Cholesterol Management Issues 2015 (Lower *is* Better)

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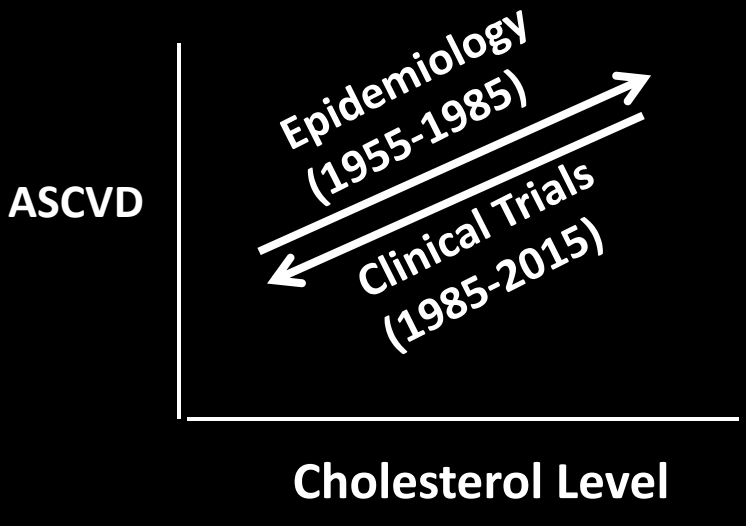
COI: None

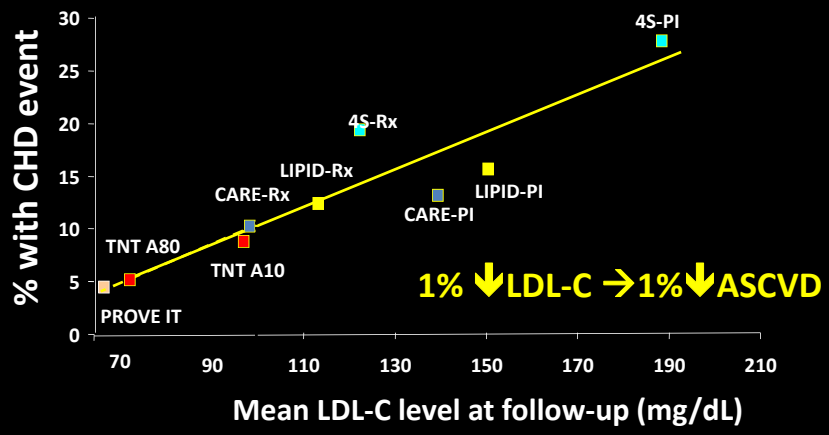
Cholesterol Hypothesis



Cholesterol Guidelines

- National Cholesterol Education Program (NCEP): ATP III (2001/04)
- European (ESC/EAS) 2011
- Canadian 2013
- International Atherosclerosis Society 2014
- ACC/AHA Guidelines 2013
- American Diabetes 2014
- AACE 2013

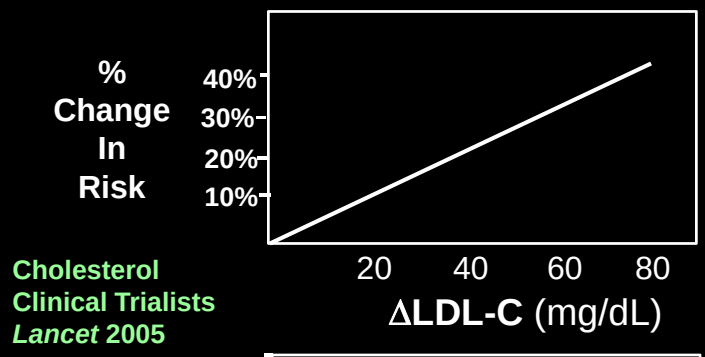
Secondary Prevention: the Lower, the Better for LDL-C



4S: Simvastatin (20-40 mg)
LIPID: Pravastatin (40 mg); CARE: Pravastatin (40 mg)
TNT: Atorvastatin (10 vs. 80 mg)
PROVE-IT: Atorvastatin (80 mg) vs Pravastatin (40 mg)

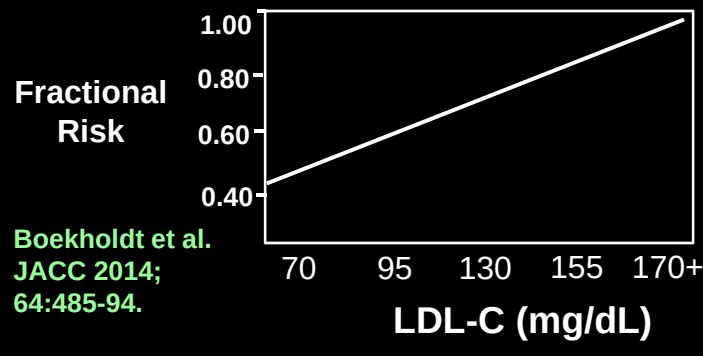
Secondary Prevention Guidelines for Cholesterol Management

- Driven by meta-analysis of randomized clinical trials (RCTs)
- More than 20 secondary prevention RCTs



The More, the Better (Oxford) (ACC/AHA)

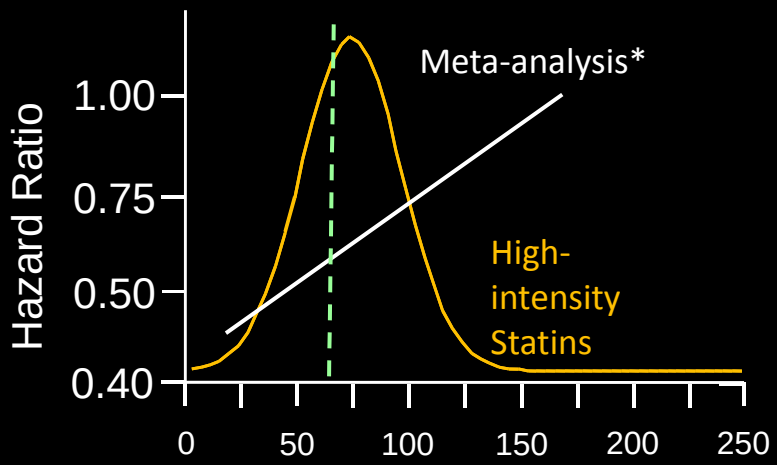
Cholesterol Clinical Trialists *Lancet* 2005



The Lower, the Better

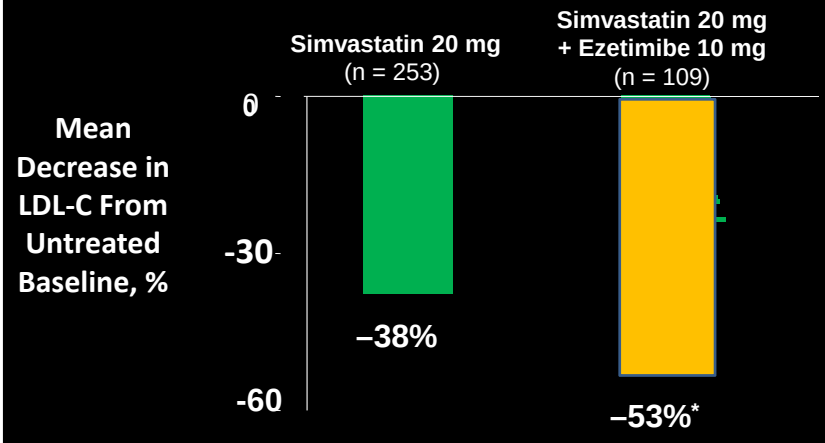
Boekholdt et al. JACC 2014; 64:485-94.

Secondary Prevention: "the Lower, the Better" Model



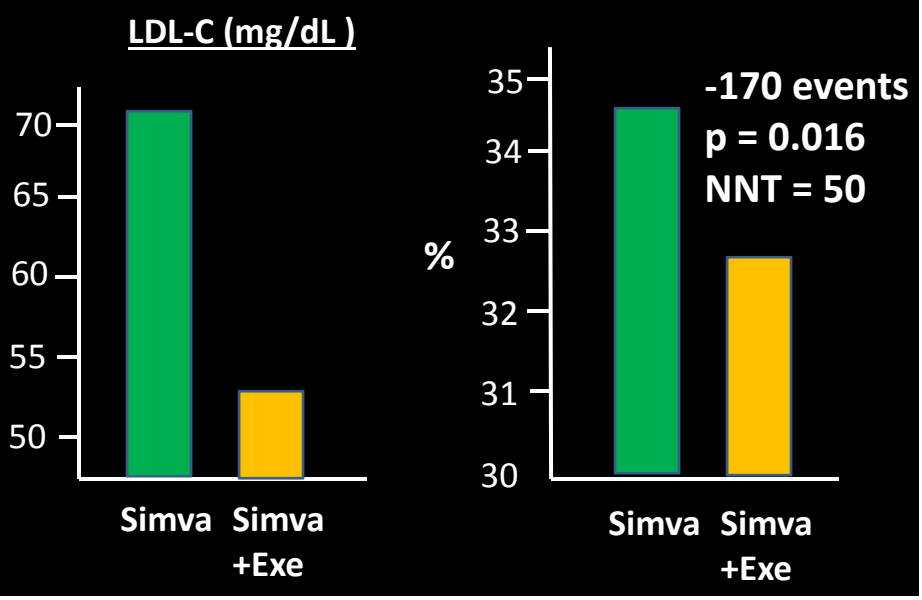
*Boekholdt et al. JACC 2014; 64:485-94.

Beyond Statins (Simvastatin 20 mg ± Ezetimibe 10 mg)



*P<0.001 vs simvastatin 20 mg.
Feldman T et al. *Am J Cardiol*. 2004;93:1481–1486.

IMPROVE-IT Trial



In secondary prevention, should ezetimibe be added to maximally tolerated statin?

- Yes*
- "The lower, the better" for cholesterol

* The IMPROVE-IT trial

In secondary prevention, should maximal lifestyle intervention be added to statin therapy?

- Yes
- "The lower, the better" for cholesterol

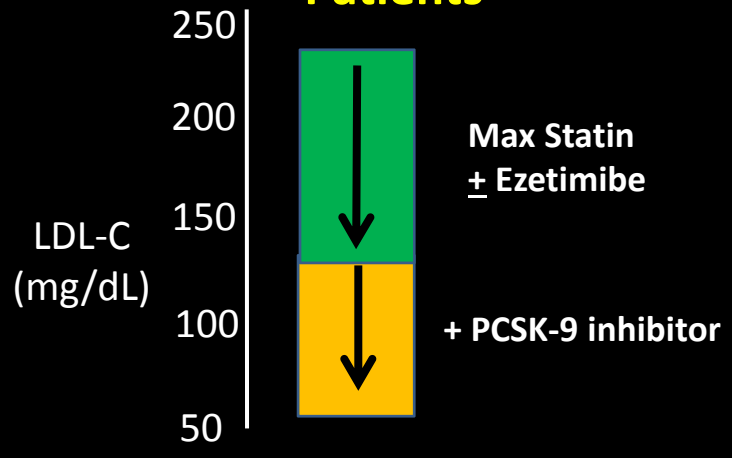
Secondary Prevention Today

- The lower, the better
- LDL-C < 70 mg/dL reasonable
- Maximally tolerated statin
- + Ezetimibe (IMPROVE-IT)
- + Maximize lifestyle therapies

PCSK-9 Inhibitors

- PCSK-9: proteins that promote degradation of LDL receptors
- PCSK-9 inhibitors: antibodies that inhibit PCSK-9
  - Preserve LDL receptors
  - Dramatically lower LDL-C

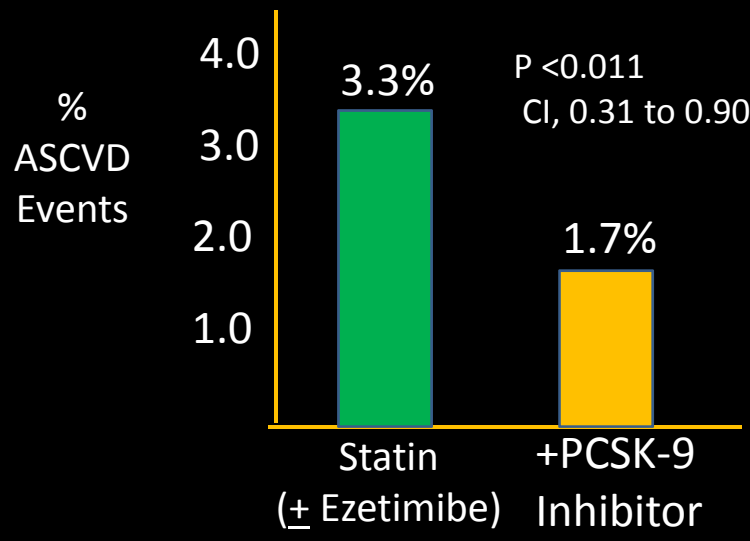
PCSK-9 Inhibitor in Hypercholesterolemic/High Risk Patients



Robinson et al. (ODYSSEY) NEJM Mar 15, 2015

ODYSSEY PCSK-9 RCT 18-mo Analysis

Hypercholesterolemia/High-Risk Patients



Robinson et al. (ODYSSEY) NEJM Mar 15, 2015

Statin-Intolerant Patient (10%)

- Maximize lifestyle therapies
- Re-challenge with same statin
- If statin not tolerated,
  - Try different statins (fluvastatin best)
  - Try every other day or twice weekly statins
  - Add ezetimibe
  - Add bile acid sequestrants (resins)
  - Add or substitute PCSK9 inhibitor (when approved by FDA)

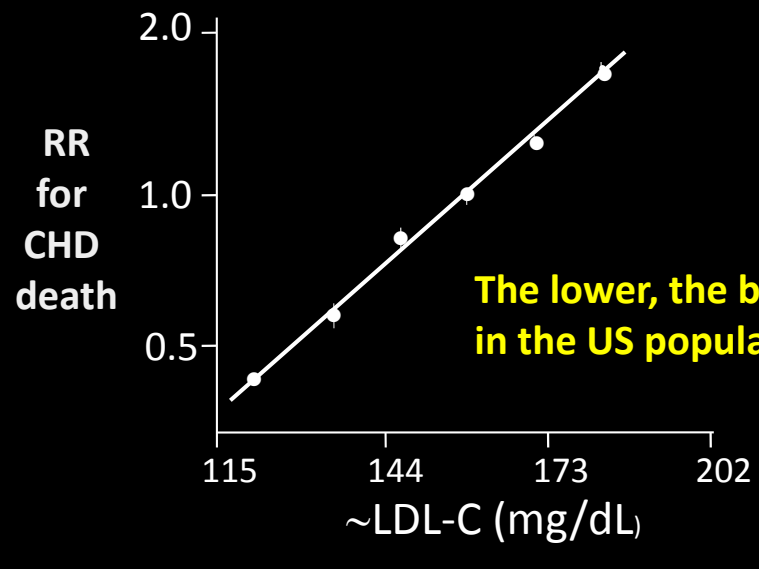
Primary Prevention

Patients without ASCVD

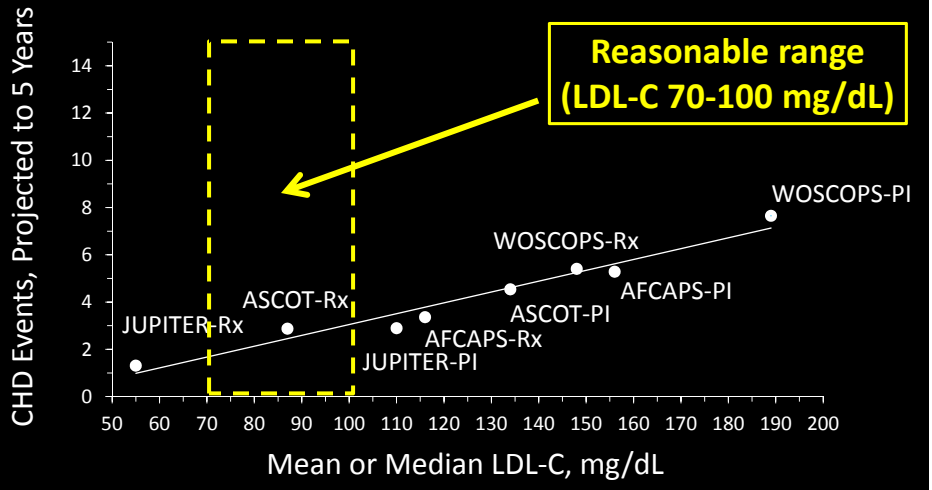
AHA/ACC Guidelines 2013

- Statin-dominated guidelines (RCTs only)
- New risk assessment algorithm
  - Based on 5 older population studies
- Start statins at lower risk than other guidelines
  - Estimated 10-year risk for ASCVD of 7.5
- Use maximally tolerated statin: No LDL goals
- Shifts statin therapy to older persons
  - Most men at 65 and most women at 70

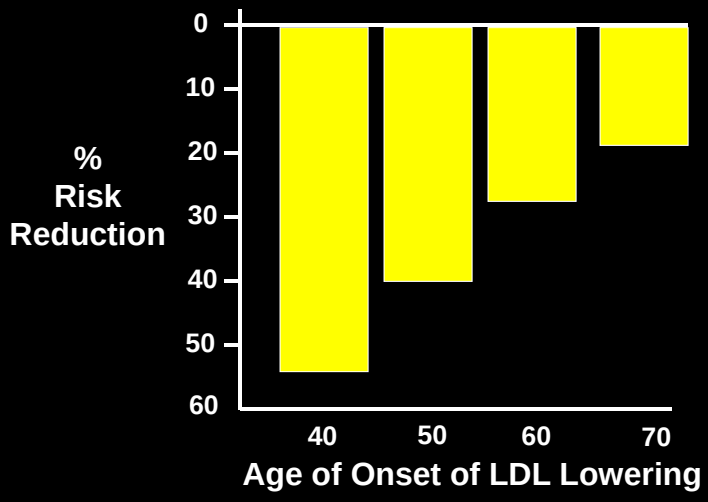
Population relationship between CHD mortality and cholesterol level (350,000 US men in MRFIT)



RCT Evidence in Primary Prevention: The Lower the Better

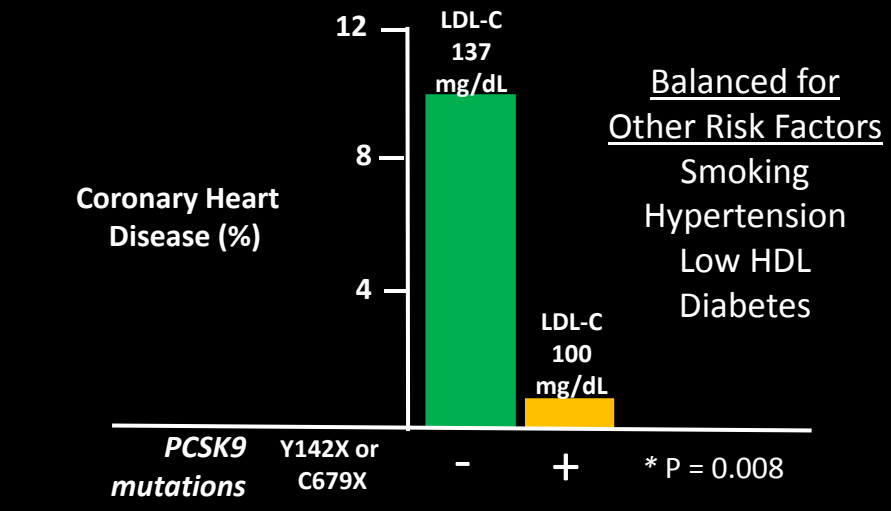


CHD Risk Reduction and Age of Onset of LDL-Lowering (by 10%): the Earlier the Better



Law *et al.* **BMJ.** 1994 Feb 5;308:367-72

Primary Prevention: the Earlier the Better for Low LDL-C



Balanced for Other Risk Factors
Smoking
Hypertension
Low HDL
Diabetes

1% ↓LDL-C →>3%↓ASCVD

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

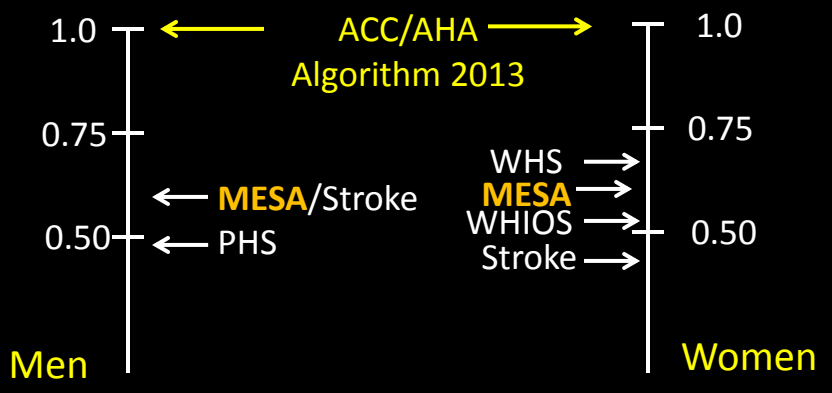
Primary Prevention: Cholesterol-Lowering Therapy

- The lower the better
  - Shown by epidemiology and clinical trials
  - **1% ↓LDL-C → 1%↓ASCVD**
- The earlier the better
  - Shown by population and genetic epidemiology
  - **1% ↓LDL-C → >3%↓ASCVD**

Risk Assessment to Inform Use of Cholesterol-Lowering Drugs

- ATP III: The greater the risk, the more intense the therapy
- ACC/AHA 2013: Single risk threshold (≥ 7.5% 10-year risk) (One size fits all)
- How best to assess risk?

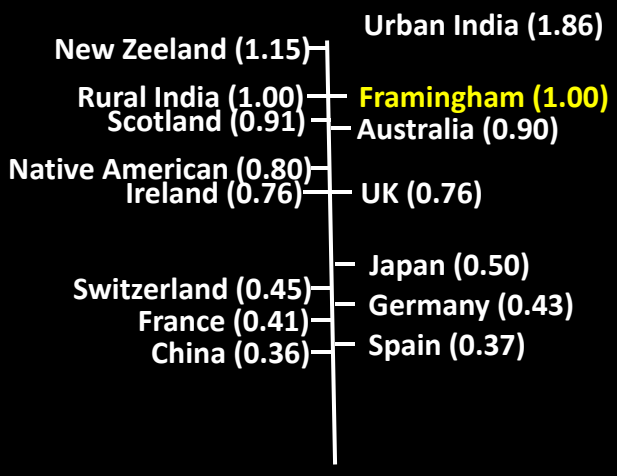
Relative Population Baseline Risks in US Cohorts



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

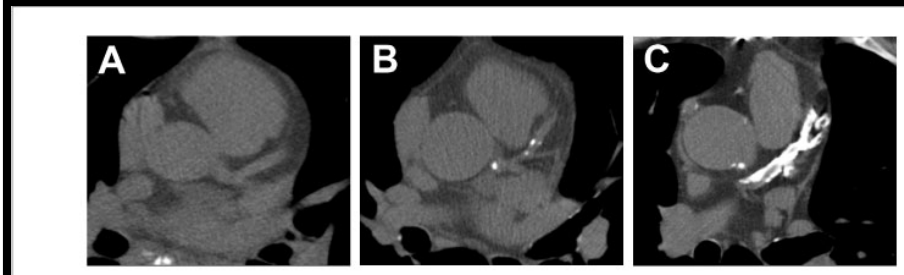
Risk Assessment: Population baseline risks for CHD



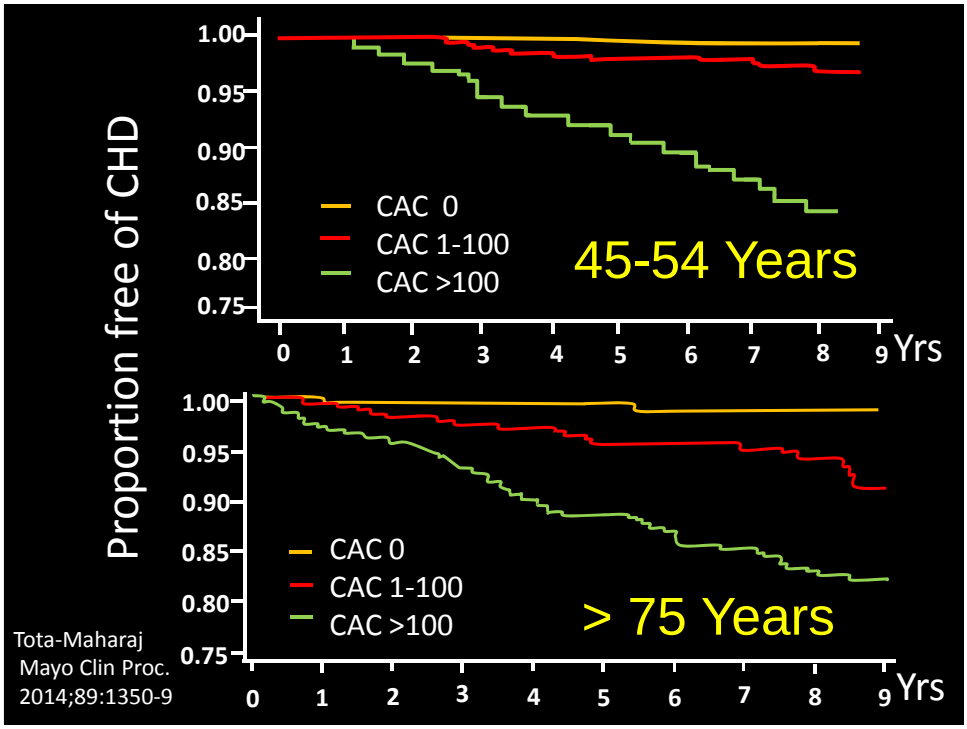
Age as a Risk Factor

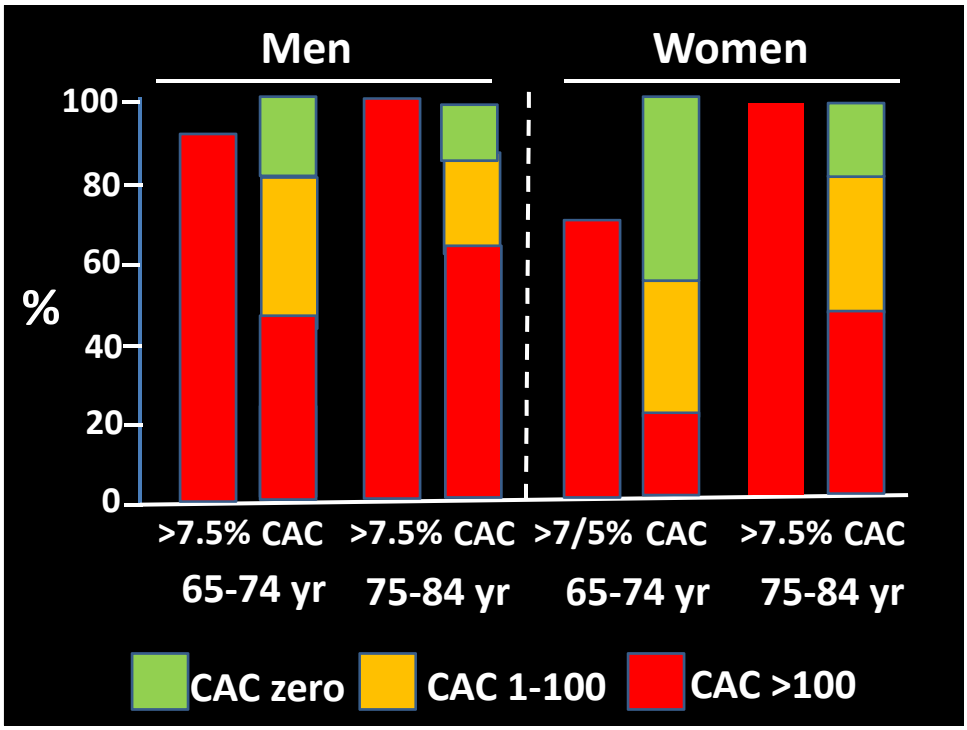
- Age dominates risk assessment in ACC/AHA guidelines
- Use of age as a risk factor shifts drug treatment mainly to older people
- Age as a risk factor is a substitute for subclinical atherosclerosis
- At a given age, atherosclerosis varies greatly in the general population.

You are as Old as Your Arteries (Grundy, Am J Cardiol. 1999 ;83:1455-7)



A: No calcification (CAC = Zero)
B: Mild calcification (CAC = 1-100)
C: Severe Calcification (CAC >100)


Proportion free of CHD
1.00
0.95
0.90
0.85
0.80
0.75
CAC 0
CAC 1-100
CAC >100
45-54 Years
0 1 2 3 4 5 6 7 8 9 Yrs
> 75 Years
Tota-Maharaj
Mayo Clin Proc.
2014;89:1350-9


Men
Women
100
80
60
40
20
0
%
>7.5% CAC
>7.5% CAC
>7/5% CAC
>7.5% CAC
65-74 yr
75-84 yr
65-74 yr
75-84 yr
CAC zero
CAC 1-100
CAC >100

Who are potential candidates for cholesterol-lowering drugs in primary prevention?

Higher Risk Conditions

- Diabetes mellitus (29.1M) (CARDS)
- Metabolic syndrome (77-86M) (JUPITER/ AFCAPS/MEGA)
- Chronic kidney disease (20M) (SHARP)

Major Risk Factors

- Hypertension (70M) (ASCOT)
- Hypercholesterolemia (31M)(WOSCOPS)
- Cigarette smoking (42M)(Multiple RCTs)

Primary Prevention: Starting Early

- Treat higher risk and/or major risk factors
- Maximize lifestyle therapy
- If other risk factors or elevated cholesterol remains, consider low-intensity cholesterol-lowering drug

Higher Risk Conditions

- Diabetes mellitus
- Metabolic syndrome
- Chronic kidney disease

Major Risk Factors

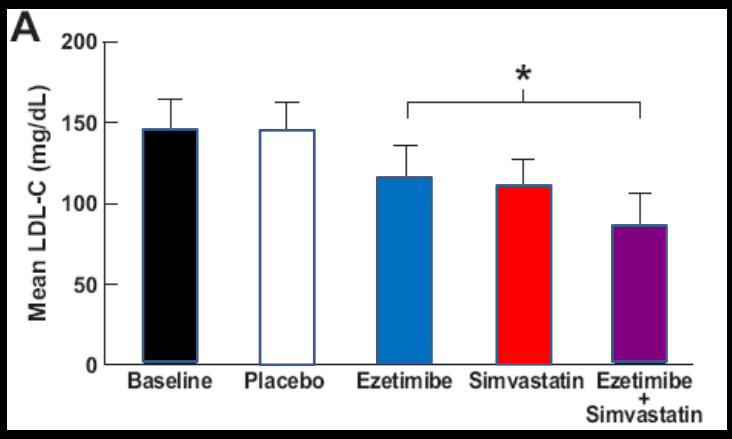
- Hypertension
- Hypercholesterolemia
- Cigarette smoking

Start Early: How to lower LDL-C by 20% (and reduce lifetime risk)

• Dietary cholesterol	< 300 mg/day
• Saturated fatty acids	< 7% of total calories
• Trans fatty acids	< 1% of total calories
• Dietary soluble fiber	10 g/day
• Dietary plant sterols/stanols	2 g/day (optional)
• Total calorie intake	Sustain desirable body weight
• Regular physical activity	30 minutes/day

Starting Early: Low Intensity Cholesterol-Lowering Drug

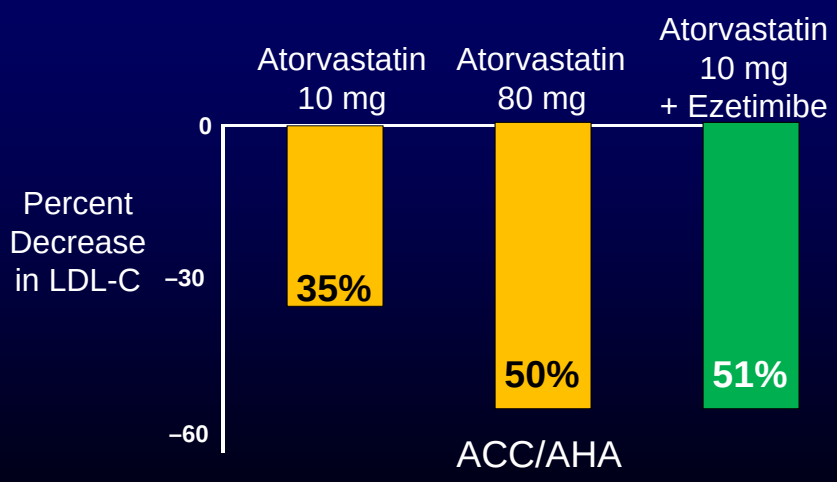
- Ezetimibe ± Low dose statin (simvastatin 10 mg)



-20% -26% -44%

Lakoski et al. JCEM 2010, 95: 800-809

Starting Later: Alternatives for Drug Therapies



Ballantyne et al. Circulation. 2003; 107(19):2409-15.

Summary

- Secondary prevention
  - Treat cholesterol aggressively
  - The lower, the better
  - Consider combined drug therapy
- Primary prevention
  - The earlier the better
  - Treat all risk factors
  - Lifestyle therapy and consider drugs for elevated LDL-C