2013 ACC/AHA Cholesterol Guidelines

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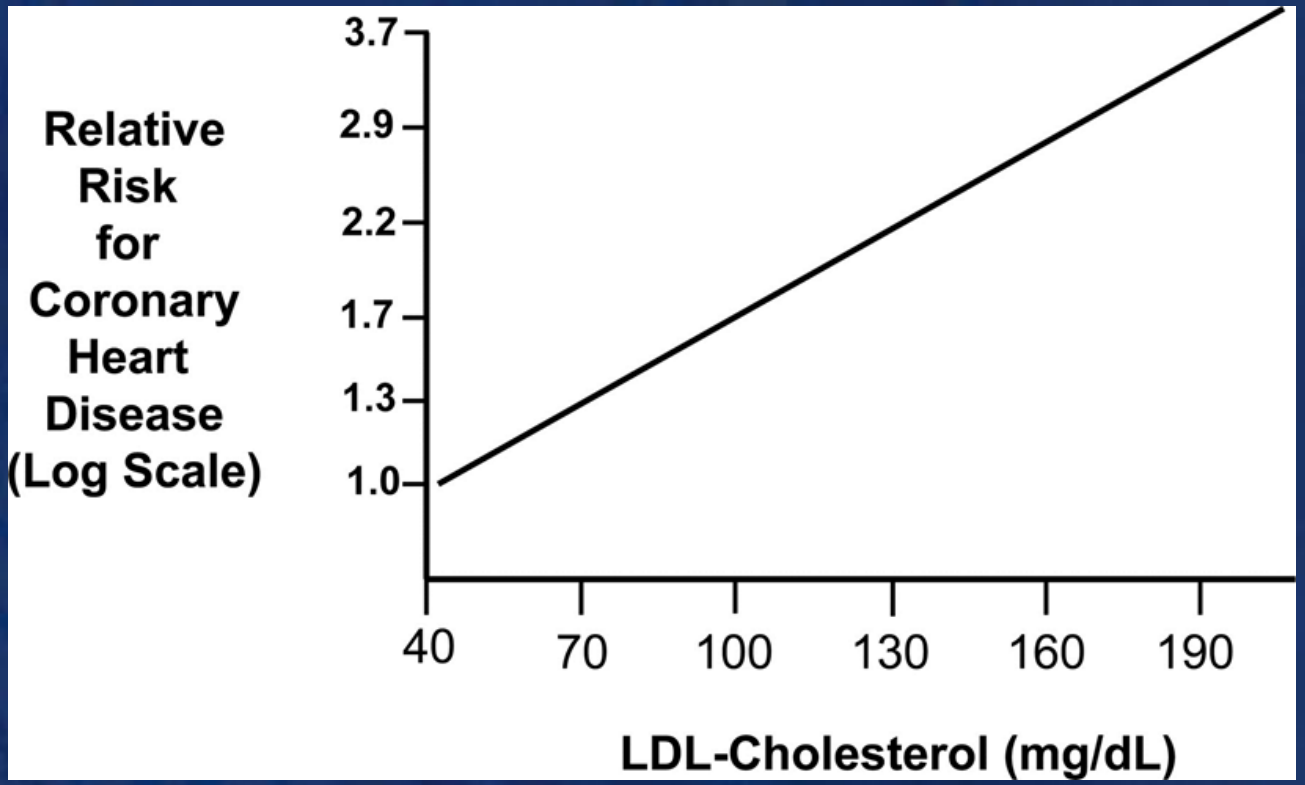
Objectives

- Epidemiology- Dyslipidemia and ASCVD
- Class Review: HMG-CoA Reductase Inhibitors
- ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
- Compare with 2014 ADA Clinical Practice Recommendations

Dyslipidemia Epidemiology

- Total cholesterol > 240 (>90th percentile)
  - 1 in 5 U.S. Adults (NHANES 1994)
  - 1 in 7 U.S. Adults (NHANES III 2010) – due to treatment
- Log-linear relationship
  - Lipid levels (total cholesterol & sub-fractions) & risk of atherosclerotic cardiovascular disease.
- 2013 ACC/AHA Guideline: Focus on LDL-C and risk of ASCVD

Log-linear Relationship Between LDL-C Levels and Relative Risk for CHD

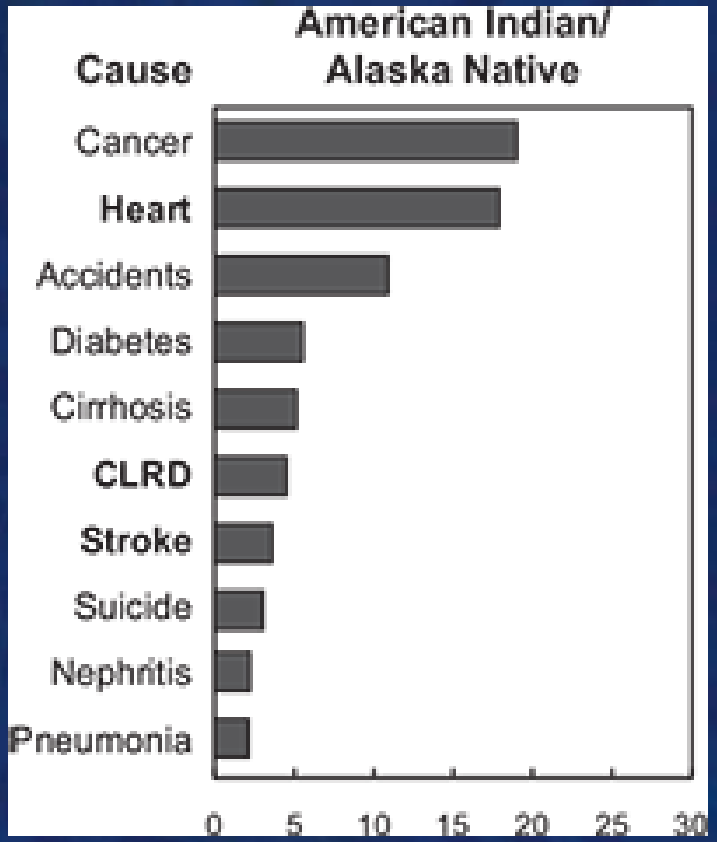


Grundy S M et al. *Circulation*. 2004;110:227-239

Health Disparities in the AI/AN Population

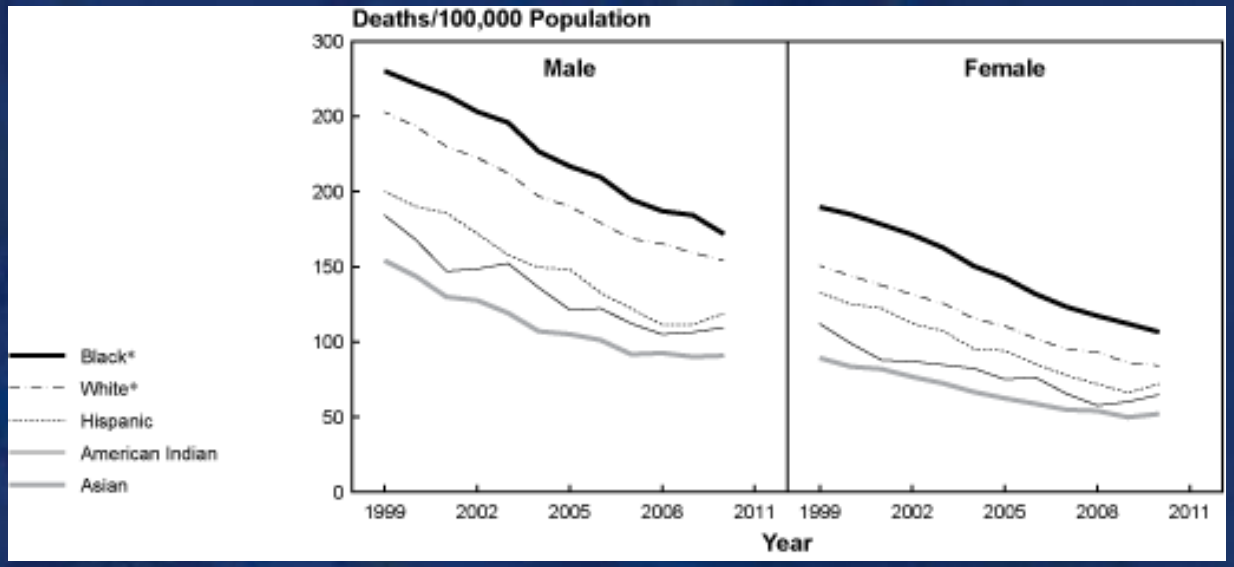
CARDIOVASCULAR DISEASE EPIDEMIOLOGY

AI/AN Cardiovascular Mortality



Source: NHLBI Fact Book 2012

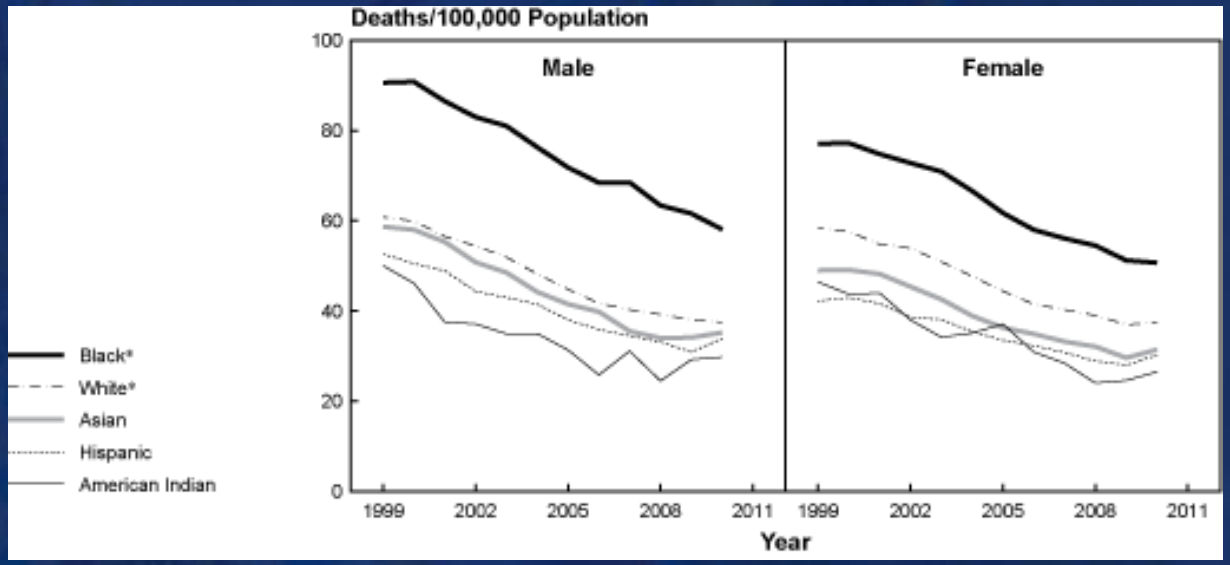
Coronary Heart Disease Trends



Age-Adjusted Death Rates for Coronary Heart Disease by Race/Ethnicity and Sex, U.S., 1999–2010

Source: NHLBI Fact Book 2012

Stroke Trends



Age-Adjusted Death Rates for Stroke by Race/Ethnicity and Sex, U.S., 1999–2010

Source: NHLBI Fact Book

HMG CoA Reductase Inhibitors

DRUG CLASS REVIEW

Drug Class: Statins
HMG CoA Reductase Inhibitors

- Agents: Lovastatin, rosuvastatin, fluvastatin, atorvastatin, pravastatin, simvastatin, pitavastatin
- Mechanism of Action: Inhibit the rate-limiting step in cholesterol biosynthesis by competitive blockade of HMG CoA reductase
- Effects
  - Lower circulating LDL-C
  - Reduced VLDL synthesis
  - Raises HDL
  - Reduced Triglycerides

Other Proposed Statin Benefits

- Regression of atherosclerotic plaques
- Reduced progression and stabilization of plaques
- Reduced inflammation (independent of lipid lowering)
- Reduced endothelial dysfunction
- Reduced thrombogenicity
- Reduced ventricular arrhythmia and cardiac death

Statin Adverse Reactions

- Hepatic Dysfunction
  - Low rate aminotransferase elevations (0.5-3 %)
  - Usually in first few months of therapy
  - Kaiser Study in Colorado (Amer J Med 2005): 23,000 statin treated patients
    - 0.3% with ALT > 10x ULN
    - 0.1% (17 patients) with severe transaminitis felt due to statin use (all but 4 associated with drug interactions)
  - FDA revised labeling 2012: Hepatic profile before initiation of statin therapy and only for clinical indications thereafter.

Evaluation of cases of severe statin-related transaminitis within a large health maintenance organization. Charles EC, Olson KL, Sandhoff BG, McClure DL, Merenich JA. Am J Med. 2005;118(6):618.

Statin Adverse Reactions (cont.)

- Muscle Injury
  - Myalgia, Myositis, and Rhabdomyolysis
  - Uncommon with statin therapy alone unless other risks
    - Caution if: Hypothyroidism, Obstructive liver disease, CRF, Inflammatory Myopathy, Elderly, Drug interactions (esp CYP3A4 drugs and Fibrates)
  - MEDLINE search 1966-2005 (Circulation 2006)
    - 74,102 subjects in 35 Statin RCTs (Statin Monotherapy)
    - No statistically significant absolute increase in risk of myalgia, creatinine kinase elevations, or rhabdomyolysis (except cerivastatin- off market).
  - Higher rates of myalgia reported in clinical practice (up to 11%)

Risks associated with statin therapy: a systematic overview of randomized clinical trials. Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, Krumholz HM. Circulation. 2006;114(25):2788

Statin Adverse Effects

- Development of Type 2 Diabetes Mellitus
  - JUPITER (17,802 patients)
    - Increased rate (3.0% versus 2.4%) of physician diagnosed DM2 in Rosuvastatin treatment group compared to placebo.
  - 2011 (JAMA) meta-analysis (32,752 patients)
    - Increased incidence DM2 with intensive statin therapy compared to moderate statin therapy.
    - 2 additional case per 1000 patient-years (NNH = 448)
    - 6.5 fewer CVD events per 1000 patient-years (NNT = 155)
  - Statin-therapy CVD benefit exceeds DM2 risk

1. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, JUPITER Study Group. N Engl J Med. 2008;359(21):2195

2. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP, Sabatine MS, Braunwald E, Kastelein JJ, de Lemos JA, Blazing MA, Pedersen TR, Tikkanen MJ, Sattar N, Ray KK. JAMA. 2011;305(24):2556.

Statin Adverse Reactions

- Renal Dysfunction (benign proteinuria)
- Behavioral/Cognitive
  - Case reports: Cognitive impairment, memory loss depression, suicidality, irritability, aggression
  - Causal relationships not well established
- Cancer
  - No convincing evidence unless you are a mouse on high dose statin therapy
- Hemorrhagic stroke (annual risk 0.5 per 1000 patients)
- Teratogenicity (Pregnancy Category X)
- Other (case reports): Cataract, Neuropathy, Lupus, Androgen reduction

2013 ACC/AHA Cholesterol Guideline

CAVEATS

- Systematic review generally did not consider evidence beyond 2011
  - Expert panels discussed major RCTs and meta-analyses published through July 2013.
  - Plan to begin guideline updates in 2014
- Recommendations derived from;
  - Randomized trials, meta-analyses, and observational studies
  - Only when sufficient evidence available

2013 ACC/AHA Cholesterol Guideline

CAVEATS (cont.)

- Grading according to;
  - Level of Evidence (Certainty of Treatment Effect)
  - Class of Recommendation (Size of Treatment Effect)
- Secondary causes of hyperlipidemia and triglycerides > 500 were exclusion criteria in studies reviewed.
- Reminder
  - “Guidelines are not a replacement for clinical judgment”

Scope of Guideline

- Primary and secondary prevention of ASCVD in adults (age 21 and older)
- Treatment of blood cholesterol levels to reduce ASCVD risk.
  - ASCVD (Coronary Heart Disease, Stroke, PAD)
- Not intended to be a comprehensive approach to lipid management

Expert Panel: Focus on Statins

- “Significant departure” from current strategies.
- Represents change in a “long standing paradigm.”

Treatment Strategy

- ***Fixed-dose*** statin therapy to reduce ASCVD risk
  - Supported by multiple RCTs
- No evidence to support other popular strategies
  - Treat to target
  - Lower cholesterol is better
  - Risk based treatment approaches

Overview: Treatment

- Consistent reduction in ASCVD events from statins in primary/secondary prevention populations
  - Exception: No benefit observed in hemodialysis patients and NYHA II-IV heart failure
- Lifestyle modification as “background therapy” prior to and during statin therapy
- Additional therapy (e.g. Niacin) to further lower non-HDL cholesterol once LDL goal achieved ***did not further reduce*** ASCVD events.

Overview: Dose

- Evidence supports
  - “Appropriate intensity” of statin therapy should be used
- No RCT evidence to support
  - Dose titration to achieve specific LDL or HDL goals

Definitions

- Clinical ASCVD (For secondary prevention)
  - Acute coronary syndromes, history of MI, stable or unstable angina, coronary or arterial revascularization, stroke, TIA, or PAD presumed due to ASCVD.
  - Based on RCT inclusion criteria
- ASCVD Risk (For primary prevention)
  - Non-fatal MI, CHD death, non-fatal and fatal stroke

General Findings
Statin Therapy

- ASCVD events decreased across a spectrum of baseline LDL-C > 70.
- Consistent relative risk reduction for;
  - All clinical subgroups
  - Primary and secondary prevention of ASCVD events
- Absolute reduction in events proportional to absolute ASCVD risk.

Major Statin Benefit Groups

Benefit "clearly outweighs" risks of adverse events

- Clinical ASCVD
- Primary elevation of LDL-C ≥ 190
- Diabetes mellitus and LDL-C 70-189 without ASCVD
  - If estimated 10 year ASCVD risk ≥ 7.5%
- LDL-C 70-189 without ASCVD or diabetes mellitus
  - If estimated 10 year ASCVD risk ≥ 7.5%

* Using Pooled Cohort Equations

Statin Benefits
Expert Panel Conclusions

- Secondary Prevention
  - ***High*** level of evidence
  - Reduced total mortality in persons with prior ASCVD events
- Primary Prevention
  - ***Moderate*** level of evidence
  - Reduced total mortality in persons with increased ASCVD risk

SUMMARY OF RECOMMENDATIONS

Level of Evidence

- Strong
- Moderate
- Weak
- Expert
- No recommendation

Treatment Targets

- ***No recommendation*** is made (lack of evidence);
  - For or against LDL-C or non-HDL-C targets;
  - For primary or secondary prevention of ASCVD

Secondary Prevention

Clinical ASCVD (Age ≤ 75 years)

- Strong evidence to support…
  - ***High-intensity statin therapy or;***
  - Moderate-intensity statin therapy if;
    - Poor tolerance, contraindications, or risks with high-intensity statin therapy
  - Initiate high-intensity statin therapy or increase intensity, as tolerated, if already on low/moderate intensity statin therapy.

Secondary Prevention

Clinical ASCVD (Age > 75 years) (cont.)

- Weigh risk-reduction benefits versus adverse effects and patient preference when considering high or moderate intensity statin therapy (Expert).
  - No clear evidence of additional risk reduction with high intensity versus moderate intensity statin therapy.
  - Moderate-intensity statin therapy did reduce ASCVD events compared to control.
  - Advised consider moderate intensity statin therapy and continuation of statin therapy if being tolerated.

Primary Prevention
Adults (21 y) with LDL-C ≥ 190

- Moderate evidence to support…
  - ***High-intensity statin therapy*** (or maximum stain therapy tolerated).
  - If LDL-C ≥ 190 or Trigs ≥ 500, then evaluate for secondary causes of hyperlipidemia.
  - Evidence shows for every 39 mg/dL reduction in LDL-C there is 20% reduction in ASCVD risk.
- Expert opinion supports…
  - For untreated LDL-C ≥ 190, intensify statin therapy to achieve 50% LDL-C reduction.
  - After maximum intensity statin therapy achieved, consider non-statin drug to further lower LDL-C.

Primary Prevention
Diabetes Mellitus and LDL-C = 70-189

- Strong evidence to support…
  - Age 40-75 years: ***Moderate-intensity statin therapy***
- Expert opinion supports…
  - Age 40-75 years: Consider ***high-intensity statin therapy***
    - If 10 year ASCVD risk > 7.5% (unless contraindicated)
  - Age < 40 or > 75 y: Consider ***mod-intensity statin therapy***
    - After weighing risk-reduction benefits versus risk of adverse effects and patient preference

Primary Prevention
No Diabetes Mellitus and LDL-C = 70-189

- Expert opinion supports…
  - Use Pooled Cohort Equations to estimate 10 year ASCVD risk.

Note: All further evidence-based decision making in this group is based on the expert opinion recommendation to use the Pooled Cohort Equations.

Measuring Risk: When/Who

Recommendations of Risk Assessment Work Group

- Persons age 20-79 years.
- Measurement of risk factors every 4-6 years.
  - Total and HDL cholesterol
  - Blood pressure
  - Diabetes mellitus
  - Current smoking status
- Calculate risk in persons age 40-79 years using pooled cohort equations.

Pooled Cohort Equations

- New risk assessment tool to estimate 10 year ASCVD risk
  - Expert Panel Definition:
    - First occurrence non-fatal and fatal MI (“hard CHD”) ***and stroke***
- Global assessment of ASCVD risk rather than risk factor counting or RCT risk factor inclusion criteria
- Intended for use to predict stroke and CHD events in;
  - Non-Hispanic Caucasian and African American
  - Women and men
  - Age 40-79 years
  - With or without diabetes
  - LDL-C 70-189

Online CV Risk Calculator

http://my.americanheart.org/cvriskcalculator

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. Circulation, 2013 Nov 12.

Risk Calculator Development
Risk Assessment Work Group

- Pooled cohorts included only African-American or White participants with at least 12 years follow-up.
  - Atherosclerosis Risk in Communities (ARIC) Study
  - Cardiovascular Health Study
  - Coronary Artery Risk Development in Young Adults (CARDIA)
  - Framingham original and offspring study cohorts
- "Insufficient data" for other race/ethnic groups
  - "But 10-yr ASCVD risk can be substantially higher" in AI/AN

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.. Goff et al. *J Am Coll Cardiol*. 2013;():. doi:10.1016/j.jacc.2013.11.005

Risk Calculator Development
Risk Assessment Work Group (cont.)

- Variables (of "statistical merit") in 4 pooled equations
  - Age
  - Total and HDL Cholesterol
  - Systolic BP, treated or untreated
  - Diabetes mellitus
  - Current smoking status

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.. Goff et al. *J Am Coll Cardiol*. 2013;():. doi:10.1016/j.jacc.2013.11.005

Risk Calculation Controversy
Lancet: Nov 2013 (Online)

- Paul Ridker, MD (Cardiologist)- Brigham and Women's
- Nancy Cook (Statistician)- Harvard
- Risk calculations based on epidemiologic models:
  - Not properly calibrated (overestimate risk by double)
  - Do not use RCT study inclusion data (evidence based)
  - Not externally validated for contemporary populations
  - Do not account for patients with high CV risk who may not benefit from statin therapy
- HTN and smoking (major drivers of global risk) are better treated directly than indirectly by statin therapy

- Statins: new American guidelines for prevention of cardiovascular disease. Ridker, PM, Cook, NR. *The Lancet*. Volume 382, Issue 9907, Pages 1762 – 1765, 30 November 2013

Risk Calculation Controversy
Lancet: Nov 2013 (Online) (cont.)

- Pooled Cohort Equations overestimate risk (by double)
  - When applied to primary prevention cohorts
    - Women's Health Study
    - Physician's Health Study
    - Women's Health Initiative Observational Study
- Statin estimates for primary prevention (from pooled cohort equations):
  - >7.5 10-year risk: 33 million adults
  - 5-7.4% 10 year risk: 12.7 million adults
- 45 million middle-aged Americans
- One in every three American adults

Statins: new American guidelines for prevention of cardiovascular disease. Ridker, PM, Cook, NR. *The Lancet*. Volume 382, Issue 9907l P{ages 1762 – 1765, 30 November 2013

Primary Prevention

No Diabetes Mellitus and LDL-C = 70-189 (cont.)

- Strong evidence to support…
  - Age 40-75 years and ASCVD risk > 7.5%: ***Moderate or high-intensity statin therapy***.
  - Regardless of sex, race, or ethnicity
- Weak evidence to support…
  - Age 40-75 years and ASCVD risk 5-7.5%: ***Moderate intensity statin therapy***
    - Adverse event rate felt to possibly outweigh ASCVD risk reduction benefit on high-intensity statins

Basis for Recommendations

1^0 Prevention: No Diabetes Mellitus and LDL-C 70-189

- Three exclusively primary prevention RCTs including individuals with LDL-C 70-189.
- 10y estimated ASCVD event rates derived from placebo groups.
- Compared excess ASCVD event rates in statin-treated groups (from statin RCTs).
- ASCVD risk reduction benefit observed following initiation of mod/high intensity statin therapy with 10 year estimated ASCVD risk ≥ 7.5%.
- Risk reduction benefit felt to exceed risk of adverse events.

Special Populations

Hemodialysis and NYHA II-IV Heart Failure

No recommendation is made regarding initiation or discontinuation of statins.

Race/Ethnicity
AI/AN Population

- Full Panel acknowledges higher rate of ASCVD in AI/AN compared to whites.
- Recommends
  - "Future trials should be powered for subgroup analysis by race and ethnicity."
- Risk Assessment Work Group recommendation:
  - Expert opinion (level of evidence)
  - "Pooled Cohort Equations may be considered when estimating risk in patients from populations other than African Americans and non-Hispanic Whites."

Native American Cardiology Program

- Assume higher ASCVD risk for AI/AN
- Simultaneous risk calculation using PCE and SHS may lead to differences that do not affect treatment decisions based upon new guidelines.
- SHS data/population may no longer be representative of current service population (new ASCVD mortality data pending release/publication soon).
- Recommend use of PCE in risk assessment

Additional Evidence
Statins and Primary Prevention

- Two meta-analyses published after ACC/AHA Task Force systematic review
  - Cochrane database (2013)
  - Lancet (2012)

Cochrane Database 2013

Statins for the Primary Prevention of Cardiovascular Disease

- Study Selection Criteria
  - New trials since last Cochrane review 2011
  - RCTs: Statins versus Placebo or Usual Care
  - Minimum treatment duration 1 year with 6 mo F/U
  - Adults without restrictions and <10% history of CVD
- Outcomes
  - All-cause mortality, fatal and non-fatal CHD, stroke, combined endpoints, revascularization, total and LDL-C concentrations, adverse effects, QOL, and costs.

Taylor F, Huffman MD, Macedo AF et al. Statins for the primary prevention of cardiovascular disease. The Cochrane database of systematic reviews 2013;1:CD004816.

Cochrane Database 2013

Statins for the Primary Prevention of Cardiovascular Disease (cont.)

- Identified 4 new trials and updated follow-up data from 3 trials.
- Results
  - Reductions in all-cause mortality, major vascular events, and revascularizations
  - Reductions in both total and LDL-C (with heterogeneous effects)
  - No excess adverse events
  - Statins determined “likely cost effective”

Taylor F, Huffman MD, Macedo AF et al. Statins for the primary prevention of cardiovascular disease. The Cochrane database of systematic reviews 2013;1:CD00481

Lancet 2012

Statins for the Primary Prevention of Cardiovascular Disease

- Meta-analysis (CTT): 27 Randomized Trials (174,149 people)
  - 22 Trials: Statin vs. Control
  - 5 Trials: More Statin vs. Less Statin (control group)
- Outcomes
  - Fatal and non-fatal CHD, stroke, revascularization
- Subjects assigned to categories for 5 year risk of major vascular events (range <5% to >30%) on control therapy.

Cholesterol Treatment Trialists Collaboration, Mihaylova B, Emberson J et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380:581–90.

Lancet 2012

Statins for the Primary Prevention of Cardiovascular Disease (cont.)

- Statins reduced risk of major vascular events and both vascular and all-cause mortality in all groups.
- Proportional reduction of risk of major vascular events was at least as high in the low risk groups as high risk groups.
- Individuals with 5 year risk < 5% for major vascular events
  - For each 1 mmol/L reduction in LDL;
  - Absolute reduction of 11 major vascular events per 1000 persons per 5y.
- Summary: Statins highly effective for primary prevention even in relatively low risk groups

Cholesterol Treatment Trialists Collaboration, Mihaylova B, Emberson J et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380:581–90.

Intensity of Statin Therapy

For Primary and Secondary Prevention

- Expert panel definitions based upon average expected response to a specific statin and dose.
  - High-intensity Statin Therapy: LDL-C reduced ≥ 50%
  - Moderate-intensity Statin Therapy: LDL-C reduced 30-50%
  - Low-intensity Statin Therapy: LDL-C reduced < 30%
- Percent reductions based upon 2010 meta-analysis performed by Cholesterol Treatment Trialists
  - In which statin therapy reduced ASCVD events

Summary of Statin Intensity

By percentage reduction of LDL-C

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C by approximately ≥50%	**Daily does lowers LDL-C approximately 30% to <50%**	**Daily dose lowers LDL–C by <30%**
Atorvastatin 40-80 mg **Rosuvastatin 20 (*40*) mg**	**Atorvastatin 10 (*20*) mg** **Rosuvastatin (*5*) 10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40 (*80*) mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

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. Circulation, 2013 Nov 12.

Conclusions
ACC/AHA Guideline

- Statins in proper dose are the most effective medications for reduction of ASCVD risk in both primary and secondary prevention.
- Statins are safe, adverse events are uncommon, and monitoring can be simplified.

Conclusions
ACC/AHA Guideline (cont.)

- Data support a simplified treatment strategy of fixed-dose statin therapy instead of statin titration to specific cholesterol targets.
- High-intensity statin therapy, as tolerated and unless contraindicated, is preferred for secondary ASCVD prevention and certain high-risk primary prevention groups.
- There is a role for moderate and low intensity statin therapy under certain circumstances.

Conclusions
ACC/AHA Guideline (more)

- New risk calculators are controversial and may overestimate risk in the primary prevention population.
- New risk calculators are not generalized to the AI/AN population.
- AI/AN have higher rates of ASCVD disease than other subgroups.
- Expert opinion favors use of new risk calculators in determining risk and making statin treatment decisions for primary prevention in the AI/AN population.

WHAT ABOUT THE ADA?

ADA 2014 Guidelines
Lipid Management For Diabetics

- Screening Lipid Profile Annually
  - Biennially if low risk lipid profile
- Lifestyle/Dietary Modification to reduce intake of trans and animal fats.
- Recommend statin therapy for primary and secondary prevention “regardless of baseline lipid levels” based upon other risk factors.
- Recommend against combination therapy (non statin medications) for further CVD risk reduction.

ADA 2014 Guidelines
Lipid Management for Diabetics (cont.)

- Secondary Prevention
  - Statin therapy for all diabetics with coronary vascular disease (Class A).
  - Target LDL < 100 (Class A) or alternate target goal LDL < 70 (Class B) with a high dose statin.

ADA 2014 Guidelines
Lipid Management in Diabetics (more)

- Primary Prevention
- Diabetic statin benefit groups
  - Age > 40 years with one other CVD risk factor (Class A).
  - Age < 40 years with multiple CVD risk factors or LDL > 100 (Class C).
- Goal of therapy is treat to target LDL < 100.

Comparing ADA and AHA
Lipid Management in Diabetics

- Common ground
  - Statin therapy is indicated for both primary and secondary prevention of CVD in diabetics.
  - Addition of non-statin lipid agents provides no additional CVD risk reduction benefit.
- Main difference
  - AHA supports fixed-dose, “appropriate intensity,” statin therapy.
  - ADA supports treat to target strategy (LDL < 100 or alternate goal of LDL < 70).

QUESTIONS?

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- Up To Date
- Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, Gillespie C, Merritt R, Hu FB. JAMA. 2012 Mar;307(12):1273-83. Epub 2012 Mar 16.
- Rising tide of cardiovascular disease in American Indians: the Strong Heart Study Howard BV, Lee ET, Cowan LD, Devereux RB, Galloway JM, Howard WJ, Rhoades ER, Robbins DC, Sievers ML, Welty TK. Circulation. 1999;99:2389 –2395.
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