hsCRP Should not be included in a Global Cardiovascular Risk Assessment.

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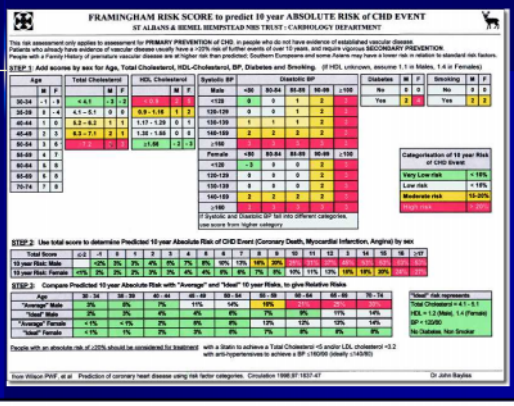
Global risk

- An attempt to quickly and accurately predict a person's 10 year risk of a cardiovascular event based on a summation of significant risk factors
  - Framingham risk score
  - Reynolds risk score
  - QRISK2
  - SCORE

Risk factors:

- Age-?chronological or biological
- Cholesterol
- HTN
- Tobacco use
- Diabetes
- Early family history
- Diet
- Exercise
- Renal disease
- Peripheral vascular disease
- Biomarkers
- EBCT
- Carotid IMT
- ???



FRAMINGHAM RISK SCORE to predict 10 year ABSOLUTE RISK of CHD EVENT

ST ALBANS & HEMEL HEMPSTEAD NHS TRUST : CARDIOLOGY DEPARTMENT

Strengths of FRS

- Uses a few readily available clinical and lab variables to predict risk
- 10 year risk can be calculated with discriminate accuracy of 75%
  - Inexpensive, rapid and offers therapeutic targets

Weintraub, W et al NEJM March 2008

Limitations

- Up to 20% of coronary events occur in women with none of these risk factors
- Those people misclassified at low risk may not receive the benefits of recommended lifestyle modifications and therapies.
- Prediction of longer term risk limited

Khot, UN et al, JAMA 2003

CVD risk predictor: desirable characteristics

- Standardized assay with limited variability
- Presence of population norms to guide interpretation
- Independence from established risk factors
- Association with CVD clinical end points and type of relationship (linear/nonlinear/dichotomous
- Ability to improve overall prediction beyond traditional risk factors
- Generalization of results to various population groups
- Acceptable cost of assays

Assay:

- Hs-CRP has a rapid, widely available, standardized assay
  - Patented by Brigham and Women's Hospital
    - "Dr Ridker is named as a coinventor on patents filed by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes."
  - Elevated levels seen in acute infection, inflammatory conditions, chronic kidney disease, pulmonary hypertension, etc

JUPITER: Exclusion criteria

- Exclusion criteria were previous or current use of lipid-lowering therapy, current use of postmenopausal hormone-replacement therapy, evidence of hepatic dysfunction (an alanine aminotransferase level that was more than twice the upper limit of the normal range), a creatine kinase level that was more than three times the upper limit of the normal range, a creatinine level that was higher than 2.0 mg per deciliter (176.8 μmol per liter), diabetes, uncontrolled hypertension (systolic blood pressure >190 mm Hg or diastolic blood pressure >100 mm Hg), cancer within 5 years before enrollment (with the exception of basal-cell or squamous-cell carcinoma of the skin), uncontrolled hypothyroidism (a thyroid-stimulating hormone level that was more than 1.5 times the upper limit of the normal range), and a recent history of alcohol or drug abuse
- patients with inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease were excluded, as were patients taking immunosuppressant agents such as cyclosporine, tacrolimus, azathioprine, or long-term oral glucocorticoids.

Ridker, P et al NEJM 2008

High Sensitvity C-Reactive Protien is most often used to help predict a healthy person's risk of cardiovascular disease.

Population norms:

- JUPITER targets:
  - Hs-CRP < 1 mg/dl = low risk
  - Hs-CRP 1-2 mg/dl = moderate risk
  - Hs-CRP > 2 mg/dl = high risk

Ridker, P et al NEJM 2008

Table 1. Distribution of C-Reactive Protein Levels in the U.S. Population Overall and According to Sex, Age, and Race or Ethnic Group.*

Characteristic	CRP Category				CRP Level	
	0–1.9 mg/liter	2.0–2.9 mg/liter	3.0–9.9 mg/liter	≥10.0 mg/liter	Mean ±SD	Median (IQR)
	% of adults					
All adults	48	14	29	10	4.3±7.7	2.1 (0.8–4.7)
Sex						
Male	56	14	24	6	3.4±7.1	1.6 (0.7–3.5)
Female	40	13	33	13	5.1±8.2	2.7 (1.0–6.0)
Age (yr)						
20–29	59	12	22	7	3.5±6.8	1.4 (0.5–3.6)
30–39	51	13	27	9	3.9±7.4	1.9 (0.7–4.2)
40–49	50	13	27	10	3.9±6.3	1.9 (0.8–4.5)
50–59	41	15	33	11	4.7±7.8	2.6 (1.0–5.4)
60–69	36	14	36	13	5.3±8.7	2.9 (1.2–6.1)
70–79	35	18	34	13	5.7±10.5	2.9 (1.4–5.6)
≥80	38	16	34	13	5.4±10.4	2.7 (1.3–5.4)
Race or ethnic group†						
White	48	14	29	9	4.1±6.8	2.1 (0.8–4.5)
Black	44	12	29	15	5.9±11.6	2.5 (0.9–6.2)
Hispanic‡	47	14	29	10	4.5±8.9	2.2 (0.8–4.7)
Other	51	13	26	10	3.9±6.1	1.9 (0.7–4.5)

* Percentages may not total 100 because of rounding. CRP denotes C-reactive protein, and IQR interquartile range (i.e., 25th to 75th percentile).
† Race or ethnic group was self-reported.
‡ "Hispanic" includes the National Health and Nutrition Examination Survey categories "Mexican Americans" and "Other Hispanics."

Woloshin S and Schwartz L. N Engl J Med 2005;352:1611-1613

The NEW ENGLAND JOURNAL of MEDICINE

Distribution of hs-CRP

- 52% of adult population likely has hs-crp > 2mg/dl
- Identification of people meeting JUPITER criteria could include an additional 6.5 million adults as candidates for statin therapy

Woloshin et al, NEJM 2005
Michos, E et al JACC 2009

Population norms:

- Estimated 17.4 million adults age > 20 years have LDL above the NCEP/ATP-III goal
  - "The JUPITER study might serve as an incentive to patients and providers to achieve their recommended LDL goals"

Michos, E et al JACC 2009

Independence from traditional risk factors?

- Elevations in hs-CRP
  - Hormone replacement
  - Obesity/Elevated BMI
  - Metabolic syndrome
  - Physical inactivity
  - Elevated BP
  - Cigarette smoking
  - Low HDL/High Triglycerides
  - Chronic infections
  - Chronic inflammation

Independent?

- Reductions in hs-CRP seen with:
  - Exercise and increasing level of fitness
  - Weight loss
  - Moderate alcohol intake
  - Use of aspirin
  - Dietary changes
  - Use of statins, fibrates and niacin

Independent?

- No currently available CRP inhibitors
- Drug therapy available also treats lipids and platelet function

Independent?

- Heterogeneous response to statin therapy
  - Statistically significant but individually unpredictable response
  - Dose and potency of statin does not predict hsCRP reduction
  - Dose or potency titration does not necessarily result in hsCRP reduction

Lipid and High-Sensitivity C-Reactive Protein Levels during the Follow-up Period, According to Study Group

Table 2. Lipid and High-Sensitivity C-Reactive Protein Levels during the Follow-up Period, According to Study Group.*

Level	12 Mo		24 Mo		36 Mo		48 Mo	
	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo
High-sensitivity C-reactive protein (mg/liter)								
Median	2.2	3.5	2.2	3.5	2.0	3.5	1.8	3.3
Interquartile range	1.2–4.4	2.0–6.2	1.2–4.3	2.0–6.1	1.1–3.9	1.8–6.0	1.1–3.7	1.7–6.1
LDL cholesterol (mg/dl)								
Median	55	110	54	108	53	106	55	109
Interquartile range	44–72	94–125	42–69	93–123	42–69	90–121	44–70	94–124
HDL cholesterol (mg/dl)								
Median	52	50	52	50	50	49	50	50
Interquartile range	43–64	41–61	44–65	42–61	41–62	40–59	43–61	42–60
Triglycerides (mg/dl)								
Median	99	119	99	116	106	123	99	118
Interquartile range	74–137	87–167	73–134	83–165	77–148	90–173	74–140	87–164

* P<0.001 for all between-group comparisons except for high-density lipoprotein (HDL) cholesterol at 36 months (P=0.003) and at 48 months (P=0.34). The mean difference in low-density lipoprotein (LDL) cholesterol levels between the two groups at 12 months was 47 mg per deciliter (1.2 mmol per liter). To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

Ridker P et al. N Engl J Med 2008;359:2195-2207

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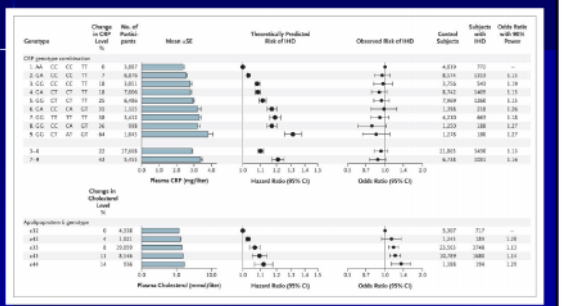

Zacho J et al. N Engl J Med 2008;359:1897-1908

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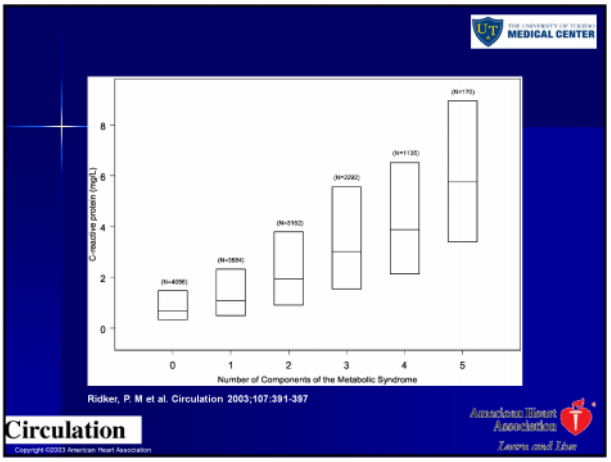
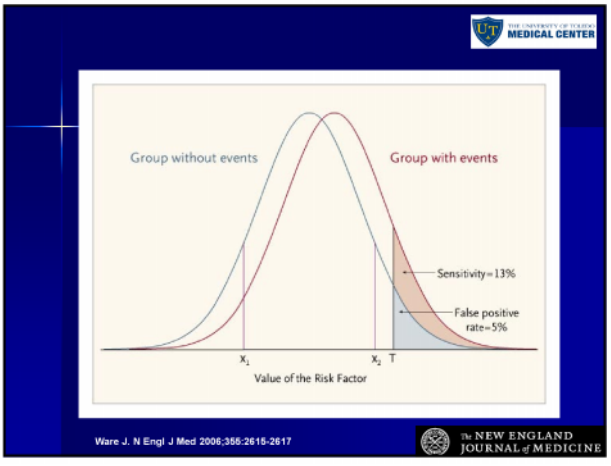


Prediction of clinical events

- hsCRP predicts coronary events in healthy populations
  - Comparing lowest v. highest tertile of hsCRP, a relative odds of 2% for major CV events was noted

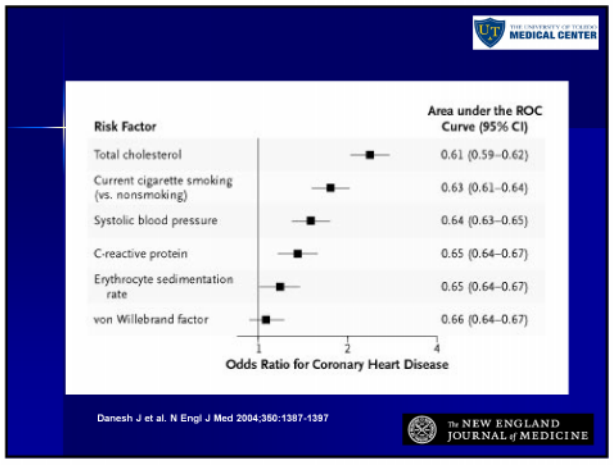
Danesh, J et al BMJ 2000



Prediction of events: Insignificant

- With adjustment for other risk factors, such as age, total cholesterol, HDL cholesterol, smoking, HTN, FH, the magnitude of risk is attenuated
- Relatively few studies have adjusted for BMI or for measures of diabetes or glucose metabolism

Pearson, T et al, Circ 2003



Danesh J et al. N Engl J Med 2004;350:1387-1397

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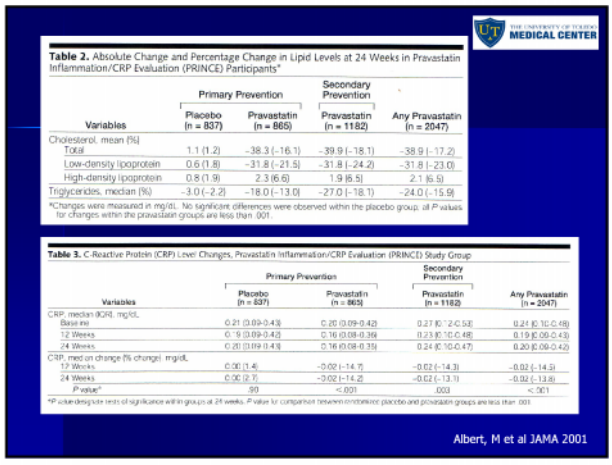


Table 2. Absolute Change and Percentage Change in Lipid Levels at 24 Weeks in Pravastatin Inflammation/CRP Evaluation (PRINCE) Participants*

Variables	Primary Prevention: Placebo (n = 837)	Primary Prevention: Pravastatin (n = 865)	Secondary Prevention: Pravastatin (n = 1182)	Any Pravastatin (n = 2047)
Cholesterol, mean (%)				
Total	1.1 (1.2)	−38.3 (−16.1)	−39.9 (−18.1)	−38.9 (−17.2)
Low-density lipoprotein	0.6 (1.8)	−31.8 (−21.5)	−31.8 (−24.2)	−31.8 (−23.0)
High-density lipoprotein	0.8 (1.9)	2.3 (6.6)	1.9 (6.5)	2.1 (6.5)
Triglycerides, median (%)	−3.0 (−2.2)	−18.0 (−13.0)	−27.0 (−18.1)	−24.0 (−15.9)

*Changes were measured in mg/dL. No significant differences were observed within the placebo group; all P values for changes within the pravastatin groups are less than .001.

Table 3. C-Reactive Protein (CRP) Level Changes, Pravastatin Inflammation/CRP Evaluation (PRINCE) Study Group

Variables	Primary Prevention: Placebo (n = 837)	Primary Prevention: Pravastatin (n = 865)	Secondary Prevention: Pravastatin (n = 1182)	Any Pravastatin (n = 2047)
CRP, median (IQR), mg/dL				
Baseline	0.21 (0.09–0.43)	0.20 (0.09–0.42)	0.27 (0.12–0.53)	0.24 (0.10–0.48)
12 Weeks	0.19 (0.09–0.42)	0.16 (0.08–0.36)	0.23 (0.10–0.48)	0.19 (0.09–0.43)
24 Weeks	0.20 (0.09–0.43)	0.16 (0.08–0.35)	0.24 (0.10–0.47)	0.20 (0.09–0.42)
CRP, med on change (% change), mg/dL				
12 Weeks	0.00 (1.4)	−0.02 (−14.7)	−0.02 (−14.3)	−0.02 (−14.5)
24 Weeks	0.00 (2.7)	−0.02 (−14.2)	−0.02 (−13.1)	−0.02 (−13.6)
P value*	.90	<.001	.003	<.001

*P value designates tests of significance within groups at 24 weeks. P value for comparison between combined placebo and pravastatin groups are less than .001.

Albert, M et al JAMA 2001

Ability to improve overall risk prediction

- Relative v. absolute risk
  - JUPITER
    - Relative risk reduction
    - Absolute risk reduction
      - Risk of participants reduced from 1.8% to 0.9% for hard cardiac endpoints
      - 120 participants had to be treated for 1.9 years to prevent one event

Ability to improve overall risk prediction

- Discrimination = the ability to predict who and who will not have an event
  - C-index or area under the receiver operating characteristic curve
    - 0.5 = no ability to discriminate
    - 1.0 = perfect discrimination
  - FRS predicts approximately 75%
    - C index = 0.75

Risk factor or Prognostic Tool?

- Any new index must have high relative risk and offer a therapeutic target in order to significantly improve FRS
- Coronary calcium scoring
  - Relative risk of 9.67 for Ca score > 300
- hsCRP
  - Relative risk of 1.3 to 1.8 for hsCRP > 2
- 5 Biomarkers
  - Relative risk of 4 in highest quintile

Weintraub, W et al NEJM 2008
Wang, T et al NEJM 2006

Risk factor or Prognostic tool?

- Age and sex only
  - c = 0.68
- Age, sex and biomarkers
  - c = 0.70
- Age, sex and traditional CV risk factors
  - C = 0.76
- Age, sex, biomarkers and traditional RF
  - C = 0.77
- CV risk factors
  - 0.79
- CV risk factors and calcium scoring
  - 0.83

Weintraub, W et al NEJM 2008
Wang, T et al NEJM 2006

Risk Factor or Prognostic Tool?

- Although biomarkers are associated with a high relative risk of adverse events, they add insignificantly to risk prediction in an individual person.
- Distributions of biomarker levels in persons with and in persons without cardiovascular events may overlap, even when large relative differences are present
- Relative risk ratios may not reflect the fact that most persons can be effectively risk stratified with conventional risk factors.

Wang, T et al NEJM 2006

Cost

- Cost of testing
- Cost of therapy
- Cost of retesting
- Cost of follow-up for therapy
- Cost of adverse events
- Indirect costs

Table 2. Age-Specific Gains in Life Expectancy Resulting From Statin Therapy in Men and Women in the Low LDL/High CRP Group

Outcome	Men					Women				
	Age (yrs)					Age (yrs)				
	35	45	55	65	75	35	45	55	65	75
Life expectancy without treatment (yrs)	38.60	29.93	21.88	14.96	9.51	44.77	35.43	26.57	18.69	12.16
Gain in life expectancy with treatment (months)	10.2	9.4	7.4	5.3	3.4	7.9	7.7	7.0	5.8	3.8

Abbreviations as in Table 1.

Blake, G et al JACC 2002

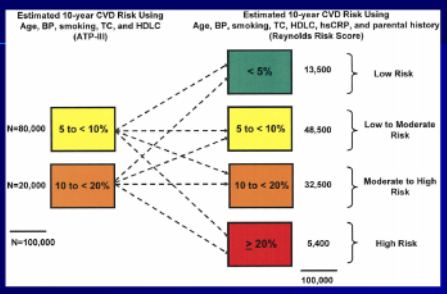
Rebuttal:

JUPITER

- Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

Ridker, P et al NEJM 2008

Risk Reclassification Using hsCRP and Parental History



Ridker, P. M. J Am Coll Cardiol 2007;49:2129-2138

Relation of Multimarker Risk Score to Outcomes

Table 3. Relation of Multimarker Risk Score to Outcomes.*

Multimarker Score	Death	Major Cardiovascular Events
	adjusted hazard ratios (95% CI)	
Low	1.0 (reference group)	1.0 (reference group)
Intermediate	1.34 (0.83–2.18)	1.54 (0.98–2.40)
High	4.08 (2.51–6.62)	1.84 (1.11–3.05)
P value for trend	<0.001	0.02

* Hazard ratios were adjusted for age; sex; body-mass index; categories of blood pressure, total cholesterol, and high-density lipoprotein cholesterol; smoking status; presence or absence of diabetes; serum creatinine level; and presence or absence of prevalent cardiovascular disease (for the model with death).

Wang T et al. N Engl J Med 2006;355:2631-2639

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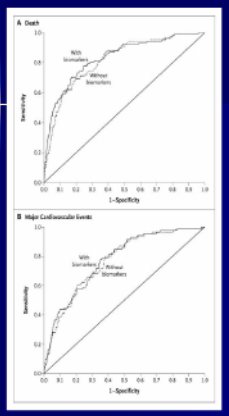

Receiver-Operating-Characteristic Curves for Death (Panel A) and for Major Cardiovascular Events (Panel B) during 5-Year Follow-up

Wang T et al. N Engl J Med 2006;355:2631-2639

Physicians Health Study

- Cost of CRP assessment
  - 14,916 x $50.00 = $74,800
- Cost of aspirin therapy (qod for 8 years)
  - 1086 x $21.90 = $23, 783

JUPITER

- Cost of hs-CRP assessment:
  - 17,802 x $50 = $890,100
- Cost of crestor treatment for 2 years
  - 8901 x $26,703,000
    - Does not include cost of follow-up lipids, LFT's, adverse events, repeat crp levels

Generic statins:

- Simvastatin $30/month
  - 8901 people treated for 1.9 years
  - $5,607,630
- Lab tests
  - hsCRP $50, LFT's $31, Lipids $32
    - Assume testing twice
  - $2,011,626

Generic statins:

- Clinical outcomes data that support high dose, high potency statin therapy
  - REVERSAL
  - TACTICS TIMI 22
  - A to Z
  - TNT

Summary:

- hsCRP is not an independent CV risk factor
- hsCRP does not provide a therapeutic target
- hsCRP is not cost-effective
- hsCRP does not significantly add to an individual's prognostic assessment

- "The thoughtful clinician takes it to be self evident that intensity of therapy should be proportional to risk of disease."
- "However, that disease is common or expensive is not in itself sufficient reason to try to predict it. What is necessary is that reasonable steps can be taken to prevent events."
- "The cost-effectiveness of [screening tests] will depend on choosing cost-effective strategies, which are not necessarily related to the test."

Weintraub, W et al NEJM 2008