Best of ACC.22: Optimizing LDL-C for Primary and Secondary Prevention of Cardiovascular Disease

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DISCLOSURES

- Consulting
  - Genentech

- Medical Advisory Board
  - Clocktree
  - Measure Labs

- Research Funding
  - Amgen (Principal Investigator for FOURIER and FOURIER-OLE studies)
  - Microsoft Research

ACKNOWLEDGEMENTS

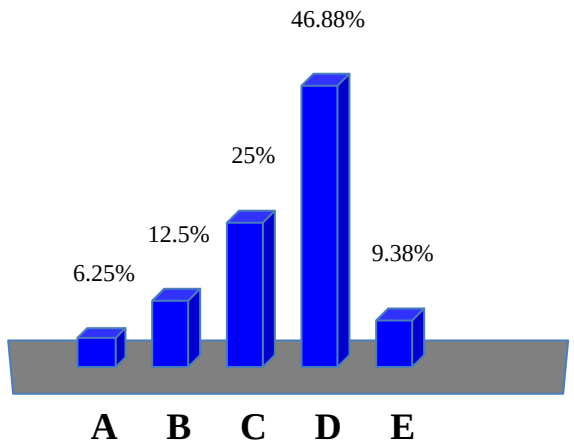
- Special thanks to Dr. Nihar Desai from Yale University School of Medicine for providing slides used for this presentation

Case #1

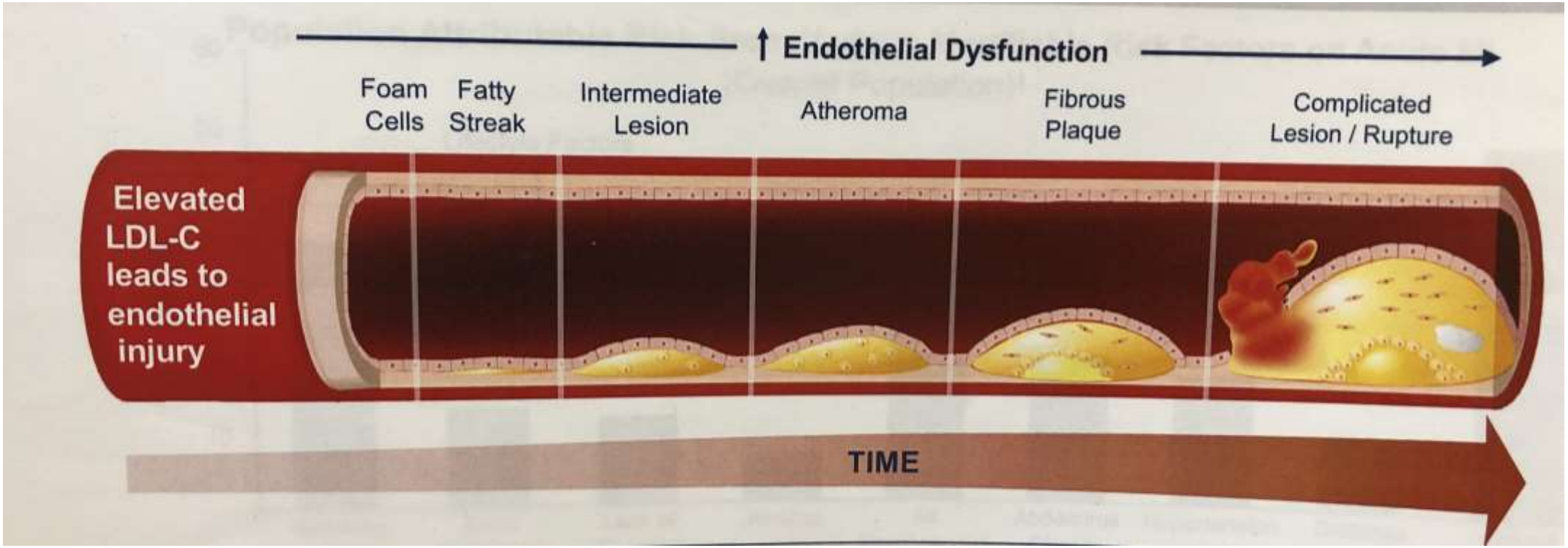
- 58 African American female with a history of rheumatoid arthritis who presents for outpatient evaluation and concern for “high cholesterol.” She has 2 children (age 28 and 24), denies smoking, diabetes. Her family history is significant for CAD in her father who had an MI at age 62.
- Exam:
  - BP 138/86; HR 72 (sinus); 99% RA; RR 14; BMI 28.2 kg/m^2
  - Unremarkable cardiovascular exam
- Labs:
  - Total cholesterol: 220 mg/dL
  - LDL-C: 150 mg/dL
  - HDL: 34 mg/dL
  - TG: 205 mg/dL
  - HbA1c: 5.2%
  - TSH: normal

What is the Next Best Step for Primary ASCVD Prevention for This Patient?

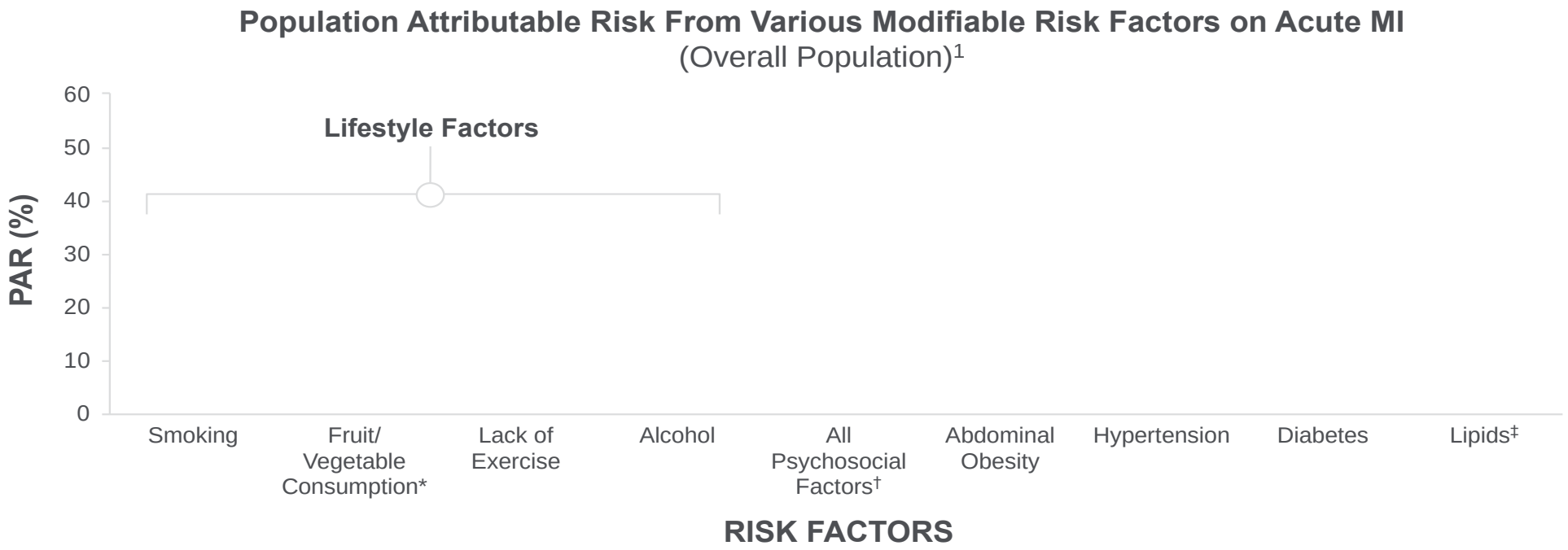
A. Perform an exercise stress test
B. Check a Lp(a) level and CAC score
C. Try lifestyle changes and reassess labs in 3-6 months
D. Initiate atorvastatin 20 mg
E. Initiate atorvastatin 20mg and clopidogrel 75mg daily



The Central Role of Lipids in Atherosclerosis



The Central Role of Lipids in Atherosclerosis



PAR=population attributable risk, which indicates the number or proportion of cases that would not occur in a population if the risk factor were eliminated.[2]

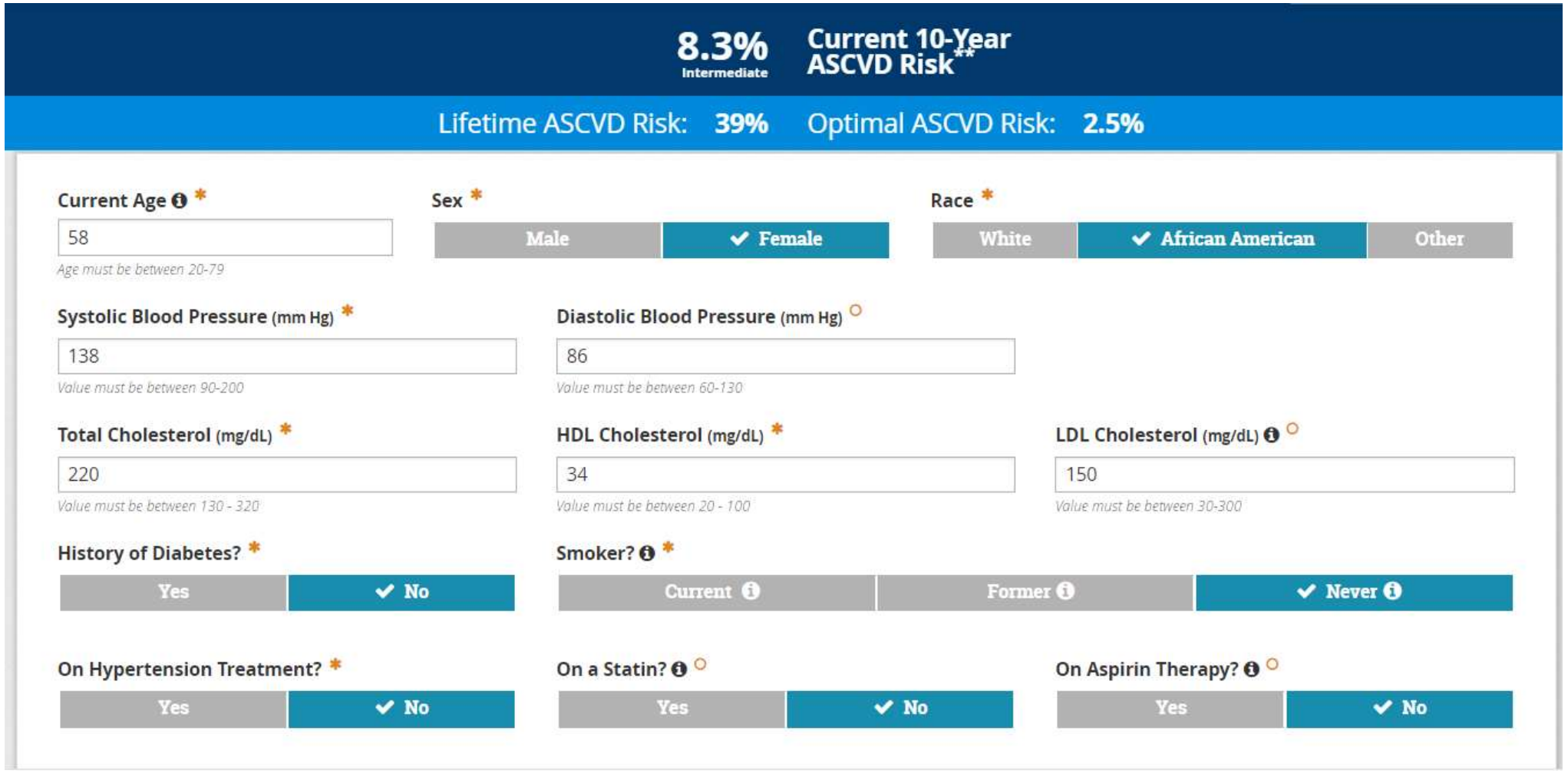
PARs from individual risk factors are reported. Note that the sum of individual PARs is greater than 100% because "cases" can simultaneously be attributed to more than one risk factor and be counted twice. PAR percentages reflected here do not indicate the amount of risk that would decrease by addressing the identified risk factors.[1]

*Irregular consumption of fruits and vegetables; †A model-dependent index combining positive exposure to depression, perceived stress at home or work (general stress), low focus of control, and major life events, all referenced against non-exposure for all 5 factors. ‡ApoB/ApoA1 ratio; INTERHEART study; n=15,152 patients and 14,820 controls in 52 countries.[1]

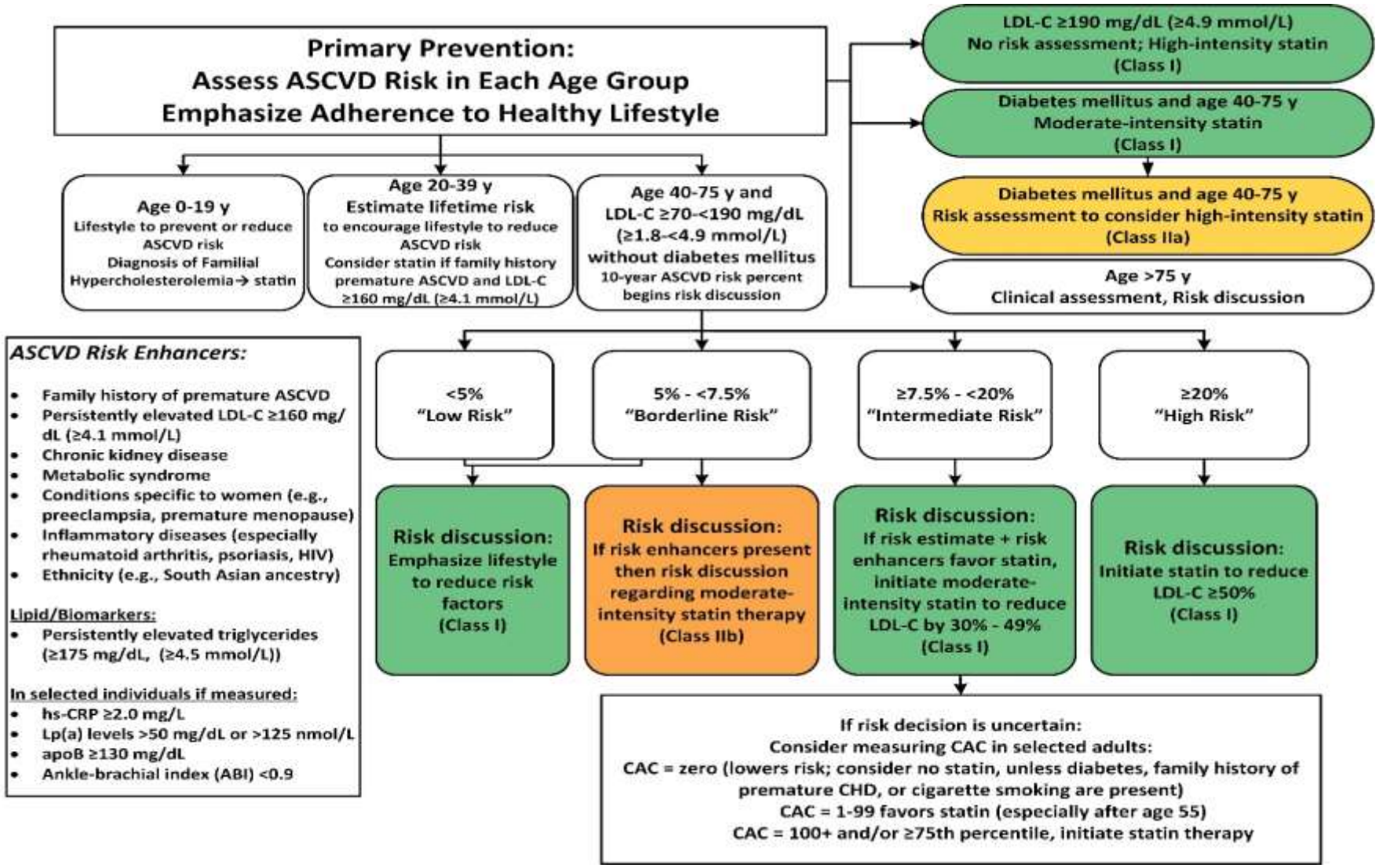
Apo=apolipoprotein; MI=myocardial infarction.

1. Yusuf S, et al. *Lancet*. 2004;364:937-952.. 2. Rockhill B, et al. *Am J Public Health*. 1998;38:15-19.

ASCVD Risk Estimator



2019 ACC/AHA Guideline on 1° Prevention of CV Disease



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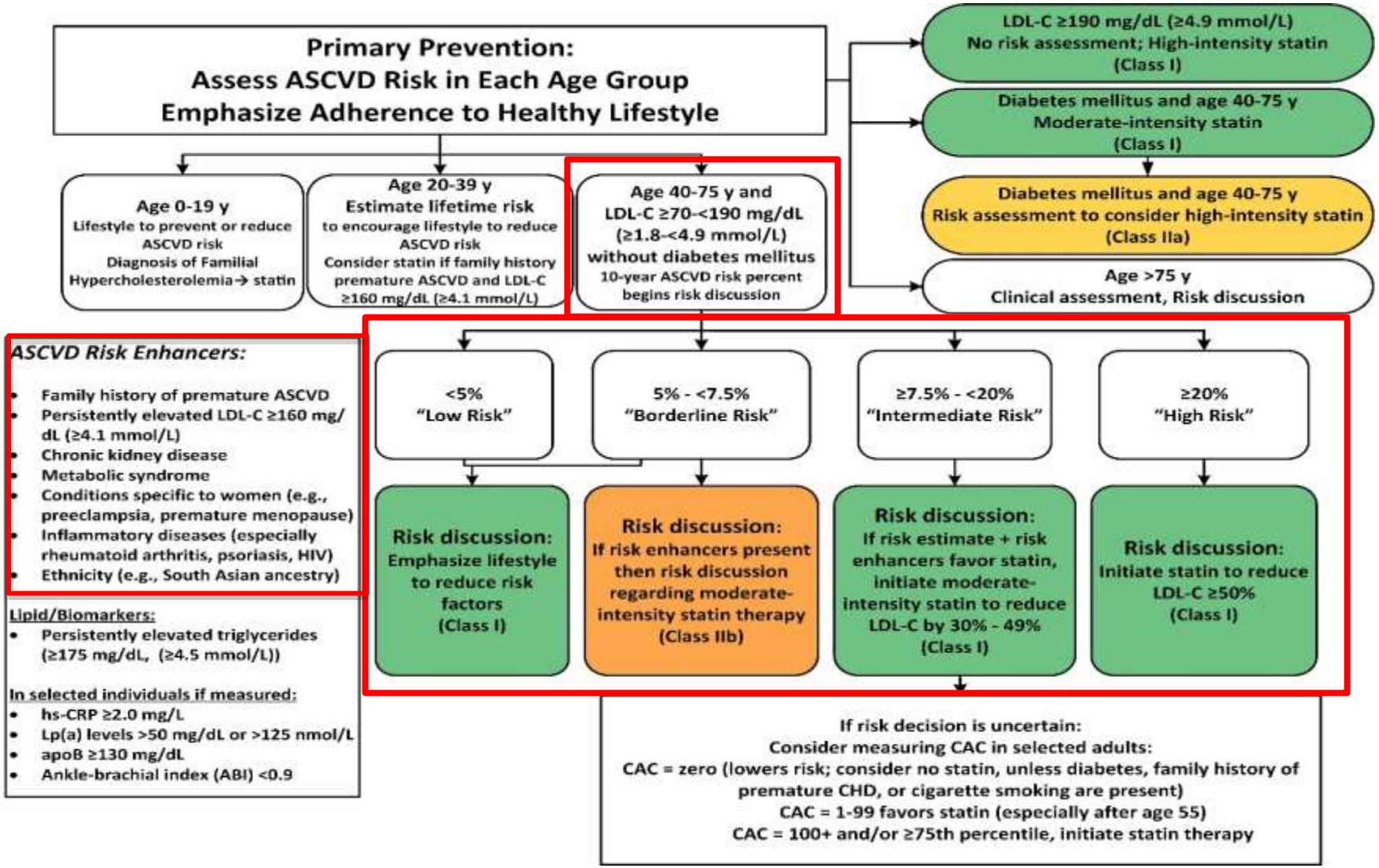
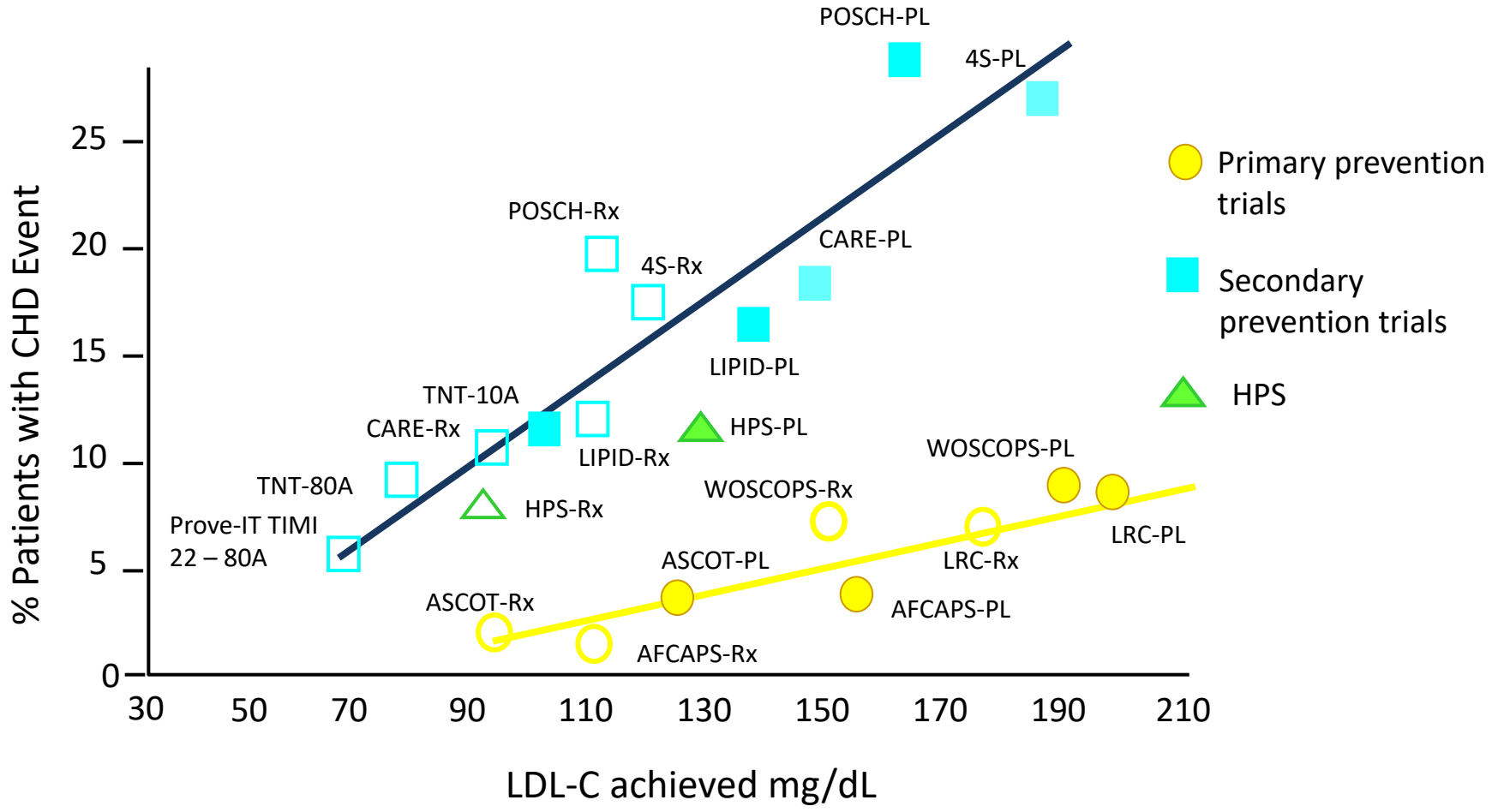


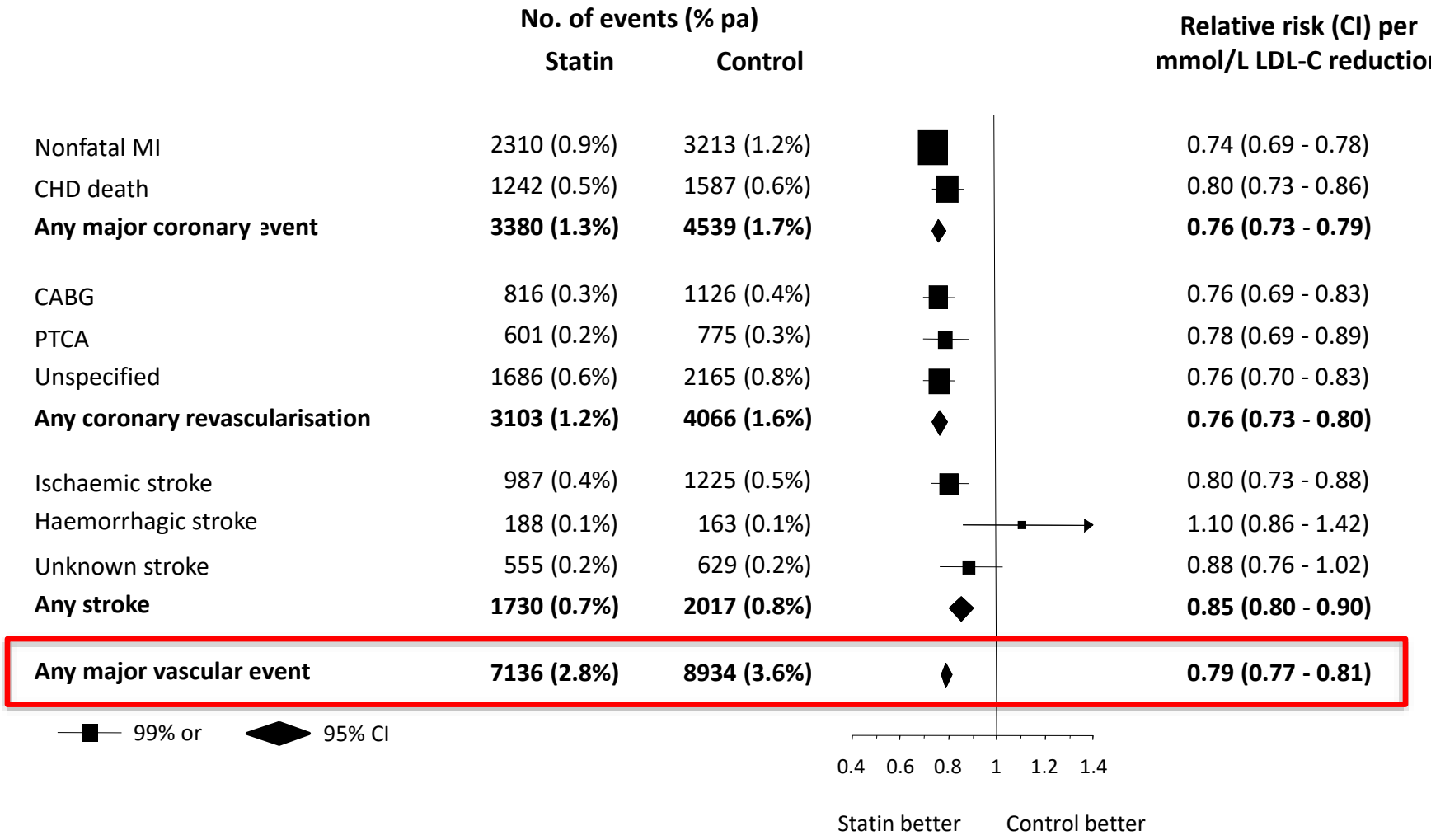
Reducing LDL-C Reduces CV Events



PL = placebo
Rx = active treatment

Ballantyne CM. *Am J Cardiol*. 1998;82:737-743.
O'Keefe JH, et al, *J Am Coll Cardiol*. 2004;43:2142-2146.

Reducing LDL-C Reduces CV Events
Statin v. Control



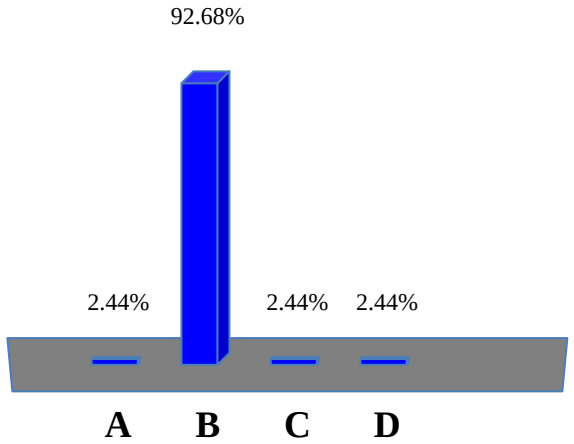
CTT Meta-analysis. Lancet 2016

Case #2

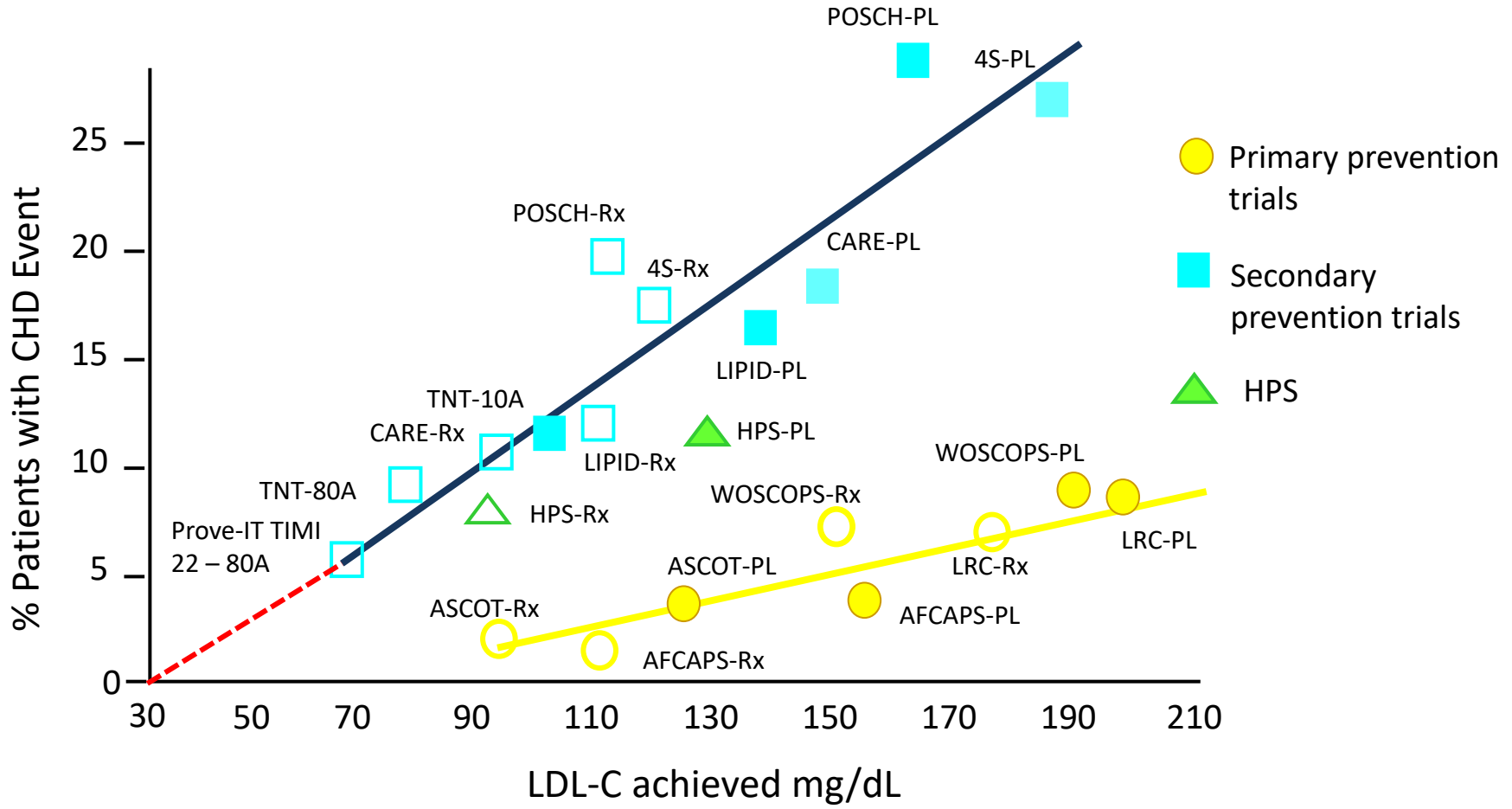
- 68M with history of inferior wall STEMI 2 years ago (DES x 2 to RCA), NSTEMI 1 year (DES to LAD and diagonal), PAD (PCI 3 months ago for symptomatic claudication), HTN, and hyperlipidemia presents for outpatient follow-up.
- Denies chest pain, exertional dyspnea, PND/orthopnea, claudication.
- Exam:
  - 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 90mg PO BID, atorvastatin 80mg, lisinopril 40mg, metoprolol succinate 100mg 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 10mg daily and consider adding PCSK9 inhibitor
C. Add icosapent ethyl
D. No change required



The Big Questions…



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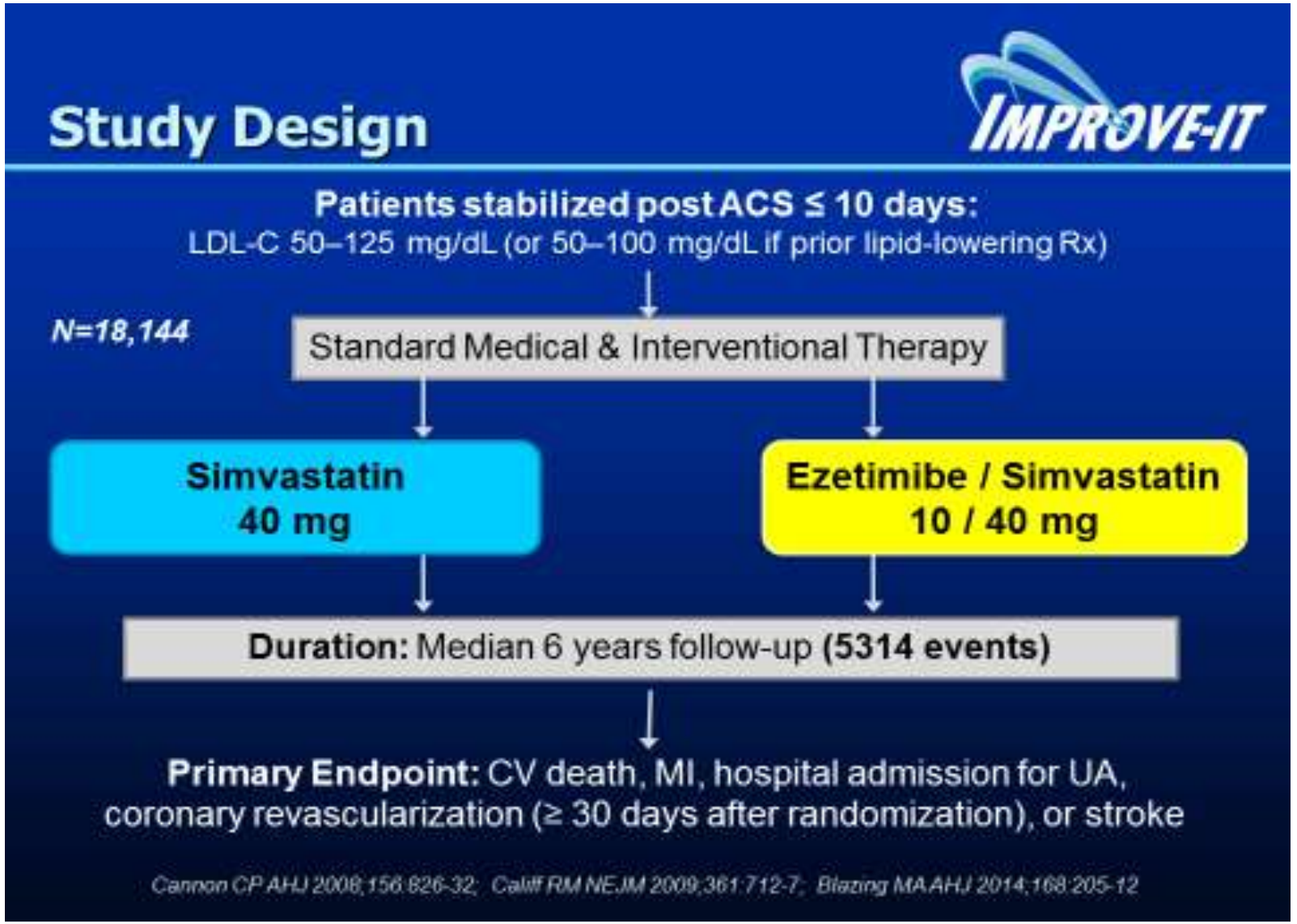
Some Answers…
IMPROVE-IT Trial



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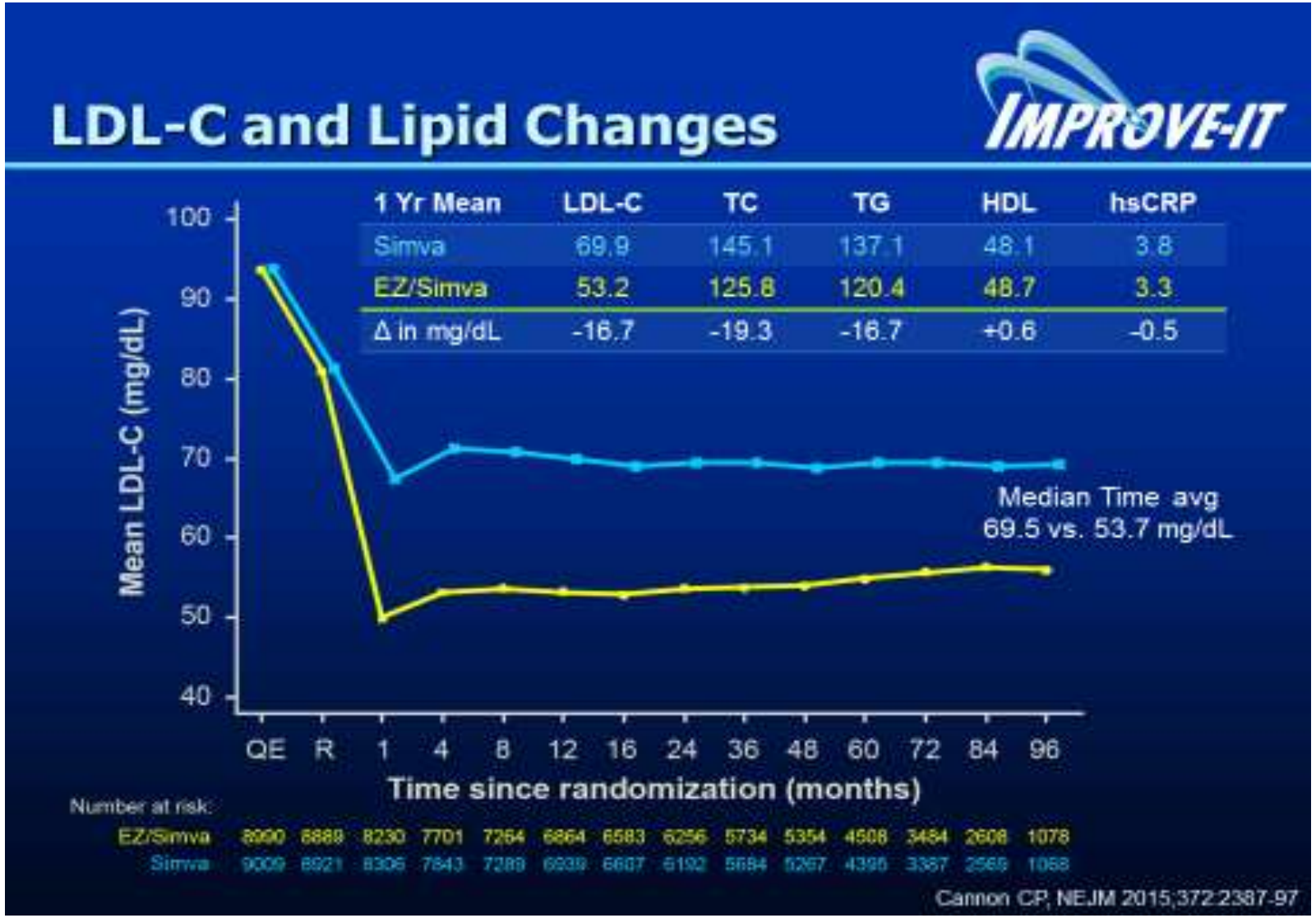

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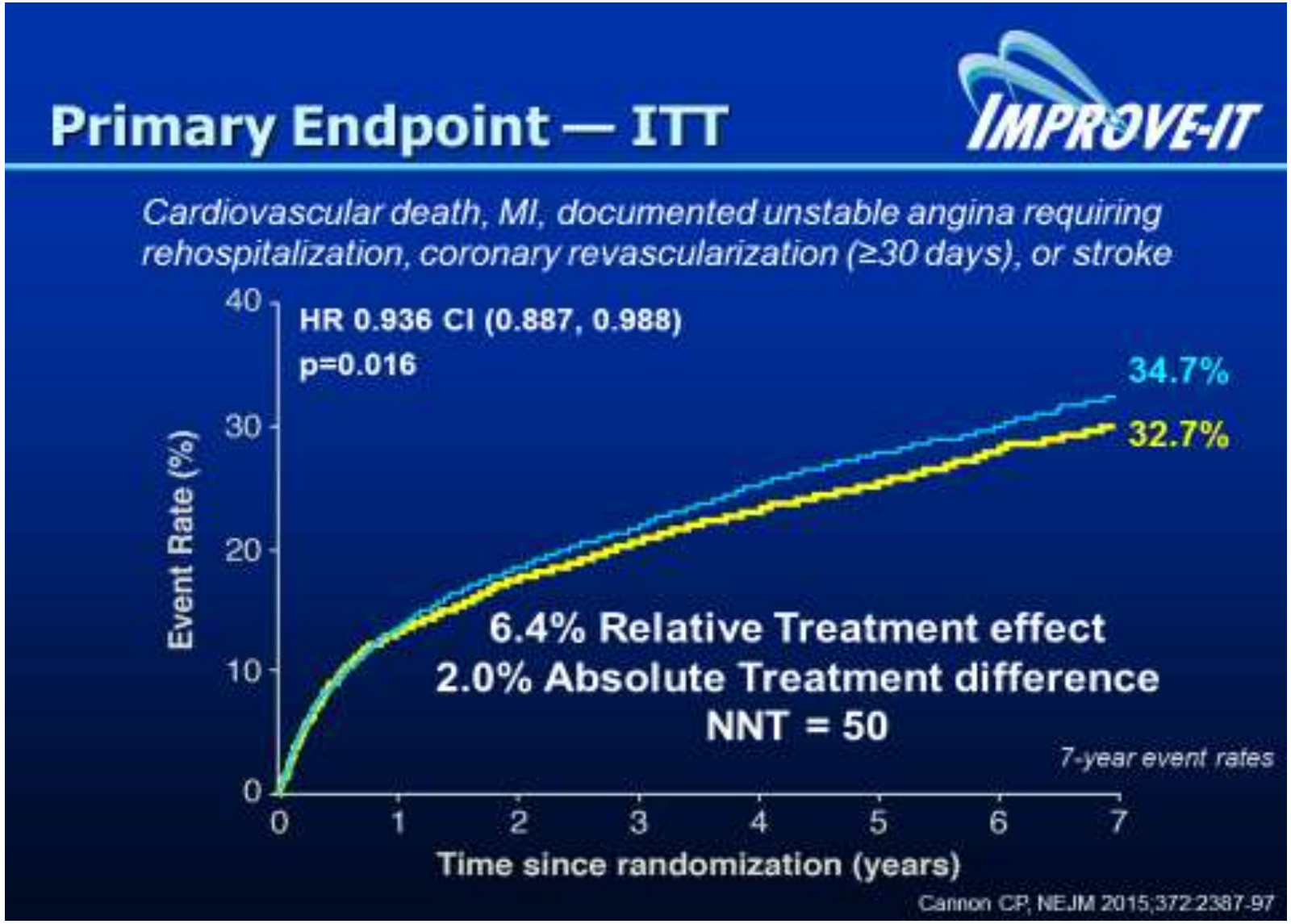
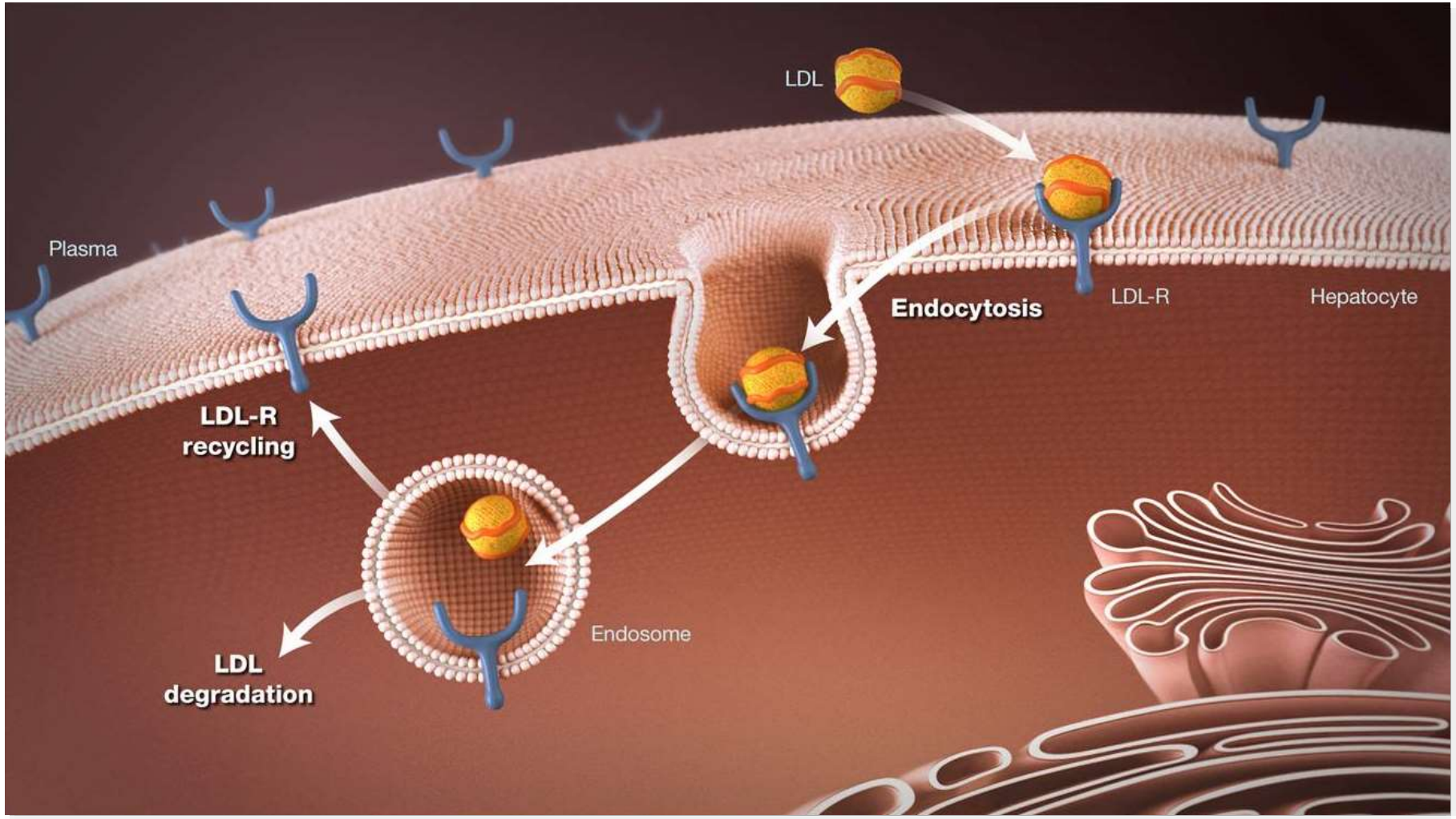


LDL-Cholesterol Biology



1. Brown MS, Goldstein JL. *Proc Natl Acad Sci* U S A. 1979;76:3330-3337.
2. Steinberg D, Witztum JL. *Proc Natl Acad Sci* U S A. 2009;106:9546-9547.
3. Goldstein JL, Brown MS. *Arterioscler Thromb Vasc Biol*. 2009;29:431-438.

The First Observation

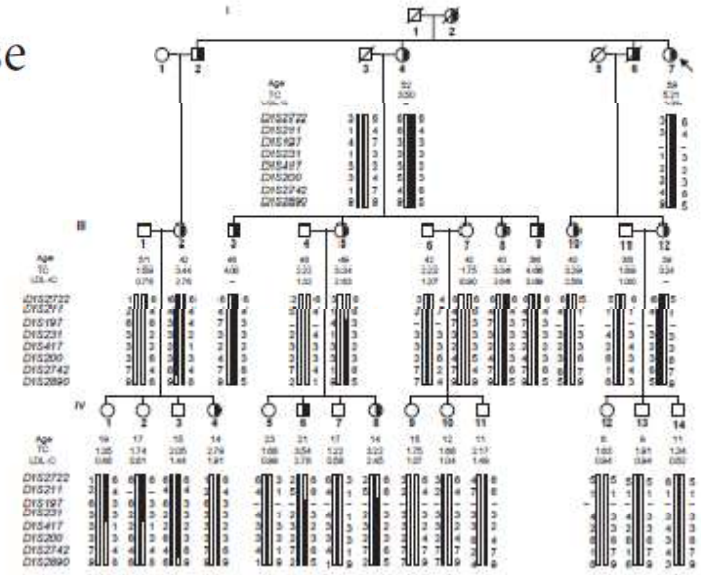
nature

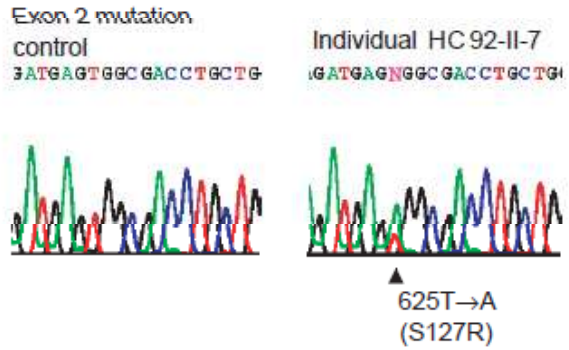
Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Affected family members with:

- **Total chol in 90th percentile**
- **Tendon xanthomas**
- **CHD, Early MI**
- **Stroke**

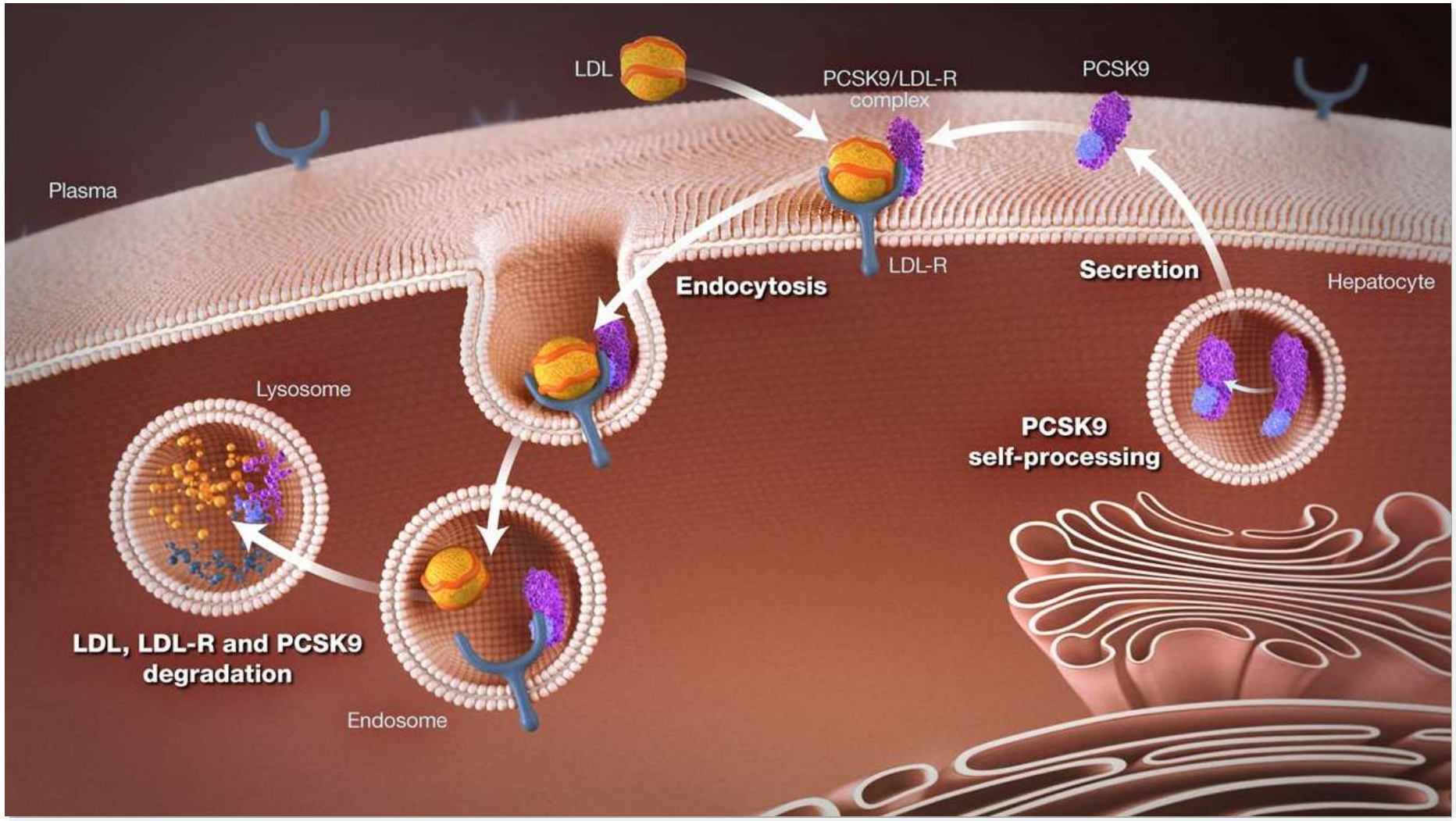
Family HC92 Pedigree





Abifadel M, et al. *Nature Genet*. 2003;34:154-156.

PCSK9 and LDL-R Recycling

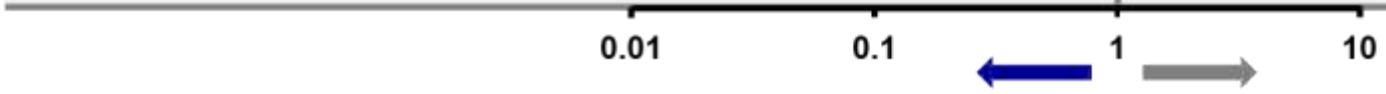


1. Qian YW, Schmidt RJ, Zhang Y, et al. *J Lipid Res*. 2007;48:1488-1498.
2. Horton JD, Cohen JC, Hobbs HH. *J Lipid Res*. 2009;50(suppl):S172-S177
3. Rashid S et al. *PNAS* 2005;102:5374-5379

Impact of PCSK9 Loss of Function Mutation on Risk of MI

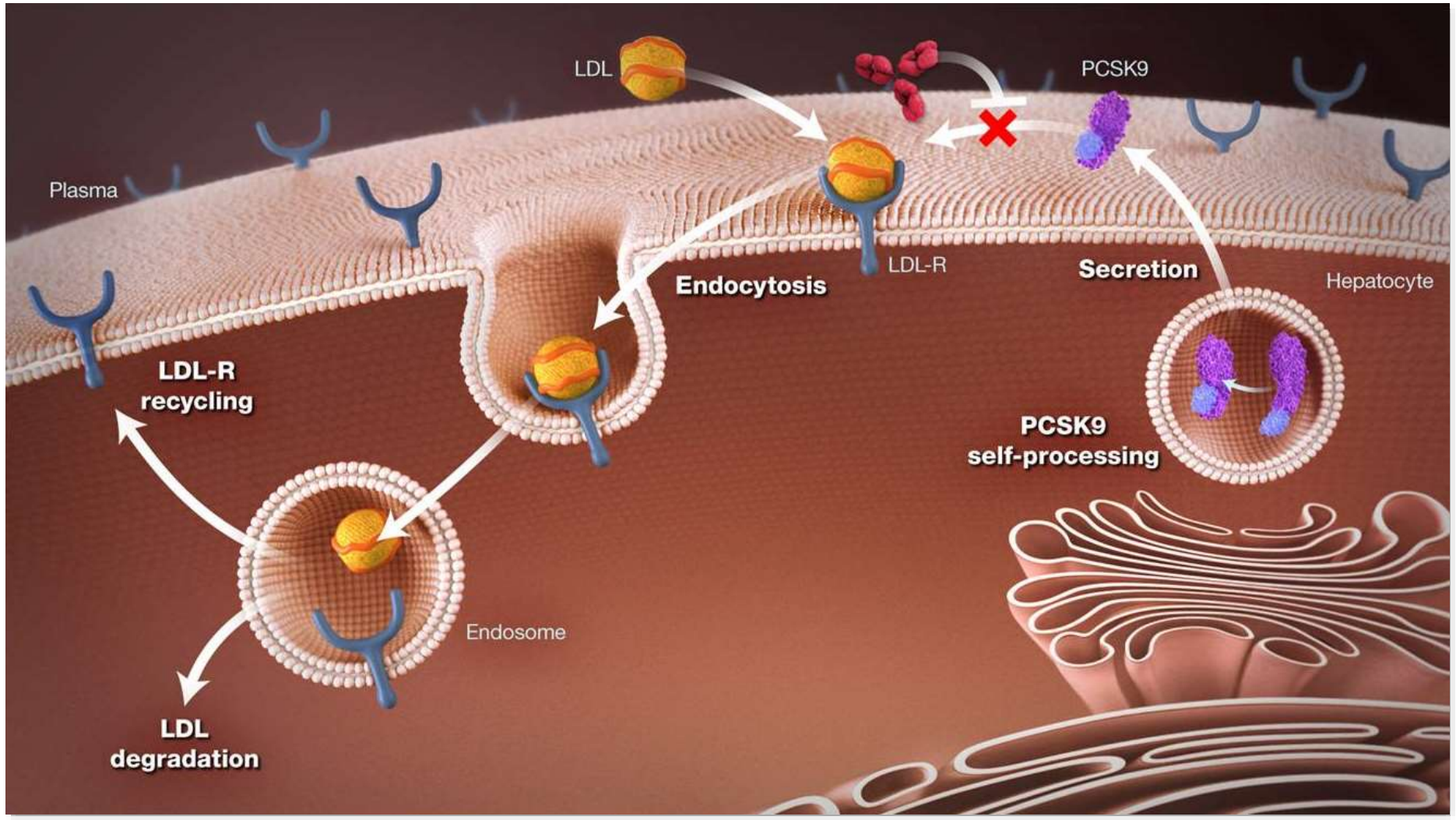
Lifelong Impact of 16% Lower LDL translates into 60% Lower Risk

Site	Study	OR for MI	95% CI	p-value
Finland	FINRISK	0.30	(0.11, 0.84)	0.02
Sweden	Malmo Diet and Cancer Study CV cohorts	0.32	(0.07, 1.61)	0.17
Spain	Registre Gironi del Cor (REGICOR)	0.35	(0.15, 0.82)	0.02
Seattle	Heart Attack Risk in Puget Sound	0.45	(0.21, 0.98)	0.049
Boston	MGH Premature CAD Study	0.59	(0.21, 1.69)	0.46
Combined analysis		0.40	(0.26, 0.61)	0.0002



N Engl J Med. 2008;358:2299-2300

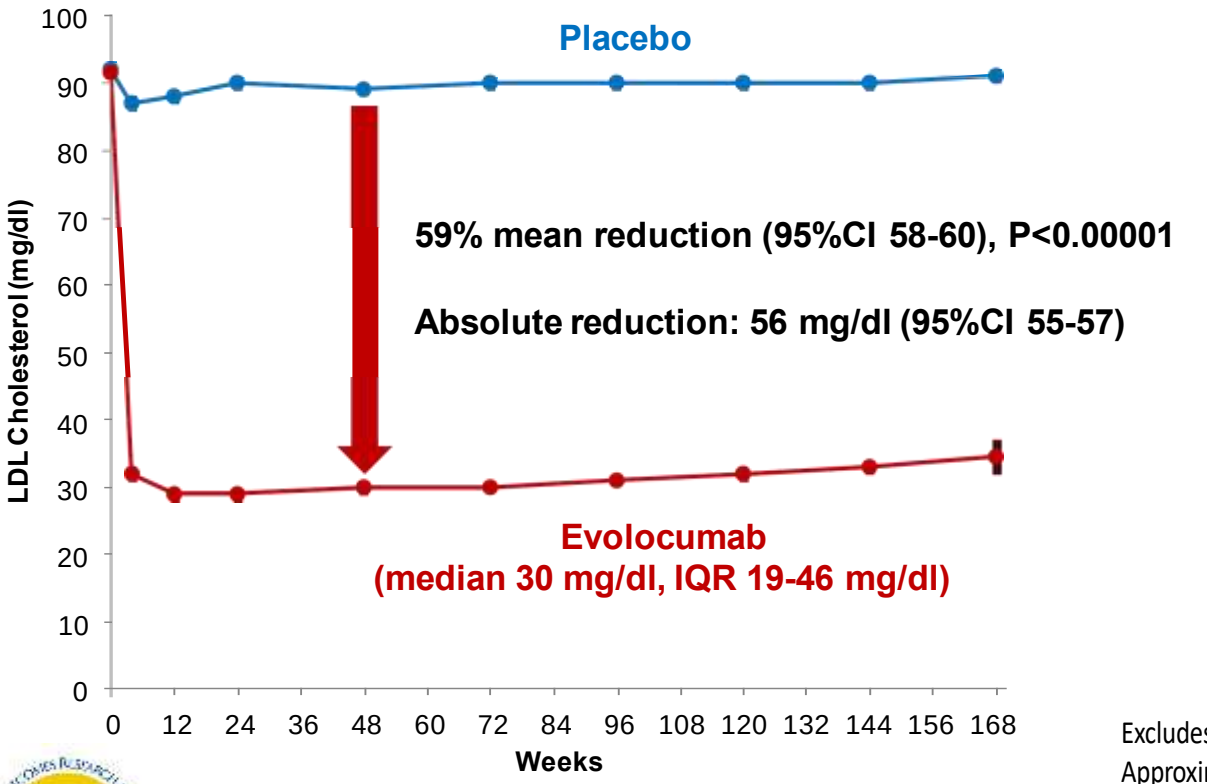
Monoclonal Antibody Against PCSK9 Blocks The PCSK9/LDL-R Interaction



1. Chan JC, Piper DE, Cao Q, et al. *Proc Natl Acad Sci U S A.* 2009;106:9820-9825.

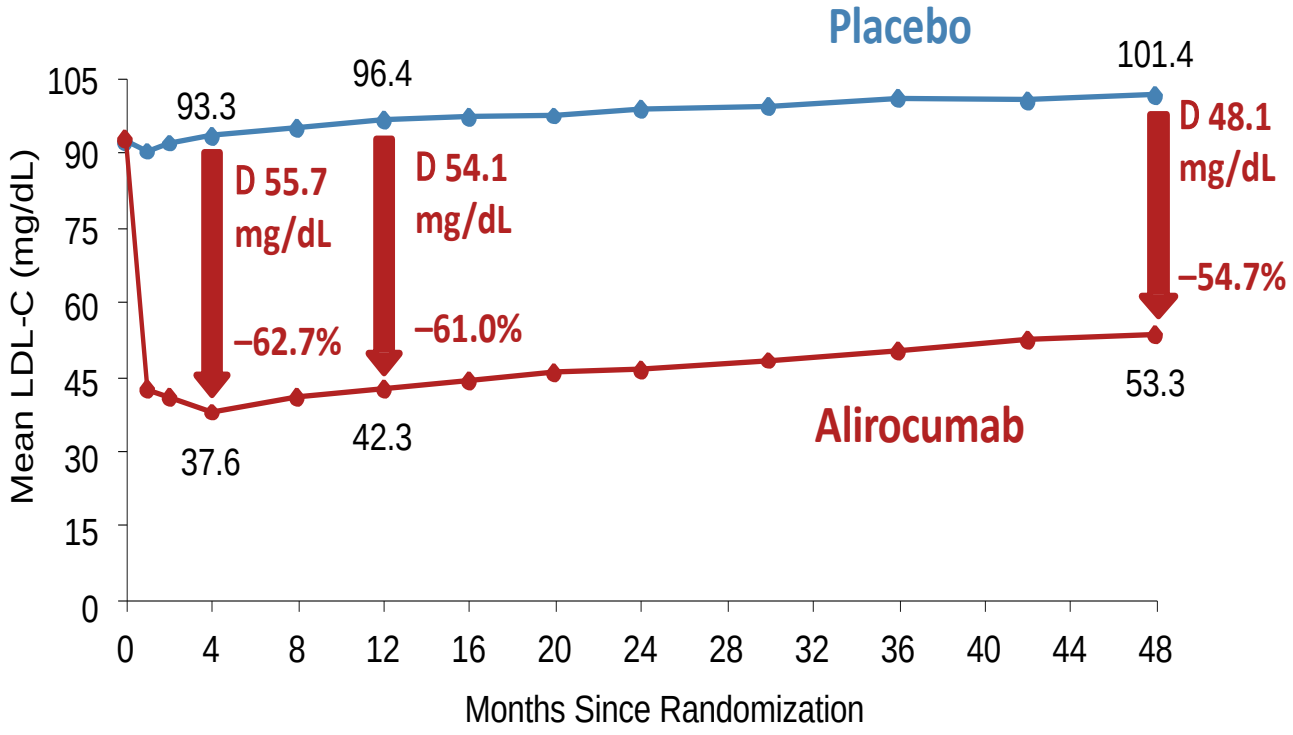
LDL-C Effects Of PCSK9 Inhibitors

FOURIER Trial



Schwartz, GC et al. NEJM 2018.

ODYSSEY Outcomes Trial

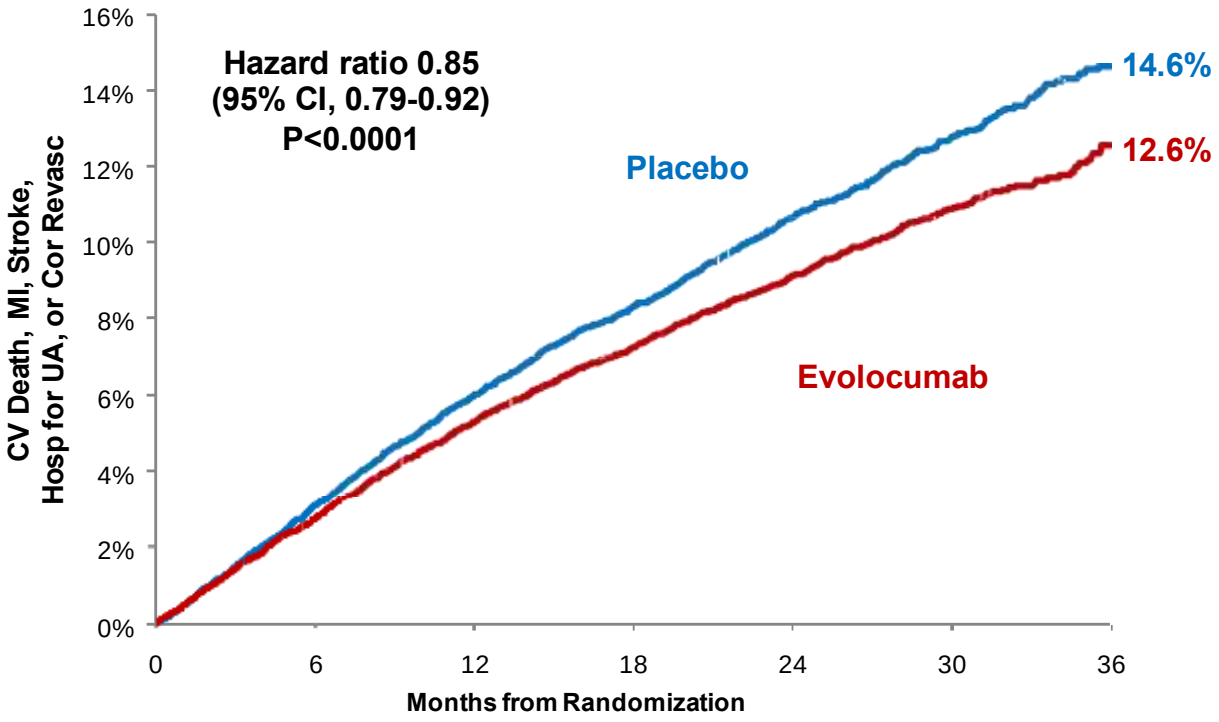


Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose

Sabatine MS et al. *NEJM* 2017;177.

Clinical Event Reductions with PCSK9 Inhibitors

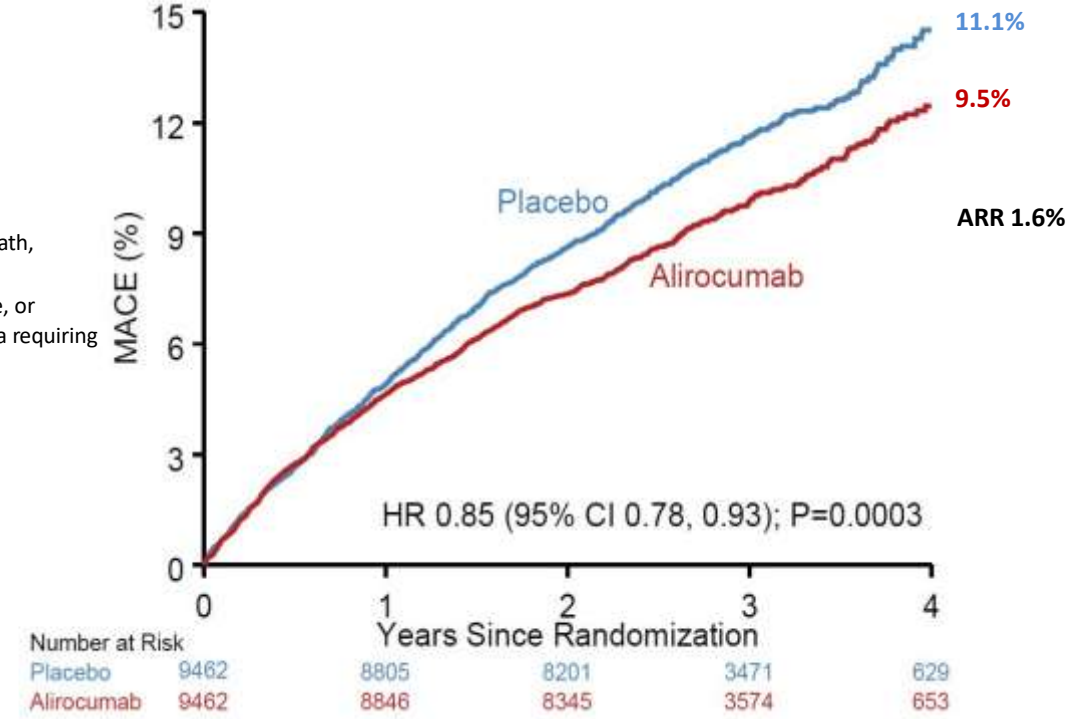
FOURIER Trial



Sabatine MS et al. *NEJM* 2017;epub ahead of print

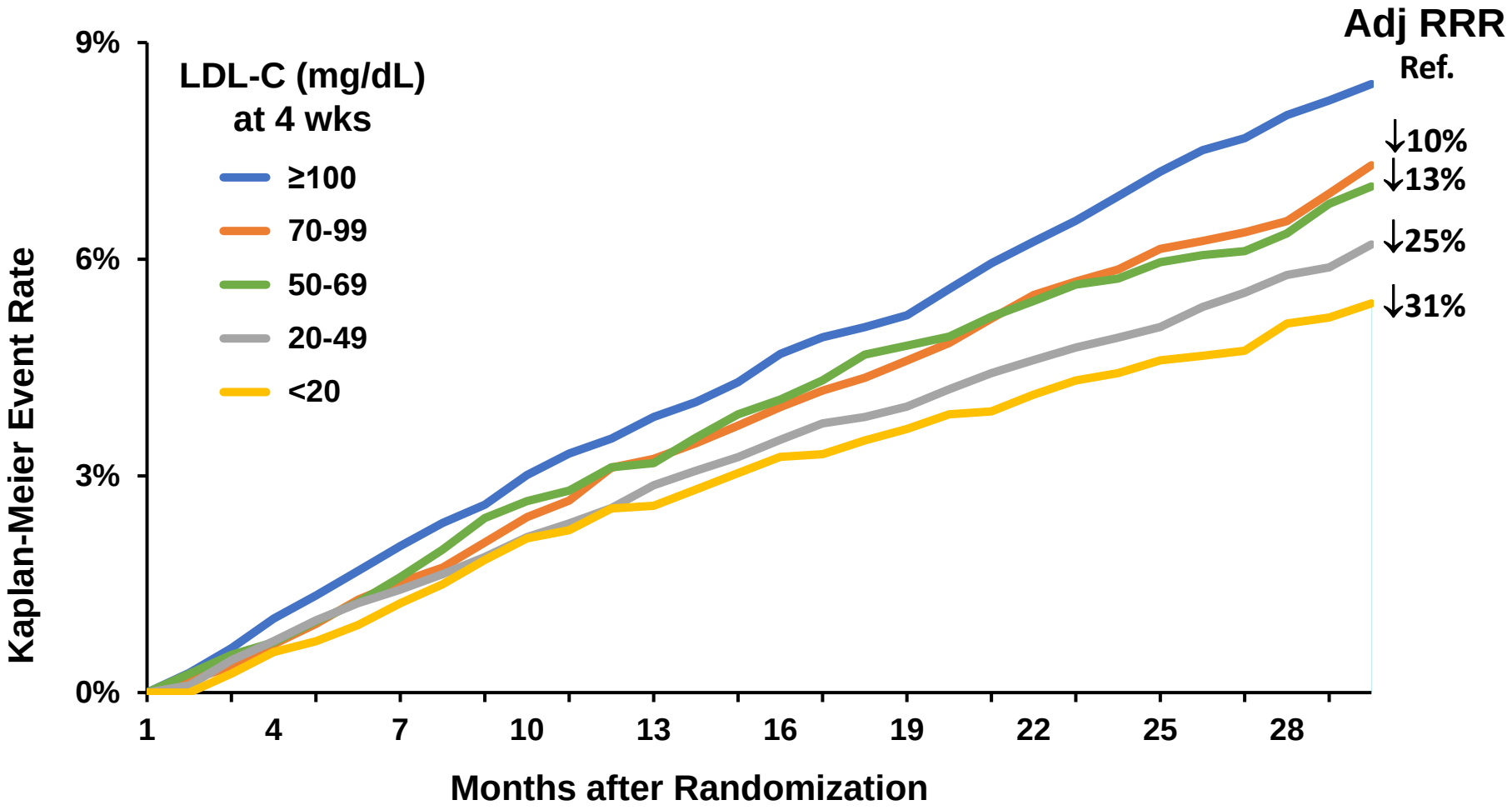
ODYSSEY Outcomes Trial

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization



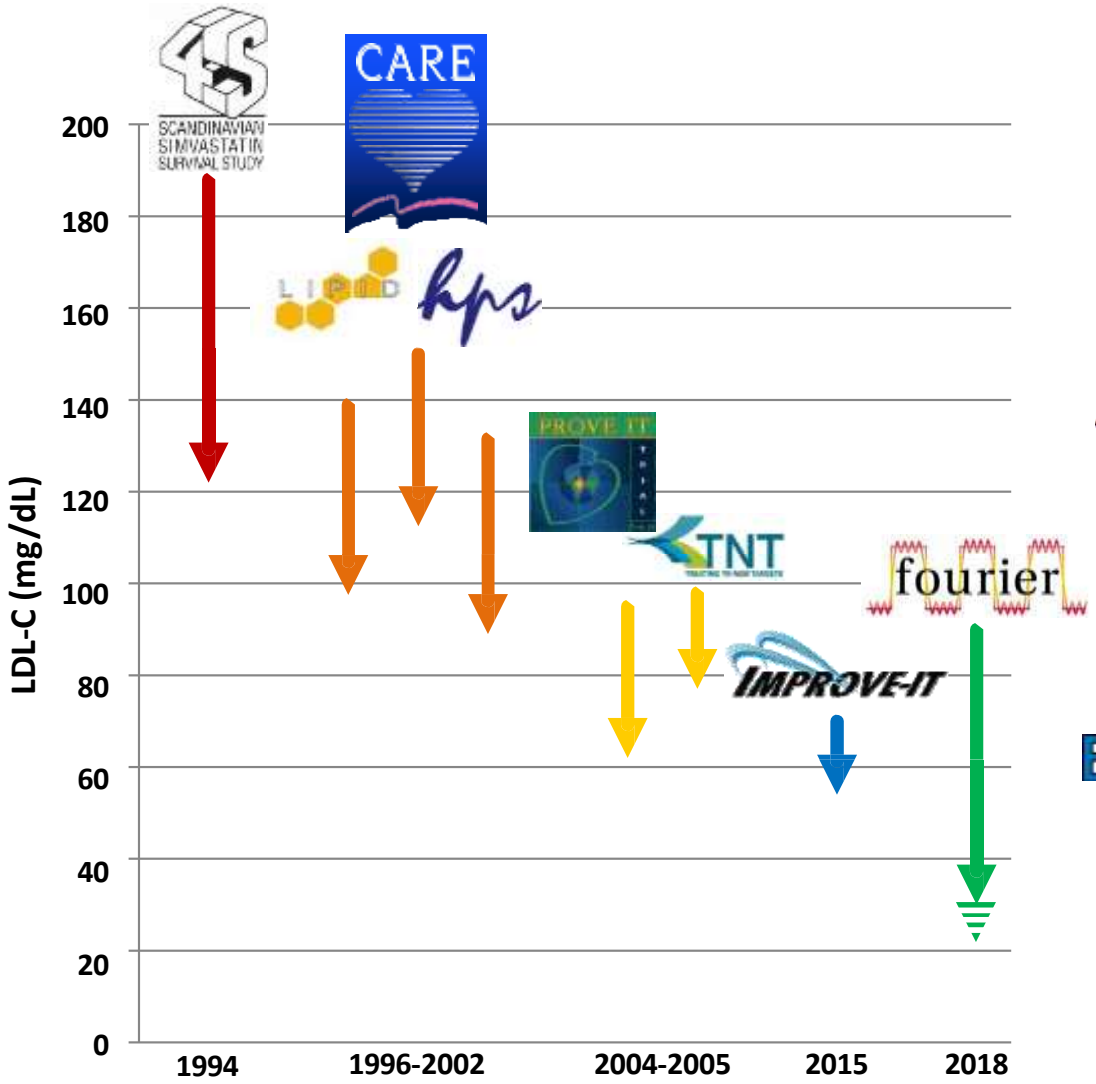
Schwartz, GC et al. NEJM 2018; Nov. 29 [Epub ahead of print]

Putting It All Together
FOURIER Trial: Achieved LDL-C



LDL-C=low-density lipoprotein cholesterol; RRR=relative risk ratio. Giugliano RP et al. *Lancet.* 2017;390:1962-71.

Evolving Paradigm of LDL-C Management



High is bad

Average is not good

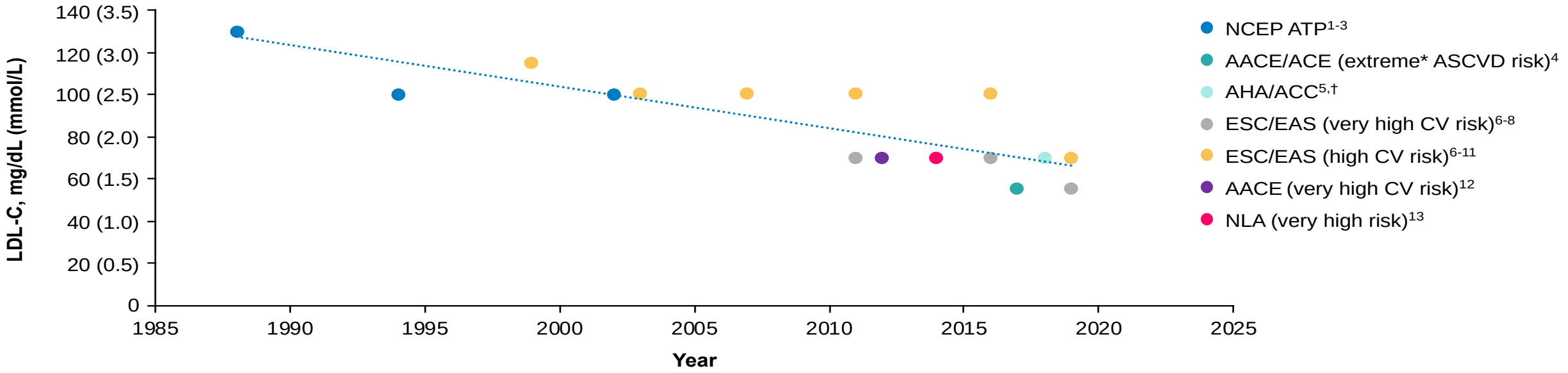
Lower is better

Even lower is even better

Lowest is best

Guidelines Reflect Evolving Evidence of Lowering LDL-C

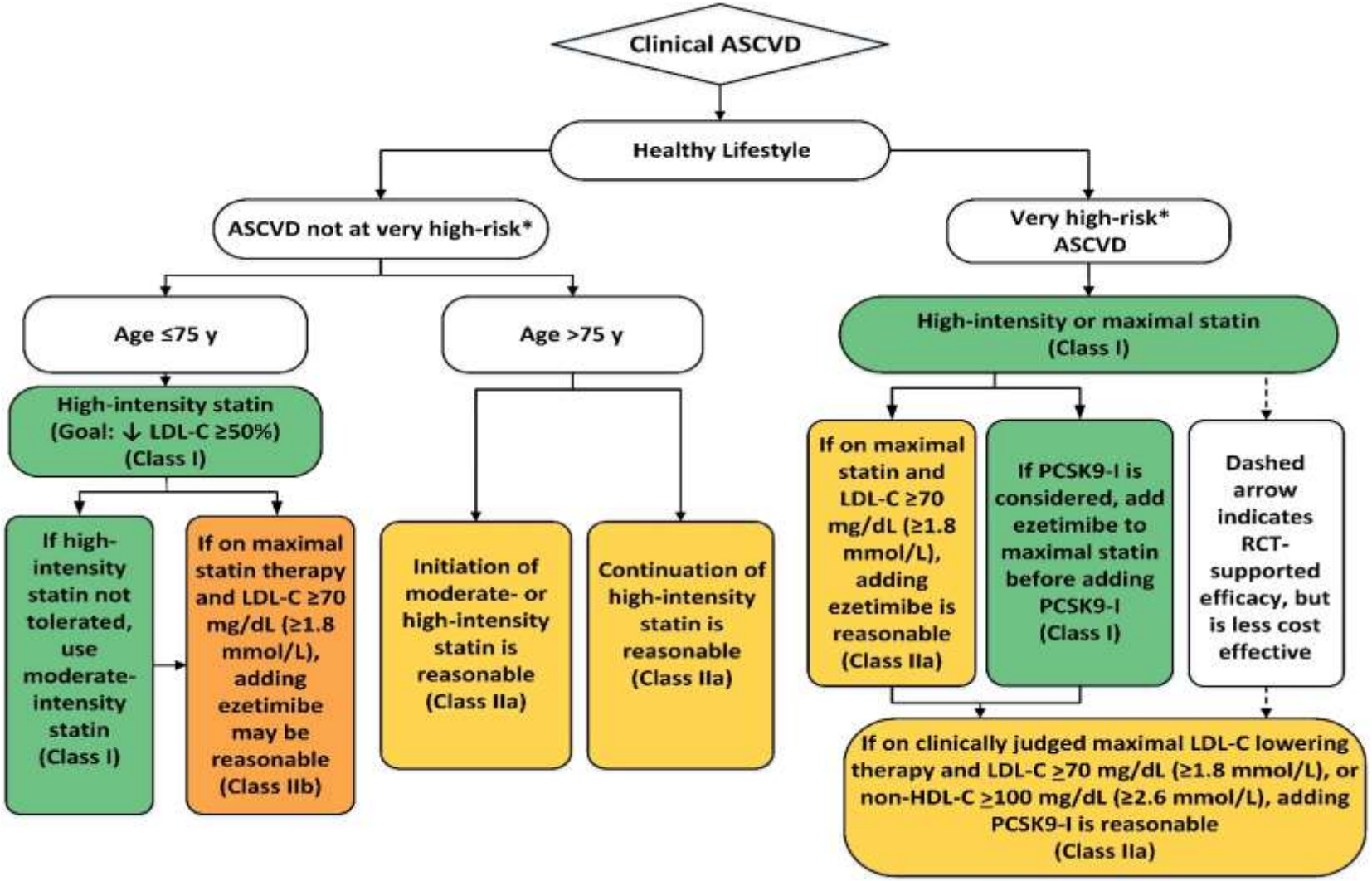
Historical Perspective of LDL-C Targets/Thresholds as Recommended by Globally Recognized Guidelines[1-13]



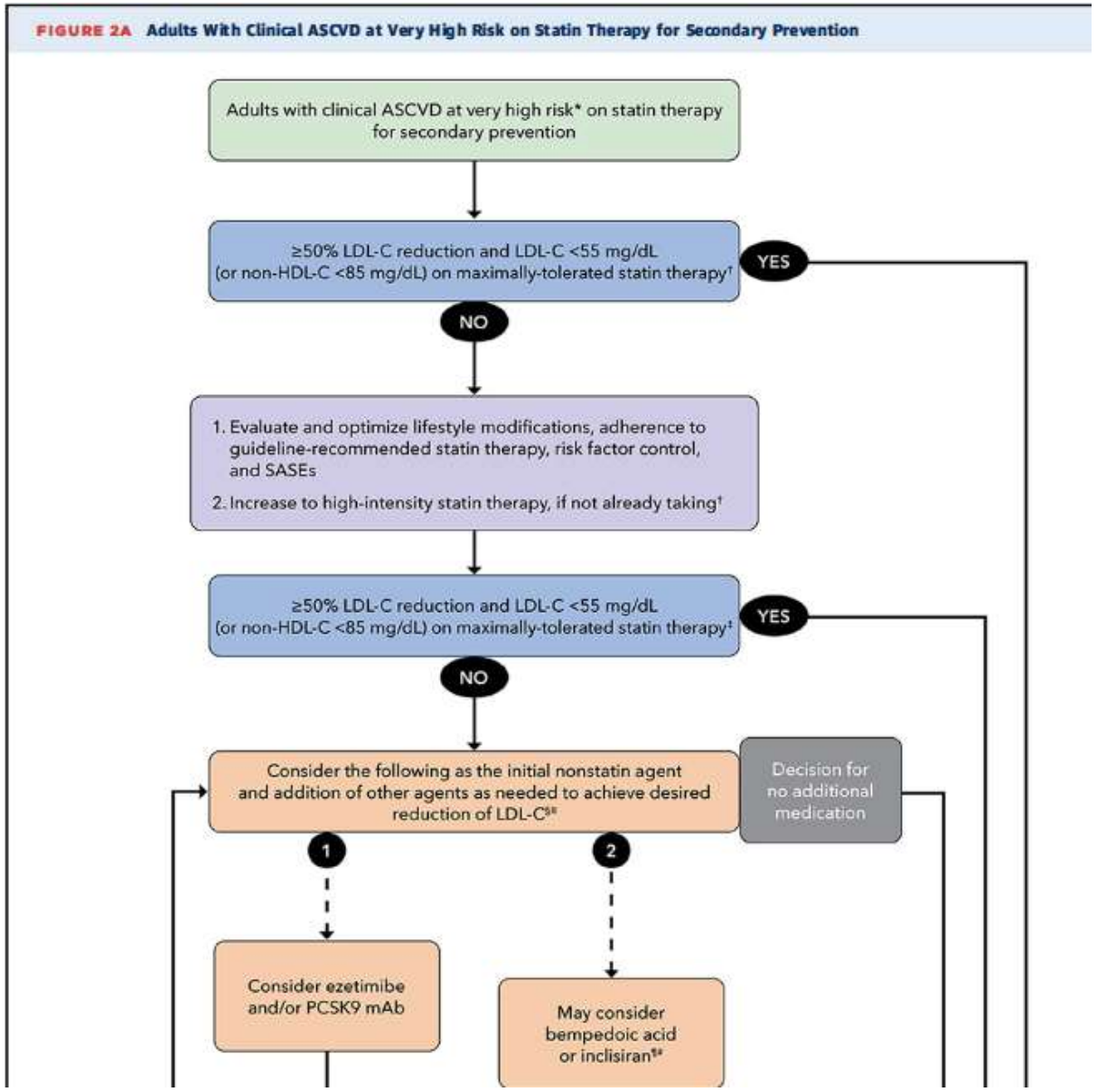
Progressive ASCVD, including UA that persists after achieving an LDL-C < 70 mg/dL (1.8 mmol/L), or established clinical ASCVD in individuals with diabetes, CKD stage 3 or 4, and/or HeFH, or in individuals with a history of premature ASCVD (< 55 years of age for males or < 65 years of age for females). †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



2022 ACC Expert Consensus Decision Pathway



2022 LIPID ASSOCIATION OF INDIA GUIDELINES

Updated Risk Stratification Approach Recommended by Lipid Association of India

Risk factors/markers

Major ASCVD risk factors	Other high-risk features	Moderate risk non-conventional risk factors
1. Age ≥45 years in males and ≥55 years in females	1. Diabetes with 0-1 other major ASCVD risk factors and no evidence of target organ damage	1. Coronary calcium score 100–299 HU
2. Family history of premature ASCVD	2. CKD stage 3B or 4	2. Increased carotid IMT
3. Current cigarette smoking or tobacco use	3. Familial hypercholesterolemia (other than familial homozygous hypercholesterolemia)	3. Lipoprotein (a) 20–49 mg/dL
4. High blood pressure	4. Extreme of a single risk factor	4. Impaired fasting glucose*
5. Low HDL-C	5. Coronary calcium score >300 HU	5. Increased waist circumference**
	6. Non-stenotic carotid plaque	6. Apolipoprotein B≥110 mg/dL
	7. Lipoprotein (a) ≥50 mg/dL	7. hsCRP ≥2 mg/L***

Risk group

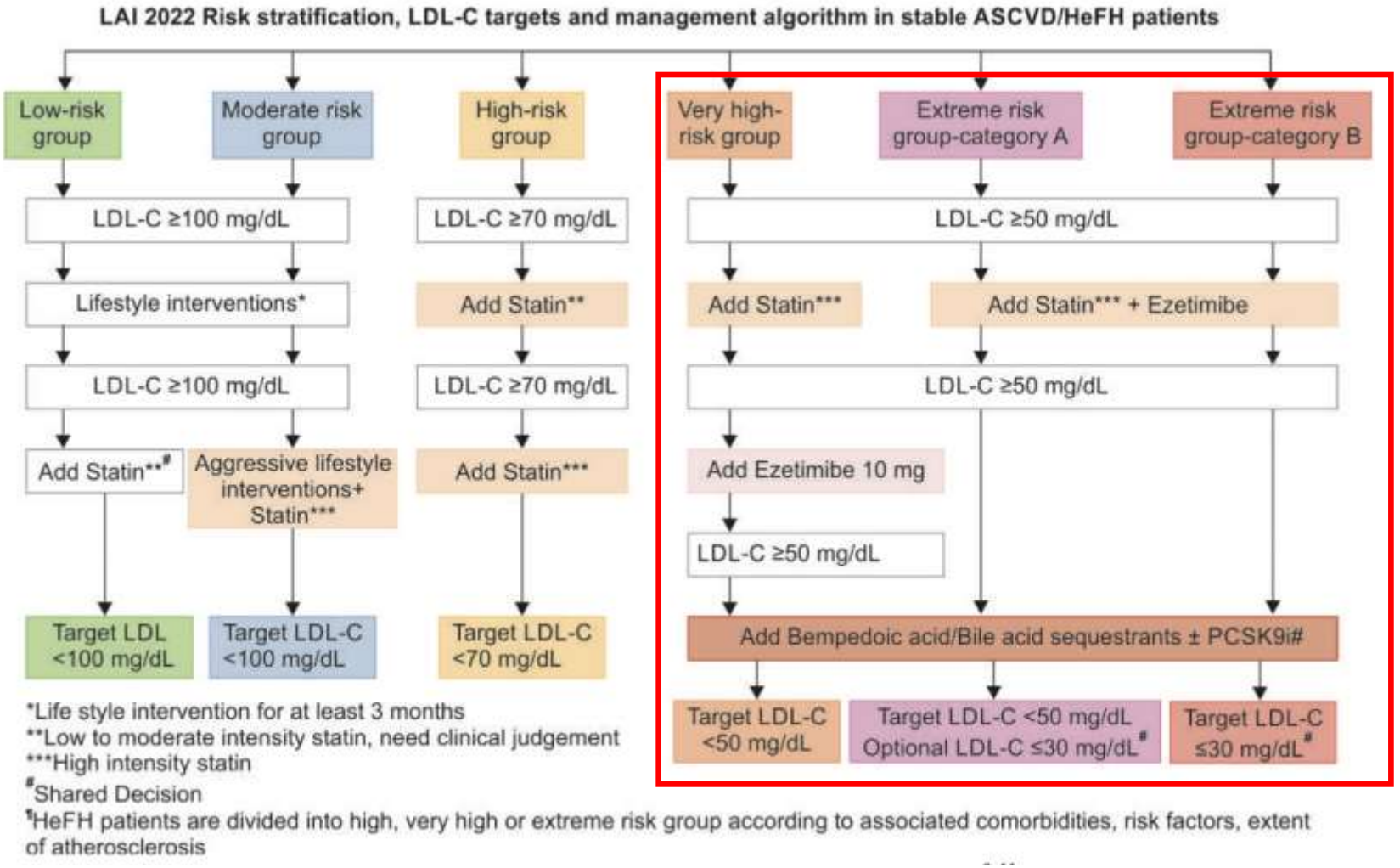
Low-risk	Moderate risk	High-risk	Very high-risk	Extreme risk	
				Category A	Category B
0-1 major ASCVD risk factor and life-time CVD risk <30%	• 2 major ASCVD risk factors • Low risk group with ≥1 moderate risk non-conventional risk factor • Life-time CVD risk ≥30%	• ≥3 major ASCVD risk factors • 2 major ASCVD risk factors with ≥1 moderate risk non-conventional risk factor • ≥1 other high-risk features	• Preexisting ASCVD • Diabetics with ≥2 other major ASCVD risk factors or evidence of target organ damage • Familial homozygous hypercholesterolemia	CAD with ≥1 feature of ***high risk group***	CAD with ≥1 feature of ***very high risk group*** or recurrent ACS (within one year) despite LDL-C <50 mg/dL or polyvascular disease

Clinical judgment to be used if patient has atherosclerotic peripheral arterial disease instead of coronary artery disease.
*A fasting blood sugar level from 100 to 125 mg/dL. It should be confirmed by repeat testing.
**Waist circumference is to be measured at the superior border of the iliac crest just after expiration. Increased waist circumference is defined as >90 cm in men and >80 cm in women. If increased waist circumference is the only risk factor, it should again be measured after 6 months after initiating heart healthy lifestyle measures.
***On two occasions at least 2 weeks apart. For reclassifying moderate risk group only.

Fig. 1: Risk stratification algorithm recommended by the LAI[10,11]

J Assoc Physicians India 2022;70:67–75.

2022 LIPID ASSOCIATION OF INDIA GUIDELINES



J Assoc Physicians India 2022;70:67–75.

They Knew It All Along…

A Receptor-Mediated Pathway for Cholesterol Homeostasis

MICHAEL S. BROWN AND JOSEPH L. GOLDSTEIN

The LDL-receptor studies lend experimental support to the epidemiologists' suggestion that the levels of plasma cholesterol usually seen in Western industrialized societies are inappropriately high (*9*). This support derives from knowledge of the affinity of the LDL receptor for LDL. The receptor binds LDL optimally when the lipoprotein is present at a cholesterol concentration of 2.5 mg/dl (*28*). In view of the 10-to-1 gradient between concentrations of LDL in plasma and interstitial fluid, a level of LDL-cholesterol in plasma of 25 mg/dl would be sufficient to nourish body cells with cholesterol (*118*). This is roughly one-fifth of the level usually seen in Western societies (Fig. 16) (*119*). Several lines of evidence suggest that plasma levels of LDL-cholesterol in the range of 25 to 60 mg/dl (total plasma cholesterol of 110 to 150 mg/dl) might indeed be physiologic for human beings.

Adapted from Nobel Prize Lecture, Stockholm, Sweden, 1985.
Science 1986;232:34.

Case #1

- 58 African American female with a history of rheumatoid arthritis who presents for outpatient evaluation and concern for “high cholesterol.” She has 2 children (age 28 and 24), denies smoking, diabetes. Her family history is significant for CAD in her father who had an MI at age 62.
- Exam:
  - BP 138/86; HR 72 (sinus); 99% RA; RR 14; BMI 28.2 kg/m^2
  - Unremarkable cardiovascular exam
- Labs:
  - Total cholesterol: 220 mg/dL
  - LDL-C: 150 mg/dL
  - HDL: 34 mg/dL
  - TG: 205 mg/dL
  - HbA1c: 5.2%
  - TSH: normal

What is the Next Best Step for Primary ASCVD Prevention for This Patient?

1. Perform an exercise stress test
2. Check a Lp(a) level and CAC score
3. **Try lifestyle changes and reassess labs in 3-6 months**
4. **Initiate atorvastatin 20 mg**
5. Initiate atorvastatin 20mg and clopidogrel 75mg daily

Case #2

- 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
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  - HbA1c: 6.2%
- Medications: aspirin 81, ticagrelor 90mg PO BID, atorvastatin 80mg, lisinopril 40mg, metoprolol succinate 100mg 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 10mg daily and consider adding PCSK9 inhibitor (bempedoic acid in India?)

C. Add icosapent ethyl

D. No change required

Summary and Conclusions

- Reducing LDL-C with statin therapy is the cornerstone of hyperlipidemia management and prevention of CV events.
- It is important to start early in terms of primary prevention and critical to aggressively lower LDL-C for secondary prevention.
- The ACC/AHA guidelines recommend additional lipid lowering therapy (with ezetimibe and PCSK9i) in high-risk patients who have LDL > 55mg/dL.
  - Indian guidelines target LDL <50 mg/dL or <30 mg/dL (extreme risk patients)