All Patients Should Have an hs-CRP Level Drawn as Part of a Cardiac Risk Assessment Strategy

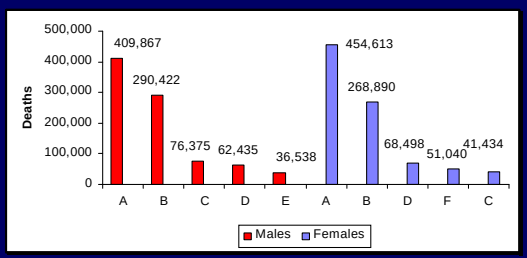
John A. Larry, MD
Section Chief of Cardiovascular Medicine
Ohio State University East Hospital
Associate Professor of Clinical Medicine
Director of Cardiac Rehabilitation
The Ohio State University Medical Center

Disclosures

- No ongoing relationships with industry sponsors and no conflicts of interest regarding the information presented today

CVD and other major causes of death for all males and females (United States: 2005).

Source: NCHS



A Total CVD
B Cancer
C Accidents
D Chronic Lower Respiratory Diseases
E Diabetes Mellitus
F Alzheimer's Disease

Coronary Artery Disease Facts (American Heart Association)

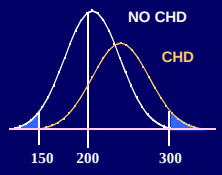
- Mortality — 445,687 deaths from coronary heart disease in the United States in 2005.
- The state of Ohio is in the top quartile for coronary heart disease mortality and second quartile for overall cardiovascular mortality
- Incidence — 1,260,000 new and recurrent coronary attacks per year. (NHLBI's Atherosclerotic Risk in Communities [ARIC] Study and Cardiovascular Health Study (CHS).
  - ~785,000 are an initial episode
  - ~470,000 are due to recurrent events
- About 37 percent of people who experience a coronary attack in a given year die from it. Approximately half of those occur prior to reaching a hospital.

Limitations of Lipid Assessment in Predicting Coronary Heart Disease

Significant overlap of LDL-cholesterol levels exists between populations with and without CHD

- Framingham Heart Study - 26 year follow-up data

  80% of MI patient population had similar cholesterol levels as those who did not have an MI



[1]Castelli W, *Atherosclerosis* 1996; 124: S1-S9

Cardiac Risk Assessment

"Prediction is very difficult, especially if it's about the future."

Niels Bohr, renowned physicist

Unfortunately for clinicians, risk stratification for future events is a mainstay of preventive medicine.

NCEP ATP III Risk Assessment

Positive

- Cigarette smoking
- HDL < 40 mg/dL
- Hypertension (blood pressure > 140/90 mm Hg or use of antihypertensive agents)
- Family history of premature coronary artery disease (CAD in male first-degree relative < 55 yrs; CAD in female first-degree relative < 65 yrs)
- Age (men > 45 yrs, women > 55 yrs)

Negative

- HDL-C > 60 mg/dL

Count the risk factors (less one for HDL greater than 60)

0-1 low risk

2 or more→ Framingham risk assessment and add up the points

ATP III Framingham Risk Scoring

Assessing CHD Risk in Women

Step 1: Age

Years	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Step 2: Total Cholesterol

TC Points at (mg/dL)	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1

Step 3: HDL-Cholesterol

HDL-C (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Step 4: Systolic Blood Pressure

Systolic BP (mm Hg)	Points if Untreated	Points if Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Step 5: Smoking Status

	Points at Age 20-39	Points at Age 40-49	Points at Age 50-59	Points at Age 60-69	Points at Age 70-79
Nonsmoker	0	0	0	0	
Smoker	9	7	4	2	

Step 6: Adding Up the Points

Age	
Total cholesterol	
HDL-cholesterol	
Systolic blood pressure	
Smoking status	
Point total	

Step 7: CHD Risk

Point Total	10-Year Risk	Point Total	10-Year Risk
<9	<1%	20	11%
9	1%	21	14%
10	1%	22	17%
11	1%	23	22%
12	1%	24	27%
13	2%	≥25	≥30%
14	2%		
15	3%		
16	4%		
17	5%		
18	6%		

Note: Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497.

LDL-C Therapy by Risk Categories Based on Clinical Trial Evidence

Risk Category	LDL-C Goal	Initiate Therapeutic Lifestyle Changes (TLC)	Consider Drug Therapy
Very high risk (established vascular disease)	<100 mg/dL, (reasonable goal <70mg/dL)	Everyone	≥70 mg/dL
CHD risk equivalents (DM, PVD or 10-year risk >20%)	<100 mg/dL	Everyone	>100 mg/dL
Moderately high risk: ≥2 risk factors (10-year risk 10%–20%)	<130 mg/dL (optional goal <100 mg/dL)	≥130 mg/dL	≥130 mg/dL (consider drug options if LDL-C 100–129 mg/dL)
Moderate risk: ≥2 risk factors (10-year risk <10%)	<130 mg/dL	≥130 mg/dL	>160 mg/dL
Low risk: ≤1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (consider drug options if LDL-C 160–189 mg/dL)

Adapted from Grundy SM et al. *Circulation*. 2004;110:227–239, and Smith et al JACC 2006;47:2130-9

Words of Caution

- You've got to be very careful if you don't know where you are going, because you might not get there.

- Yogi Berra, NY Yankee baseball great

Framingham Risk Equation Underestimates Subclinical Atherosclerosis in Asymptomatic Women

- 2447 non-diabetic females (55+/-10yrs)
- Global risk by Framingham
  - 90% low risk (10yr risk below 10%)
  - 10% intermediate risk (10yr risk 10-20%)
- Coronary calcium identified in 33%, 20% who had scores >75th percentile
- 84% of women with calcium scores >75th percentile were classified as low risk

Michos, et al. Atherosclerosis 2006; 184:201-6.

Preventing MI in the Young Adult in the First Place: How do the National Cholesterol Education Panel III Guidelines Perform?

Ten-Year CHD Risk Profile

	LDL Cholesterol (mg/dl)				Total
	< 100	100-129	130-159	≥ 160	% Cohort
2+ risk factors 10-year risk > 20%	**2 (1%)**	**11 (5%)**	7 (3%)	7 (3%)	27 (12%)
2+ risk factors 10-year risk 10%-20%	**6 (3%)**	**12 (5%)**	13 (6%)	8 (4%)	39 (18%)
2+ risk factors 10-year risk < 10%	**12 (5%)**	**22 (10%)**	**9 (4%)**	3 (1%)	45 (20%)
0-1 risk factor	**31 (14%)**	**33 (15%)**	**28 (13%)**	18 (8%)	110 (50%)
Total (% cohort)	51 (23%)	78 (35%)	57 (29%)	36 (16%)	

Akosah, et al. JACC. 2003; 41: 1475-1479

Limitations of current assessment strategies

- Khot, et al reported in a review of 87,000 males that 62% of individuals had 0 or 1 conventional modifiable risk factor
  - 19% had no risk factors
  - 43% had 1 conventional risk factor

- Khot, et al JAMA 2003;290:898-904.

Traditional Clinical Risk Assessment Tools Do Not Accurately Predict Coronary Atherosclerotic Plaque Burden: A CT Angiography Study

- **1,653 patients (1,089 men, 564 women) without a history of coronary heart disease**
- **Obtained FRS**
- **Correlation of plaque scores with the Framingham 10-year risk estimates were modest: Spearman's rho was 0.49-0.55.**
- **Overall, 21% of the patients would have their perceived need for statins changed by using the coronary CTA plaque estimates in place of the NCEP core risk categories; 26% of the patients on statins had no detectable plaque.**

Kevin M. Johnson, David A. Dowe and James A. Brink *AJR* 2009; 192:235-243

Criticisms of Framingham Risk Assessment

- Underrepresented minority population
- Triglycerides not included
- Family history not included
- Females underestimated in risk severity

CRP

- CRP, discovered in 1930, is an acute-phase protein produced by the liver in response to cytokine production (IL-6, IL-1, tumor necrosis factor) during tissue injury, inflammation, or infection.

Standard CRP assays cannot detect levels of CRP below 5 or 10mg/L

High-sensitivity CRP (hs-CRP) assays detect levels of CRP within the normal range, levels proven to predict future cardiovascular events.

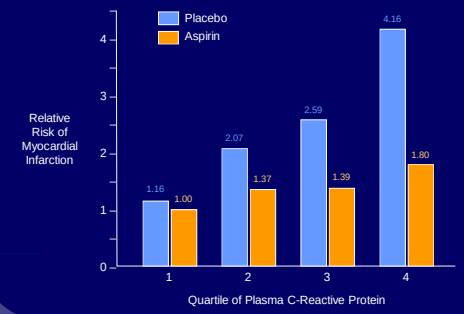
While varying studies reported levels in quartiles or quintiles, it is now commonly accepted that

<1 low risk, 1-3 intermediate risk, >3 high risk

Epidemiologic Studies of hs-CRP

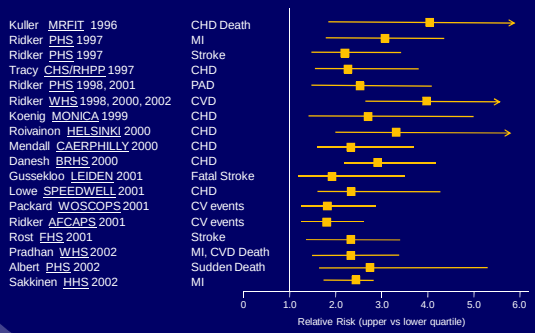
- "You can see a lot just by observing."
  - Yogi Berra, famous NY Yankees' catcher

Relative Risk of a First Myocardial Infarction Associated with Baseline Plasma Concentrations of C-reactive Protein Stratified According to Randomized Assignment to Aspirin or Placebo Therapy (Physician's Health Study)



Ridker et al. *NEJM*. 1997; 336: 973-979

Prospective studies relating baseline CRP levels and the risk of first cardiovascular event

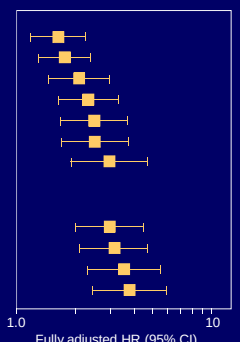


Ridker, P. *Circulation*. 2003; 107: 363-369

Risk Factors for Cardiovascular Events

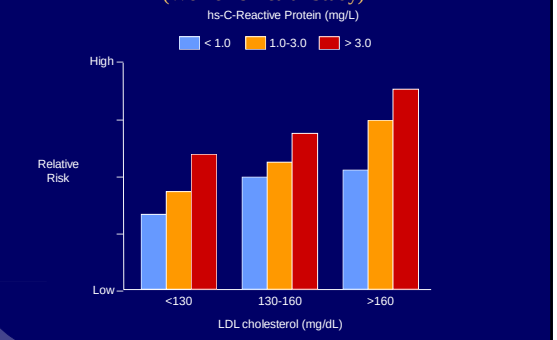
Individual variables
- LDL-C
- $ApoA_1$
- Total chol.
- HDL-C
- $ApoB_{100}$
- Non-HDL-C
- **High-Sensitivity CRP**

Lipid ratios
- $ApoB_{100}$ to $ApoA_1$
- LDL-C to HDL-C
- $ApoB_{100}$ to HDL-C
- Total chol. to HDL-C



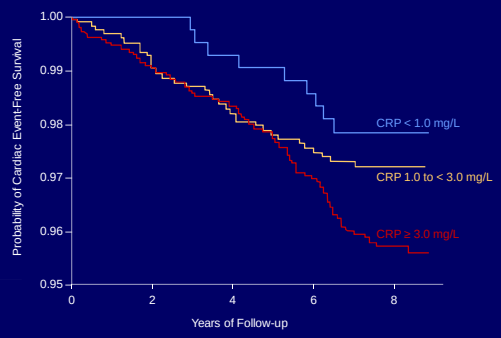
Ridker PM et al. *JAMA*. 2005; 294: 326

hs-CRP Improves Risk Prediction at all Levels of LDL Cholesterol (Women's Health Study)



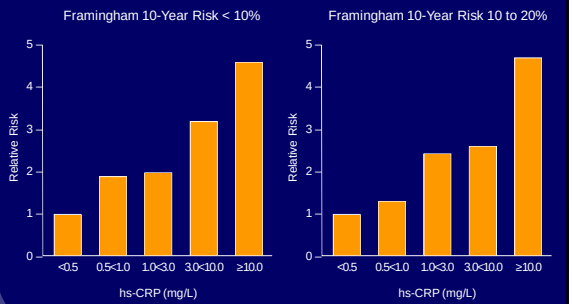
Ridker et al. *NEJM.* 2000; 342: 836-843

Cardiovascular event-free survival according to baseline CRP levels among individuals already defined as having the metabolic syndrome

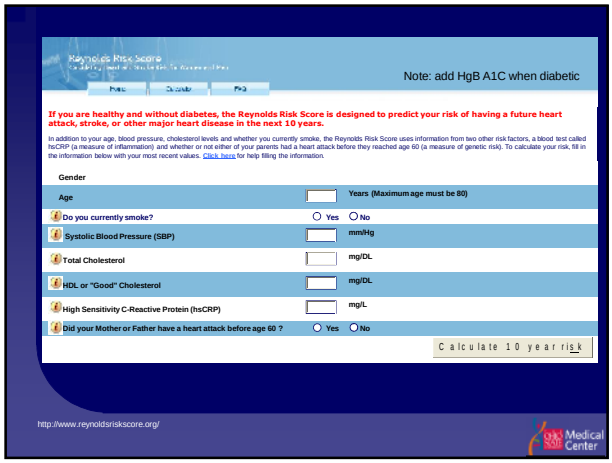


Ridker et al. *Circulation* 2003. 107; 391-397

Relative Risk of Future Cardiovascular Events Among Those with Calculated 10-Year Framingham Risk < 10% and Between 10% and 20% (Women's Health Study)

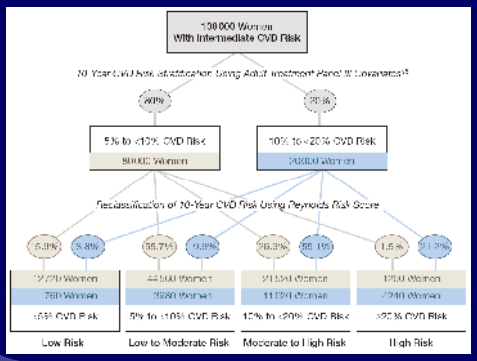


Ridker et al. *Circulation.* 2004; 109: 1955-1959



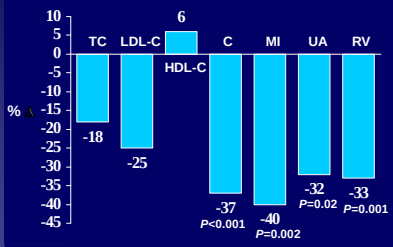
http://www.reynoldsriskscore.org/

Reclassification of risk using the Reynolds Risk Score for a representative population of 100,000 intermediate-risk U.S. women without diabetes



Ridker, et al. *JAMA* 2007. 297; 611-619

AFCAPS/TexCAPS: Effects of LDL-C Lowering in Patients With Average Cholesterol Levels

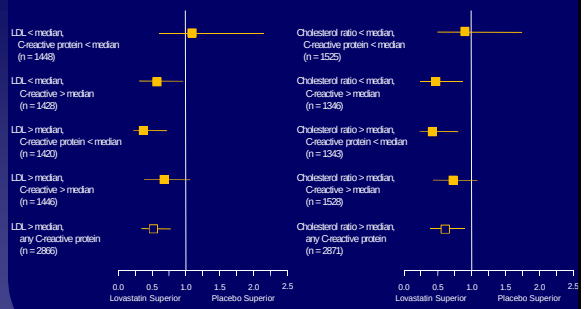


Subjects: 6,605
85% men, 45-73 yr
15% women, 55-73 yr
Baseline lipids:
TC: 221 mg/dL
LDL-C: 150 mg/dL
HDL-C: men, 36 mg/dL
women, 40 mg/dL
Intervention: Lovastatin 20-40mg/day

C=coronary events defined as fatal/nonfatal myocardial infarction, sudden death, and unstable angina;
MI=fatal/nonfatal myocardial infarction; UA=unstable angina;
RV=revascularizations.

Downs JR et al. *JAMA.* 1998;279:1615-1622.

AF CAPS/Tex CAPS: Relative Risks Associated with Lovastatin According to Baseline Lipid and CRP Levels



Ridker, et al. *NEJM.* 2001; 344: 1959-1965

Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)

- Nearly 18,000 patients
- Men >50 years and women > 60 years
- No history of diabetes, heart attack, stroke, or other serious cardiovascular event, with LDL cholesterol levels less than 130 mg/dL (3.36 mmol/L) and hs-CRP levels of >2 mg/L
- 7000 females, 5000 minority
- Low Framingham risk scores

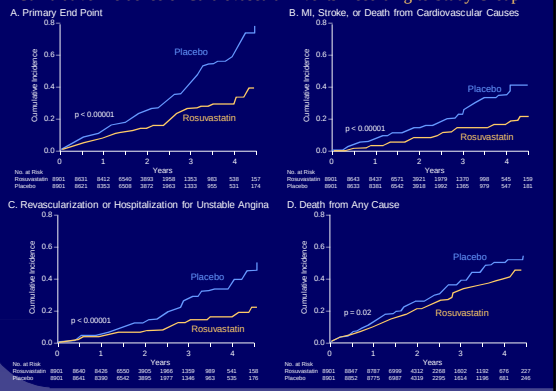
- Ridker, et al. *NEJM.* 2008; 359: 2195-2207

Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)

- Randomized to Rosuvastatin 20 mg vs. placebo
- Primary endpoint (summation of CV death, MI, unstable angina, CABG, PCI)
- Secondary endpoints (overall mortality)
- Trial stopped prematurely by DSB after 1.9 yrs

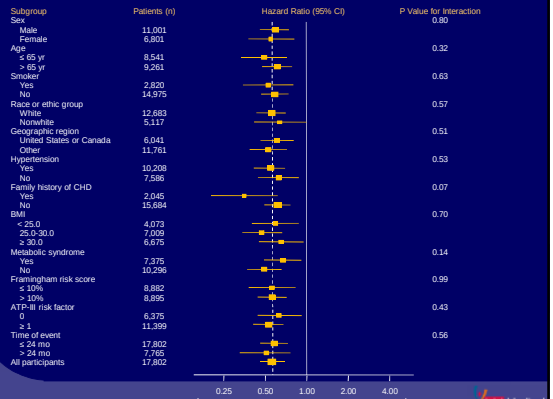
♥ Ridker, et al. *NEJM*. 2008; 359: 2195-2207

Cumulative Incidence of Cardiovascular Events According to Study Group



Ridker, et al. *NEJM*. 2008; 359: 2195-2207

Effects of Rosuvastatin on the Primary End Point, According to Baseline Characteristics



Ridker, et al. *NEJM*. 2008; 359: 2195-2207

Estimated 5-Year NNT Values of Interventions for the Primary Prevention of Cardiovascular Disease Among Middle-Aged Populations

Intervention	Population	End Point	5-year NNT	Reference
Rosuvastatin	Elevated hsCRP, low LDL	MI, stroke, arterial revasc., death	20	Current article
Rosuvastatin	Elevated hsCRP, low LDL	MI, stroke, death	29	Current article
Pravastatin	Hyperlipidemia	MI (including silent) and cardiac death	44	7, 9
Lovastatin	Hyperlipidemia	Unstable angina, MI and cardiac death	49	6, 9
Lovastatin	Hyperlipidemia	Any coronary event†	63	6, 8
Diuretics*	Hypertension	MI, stroke or any death	86	12
β-blockers*	Hypertension	Fatal or nonfatal CHD and stroke	140	13
Aspirin	Men	MI, stroke or cardiovascular death	346‡	16
	Women	MI, stroke or cardiovascular death	426‡	16

*Based on meta analysis including trials that randomized individuals with prior cardiovascular disease.

†Includes fatal or nonfatal MI, sudden death, stable or unstable angina, coronary revascularization and congestive heart failure.

‡For the aspirin analysis, 5-year NNTs were obtained from estimated NNTs for 6.4 years of 270 for men and 333 for women by the method of Altman and Anderson.

Ridker et al. *Circulation*. 2009; 2: Cardiovascular Quality Outcomes (online release Sept. 22, 2009)

Potential Jupiter Impact

- It has been estimated that between 6 and 11 million people in the US would fit into the entry criteria for the Jupiter and thus be candidates for statin therapy
- It has been estimated that this would result in 250,000 less coronary events in a 5 year period of time
- This does not include the potential impact of reclassification of risk status for those who are currently intermediate risk by ATP 3 criteria

Conclusion

- Cardiovascular disease remains the most prevalent and the number one cause of mortality in the US.
- Traditional risk assessment strategies have shortcomings, especially in women and minority groups.
- Epidemiologic studies have consistently demonstrated a relationship between levels of hs-CRP and cardiovascular risk and the use of hs-CRP can reclassify individuals into a more appropriate risk category.
- The AFCAPS/TEXCAPS and Jupiter trials demonstrate the clinical utility of CRP measurement.
- Utilization of statin therapy in those with LDL levels below the median but elevated CRP levels reduces non-fatal and fatal cardiovascular events.
- For all the above reasons, hs-CRP should be adopted as part of a cardiovascular risk screening strategy.

Thank You !

THE OHIO STATE UNIVERSITY Medical Center