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

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
Drugs 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
    - 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.

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%)

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

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 \( \geq 190 \)
- Diabetes mellitus and LDL-C 70-189 without ASCVD
  - If estimated 10 year ASCVD risk \( \geq 7.5\% \)
- LDL-C 70-189 without ASCVD or diabetes mellitus
  - If estimated 10 year ASCVD risk \( \geq 7.5\% \)

* 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

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

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

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
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

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\textsuperscript{st} 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 $\geq 7.5\%$.
- Risk reduction benefit felt to exceed risk of adverse events.
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.

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”

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.

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

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

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
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<tbody>
<tr>
<td>Daily dose lowers LDL-C by approximately ≥50%</td>
<td>Daily does lowers LDL-C approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C by &lt;30%</td>
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<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10 (20) mg</td>
<td>Simvastatin 10 mg</td>
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<td>Rosuvastatin 20 (40) mg</td>
<td>Rosuvastatin (5) 10 mg</td>
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<td>Simvastatin 20–40 mg‡</td>
<td>Lovastatin 20 mg</td>
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<td>Lovastatin 40 mg</td>
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<td>Pitavastatin 2–4 mg</td>
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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.
• 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?
REFERENCES


• Up To Date


REFERENCES (more)

- ADA 2014 Clinical Practice Guidelines