Usefulness of the Lipid Panel: From NCEP to ACC/AHA

Janelle M. Chiasera, PhD
Professor and Chair
University of Alabama at Birmingham

Outline

- Statistics
- History
- NHLBI, NCEP-ATP, ACC/AHA vs. ESC/EAS
- Risk Calculator & Results
- Questions

Objectives

- Describe the major differences between the ATPIII/NCEP and ATP IV/ACC-AHA recommendations
- Describe the role of inflammatory markers in ATP IV/ACC-AHA recommendations
- Use the ATP IV/ACC-AHA Risk Calculator

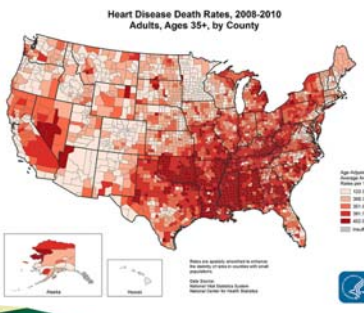
The Issue

- Heart disease is the leading cause of death in the U.S. (610,000; 1 in 4 deaths)
  - Every 90 seconds
- 86 M Americans are living with cardiovascular disease or after-effects of stroke
  - Direct and Indirect Costs total more than $440B
- Coronary Heart Disease is the most common type of heart disease (370,000 deaths annually)

Xu J, Murphy SL, Kochanek KD, Bastian BA. Deaths: Final Data for 2013. National Vital Statistics Reports, Vol 64 No 2, Feb 2016.

The Issue

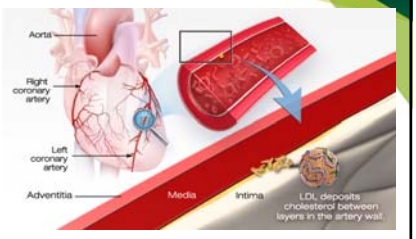
- 2001 – Present
  - Death rate↓ 39%; Operations and procedures ↑ 28%
- 735,000 Americans have a heart attack annually
  - Majority first heart attack (600,000)
  - 120,000 die
- Remains the leading cause of death for people in most ethnicities



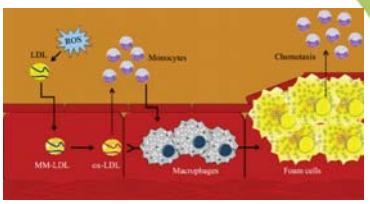
Atherosclerotic Cardiovascular Disease (ASCVD)

- Plaque buildup
  - Coronary Heart Disease
  - Cerebrovascular Disease
  - Peripheral Artery Disease
  - Aortic Atherosclerotic Disease

- CAD: Inside lumen narrows
- Begins with cholesterol deposition
- Immune response to the invasion.

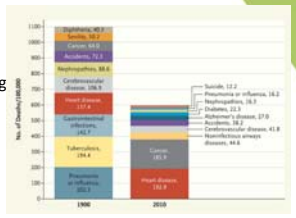


- LDL undergoes oxidation (mm-LDL)
- ox-LDL activates monocytes (macrophages)
- Macrophages engulf lipids (foam cells)
- Collection of foam cells = fatty streak



Background

- Chronic conditions replaced infectious diseases as primary cause of death
- CVD: inevitable consequence of aging
- NHLBI launched Framingham Heart Study
  - 5,209 men and women (1948 – 1952)
  - Identify risk factors for CVD
  - This set of factors is still used today



David S. Jones, M.D., Ph.D., Scott H. Podolsky, M.D., and Jeremy A. Greene, M.D., Ph.D. The Burden of Disease and the Changing Task of Medicine, N Engl J Med 2012; 366:2333-2338June 21, 2012DOI: 10.1056/NEJMp1113569

Risk Factors for CVD

- Age
- Male sex
- Smoking status
- Diabetes mellitus
- Hypertension
- Elevated levels of cholesterol

2013 Risk Calculator

- Additional risk Factors
  - LDL-C greater than 160 mg/dL (or genetic dyslipidemia)
  - family history of premature ASCVD with onset less than 55 or 65 years of age in a first degree male or female relative
  - high-sensitivity C-reactive protein greater than 2 mg/L,
  - CAC score greater than 300 Agatston units or greater than 75 percentile for age, sex, and ethnicity
  - ankle-brachial index less than 0.9, or elevated lifetime risk of ASCVD.

Other Important Points

- 1985 NCEP of NHLBI formed
- 1988 NCEP-ATP guidelines published (ATP I)
- 1993 NCEP-ATP updated recommendations (ATP II)
- 1998 Rigid analytical goals
- 2002 NCEP-ATP III
- 2005 Updated ATP III
- 2013 The great divide
  - ESC/EAS (2012) vs. ACC/AHA (2013)

Lipid Standardization Program (LSP)

- CDC
- Accuracy-based standards for TC, TG, HDL, apo A-I, apo B
- Primary objective
  - Standardize analysis to ensure that results of all clinical trails and population studies are comparable and traceable to well-defined standards
- https://www.cdc.gov/labstandards/lsp.html

Lipid Standardization Program (LSP)

- Provides traceability to CDC's reference measurement procedures
  - TC: Modified Abell-Kendall
  - TG: GC-IDMS
  - HDL: Ultracentrifugation, selective precipitation, and modified Abell-Kendall
  - Apo-AI and Apo-B: Northwest Lipid Metabolism and Diabetes research Laboratories (Siemens-Behring on BNII)

NCEP-ATP

- ATP I (1988)
  - Outlined strategy for primary prevention of CHD in those with high LDL
- ATP-II (1993)
  - ATP-I plus intensive management in those with CHD
  - New lower LDL-cholesterol value (≤ 100 mg/dL)

NCEP-ATP

- ATP-III (2002 & 2005)
  - ATP-I and ATP-II plus:
    - Focus on those with multiple risk factors
    - Lipoprotein profile
    - New HDL level
    - New set of "therapeutic lifestyle changes"
    - Increased focus on risk factors known as "the metabolic syndrome"
    - Increased attention to the treatment of high triglycerides

ATP-III

- Raised people with DM to risk level of CHD
- Used Framingham projections to identify people for more intensive therapy
- Identified people with metabolic syndrome as candidates for TLC

- Identified LDL<100 mg/dL as optimal
- Raised HDL recommendation from 35 mg/dL to 40 mg/dL
- Lowered the TG classification cutpoint

- Recommended lipoprotein analysis (TC, LDL-c, HDL-c, and TG)
- Encouraged plant and fiber as dietary option
- Recommended treatment beyond LDL lowering for those with increased TG

NCEP-ATP III

Table 4. Three Categories of Risk that Modify LDL Cholesterol Goals

Risk Category	LDL Goal (mg/dL)
CHD and CHD risk equivalents	<100
Multiple (2+) risk factors*	<130
Zero to one risk factor	<160

* Risk factors that modify the LDL goal are listed in Table 3

NECP-ATP III

Table 5: LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

† Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

NCEP-ATP III

Identify metabolic syndrome and treat, if present, after 3 months of TLC.

Clinical Identification of the Metabolic Syndrome – Any 3 of the Following:

Risk Factor	Defining Level
Abdominal obesity*	Waist circumference†
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

* Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

† Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

Samples

ATP II	ATP III	ACC/AHA
Non-fasting sample	9-12 hour fasting sample	9-12 hour fasting sample
TC HDL	TC HDL LDL TG	TC HDL LDL TG

Lipid Panel

- **LDLc** – Cholesterol associated with low density lipoproteins, directly linked to cardiovascular disease (CVD): calculated or detergent based assay
- **HDLc** – Cholesterol associated with high density lipoproteins, inversely associated with CVD, detergent based assay (others)
- **Total Cholesterol** – Esterified and non-esterified cholesterol, necessary for calculating LDLc, enzymatic assay (others)
- **Triglyceride** – Circulating triglycerides, enzymatic assay actually measures glycerol, also atherogenic and high concentrations (>500 mg/dL) associated with pancreatitis

Calculating LDL-C

Friedewald calculation:

LDLc = TC - HDLc - VLDLc

(VLDLc = TG*/5)

***TG<400 mg/dL**

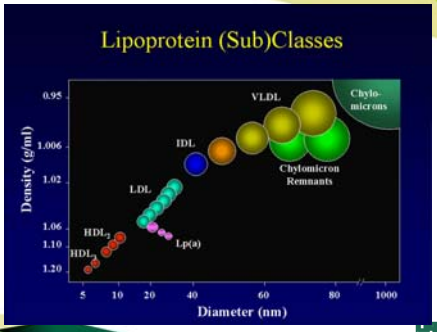
Non-HDL cholesterol:

TC – HDLc = Non-HDLc

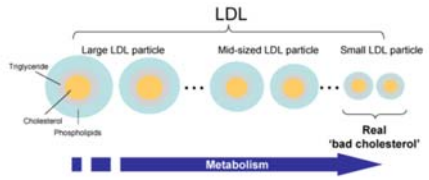
NOTE: Other species are atherogenic

Recent CAP survey indicates 3,100 labs calculated LDLc (54%) and 2,589 labs (46%) measured it directly

Lipoprotein (Sub)Classes



Size Does Matter!



How Good Is NCEP III At Predicting MI?

JACC 2003:41 1475-9

88% of these "young" patients who suffered a first Myocardial Infarction were in the Low to Intermediate "risk" category according To Framingham Risk Assessment and would have been missed as truly "High Risk" individuals who should have been treated "aggressively".

2013: The Year of the Great Divide

- ESC/EAS (2012) vs. ACC/AHA (2013)
- ESC/EAS (Europe)
  - Recommended statin therapy based on LDL-cholesterol and a risk estimator
  - Singled out adults with severe HTN and chronic kidney disease
- ACC/AHA (U.S.)
  - Abandoned specific cholesterol levels
  - Recommended statin therapy based on 10-year risk ≥7.5% (≥5%)
  - Used the Blood Cholesterol Expert Panel

ACC/AHA

- Goals
  - Prevent cardiovascular disease
  - Improve management
  - Develop guidelines, standards, policies
- Collaborated with the NHLBI
  - Cardiovascular risk
  - Lifestyle modification
  - Management of blood cholesterol in adults
  - Management of overweight and obesity in adults

ACC/AHA

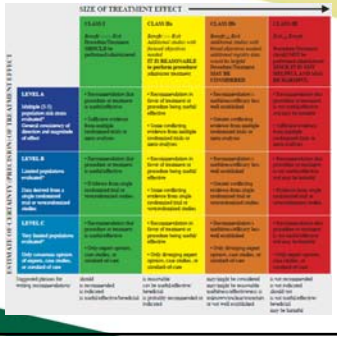
- Deviations from the guidelines may be appropriate

"I don't think it's anything serious, but, just to be sure, I'm going to bill you as if it is."

The Panel and Document Review

- Expert Panel
  - Convened to be the ATP IV (13 members plus 3)
  - Recused for conflict of interest
  - All 16 members became the ACC/AHA guideline Expert Panel
- Document Review and Approval
  - 23 expert reviewers
  - 4 experts from ACC and AHA

- American Academy of Physician Assistants
- Am Assoc of Cardiovascular and Pulmonary Rehabilitation
- American Pharmacists Association
- Am Society for Preventive Cardiology
- Association of Black Cardiologists
- Preventive Cardiovascular Nurses Association
- WomenHeart



LOE and COR

Level of Evidence (LOE)		Classification of Recommendation	
A	High quality evidence	I	Benefit > > > Risk Recommended; Should be performed
B-R	Moderate-quality evidence from RCT	IIa	Benefit > > Risk Reasonable to perform; Can be useful
B-NR	Moderate-quality evidence from non-RCT	IIb	Benefit ≥ Risk May be considered
C-LD	Randomized or nonrandomized observational or registry studies with limitations of design or execution	III NB	Is not indicated/useful/beneficial/effective
C-EO	Consensus of expert opinion based on clinical experience	III H	Potentially harmful

ACC/AHA 2013 Guidelines

- Updated the NCEP-ATP III; NHLBI (so-called ATP-IV)
- Followed rules for guideline development (IOM)
  - Evidence-based decisions vs. all scientific data
- LDL is NOT the centerpiece; Statins are the linchpin
  - Four statin benefit groups
    - Clinical ASCVD, LDL-c ≥190 mg/dL, DM and LDL-c 70-189 mg/dL, LDL-c 70-189 mg/dL and 10 year risk ≥ 7.5%
  - Absolute risk reduction calculation
    - 10 Year risk x Relative reduction risk based on statin intensity (30%/45%)

- Statin intensity
  - High intensity: lowers LDL ≥ 50%
  - Moderate: lowers LDL 30-50%
  - Low: lowers LDL < 30%
- Recommended a new algorithm for 10-year risk assessment for ASCVD
  - http://www.cvriskcalculator.com/

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease

Helping Cardiovascular Professionals Learn. Advance. Heal.

American Heart Association.

Recommendation A

- Heart healthy lifestyle habits should be encouraged for all
  - Heart-healthy diet
  - Regular exercise
  - No tobacco products
  - Maintenance of healthy weight

Recommendation B

Statin-benefit Group		Statin Intensity	COR	LOE
1) Clinical ASCVD	Age ≤ 75 y, no safety concerns	High	I	A
	Age > 75 y or safety concerns	Moderate	I	A
2) LDL-C ≥ 190 mg/dL	Rule out secondary cause Age ≥ y Achieve 50% reduction in LDL-C	N/A High N/A	I I IIa	B B B
3) DM, 40-75 y, LDL-C 70-189 mg/dL	< 7.5% 10-y ASCVD risk ≥ 7.5% 10-y ASCVD risk	Moderate High	I IIa	A B
4) 40-75 y, LDL-C 70-189 mg/dL	Estimate 10-y ASCVD risk (not on a statin) Client-patient conversation ≥ 7.5% 10-y ASCVD risk 5 – 7.5% 10-y ASCVD risk Other Factors	 Mod or High Moderate	I IIa I IIa IIb	B C A B C

Recommendation C

- Regularly monitor adherence (IA)

		COR	LOE
Fasting Lipid Panel		I	A
Do not measure CK ALT, unless symptomatic		IIa	C
Screen and treat for T2DM		I	B
Less than anticipated response	Reinforce adherence Evaluate for secondary causes Increase statin intensity	I I IIb	A A C
Regularly monitor adherence 3-12 mo.		I	A

Recommendation D

- In those who are tolerant, use maximum intensity of statin recommended (IB)
- Muscle or other symptoms, establish they are statin related (IIaB)

To Summarize the Recommendations…

- followed the rules of guideline development by IOM (RCT's excluding other types of evidence)
  - Made LDL irrelevant to guideline development (unknown benefit of treat-to-target approach)
  - Made statins the linchpin of recommendations
- New guidelines abandoned LDL targets in favor statin therapy
  - Less detailed; more clinical judgement required
  - Exception: they use LDL-C to initiate therapy

To Summarize the Recommendations…

- ATP III considered drug treatment when risk ≥10%
- ACC/AHA set threshold for statin treatment at 7.5% and set 5% to consider statins as a therapeutic option.
- Fvhduauilgrf
- ACC/AHA developed a new calculator
  - Criticism: May overestimate risk ~2 fold (Ridker and Europe).
  - May mean that more low risk people will be put on statins.

To Summarize the Recommendations…

- ACC/AHA discards the metabolic syndrome due to a lack of clinical trials that target it with drug therapy
  - ATP III acknowledges the metabolic syndrome as essentially doubling the risk for ASCVD and is a big target for TLC.
  - May leave the clinician to make the call
    - Perhaps ATPIII is useful for guiding judgement

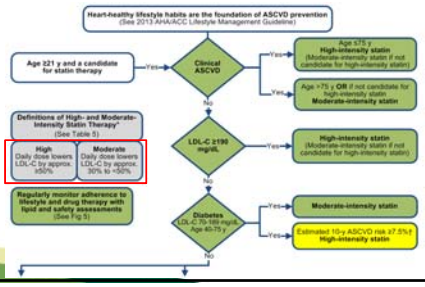
Guidelines and Metabolic Syndrome

Prevalence of the Metabolic Syndrome in the United States, 2003-2012

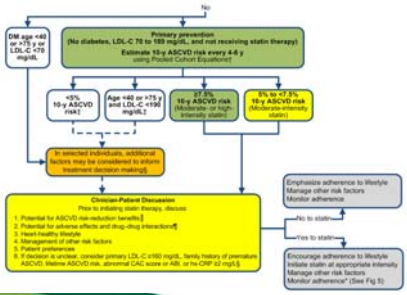
The metabolic syndrome contributes to cardiovascular morbidity and mortality.[1-4] Data from the National Health and Nutrition Examination Survey (NHANES) 1999-2006 reported a metabolic syndrome prevalence of 34%.[5] Understanding updated prevalence trends may be important given the potential effect of the metabolic syndrome and its associated health complications on the aging US population. We investigated trends in the prevalence of the metabolic syndrome through 2012.

JAMA May 19, 2015 Volume 313, # 19

Statin Initiation Recommendations (Revised Figure)



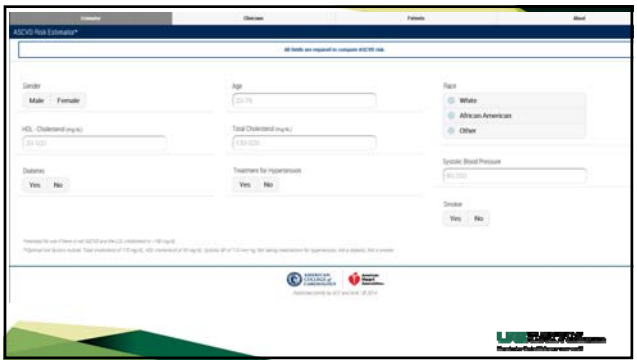
Continued

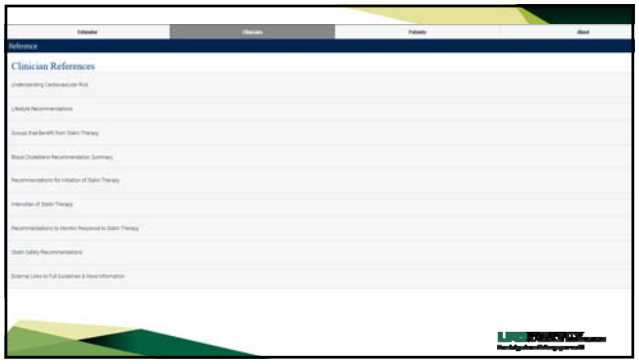


Risk Calculator

http://tools.acc.org/ascvd-risk-estimator/

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *J Am Coll Cardiol.* 2014;63(25_PA):2889-2934. doi:10.1016/j.jacc.2013.11.002





Risk Calculator

http://tools.acc.org/ascvd-risk-estimator/

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *J Am Coll Cardiol.* 2014;63(25_PA):2889-2934. doi:10.1016/j.jacc.2013.11.002

Intensity for Statin Therapy

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C on average, by approximately ≥50%	Daily dose lowers LDL-C on average, by approximately 30% to <50%	Daily dose lowers LDL-C on average, 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*

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

THE BOTTOM LINE

- **Still require LDLc measurements which means for 60% of the country a lipid profile still needs to be done and LDLc will continue to be needed for treatment and monitoring purposes (but likely not as often since not treating to target levels)**
- **Need HDLc and Total Cholesterol to do risk assessment so these tests will also continue to be done (strange that they discredit non-HDLc as being useful but it appears to be a part of their risk assessment).**

USPSTF Recommendations for Screening

- Men ≥ 35: Fasting lipid panel
- Men 20-35: Screen if at an increased risk for CHD
- Women ≥ 45: Fasting lipid panel only if at an increased risk for CHD
- Women 20-45: Screen if at an increased risk
- Routine screening for men and women not at an increased risk for CHD is at the discretion of the physician
- Repeat screening in 5 years for those with normal lipids

Recommendations for Statin Safety

- Avoid treatment in women of childbearing potential unless they are using an effective contraception and are not nursing
- Liver tests:
  - Check ALT at baseline
  - Routine hepatic monitoring not recommended
  - Check liver tests on treatment if symptoms arise

"To prevent a heart attack, take one aspirin every day. Take it out for a run, then take it to the gym, then take it for a bike ride..."

Questions

Thank you