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

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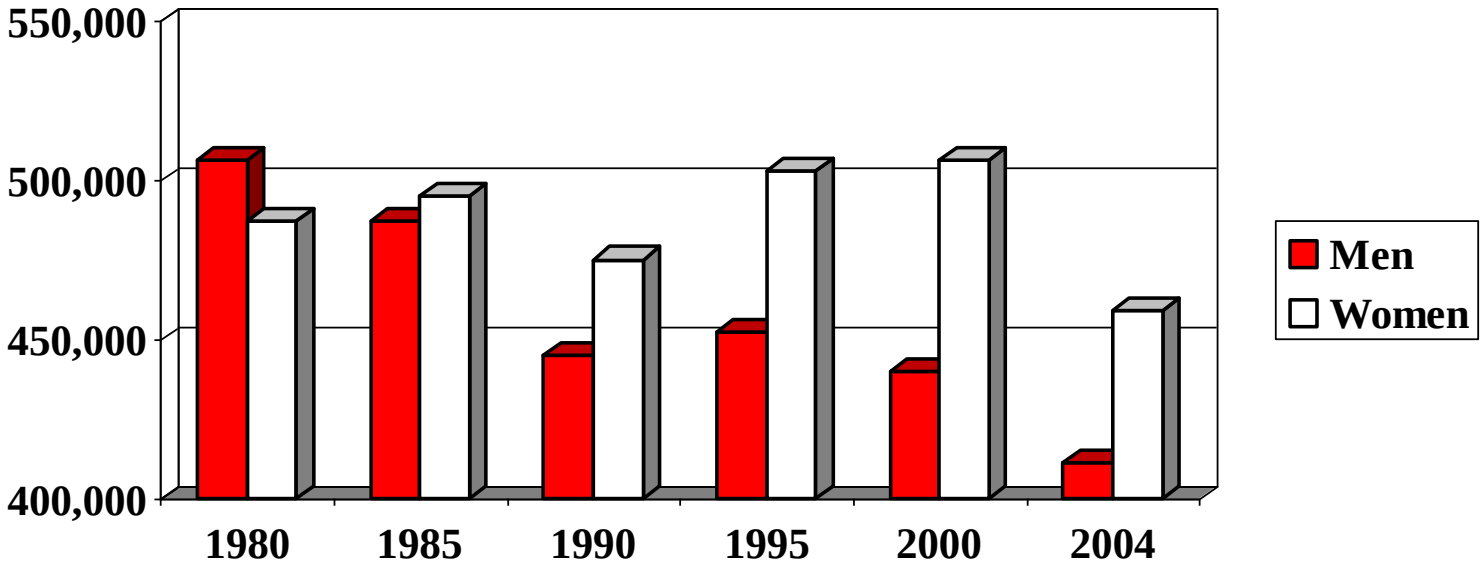
Objectives

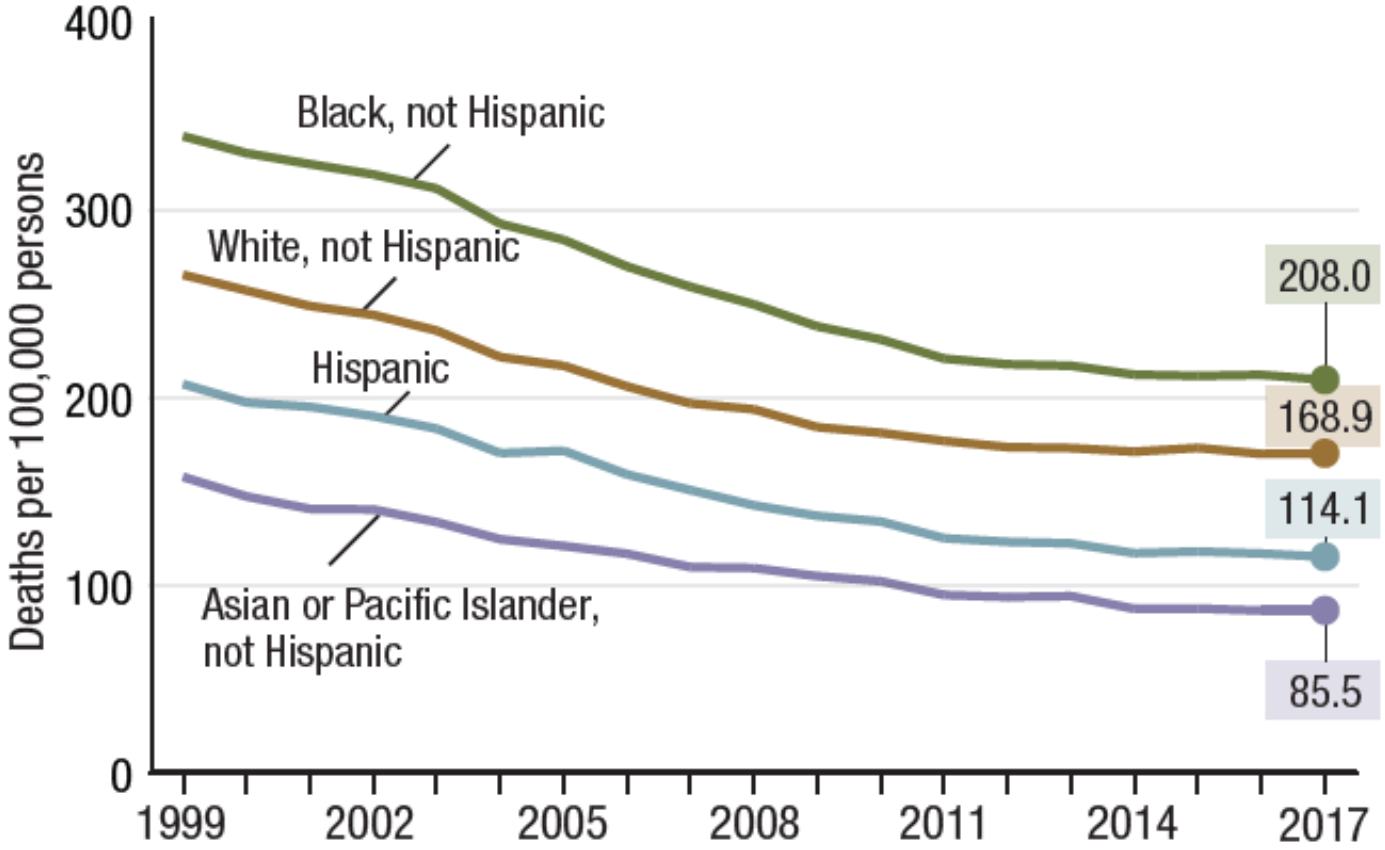
- Cardiovascular disease risk and Diabetes: scope of the problem
- Estimating individual CVD risk
- Risk factor modification > LDL reduction

Cardiovascular Disease Mortality: U.S. Males and Females 1980-2004



Source: Adapted from Rosamond 2008

Age-adjusted death rates for heart disease, by race and Hispanic origin: 1999–2017



- Cardiovascular disease is the leading cause of death for African Americans, Latinos, Asian Americans, Pacific Islanders, and American Indians
- African American women are at the highest risk for death from heart disease among all racial, ethnic, and gender groups

National Center for Health Statistics (NCHS), National Vital Statistics System (NVSS).

WELL-AHEAD

Project ECHO

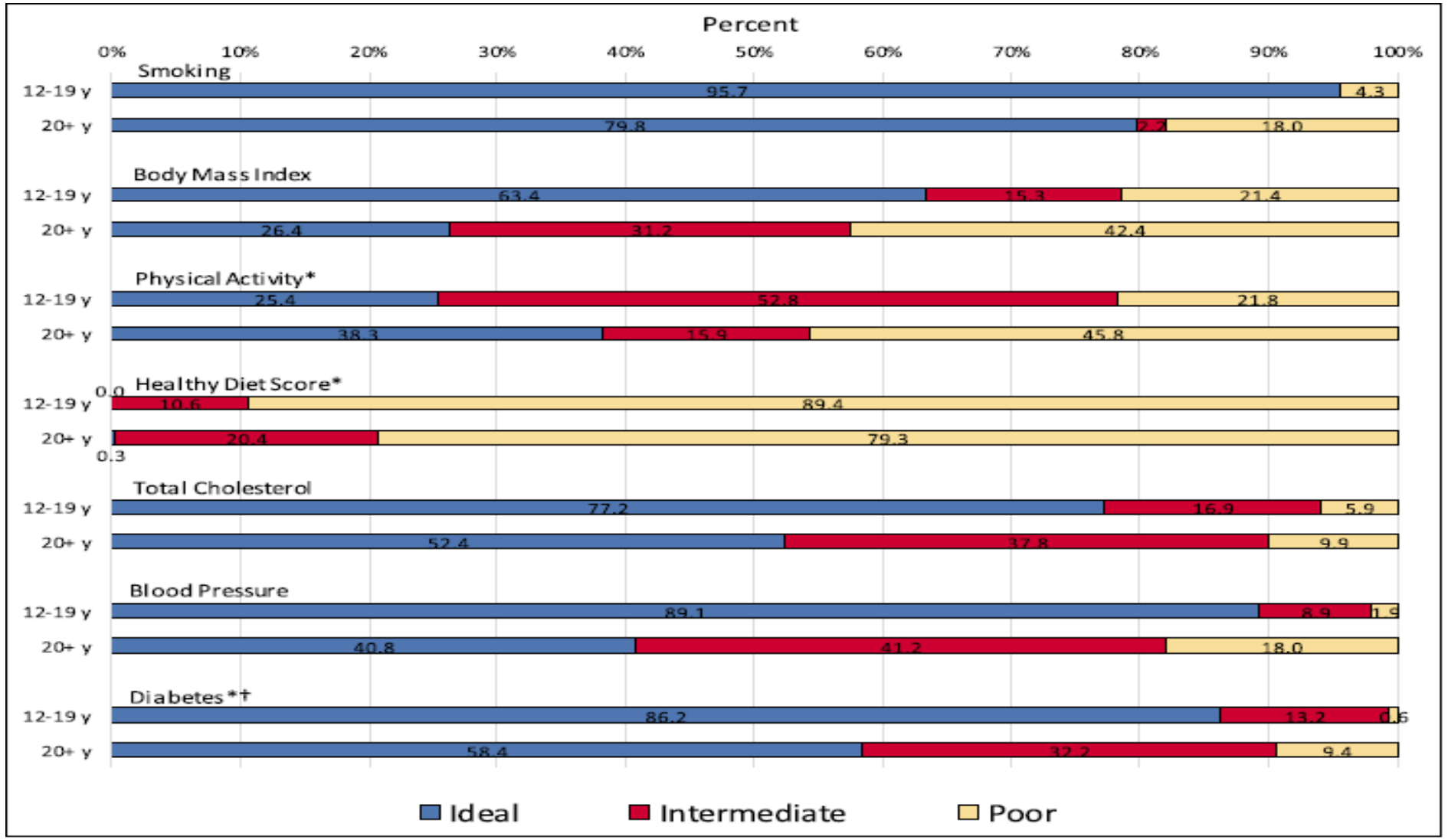
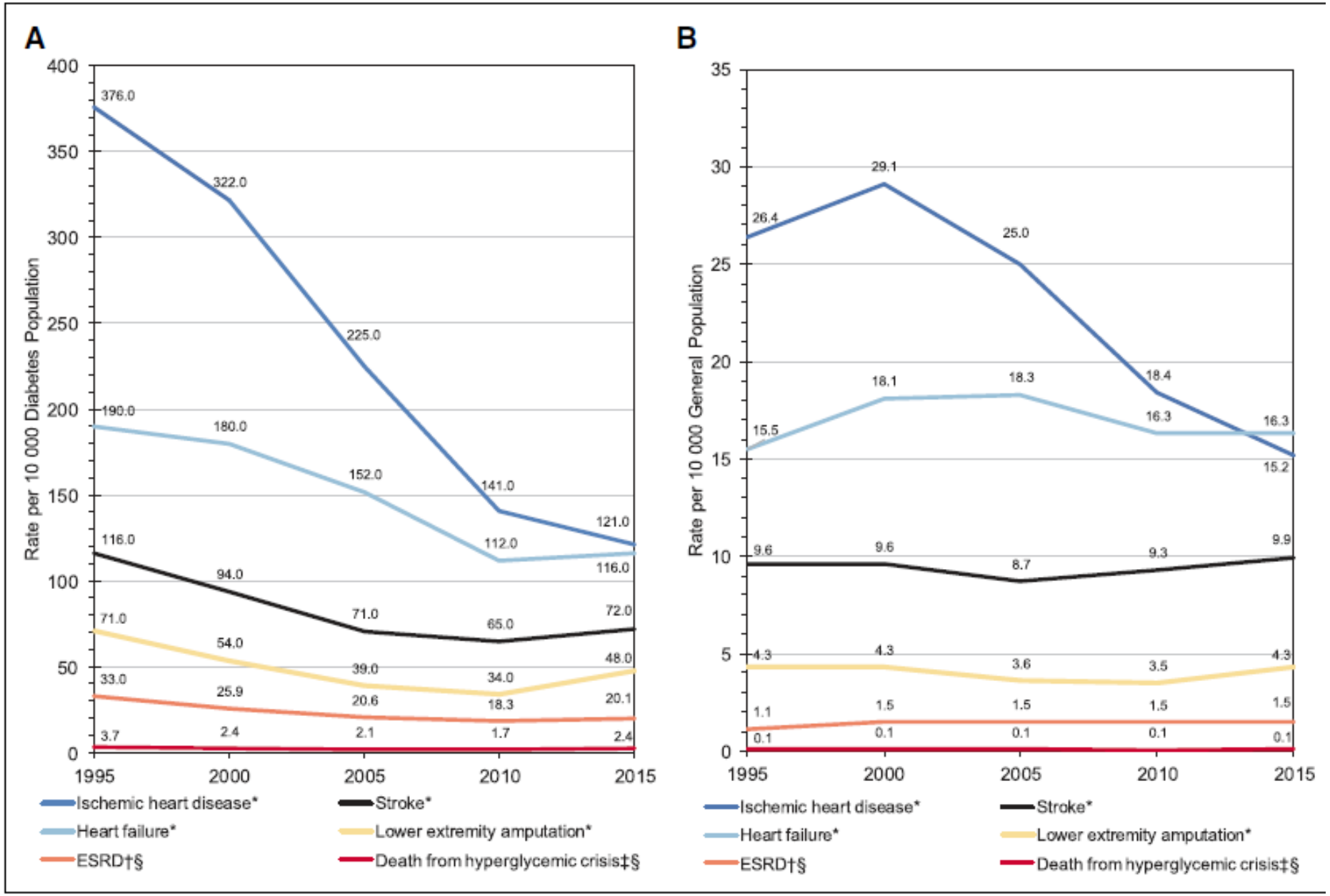


Chart 2-1. Prevalence estimates of poor, intermediate, and ideal cardiovascular health (CVH) for each component of CVH among US children 12 to 19 years of age and US adults ≥20 years of age, 2015 to 2016 and 2017 to 2018.

AHA Heart Disease and Stroke Statistics – 2021 Update. Virani et.al. Circ. 2021; 143:e254-e743.



Trends in age-standardized rates of diabetes-related complications among US adults ≥18 years of age from 1995 to 2015.

TRADITIONAL RISK FACTORS

- Age > 65 years
- Male sex
- Family history
- Others

- High Blood Pressure
- High Cholesterol
- Smoking
- Physical inactivity
- Diabetes

IRREVERSIBLE

REVERSIBLE

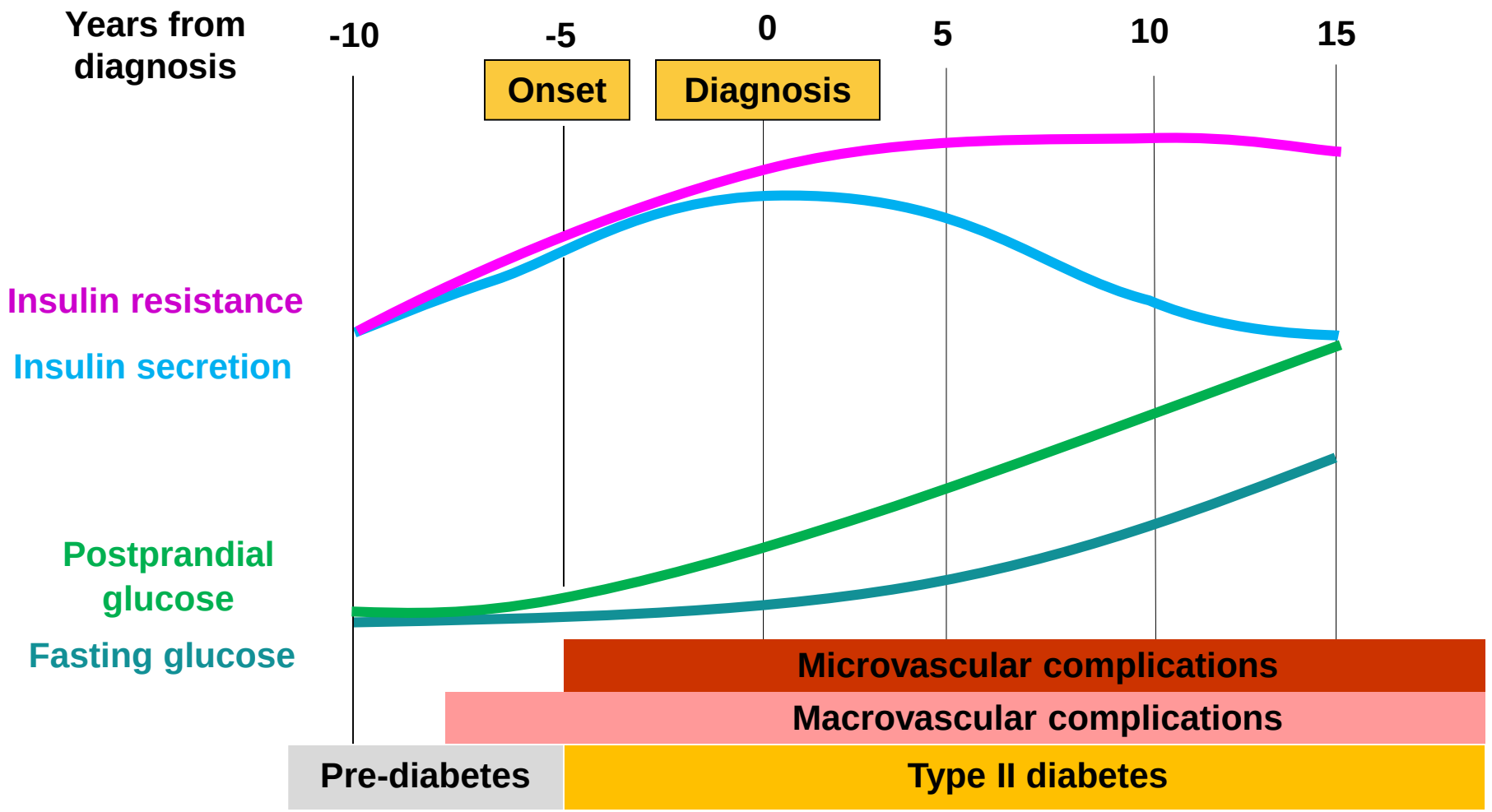
Estimating Individual risk

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

Diabetes and Cardiovascular Disease

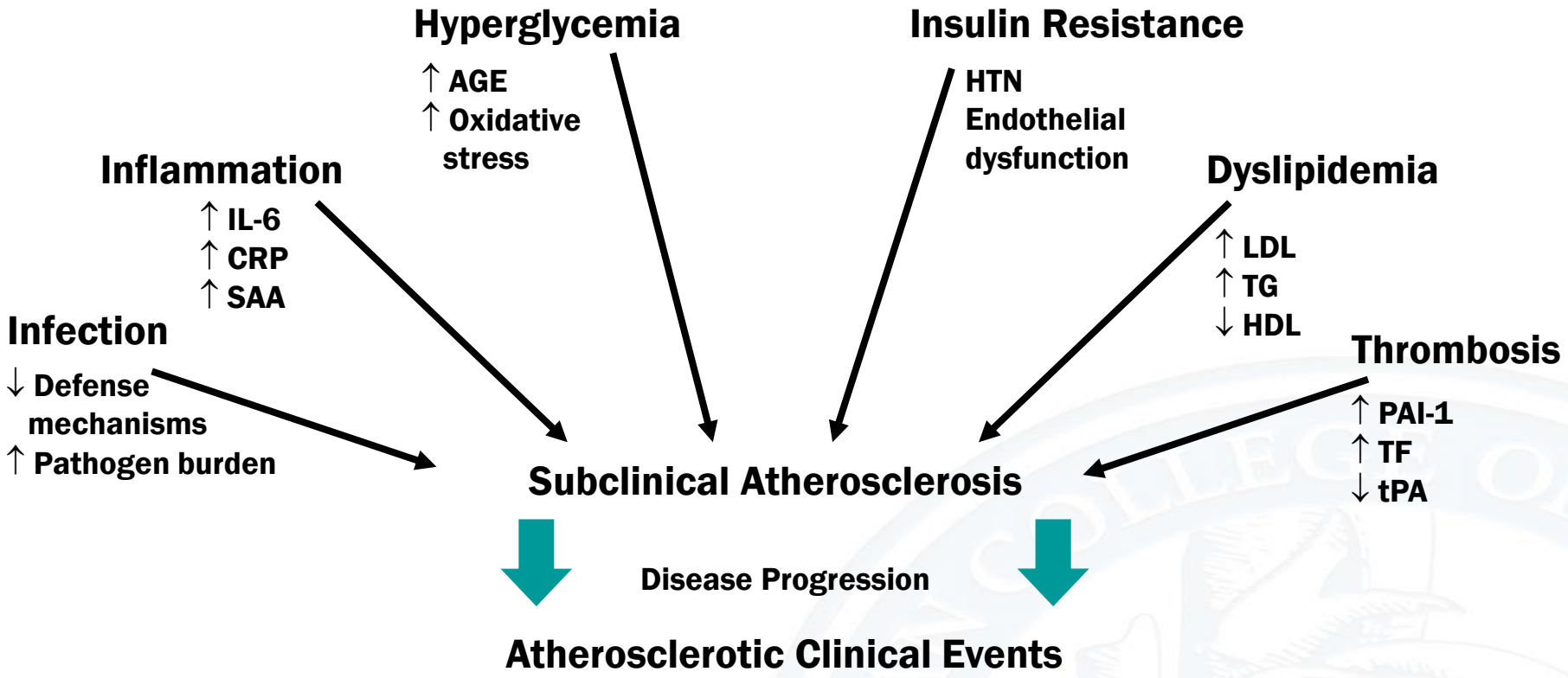
- Diabetes
- Pre-Diabetes
- Metabolic Syndrome

Natural History of Type II Diabetes Mellitus



Sources:
Ramlo-Halsted BA et al. *Prim Care.* 1999;26:771-789
Nathan DM et al. *NEJM* 2002;347:1342-1349

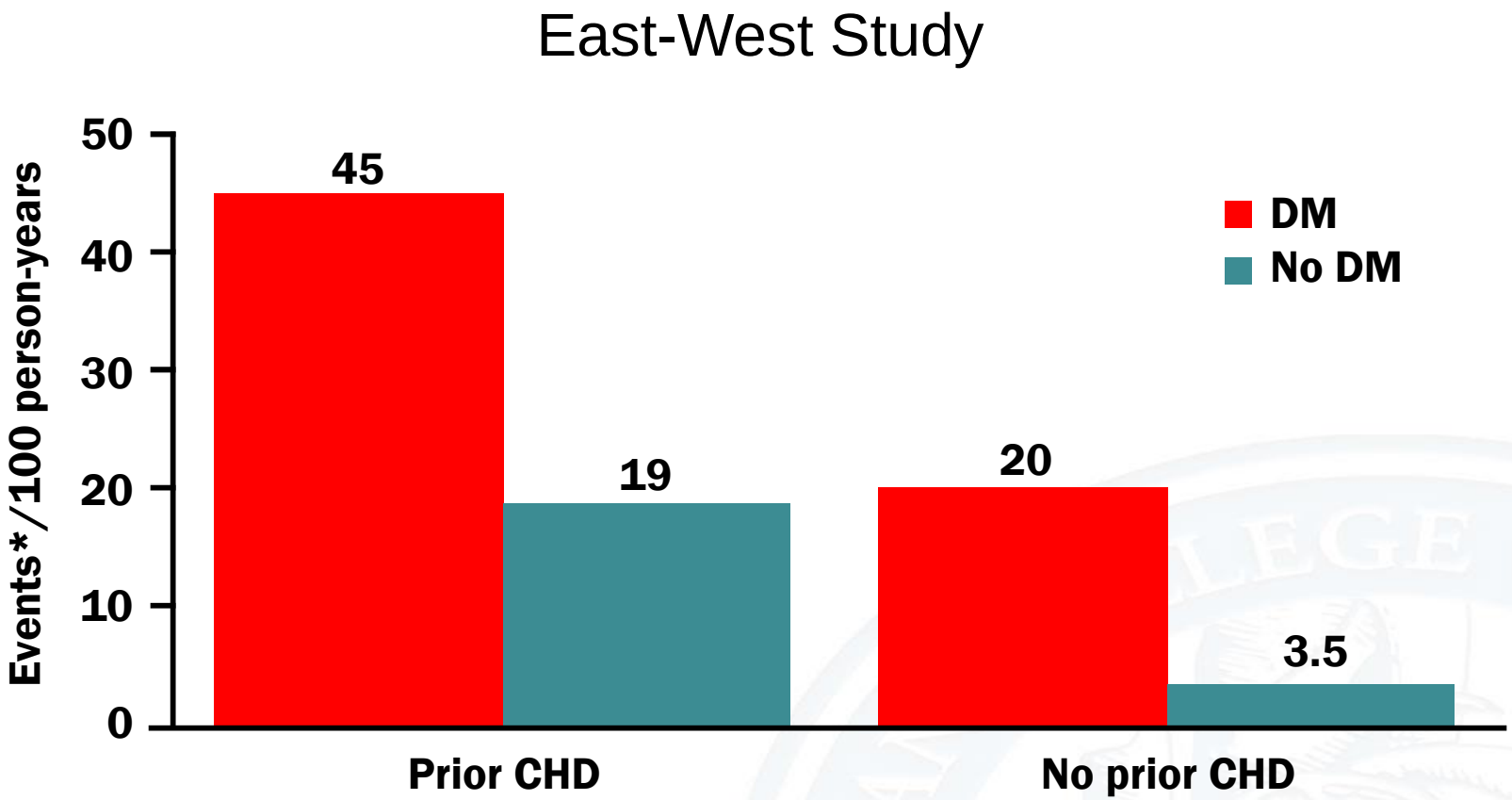
Mechanisms by which Diabetes Mellitus Leads to Coronary Heart Disease



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

Diabetes Mellitus: Risk of Myocardial Infarction



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

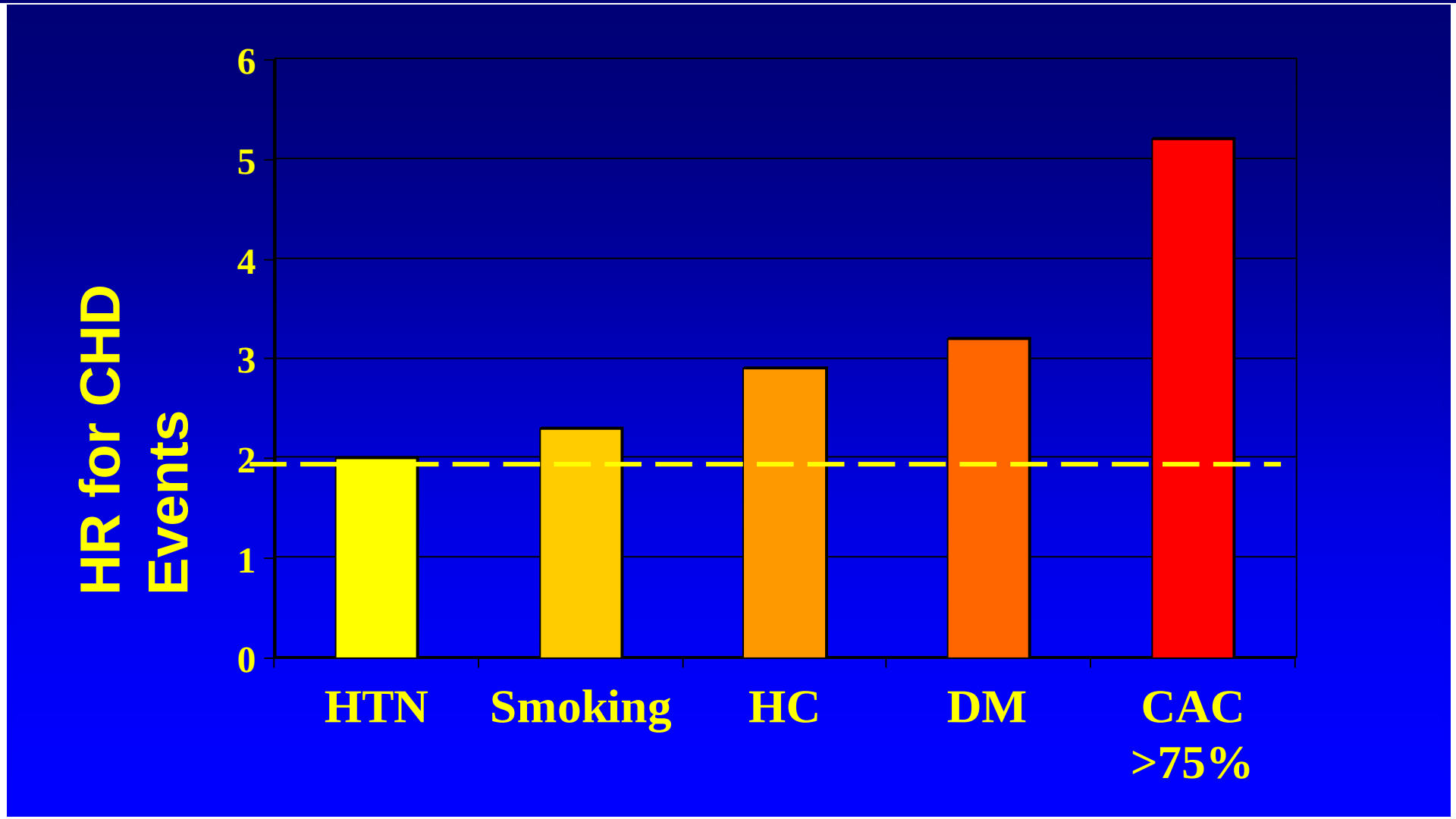
*Fatal or non-fatal MI

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

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

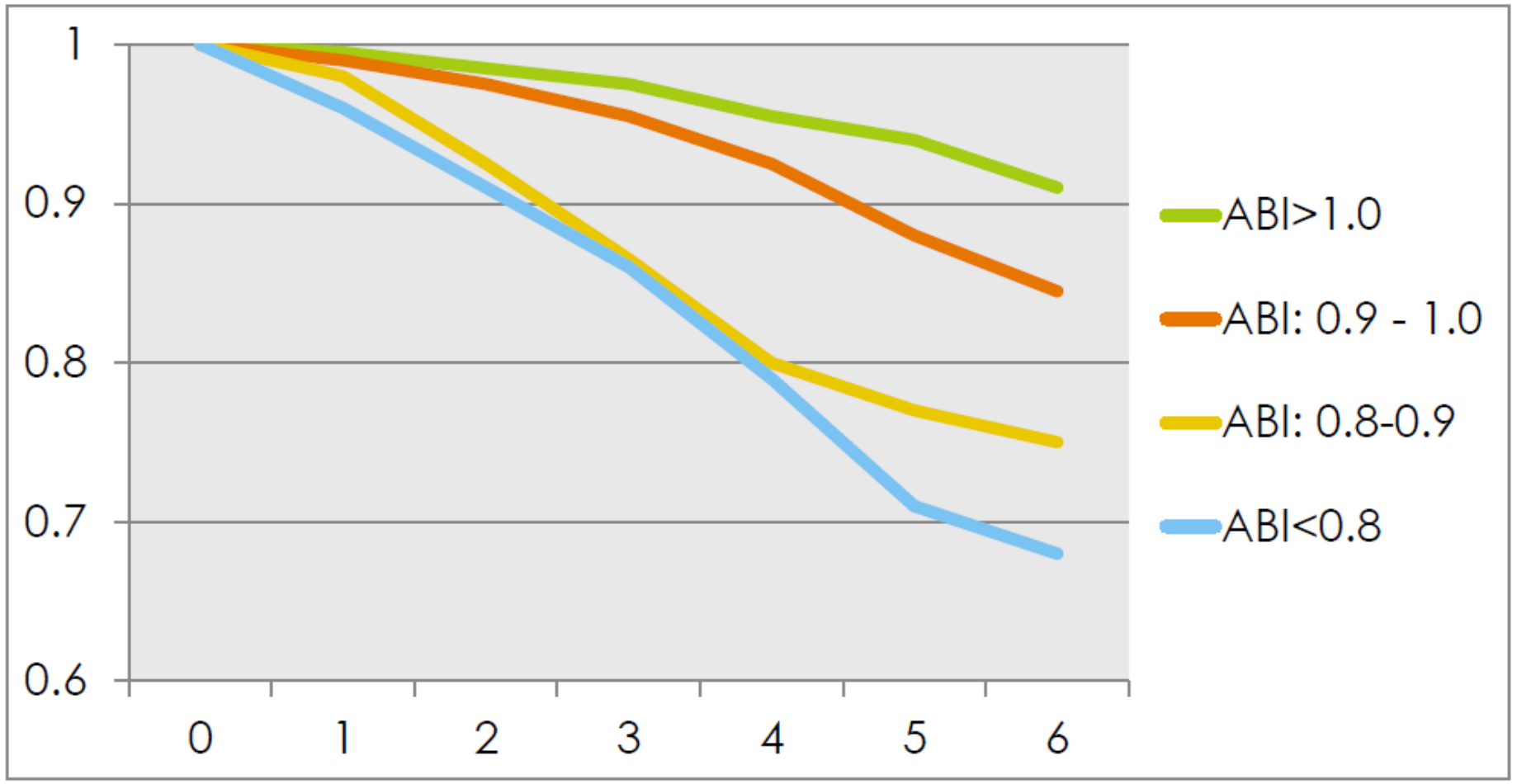
Leber A et al, Am Heart J 2007 (in press)

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



Ankle-Brachial Index (ABI)

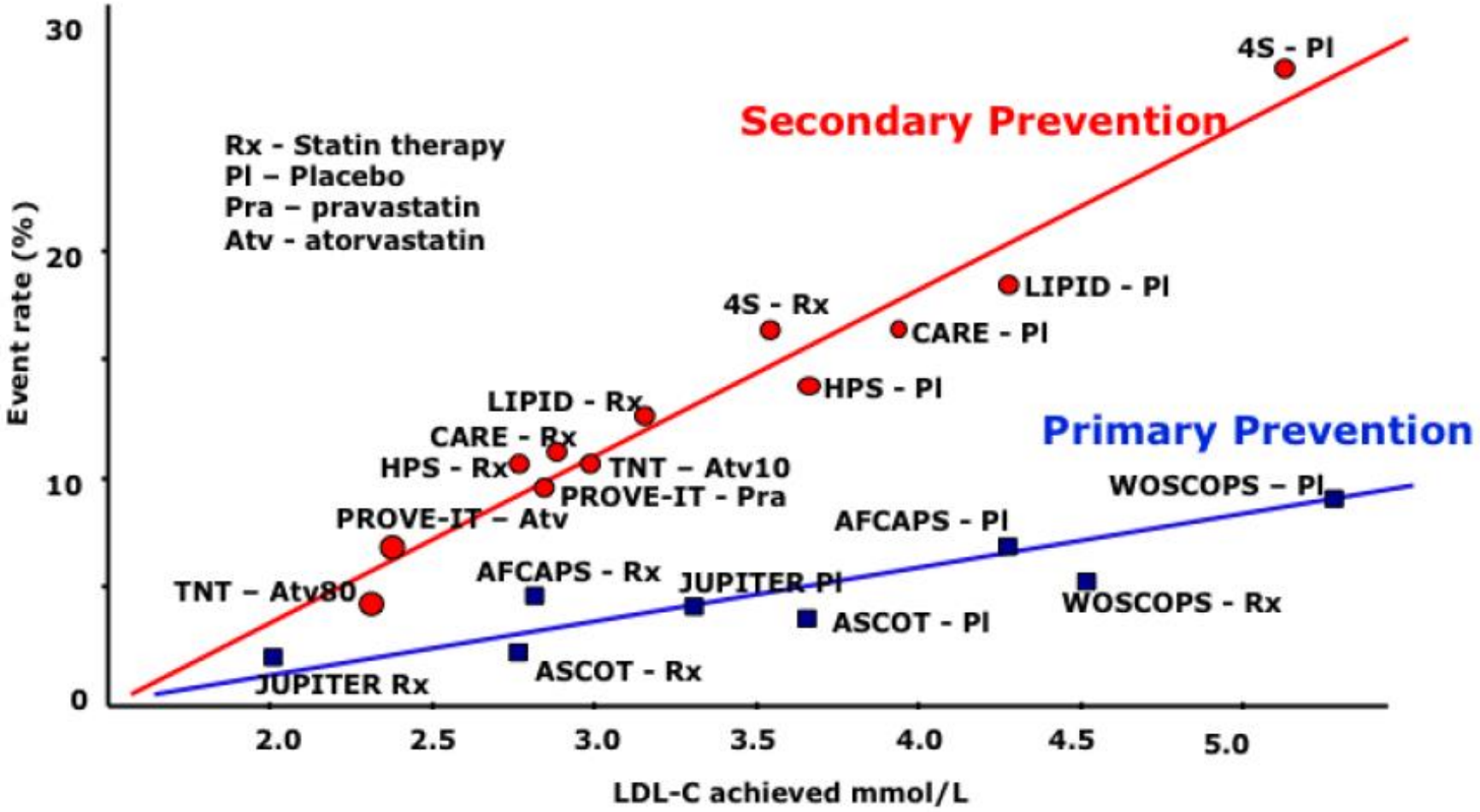
Patient survival by ABI in Cardiovascular Health Study…



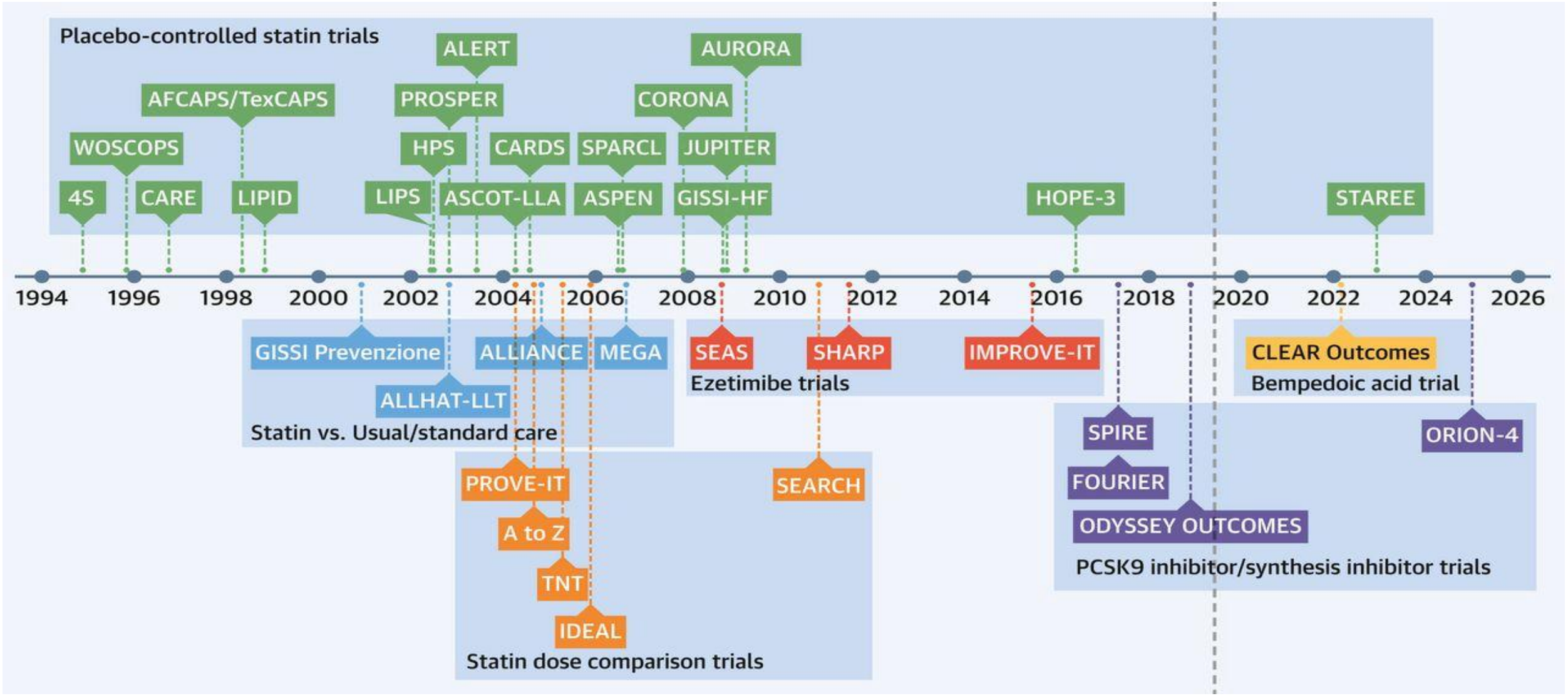
Newman et al ATVB 1999;19; 538-545

LDL Reduction

Reducing LDL > Reduced CV events

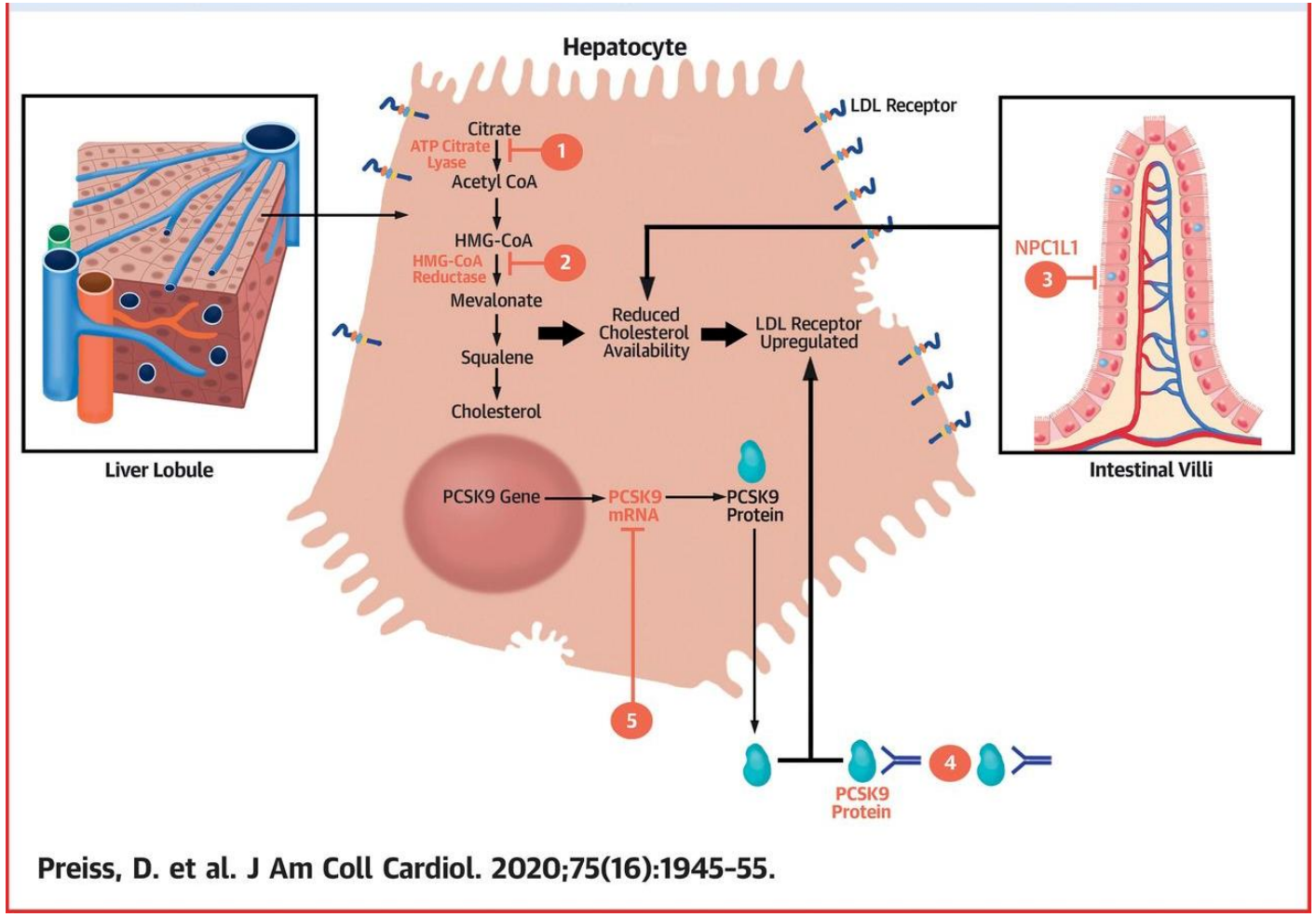


New Engl J Med 2005;352:1425



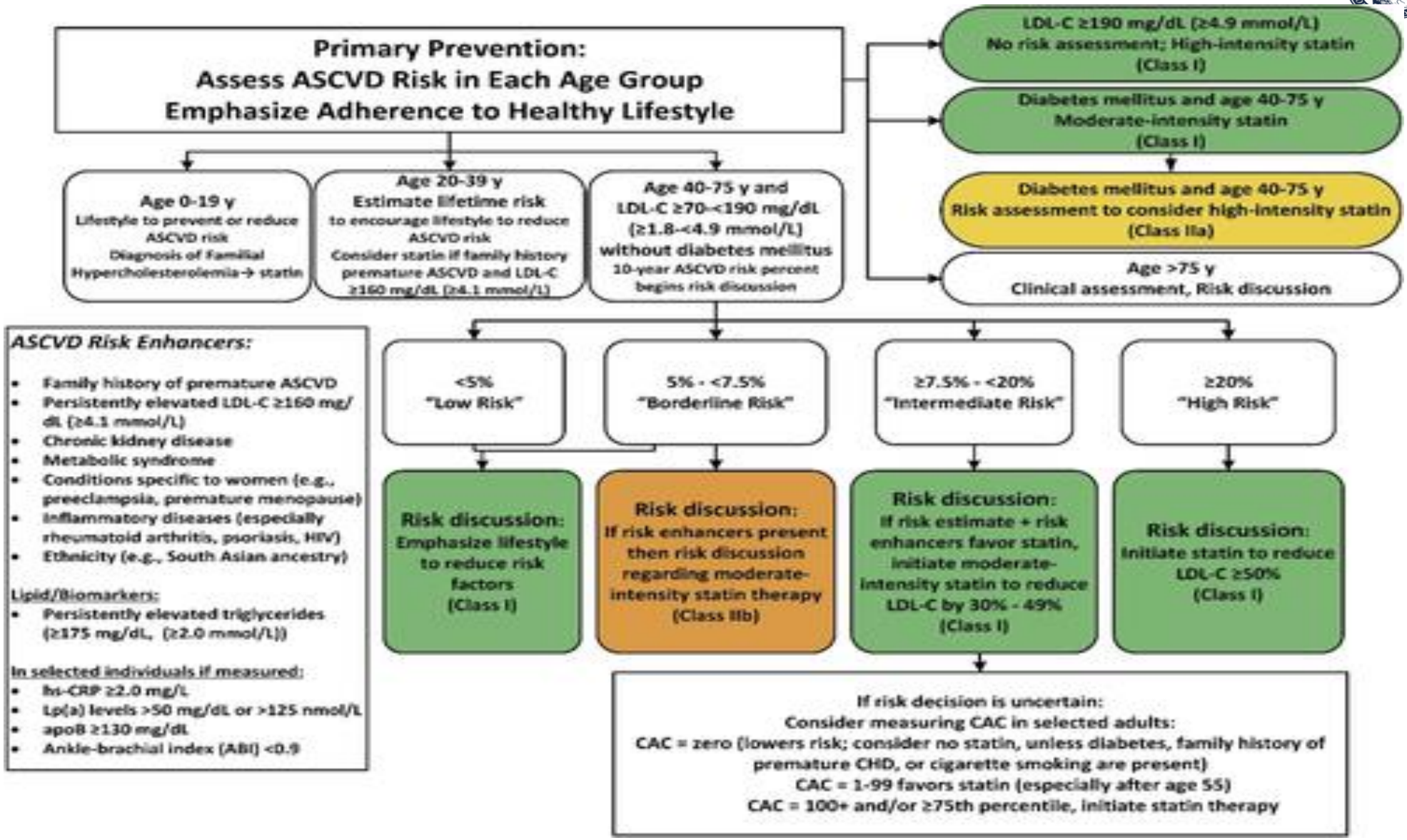
David Preiss et al. J Am Coll Cardiol 2020;75:1945-1955

Many therapeutic options to reduce LDL…

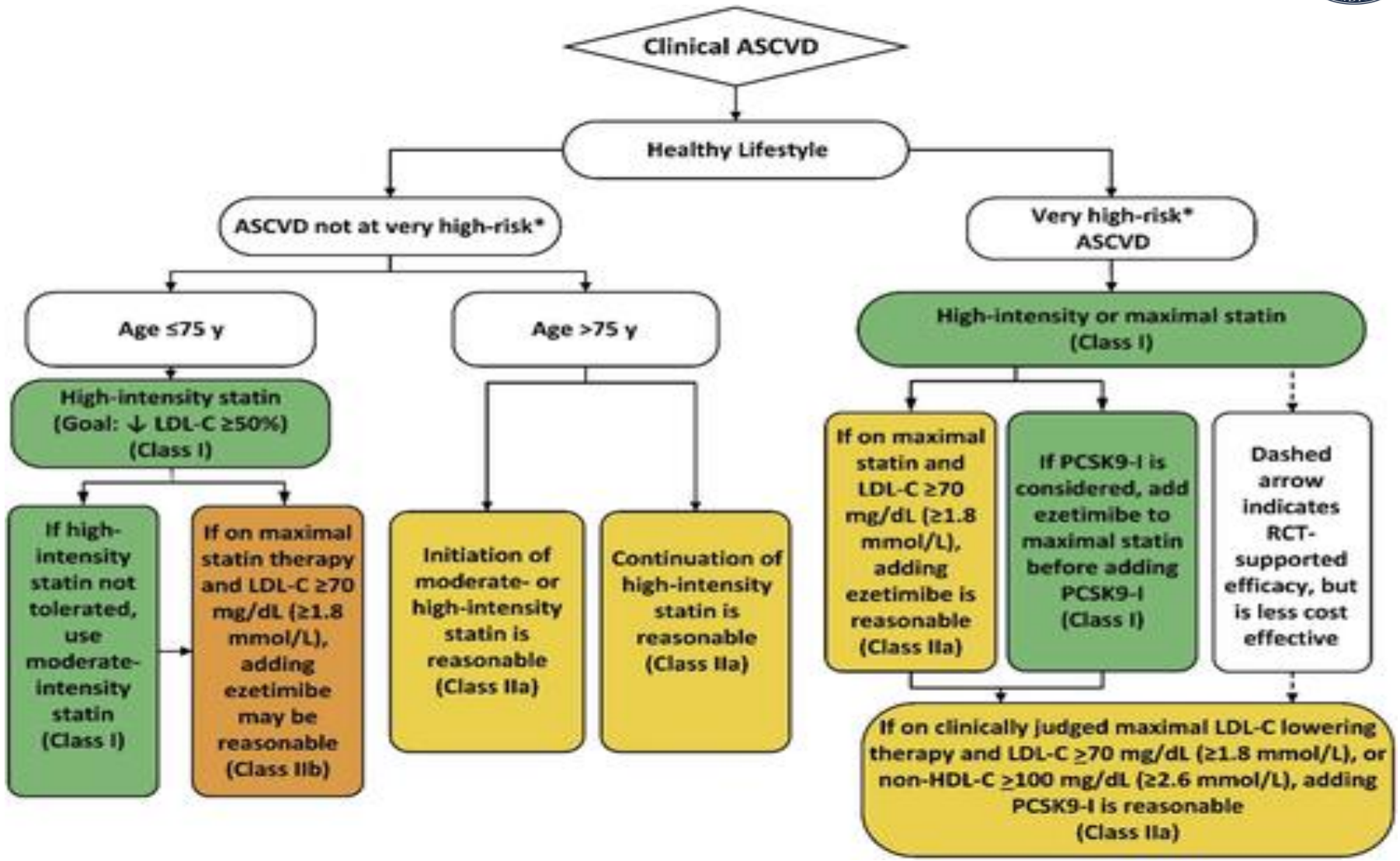


1. **Bempedoic acid (Nexletol)**
2. **Statins**
3. **Ezetemibe (Zetia)**
4. **PCSK9 Inhibitors**
5. **Inclisiran (Leqvio)**

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



Scott M. Grundy et al. *J Am Coll Cardiol* 2018; 73:e285-e350.

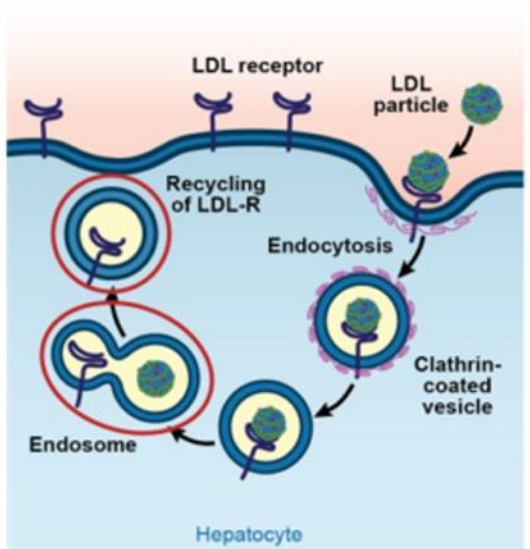


Scott M. Grundy et al. *J Am Coll Cardiol* 2018; 73:e285-e350.

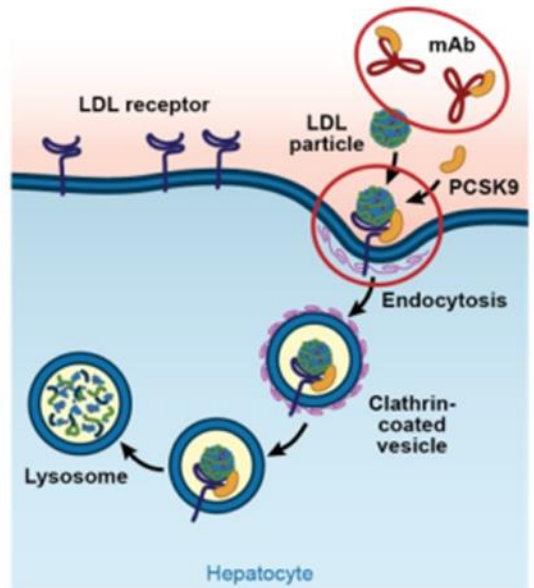
Background

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.

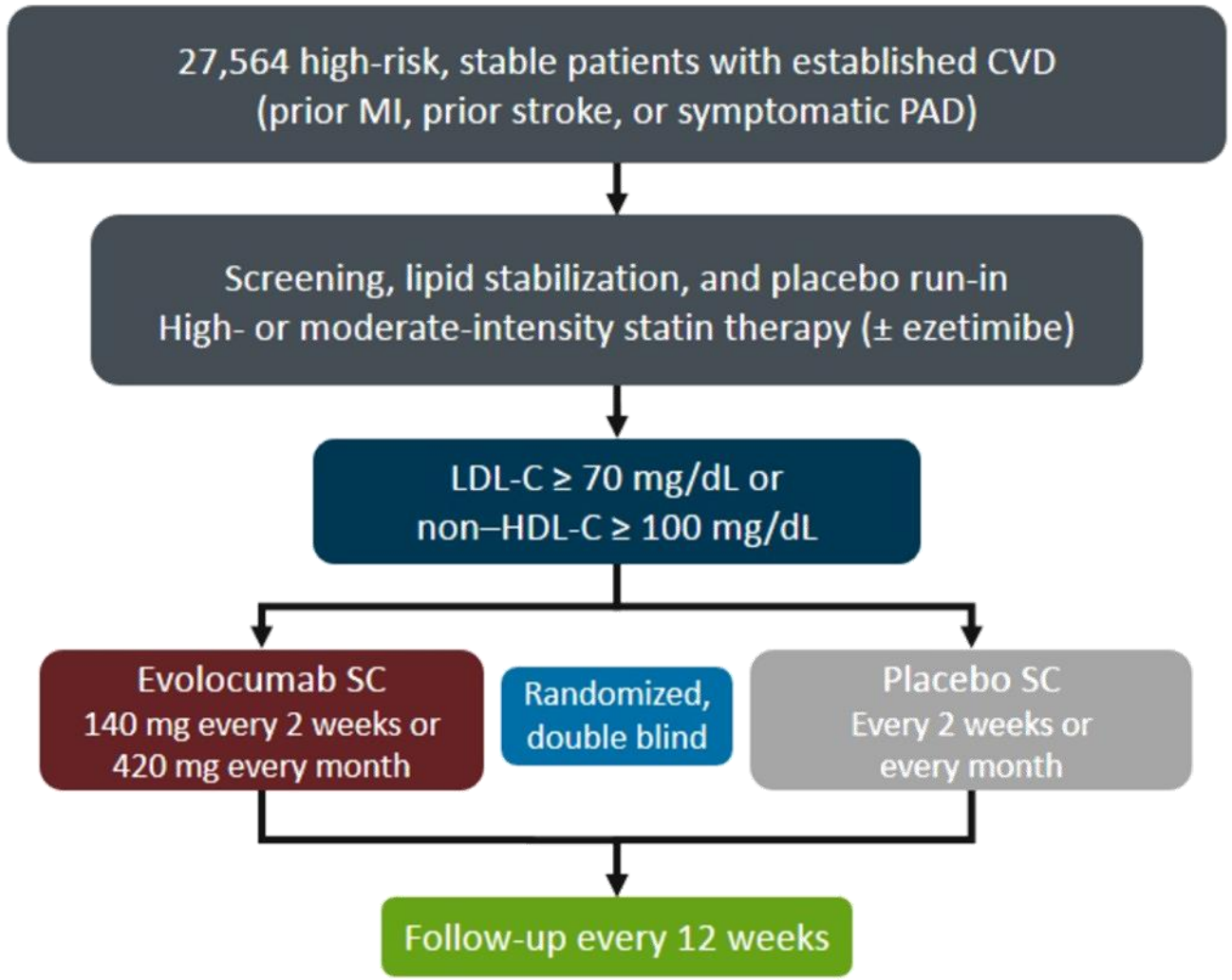
Alirocumab (Praluent)

- 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 ½ = 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 ½ = 11-17 days
- Hepatic elimination

FOURIER Trial Design

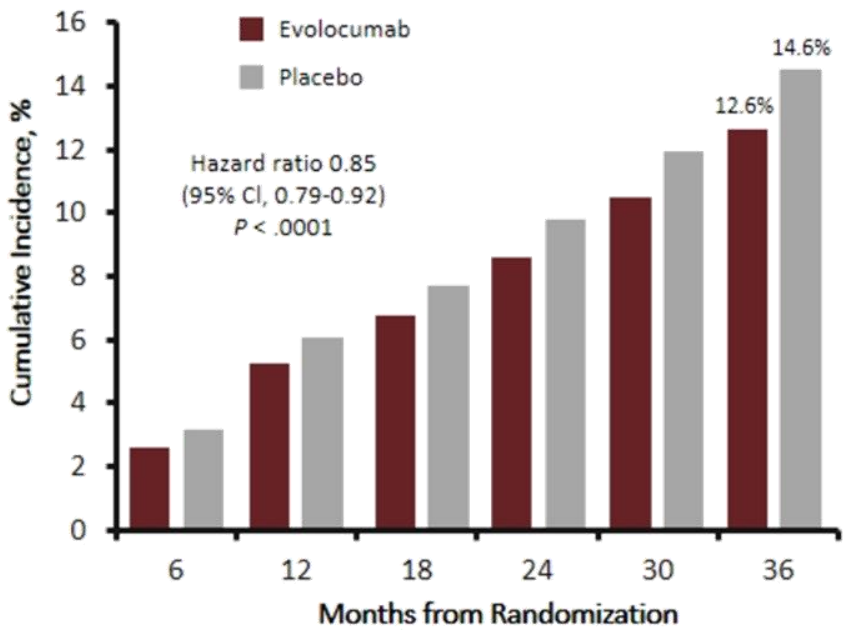


Sabatine MS, et al. *Am Heart J.* 2016;173:94-101.

FOURIER: Results

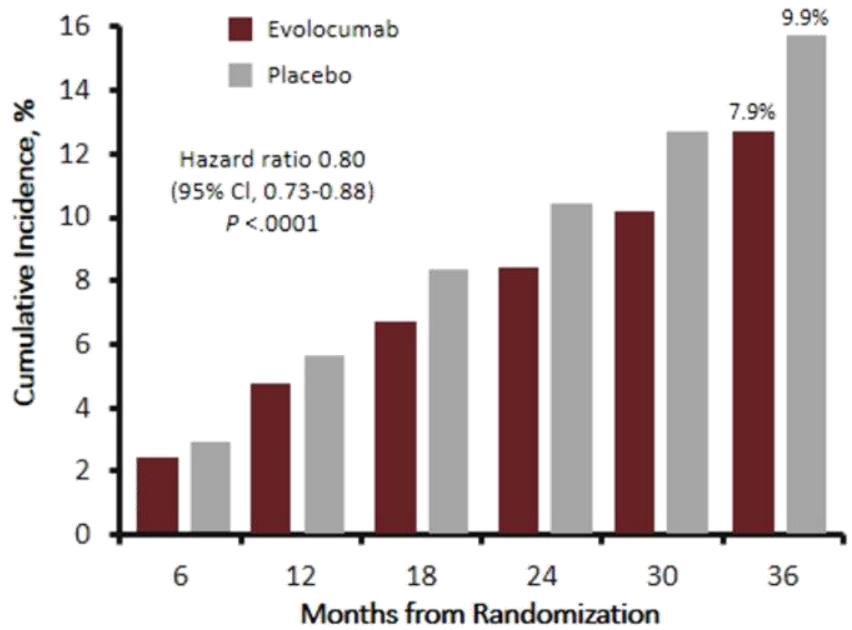
Primary Outcome

CV Death, MI, Stroke, Revascularization, or Hospitalization for UA



Secondary Outcome

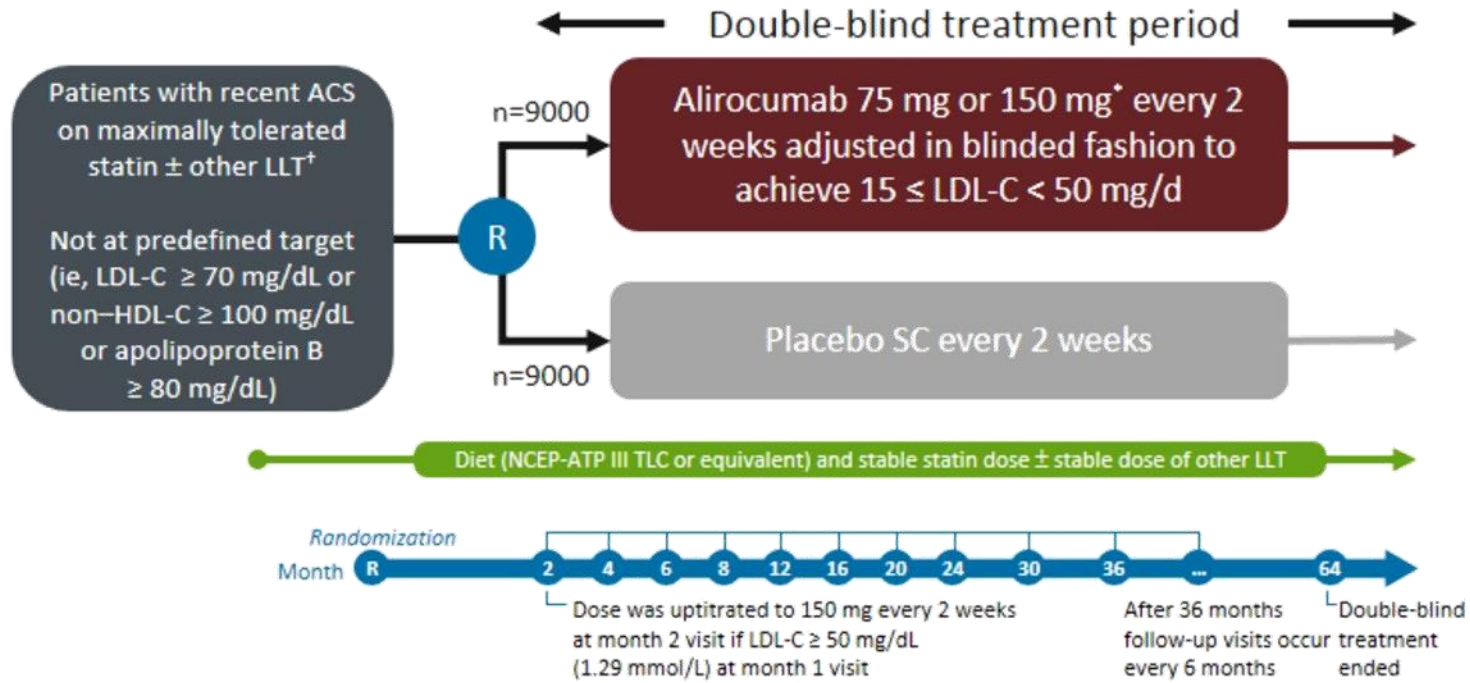
CV Death, MI, or Stroke



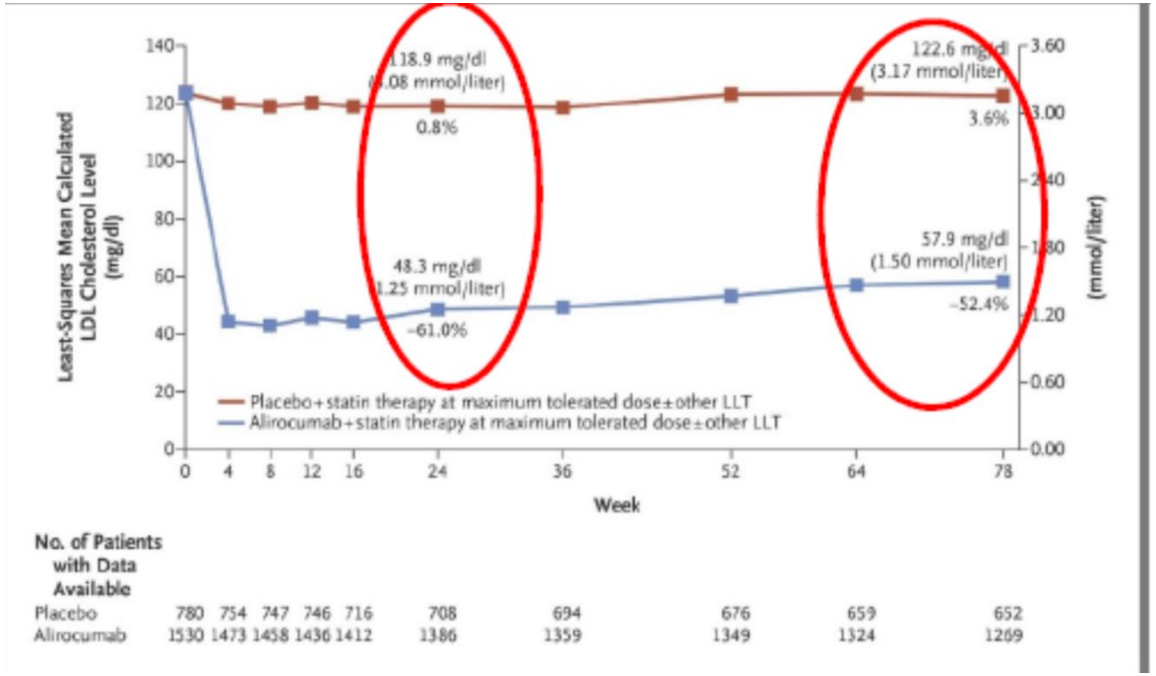
Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.

ODYSSEY OUTCOMES: Study Design

A randomized, double-blind, placebo-controlled study



*Dose titrated up to 150 mg every 2 weeks at month 2 if LDL-C ≥50 mg/dL (1.29 mmol/L) at month 1 visit.
†Atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg OR maximally tolerated dose of statin (can be 0 mg).
If LDL-C < 25 mg/dL on any 2 consecutive measurements on alirocumab 150 mg, the dose is reduced to 75 mg.
If LDL-C < 15 mg/dL on 2 consecutive measurements with alirocumab 75 mg, active treatment is discontinued at the next study visit and substituted with placebo.
Schwartz GG, et al. *Am Heart J*. 2014;168:682-689.e1; ClinicalTrials.gov. NCT01663402.



Cardiovascular adverse events of interest — no. of patients (%)			
Death from coronary heart disease, including death from unknown cause	4 (0.3)	7 (0.9)	0.26
Nonfatal myocardial infarction	14 (0.9)	18 (2.3)	0.01
Fatal or nonfatal ischemic stroke	9 (0.6)	2 (0.3)	0.35
Unstable angina requiring hospitalization	0	1 (0.1)	0.34
Congestive heart failure requiring hospitalization	9 (0.6)	3 (0.4)	0.76
Ischemia-driven coronary revascularization procedure	48 (3.1)	24 (3.0)	1
Positively adjudicated cardiovascular events, including all cardiovascular adverse events listed above	72 (4.6)	40 (5.1)	0.68
Adjudicated major adverse cardiovascular events in post hoc analysis‡	27 (1.7)	26 (3.3)	0.02

GLAGOV

(Nicholls SJ, Puri R, Anderson T, et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. *JAMA* 2016;316:2373-84)

- Evolocumab/statin Vs Placebo/statin in non-obst CAD
- 968 patients followed with serial IVUS studies
- Evolocumab arm mean LDL 37 Vs 93
- PAV (percent atheroma volume):
    - 0.05% increase in statin arm
    - 0.95% DECREASE in PCSK9 arm
    - 64% in Evolocumab arm showed plaque regression
- Regression was more likely when LDL was < 60

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 Cardiovascular risk of Diabetes
- Err on the side of starting “high-intensity” statin tx if patient is able to tolerate
- Novel Anti-lipidemic therapies: PCSK9 Inhibitor tx

THANK YOU