

Cardiovascular Risks and Treatment Options

Satish Gadi, MD FACC FSCAI

Interventional Cardiologist, Cardiovascular Institute of the South, Baton Rouge, LA.

Adjuvant Asst. Clinical Professor, Tulane University School of Medicine





Disclosures: Speaker – Astrazeneca, Amgen

Disclosure Statement: Project ECHO®, in compliance with the ACCME Standards for Integrity and Independence in Accredited Continuing Education, requires that anyone who is in a position to control the content of an educational activity disclose all relevant financial relationships they have had within the last 24 months with an ineligible company. The following planners and presenters listed below have disclosed that they have a relevant financial relationship with an ineligible company: Satish Gadi, MD (Speaker, AstraZeneca). All of the relevant financial relationships listed for these individuals have been mitigated.

Objectives

- Assessment of risk – going beyond the traditional
- Risk Reduction – LDL reduction

TRADITIONAL RISK FACTORS

- Age > 65 years
- Male sex
- Family history
- Others
- High Blood Pressure
- High Cholesterol
- Smoking
- Physical inactivity
- Diabetes

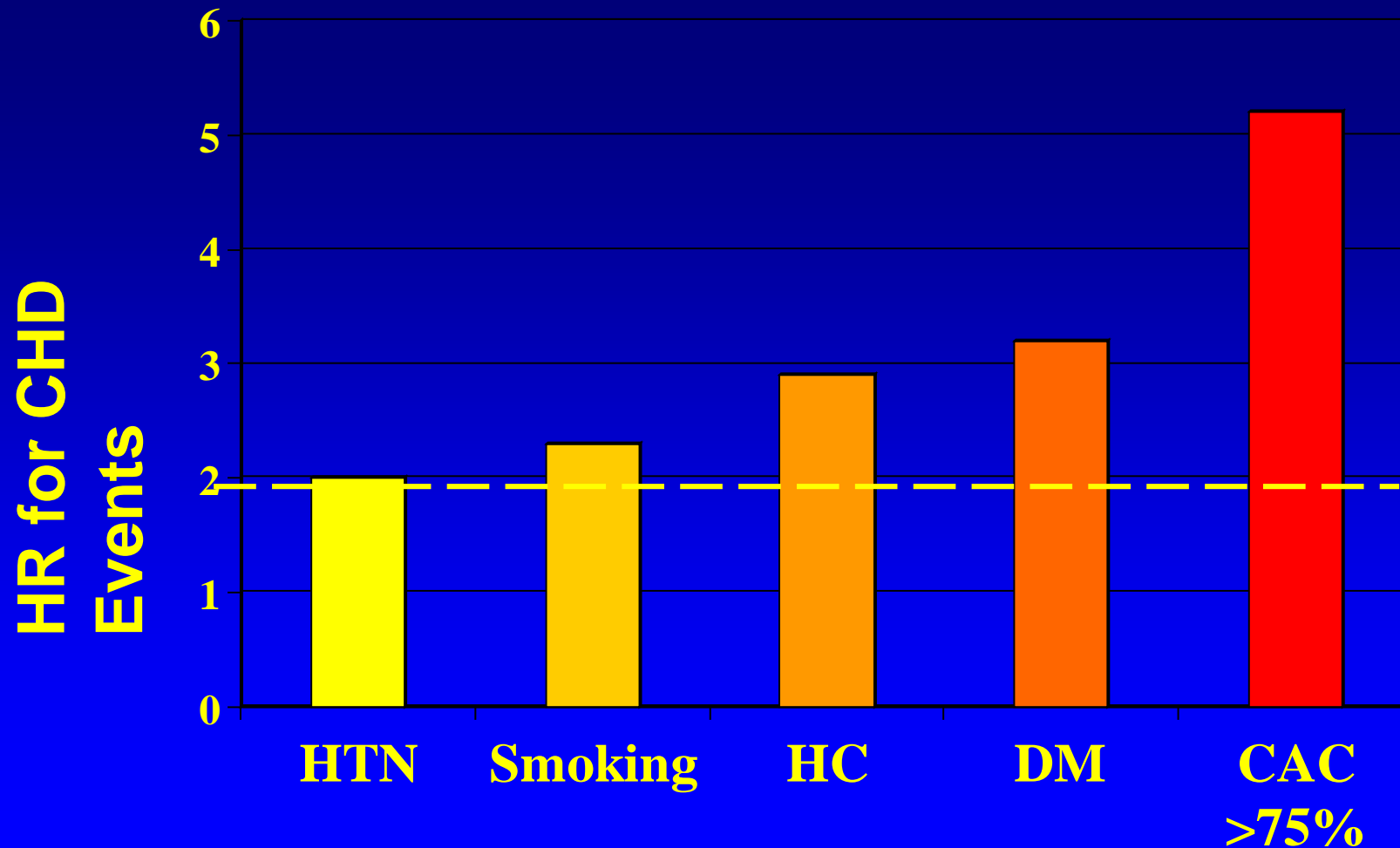
IRREVERSIBLE

REVERSIBLE

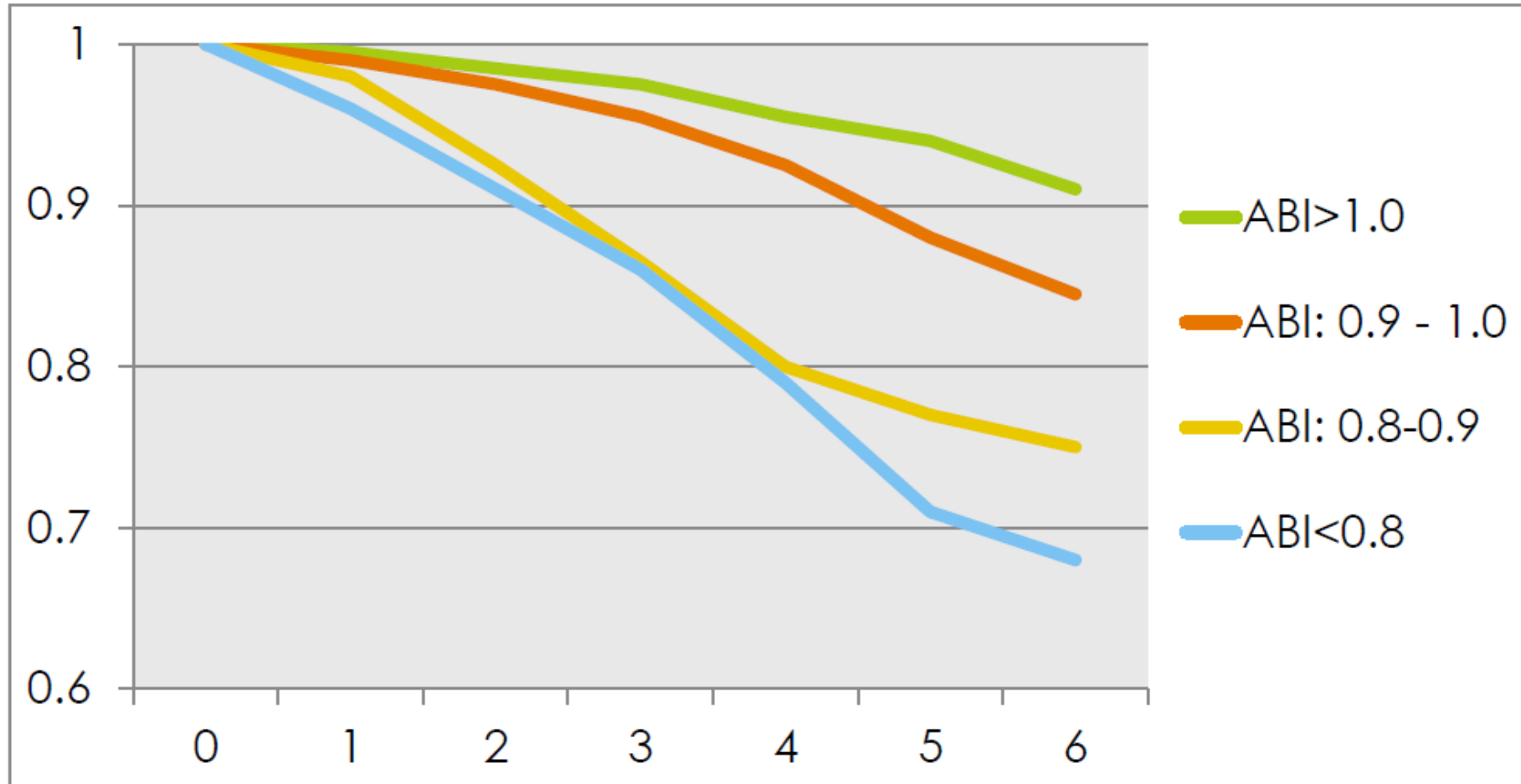
Estimating Individual risk

- ASCVD Risk Estimator (pooled cohort risk estimates)
- Non-traditional risk factors: Ankle-Brachial Index (ABI), Coronary Calcium score

Relative Predictive Value of CAC and Traditional Risk Factors for CHD in 1726 Asymptomatic Subjects over 40 Months: Dichotomous Analysis




Patient survival by ABI in Cardiovascular Health Study...



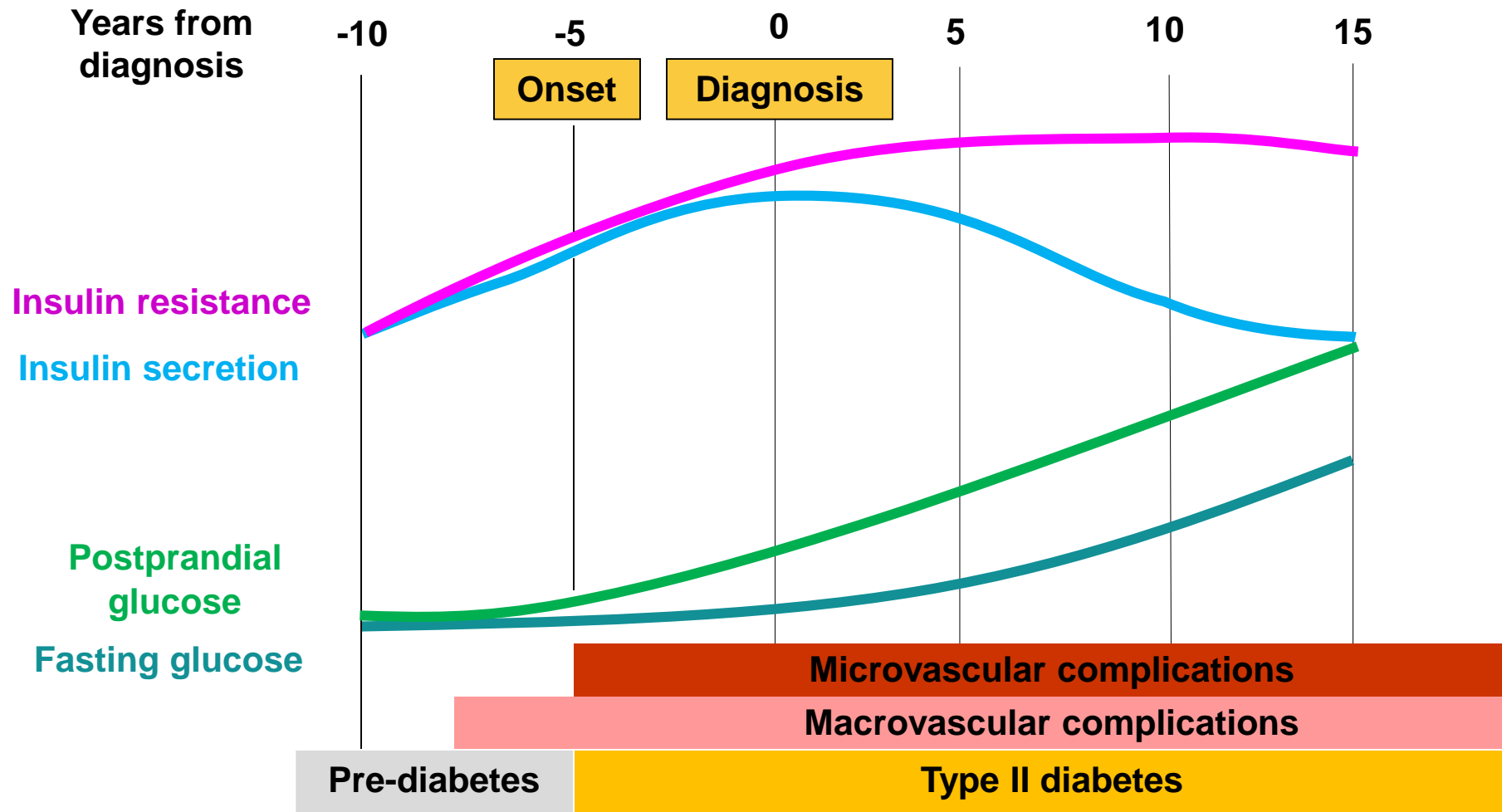
Newman et al ATVB 1999;19; 538-545



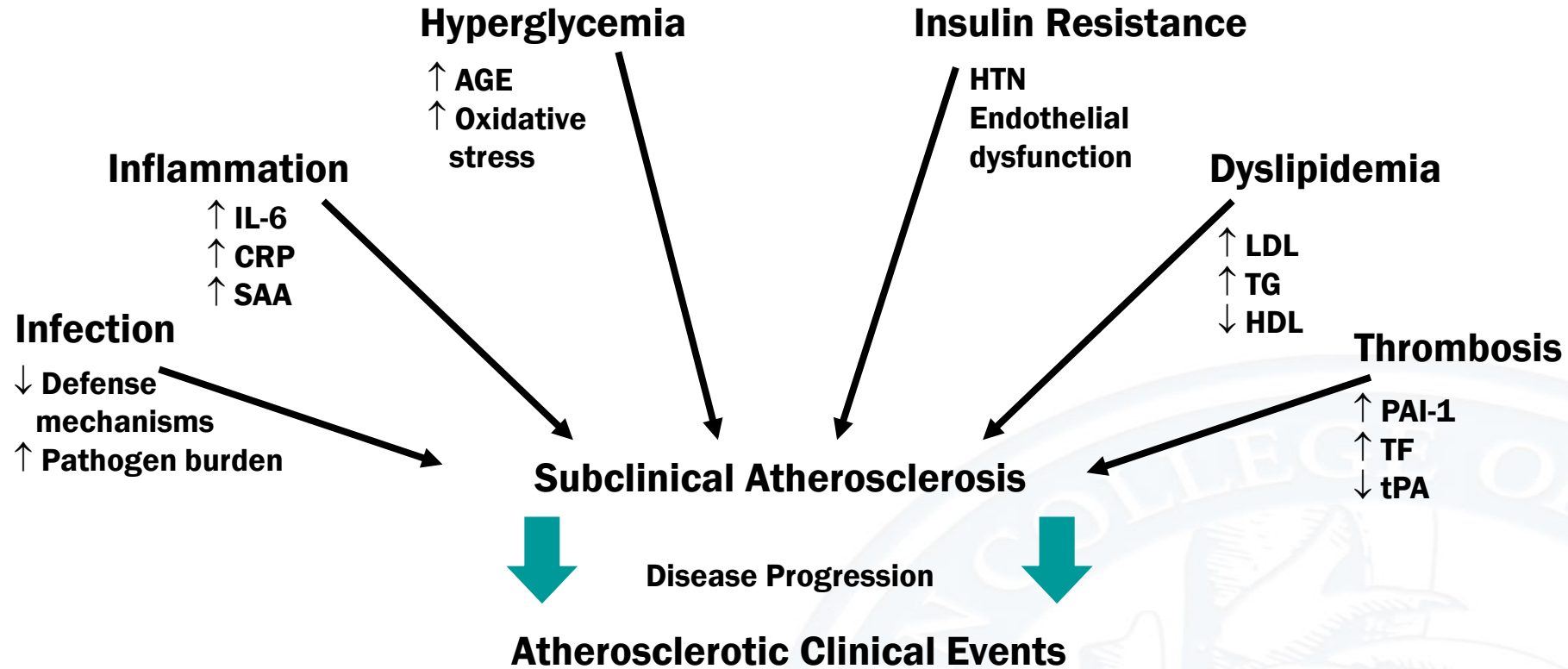
Diabetes and Cardiovascular Disease

- 
- Diabetes
 - Pre-Diabetes
 - Metabolic Syndrome

Natural History of Type II Diabetes Mellitus



Mechanisms by which Diabetes Mellitus Leads to Coronary Heart Disease



AGE=Advanced glycation end products, CRP=C-reactive protein, CHD=Coronary heart disease HDL=High-density lipoprotein, HTN=Hypertension, IL-6=Interleukin-6, LDL=Low-density lipoprotein, PAI-1=Plasminogen activator inhibitor-1, SAA=Serum amyloid A protein, TF=Tissue factor, TG=Triglycerides, tPA=Tissue plasminogen activator

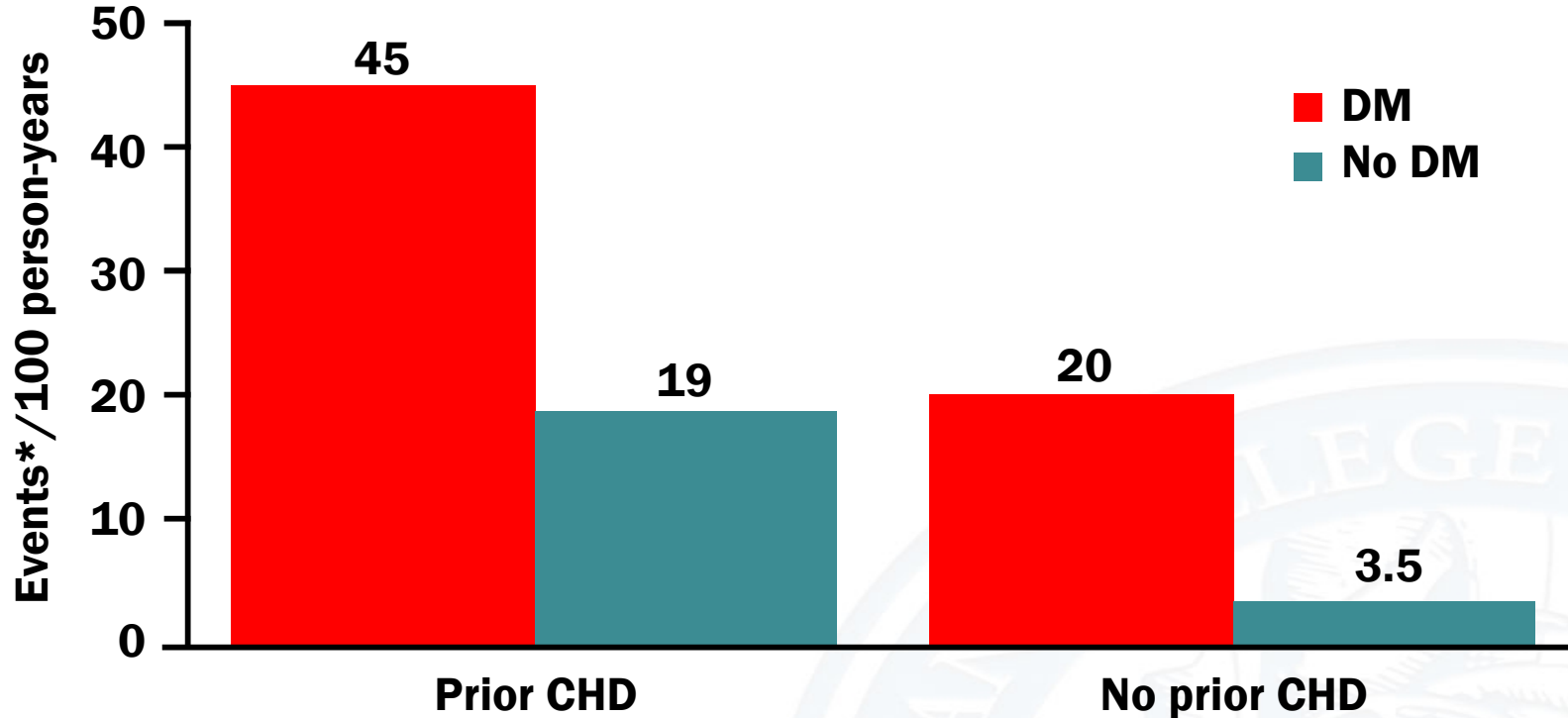
Source: Biondi-Zoccai GGL et al. JACC 2003;41:1071-1077



*Helping Cardiovascular Professionals
Learn. Advance. Heal.*

Diabetes Mellitus: Risk of Myocardial Infarction

East-West Study



Patients with DM but no CHD experience a similar rate of MI as patients without DM but with CHD



*Helping Cardiovascular Professionals
Learn. Advance. Heal.*

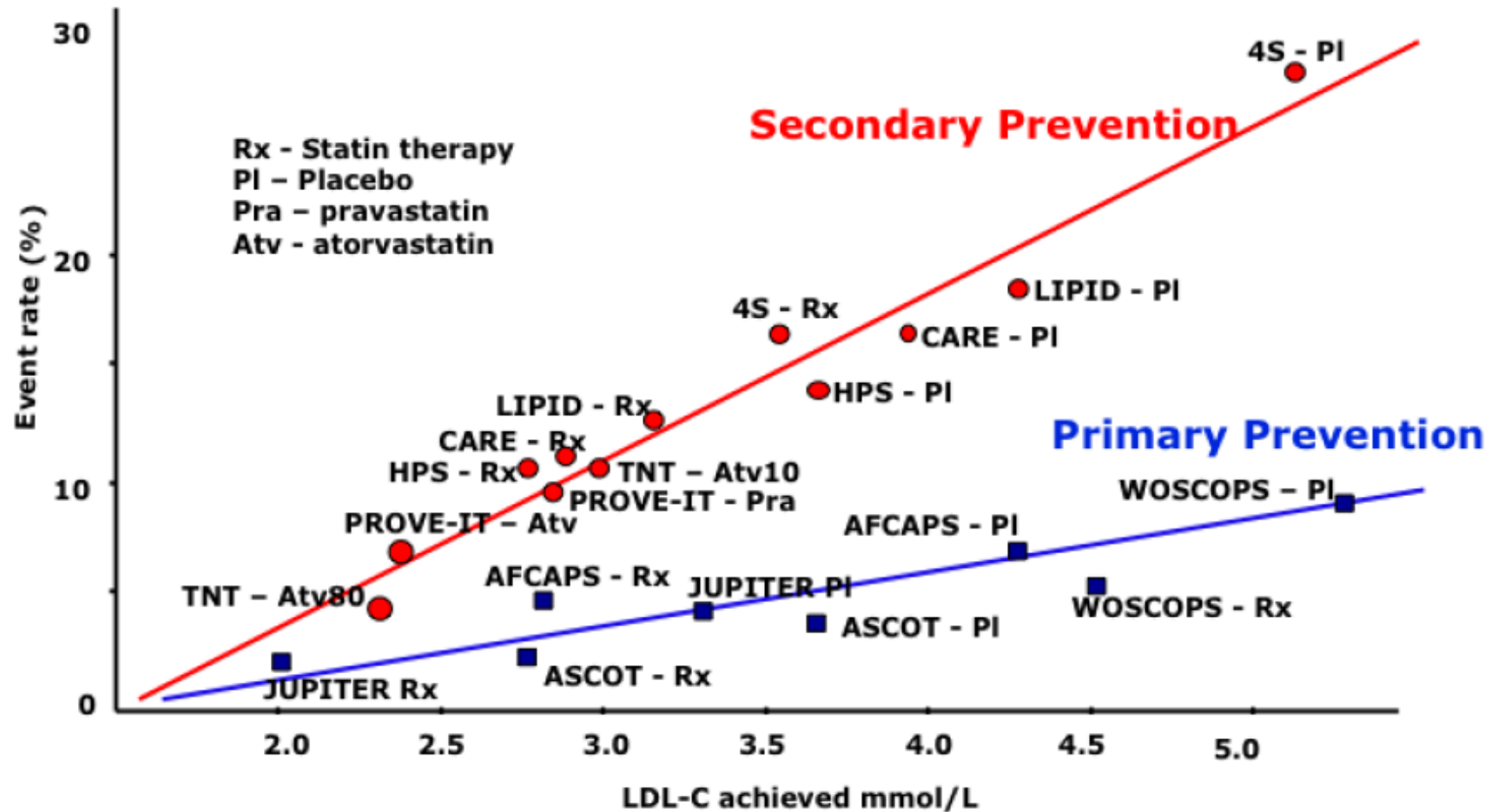
*Fatal or non-fatal MI

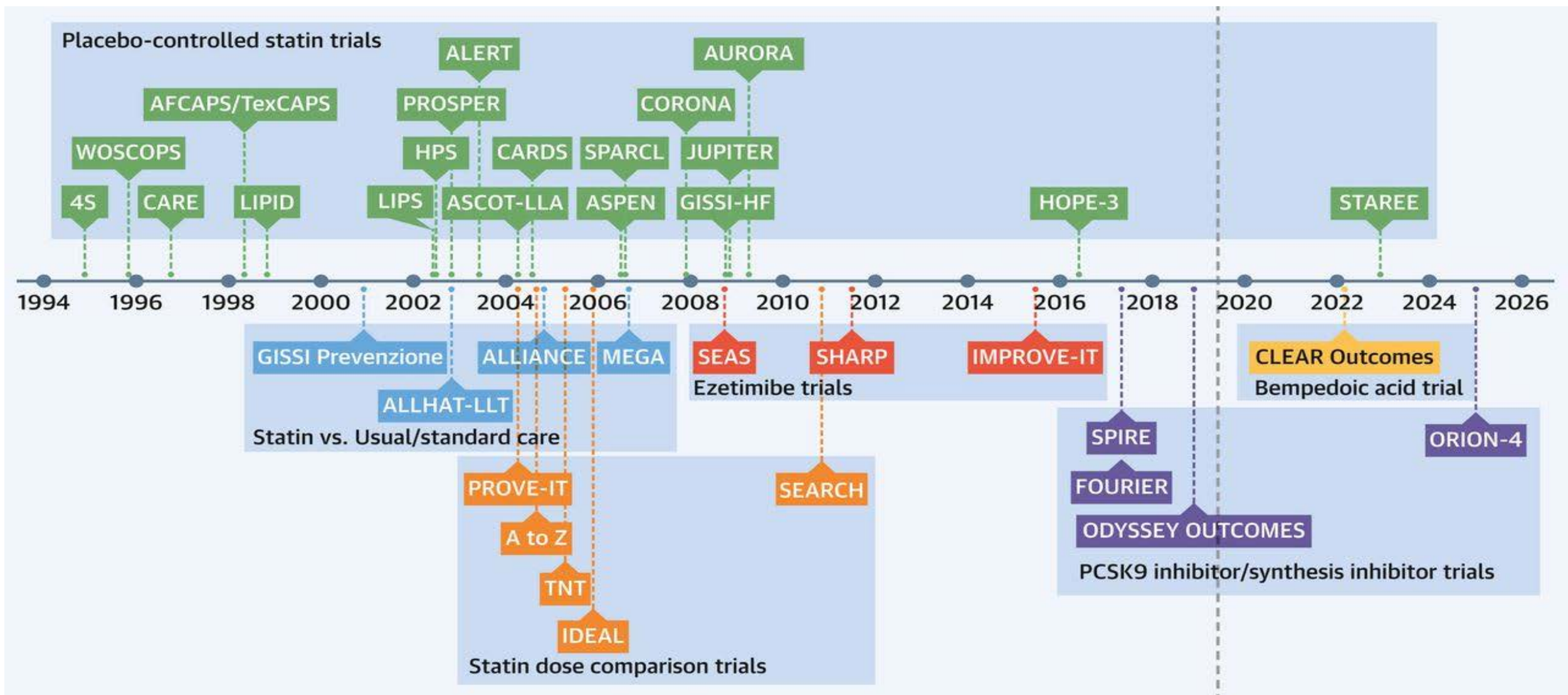
CHD=Coronary heart disease, DM=Diabetes mellitus, MI=Myocardial infarction

Source: Haffner SM et al. *NEJM* 1998;339:229–234

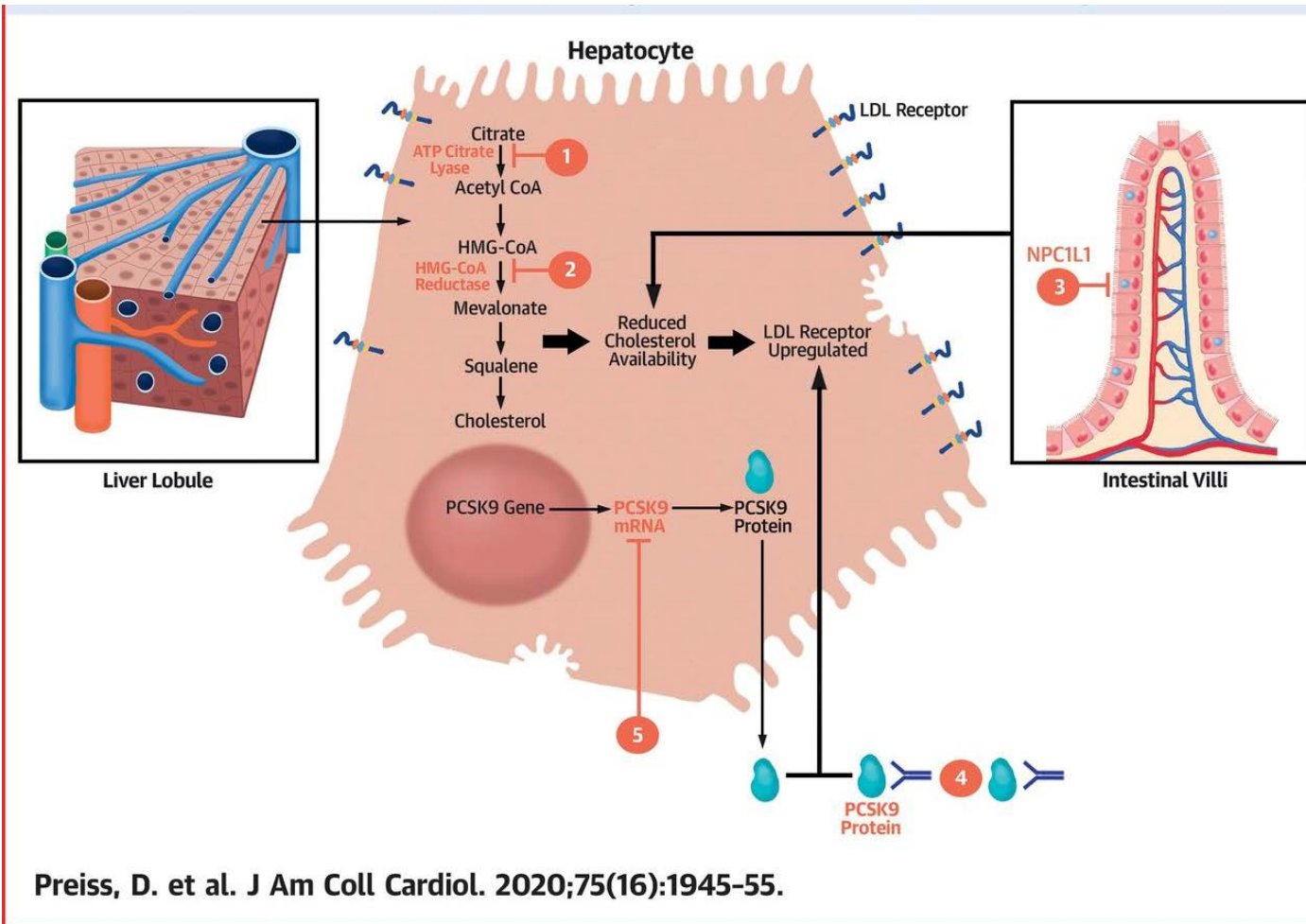
LDL Reduction

Reducing LDL > Reduced CV events



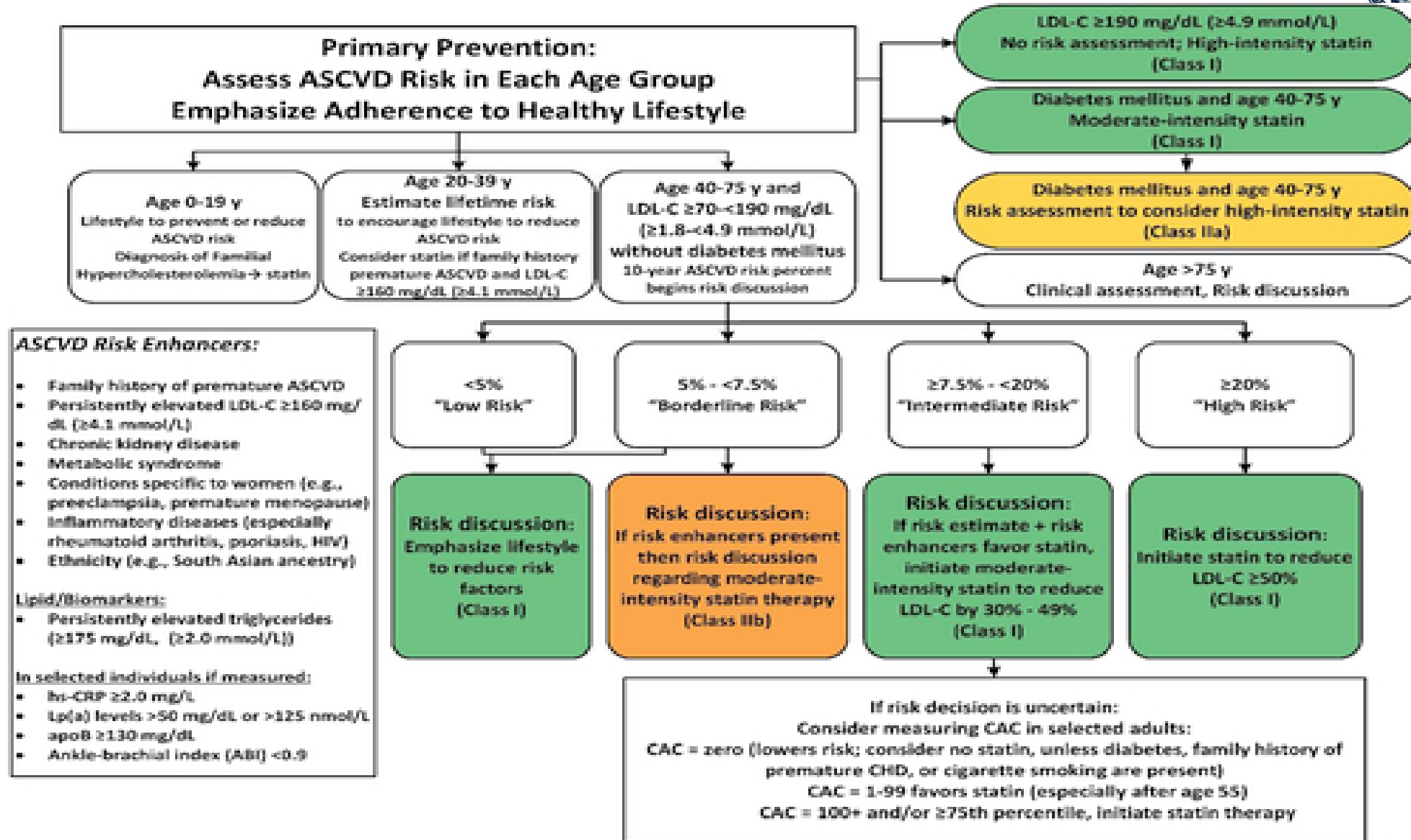


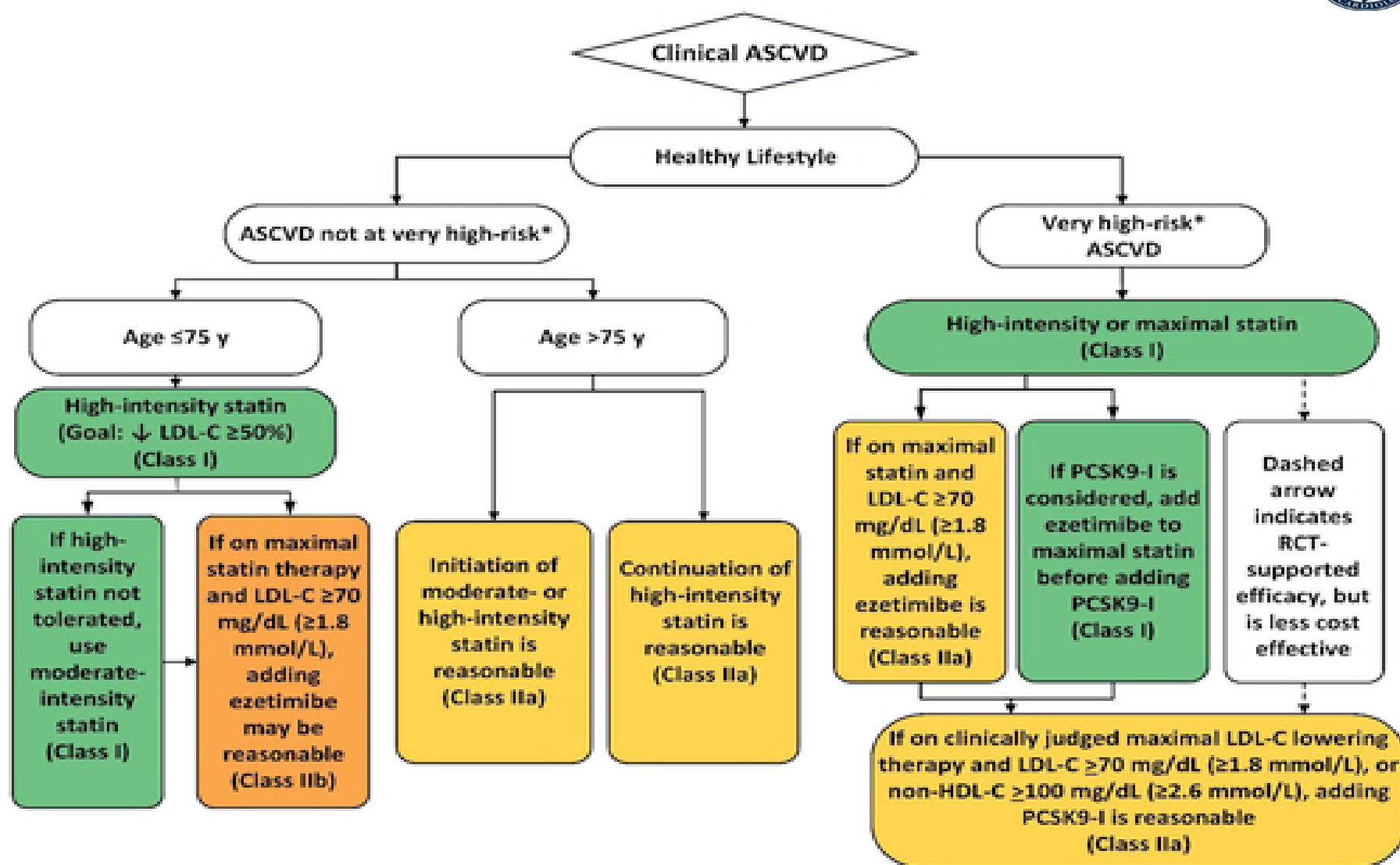
Many therapeutic options to reduce LDL...



1. Bempedoic acid (Nexletol)
2. Statins
3. Ezetemibe (Zetia)
4. PCSK9 Inhibitors
5. Inclisiran (Leqvio)
6. Evinacumab

| High, Moderate, and Low Intensity Statins | | | |
|---|--|--|--|
| | High Intensity | Moderate Intensity | Low Intensity |
| LDL-C Lowering | >/= 50% | 30-49% | < 30% |
| | Atorvastatin 40-80 mg Rosuvastatin 20-40 mg | Atorvastatin 10-20 Rosuvastatin 5-10 Simvastatin 20-40 | Simvastatin 10 mg |
| | | Pravastatin 40-80 Lovastatin 40-80 Fluvastatin XL 80 BID Pitavastatin 1-4 | Pravastatin 10-20 Lovastatin 20 mg Fluvastatin 20-40 |





Evolution of Guidelines

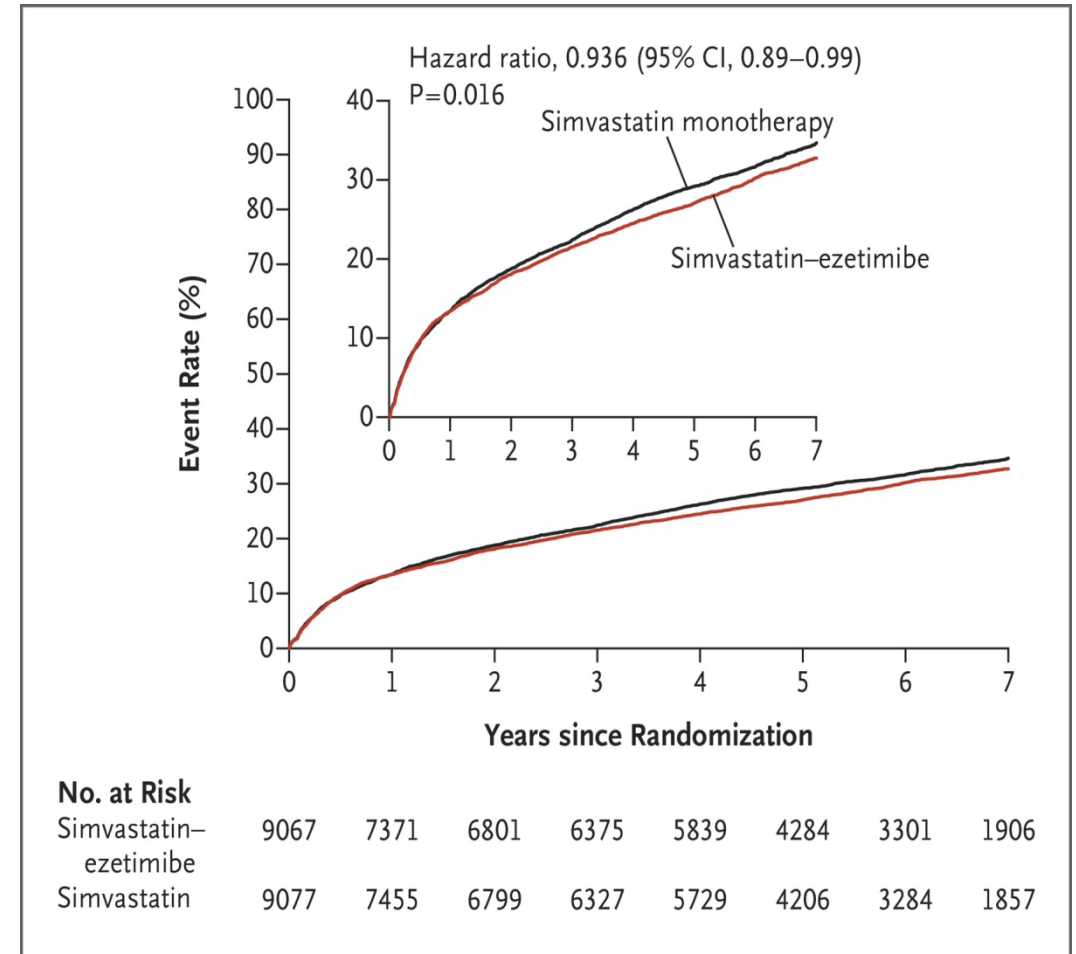
- 2016 ACC Expert Consensus Decision Pathway on the Role of Non-statin Therapies for LDL-Cholesterol Lowering: Ezetemibe
- 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-statin Therapies for LDL-Cholesterol Lowering: first incorporation of PCSK9 Inhibitors
- 2018 ACC/AHA Guidelines: LDL < 70 (add non-statin if LDL continues to be ≥ 70)
- Ezetemibe was first-choice non-statin tx

Value-based Care

- The 2018 AHA/ACC/multisociety cholesterol guideline includes the following value statement: “At mid-2018 list prices, PCSK9 mAbs have a low cost value (>\$150,000 per quality-adjusted life year [QALY]) compared with good cost value (<\$50,000 per QALY).”
- Since publication of the 2018 AHA/ACC/multisociety cholesterol guideline, 3 additional nonstatin therapies—bempedoic acid, evinacumab, and inclisiran—have received FDA approval for management of hypercholesterolemia.

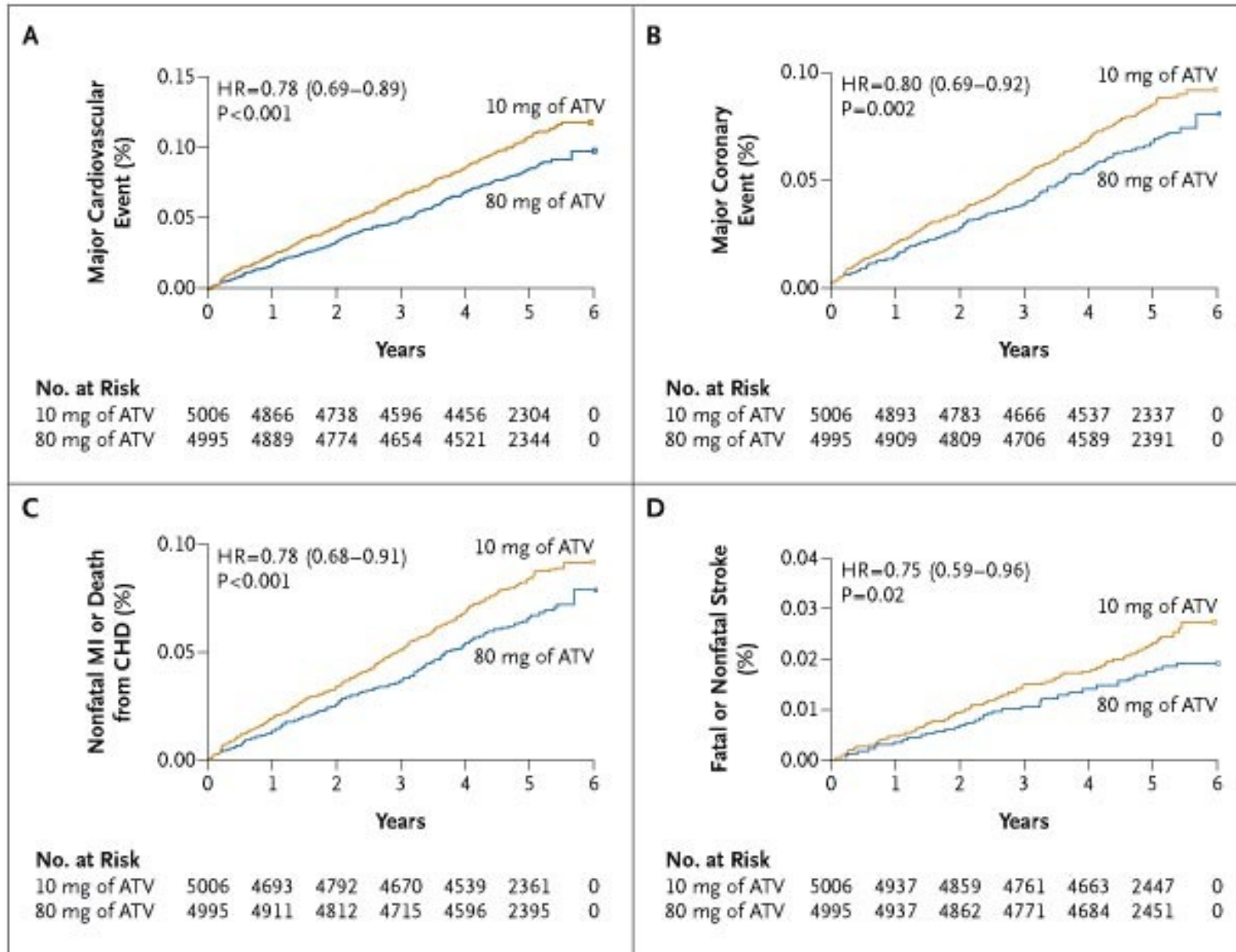
How low can we go?

- Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes (IMPROVE-IT): N Engl J Med 2015; 372:2387-2397
- > 18k patients
- Mean LDL: 93
- Statin: 69.9
- Combo: 53.2
- 24% further lowering of LDL cholesterol level when ezetimibe was combined with simvastatin than when simvastatin was administered alone

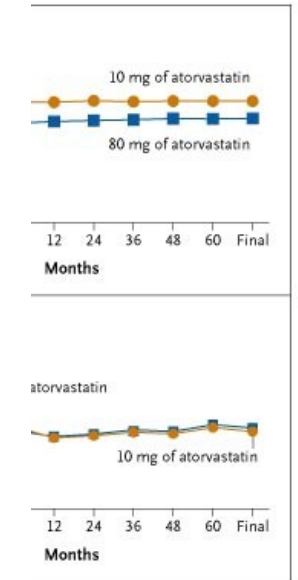


Intensive Lipid Treatment

- > 10k patients with CHD and mean age less than 130 years
- Atorvastatin 10 mg or 80 mg daily
- 4.9 years of follow-up
- The mean baseline LDL-C was 177 mg/dL
- of atorvastatin treatment



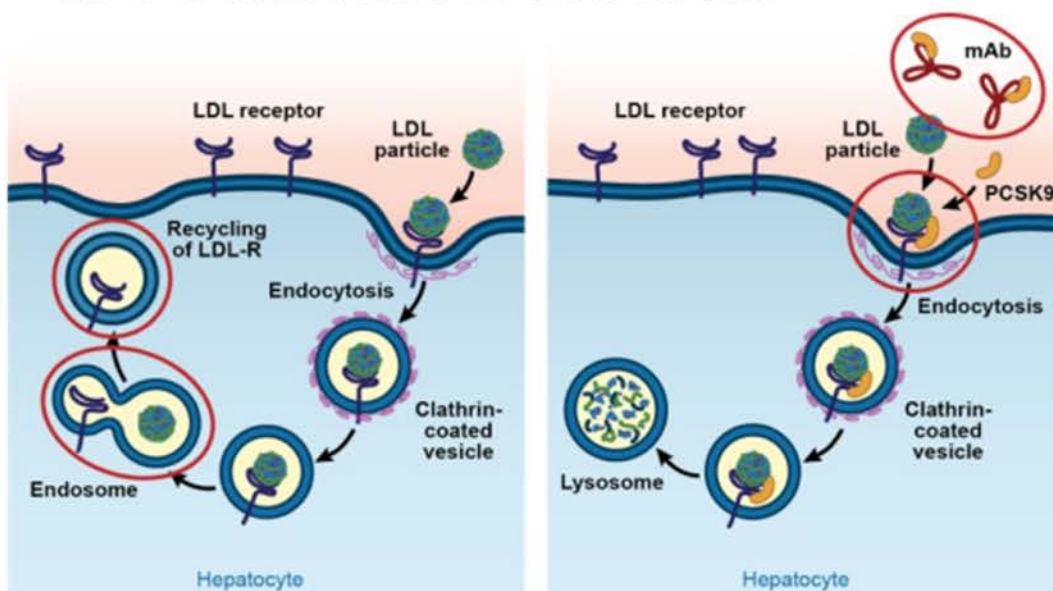
My Disease: 35



Background

PCSK9: Proprotein convertase subtilisin/kexin type 9

- Chaperones LDL-R to destruction → increase circulating LDL-C
- Loss-of-function genetic variants → increase LDL-R → reduce LDL-C and reduce risk of MI



LDL degradation and recycling of LDLR

PCSK9-mediated degradation of LDLR

Evolocumab and Alirocumab

- Human anti-PCSK9 mAb
- 50% to 60% reduce LDL-C^[a]
- Safe and well-tolerated in Phase 2 and 3 studies^[b]

a. Giugliano RP, et al. *Lancet*. 2012;380:2007-2017.

b. Sabatine MS, et al. *N Engl J Med*. 2015;372:1500-1509.

Evidence for PCSK9 Inhibitors

- FOURIER (Sabatine MS NEJM 2017; 316:1713-1722): > 27 k patients randomized; Evolocumab significantly reduced primary outcome (CV death, MI, stroke, revascularization, or hospitalization for UA)
- ODYSSEY (NEJM 2018 Nov 29;379(22):2097-2107): 18k patients randomized post-recent ACS; Alirocumab significantly reduced nonfatal MI
- Plaque reduction/modification: GLAGOV, HUYGENS, and ARCHITECT trials
- > 50 mg/dl LDL reduction over and above maximally tolerated statin dose

Alirocumab (Praluent)

- 75 mg q 2weeks or 150 mg q 2weeks
- Pre-filled syringe
- Store in refrigerator; room temperature for 30 days
- Nasopharyngitis is most common side effect
- $T_{1/2} = 17-30$ days
- Hepatic elimination

Evolocumab (Repatha)

- 140 mg q 2weeks or 420 mg q 4weeks
- Pre-filled syringe Sureclick Autoinjector / Pushtronex on-body infusor
- Store in refrigerator; room temperature for 30 days
- Nasopharyngitis is most common side effect
- $T_{1/2} = 11-17$ days
- Hepatic elimination

Main Indications for PCSK9 Inhibitor therapy

- Statin Intolerance
- Familial Hypercholesterolemia
- Failure to achieve target LDL in the setting of known ASCVD despite maximally tolerated statin

Take home points...

- Appreciate the specific Cardiovascular risk of Diabetes
- Look beyond the traditional risk factors
- High-intensity Statin therapy
- Novel Anti-lipidemic therapies: PCSK9 Inhibitor tx
- Lower the better!

| Lipid Panel | |
|----------------------|-----|
| Cholesterol, Total | 73 |
| Triglycerides | 118 |
| HDL Cholesterol | 39 |
| LDL Cholesterol Cal | 21 |
| LDL Chol Calc (NIH) | 13 |
| Hemoglobin A1c | |
| Hemoglobin A1c | 9.7 |
| Alkaline Phosphatase | |

Board

Clinical Summary

Progress Notes

Notes

Mes

as : Gadi, Satish

| Test | Current Result and Flag | |
|------------------------------------|-------------------------|----------|
| Cholesterol, Total ⁰¹ | 72 | |
| Triglycerides ⁰¹ | 180 | High |
| | Normal | |
| | Borderline High | 150 - 1 |
| | High | 20 |
| | Very High | |
| HDL Cholesterol ⁰¹ | 43 | |
| VLDL Cholesterol Cal ⁰¹ | 28 | |
| LDL Chol Calc (NIH) ⁰¹ | 1 | |
| | Optimal: | |
| | Near Optimal: | 100 - 12 |
| | Borderline High: | 130 - 15 |
| | High: | 160 |
| | Very High: | |

THANK YOU