Updates in Atherosclerotic Cardiovascular Risk Management

Sally A. Arif, Pharm.D., BCPS (AQ Cardiology)
Assistant Professor of Pharmacy Practice
Midwestern University, Chicago College of Pharmacy
Cardiology Clinical Specialist, Rush University Medical Center
sarif@midwestern.edu

RUSH UNIVERSITY MEDICAL CENTER

Speaker has no conflicts of interest to disclose.

Learning Objectives

Pharmacists

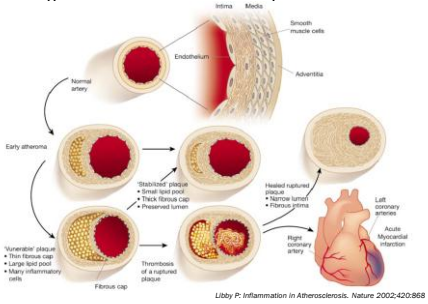
1. Describe key aspects from the new cholesterol guidelines for cardiovascular risk reduction.
2. Compare and contrast the Framingham risk assessment tool and the pooled cohort equation in estimating a patient's risk for an atherosclerotic event.
3. Review a patient plan to incorporate an evidence-based approach to reduce cardiovascular risk.

Technicians

1. Identify high and moderate intensity doses for statins.
2. Describe monitoring parameters associated with lipid therapy.

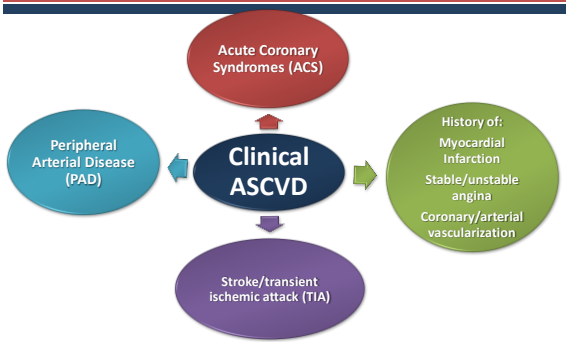
Atherosclerotic Disease

- Leading cause of death and disability in United States



Libby P: Inflammation in Atherosclerosis. Nature 2002;420:868

AtheroSclerotic CardioVascular Disease



ATP-III Guidelines

- Adult Treatment Panel III (ATP-III) published in 2001, updated in 2004
  - Based on treating to **LDL target**
    - LDL targets based on coronary heart disease (CHD) risk
    - Statins preferred but other LDL-lowering drugs could be used to get targets
    - Framingham risk assessment used to determine a patient's 10-year & lifetime risk of CHD

CHD Risk	LDL Goal
Primary Prevention (0-1 risk factors)	< 160 mg/dl
Primary Prevention (≥ 2 risk factors)	< 130 mg/dl
Secondary Prevention or CHD risk equivalents (e.g. DM, carotid disease, PAD)	<100 mg/dl or <70mg/dl

JAMA 2001;285:2486-97.

Framingham CHD 10-year Risk Assessment

- Based on data from predominately white population 30 to 74 years of age without heart disease or diabetes
- Validated in Caucasian and African American populations
  - May over- or underestimate risk in other ethnic groups
- Less precise in:
  - Patients < 30 or > 65 years of age
  - Patients with diabetes, severe hypertension, or left ventricular hypertrophy
- Only predicts coronary events (not stroke/TIA)

J Gen Intern Med 2003;18:1039-52

2013 ACC/AHA Evidence Based Guidelines

- Released by American College of Cardiology (ACC) and American Heart Association (AHA) in collaboration with National Heart, Lung and Blood Institute (NHLBI)
- **Evidence based approach** using high quality RCTs with ACSVD outcomes
- Goals:
  - Identify patients would benefit most from clinically-proven therapy
  - Identify drugs are clinically proven to reduce ASCVD
  - Recommend assessing risk factors (e.g. BP, Lipids, Glucose) ~5 years in adult population (20 - 79 years of age)

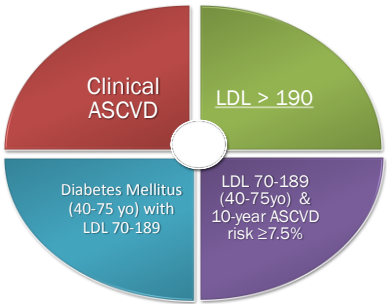
Circulation 2013 ACC/AHA Guidelines on Cholesterol (e-publication).

2013 ACC/AHA Guidelines- A practice change

- No need to titrate to a specific LDL or non-HDL targets
- Measure lipids during follow-ups to assess adherence to treatment, not to achieve a specific LDL target
- Goal to initiate either **moderate-intensity** or **high-intensity statin** therapy for patients who would benefit from statin therapy

Who benefits from Statin therapy?

ACC/AHA Guidelines identified **4 groups**



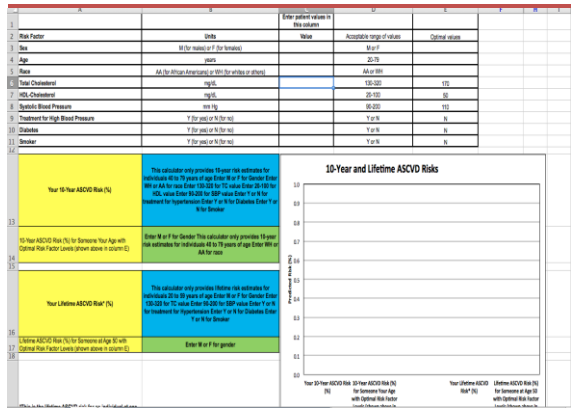
Who has been excluded from the updated guidelines?

1. Patients with Class II – IV heart failure
   - Heart Failure guidelines: HF alone not indication for statin therapy; use if documented ASCVD
2. Patients with ESRD on hemodialysis
   - KDIGO guidelines: Do not start statins in dialysis-dependent CKD; Patients already taking statins before dialysis started should continue drug therapy
3. Patients with TG > 500 mg/dl – (risk for pancreatitis)
   - Lipid guidelines: Refer to AHA Statement on TG and CV disease
   - Screen for secondary causes
   - Treat with lifestyle changes/drug therapy specific to hypertriglyceridemia
     - Once TG controlled then evaluate patient for benefit from statin therapy

J Am Coll Cardiol 2013;62:e147-239
Ann Intern Med 2014;160:182-9.
Circulation 2011;123:2292-333.

Pooled Cohort Cardiovascular Risk Calculator

- Estimates 10 year ASCVD Risk
- Developed using data from 5 NHLBI sponsored, longitudinal, population-based cohorts
  - Data from men (white and African American) and women, with or without diabetes, 40 to 79 years of age.
- Based on **age, sex, race, smoking status, TC level, HDL level, systolic blood pressure, HTN treatment, and DM**
- Estimate risk for first MI, CHD death, or fatal/nonfatal stroke (primary prevention only) in ages 40-75 years and need for statin therapy
- Difference from earlier Framingham equations
  - Includes stroke as an outcome
  - Provides race specific recommendations



American Heart Association. | AMERICAN COLLEGE of CARDIOLOGY

2013 Prevention Guidelines Tools

CV RISK CALCULATOR

- Web based calculator
  - http://myamericanheart.org/cvriskcalculator
- Mobile Apps :

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Assessment Question: CV Risk Calculators

Which of the following outcomes is predicted by the Pooled Cohort ASCVD Risk calculator, but NOT by the Framingham Risk Assessment?

A. Myocardial infarction

B. Death from coronary event

C. Stroke

Controversy with Pooled Cohort Calculator

- Has not been tested in clinical trials
  - Not evaluated prospectively in primary prevention trials
- Possibly overestimates risk?
  - Age alone can increase the risk significantly
  - Mexican Americans, Asian Americans of East Asian ancestry
  - Other risk factors such as smoking and elevated BP increase risk which statins would not necessarily address
- Possibly underestimates risk?
  - American Indians, Puerto Ricans, Asian Americans of South Asian ancestry
- Does not include other risk factors into the calculation

Lancet 2013;382:1762-5.

Lifestyle Management

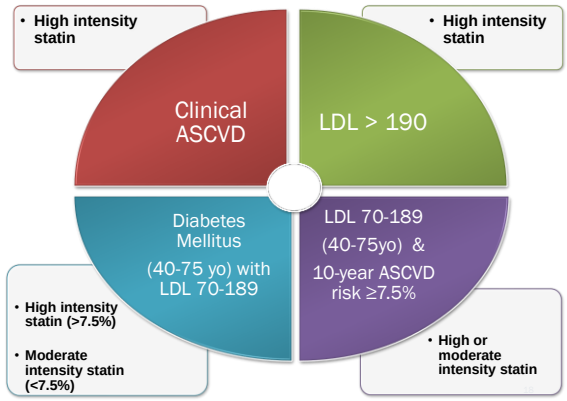
- Heart healthy lifestyle habits recommended for ALL patients regardless of risk
  - Dietary approaches
  - Physical Activity
  - Smoking Cessation
  - Weight Loss

2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013.

Pharmacotherapeutic Approach

- Use drug therapy that has been proven to reduce ASCVD risk
  - **STATINS!**
- For primary prevention, approach is "patient-centered"
  - Clinician-patient discussion needed
- Non-statin drug therapy has not demonstrated significant ASCVD risk reduction
  - Ezetimibe – ENHANCE trial
  - Nicotinic Acid – HPS2-Thrive and AIM-HIGH Trials
  - Fibrates – ACCORD trial

NEJM 2008;358:1431-43.
Eur Heart J 2013;34:1279-91.
NEJM 2011;365:12255-67.
NEJM 2010;362:1563-74.



Statins - Dosing Strategies

- High-intensity: decrease LDL ≥ 50%
- Moderate-intensity: decrease LDL 30% to < 50%
- Low-intensity: decrease LDL < 30%

- **High-intensity or moderate-intensity** are the most studied and recommended

- Low-intensity is reserved for patients who can NOT tolerate moderate- or high-intensity statin doses

Statin Regimens

Statin	Moderate Intensity	High Intensity
Atorvastatin (Lipitor®)	**10** - 20mg	**40 - 80 mg**
Rosuvastatin (Crestor®)	5 - **10**mg	**20** - 40mg
Simvastatin (Zocor®)	**20 - 40** mg	--
Pravastatin (Pravachol®)	**40** - 80mg	--
Lovastatin (Mevacor®)	**40 mg**	--
Fluvastatin XL(Lescol XL®)	80 mg	--
Fluvastatin (Lescol®)	**40 mg BID**	--
Pitavastatin (Livalo®)	2-4 mg	--

Doses in **bold have been studied in ASCVD outcome trials*

Ann Intern Med. 2014;160(5):339-343.

Assessment Question: Optimal Plan

A 48 yo white female (non-smoker) with diabetes mellitus.
- Total cholesterol 180
- LDL 70
- HDL: 55
- BP: 130/89
- Calculated 10 yr risk ASCVD : 1.8%

Which of the following approaches should be taken to reduce her cardiovascular risk?

A. Start a **low** intensity statin
B. Start a **moderate** intensity statin
C. Start a **high** intensity statin
D. No statin therapy is needed at this time

Assessment Question: Optimal Plan

A 22 yo African American male (non-smoker) with NO PMH of DM or HTN.
- LDL: 195
- BP: 120/85

Which of the following approaches should be taken to reduce his cardiovascular risk?

A. Start a **low** intensity statin
B. Start a **moderate** intensity statin
C. Start a **high** intensity statin
D. No statin therapy is needed at this time

Assessment Question: Optimal Plan

A 66 yo white female with hypertension who is non-smoker.
- Total cholesterol: 230
- LDL 125
- HDL: 55
- SBP: 110/79
- Calculated 10 yr risk of ASCVD : 6.6 %

Which of the following approaches should be taken to reduce her cardiovascular risk?

A. Start a **low** intensity statin
B. Start a **moderate** intensity statin
C. Start a **high** intensity statin
D. No statin therapy is needed at this time

Statin Safety Considerations

- Select the appropriate dose

- Predict potential adverse effects and drug-drug interaction

- If high or moderate intensity statin not tolerated, use the maximum tolerated dose instead

When to use lower intensity statin doses?

- Consider decreasing statin dose if 2 consecutive LDL levels are < 40 mg/dl (Grade C recommendation)
- Consider moderate-intensity doses for patients who would qualify for high-intensity but have certain characteristics that predispose them to side effects
  - > 75 years old
  - Multiple or serious comorbidities, including impaired renal or hepatic impairment
  - History of previous statin intolerance or muscle disorders
  - Unexplained ALT elevations > 3x ULN
  - Concomitant drugs that affect statin metabolism

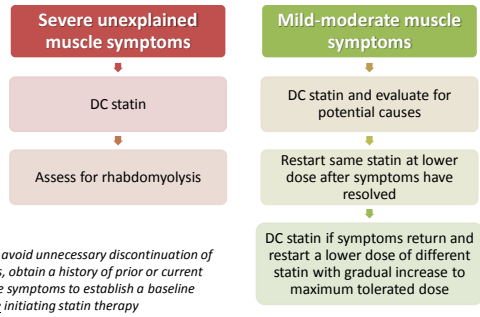
Utility of Biomarkers

- What if an individual is **not** in a statin benefit group and decision to initiate statin therapy is unclear?
  - ASCVD risk < 7.5%, no DM, or LDL < 190
- Consider other risk factors:
  - LDL≥ 160 mg/dL or genetic hyperlipidemia
  - Family history of premature ASCVD
  - High-sensitivity C-reactive protein > 2 mg/L
  - Coronary Artery Calcium (CAC) score ≥ 300 or >75th percentile for age, sex and ethnicity
  - Ankle-brachial index <0.9
  - Elevated lifetime risk of ASCVD

Monitoring

- Prior to initiation of statin therapy:
  - Fasting Lipid Panel (FLP)
  - ALT
  - Creatine kinase (CK) only if high risk for myalgia
- Follow-up
  - FLP only to assess adherence!
    - Repeat 4-12 weeks after starting or changing dose, then q 3-12 months
  - ALT only if symptoms of hepatotoxicity
  - CK should not be routinely measured

Muscle Symptoms



****To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy*

Assessment Question: Monitoring

Four weeks after initiating statin therapy, your patient has no muscle complaints. Which of the following lab test(s) should be ordered at this time?

A. Fasting Lipid Panel
B. ALT
C. CK
D. All of the above
E. None of the above

Summary of Guideline Updates

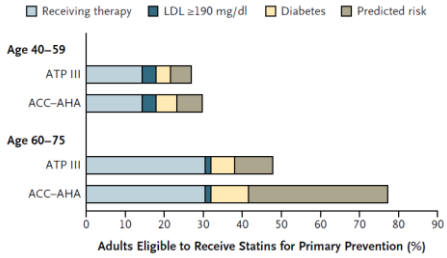
ATP III Guidelines (2004)	ACC/AHA Guidelines (2013)
• Based on idea that lowering cholesterol lowers ASCVD risks (LDL goal based approach) • Framingham Risk Assessment used • RCTs supporting targeted LDL goals are lacking • Non-statin therapy can be used to reach target goals	• Based on idea that appropriate statin intensity should be abased on ASCVD risk (Dose based approach) • Pooled Cohort Equations used to calculate 10-year ASCVD risk • Recommendations based on high quality evidence based trials • Identified 4 statin benefit groups • Evidence to support adding non-statins to reduce ASCVD risk is lacking

Accepting Change in Practice…

- ATP III has been in practice for over a decade
  - Clinicians are comfortable with treating to targets
  - Patients understand why to take medicine based on abnormal cholesterol levels
  - Clinical practice has been based on "goals of therapy"
- Agreement on ACC/AHA guidelines approach
  - Other guidelines still recommend treat to goal LDL

Risk of Overtreatment?

- Statin Eligible: 43.2 million (ATP III) vs. 56 million adults (ACC/AHA)



Pencina MJ, Navar-Boggan AM, D'Agostino RB, et al. N Engl J Med 2014;370:1422-31.

Where do we go from here?

"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning"

-Winston Churchill 1942

Summary

- "Treat to target" and "lower is best" strategies are *no longer advocated*
- Identify patients at highest risk (know the 4 high risk groups)
- Use medications proven to reduce risk (e.g. statins)
- Encourage healthy lifestyle
- Recognize that questions and concerns remain

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