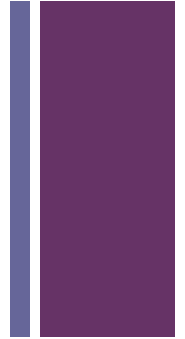


Update on Lipid Management

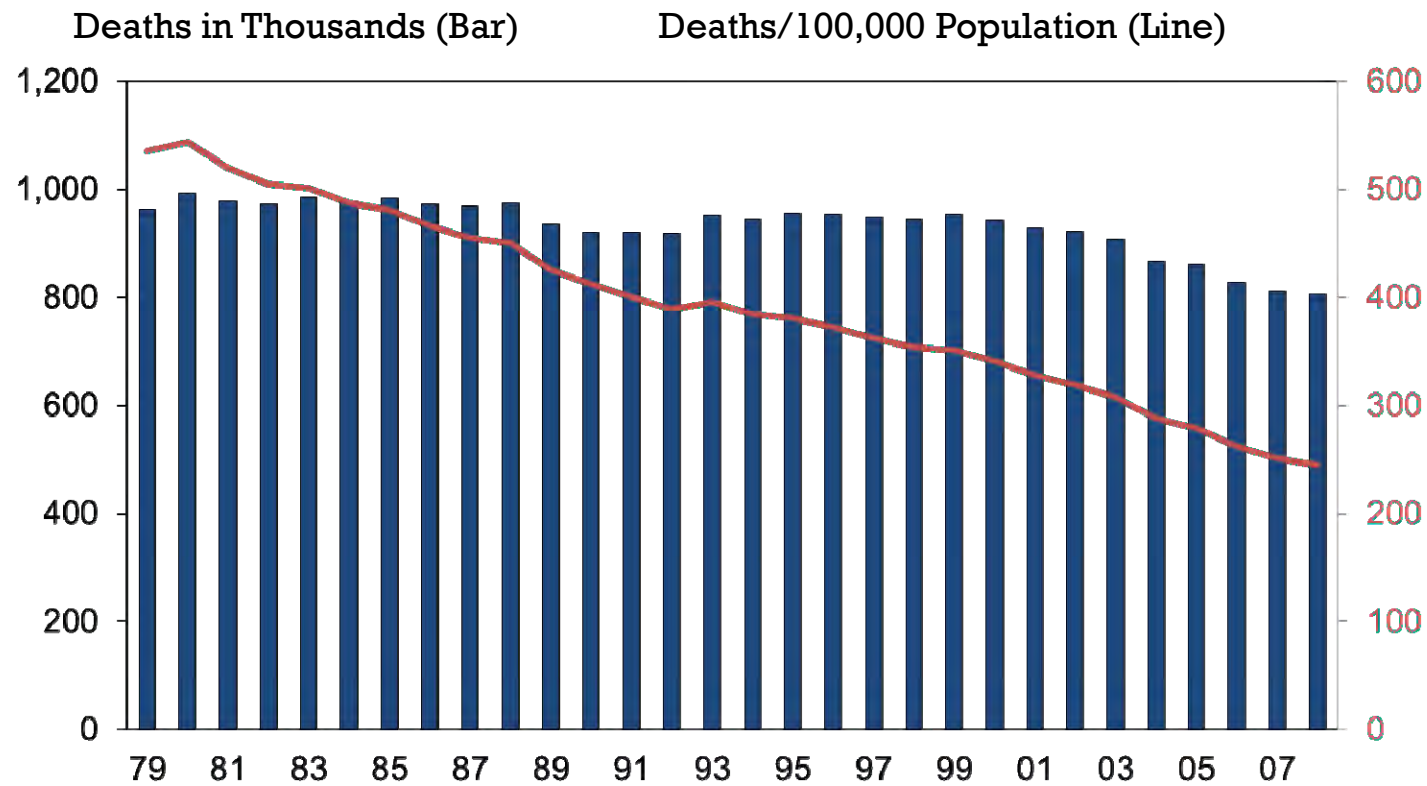
Stacey Gardiner, MD
Assistant Professor
Division of Cardiovascular Medicine
Medical College of Wisconsin

+ The stats on heart disease



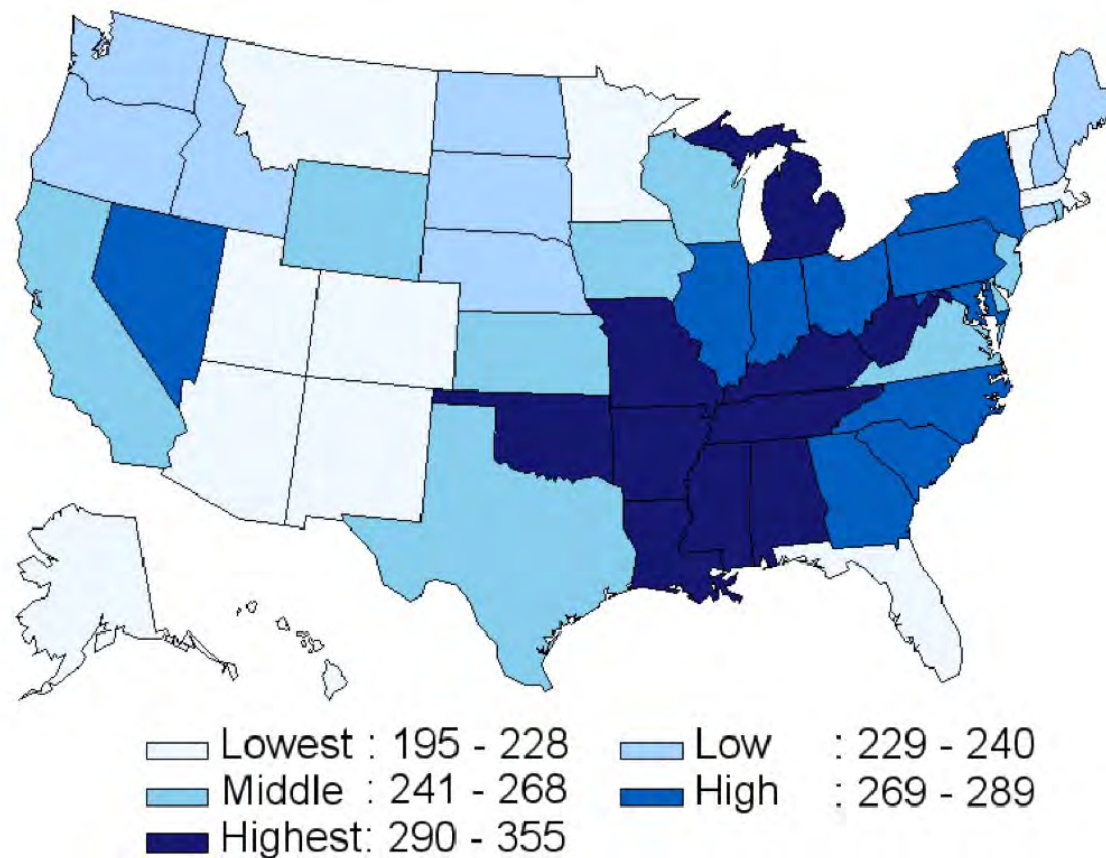
- Over the past 10 years for which statistics are available, the death rate from heart disease has fallen about 39 percent – but the burden and risk factors remain alarmingly high.
- Heart disease strikes someone in the U.S. about once every 34 seconds.
- Heart disease is the No. 1 cause of death in the United States, killing almost 380,000 people a year.
- **Heart disease is the No. 1 killer of women, taking more lives than all forms of cancer combined.**
- Over the past 10 years for which statistics are available, the death rate from heart disease has fallen about 39 percent.

+ Deaths & Age-Adjusted Death Rates for Cardiovascular Diseases, U.S., 1979–2008

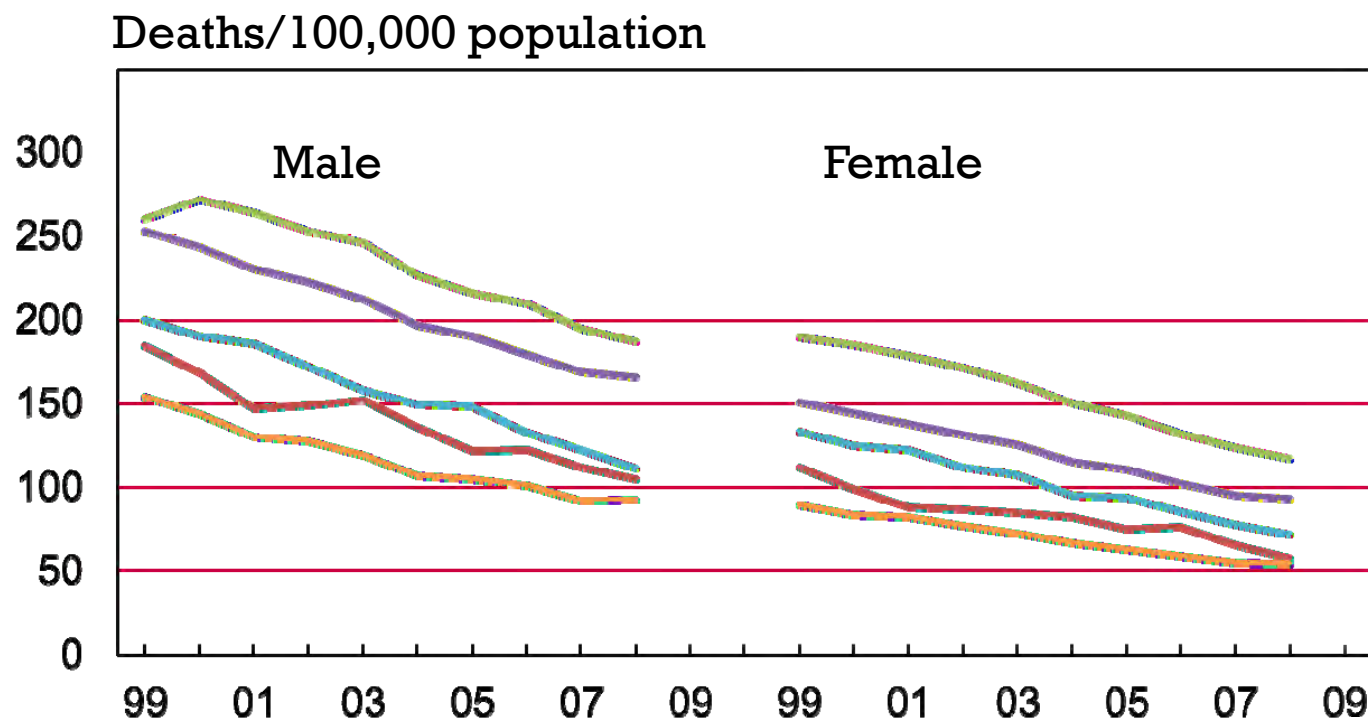


Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases, NHLBI, February 2012

+ Death Rates* for Cardiovascular Diseases[‡] by State, U.S., 2005–2007



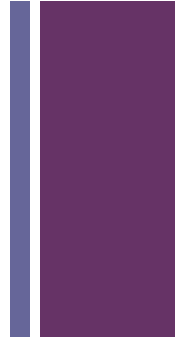
+ Age-Adjusted Death Rates for CHD[‡] by Race/Ethnicity & Sex, U.S., 1999–2008



Green - Black , Purple -White , Blue - Hispanic, Red- American Indian, Orange - Asian

Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases, NHLBI, February 2012

+ The statistics, continued

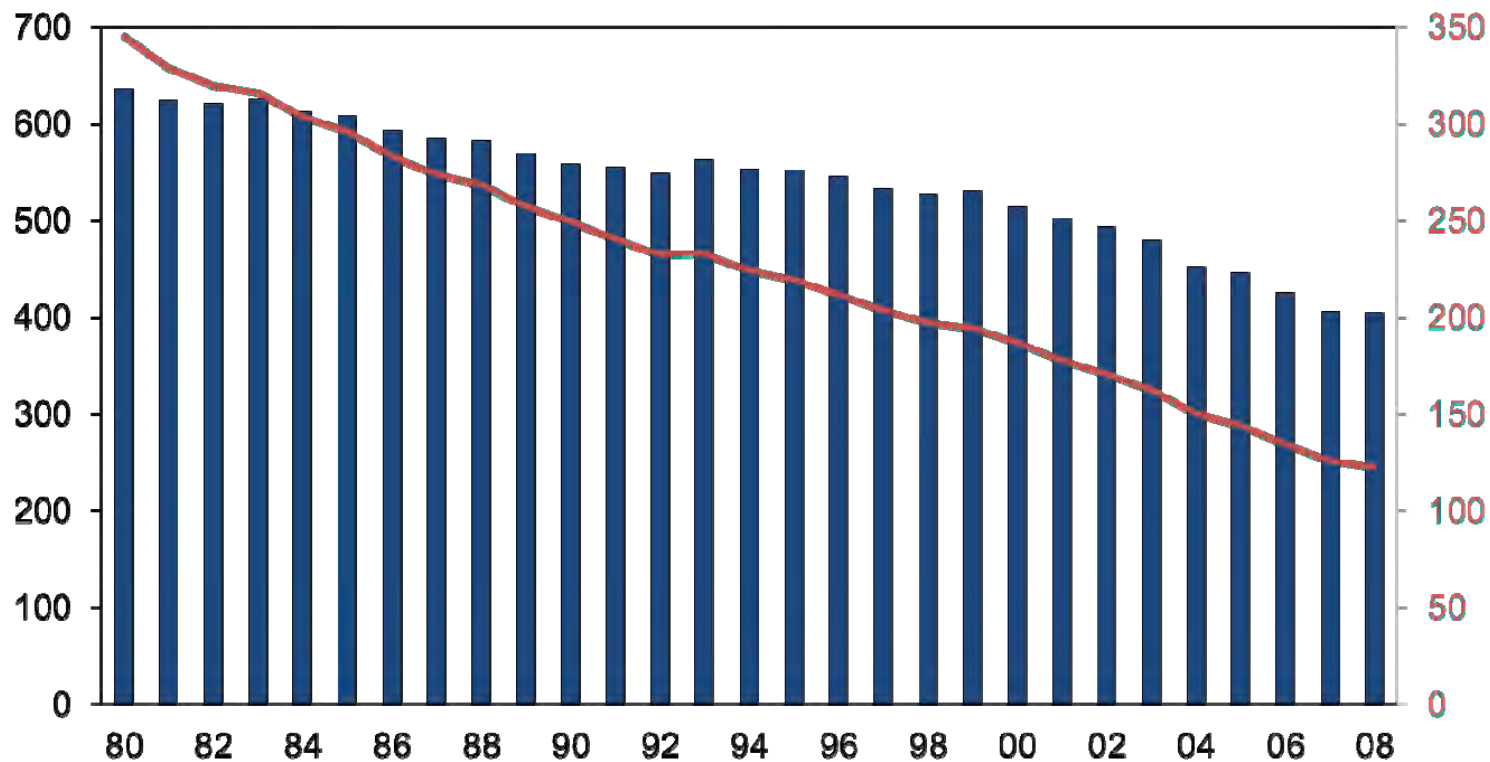


- Over 39,000 African-Americans died from heart disease in 2010, the most recent year for which statistics are available.
- Cardiovascular operations and procedures increased about 28 percent from 2000 to 2010, according to federal data, totaling about 7.6 million in 2010.
- About 720,000 people in the U.S. have heart attacks each year. Of those, about 122,000 die.
- About 620,000 people in the U.S. have a first-time heart attack each year, and about 295,000 have recurrent heart attacks.

+ Deaths & Age-Adjusted Death Rates for Coronary Heart Disease, U.S., 1980–2008

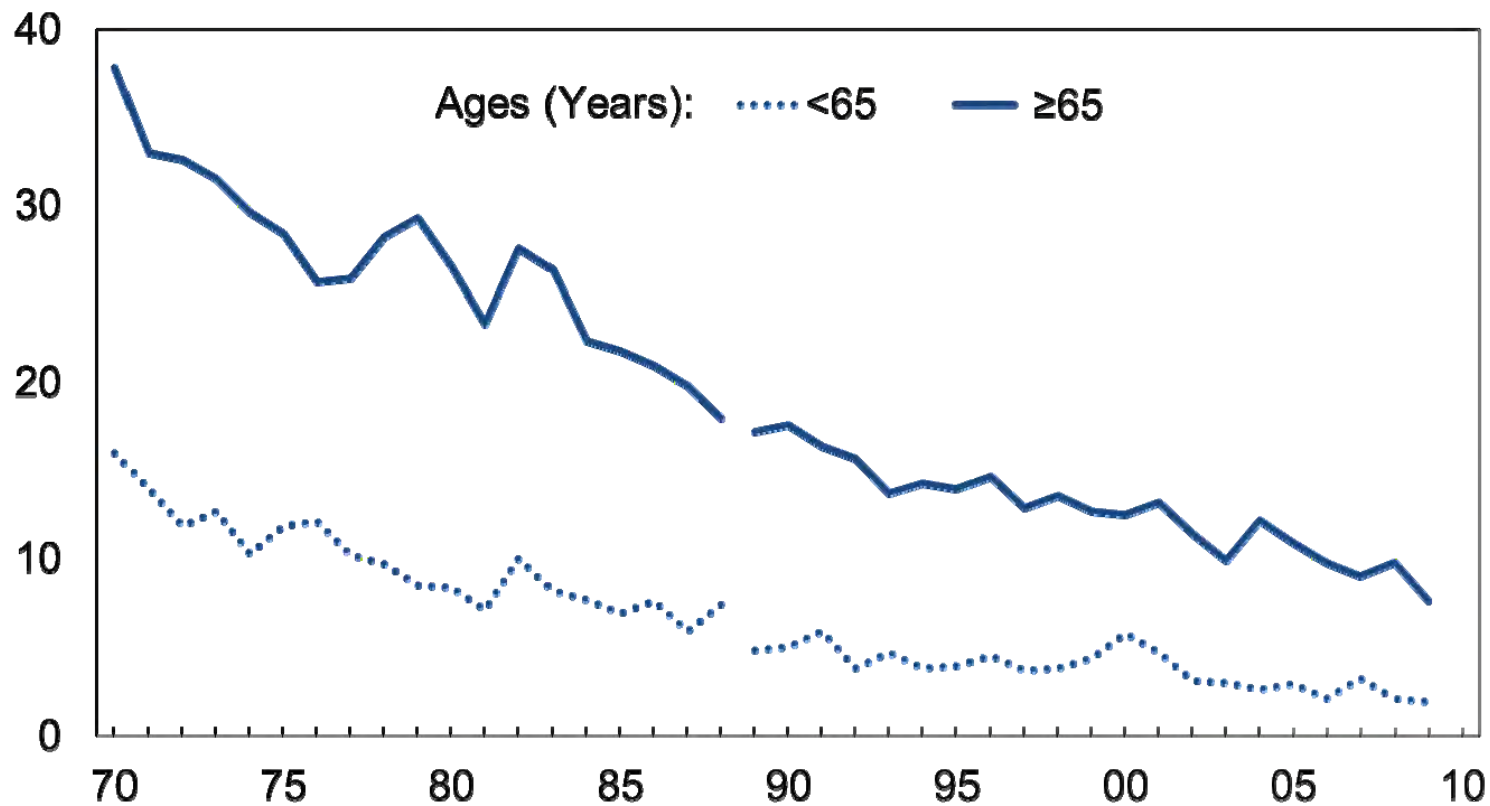
Deaths in Thousands (Bar)

Deaths/100,000 Population (Line)



Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases, NHLBI, February 2012

+ Hospital Case-Fatality Rates for Acute MI*, Ages < 65 & ≥ 65, U.S., 1970–2009



Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases, NHLBI, February 2012

+ What accounts for the decline in CV deaths?

THE NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Explaining the Decrease in U.S. Deaths from Coronary Disease, 1980–2000

Earl S. Ford, M.D., M.P.H., Umed A. Ajani, M.B., B.S., M.P.H., Janet B. Croft, Ph.D., Julia A. Critchley, D.Phil., M.Sc., Darwin R. Labarthe, M.D., M.P.H., Ph.D., Thomas E. Kottke, M.D., Wayne H. Giles, M.D., M.S., and Simon Capewell, M.D.

ABSTRACT

BACKGROUND

Community and the
Prevention Center
Health Control
Institute of

Mortality from coronary heart disease in the United States has decreased substantially in recent decades. We conducted a study to determine how much of this decrease could be explained by the use of medical and surgical treatments as opposed to changes in cardiovascular risk factors.

+ Explaining decrease in CV deaths

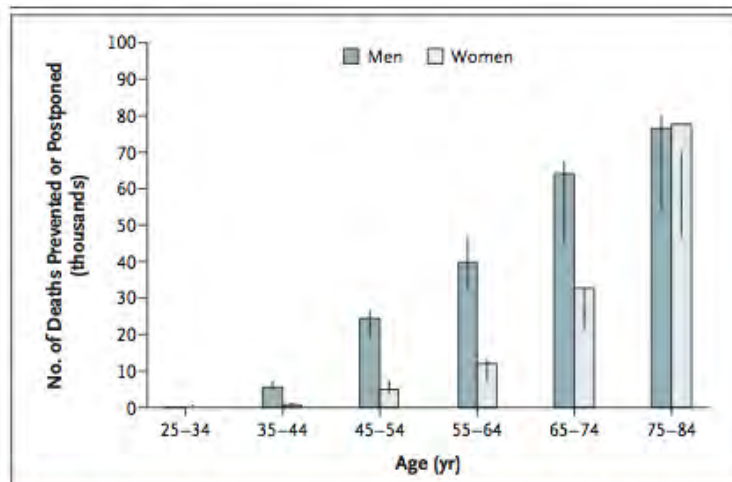


Figure 1. Estimated and Observed Reductions in Deaths from Coronary Heart Disease in the United States between 1980 and 2000, Stratified According to Age and Sex.

The bars show the observed decrease in deaths in each age group, and the vertical lines the extreme minimum and maximum estimates in the sensitivity analysis.

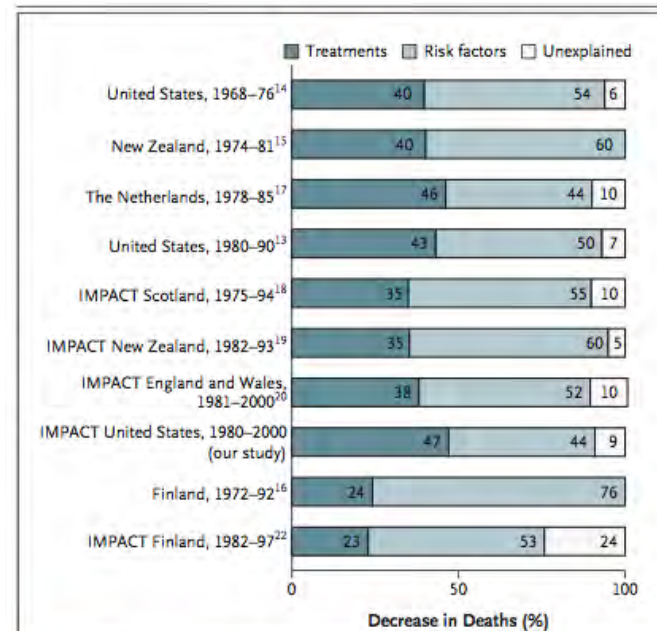
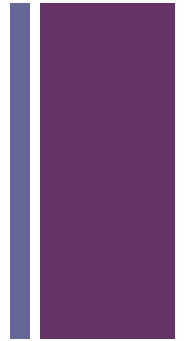


Figure 2. Percentage of the Decrease in Deaths from Coronary Heart Disease Attributed to Treatments and Risk-Factor Changes in Our Study Population and in Other Populations.

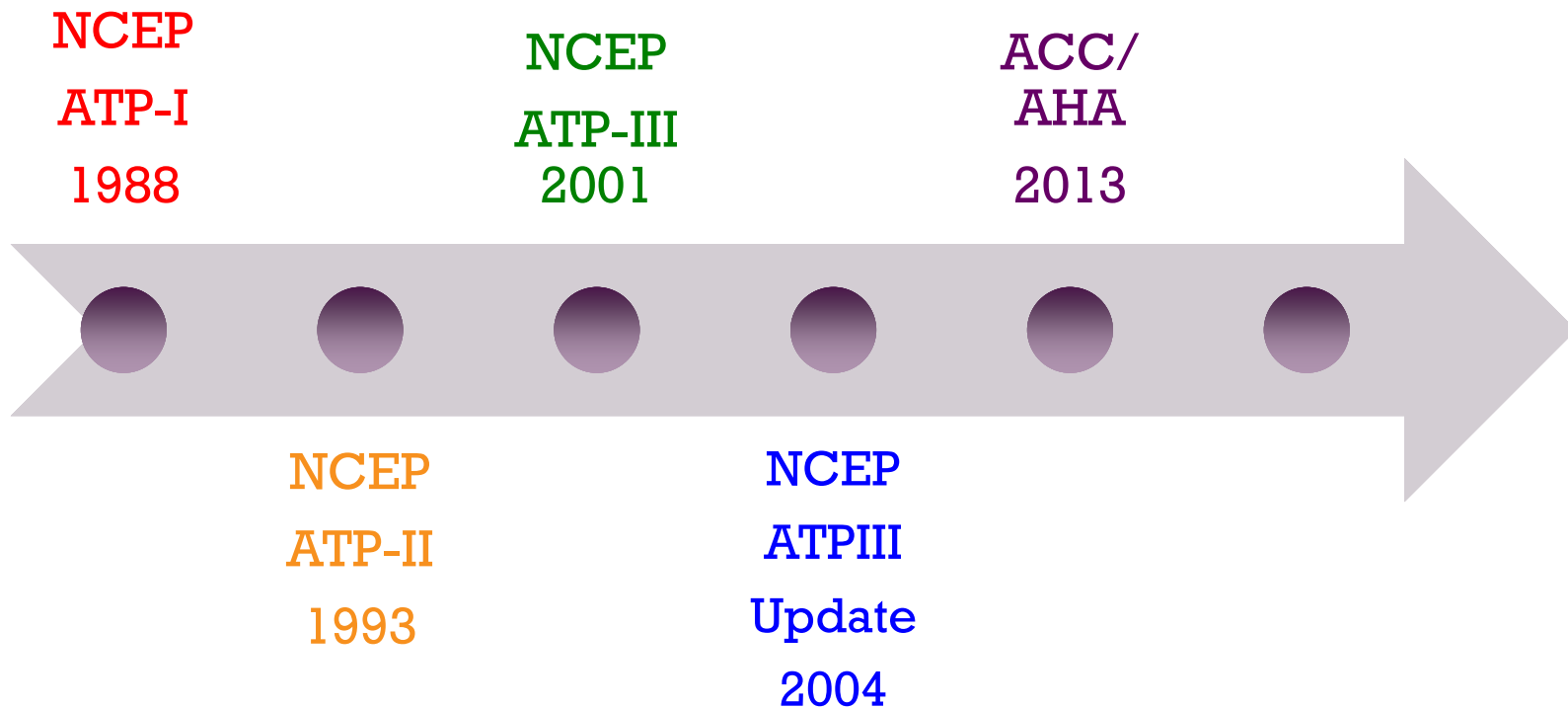
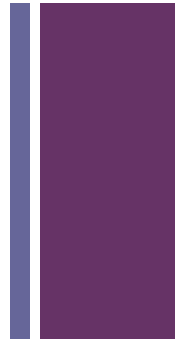
In the New Zealand study, 1974 to 1981 (Beaglehole¹⁵), the analysis focused on specific treatments and inferred contribution from risk factors. In the Finland study, 1972 to 1992 (Vartiainen et al.¹⁶), the analysis focused on risk factors and inferred contribution from treatments.

+ Decrease in CV deaths



- Reductions in major risk factors accounted for about $\frac{1}{2}$ of the decrease in deaths from coronary heart disease
- The largest contributions for medical therapies came for secondary prevention, treatments for ACS and heart failure
- Revascularization by means of CABG or angioplasty accounted for 7% of overall drop in deaths

+ Evolution of Lipid Guidelines



+ The previous guidelines ATP III (2001)

Primary goal for treatment: LDL

- <100 Optimal
- 100-129 Near Optimal/Above Optimal
- 130-159 Borderline High
- 160-189 High
- 190 Very high



+ ATP III



Total Cholesterol

- <200 Desirable
- 200-239 Borderline
- >240 High

HDL cholesterol

- <40 Low
- >60 High

+ Assessment of risk

CHD equivalents

- Clinical CHD
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm.

Major risk factors

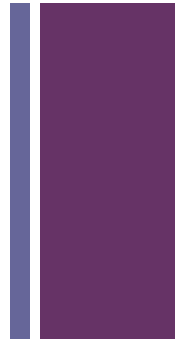
- Smoking
- Hypertension (BP 140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dl)
- Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
- Age (men 45 years; women 55 years)

+ LDL cholesterol goals and cutpoints for TLC and drug therapy

Risk Category	LDL goal	When to initiate TLC	When to consider drug therapy
High risk > 20% 10 year risk CHD, and equivalents	< 100	> 100	➤ 130 ➤ (100-129 –drug optional)
2+ risk factors	< 130	> 130	10-20% risk - > 130 < 20% risk - > 160
0-1 risk factors	<160	> 160	➤ 190 ➤ (160-189 – drug optional)

+ ATP-III update 2004

- Option to lower LDL-C levels to less than 70 mg/dL in high risk patients



+ November 2013

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Neil J. Stone, Jennifer Robinson, Alice H. Lichtenstein, C. Noel Bairey Merz, Conrad B. Blum, Robert H. Eckel, Anne C. Goldberg, David Gordon, Daniel Levy, Donald M. Lloyd-Jones, Patrick McBride, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Jr, Karol Watson and Peter W.F. Wilson

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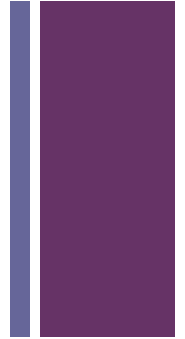


Bacon Good For You, Reports Best Scientist Ever

RADIO NEWS • Science & Technology • ISSUE
45•35 • Aug 26, 2007

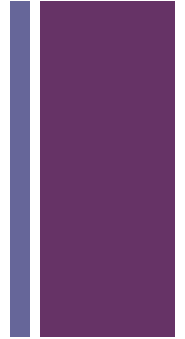


+ New cholesterol guidelines



- The ACC and AHA in collaboration with the NHLBI of the NIH formed an expert panel in 2008 to draft new cholesterol guidelines
- They used evidence from RCTs, reviews and meta-analyses and the predetermined outcomes of these trials (not post-hoc analyses)
- The NHLBI removed itself from the process, and other members removed themselves because of disagreement
- The guidelines and the new cardiovascular risk calculator were released in late 2013 without a preliminary period for discussion or criticism
- No attempt to harmonize the guidelines with previous versions of guidelines or with international guidelines

+ What's new?



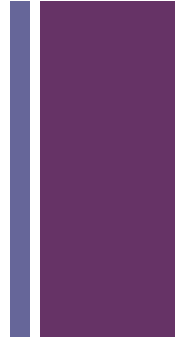
- Elimination of targets
- High intensity statin therapy emphasized and low intensity statin therapy eliminated
- ASCVD is now inclusive of stroke
- Non-statin therapies markedly de-emphasized
- No guidelines for triglycerides
- **Four treatment groups identified**

+ Group 1: Individuals with Clinical
ASCVD

■ CAD

■ PAD

■ Cerebrovascular Disease



+ Group 1 recommendation

Advantages

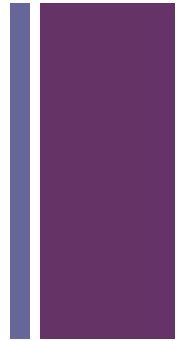
- Statins are recommended in the highest tolerated doses in this high risk group
- Without targets, treatment is simpler and requires less monitoring
- Cerebrovascular disease is included

Potential Limitations

- Follow up LDL levels irrelevant
- Less individualized approach to minimize residual risk
- Patients no longer have a goal -discourages self-management
- Eliminate consideration of multi-drug consideration
- This undermines potential development of new therapies

+ Group 2: People with LDL > 190

- These patients should receive statins in maximally tolerated doses
- New guidelines suggest consideration of additional agents if LDL remains above 190 with maximally tolerated statin therapy



+ Group 3: Diabetics

■ Who:

- Age 40-75
- LDL-C 70-189
- No Clinical ASCVD

■ How much:

- If 10 year risk $> 7.5\%$ - high intensity therapy
- If 10 year risk $< 7.5\%$, then moderate intensity statin

■ Disadvantages

- Does not address patients younger than 40 or older than 75
- Some patients may be overtreated
- These patients have high residual risk and may require more aggressive LDL lowering or non-LDL targets for therapy

■ Advantages

- Aggressive treatment of a high risk group



+ Statin dosing

High Intensity

- Atorvastatin 40-80 mg
- Rosuvastatin 20 mg – 40 mg
- **Lowers LDL-C \geq 50%**

Moderate Intensity

- Atorvastatin 10-20 mg daily
- Rosuvastatin 5-10 mg daily
- Simvastatin 20-40 mg daily
- Pravastatin 40-80 mg daily
- Lovastatin 40 mg daily
- **Lowers LDL-C 30-50%**

+ **Group 4:**
Patients with 10 year risk > 7.5%

- Age 40-75
- LDL 70-189
- No ASCVD
- 10 year risk of >7.5% by new risk calculator



There's an app for it!

+ Risk Calculator

AT&T 11:03 PM

Estimator Clinicians Patients About

ASCVD Risk Estimator*

10-Year ASCVD Risk	Lifetime ASCVD Risk
8.7% <small>calculated risk</small>	50% <small>calculated risk</small>
0.4% <small>risk with optimal risk factors**</small>	8% <small>risk with optimal risk factors</small>

Recommendation Based On Calcul... >

Age

Race

- White
- African American
- Other

Total Cholesterol (mg/dL)

AT&T 11:04 PM

10-Year ASCVD Risk	Lifetime ASCVD Risk
8.7% <small>calculated risk</small>	50% <small>calculated risk</small>
0.4% <small>risk with optimal risk factors**</small>	8% <small>risk with optimal risk factors</small>

Recommendation Based On Calcul... >

HDL - Cholesterol (mg/dL)

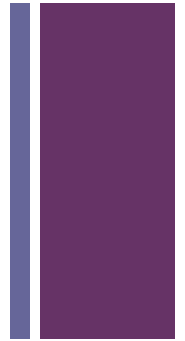
Systolic Blood Pressure

Treatment for Hypertension Y N

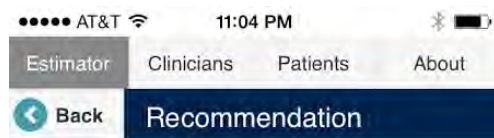
Diabetes Y N

Smoker Y N

*Intended for use if there is not ASCVD and



+ Risk Calculator



Based on the data entered (assuming no clinical ASCVD and LDL-C 70-189 mg/dL):

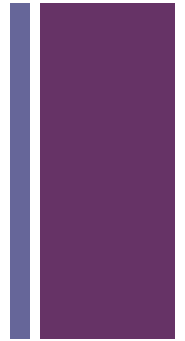
- Gender: Female
- Age: 42
- Race: African American
- Total Cholesterol: 190
- HDL-Cholesterol: 42
- Systolic Blood Pressure: 138
- Hypertension Treatment: Yes
- Diabetes: No
- Smoker: Yes

Moderate to High-Intensity
Statin Recommended

Before initiating statin therapy, it is reasonable for clinicians and patients to engage in a discussion



+ Statins in Primary Prevention



- Recommendation that statins be initiated in primary prevention patients with a 10 year risk of events $\geq 7.5\%$
- Consideration of statin therapy recommended in patients with 10 year risks of 5-7.5%
- In patients with Diabetes Mellitus, the threshold of greater than or equal to 7.5% is used to determine whether high intensity or moderate intensity statin therapy recommended
- **In the guidelines, the new criteria could result in more than 45 million middle aged Americans who do not have cardiovascular disease being recommended for statin therapy**
- This is about 1:3 adults (many of which are already on statin)

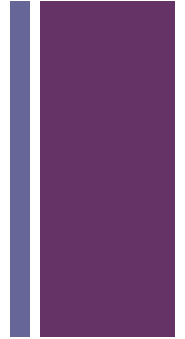
+ Primary prevention trials

Reduction of MI and stroke in those with increased LDL
(WOSCOPS, MEGA)

Reduced HDL cholesterol
(AFCAPS/TexCAPS)

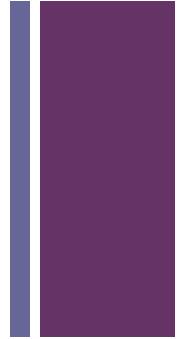
Raised concentrations of CRP (JUPITER), Diabetes (CARDS) or HTN (ASCOT-LLA)

+ Primary Prevention



- Between 1995-2008 six major primary prevention trials, which included greater than 55,000 men and women showed that statins were effective in primary prevention of MI, CVA among those with elevated LDL, reduced HDL, increased CRP, DM, or HTN.
- No trial of statin therapy has used a global risk prediction score as enrollment criterion
- **Statins CANNOT be recommended simply based on high risk without regard for individuals and specific clinical conditions**

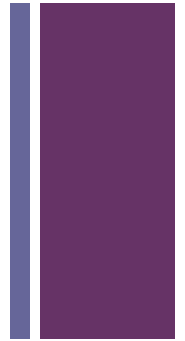
+ Special Populations: CORONA trial



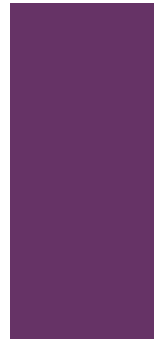
- Daily treatment with 10 mg of rosuvastatin did not reduce the composite outcome of death from cardiovascular causes or nonfatal myocardial infarction or stroke in vulnerable, elderly patients **with ischemic, systolic heart failure** who had already received extensive treatment with drugs for cardiovascular disease.
- However, rosuvastatin reduced the number of hospitalizations for cardiovascular causes, in addition to effectively reducing levels of LDL cholesterol and high-sensitivity C-reactive protein.

+ Special populations: AURORA trial

- In patients undergoing hemodialysis, the initiation of treatment with rosuvastatin lowered the LDL cholesterol level
- However, there was no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.



+ Special Populations:



Heart Failure and Hemodialysis				
1. The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II–IV ischemic systolic heart failure or in patients on maintenance hemodialysis.	N (No Recommendation)	71, 72		

- **Expert panel does not make a recommendation in patients with ischemic HF or in patients on maintenance HD**

+ The risk calculator is controversial

- “It is in the realm of primary prevention that the new guidelines are likely to be more controversial.”



- www.thelancet.com, Volume 382, November 30, 2013

+ Which of these two patients would be considered for statin therapy ?

- 55 year old male

- Smoker

- HTN, untreated

- LDL 75, HDL 50

- **9.6% 10 year risk**

- 60 year old female

- No HTN

- Non-smoker

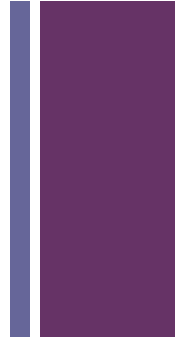
- LDL 180, HDL 50

- **3.8% 10 year risk**

The context is KEY

More important than absolute risk is the projected treatment effect for the INDIVIDUAL.

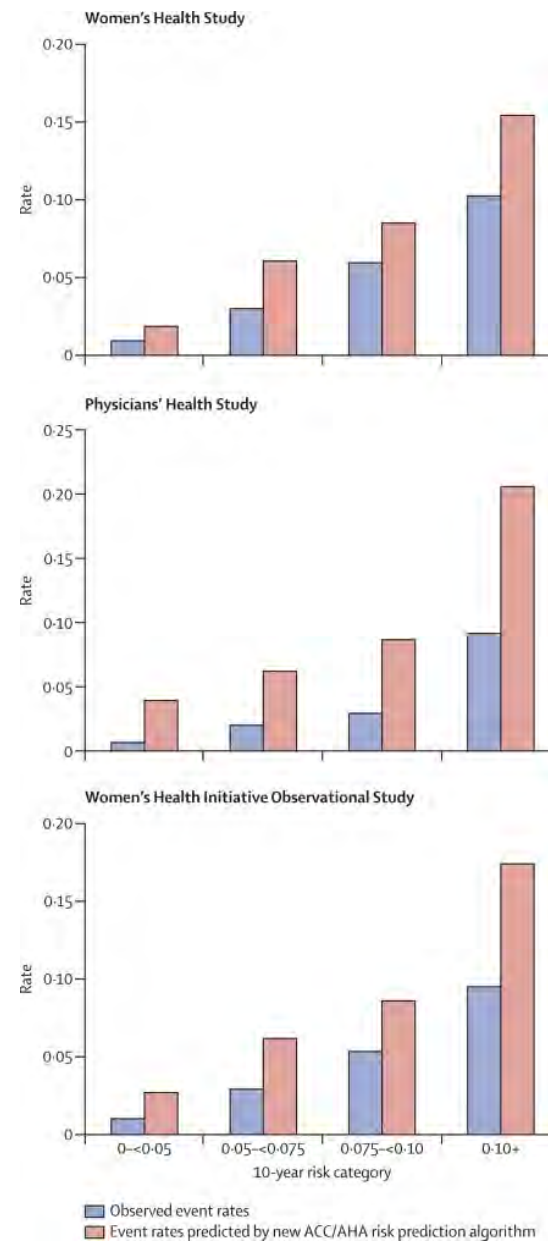
+ Overestimation of risk?



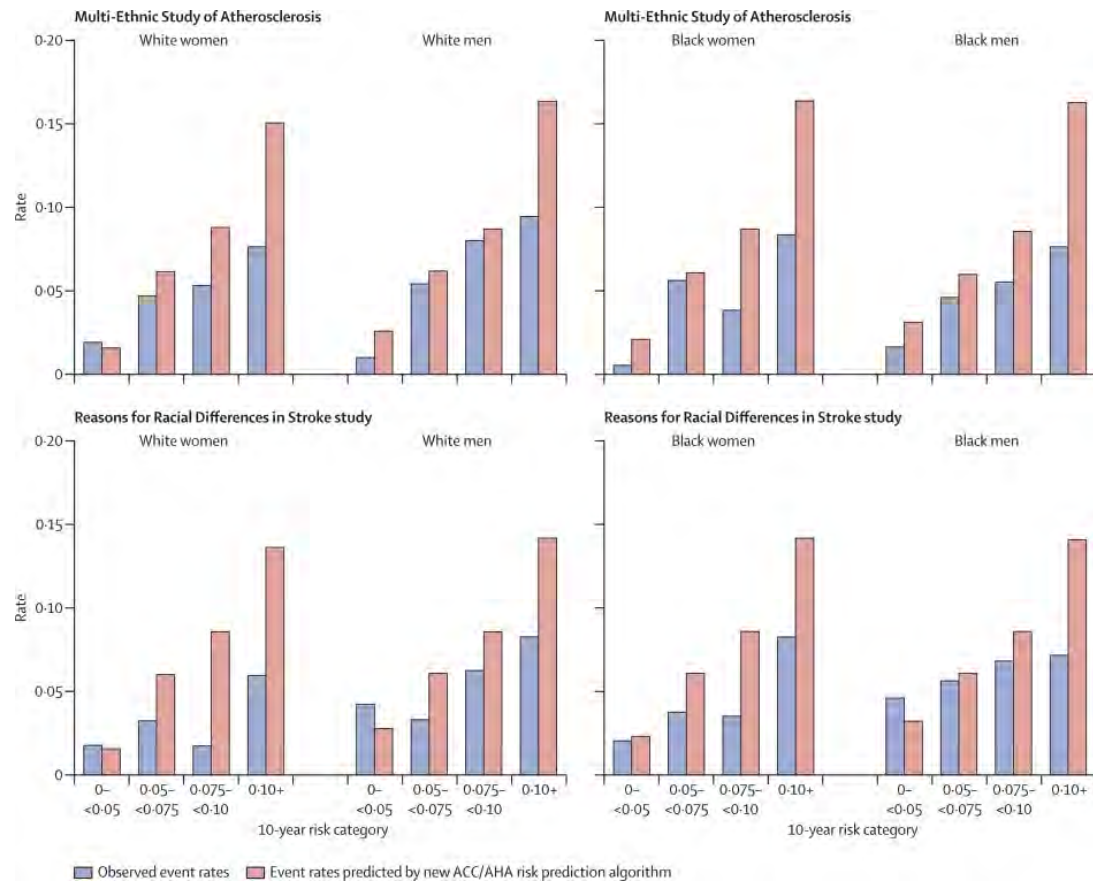
- The predicted 10 year risks of atherosclerotic events using the ACC/AHC algorithm were compared to observed event rates in three large primary prevention cohorts
 - The Women's Health Study
 - The Physicians' Health Study
 - Women's Health Initiative Observational Study
- The ACC/AHA risk prediction calculatory systematically overestimated observed risks by 75-150%

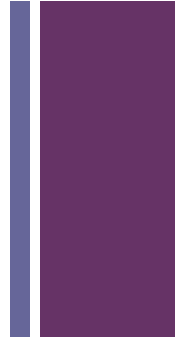


Does the risk predictor correctly assess vascular risk?



+ Comparison of observed event rates with predicted event rates in two external validation cohorts





- On the basis of the data from five external validation cohorts, it is possible that 40-50% of 33 million Americans targeted by new ACC/AHA guidelines do not have risk thresholds that are greater than 7.5%

ORIGINAL ARTICLE

Application of New Cholesterol Guidelines to a Population-Based Sample

Michael J. Pencina, Ph.D., Ann Marie Navar-Boggan, M.D., Ph.D.,
Ralph B. D'Agostino, Sr., Ph.D., Ken Williams, M.S., Benjamin Neely, M.S.,
Allan D. Sniderman, M.D., and Eric D. Peterson, M.D., M.P.H.

ABSTRACT

BACKGROUND

The 2013 guidelines of the American College of Cardiology and the American Heart Association (ACC–AHA) for the treatment of cholesterol expand the indications for statin therapy for the prevention of cardiovascular disease.

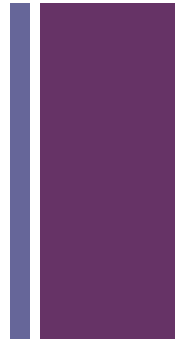
METHODS

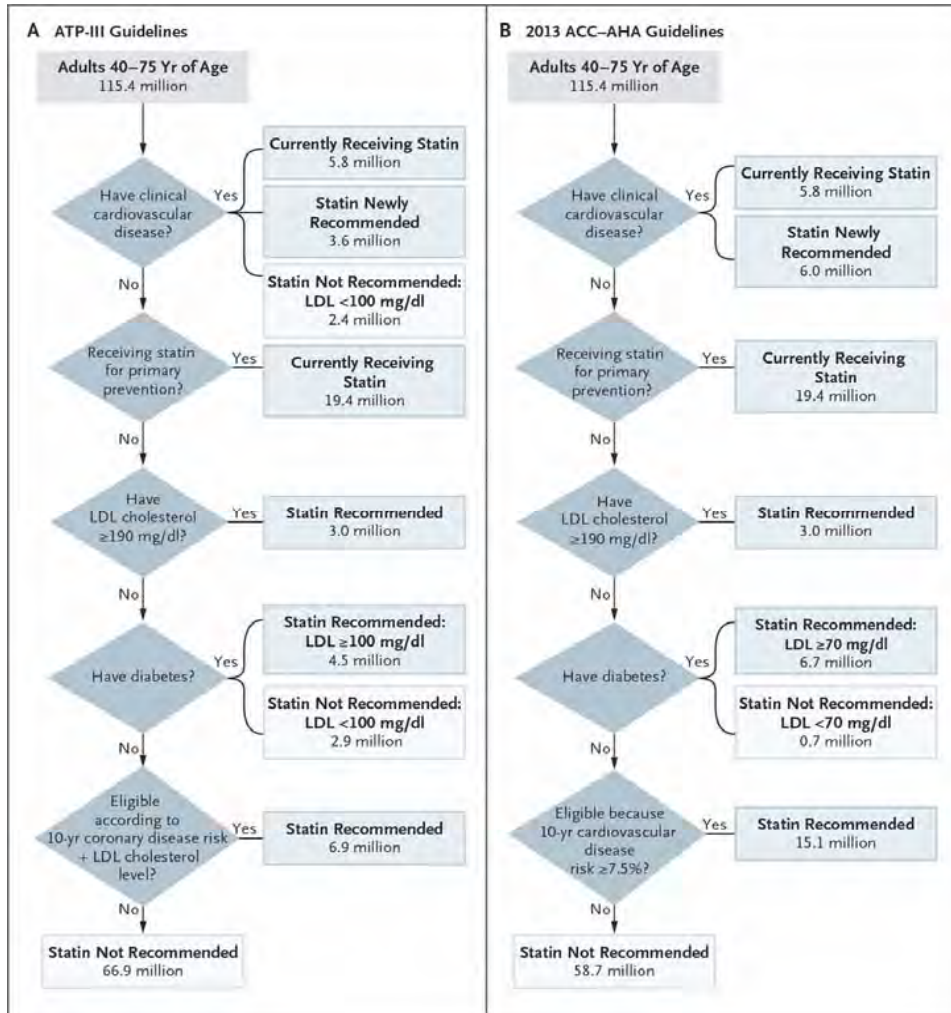
Using data from the National Health and Nutrition Examination Surveys of 2005 to 2010, we estimated the number, and summarized the risk-factor profile, of persons for whom statin therapy would be recommended (i.e., eligible persons) under the new ACC–AHA guidelines, as compared with the guidelines of the Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program, and extrapolated the results to a population of 115.4 million U.S. adults between the ages of 40 and 75 years.

From the Duke Clinical Research Institute (M.J.P., B.N., E.D.P.), Department of Biostatistics and Bioinformatics (M.J.P.) and Division of Cardiology (A.M.N.-B.), Duke University, Durham, NC; the Department of Mathematics and Statistics, Boston University and the Harvard Clinical Research Institute — both in Boston (R.B.D.); KenAnCo Biostatistics, San Antonio, TX (K.W.); and Royal Victoria Hospital, McGill University, Montreal (A.D.S.). Address reprint requests to Dr. Pencina at Duke University, Duke Clinical Research Institute, Biostatistics and Bioinformatics, 2400 Pratt St., Durham, NC 27705, or at michael.pencina@duke.edu.

+ Application of New Cholesterol Guidelines to a Population-Based Sample

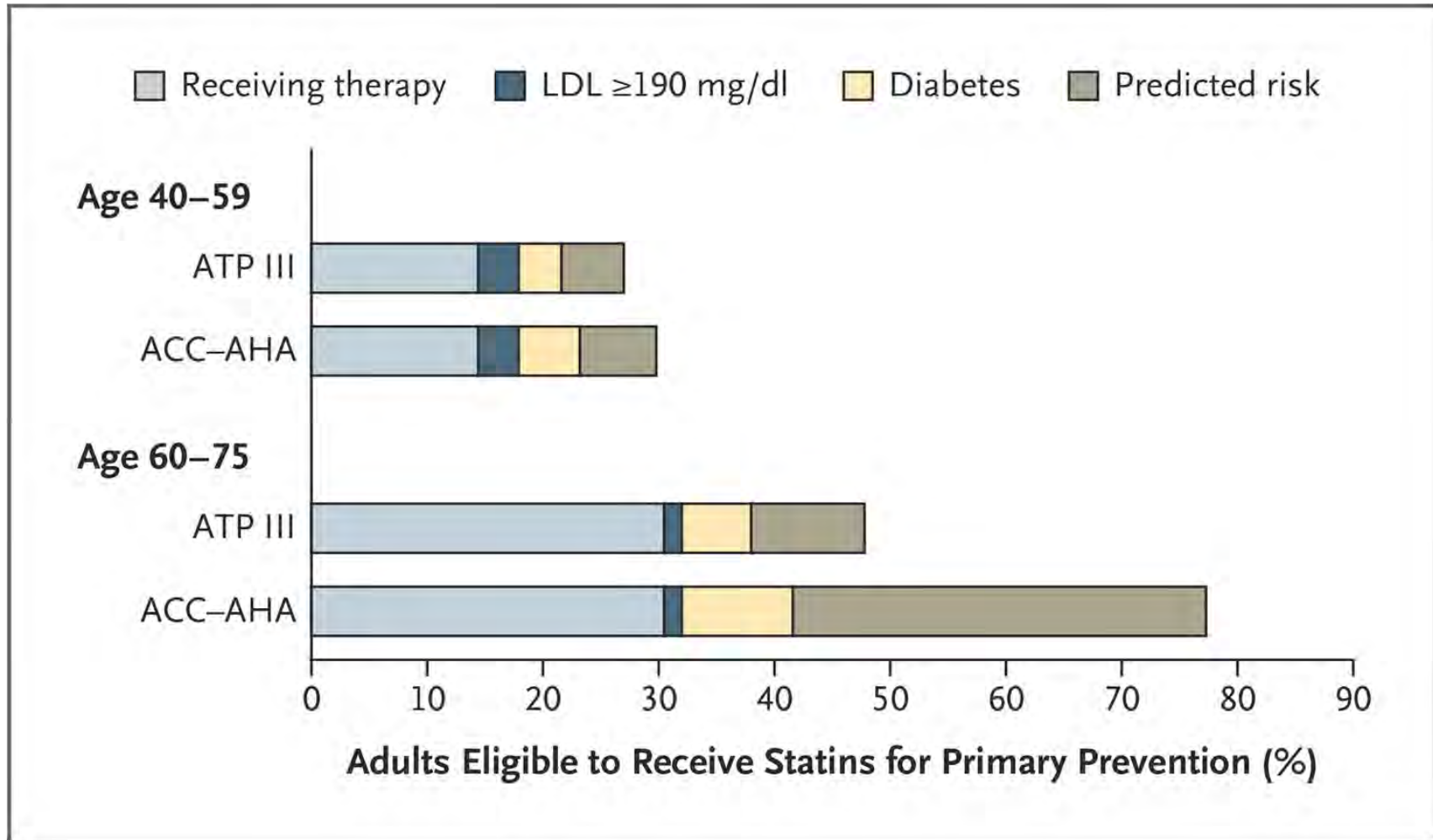
- Pencina, MJ, et al used data from NHANES (National Health and Nutrition Examination Surveys) 2005-2010, estimated the number and summarized risk factor profile of persons from whom statin therapy would be recommended under new guidelines compared to ATP III
- New guidelines would increase the number of US adults receiving or eligible for statin therapy from 37.5% (43.2 million) to 48.6% (56 million)
- Effect would largely be driven by increased number of adults who would be classified solely on their 10 year risk





**Pencina MJ et al. N Engl J Med 2014. DOI:
10.1056/NEJMoa1315665**

Percent of U.S. Adults Who Would Be Eligible for Statin Therapy for Primary Prevention, According to Set of Guidelines and Age Group.



+ All statin recommendations must be made with LIFESTYLE counseling!!

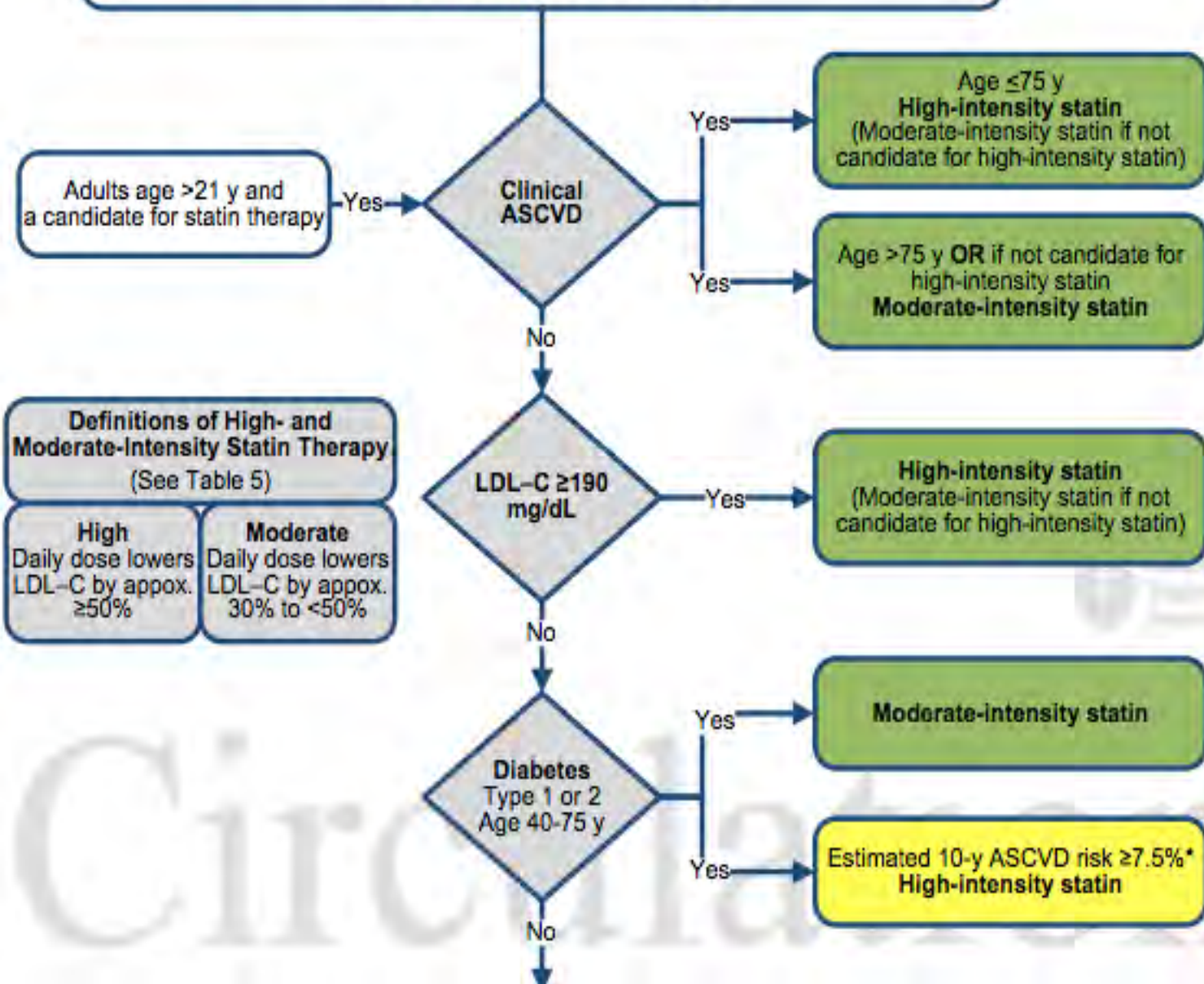
■ “Lifestyle counseling should occur at the initial and follow-up visits as the **foundation** for statin therapy and may improve the overall risk factor profile”

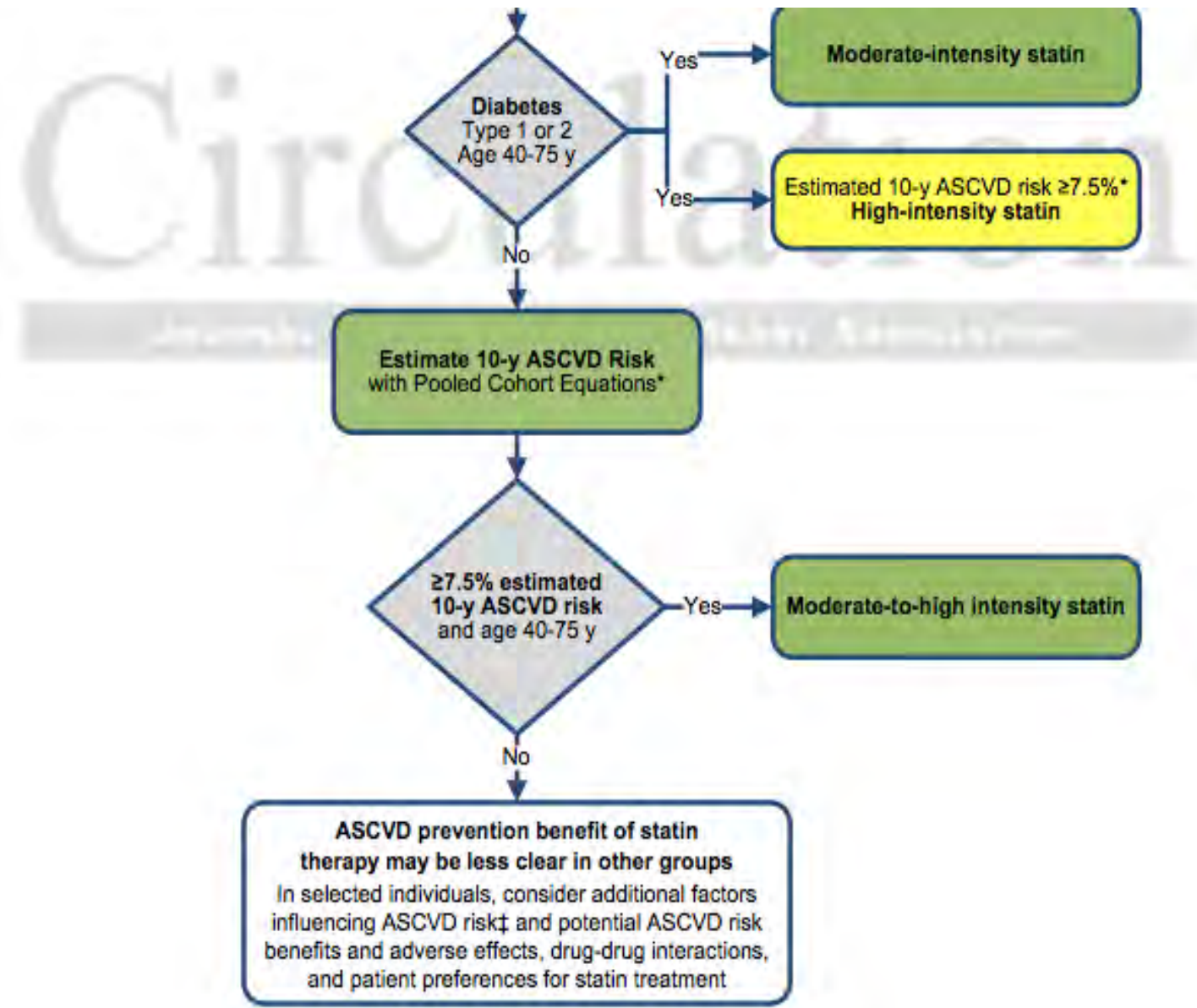


Lunch in Milwaukee 😊

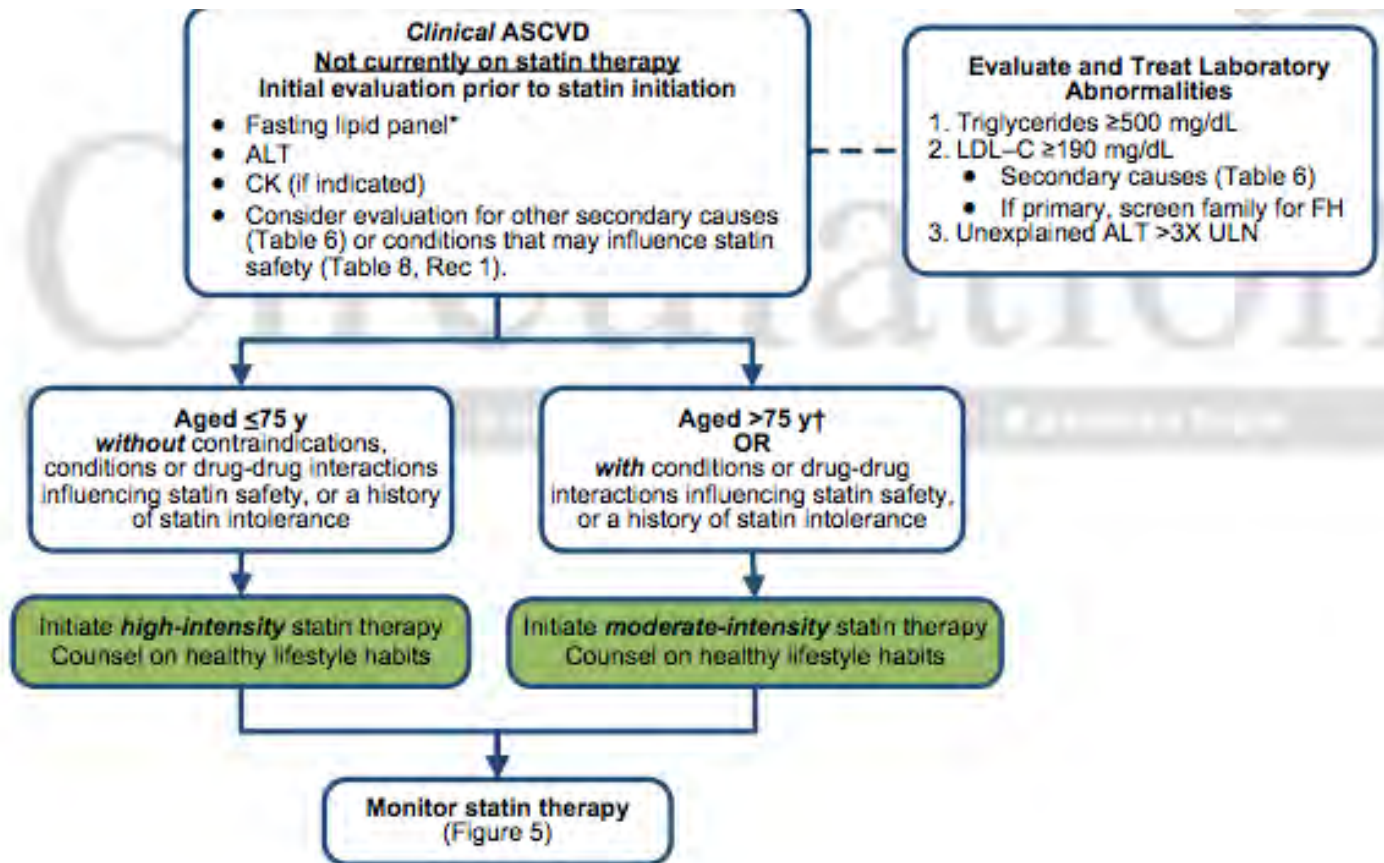
ASCVD Statin Benefit Groups

Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C 70-189 mg/dL.

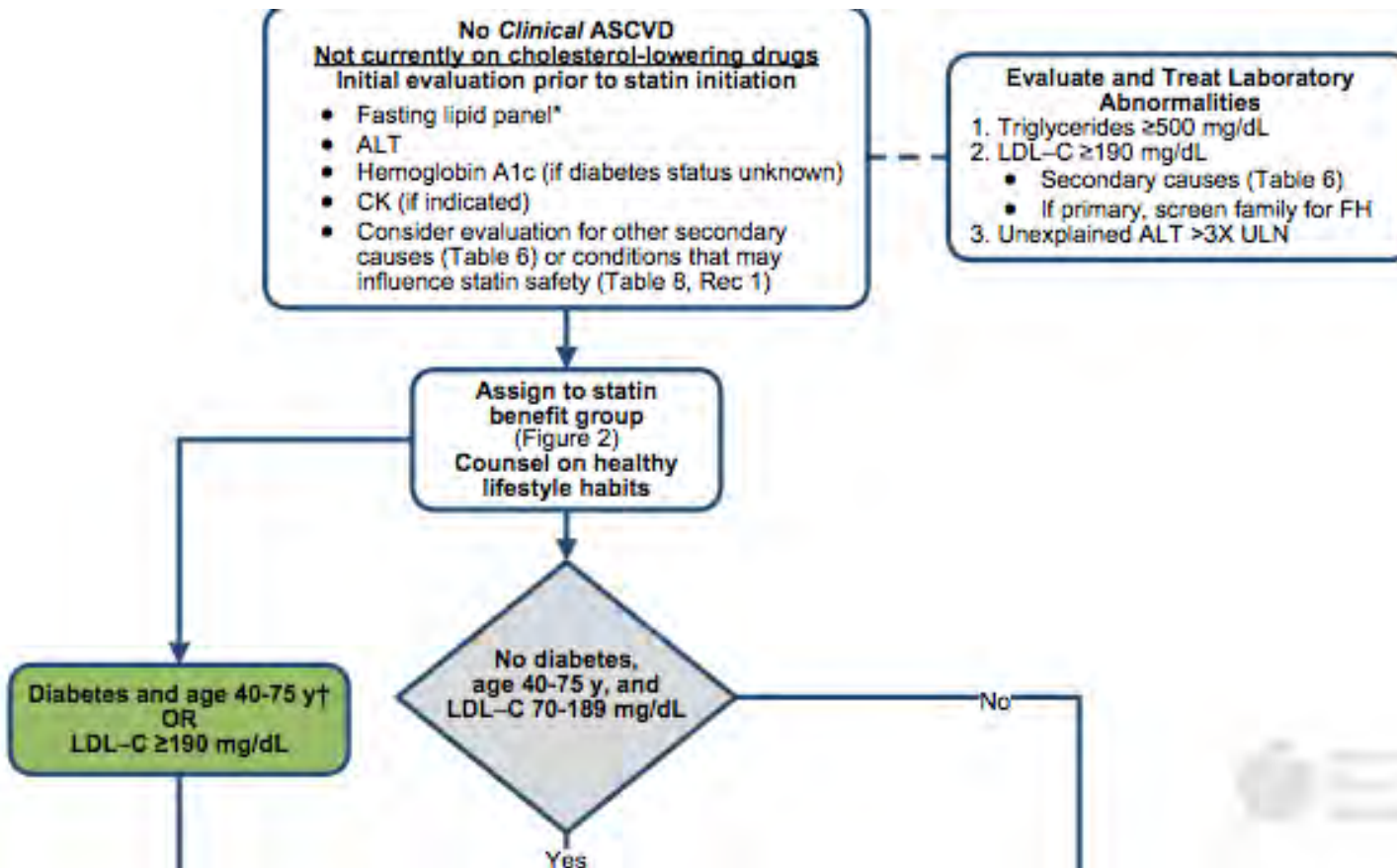




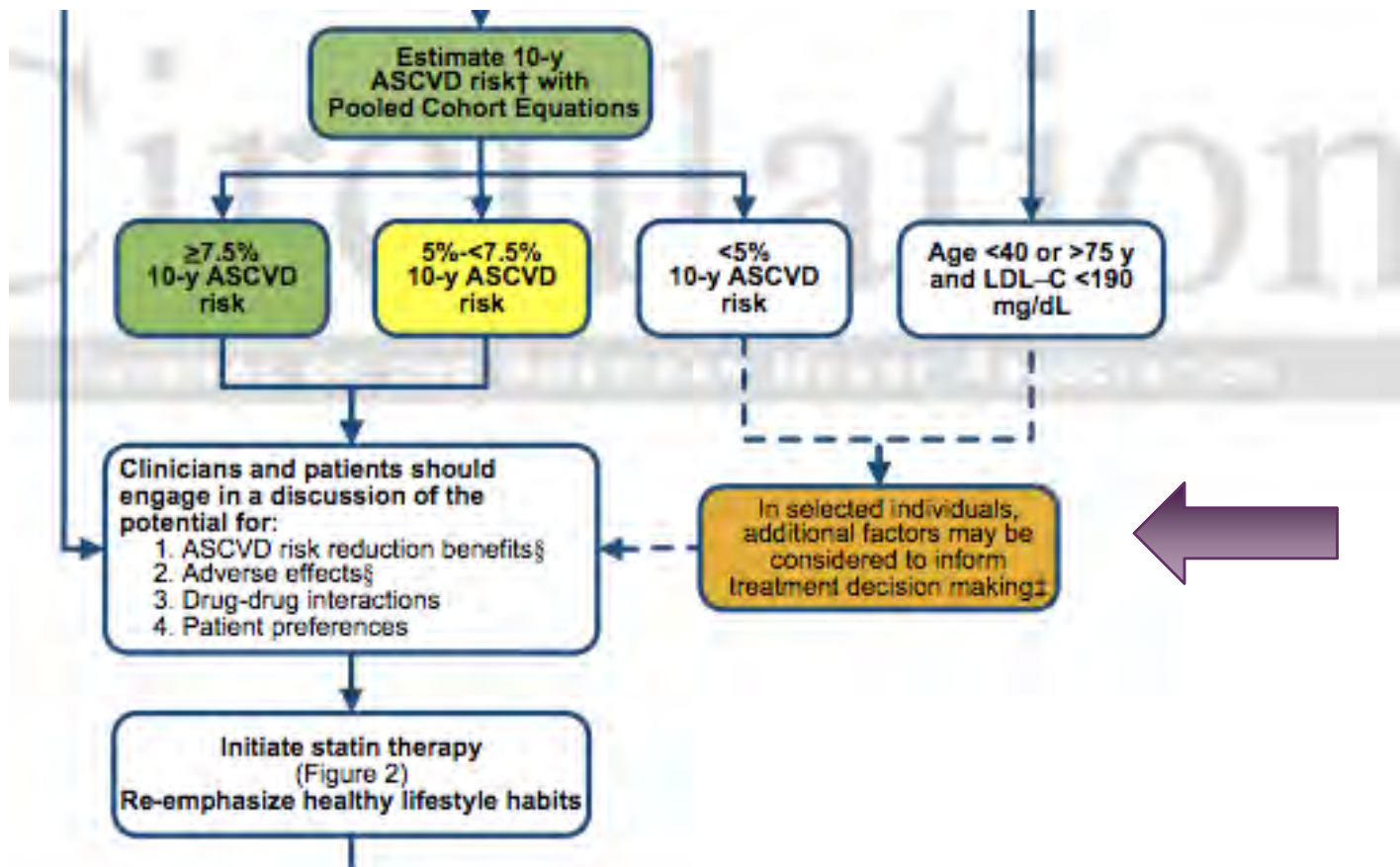
+ Clinical ASCVD



+ No history of Clinical ASCVD



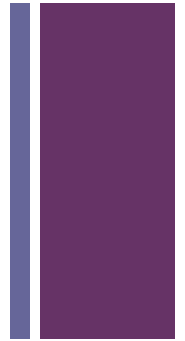
+ No clinical History of ASCVD



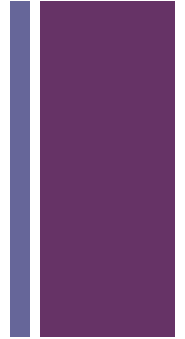
+ Additional factors to consider in treatment decisions

Primary LDL-C >160 mg/dL or other evidence of genetic hyperlipidemias,

- Family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative,
- Elevated C-reactive protein >2 mg/L
- ABI <0.9, or lifetime risk of ASCVD.



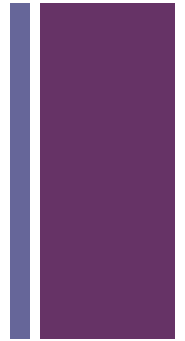
+ Safety Considerations



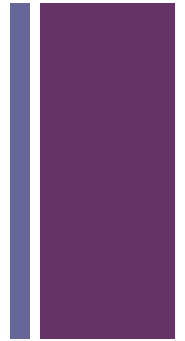
- In patients recommended for high intensity therapy, consider moderate intensity therapy if patients have characteristics that predispose individuals to statin adverse effects
 - Multiple or serious comorbidities, including impaired renal or hepatic function.
 - History of previous statin intolerance or muscle disorders.
 - Unexplained ALT elevations >3 times ULN.
 - Patient characteristics or concomitant use of drugs affecting statin metabolism.
 - >75 years of age

+ Safety and Monitoring

- Other patients that may warrant consideration to decrease statin intensities may include, but are not limited to:
 - History of hemorrhagic stroke.
 - Asian ancestry.

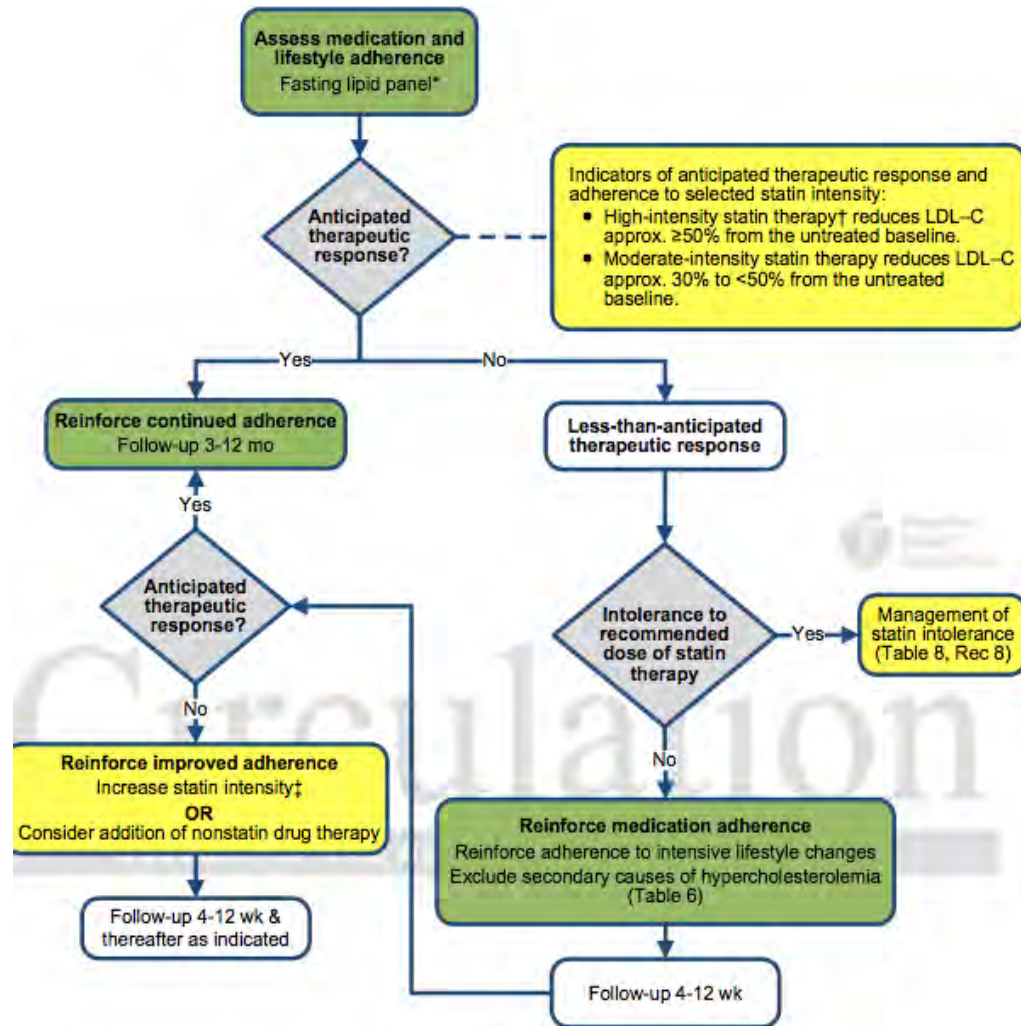


+ Safety Considerations (continued)

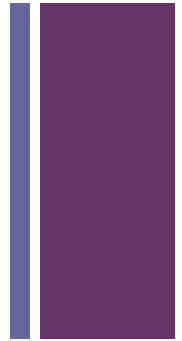


- CK levels should not be routinely measured – Class III (no benefit)
- Can consider checking CK level in individuals with personal history of muscle events, increased risk for myopathy
- ALT levels should be monitored prior to initiation, but no further follow up levels unless concern for hepatotoxicity
- Should not initiate simvastatin at 80 mg or increase to 80 mg – Class III (harm)

+ Monitoring and reassessment

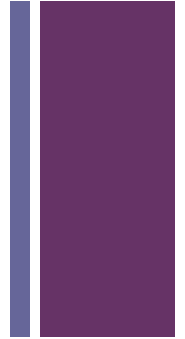


+ In summary....



- Despite ongoing decline in cardiovascular death rates, the burden of CV disease remains alarmingly high.
- Reduction of CV death rates is in part due to advancement of medical therapies, including statins for both primary and secondary prevention.
- The new guidelines are a departure from old guidelines in that there is no treatment targets.
- Four treatment groups were identified, including: those with ASCVD; individuals with LDL > 190; diabetics age 40-75; and individuals without ASCVD who have estimated 10 year risk of events.
- It has been suggested that risk calculator may overestimate risk in certain patients, and that the number of patients eligible for statin therapy increases especially in the older patients.
- Guidelines guide therapy, and do not mandate it and you still need to have individualized approach in treatment decisions.

+ Thank You!!!



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