LDL-Cholesterol

How Low is Too Low?

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CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

COURSE NAME:

Medicine RSS eLearning Modules

CME eLEARNING ACTIVITY NAME:

LDL-Cholesterol: How Low is Too Low?

2018 Cholesterol Guidelines

PROGRAM DESCRIPTION, EDUCATIONAL GOAL AND RATIONALE:

Evidence based guidelines are constantly changing and being updated for several core areas of Internal Medicine throughout the year. It is important for physicians to practice the most up-to-date standard of care in all specialties to promote patient health and well-being. Our series of lectures at the medicine regularly scheduled series promotes continuing education for the practicing internist and highlights important updates in medical practice in these core areas. Physicians in general practice often and do not have the time to keep themselves up-to-date with medical advances as they are busy seeing patients in the clinical setting. The Medicine Regularly Scheduled Series gives these physicians the opportunity to learn these advances in an academic setting.

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TARGET AUDIENCE:

Physician Partners and Premium Network community-based providers

LEARNING OBJECTIVES:

- To Understand the Recent Data Regarding Treatment to Low LDL-Cholesterol and Effect on Cardiovascular Outcomes.
- To Recognize the Safety Data Regarding Cellular and Physiologic Effects Among Patients Treated to Low LDL Cholesterol.
- To Understand How Recent Studies Have Advanced Our Understanding of the Role of LDL Cholesterol Physiology.
- Identify how personal care guidelines have become more specific since 2013
- Conduct a detailed risk assessment and identify new lipid lowering options for patients with highest ASCVD risk
- New lipid lowering options for patients with highest ASCVD risk
- Learn how to utilize Risk Enhancing Factors
- Identify benefits of therapy v. side effects
- Review risk factors

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COURSE HOST:

Department of Medicine

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ESTIMATED TIME TO COMPLETE ACTIVITY:

90 minutes

ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT:

An announcement of program support will be made to all attendees at the beginning of each educational activity.

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FACULTY DISCLOSURES:

Drs. Thomas McGinn, Dr. Sandy Balwan, George Boutis, John Raimo and Sean LaVine have nothing to disclose. Dr. Hirsh's disclosures are on the next slide.

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PROGRAM EXPIRATION: 7/30/19

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Relevant Disclosures:

Consultanship: Sanofi-Regeneron

Advisory Board: AstraZeneca, Regeron

Objectives

1. To Understand the Recent Data Regarding Treatment to Low LDL-Cholesterol and Effect on Cardiovascular Outcomes.

2. To Recognize the Safety Data Regarding Cellular and Physiologic Effects Among Patients Treated to Low LDL Cholesterol.

3. To Understand How Recent Studies Have Advanced Our Understanding of the Role of LDL Cholesterol Physiology.

In your opinion, what directly measured LDL-C is considered too low?

A. 60 mg/dL
B. 40 mg/dL
C. <25 mg/dL
D. <15 mg/dL
E. There is no lower limit

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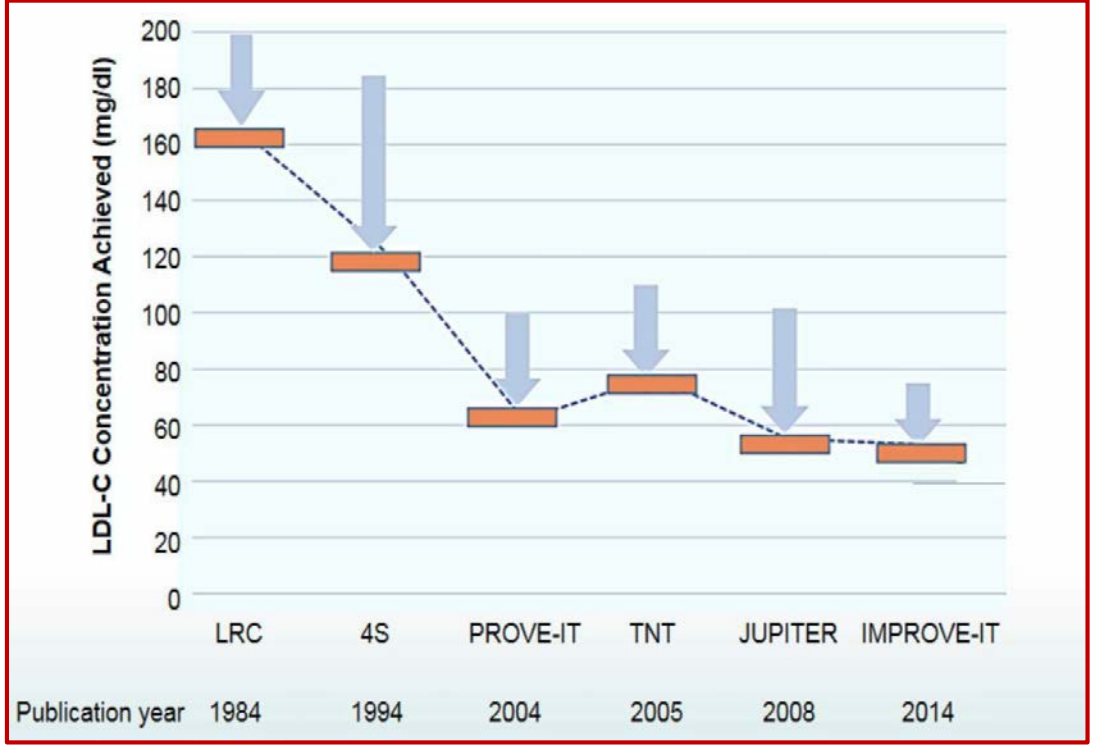
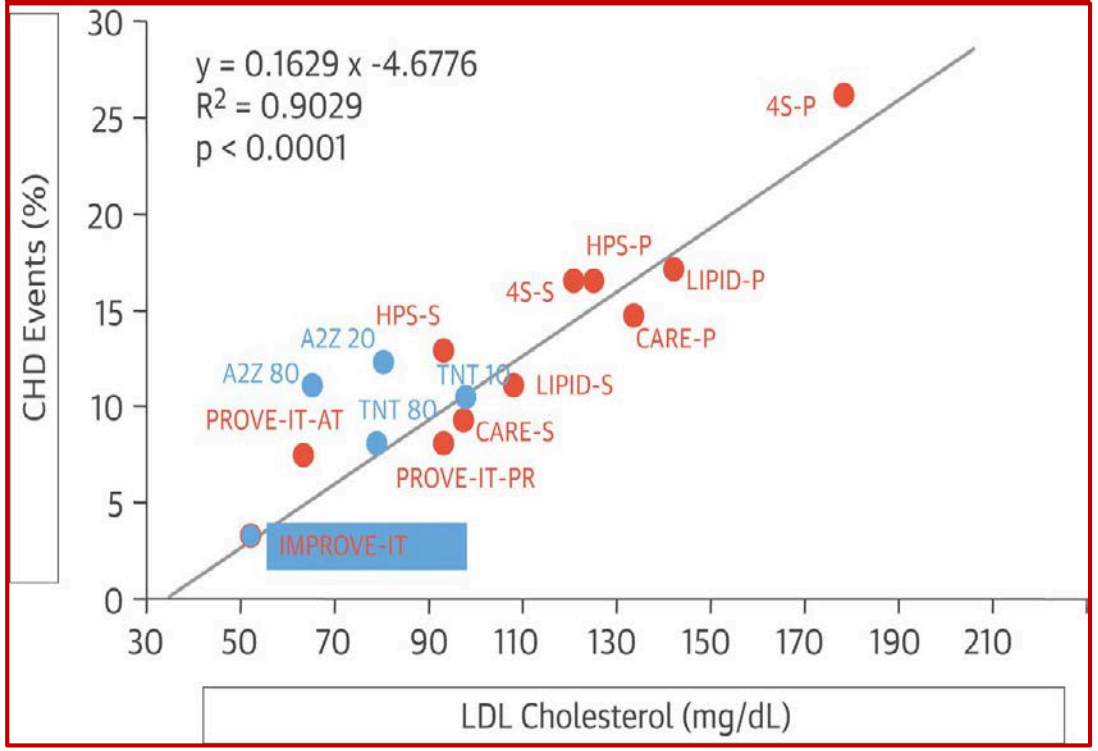
Treatment of LDL-Cholesterol to Lower CHD Events

Lessons from 3 Decades of Cholesterol Treatment Trials

Over a Quarter Century Treating LDLc in RCTs



Log-Linear Relationship: Achieved LDLc & CHD

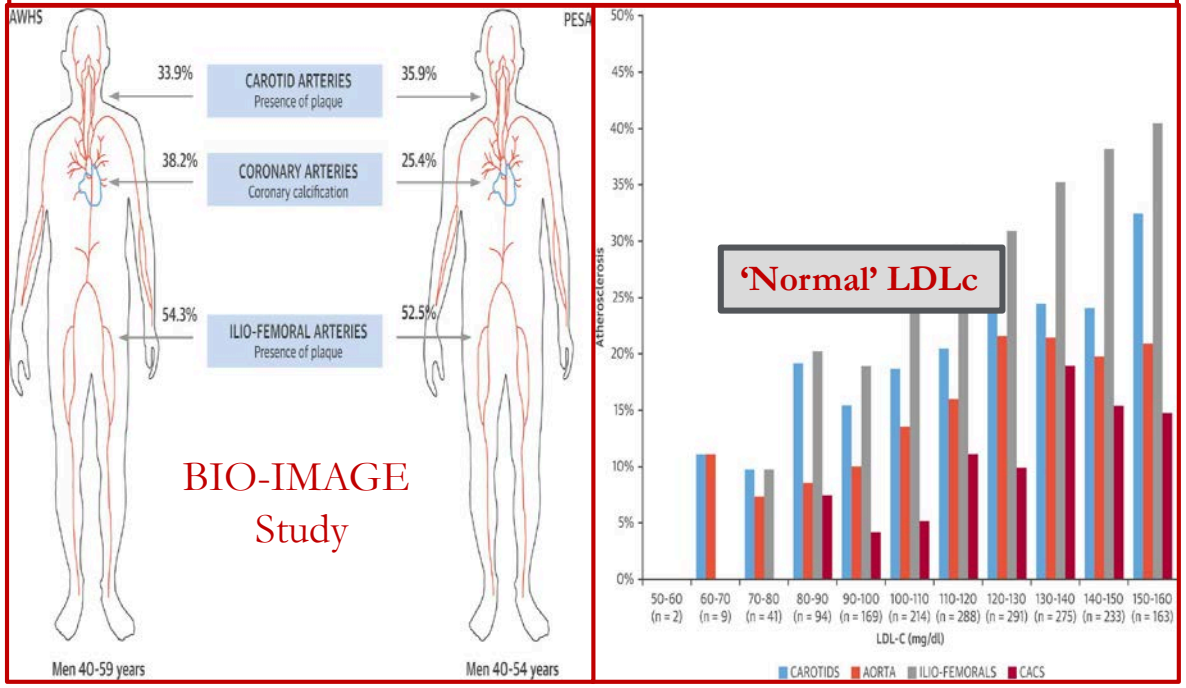


1. Masana L, Girona J, et al. Clinical and pathophysiological evidence supporting the safety of extremely low LDL levels—The zero-LDL hypothesis. J Clin Lipid 2018; 12:292-299.
2. Wright RS and Murphy J. PROVE-IT to IMPROVE-IT: Why LDL goals still matter in post-ACS patients. J Am Coll Card 2016; 67:362-365.

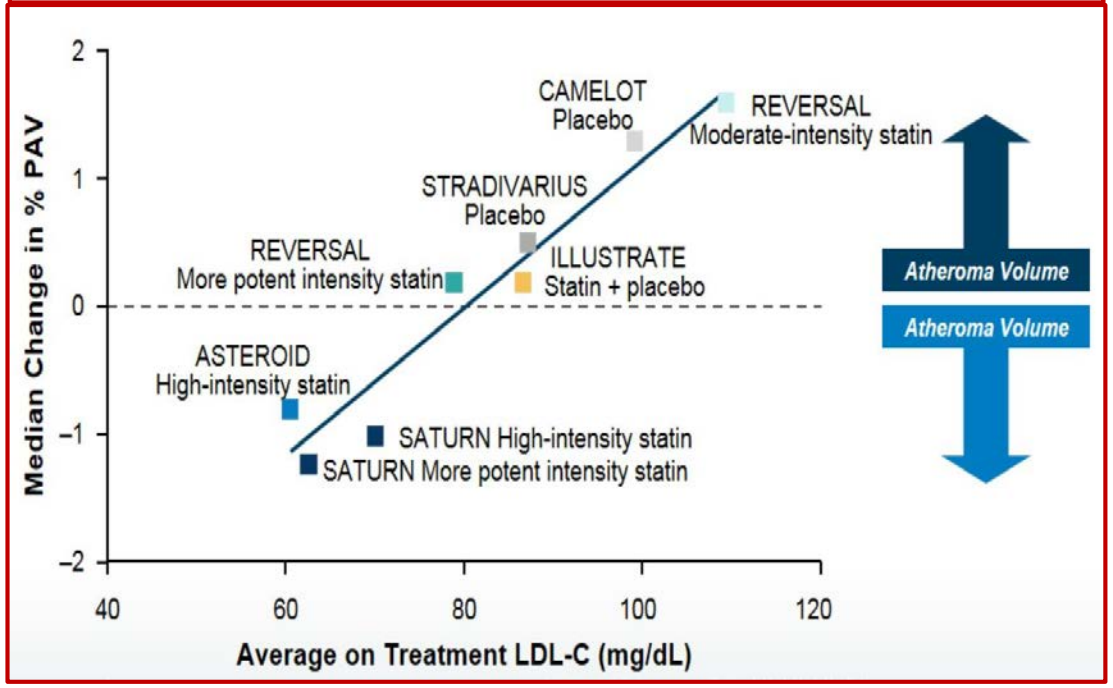
LDLc and ASCVD: Primary and Secondary Prevention

- In Absence of RFs, LDLc -ASCVD Directly-Related; Observed EVEN at **'Normal'** Levels
- In Presence of Plaque, Regression is Directly-Related to LDL-C Level

Bioimage: Atherosclerosis (Low-Risk)
CAC, Iliofemoral, Carotid, Abdominal Aorta



Plaque Regression Directly Related to
LDLc Lowering

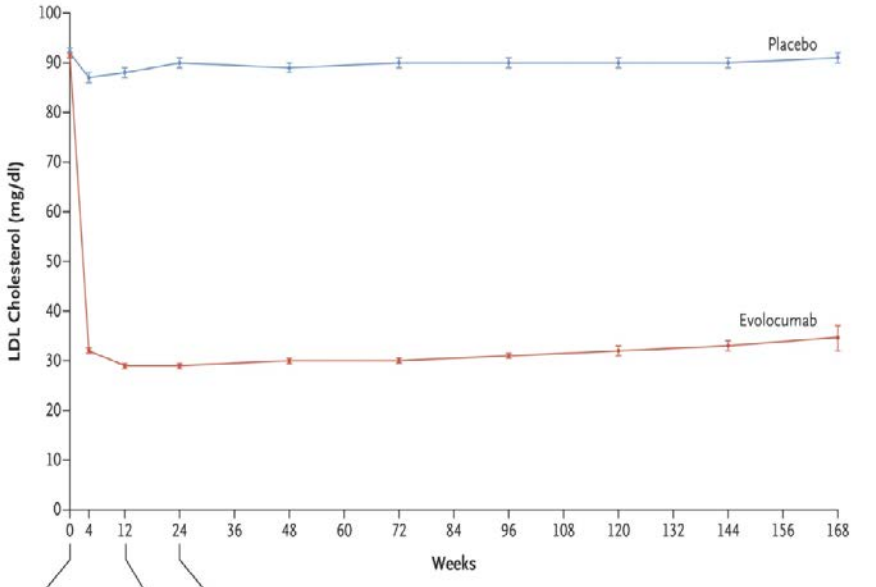


1. Fernandez L, Fuster V, et al. Normal LDL cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. JACC 2017; 70:2979-2991.
2. Nicholls SJ, Nissen SE, et al. Effect of Evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV study. JAMA 2016; 136:2373-2384.

PCSK9 Inhibitor Therapy & LDL-Cholesterol Levels

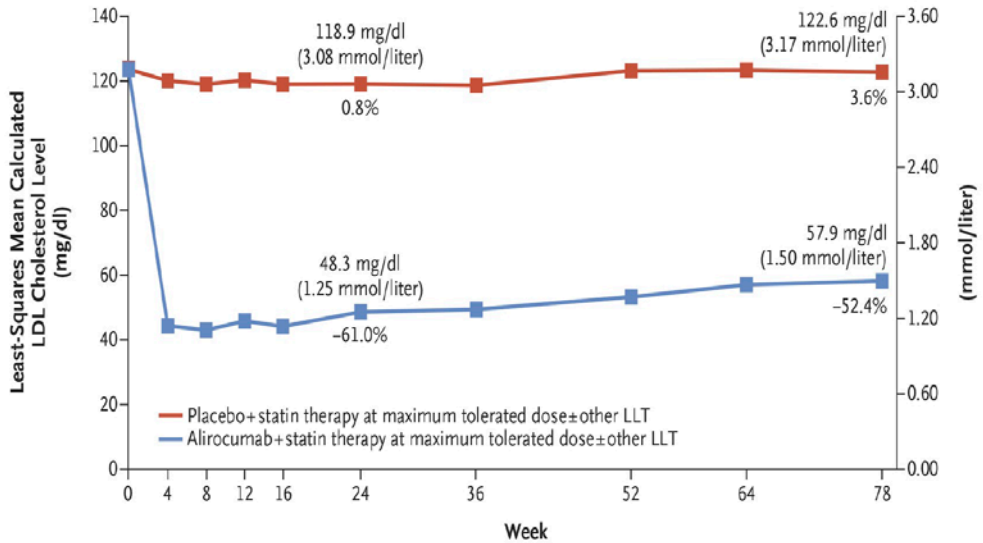
Greater Potency, Lower LDLc, And Questions Regarding Safe & Optimal LDLc Levels

FOURIER Trial: Evolocumab



No. at Risk									
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

ODYSSEY Trial: Alirocumab



No. of Patients with Data Available										
Placebo	780	754	747	746	716	708	694	676	659	652
Alirocumab	1530	1473	1458	1436	1412	1386	1359	1349	1324	1269

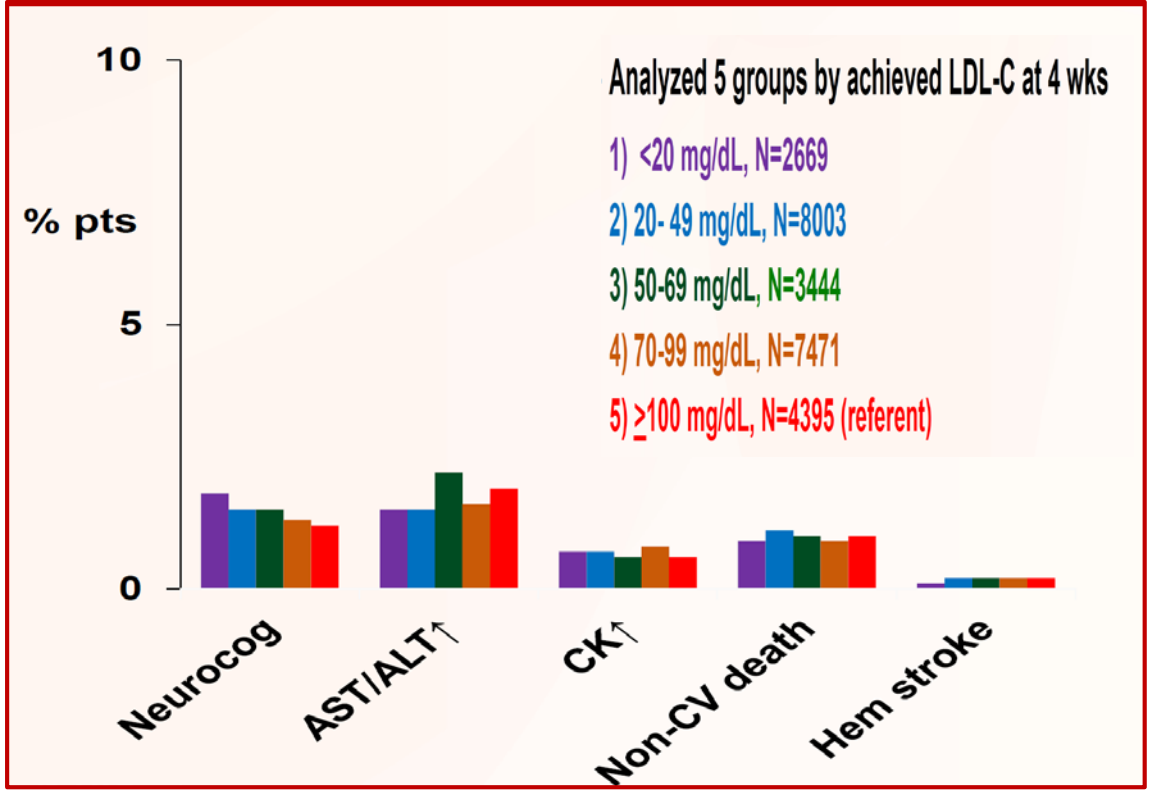
1. Sabatine MS, Giugliano RP, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017; 376:1713-1722.
2. Schwartz GG, Bhatt DL, et al. Alirocumab in patients after acute coronary syndrome. Presented at ACC March 2018, New Orleans, LA.

Very Low
Levels of
[LDL-C]
Safety & Efficacy

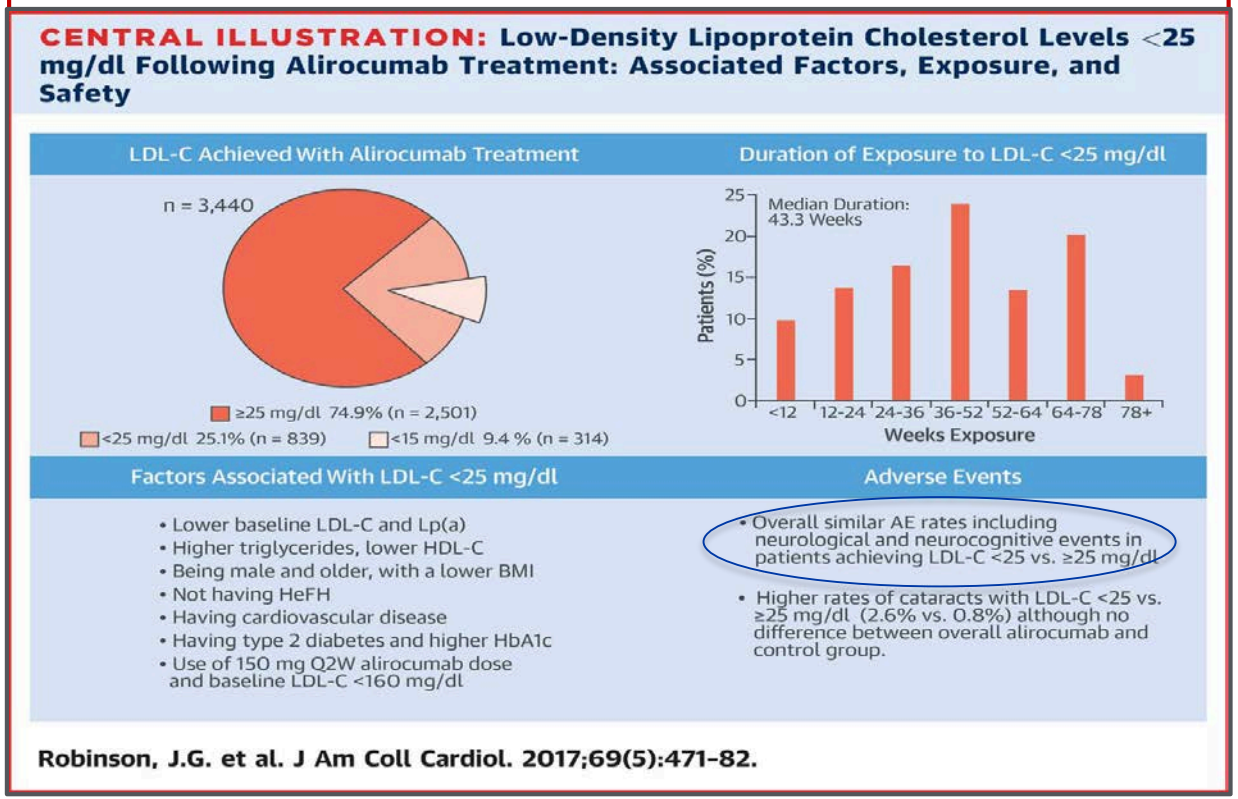
Very Low [LDLc] & Adverse Events

[LDLc] <20 – 25 mg/dL and Adverse Events in The FOURIER & ODYSSEY RCTs

FOURIER Adverse Events
[LDLc] < 20mg/dL (n=2669)



ODYSSEY Adverse Events
[LDLc] < 25 mg/dL (n=839)



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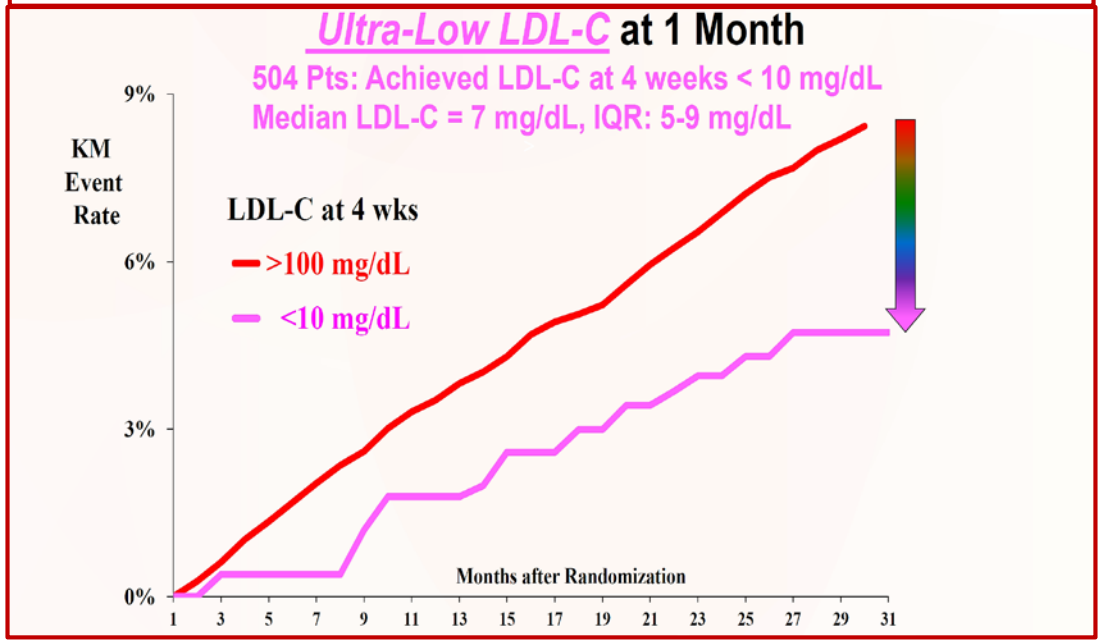
1. Giugliano RP, Sabatine MS, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet 2017; 390:1962-1971.
2. Robinson JG, Kastelein J, et al. Alirocumab reduces major cardiovascular events in individuals with atherosclerotic cardiovascular disease: A post-hoc analysis of ODYSSEY LONGTERM. J Am Coll Card 2017; 69:471-482.

Ultra Low [LDLc]: Lower is Better for Reduction in MACE

Efficacy & Safety for Patients with On-Treatment [LDLc] of < 10 mg/dL

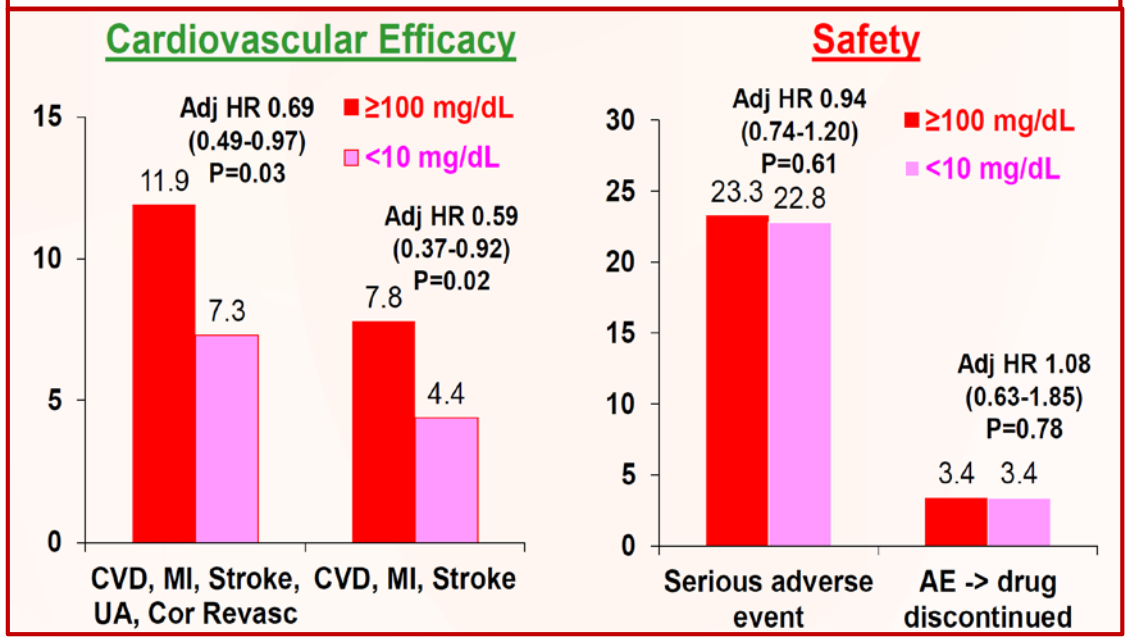
FOURIER Efficacy

[LDLc] < 10 mg/dL (n=504); Median = 7 mg/dL



FOURIER Safety

[LDLc] < 10 mg/dL (n=504)



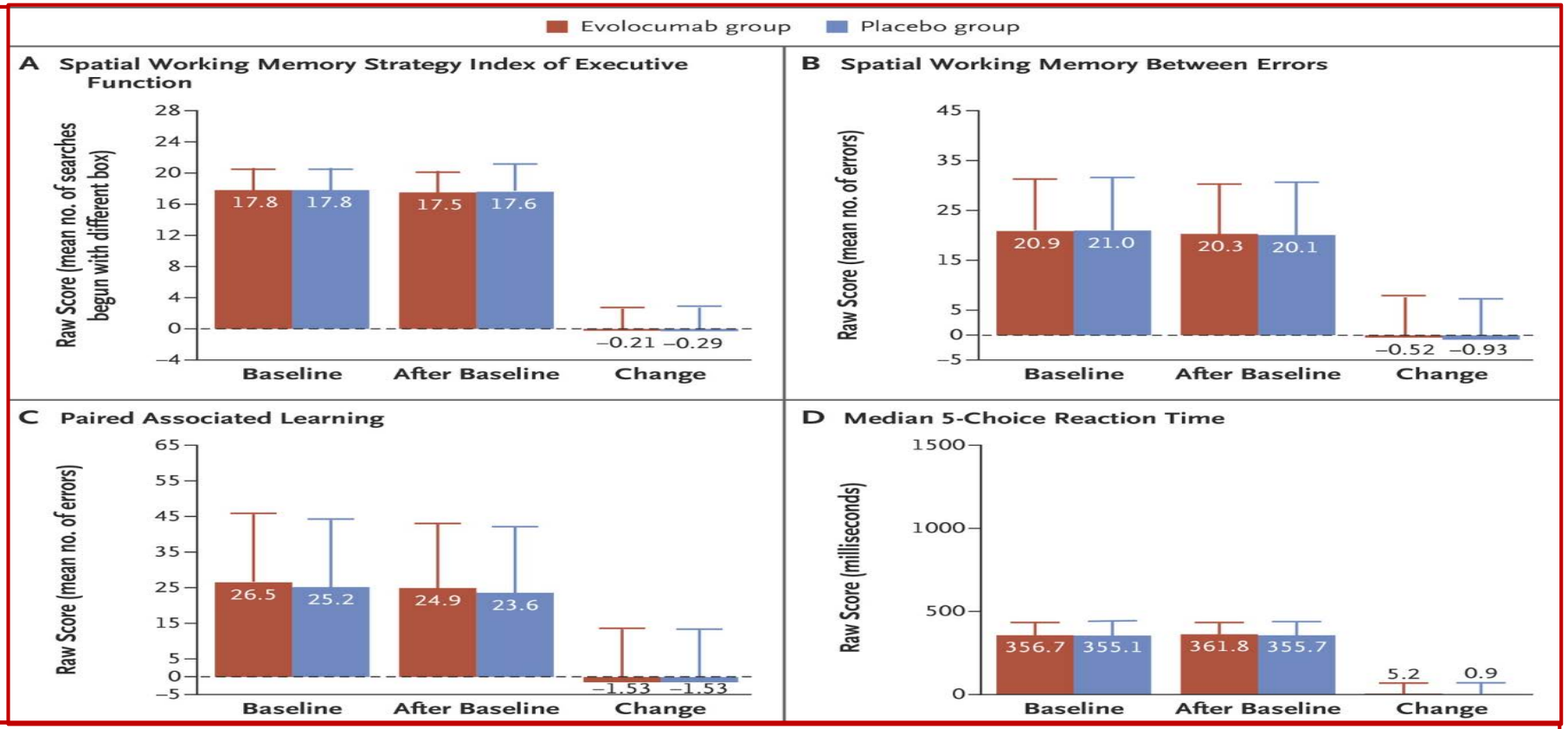
1. Giugliano RP, Sabatine MS, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet 2017; 390:1962-1971.

Neurocognitive Outcomes

Ebbinghaus: Cognitive Function in a Randomized Trial of Evolocumab.

2000 Fourier Patients

- Neurocognitive Testing
- Working Memory
- Spatial Processing
- Language Fluency
- Reaction Time
- Psychomotor Speed
- Baseline
- 6 Months
- Yearly
- 5 Years



STRATIFIED by the lowest-attained LDLc level:

- After Randomization: **No associations between LDLc level and adverse cognitive outcomes.**
- Including among **661 patients who underwent cognitive testing with LDLc levels below 25 mg/dL.**

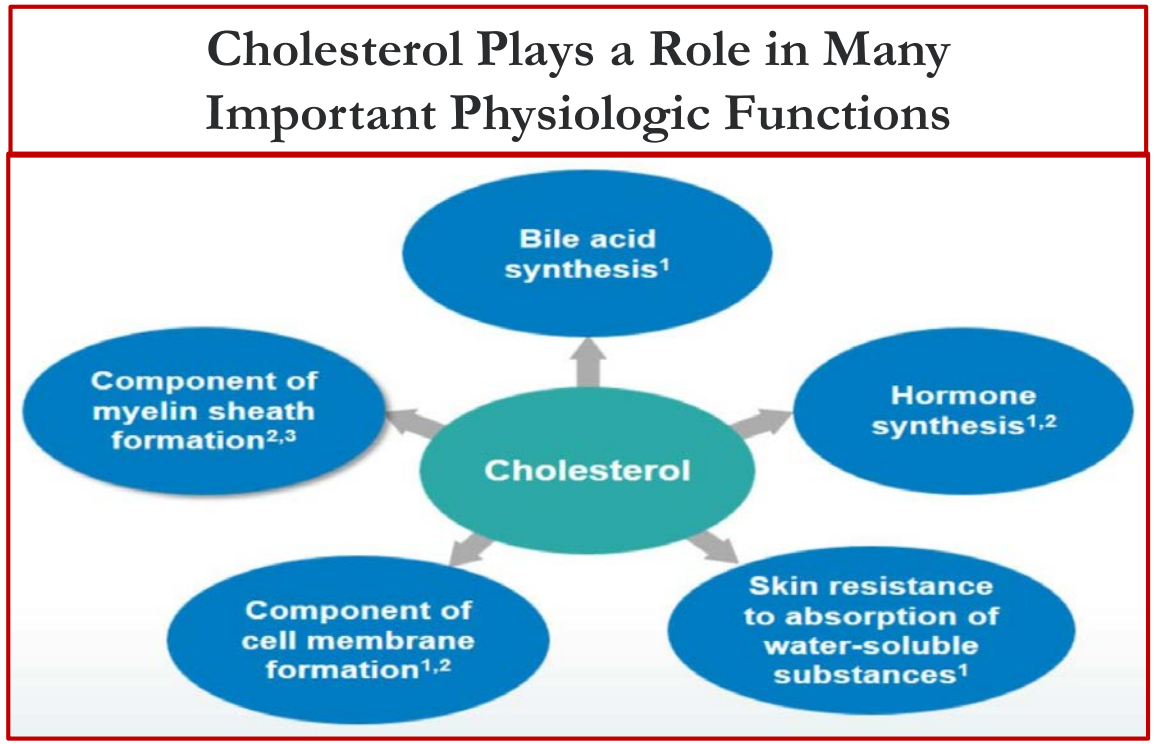
1. Giugliano RP, Sabatine MS, et al. Cognitive function in a randomized trial of evolocumab. N Engl J Med 2017; 377:633-643.

Addressing the Concerns with Treatment to Low Levels of LDLc

Addressing the concerns with treatment to very low [LDL]

Could profound reduction of LDLc deplete cholesterol stores and compromise essential functions of cholesterol, including:

- Hormone Synthesis
- Fat-Soluble Vitamin Synthesis
- Myelin Sheath Formation
- Cell-membrane Integrity
- Bile-Acid Synthesis



1. Goldstein JL and Brown MS. The LDL Receptor. Arterioscler Thromb Vasc Biol 2009; 29:431-436.
2. Saher G, Brugger B, et al. High cholesterol is essential for myelin membrane growth. Nat Neurosci 2005; 8:468-475.

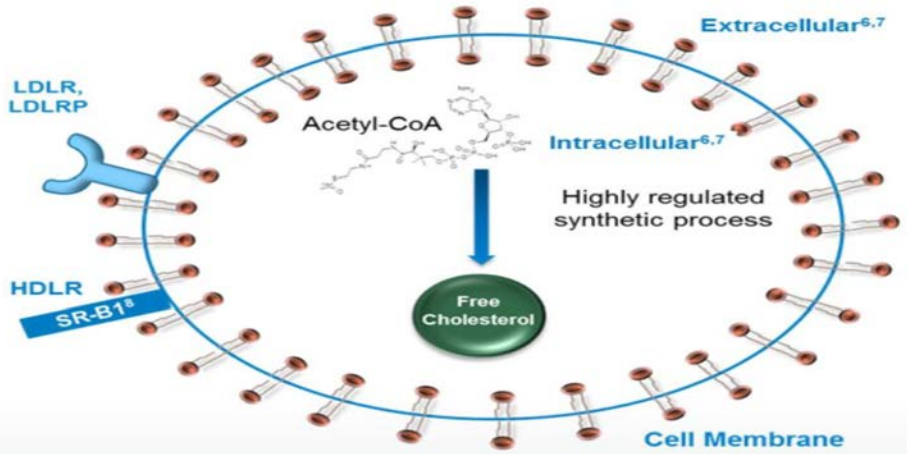
Addressing the concerns with treatment to very low [LDL]

Is LDL necessary to supply cholesterol to peripheral tissues?

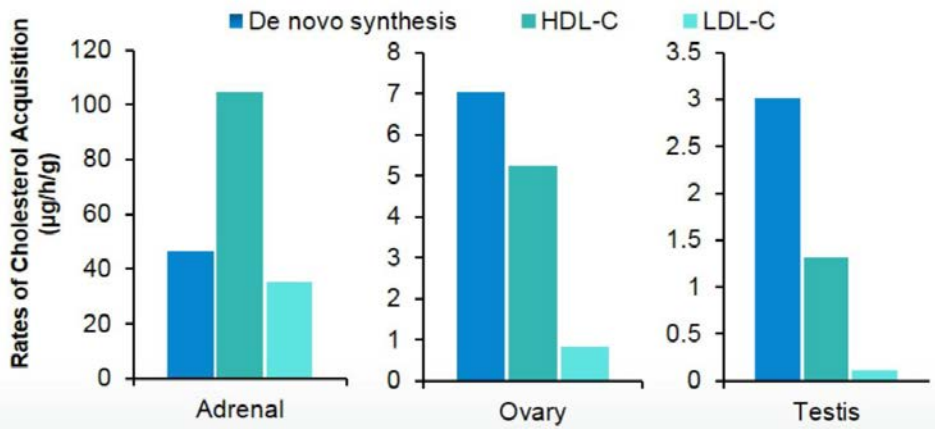
Intracellular [cholesterol] is predominantly

- Synthesized de novo or
- Acquired from HDL (significantly less is acquired from LDL)
- **LDL is an Insignificant Source of Cholesterol for Steroid Synthesis**

Process of De Novo Synthesis is Highly Regulated



Steroidogenic Tissues Predominantly Acquire Cholesterol De Novo or from HDL

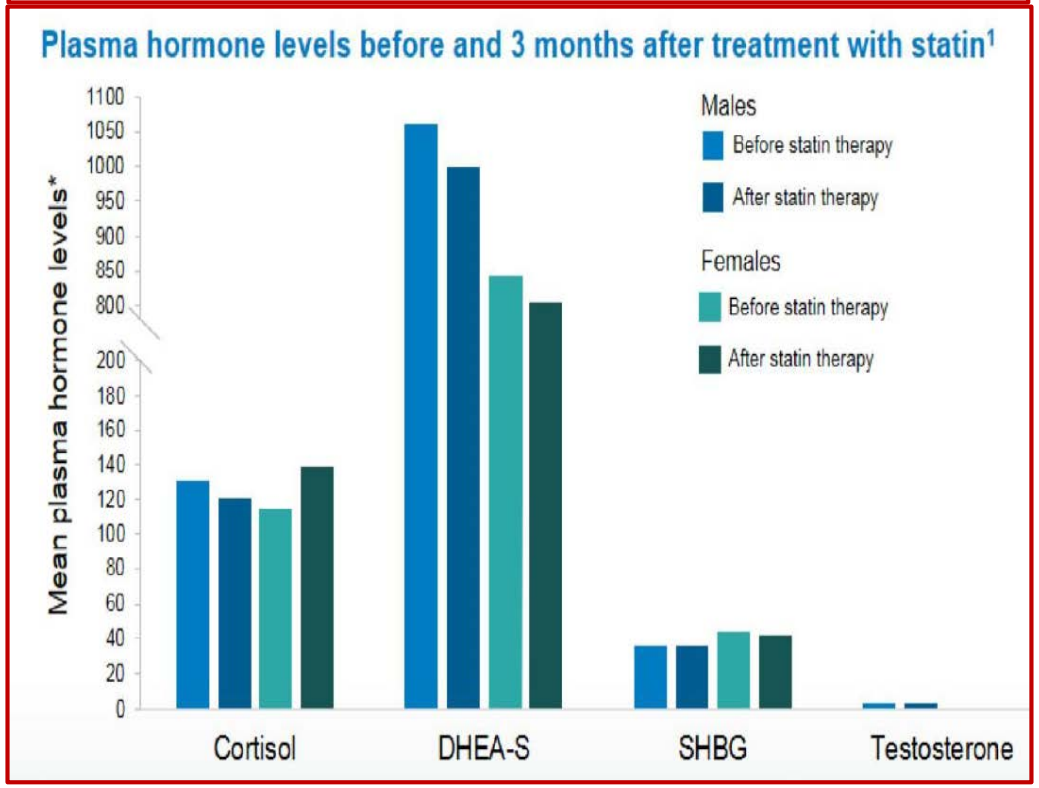


1. Xie C, Richardson JA, et al. Cholesterol substrate pools and steroid hormone levels are normal in the face of mutational inactivation of NPC1 protein. J Lipid Res 2006; 47:953-963.
2. Bochem AE, Holleboom AG, et al. High-density lipoprotein as a source of cholesterol for adrenal steroidogenesis. J Lipid Res 2013; 64:1694-1704.

Addressing the concerns with treatment to very low [LDL]

Does Cholesterol-lowering therapy affect adrenal and gonadal hormone synthesis?

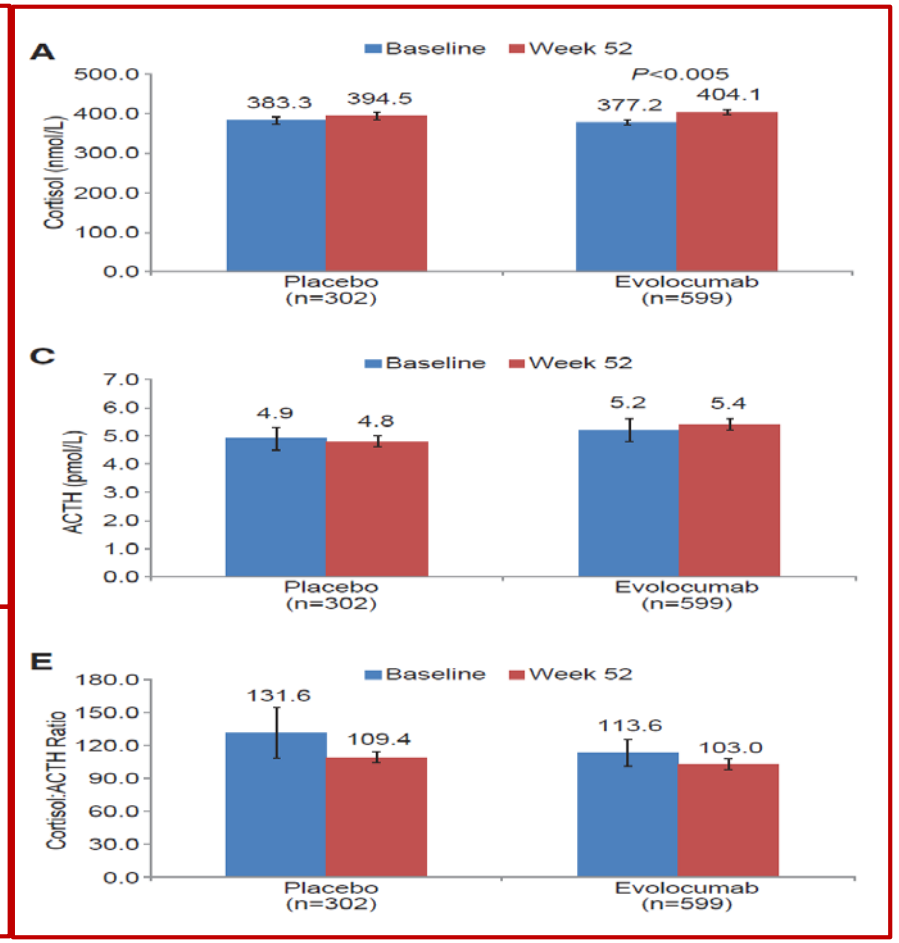
Statins (FDA). Despite Reducing LDL, Statins Do Not Alter Hormone Synthesis



PCSK9 (FDA). Despite Reducing LDL to Very Low Levels, PCSK9 Inhibitors Do Not Alter Hormone Synthesis

Blue
Baseline

Red
Post PCSK9i
Treatment



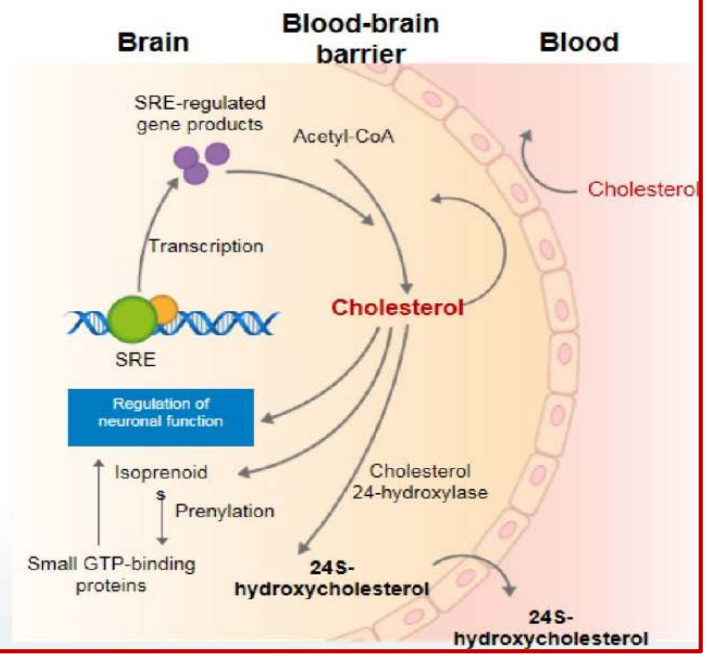
1. Sezer K, Emral R, et al. Effect of very low LDL on cortisol synthesis. J Endocrinol Invest 2008; 31:1075-1078.
2. Robinson JG, Kastelein JJ, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015; 372:1489-1499.

Addressing the predominant concerns with very low [LDL]

Is the CNS Affected by Reduced [LDL] or the use of PCSK9 Antibodies?

The CNS Predominantly Synthesizes Cholesterol De Novo. HDL Crosses Blood Brain Barrier. LDL Does Not.

- Cholesterol is a major component of the CNS[1,2]
  - The CNS predominantly synthesizes cholesterol de novo[1,2]
  - The blood-brain barrier (BBB) prevents the uptake of systemic lipoprotein cholesterol from atherogenic lipoproteins[2,3]
    - However, HDL does appear to cross the BBB[3]
  - This segregation ensures that cholesterol metabolism within the brain is isolated from changes in the circulating lipid levels due to diet or medication[2]



Concerns with regard to PCSK9 Monoclonal Antibodies in the Central Nervous System

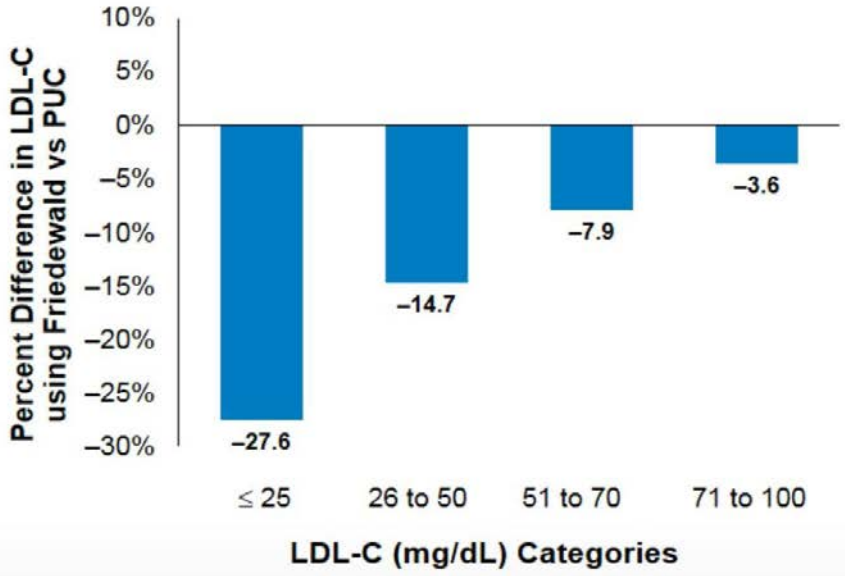
- PCSK9 Monoclonal Antibodies are too large to cross the blood brain barrier.
- No increased neurocognitive risk in a pooled analysis of 14 trials on PCSK9 inhibitors even after attaining an extremely low LDL-C level.
- Loss of function of PCSK9 is not associated with any signs of neurocognitive deficits.

1. Figure Adapted from Katsuno M, et al. Nature Med 2009.
2. Robinson JG, et al. Safety of Very Low Low-Density Lipoprotein Cholesterol Levels With Alirocumab: Pooled Data From Randomized Trials. J Am Coll Cardiol 2017; 6:471–482.

Addressing the predominant concerns with very low [LDL]

Inaccurate Measures of Calculated LDLc at low LDL-c levels and high triglycerides.

Calculated LDLc Underestimation of Actual LDLc Increases More as LDLc < 70; TG > 150



- At LDL-C levels < 100 mg/dL, calculating LDL-C by the Friedewald Equation results in a negative bias which becomes progressively more pronounced at lower LDL-C levels, with a percent difference as high as −27.6% at LDL-C levels ≤ 25 mg/dL, compared with LDL-C levels analyzed by the reference method (PUC)
- Further, as TG levels increase in patients within these low LDL-C ranges, the negative bias seen with calculated LDL-C increased to as high as 66%

As LDL-C decreased, underestimation of LDL-C by Friedewald increased

1. Baum SS, Blaha M, et al. Friedewald-Estimated Versus Directly Measured Low-Density Lipoprotein Cholesterol and Treatment Implications. J Am Coll Cardiol 2013; 62:732-739.

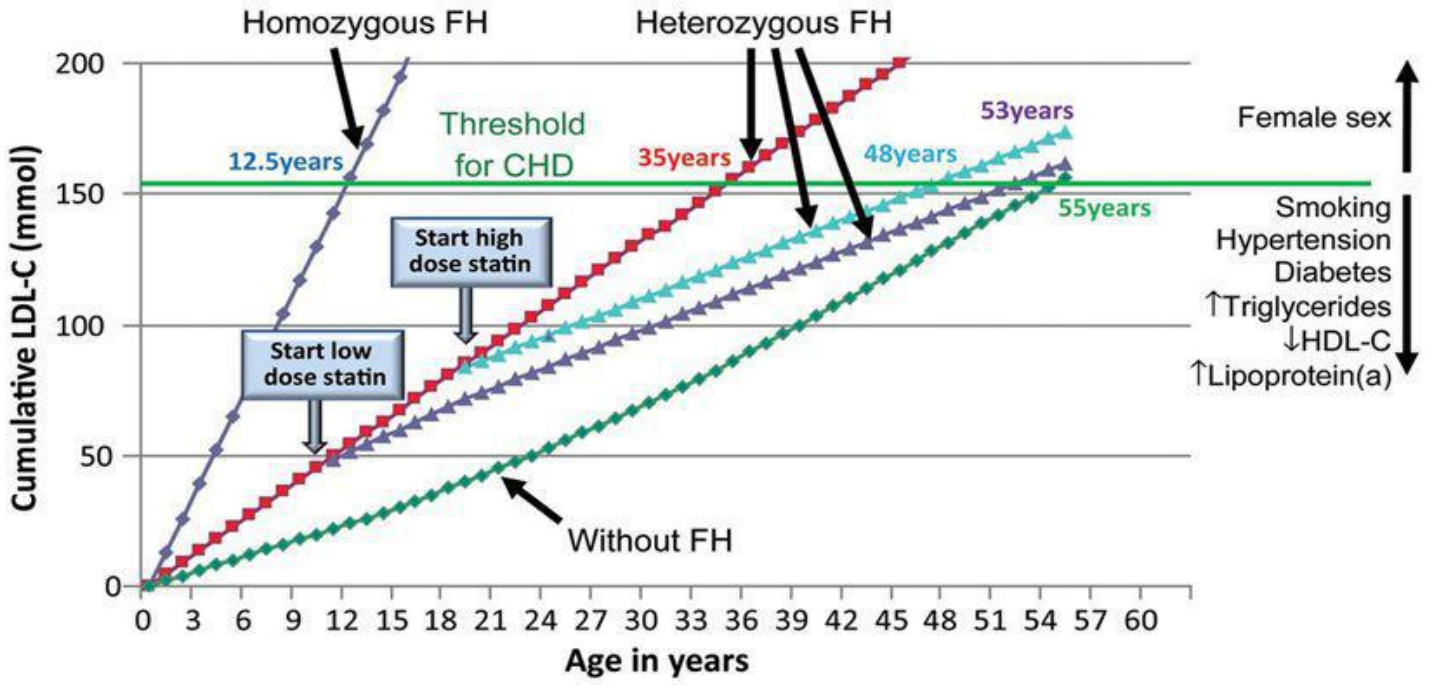
General Principles in Cholesterol Management

1. Early Identification of FH is Essential!
2. Higher-Risk Patients with Higher LDLc Benefit the Most
3. Risk Reduction Continues to Accrue Over Time

   i.e., Treatment Should be Sustained

Early Recognition of Familial Hypercholesterolemia is Essential!

LDL cholesterol burden in individuals with or without familial hypercholesterolaemia as a function of the age of initiation of statin therapy.

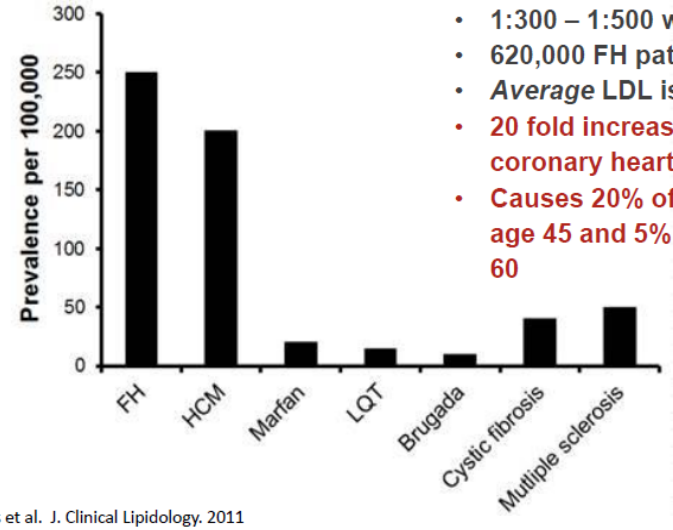


Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490

Hidden in Plain Sight

Arcus  Senilis

FH is more common than many well known genetic diseases



- 1:300 – 1:500 worldwide
- 620,000 FH patients in US
- *Average* LDL is 220 mg/dl
- 20 fold increased risk of coronary heart disease
- Causes 20% of MIs before age 45 and 5% before age 60

Hopkins et al. J. Clinical Lipidology. 2011
Goldberg et al. J. Clinical Lipidology. 2011

FH FOUNDATION
Raising Awareness. Saving Lives.

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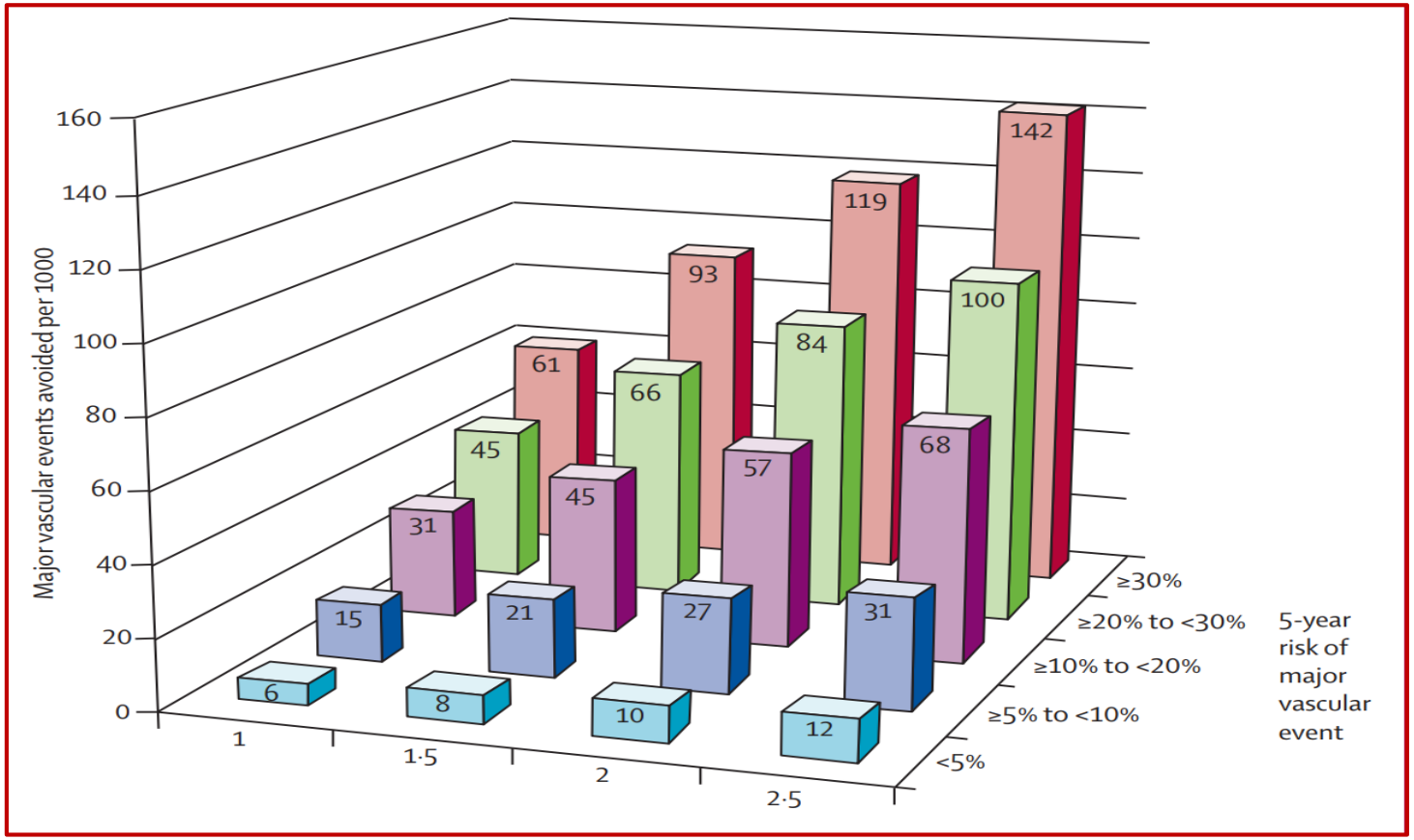
Higher-Risk Patients Benefit Most from Cholesterol Reduction



Risk & Benefit

- CTT Statin Meta-analyses
- Reduction in CVD risk is proportionally similar in patients at all levels of risk
- Greatest absolute number of events avoided in patients at highest risk
- Similar to Statins, the recent nonstatin therapies reduce ASCVD risk by extent of absolute LDL-C lowering (highest levels) & Achieved LDL-C Level

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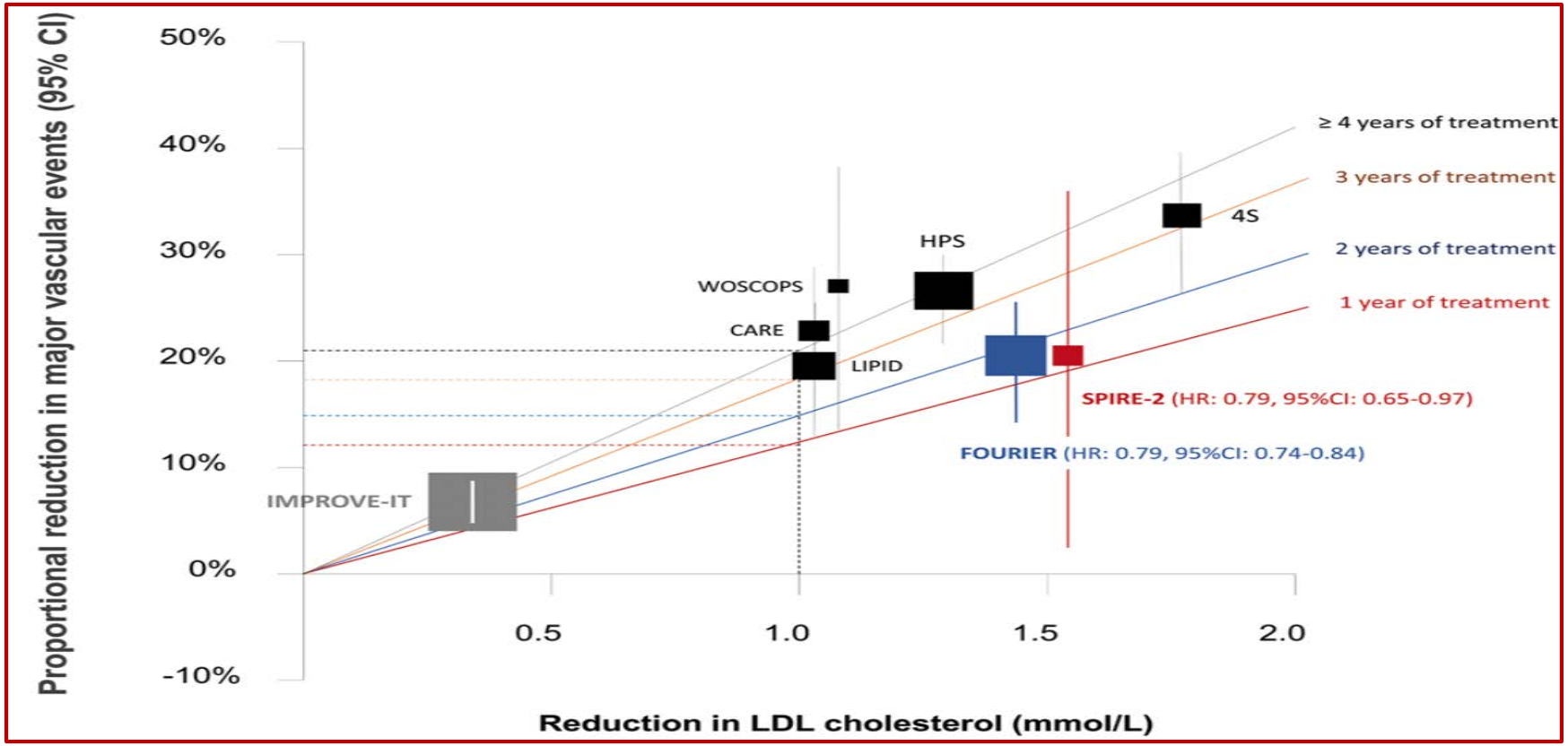
1. Cholesterol Treatment Trialists. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012. 380:581-590.

Duration of Therapy

LDL-Reduction Leads to Even Greater ASCVD Risk Reduction…**if Sustained.**



1. Ference BA, Cannon CP, et al. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration. Eur Heart Jour 2017.

Perspectives on Serum [LDL-C]

Past & Present

Key Opinion Leaders

And

The Bigger Picture

Lessons from the Past & Present

Treatment of LDL-Cholesterol – From 1984 to 2018

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 and ref. 119). Several lines of evidence suggest that plasma levels of LDL-cholesterol in the range of 25-60 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 AAAS

***Science* 1986; 232:34.**

LDL Cholesterol Treatment in the PCSK9 Era Getting Back on Target

Marc S. Sabatine and Robert P. Giugliano

- **LDL-C can now be reduced to unprecedented low levels with statin + PCSK9i (<< 40 mg/dL)**
- **Lowering LDL-C with evolocumab (while on statin) safely reduced CV events in a variety of high risk patients, mostly by reducing MI and ischemic stroke**
- **No excess in safety events, including new DM, even at very low achieved LDL-C <20 mg/dL at 2.2 years**

Based on the totality of the data, we would advocate targeting an LDL-C level of 20-25 mg/dL (0.5-0.6 mmol/L) or lower in secondary prevention in high-risk pts

Adapted from Editorial on FOURIER Trial

***JAMA Cardiol 2018*; 2:935-936.**

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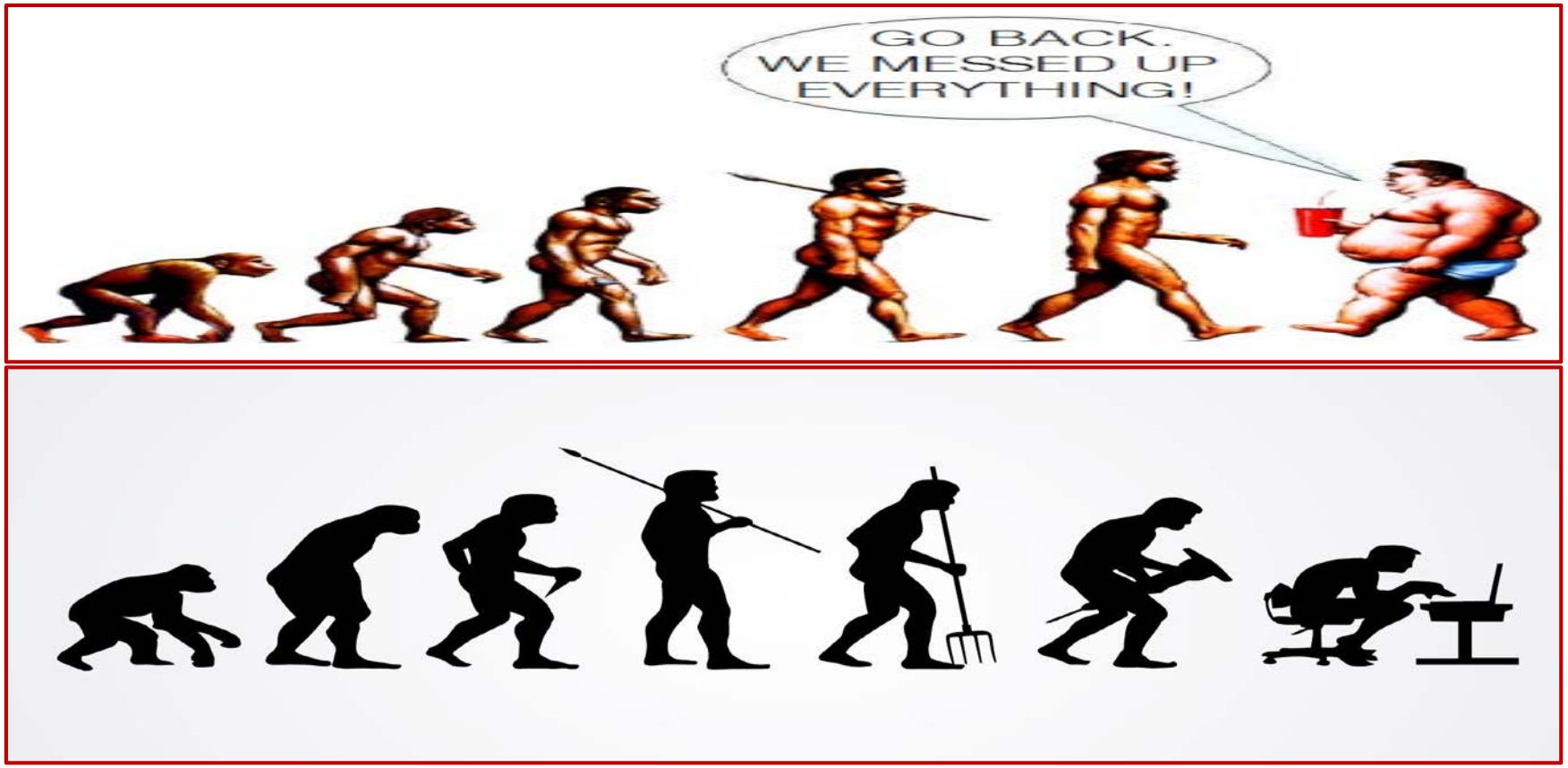
Cardiovascular Prevention

Keeping Sight of the Big Picture

Lifestyle Remains the Cornerstone of Therapy

We Are Evolving in the Wrong Direction



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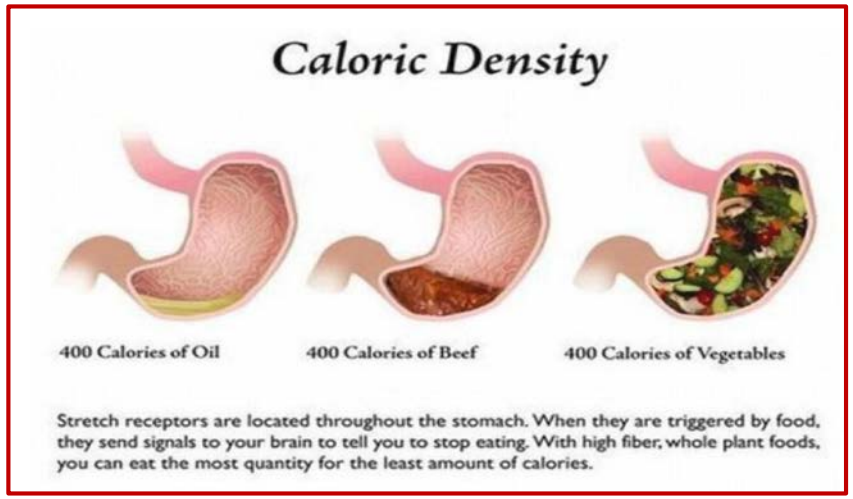
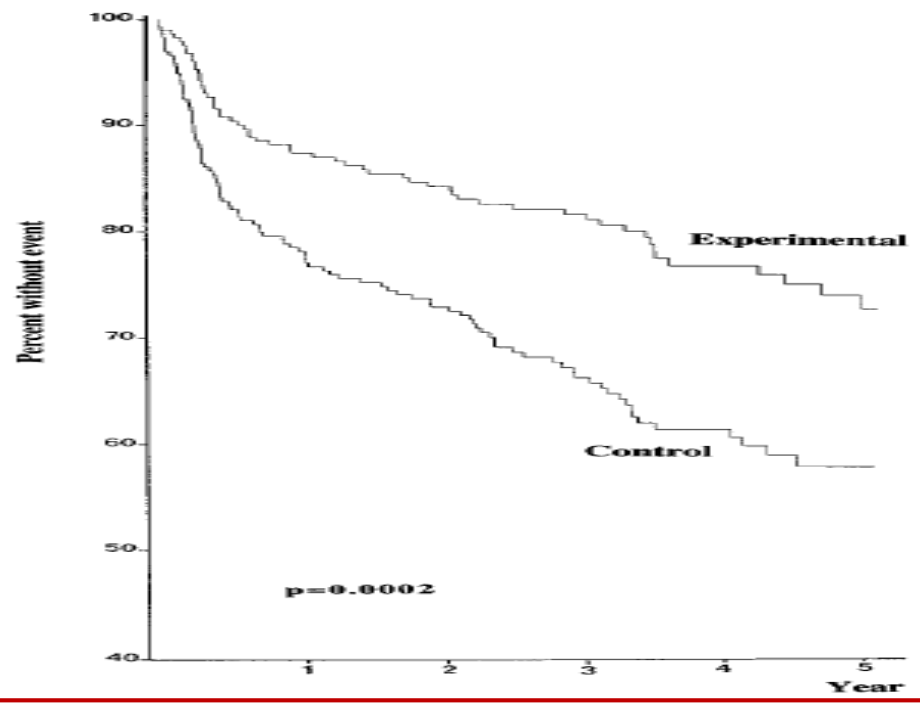
Lifestyle Remains the Cornerstone of Therapy

We Are Evolving in the Wrong Direction



LYON-HEART Study: Mediterranean Diet



MI Prior 6 Mos – Mediterranean vs Western

Reduction of Nonfatal MIs

Reduction in Overall Mortality

Subsequent studies decreased inflammation

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Lorgeril MD, Mamelle M, et al. Mediterranean Diet, Traditional Risk Factors, and the Rate of Cardiovascular Complications After Myocardial Infarction. *Circulation* 1999; 99:779-85.

Lifestyle Remains the Cornerstone of Therapy

We Are Evolving in the Wrong Direction

"Exercise can be viewed as a preventive medical treatment, like a 'pill' that should be taken on an almost daily basis."

Nanette Wenger, M.D., M.A.C.P., M.A.C.C.

2013 American Heart Association Scientific Statement

Potential Cardioprotective Effects of Regular Physical Activity

Anti-atherosclerotic	Psychologic	Anti-Thrombotic	Anti-Ischemic	Anti-Arrhythmic
Improved lipids	↓ Depression	↓ Platelet adhesiveness	↓ Myocardial O_2 demand	↑ Vagal tone
Lower BPs	↓ Stress	↑ Fibrinolysis	↑ Coronary flow	↓ Adrenergic activity
Reduced adiposity	↑ Social support	↓ Fibrinogen	↓ Endothelial dysfunction	↑ HR variability
↑ Insulin sensitivity		↓ Blood viscosity	↑ EPCs and CACs	
↓ Inflammation			↑ Nitric Oxide	

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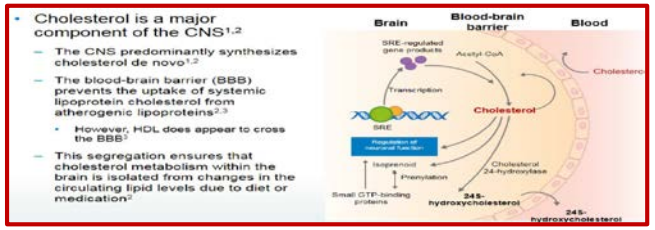
Balady GJ, Ades AP, Yancy CW, et al. Referral, Enrollment, and Delivery of Cardiac Rehabilitation/Secondary Prevention Programs at Clinical Centers and Beyond: A Presidential Advisory From the American Heart Association. *Circulation* 2013; 124:1951-60.

Wrap Up



- Recent trials demonstrate that reducing LDLc to very low levels are safe with ezetimibe and PCSK9 inhibitors (with 5 years of data).
- Cholesterol is mostly derived through de novo synthesis and HDL.
- LDL is an insignificant source of cholesterol for steroid synthesis.
- There may be no lower limit to LDL cholesterol.
- Identifying FH and high-risk patients EARLY is essential, as is long-term treatment.
- Cholesterol is one of many modifiable risk factors leading to accelerated atherosclerosis.
- Lifestyle remains the cornerstone of therapy to reduce atherosclerosis.

LIPID CENTER:

Dr. Mintz and Dr. Hirsh will be starting a lipid treatment program at North Shore.

In the meantime, feel free to reach out with questions.

Thank you!

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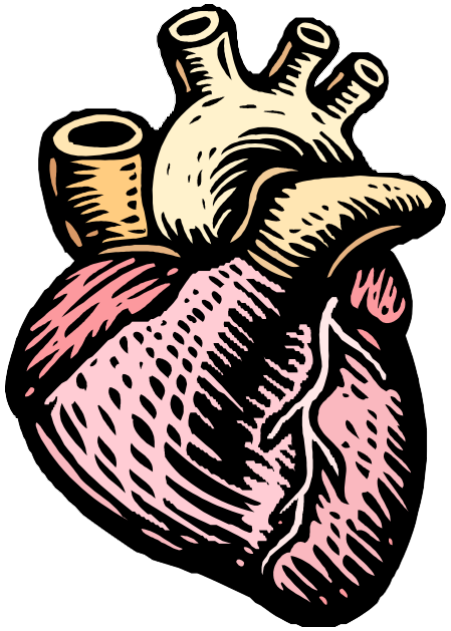
2018 Cholesterol Guidelines



Guy L. Mintz M.D., FACP, FACC, FNLA

Director of Cardiovascular Health & Lipidology

Sandra Atlas Bass Heart Hospital

North Shore University Hospital

Associate Professor of Medicine

Zucker School of Medicine

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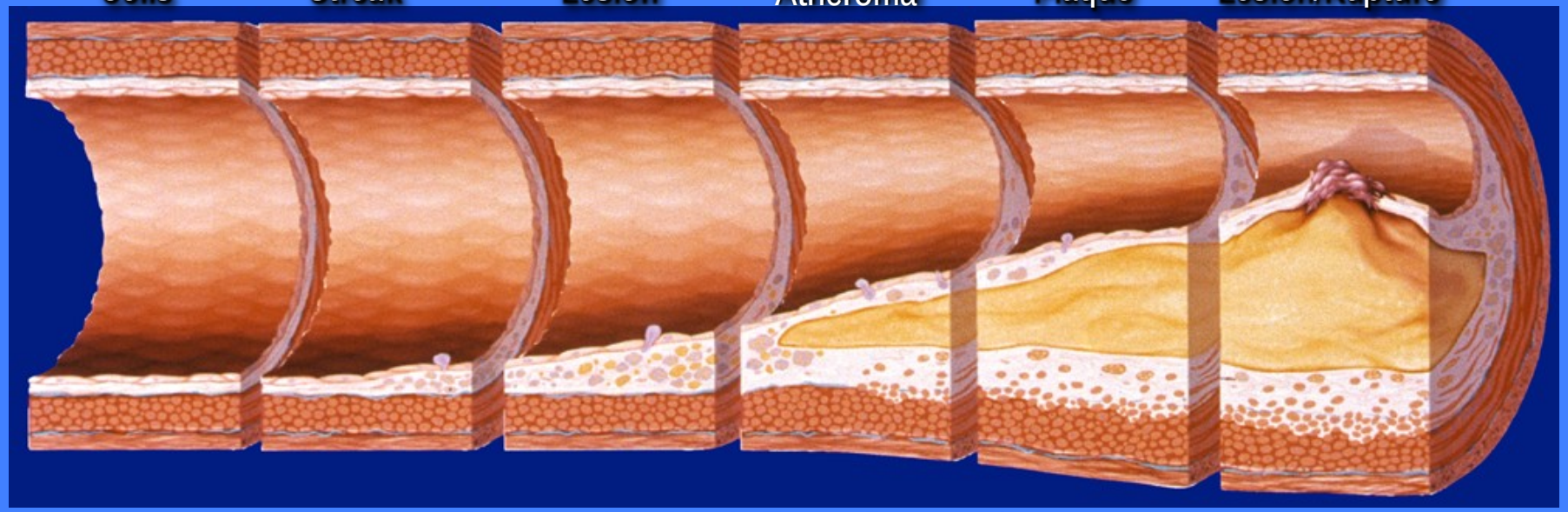
Atherosclerosis Timeline

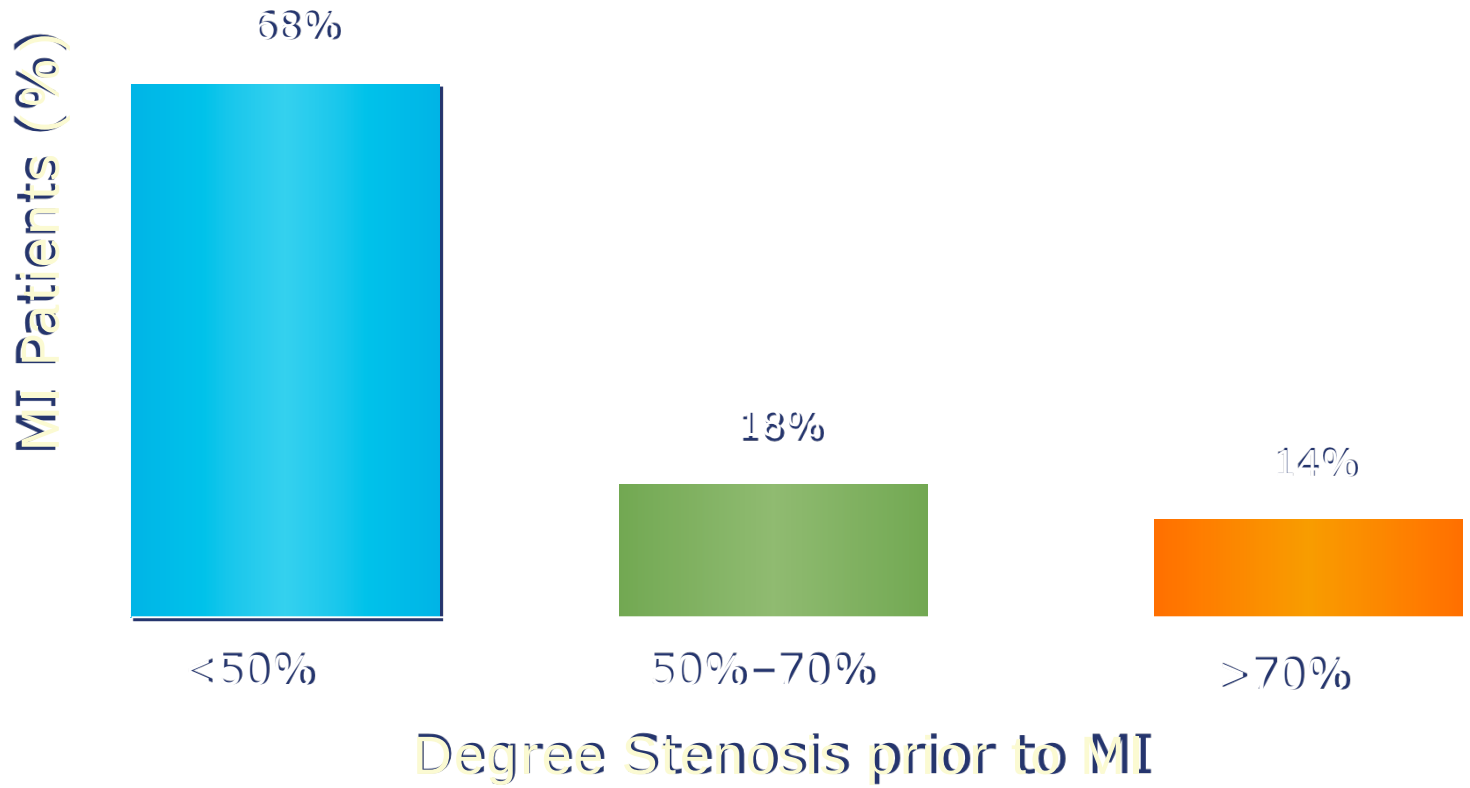


Endothelial Dysfunction →

From first decade	From third decade	From fourth decade
Growth mainly by lipid accumulation		Smooth muscle and collagen	Thrombosis, hematoma

Adapted from Stary HC et al. *Circulation*. 1995;92:1355-1374.

Myocardial Infarction
Stenosis Severity and Risk



Falk E, et al. *Circulation*. 1995;92:657-671.

Guidelines New Emphasis

1. More personalized care than 2013 guidelines

2. Detailed risk assessment

3. New lipid lowering options for patients with highest ASCVD risk

4. Utilize Risk Enhancing Factors

5. Class I Recommendation: Patient-Physician discussion
   - Benefits of therapy v. side effects
   - Potential drug-drug interaction
   - Review risk factors
   - Financial cost

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Emphasis on Heart Healthy Lifestyle

- Reduces development of risk factors
- Foundation for ASCVD risk reduction
- Primary intervention for Metabolic syndrome
- Assess lifetime risk in young adults (20-39 years of age)

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Life Style Discussion

- **In all individuals, emphasize a heart-healthy lifestyle across the life course.**

  A healthy lifestyle reduces atherosclero@c cardiovascular disease (ASCVD) risk at all ages.

- In younger individuals, healthy lifestyle can reduce development of risk factors and is the founda@on of ASCVD risk reduc@on.

  In young adults 20 to 39 years of age, an assessment of life@me risk facilitates the clinician–pa@ent risk discussion and emphasizes intensive lifestyle efforts.

- In all age groups, lifestyle therapy is the primary interven@on for metabolic syndrome.

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ATP-III Guidelines

LDL-C Goals, Levels for Lifestyle Changes, and Levels for Drug Therapy

Risk Category	LDL-C Goal (mg/dL)	LDL-C Level for Initiation of TLC (mg/dL)	LDL-C Level to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100–129: drug optional)
≥2 risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%–20%: ≥130 10-year risk <10%: ≥160
0–1 risk factor	<160	≥160	≥190 (160–189: LDL-C–lowering drug optional)

TLC, therapeutic lifestyle changes.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA.* 2001; 285:2486-2497.

Four Statin Benefit Groups

1.Primary Prevention Over Lifespan

2. Diabetes Mellitus In Adults
   -Age 40 - 75 years of Age
   -LDL- C of 70mg/dl-189 mg/dl
   - Risk Enhancers independent of other risk factors

3. Severe Hypercholesterolemia: LDL> 190 mg/dl

4.Secondary Atherosclerotic Heart Disease Prevention

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Primary Prevention for ASCVD

- 40-75 years of age
- Lifestyle modification to reduce risk factors
- Review Risk Factors: LDL-C, HBA1C, Smoking cessation, Weight loss, Hypertension
- Calculate 10 years ASCVD risk
  - AHA/ACC Pooled Cohort Risk Calculator
  - Reynolds Risk Score
  - Framingham Risk Score

Shared decision making with patient including statin side effects & cost

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ASCVD Risk Calculators

- AHA/ACC Pooled Cohort
- Reynolds Risk Score (includes hs-CRP & family history)
- Framingham Risk Score
- MESA (Multi Ethnic Study of Atherosclerosis)

10 year ASCVD Risk with Coronary Calcium calculated

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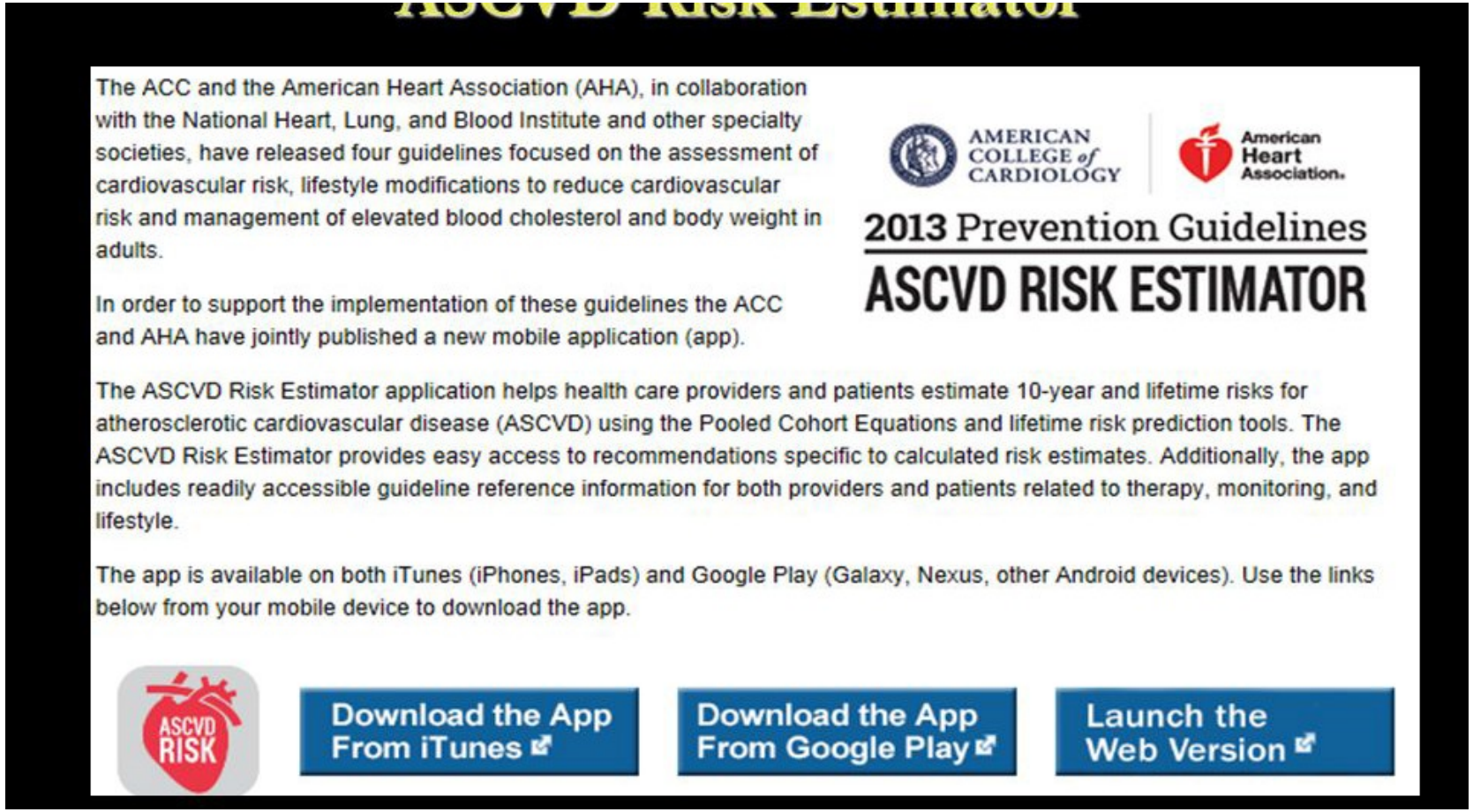
CARDIOVASCULAR RISK CALCULATORS

AHA/ ACC Pooled Cohort: 10 year ASCVD Risk (NFMI, CHD DEATH OR CVA)	Framingham Calculator: 10 year MI Risk	Reynolds Risk Score: 10 year Risk: MI, CVA, other Heart Disease
Age	Age	Age
Gender	Gender	Gender
RACE (B/W/OTHER) Under es@mate:--Am Indians, South Asia, Hispanics--PR Over es@mate: East Asia, Mexican Americans		HIGH SENSITIVITY CRP (HS--CRP)
TOTAL CHOLESTEROL	TOTAL CHOLESTEROL	TOTAL CHOLESTEROL
HDL--C	HDL--C	HDL--C
SYSTOLIC BP	SYSTOLIC BP	SYSTOLIC BP
HTN TREATMENT: Y/N	HTN TREATMENT: Y/N	MOTHER OR FATHER MI < 60 YRS
DIABETES: Y/N		
SMOKER: Y/N	SMOKER: Y/N	

AHA-ACC ASCVD Risk Calculator



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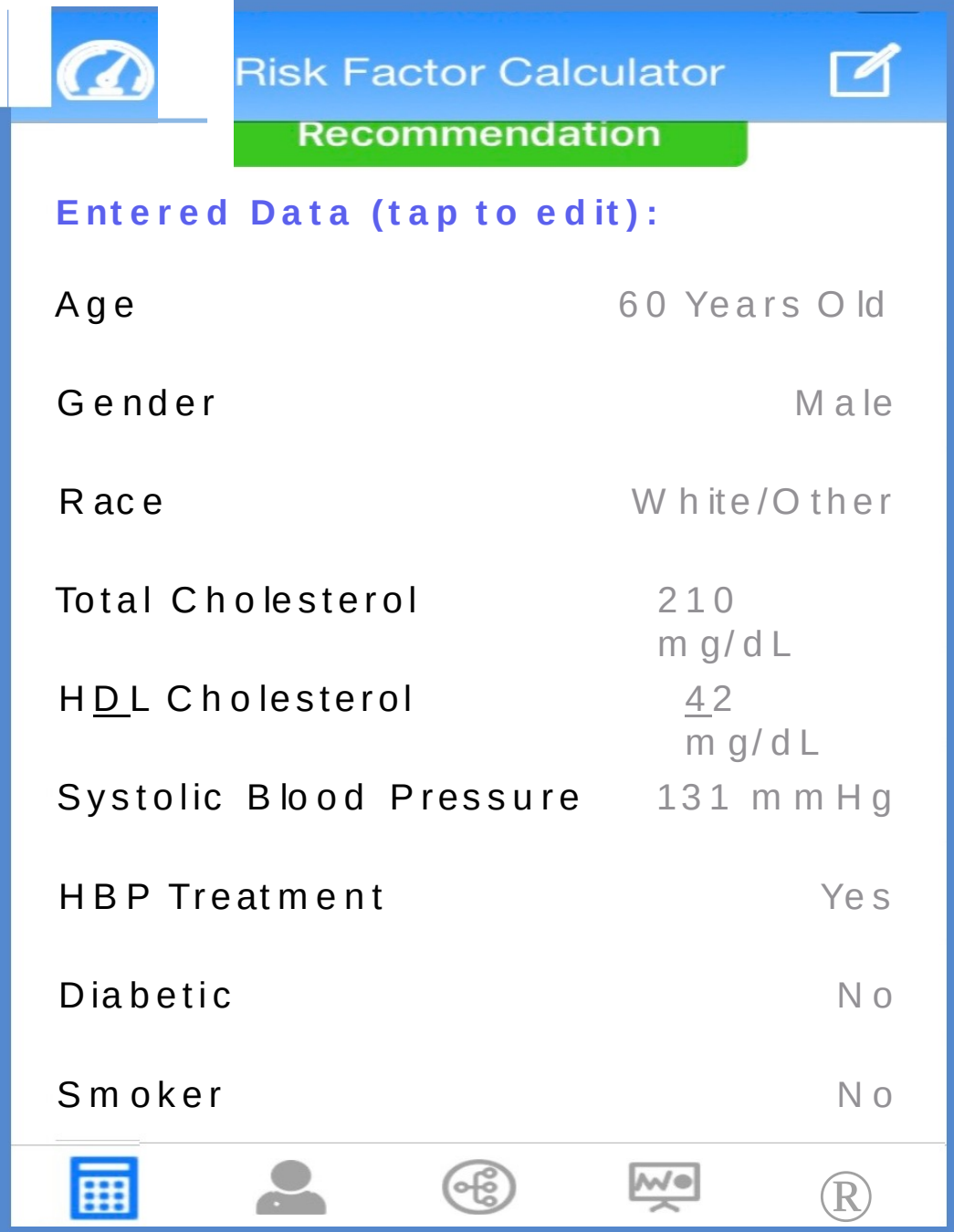
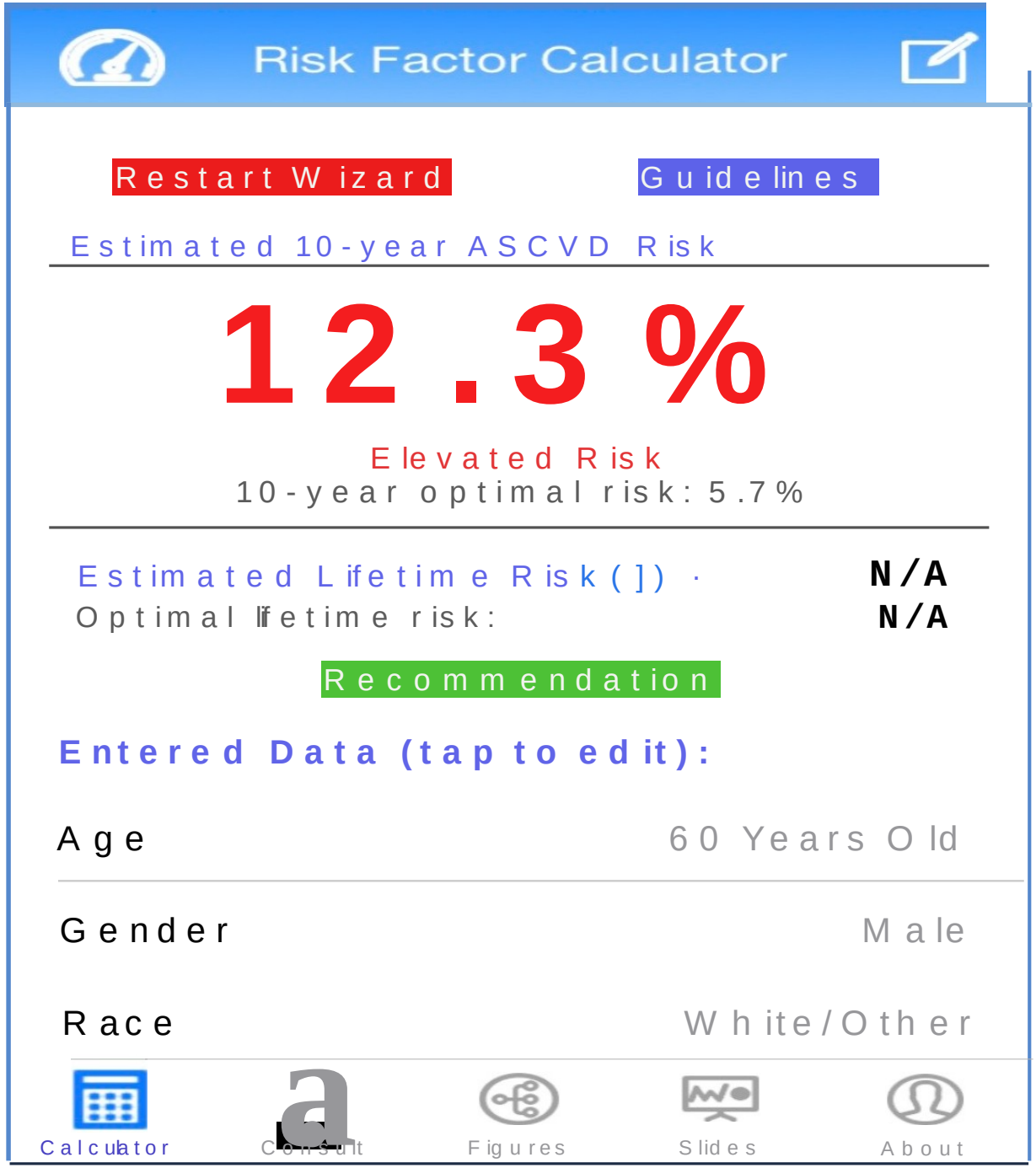

Risk Factor Calculator
Recommendation
Entered Data (tap to edit):
Age 60 Years Old
Gender Male
Race White/Other
Total Cholesterol 210 mg/dL
HDL Cholesterol 42 mg/dL
Systolic Blood Pressure 131 mmHg
HBP Treatment Yes
Diabetic No
Smoker No



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ASCVD PLUS CALCULATOR	INFORMATION OFFERED
AGE	CURRENT 10 YEAR RISK OF ASCVD
GENDER	OPTIMAL ASCVD RISK
RACE (B/W/ OTHER)	VIEW ADVICE: LIFESTYLE CHANGE, LDL--C THERAPY INTENSITY, (70--189 MG/DL), REVIEW RISK ENHANCERS
SYSTOLIC BLOOD PRESSURE	
DIASTOLIC BLOOD PRESSURE	
TOTAL CHOLESTEROL	
HDL CHOLESTEROL	
LDL CHOLESTEROL	
DIABETES Y/N	
SMOKER Y/N	
HYPERTENSION THERAPY Y/N	
STATIN Y/N	
ASPIRIN Y/N	
REFINE RISK USING PREVIOUS DATA	

Utilization of Ten Year ASCVD Risk Score

Characteristics:

- 40-75 years of age
- Non Diabetic & LDL-C ≥ 70 mg/dl

Low Risk: < 5 %

- Therapeutic lifestyle Change

Borderline Risk: 5 - < 7.5 %

- Risk discussion for statin benefit; risk enhancers

Intermediate: Moderate Risk: > 7.5 % & < 20 %

- Evaluate Risk enhancers & Coronary artery calcification if uncertain
- Moderate intensity statin, LDL-C reduction 30-50%

High Risk: > 20 %

- 10 year ASCVD Risk ≥ 20%
- High Intensity statin , Reduce LDL-C by 50%

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Primary Prevention: Assessment

- Age 40-75 years of age
- No Diabetes
- LDL-C > 70mg/dl
- 10 year ASCVD risk of > 7.5 %

- Start moderate or high intensity statin therapy

- Presence of Risk Enhancing Factors Favor Statin Therapy

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Ten Year ASCVD Risk: >7.5-19.9%

- 40-75 years of age; non-diabetic
- LDL-C ≥ 70 mg/dl – 189 mg/dl
- Intermediate Risk

Coronary Calcium Score: if risk uncertain

- CAC of zero: statins withheld or delayed unless diabetic, smoker, or strong family history of premature ASCVD
- CAC score: 1-99 : statin therapy especially ≥ 55 years old
- CAC score ≥ 100 or ≥ 75th percentile: statin therapy

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Risk-Enhancing Factors for Clinician–Patient Risk Discussion

Risk-Enhancing Factors

- Family history of premature ASCVD (males, age <55 y; females, age <65 y)
- Primary hypercholesterolemia (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*
- Metabolic syndrome (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)
- Chronic kidney disease (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
- Chronic inflammatory conditions such as psoriasis, RA, or HIV/AIDS
- History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia
- High-risk race/ethnicities (e.g., South Asian ancestry)

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Risk Enhancing Factors: Biomarkers & Clinical Assessme

Risk-Enhancing Factors
• **Lipid/biomarkers**: Associated with increased ASCVD risk o Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL); o If measured: ▬ **Elevated high–sensiSvity C-reacSve protein** (≥2.0 mg/L) ▬ **Elevated Lp(a):** A rela@ve indica@on for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L cons@tutes a risk-enhancing factor especially at higher levels of Lp(a). ▬ **Elevated apoB** ≥130 mg/dL: A rela@ve indica@on for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and cons@tutes a risk-enhancing factor ▬ **ABI** <0.9

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Selected Examples of Candidates for CAC Measurement Who Might Benefit From Knowing Their CAC Score Is Zero

CAC Measurement Candidates Who Might Benefit from Knowing Their CAC Score Is Zero
• Pa@ents reluctant to ini@ate sta@n therapy who wish to understand their risk and poten@al for benefit more precisely • Pa@ents concerned about need to reins@tute sta@n therapy amer discon@nua@on for sta@n-associated symptoms • Older pa@ents (men, 55-80 y of age; women, 60-80 y of age) with low burden of risk factors who ques@on whether they would benefit from sta@n therapy • Middle-aged adults (40-55 y of age) with PCE-calculated 10-year risk of ASCVD 5% to <7.5% with factors that increase their ASCVD risk, although they are in a borderline risk group

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Coronary Calcium Score

1. Add to risk assessment in asymptomatic patients at intermediate risk, 10-20 % if decision regarding statins is uncertain
2. Score of zero reasonable to withhold statin therapy & reassess in 5-10 years
3. Score: 1-99 Agaston units may support statin use age > 55years
4. Score: > 100 Agaston units or 75th percentile by age & gender- start statin therapy
5. Result: > 300 Agaston units-High risk scan which requires high intensity statin therapy
6. Low dose radiation with newer scanners about 1 mSv, (Chest Cat Scan 7 mSv, mammogram 0.4 mSv; CXR- 0.1 mSv, people in U.S. exposed to average of 3mSv from natural surroundings)

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Coronary Artery Calcification

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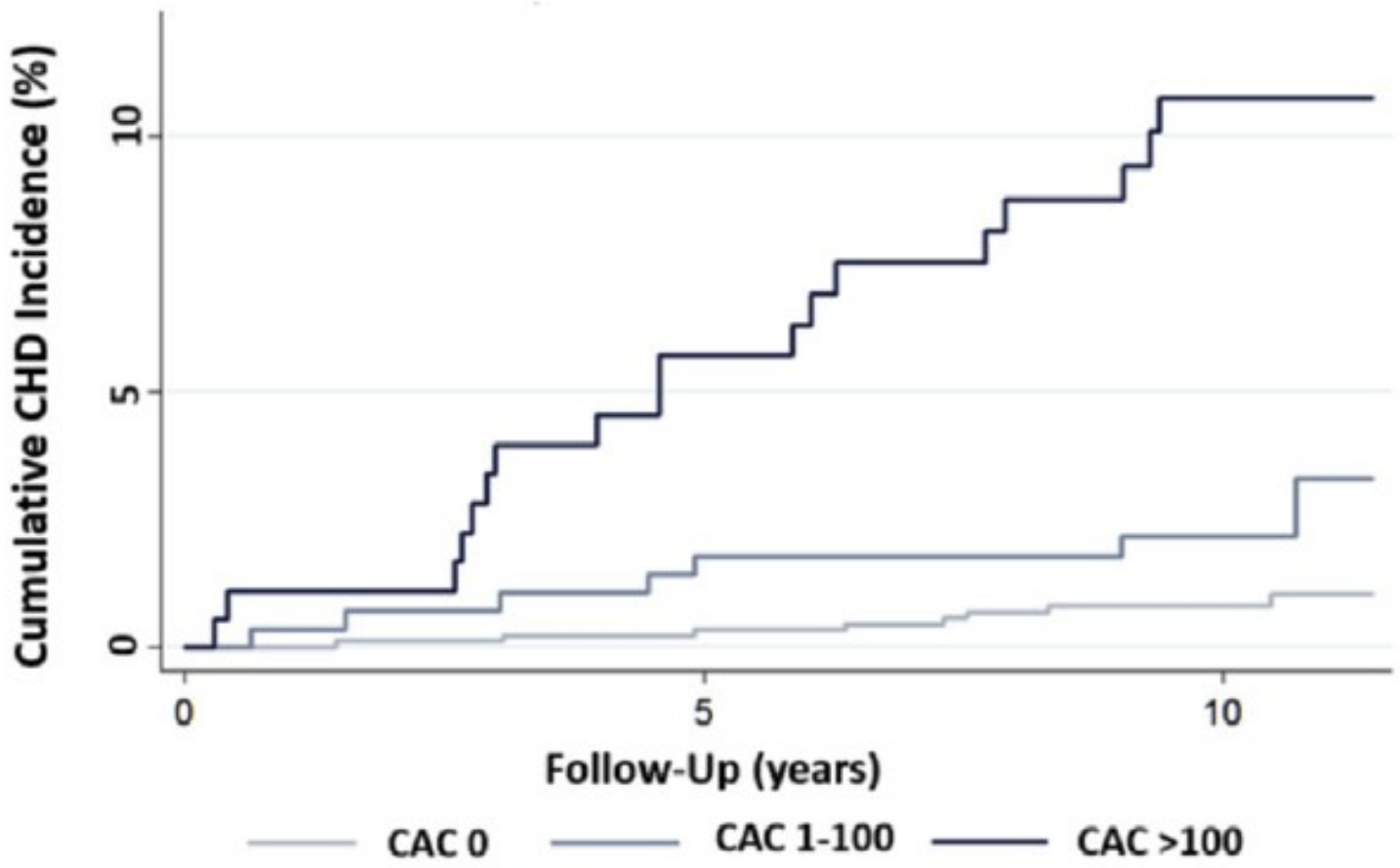
Coronary Calcium Score Risk

Coronary Calcium Score	10 Year Risk of NFMI or CHD Death	Risk StraSficaSon
0	Less than 1 %	Lower
1--99	4 %	Lower to Moderate
100 --399	13 %	Moderate
400 & Greater	24 %	High

MESA: Cumulative CHD Incidence Across Coronary Artery Calcium Categories



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Joshi PH , et al. Atherosclerosis. 2016;246:367-373

Checklist for Clinician–Patient Shared Decision-Making for Initiating Therapy

Checklist Item	RecommendaSon
ASCVD risk assessment	• Assign to sta@n treatment group; use ASCVD Risk Es@mator Plus.* o In lower--risk primary--preven@on adults 40--75 y of age with LDL--C ≥70 mg/dL (≥1.8 mmol/L). o Not needed in secondary preven@on, in those with LDL--C ≥190 mg/dL (≥4.9 mmol/L), or in those 40--75 y of age with diabetes mellitus. • Assess other pa@ent characteris@cs that influence risk. See Risk--Enhancing Factors (Sec@on 4.4.1.3. and Table 6) • Assess CAC (Sec@on 4.4.1.4.) if risk decision is uncertain and addi@onal informa@on is needed to clarify ASCVD risk. o Use decision tools to explain risk (e.g., ASCVD Risk Es@mator Plus,* Mayo Clinic Sta@n Choice Decision Aid).
Lifestyle modifica@on s	• Review lifestyle habits (e.g., diet, physical ac@vity, weight or body mass index, and tobacco use). • Endorse a healthy lifestyle and provide relevant advice, materials, or referrals. (e.g., CardioSmart, AHA Life's Simple 7, NLA Pa@ent Tear Sheets, PCNA Clinicians' Lifestyle Modifica@on Toolbox, cardiac rehabilita@on, die@@an, smoking cessa@on program).

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AHA SIMPLE 7

1. Manage Blood Pressure
2. Control Cholesterol
3. Reduce Blood Sugar
4. Get Active
5. Eat Better
6. Lose Weight
7. Stop Smoking

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Checklist for Clinician–Patient Shared Decision-Making for Initiating Therapy

Checklist Item	RecommendaSon
Poten@al net clinical benefit of pharmacotherapy	• Recommend sta@ns as first--line therapy. • Consider the combina@on of sta@n and nonsta@n therapy in selected pa@ents. • Discuss poten@al risk reduc@on from lipid---lowering therapy. • Discuss the poten@al for adverse effects or drug– drug interac@ons.

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Checklist for Clinician–Patient Shared Decision-Making for Initiating Therapy

Checklist Item	RecommendaSon
Cost considera@on s	• Discuss poten@al out--of--pocket cost of therapy to the pa@ent (e.g., insurance plan coverage, @er level, copayment).
Shared decision-- making	• Encourage the pa@ent to verbalize what was heard (e.g., pa@ent's personal ASCVD risk, available op@ons, and risks/benefits). • Invite the pa@ent to ask ques@ons, express values and preferences, and state ability to adhere to lifestyle changes and medica@ons. • Refer pa@ents to trustworthy materials to aid in their understanding of issues regarding risk decisions. • Collaborate with the pa@ent to determine therapy and follow--up plan.

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Primary Prevention in Other Age Groups (Older Adults)

RecommendaSons for Older Adults		
COR	LOE	RecommendaSons
IIb	B--R	In adults 75 years of age or older with an LDL--C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), iniSaSng a moderate---intensity staSn may be reasonable.
IIb	B--R	In adults 75 years of age or older, it may be reasonable to stop staSn therapy when funcSonal decline (physical or cogniSve), mulSmorbidity, frailty, or reduced life--expectancy limits the potenSal benefits of staSn therapy.
IIb	B--R	In adults 76 to 80 years of age with an LDL--C level of 70 to 189 mg/dL__(1.7 to 4.8 mmol/L), it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid staSn therapy.

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Primary Prevention in Other Age Groups (Older Adults)

RecommendaSons for Older Adults		
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IIb	B--R	In adults 75 years of age or older with an LDL--C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), iniSaSng a moderate---intensity staSn may be reasonable.
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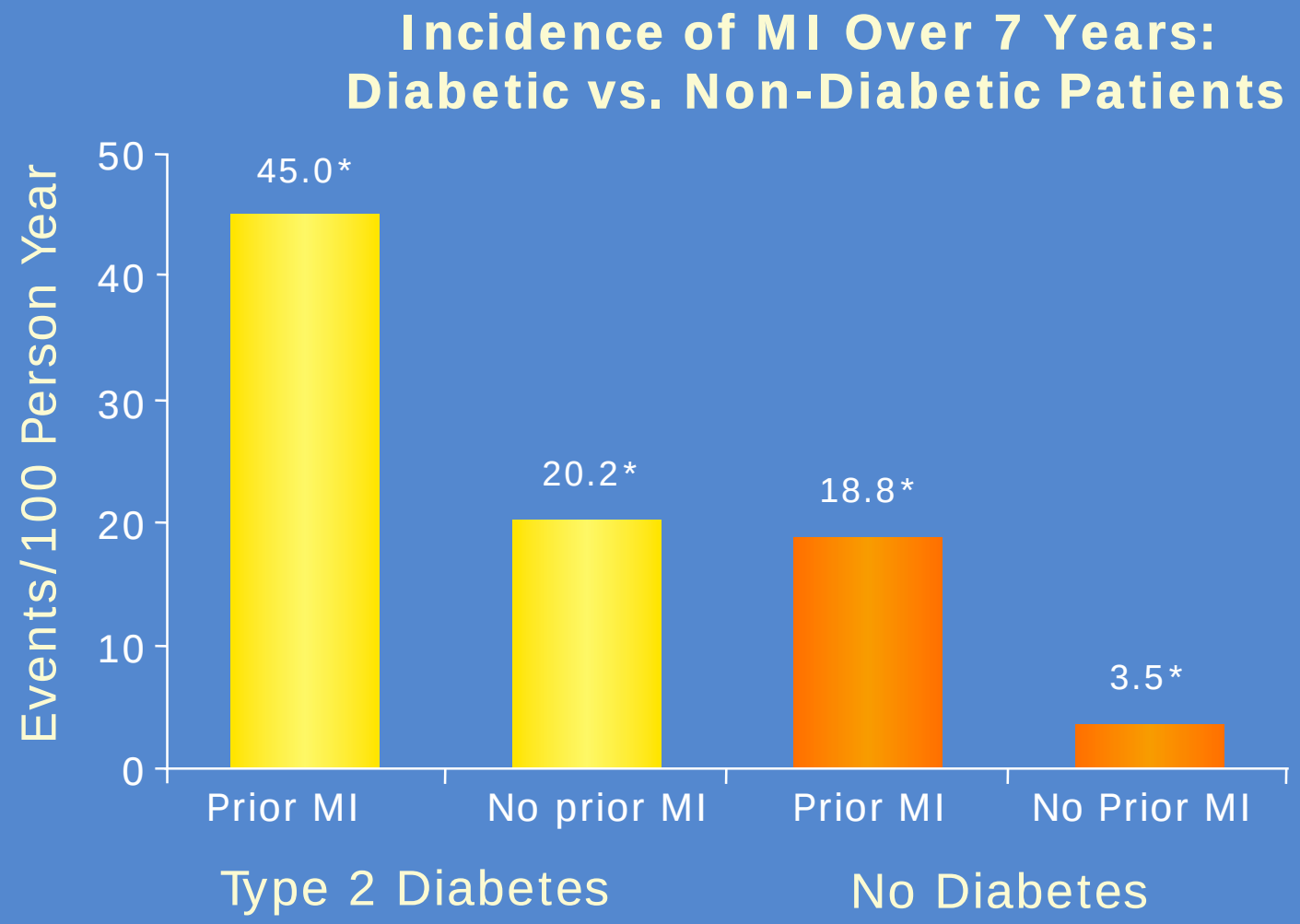
Diabetes Is a Significant Risk Factor for MI



*P<0.001

Haffner SM, et al. *N Engl J Med.* 1998;339:229-234.

Diabetic Patients

- 40-75 years of age
- LDL ≥ 70 mg/dl
- Begin moderate intensity statin therapy without calculating 10 year risk

HIGHER RISK:

- Multiple ASCVD risk factors
- 50-75 years of age
- **High Intensity Statin** therapy to **reduce LDL ≥ 50%**

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Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes

- Long duration (≥10 years for type 2 diabetes or ≥ 20 years for type 1 diabetes)
- Albuminuria ≥30 mcg albumin/mg creatinine
- eGFR <60 ml/min/1.73 m^2
- Retinopathy
- Neuropathy
- ABI <0.9

Endocrine Society: ASCVD–DiabeJc Risk Categories

- Low risk:
  - No risk factors
- Moderate risk:
  - 2 or fewer risk factors and a calculated 10–year risk of less than 10%
- High risk:
  - An ASCVD equivalent including diabetes or stage 3 or 4 CKD with no other risk factors, or individuals with 2 or more risk factors and a 10-year risk of 10%-20%
- Very high risk:
  - Established or recent hospitaliza Jon for ACS; coronary, caroJ d or peripheral vascular disease; diabetes or stage 3 or 4 CKD with 1 or more risk factors; a calculated 10-year risk greater than 20%; or HeFH
- Extreme risk:
- Progressive ASCVD, including unstable angina that persists a [er achieving an LDL–C less than 70 mg/dL, or established clinical ASCVD with diabetes, **stage 3 or 4** CKD, and/or HeFH, or in those with a history of premature ASCVD (<55 years of age for males or <65 years of age for females)
- This category was added in this CPG based on clinical trial evidence and supported by meta-analyses that further lowering of LDL-C produces bec er outcomes in individuals with ACS. IMPROVE-IT demonstrated lower rates of cardiovascular events in those with ACS when LDL-C levels were lowered to 53 mg/dL combining ezeJ mibe with staJ ns.

AbbreviaJ ons: ACS, acute coronary syndrome; ASCVD, atheroscleroJ c cardiovascular disease; CKD, chronic kidney disease; CPG, clinical pracJ ce guideline; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; IMPROVE-IT, Improved Reduc@on of Outcomes: Vytorin Efficacy Interna@onal Trial.

AACE/ACE CPG. 2017;epub ahead of print; Cannon, CP, et al. *N Engl J Med.* 2015;372(25):2387--239; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Prac*ce.* 2017;23(4):479–97.

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Endocrine: ASCVD Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors/10--year risk	Treatment goals		
		LDL--C (mg/dL)	Non--HDL--C (mg/dL)	Apo B (mg/dL)
Extreme risk	–Progressive ASCVD including unstable angina in individuals a[er achieving an LDL--C <70 mg/dL –Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	–Established or recent hospitalizaJon for ACS, coronary, caroJd or peripheral vascular disease, 10--year risk >20% – DM or stage 3 or 4 CKD with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10--year risk 10%--20% – DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10--year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.

Barter PJ, et al. *J Intern Med*. 2006;259:247–258; Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485–494; Brunzell JD, et al. *Diabetes Care*. 2008;31:811–822; Cannon CP, et al. *N Engl J Med.* 2015;372(25):2387–2397; Grundy SM, et al. *Circula; on.* 2004;110:227–239; Heart ProtecJon Study CollaboraJ ve Group. *Lancet*. 2002;360:7–22; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Prac*ce*. 2017;23(4):479–497; Lloyd-Jones DM, et al. *Am J Cardiol*. 2004;94:20–24; McClelland RL, et al. *J Am Coll Cardiol*. 2015;66(15):1643–1653; NHLBI. NIH PublicaJon No. 02–5215. 2002; Ridker PM, *J Am Coll Cardiol*. 2005;45:1644–1648; Ridker PM, et al. *JAMA*. 2007;297(6):611–619; Sever PS, et al. *Lancet*. 2003;361:1149–1158; Shepherd J, et al. *Lancet*. 2002;360:1623-1630; Smith SC Jr, et al. *Circula; on*. 2006;113:2363–2372; Stevens RJ, et al. *Clin Sci*. 2001;101(6):671–679; Stone NJ. *Am J Med*. 1996;101:4A40S–48S; Weiner DE, et al. *J Am Soc Nephrol.* 2004;15(5):1307–1315.

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Familial Heterozygous Hypercholesterolemia

- LDL ≥ 190 mg/dl
- Initiate high intensity therapy statin therapy without calculating 10 year ASCVD Risk
- LDL remains ≥ 100 mg/dl - adding ezetimibe is reasonable
- If LDL remains ≥ 100 mg/dl on high intensity statin and ezetimibe therapy consider PCSK9 therapy if multiple risk factors for ASCVD exist

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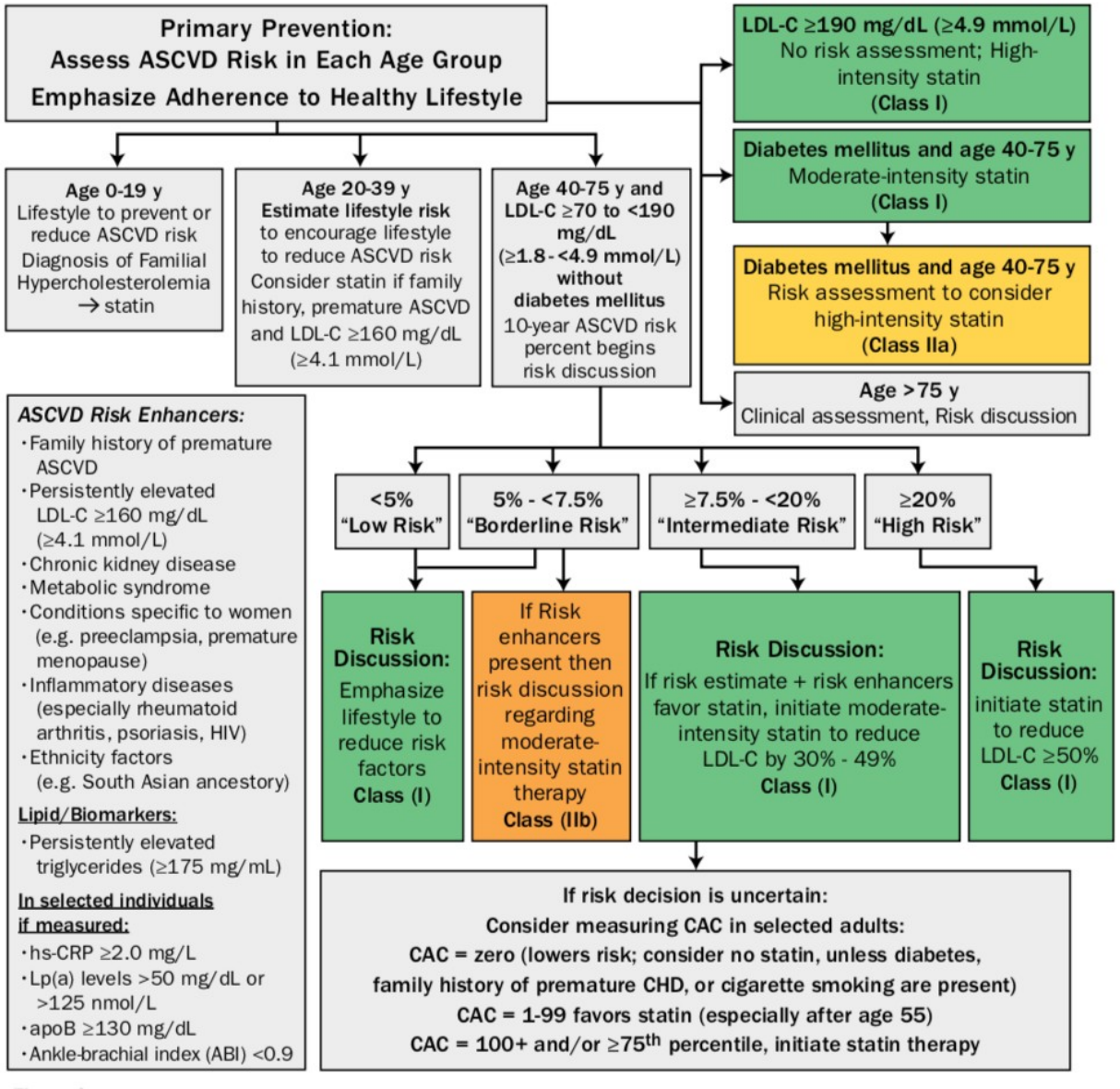
RecommendaJ ons for Primary Severe Hypercholesterolemia [LDL-C ≥190 mg/dL (≥4.9 mmol/L)]

COR	LOE	Recommendations
I	B-R	1. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended.
IIa	B-R	2. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher who achieve less than 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, ezetimibe therapy is reasonable.
IIb	B-R	3. In patients 20 to 75 years of age with a baseline LDL-C ≥190 mg/dL (≥4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≥300 mg/dL (≥3.4 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered.
IIb	B-R	4. In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.
IIb	C-LD	5. In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL (≥5.7 mmol/L) or higher who achieve an on-treatment LDL-C level of 130 mg/dL (≥3.4 mmol/L) or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.
Value Statement: Uncertain Value (B-NR)		6. Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 US list prices.

Nortl
Healt

Primary Prevention



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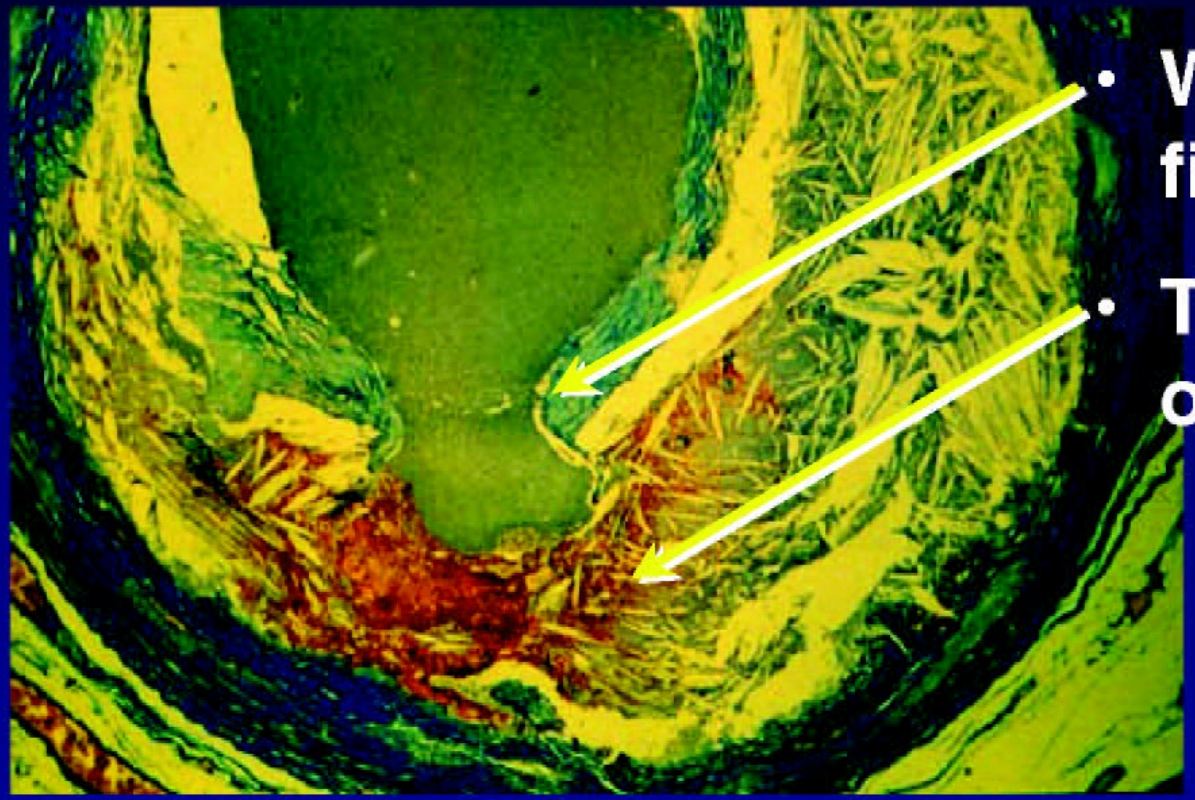
Thrombosis of a disrupted atheroma, the cause of most acute coronary syndromes, results from:



- Weakening of the fibrous cap
- Thrombogenicity of the lipid core

Secondary Prevention: Major ASCVD Events

- Recent acute coronary syndrome (≤ 12 months)
- Myocardial Infarction (≥ 12 months)
- Ischemic stroke history
- Symptomatic peripheral arterial disease
  - Claudication: ABI ≤ 0.85
  - Previous Revascularization or amputation

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High-Risk for Future ASCVD Events

Major ASCVD Events
Recent acute coronary syndrome (within the past 12 months)
History of myocardial infarction (other than recent acute coronary syndrome event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
Diabetes Mellitus
Hypertension
Chronic kidney disease (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 heart failure

*Very High Risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.

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Secondary Prevention: Very High Risk ASCVD

- Mul@ple major ASCVD events **OR**

- One major ASCVD event and mul@ple high risk condi@ons:
  - Age: ≥ 65 years old
  - Diabetes
  - Hypertension
  - CKD (GFR: 15-59 cc/min +/- albuminuria)
  - Smokers
  - Persistently elevated LDL-C ≥ 100 mg/dl
  - Prior CABG or PCI, CHF
  - Heterozygous FH

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Secondary Prevention for ASCVD

- High intensity statin therapy
- Maximally tolerated statin therapy
- Decrease coronary artery disease risk
- GOAL: reduce LDL by ≥ 50%

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Treatment of Very High Risk ASCVD Patients

- **Reasonable to add Ezetimibe to maximally tolerated statin therapy if LDL ≥ 70 mg/dl or non-HDL-C ≥ 100 mg/dl**

- **Reasonable to add PCSK-9 therapy if LDL ≥ 70 mg/dl on maximally tolerated statin and Ezetimibe therapy**

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RecommendaSons for StaSn Therapy Use in PaSents With ASCVD		
COR	LOE	RecommendaSons
IIa	B--R	In paSents older than 75 years of age with clinical ASCVD, it is reasonable to iniSate moderate-- or high--intensity staSn therapy acer evaluaSon of the potenSal for ASCVD risk reducSon, adverse effects, and drug–drug interacSons, as well as paSent frailty and paSent preferences.
IIa	C--LD	In paSents older than 75 years of age who are toleraSng high--intensity staSn therapy, it is reasonable to conSnue high--intensity staSn therapy acer evaluaSon of the potenSal for ASCVD risk reducSon, adverse effects, and drug--drug interacSons, as well as paSent frailty and paSent preferences.

RecommendaSons for StaSn Therapy Use in PaSents With ASCVD		
COR	LOE	RecommendaSons
IIb	B--R	In paSents with clinical ASCVD who are receiving maximally tolerated staSn therapy and whose LDL--C level remains 70 mg/dL (≥1.8 mmol/L) or higher, it may be reasonable to add ezeSmibe.
IIb	B--R	In paSents with heart failure (HF) with reduced ejecSon fracSon ahributable to ischemic heart disease who have a reasonable life expectancy (3 to 5 years) and are not already on a staSn because of ASCVD, clinicians may consider iniSaSon of moderate--intensity staSn therapy to reduce the occurrence of ASCVD events.

Secondary Prevention Treatment

- Patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

- The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

- Use a maximally tolerated statin to lower LDL-C levels by ≥50%.

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Intensity of Statin Therapy

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

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Intensity of Statin Therapy

	High-Intensity	Moderate-Intensity	Low-Intensity
LDL-C Lowering†	≥50%	30% to 49%	<30%
Primary Statins	Atorvastatin (40 mg‡) 80 mg Rosuvastatin 20 (40 mg)	Atorvastatin 10 mg (20 mg) Rosuvastatin *(5 mg)* 10 mg Simvastatin 20–40 mg§	*Simvastatin 10 mg*
Other Statins	–	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*

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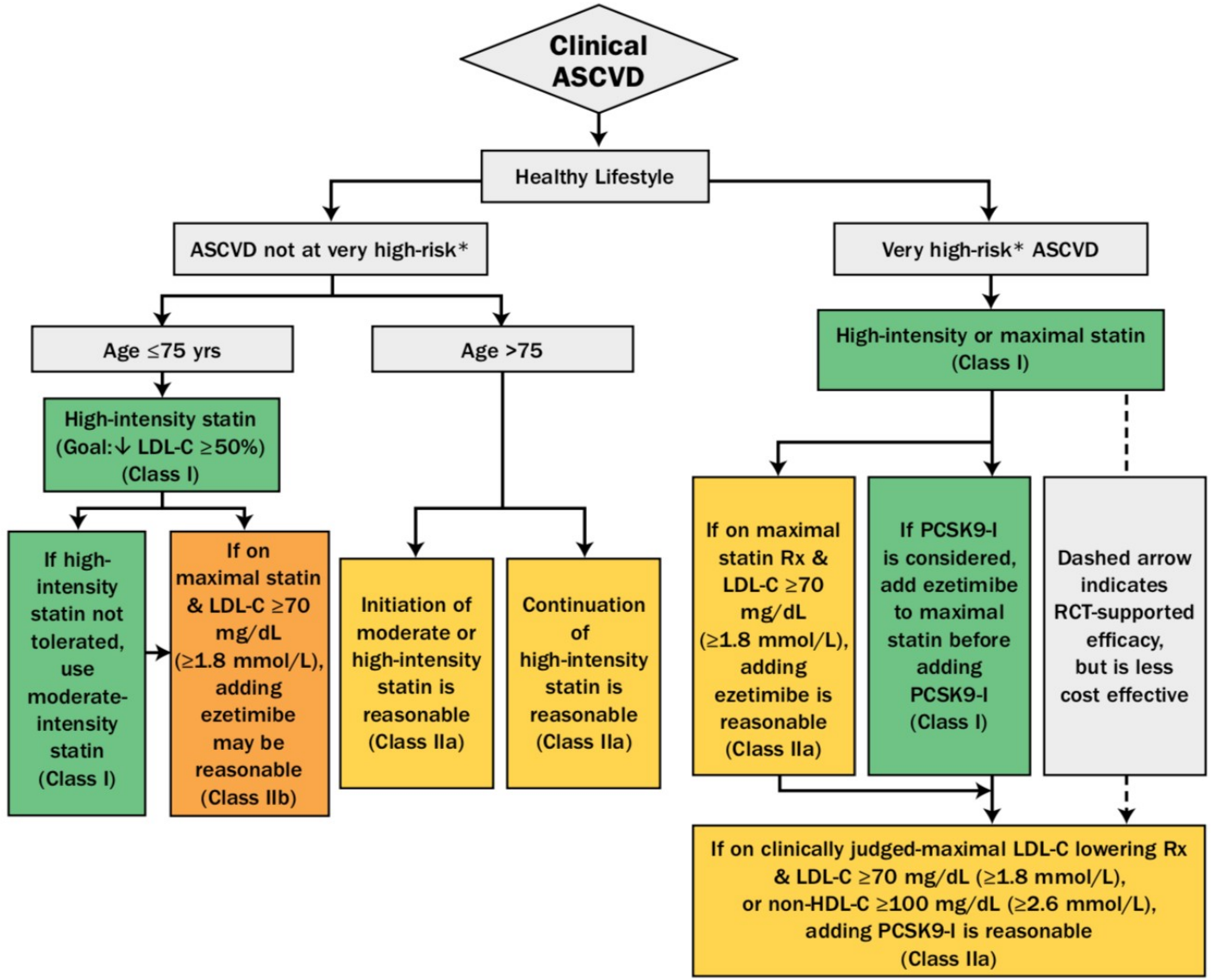
Secondary Prevention in ASCVD Patients



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Non- Statin Lipid Therapy In Guidelines

- 1. Ezetimibe

- 2 PCSK-9 Inhibitors

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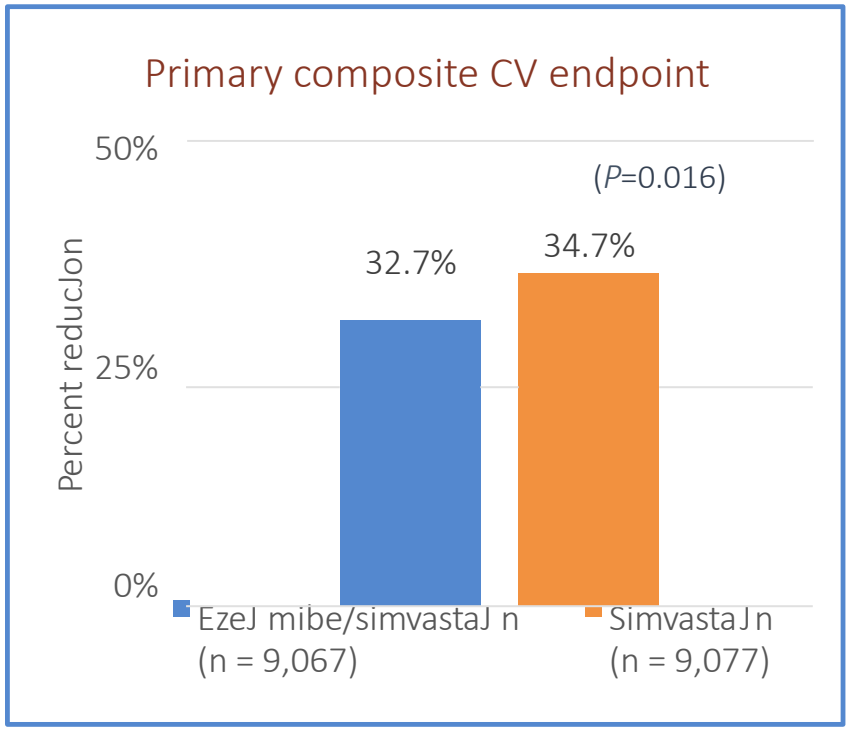
IMPROVE-IT: Improved ReducJ on of Outcomes, Vytorin Efficacy InternaJ onal Trial

Trial design: PaJ ents with recent ACS were randomized 1:1 to either ezeJ mibe 10 mg + simvastaJ n 40 mg or simvastaJ n 40 mg and followed for a median of 6 years



Results

- Primary endpoint (CV death/MI/UA/coronary revasc/stroke/moderate/severe bleeding) for ezeJ mibe/simvastaJ n vs. simvastaJ n: 32.7% vs. 34.7% (HR 0.94, 95% CI 0.89-0.99; *P*=0.016)
- MI: 13.1% vs. 14.8%, *P*=0.002; stroke: 4.2% vs. 4.8%, *P*=0.05; CVD/MI/stroke: 20.4% vs. 22.2%, *P*=0.003
- Median LDL follow-up average: 53.7 vs. 69.5 mg/dL

Conclusions

- In paJ ents with high-risk ACS, ezeJ mibe 10 mg/simvastaJ n 40 mg was superior to simvastaJ n 40 mg alone in reducing adverse CV events
- This is the first study powered for clinical outcomes to show a benefit with a non-staJ n agent
- Reaffirms the "lower is bec er" hypothesis with LDL–C

Abbrevia@ons: ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarc@on.

Cannon CP, et al. *N Engl J Med.* 2015;372:2387--2397.

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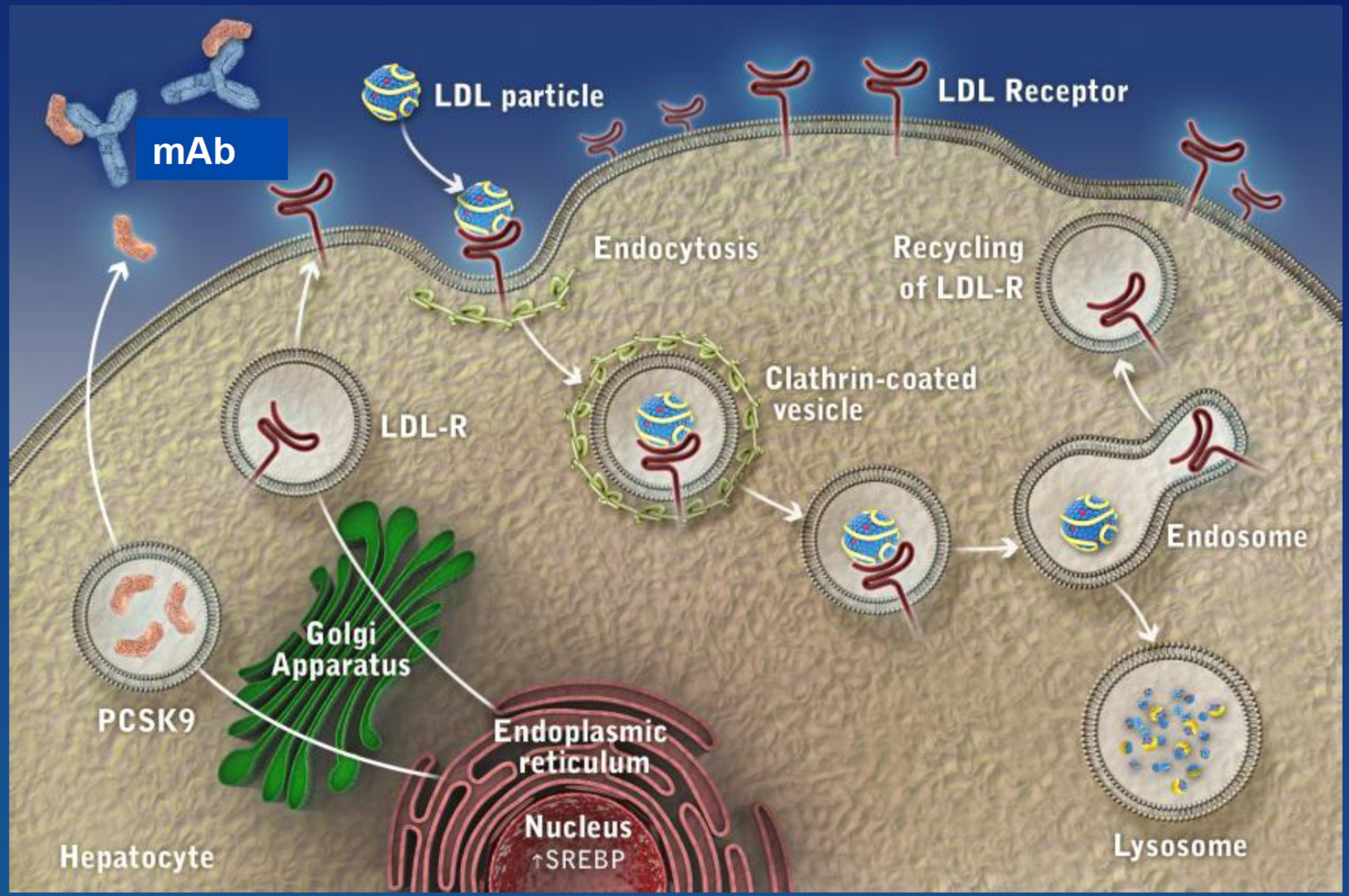
Impact of an PCSK9 mAb on LDL Receptor Expression



PCSK9 INHIBITORS: Dosages & Dosage Ranges

Agent	Usual recommended starting daily dosage	Dosage range	Method of administration
PCSK9 inhibitors Alirocumab	75 mg every 2 weeks	75--150 mg every 2 weeks, 300mg once monthly	SQ
Evolocumab	140 mg every 2 weeks or 420 mg once monthly	Not applicable	SQ

Metabolic Effects:

- ↓LDL-C 48%-71%, ↓ non-HDL-C 49%-58%, ↓TC 36%-42%, ↓Apo B 42%-55% by inhibiting PCSK9 binding with LDLRs, increasing the number of LDLRs available to clear LDL, and lowering LDL-C levels

Main Considerations:

- Require subcutaneous self-injection; refrigeration generally needed
- Overall levels of adverse reactions and discontinuation very low
- Adverse reactions with significantly different rates between drug and placebo were: local injection site reactions and influenza
- The most common adverse reactions with similar rates for drug vs. placebo were:
  - Alirocumab: nasopharyngitis, influenza, urinary tract infections, diarrhea, bronchitis, and myalgia
  - Evolocumab: nasopharyngitis, back pain, and upper respiratory tract infection

Abbreviations: apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; SQ, subcutaneous injection; TC, total cholesterol.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Pract*ce*. 2017;23(4):479-497; Praluent (alirocumab) [PI] 2015; Repatha (evolocumab) [PI]; 2016.

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PCSK9 Therapy Issues

- Long term safety ≥ 3 years uncertain
- Economic cost

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Statin Safety and Statin-Associated Side Effects

RecommendaSons for StaSn Safety and StaSn--Associated Side Effects		
COR	LOE	RecommendaSons
III: No Benefit	B--R	Coenzyme Q10 is not recommended for rouSne use in paSents treated with staSns or for the treatment of SAMS.
III: No Benefit	C--LD	In paSents treated with staSns, rouSne measurements of creaSne kinase and transaminase levels are not useful.

Evaluate Successful Statin Therapy

- Compliance with medical therapy and lifestyle
- Repeat lipid panel 4-12 weeks after statin begins
- Dose adjusted every 3-12 months as needed
- Consider addition of non-statin drugs if LDL ≥ 70 mg/dl, or

  non-HDL-C > 100mg/dl

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Bempedoic Acid

- Once-daily, oral pill
- 30% LDL-C lowering
  - Incremental 20%+ on top of statins, including high-intensity statins
  - Incremental 30% on top of PCSK9i
- 40% hsCRP reduction alone; 48% hsCRP reduction with the combination of bempedoic acid / ezetimibe + atorvastatin 20 mg
- Potential for lower occurrence of muscle-related side effects
- Safe and well-tolerated

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CLEAR Outcomes Study

Northwell Investigators: Dr. Guy Mintz & Dr. Ben Hirsh

Primary Objective:

To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduces the risk of major adverse cardiovascular events (MACE) **in patients with, or at high risk for, cardiovascular disease (CVD) who are statin intolerant**.

This will be assessed with a composite primary efficacy endpoint that includes time to first occurrence of:

- **cardiovascular (CV) death**
- **nonfatal myocardial infarction (MI)**
- **nonfatal stroke, or**
- **coronary revascularization.**

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CLEAR Outcomes Secondary Objectives

Secondary Objectives:

- To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduces the risk of other clinical endpoints of CV morbidity and mortality and all-cause mortality.
- To evaluate the effect of long-term treatment with bempedoic acid 180 mg/day versus placebo on low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein (hsCRP).
- To evaluate the long-term safety and tolerability of bempedoic acid 180 mg/day compared to placebo.

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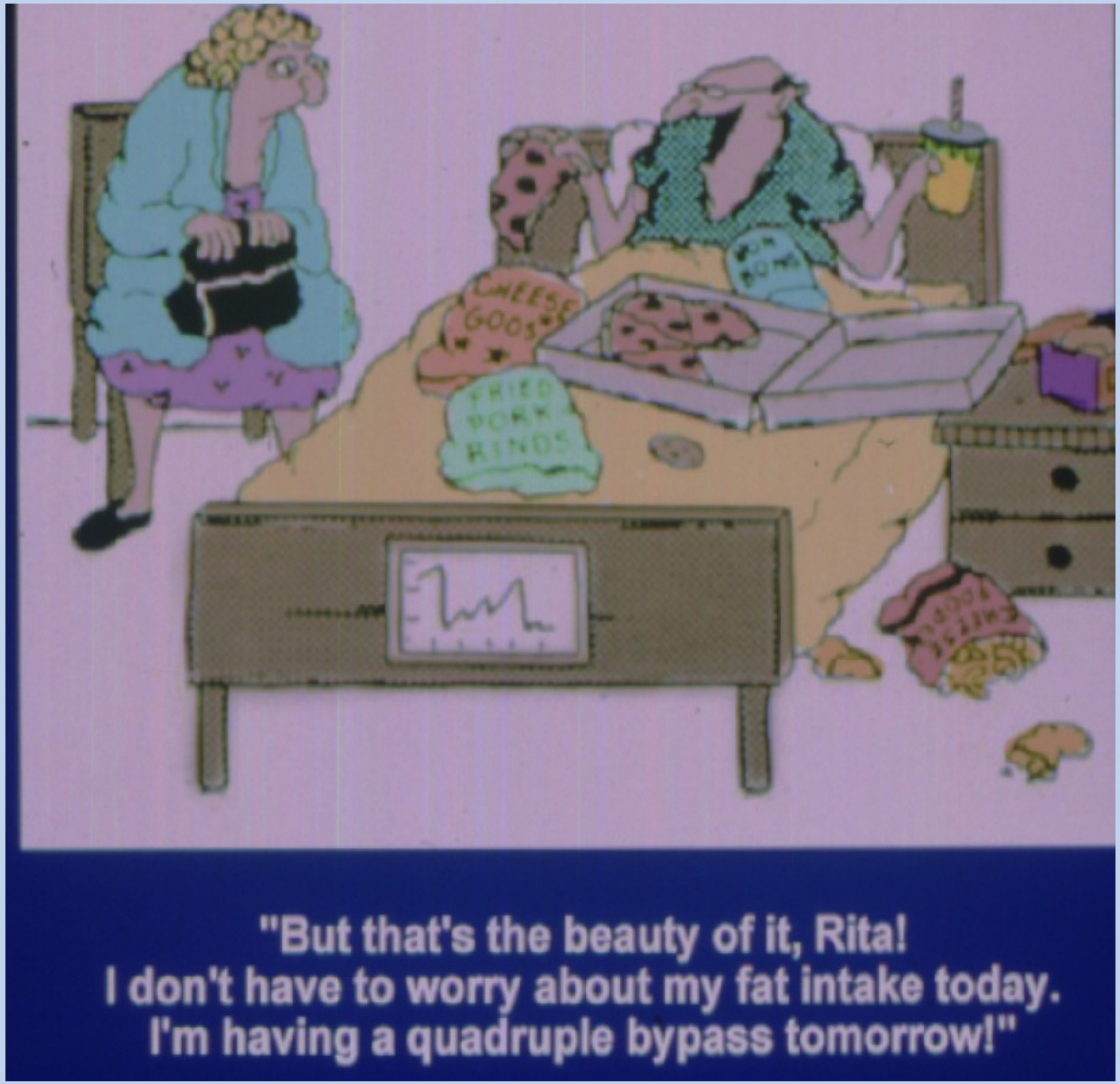
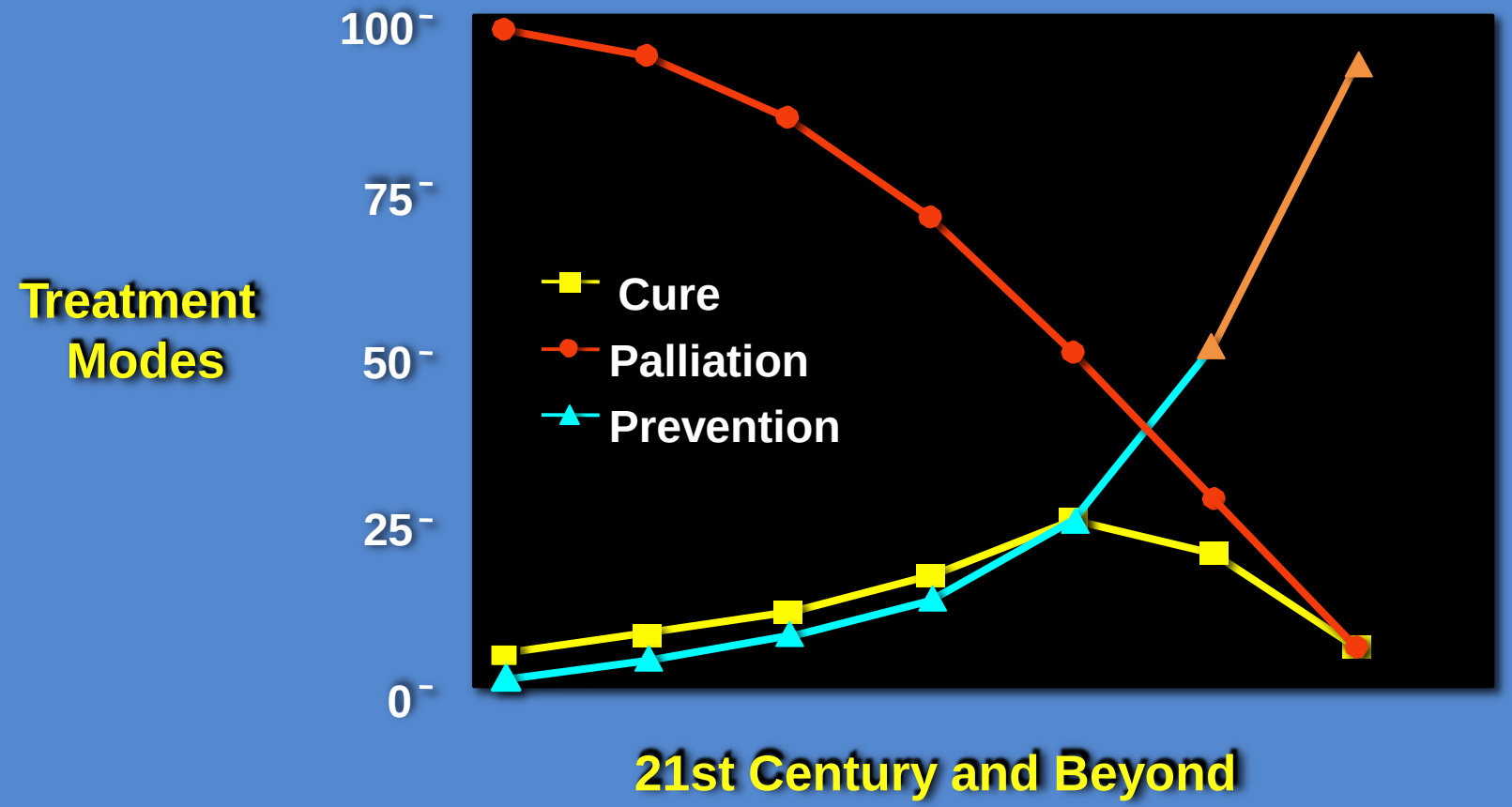

CHEESE GOOS
FRIED PORK RINDS
"But that's the beauty of it, Rita!
I don't have to worry about my fat intake today.
I'm having a quadruple bypass tomorrow!"

Cardiology: Where To Go From Here?

Expected Changes in Therapeutic Approaches to Cardiovascular Disease in the Future



Wellens HJJ. *Lancet 2000.* 1999;354:SIV8.

Top 10 Take-Home Messages

2018 Cholesterol Guidelines

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Top 10 Take Home Messages

1. In all individuals, emphasize a heart–healthy lifestyle across the life course.

A healthy lifestyle reduces atherosclero@c cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the founda@on of ASCVD risk reduc@on.

In young adults 20 to 39 years of age, an assessment of life@me risk facilitates the clinician–pa@ent risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary interven@on for metabolic syndrome.

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Top 10 Take Home Messages

2. **In paSents with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity staSn therapy or maximally tolerated staSn therapy.**

   The more LDL-C is reduced on sta@n therapy, the greater will be subsequent risk reduc@on.

   Use a maximally tolerated sta@n to lower LDL-C levels by ≥50%.

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Top 10 Take Home Messages

3. **In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addiSon of nonstaSns to staSn therapy.**

- Very high-risk includes a history of mul@ple major ASCVD events or 1 major ASCVD event and mul@ple high-risk condi@ons.
- In very high-risk ASCVD pa@ents, it is reasonable to add eze@mibe to maximally tolerated sta@n therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L).
- In pa@ents at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated sta@n and eze@mibe therapy, adding a PCSK9 inhibitor is reasonable,
  although the long-term safety (>3 years) is uncertain and cost-effec@veness is low at mid-2018 list prices.

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Top 10 Take Home Messages

4. **In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL[≥4.9 mmol/L]) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.**

   - If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable

   - If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) & the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered,
     although the long-term safety (>3 years) is uncertain and economic value is low at mid-2018 list prices.

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Top 10 Take Home Messages

5. **In paSents 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate–intensity staSn therapy without calculaSng 10-year ASCVD risk.**

   In pa@ents with diabetes mellitus at higher risk, especially those with mul@ple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity sta@n to reduce the LDL-C level by ≥50%.

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Top 10 Take Home Messages

6. **In adults 40 to 75 years of age evaluated for primary ASCVD prevenSon, have a clinician–paSent risk discussion before starSng staSn therapy.**

   Risk discussion should include a review of major risk factors (e.g., cigarez e smoking, elevated blood pressure, (LDL-C), hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);

   - the presence of risk-enhancing factors (see No. 8);
   - the poten@al benefits of lifestyle and sta@n therapies;
   - the poten@al for adverse effects and drug–drug interac@ons;
   - the considera@on of costs of sta@n therapy; and
   - the pa@ent preferences & values in shared decision-making.

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Top 10 Take Home Messages

7. **In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.**

   Risk-enhancing factors favor statin therapy (see No. 8).

   If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.

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Top 10 Take Home Messages

8. **In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).**

Risk-enhancing factors include

- family history of premature ASCVD;
- persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L);
- metabolic syndrome;
- chronic kidney disease;

- history of preeclampsia or premature menopause (age <40 yrs)
- chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV);
- high-risk ethnic groups (e.g., South Asian);
- persistent elevations of triglycerides ≥ 175 mg/dL (≥1.97 mmol/L);

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Top 10 Take Home Messages

8. **In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).**

Risk-enhancing factors include

and, if measured in selected individuals

- apolipoprotein B ≥130 mg/dL
- high-sensitivity C-reactive protein ≥2.0 mg/L
- ankle-brachial index <0.9 and l
- lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a).

Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-7.5% (borderline risk)

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Top 10 Take Home Messages

9. **In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL–189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.**

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age.
- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.

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Top 10 Take Home Messages

10. **Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after initiation or dose adjustment, repeated every 3 to 12 months as needed.**

    - Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
    - In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).

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Secondary Prevention

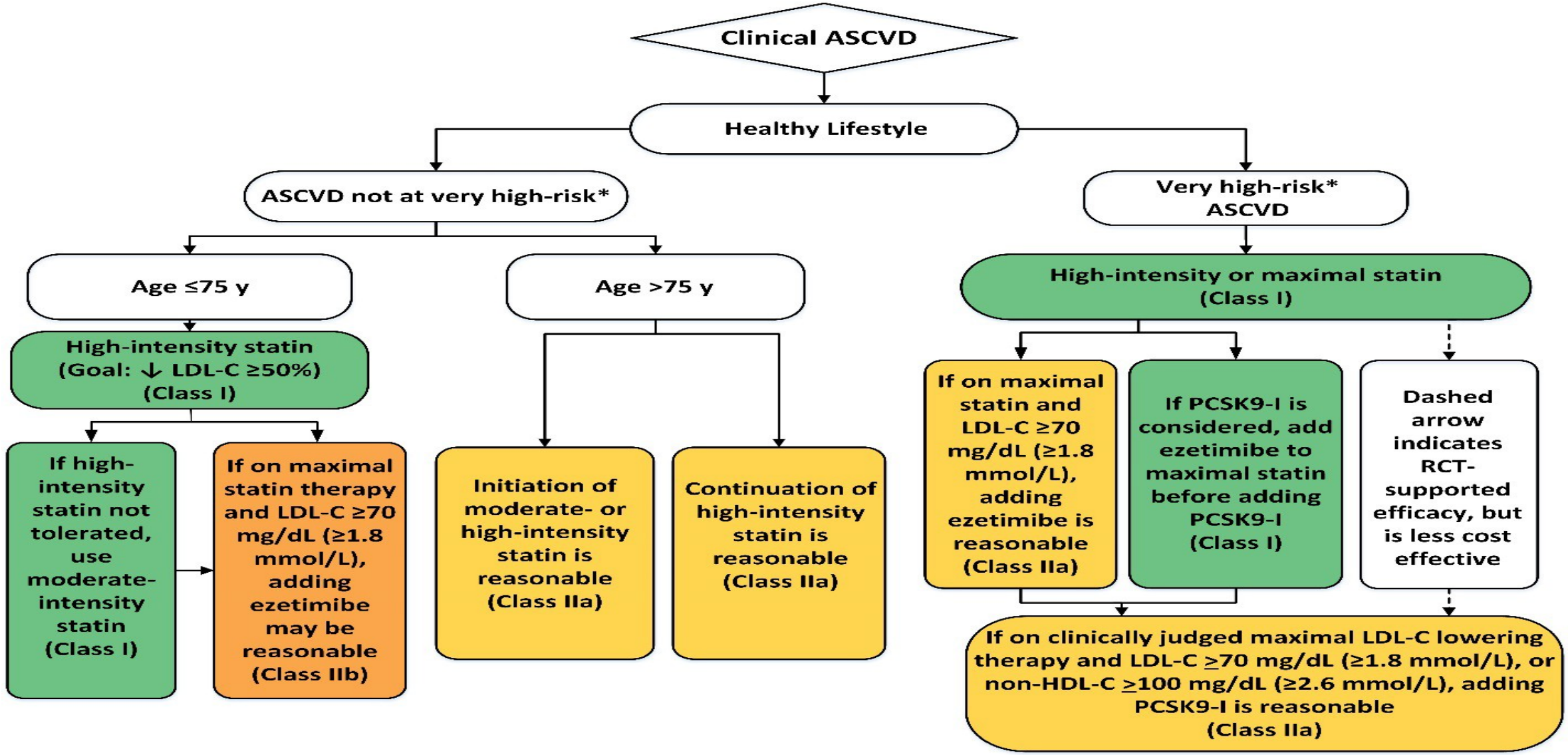

Table 6. Risk-Enhancing Factors for Clinician–Patient Risk Discussion

Risk-Enhancing Factors
• Family history of premature ASCVD (males, age <55 y; females, age <65 y) • Primary hypercholesterolemia (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])* • Metabolic syndrome (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis) • Chronic kidney disease (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation) • Chronic inflammatory conditions such as psoriasis, RA, or HIV/AIDS • History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia • High-risk race/ethnicities (e.g., South Asian ancestry)

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Table 6 conJ nued

Risk-Enhancing Factors
• **Lipid/biomarkers**: Associated with increased ASCVD risk o Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL); o If measured: ▬ **Elevated high–sensiSvity C-reacSve protein** (≥2.0 mg/L) ▬ **Elevated Lp(a):** A rela@ve indica@on for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L cons@tutes a risk-enhancing factor especially at higher levels of Lp(a). ▬ **Elevated apoB** ≥130 mg/dL: A rela@ve indica@on for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and cons@tutes a risk-enhancing factor ▬ **ABI** <0.9

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