: gemfibrozil)

Alonso R et al. J Atheroscler Thromb, 2019; 26: 207-215.

Clinical Index for SAMS

Table 3. Statin-Associated Muscle Symptom Clinical Index[36,170]

Clinical Symptoms	Score
Regional distribution/pattern	
Symmetrical hip flexors/thigh aches	3
Symmetrical calf aches	2
Symmetrical upper proximal aches	2
Nonspecific asymmetrical, intermittent	1
Temporal pattern	
Symptom onset <4 wk	3
Symptom onset 4–12 wk	2
Symptom onset >12 wk	1
Dechallenge	
Improves upon withdrawal <2 wk	2
Improves upon withdrawal 2–4 wk	1
Does not improve upon withdrawal >4 wk	0
Challenge	
Same symptoms reoccur upon rechallenge <4 wk	3
Same symptoms reoccur upon rechallenge 4–12 wk	1
Statin myalgia clinical index score	
Probable	9–11
Possible	7–8
Unlikely	<7

Ward NC et al. Circ Research; 2019;124:328-350.

Management of Statin Associated Muscle Symptoms

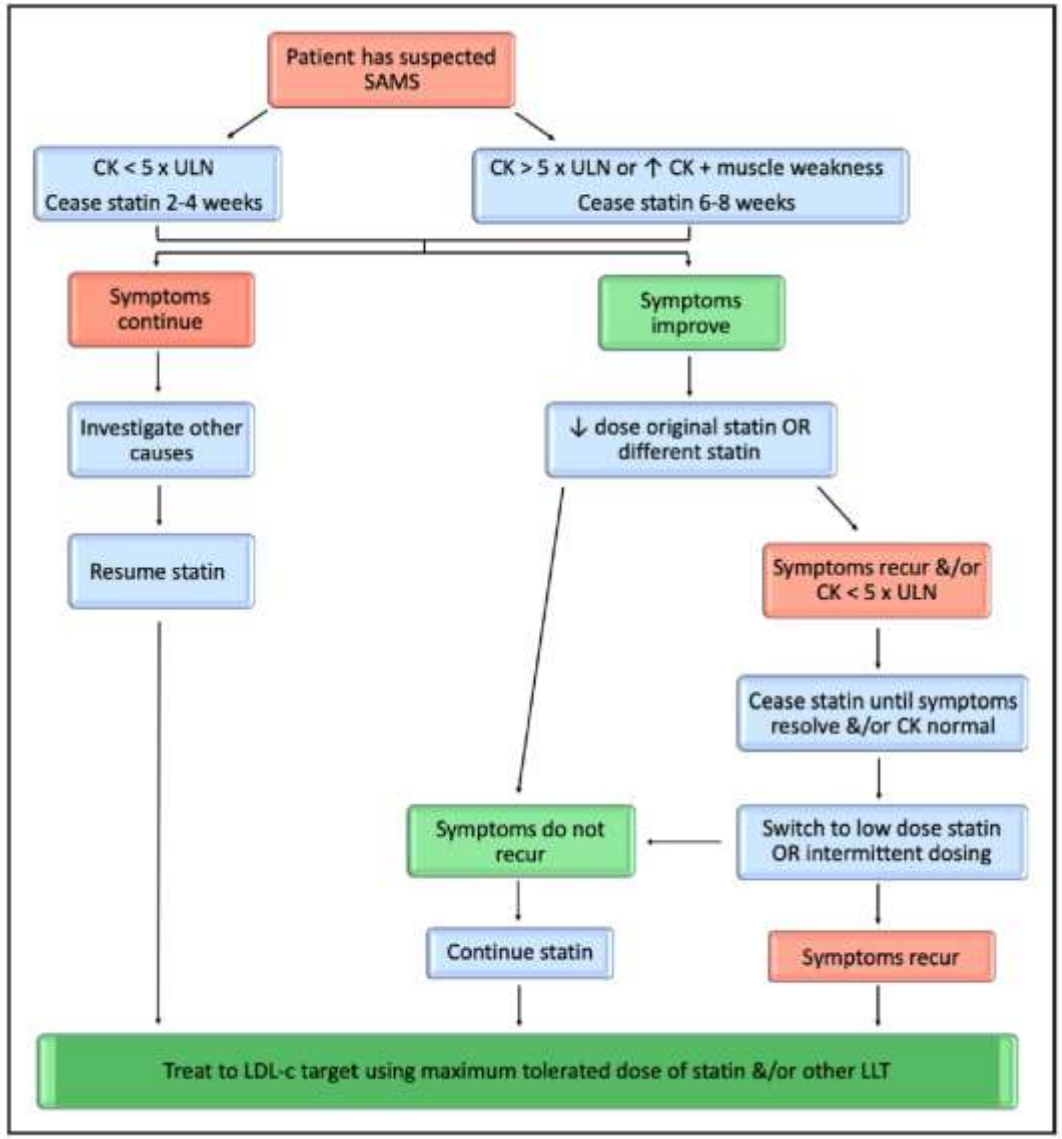


Figure 3. Statin-associated muscle symptoms (SAMS) management algorithm. CK indicates creatinine kinase; LDL-c, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; and ULN, upper limit of normal. Figure derived from www.nps.org.au and 2012 Therapeutic Guidelines: Cardiovascular and 2016 European Society of Cardiology/European Atherosclerosis Society Guidelines for the management of dyslipidemias.[23,29,36]

Ward NC et al. Circ Research; 2019;124:328-350.

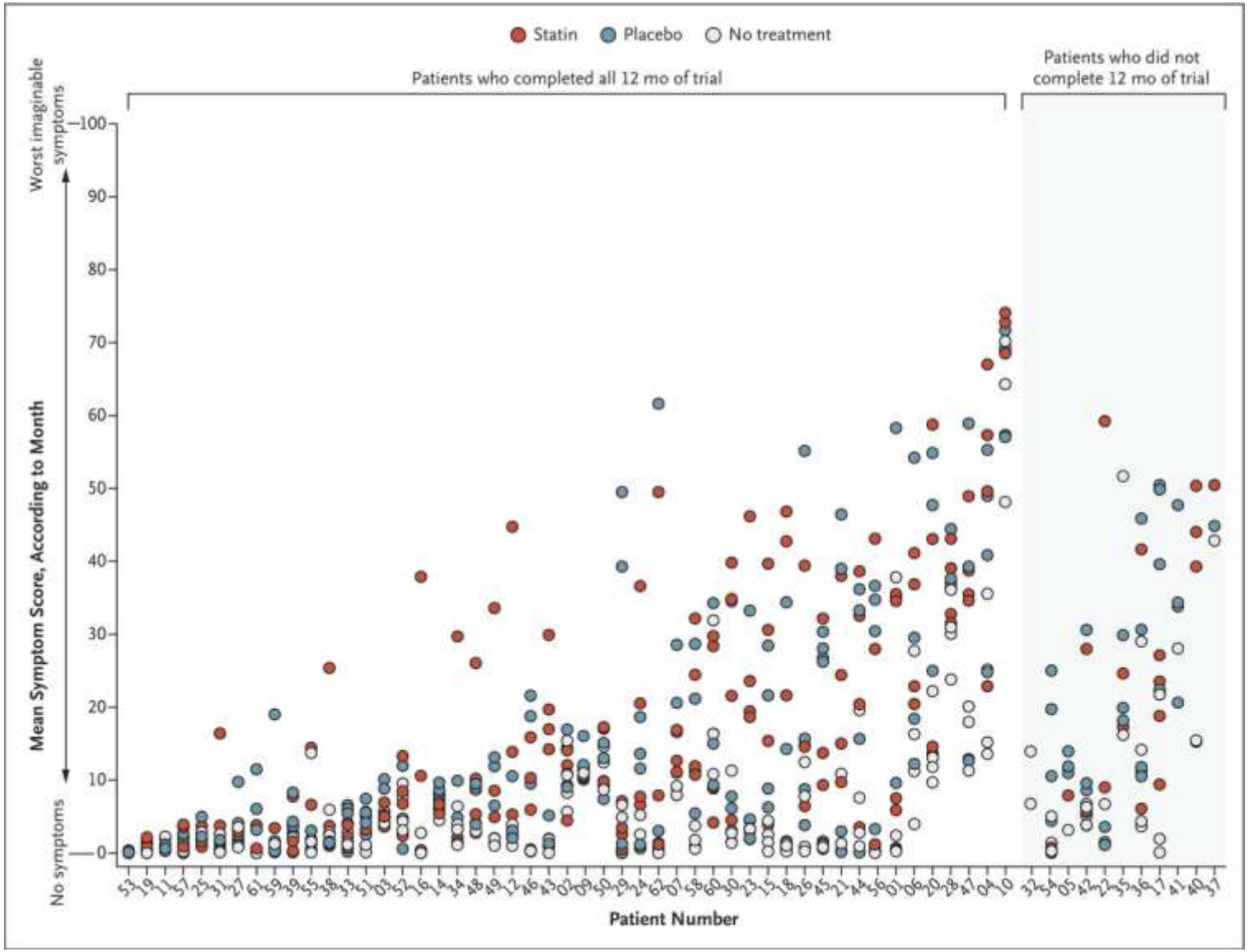
Options for LDL-Cholesterol Lowering in Statin "Intolerant" Patient

- Lower statin dose
- Switch to alternative statin
- Altered dosing regimens
  - Rosuvastatin 2.5-10 mg 3 x weekly or alternate days
  - Rosuvastatin 5-20 mg once weekly
- Low dose / alternative statin /alternating day rosuvastatin

  +

  - Ezetimibe
  - PCSK9i
  - Bempedoic Acid

Statin Intolerance: N-of-1 Trials



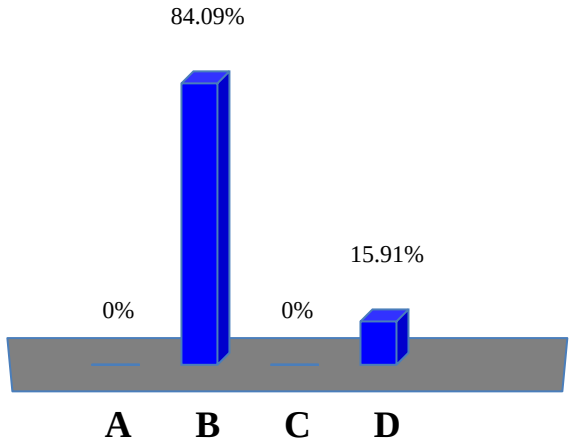
FA Wood et al. N Engl J Med 2020;383:2182-2184.

Case Presentation

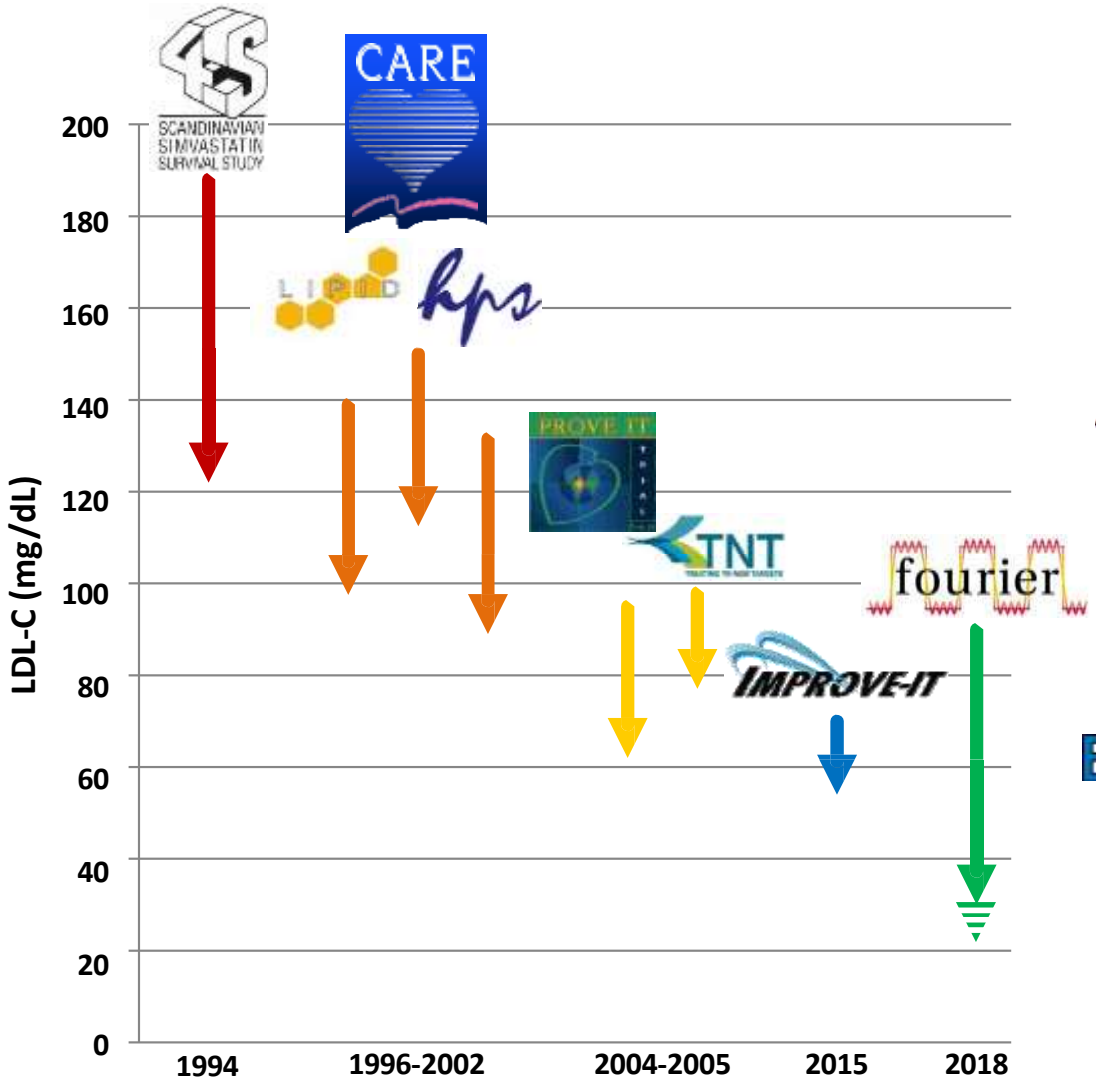
- 68M with history of inferior wall STEMI 2 years ago (DES x 2 to RCA), NSTEMI 1 year (DES to LAD and diagonal), PAD (PCI 3 months ago for symptomatic claudication), HTN, and hyperlipidemia presents for outpatient follow-up.
- Denies chest pain, exertional dyspnea, PND/orthopnea, claudication.
- Exam:
  - BP 132/78; HR 62 (sinus); 98% RA; RR 14; BMI 33.4 kg/m^2
  - JVP 8cm, lungs clear, 2/6 early peaking systolic ejection murmur, no edema
- Labs:
  - Total cholesterol: 190 mg/dL
  - LDL-C: 110 mg/dL
  - HDL: 50 mg/dL
  - TG: 150 mg/dL
  - HbA1c: 6.2%
- Medications: aspirin 81, ticagrelor 90 mg PO BID, atorvastatin 80 mg, lisinopril 40 mg, metoprolol succinate 100 mg daily.

What Would Be Your Approach for Secondary Prevention of Adverse CV Events, Particularly with Regard to Lipids?

A. Switch from atorvastatin to rosuvastatin
B. Add ezetimibe 10 mg daily and consider adding PCSK9 inhibitor
C. Add icosapent ethyl
D. No change required



Evolving Paradigm of LDL-C Management



High is bad

Average is not good

Lower is better

Even lower is even better

Lowest is best

2018 ACC/AHA Guidelines