Cholesterol-Lowering Therapy in Secondary and Primary Prevention
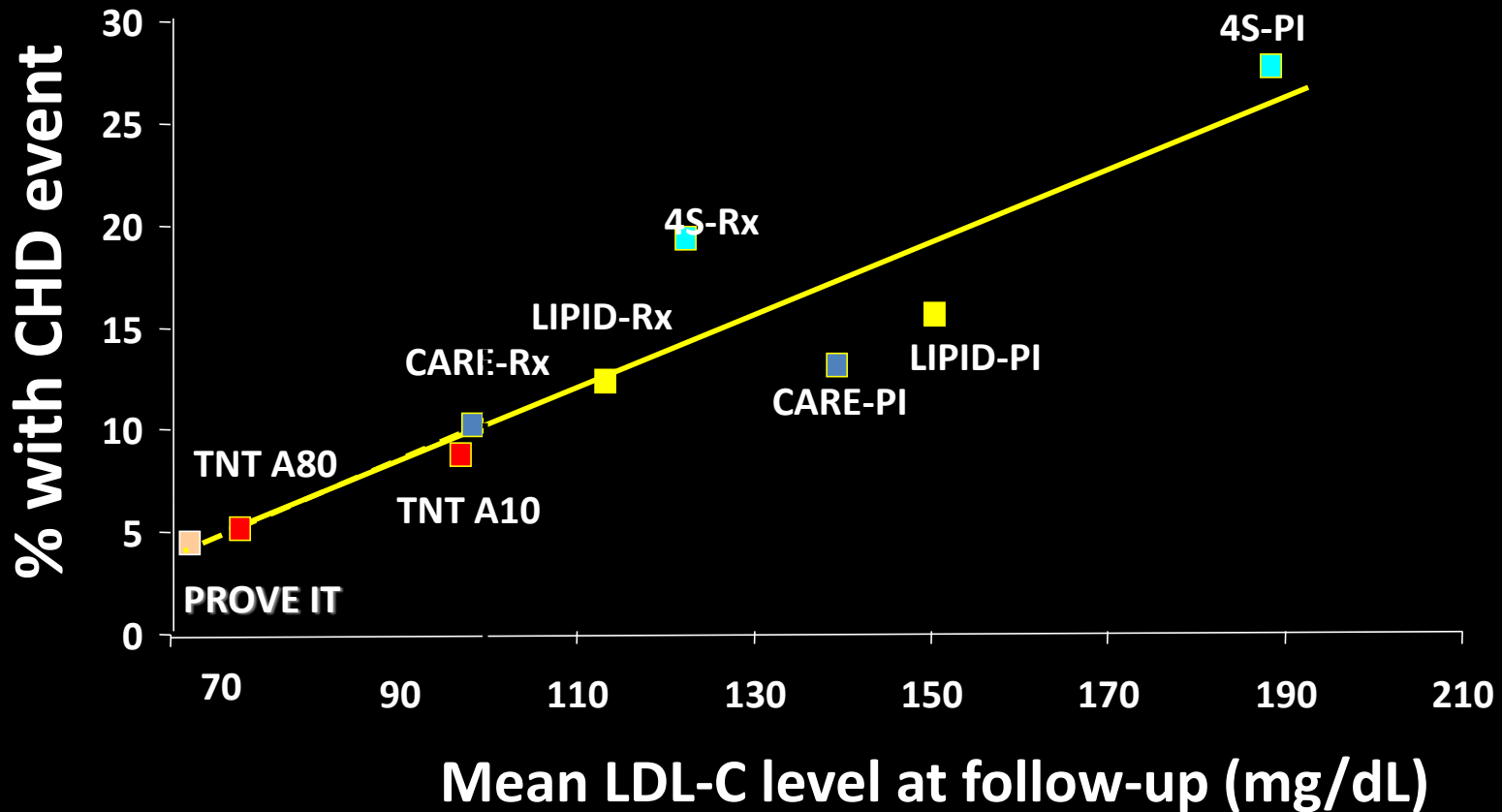
Scott M. Grundy MD PhD

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COI: None

Secondary Prevention:
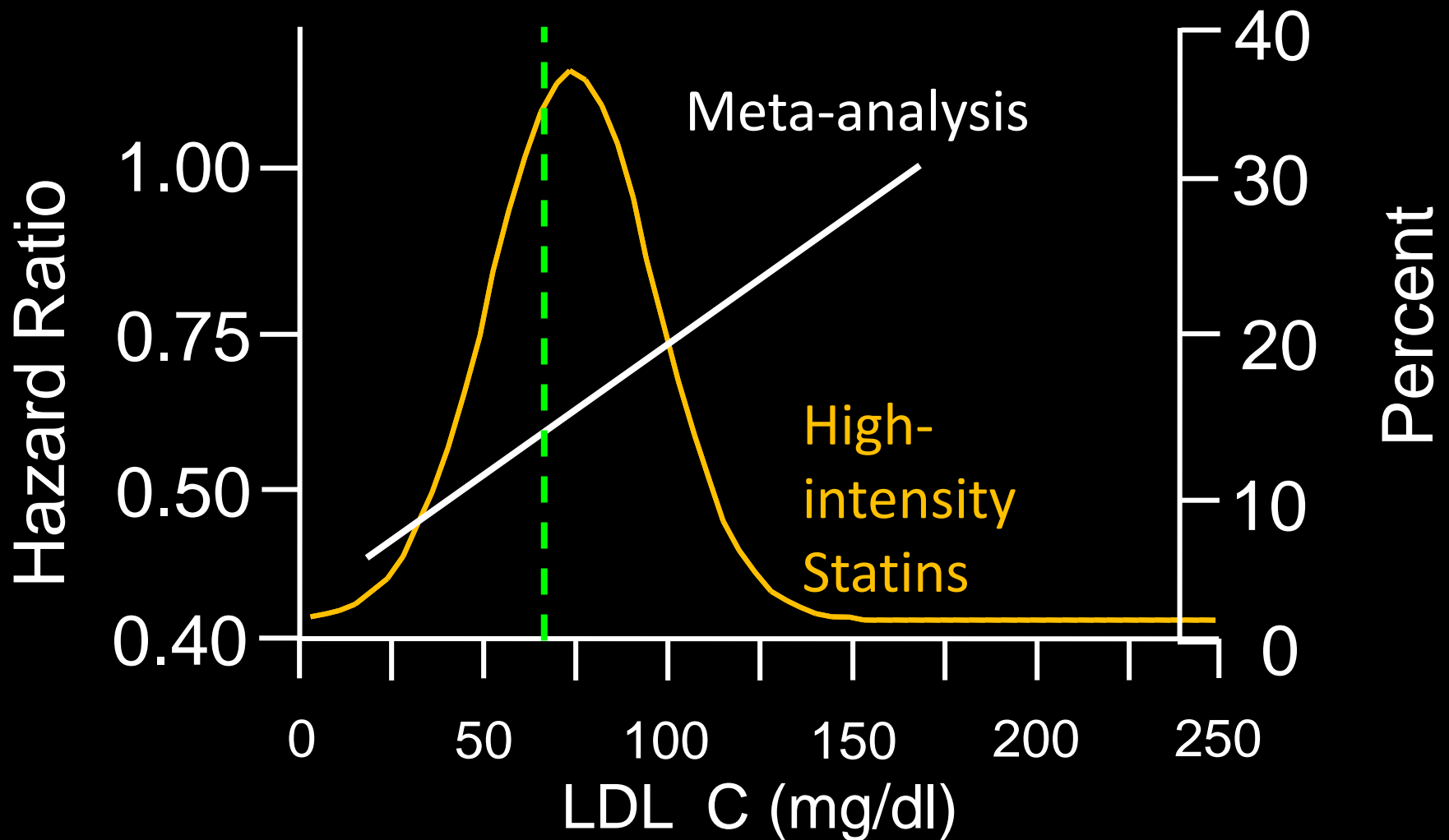# Is the Lower, the Better for LDL-C?

PI=placebo; Rx=treatment
4S Study Group. *Lancet.* 1995;345:1274-1275.
Sacks FM et al. *N Engl J Med.* 1996;335:1001-1009.
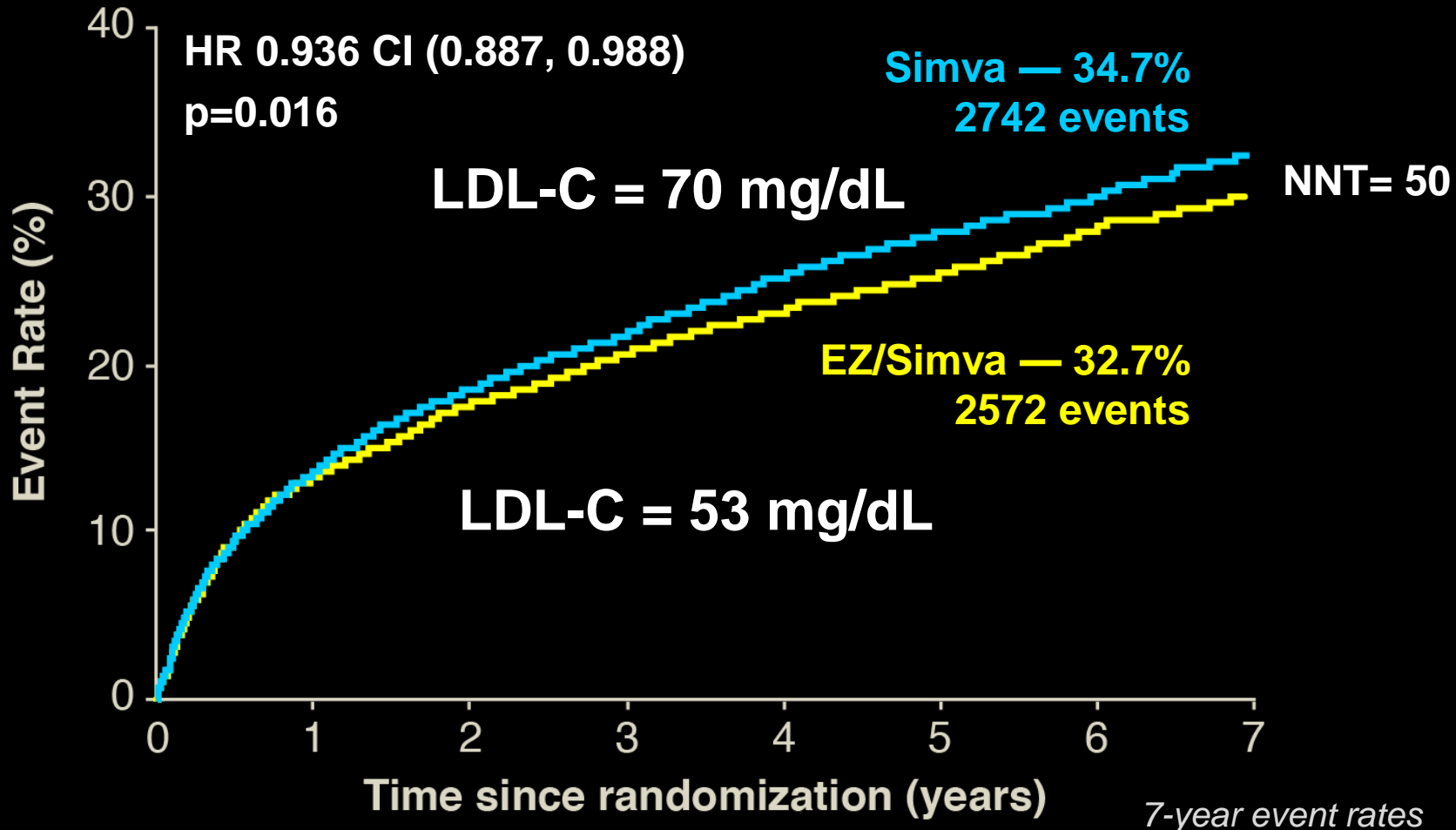LIPID Study Group *New Engl J Med. 1998:339:1349-1357,*

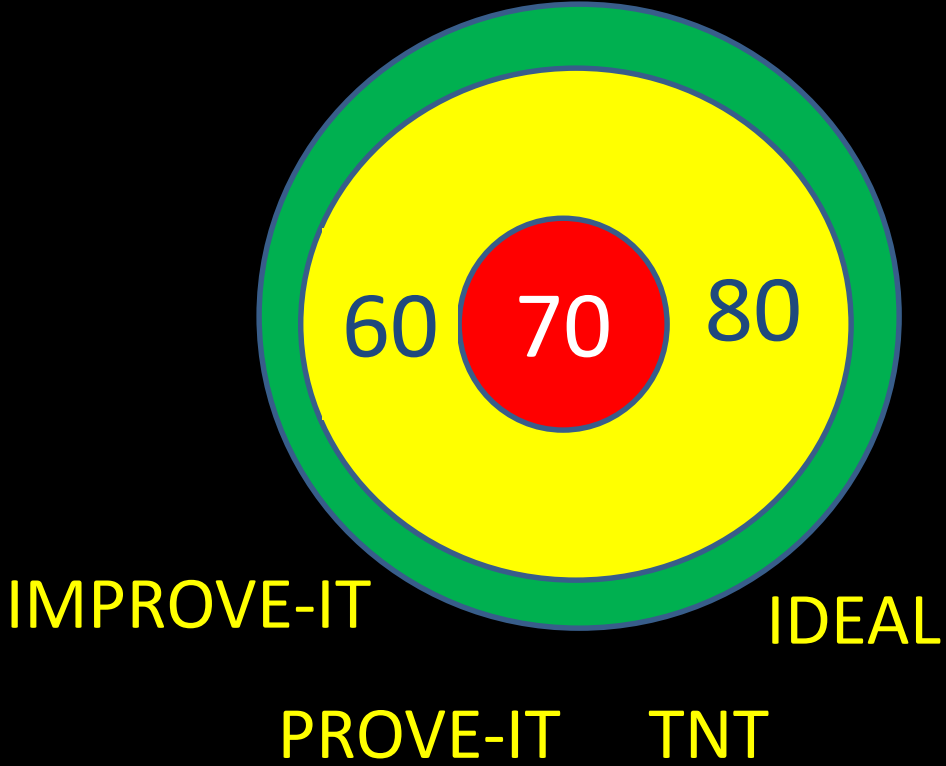# Secondary Prevention:
Is the Lower, the Better for LDL-C

Boekholdt et al. JACC 2014;64:485-94

Primary Endpoint — ITT

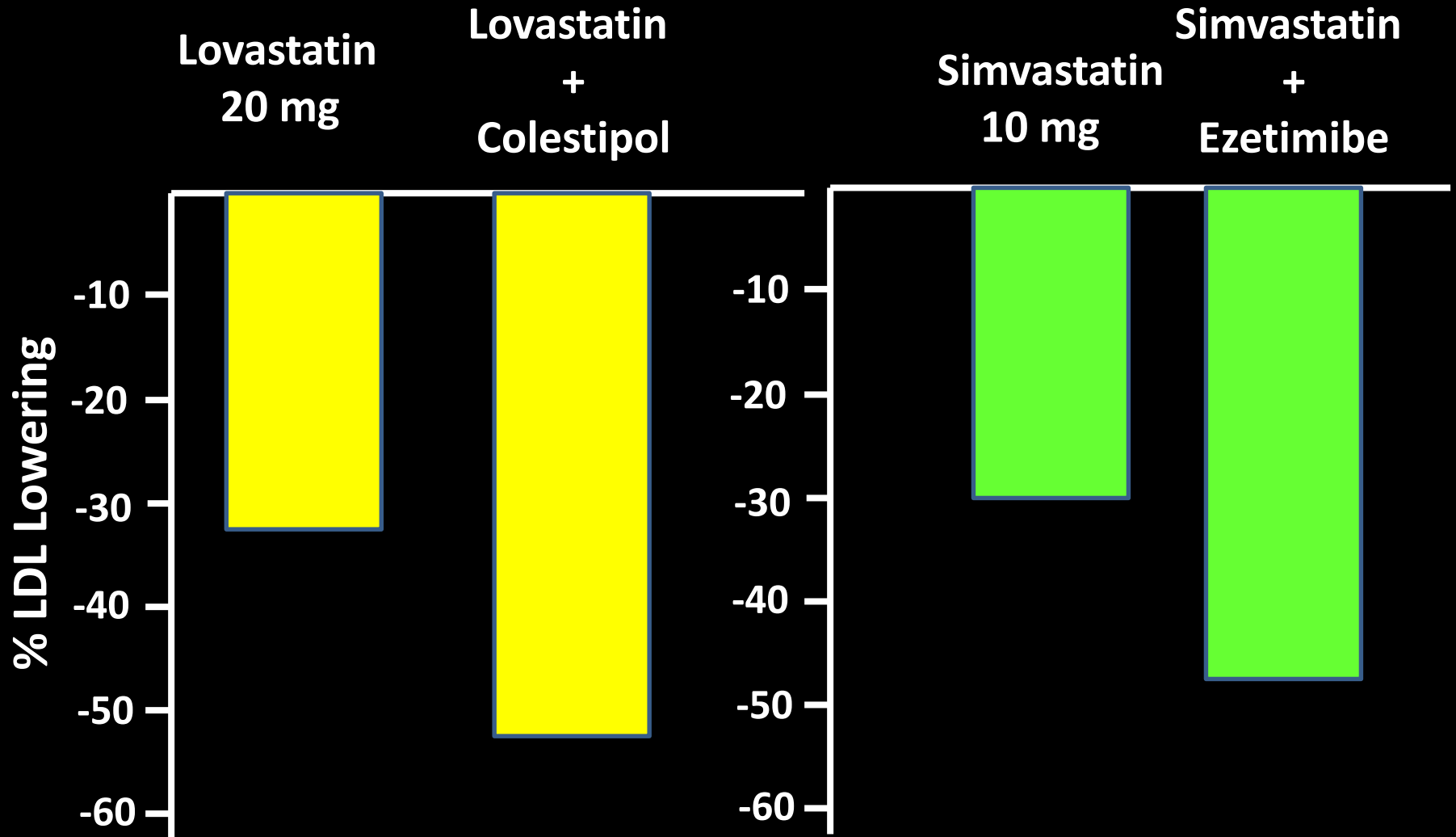*Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke*

HR 0.936 CI (0.887, 0.988)
p=0.016

Simva — 34.7%
2742 events

NNT= 50

LDL-C = 70 mg/dL

EZ/Simva — 32.7%
2572 events

LDL-C = 53 mg/dL

Event Rate (%)
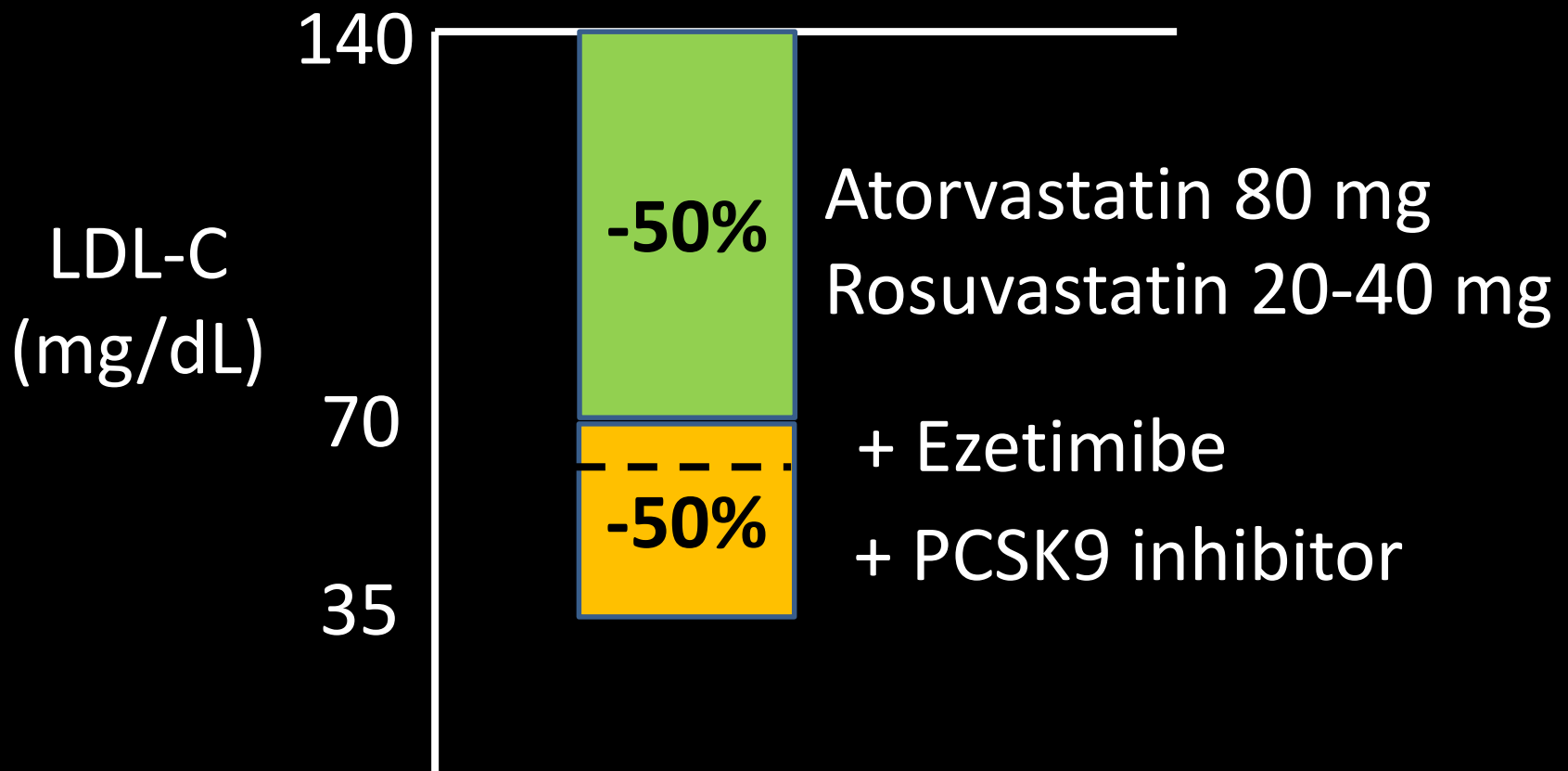
Time since randomization (years)

7-year event rates

What is a Reasonable LDL-C Target?

What are options for intolerance to high-intensity statins?

What is the Future of LDL-Lowering Therapy?

LDL-C (mg/dL)

140

-50% — Atorvastatin 80 mg
Rosuvastatin 20-40 mg

70

-50% — + Ezetimibe
+ PCSK9 inhibitor
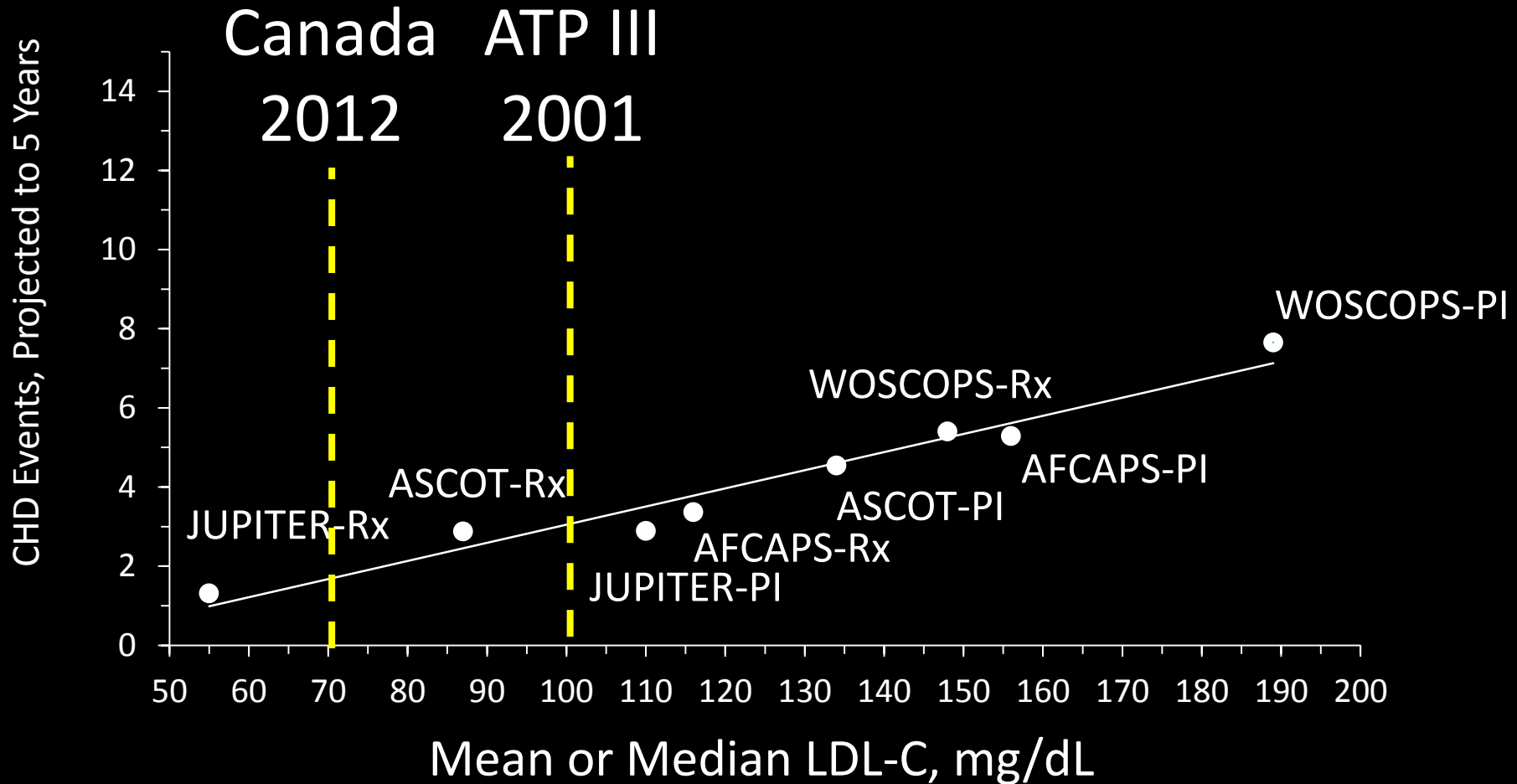
35

AHA/ACC Guidelines 2013: Primary Prevention

- Before initiation of statin therapy for the primary prevention of ASCVD in adults with LDL-C 70–189 mg/dL without clinical ASCVD or diabetes, it is reasonable for clinicians and patients to engage in a discussion that considers the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions, as well as patient preferences for treatment.
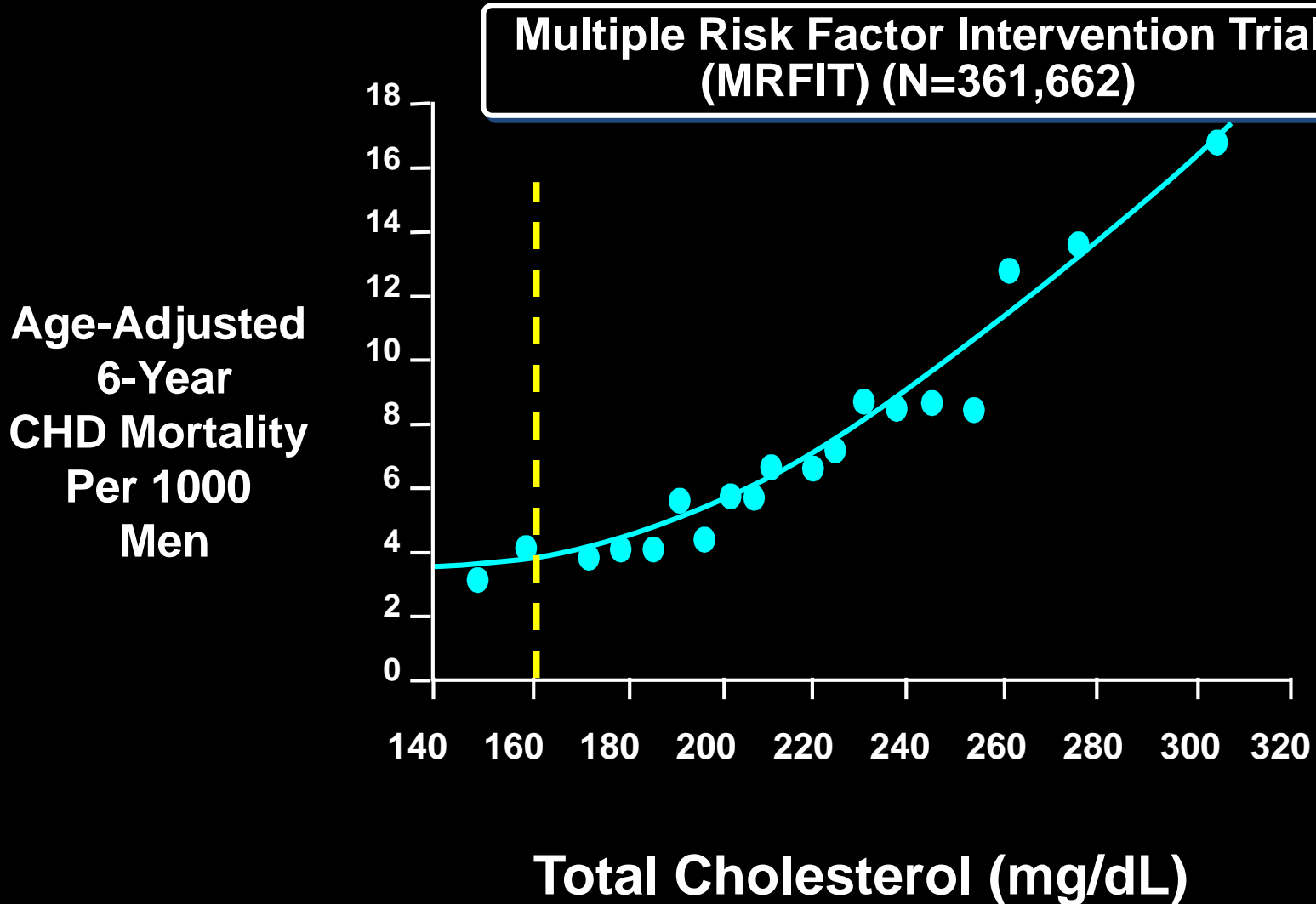
What should be discussed with patients in primary prevention?

- How low should we lower LDL-C?
- At what age should we start LDL lowering?
- What are reasonable indications for statins?
- Can we trust "quantitative" risk assessment?
- How many people need to be treated to benefit one person?
- Should we measure subclinical atherosclerosis?
- What are the LDL-lowering options?
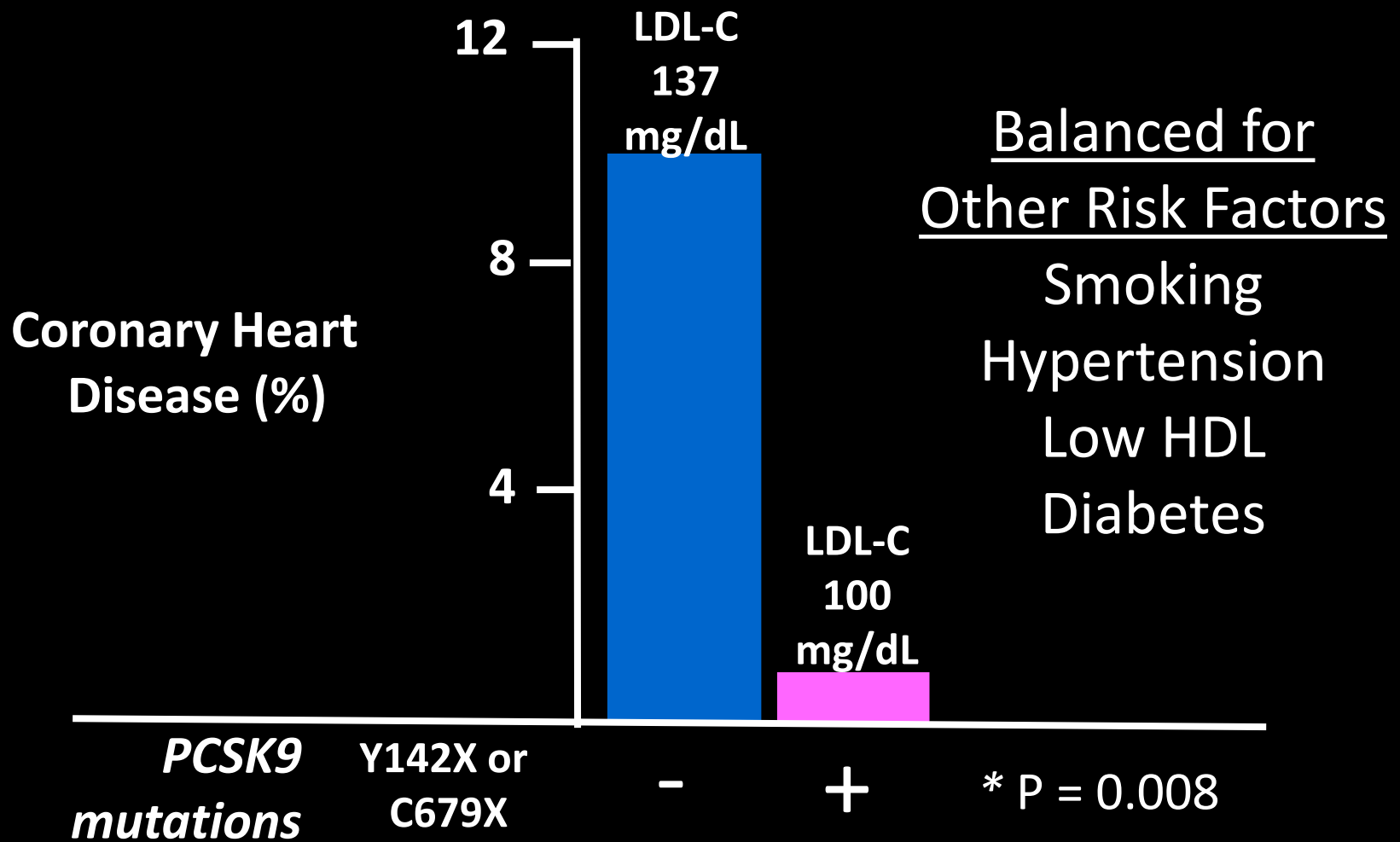
Primary Prevention: What is a reasonable LDL-C goal on drug theapy?

What does epidemiology tell us about how low to lower cholesterol?

Multiple Risk Factor Intervention Trial (MRFIT) (N=361,662)

Age-Adjusted 6-Year CHD Mortality Per 1000 Men

Total Cholesterol (mg/dL)

Primary Prevention: When should LDL-Lowering therapy be started?

Coronary Heart Disease (%)

LDL-C 137 mg/dL

LDL-C 100 mg/dL

Balanced for Other Risk Factors
Smoking
Hypertension
Low HDL
Diabetes

PCSK9 mutations   Y142X or C679X   −   +   * P = 0.008

Cohen et al. *N Engl J Med* 354:1264

When should LDL-Lowering therapy be started? CHD Risk Reduction and Age of Onset of LDL-Lowering (by 10%)

Law *et al.* **BMJ.** 1994 Feb 5;308:367-72
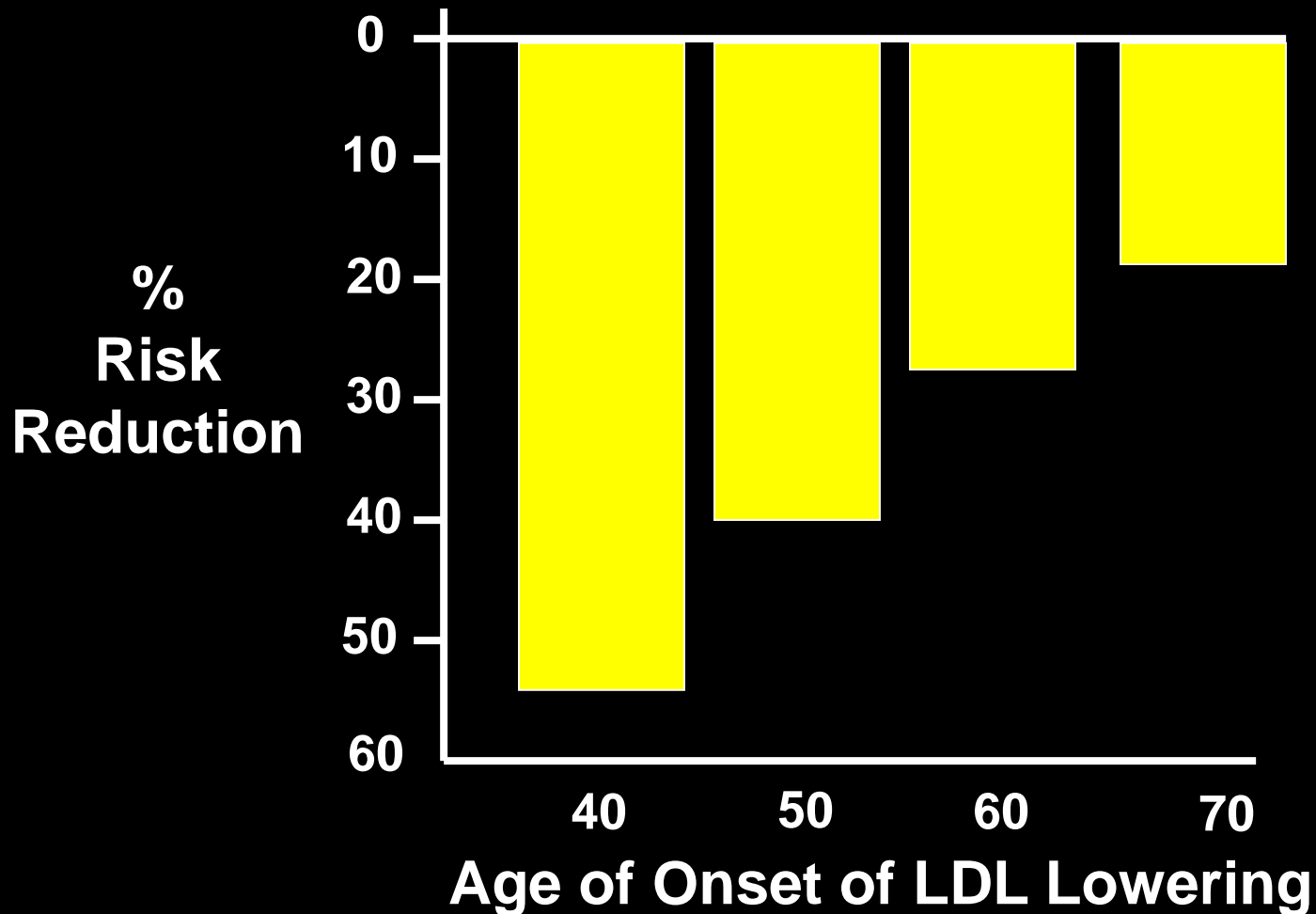
Can we trust the 2013 ACC/AHA Risk Algorithm?

1.0 ← ACC/AHA → 1.0

Algorithm 2013

0.75

← MESA/Stroke

0.50 ← PHS

WHS →
MESA →
WHIOS →
Stroke →

0.75

0.50

Men
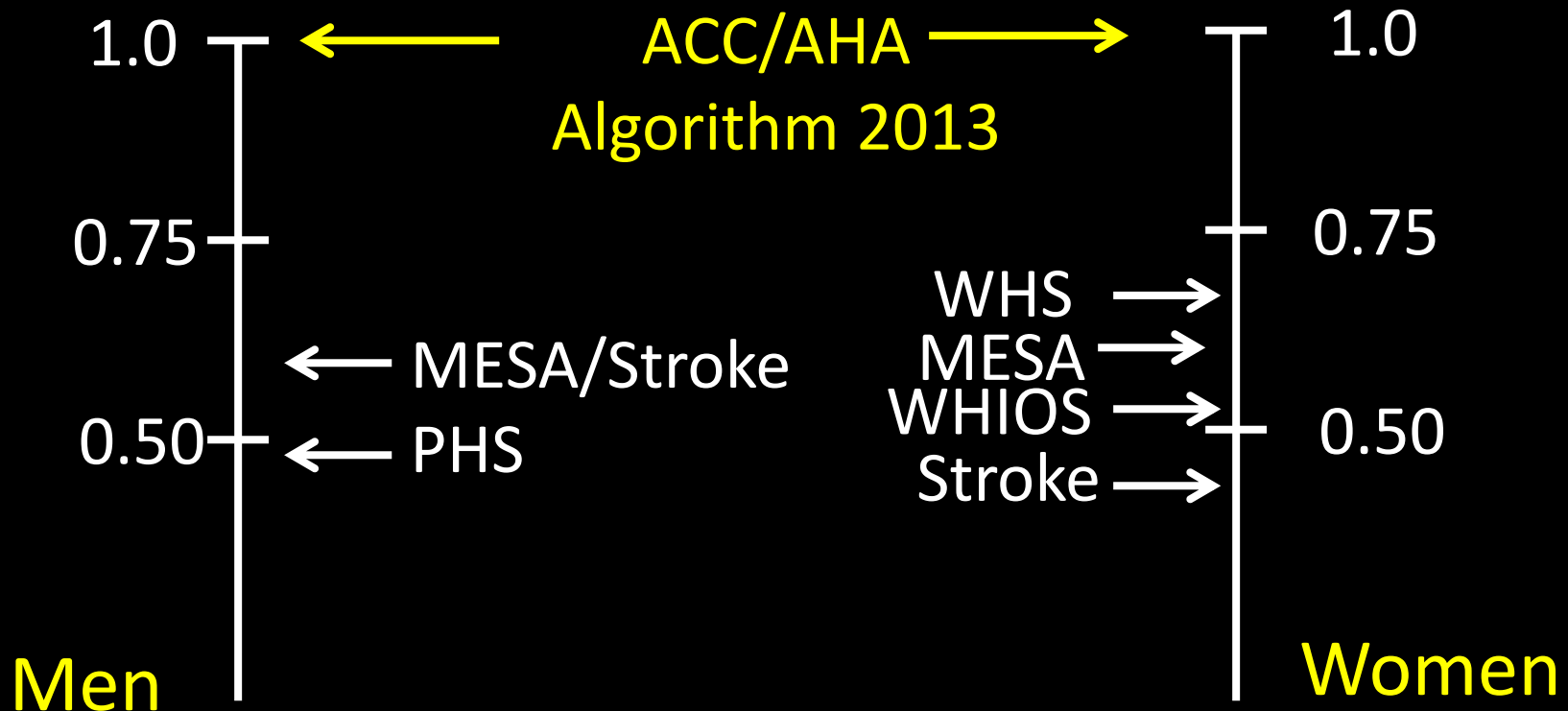
Women

MESA = Multi-Ethnic Study of Atherosclerosis   PHS = Physicians Health Study
WHS = Women's Health Study WHIOS =Women's Health Initiative Observational Study
Stroke = Reasons for Racial Differences in Stroke study

Ridker and Cook. *Lancet* November 19, 2013

What are relative baseline risks in populations worldwide?

Urban India (1.86)

New Zeeland (1.15)

Rural India (1.00)   Framingham (1.00)
Scotland (0.91)   Australia (0.90)

Native American (0.80)
Ireland (0.76)   UK (0.76)

                          Japan (0.50)
Switzerland (0.45)
France (0.41)   Germany (0.43)
China (0.36)   Spain (0.37)
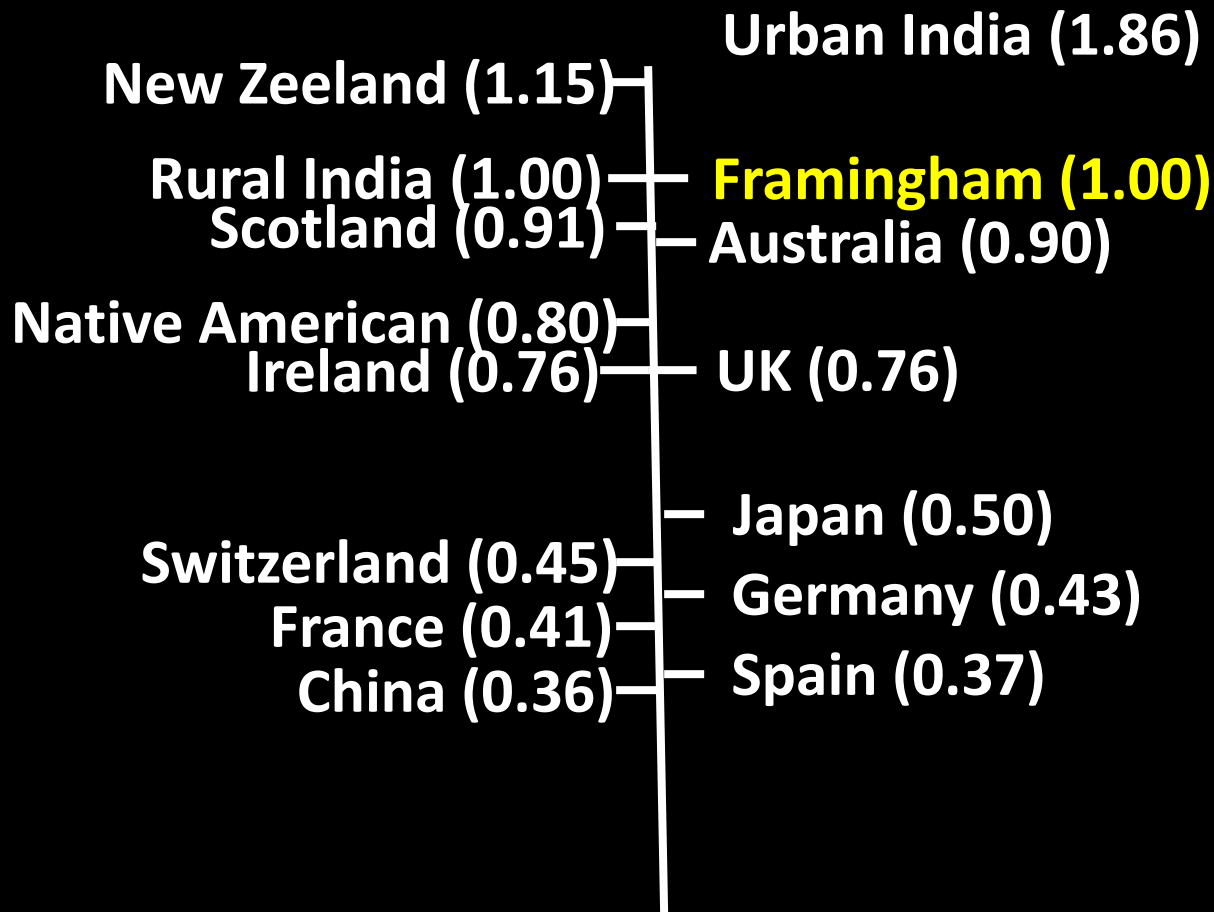
What are reasonable categorical indications for statins in primary prevention?

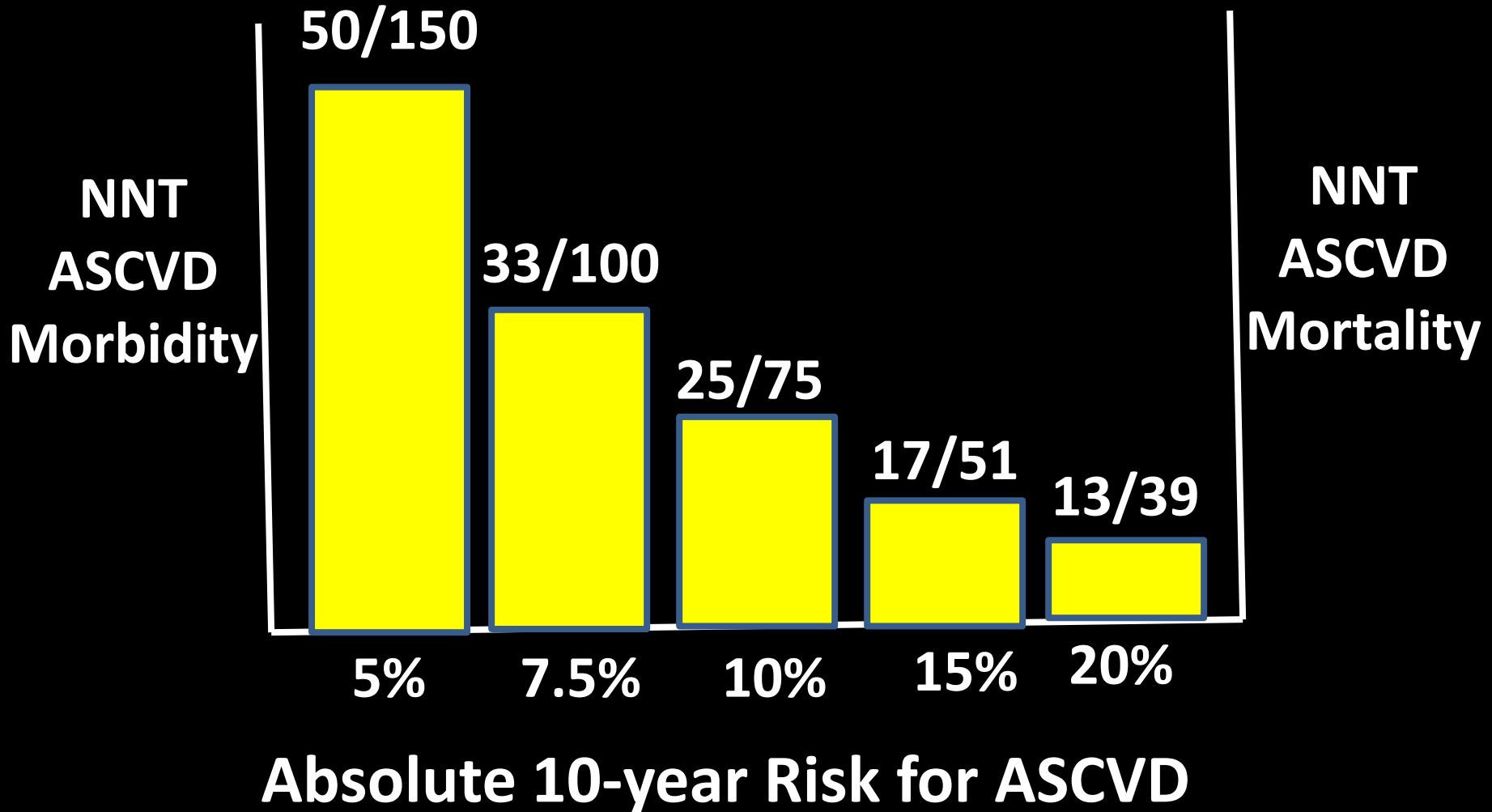## Higher Risk Conditions

- Diabetes mellitus (CARDS)

- Metabolic syndrome (JUPITER/AFCAPS/MEGA)

- Chronic kidney disease (SHARP)

Major Risk Factors

- Hypertension (ASCOT)

- Hypercholesterolemia (WOSCOPS)

- Cigarette smoking (Multiple RCTs)

Is 10-year NNT for ASCVD Morbidity/Mortality a valuable tool for patient discussion? (Individual vs. Public Health Considerations)

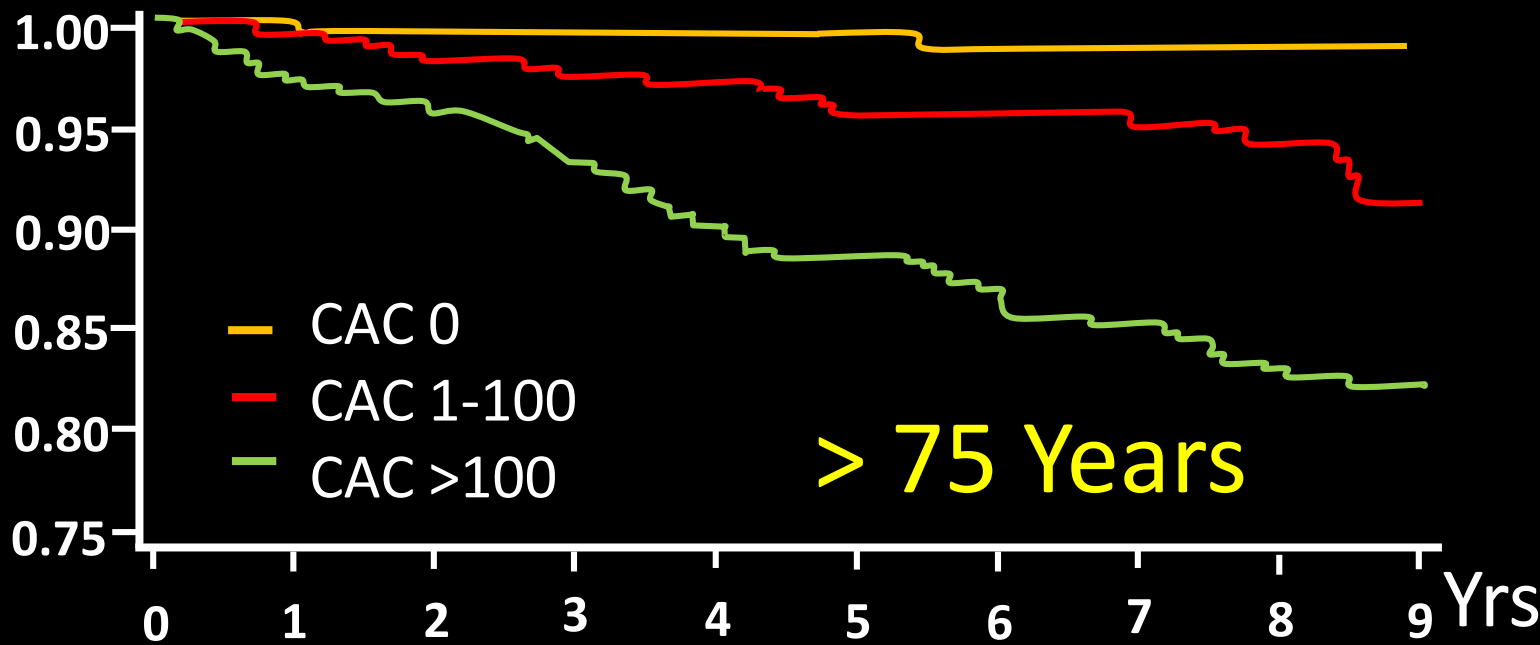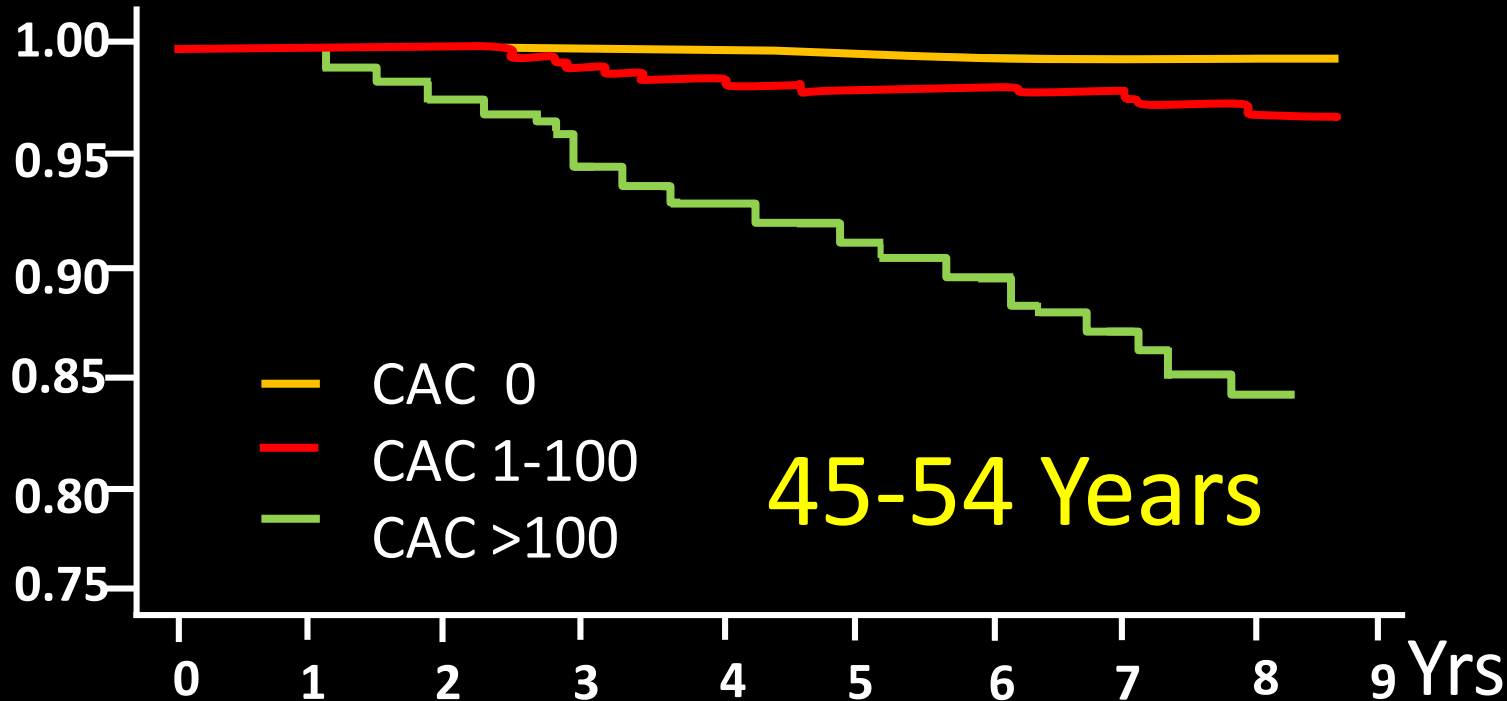# Is CAC the best single predictor for CHD?
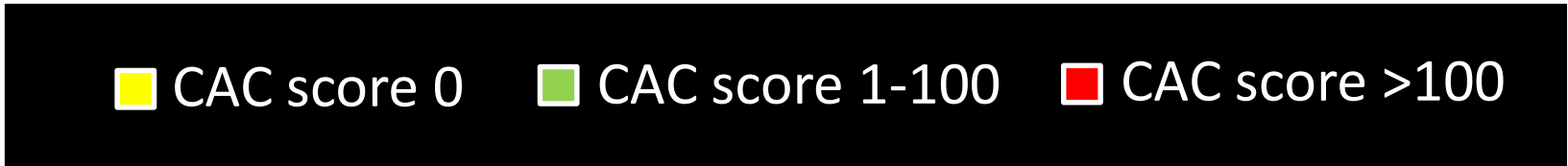

A: No calcification (CAC = Zero)
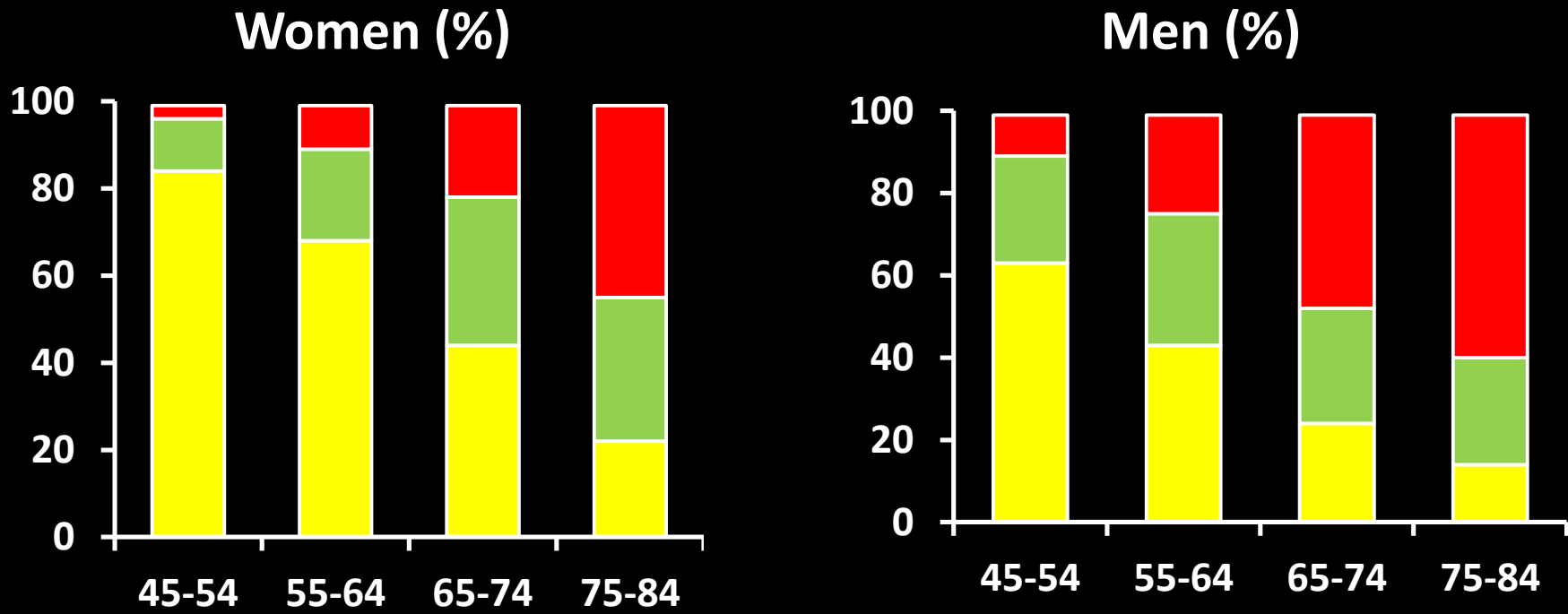
B: Mild calcification (CAC = 1-100)

C: Severe Calcification (CAC >100)

Fraction Free of CHD

45-54 Years

Legend:
- CAC 0 (orange)
- CAC 1-100 (red)
- CAC >100 (green)

> 75 Years

Legend:
- CAC 0 (orange)
- CAC 1-100 (red)
- CAC >100 (green)

Tota-Maharaj
Mayo Clin Proc.
2014;89:1350-9

What % of the population has zero CAC or low CAC levels?

Women (%)

Men (%)

Legend: CAC score 0 (yellow) ■ CAC score 1-100 (green) ■ CAC score >100 (red)

Tota-Maharaj et al. Mayo Clin Pro. 2014;89:1350-9

What are the LDL-lowering options for primary prevention?

- Reasonable goal on lifestyle RX: <100 mg/dL
- Reasonable goal on drug RX: <70 mg/dL
- First-line therapy: Statins
- Second-line therapy
  - Ezetimibe
  - Bile acid sequestrants
  - Fibrates (metabolic syndrome)
- Dietary therapy (start early)
  - Low saturated fat and *trans* fat
  - Low dietary cholesterol
  - Weight reduction