

Value of biomarkers for early detection of cardiovascular disease

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NO DISCLOSURES

What are biomarkers?

- NIH definition:
 - Characteristics that are objectively measured and evaluated as indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

3 criteria required for a biomarker to be clinically useful

- The assay should be precise, accurate, and rapidly available to clinicians at a relatively low cost.
- The biomarker must provide additional information that is not surmised from clinical evaluation.
- The absolute measured value should help in clinical decision making.

The Ideal Biomarker 2007

*Redefined 2011

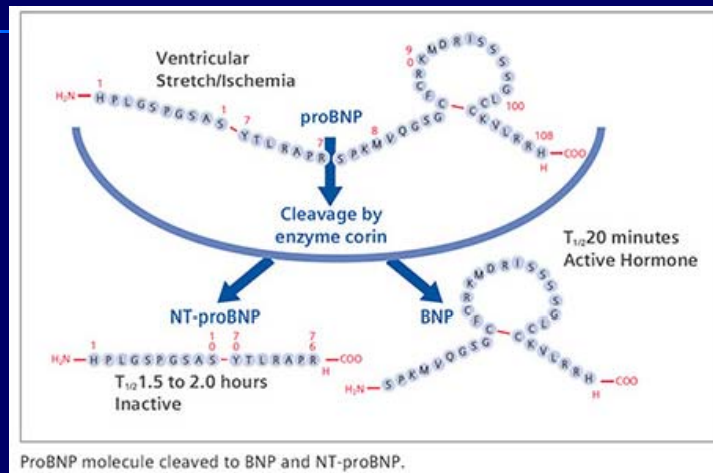
| | |
|--|---|
| Sensitive and specific | Either highly sensitive (diagnosis) or highly specific (treatment effect) |
| Reflects disease severity | Reflects abnormal physiology or biochemistry |
| Correlates with prognosis | Prognosis is most meaningful if level is clinically actionable |
| *Should aid in clinical decision making | Should be used as a basis for specific "biomarker-guided therapy" |
| *Level should decrease after effective therapy | "Biomonitoring" during treatment is an effective surrogate of improvement |

Morrow DA, de Lemos JA. Benchmarks for the assessment of cardiovascular biomarkers Circulation 2007;115:949-952
 Maisel A. J Am Coll Cardiol 2011;58:1890-92

Biomarkers

| |
|---|
| Natriuretic peptides |
| Fibrosis markers: galectin-3, soluble ST2, GDF-15 |
| Troponins |
| Matrix metalloproteinases |
| Collagen turnover markers: type I collagen telopeptide |
| Tenascin C |
| Inflammatory markers: tumor necrosis factor receptors, CRP, cardiotrophin-1 |
| Neurohormonal markers: aldosterone, aldosterone:renin ratio, angiotensin II |
| Others: tissue plasminogen activator |

proBNP => BNP + NT-proBNP



Brain natriuretic proteins

- BNP sensitive for diagnosing CHF in patients with dyspnea (Breathing Not Properly trial)
 - Wet BNP higher than Dry BNP
- Nesiritide
 - a recombinant B-type natriuretic peptide with vasodilatory properties
 - Initially approved for CHF management to reduce PCWP and dyspnea at 3 hours in acute CH
 - N Engl J Med 2000;343:246-53
 - Subsequent studies/meta-analyses suggested worse renal failure and mortality

Reference Limits for N-Terminal-pro-B-Type Natriuretic Peptide in Healthy Individuals (from the Framingham Heart Study)

- 2,285 subjects (mean age 38 years, 56% women) without CVD from Generation 3 underwent testing
- Gender, age, blood pressure, and body mass index accounted for approximately 33% of the interindividual variability in NT-pro-BNP in the reference sample
- NT-pro-BNP values were substantially higher in women compared to men at every age
 - 42.5 to 106.4 pg/ml in men
 - 111.0 to 215.9 pg/ml in women
- Levels increased with increasing age for both genders

American Journal of Cardiology
Volume 108, Issue 9, Pages 1341-1345, 1 November 2011

Future of BNP

- Early indicator of aortic regurgitation progression in patients with normal LVEF
- Target of therapy in patients with advanced CHF
- Marker of early preclinical treatment of CAD (PEACE trial)
- Not of additive value in pts with clinical CHF

Appropriate use of screening and diagnostic tests to foster high-value, cost-conscious care

- Measuring BNP in the initial evaluation of patients with typical findings of heart failure does not reflect high-value care

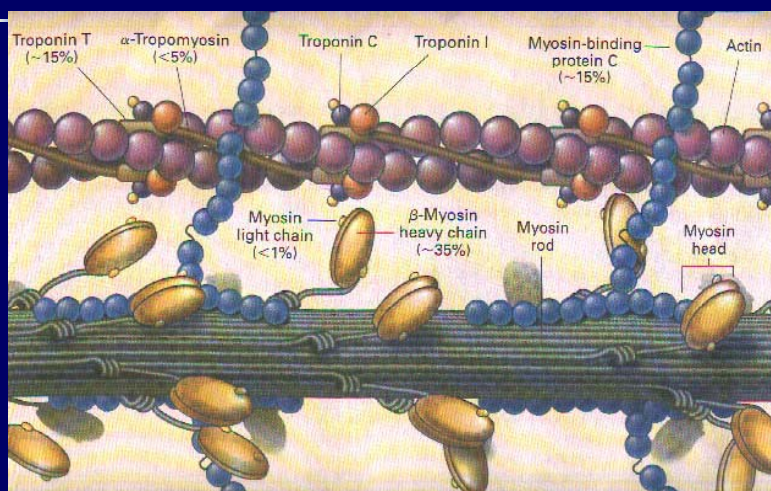
Ann Intern Med 2012;156:147-149

Association of Imaging Markers of Myocardial Fibrosis With Diabetic Cardiomyopathy

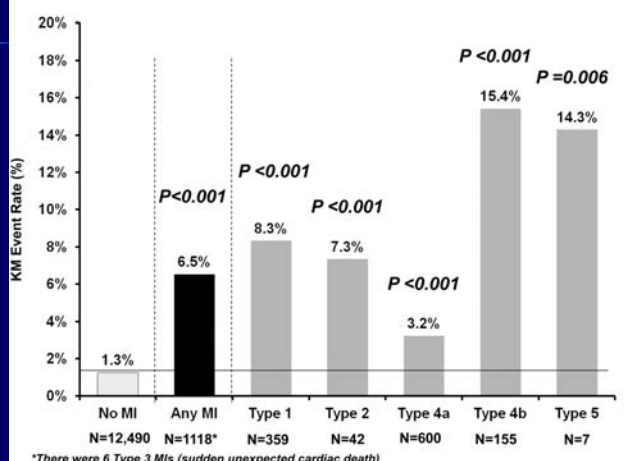
- Propeptides of procollagenase 1 and 3 were measured as a marker of fibrosis
- Elevations have been identified in small studies (67 T2DM mean age 60) with normal LV function and no CAD by stress testing and evidence of T1 fibrosis by MRI
- May be initial stages of diabetic CMP

Circulation: Cardiovascular Imaging. 2011; 4: 693-702

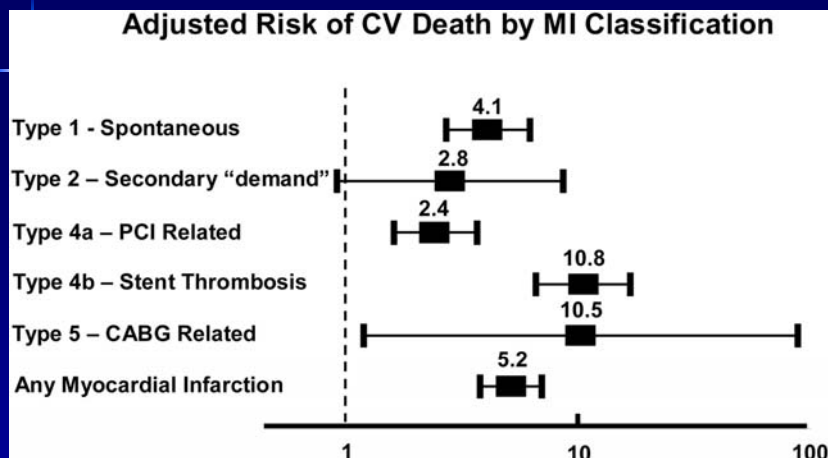
TnI



CV Death at 180 Days for by MI Subtype



Bonaca M P et al. Circulation 2012;125:577-583



Bonaca M P et al. Circulation 2012;125:577-583

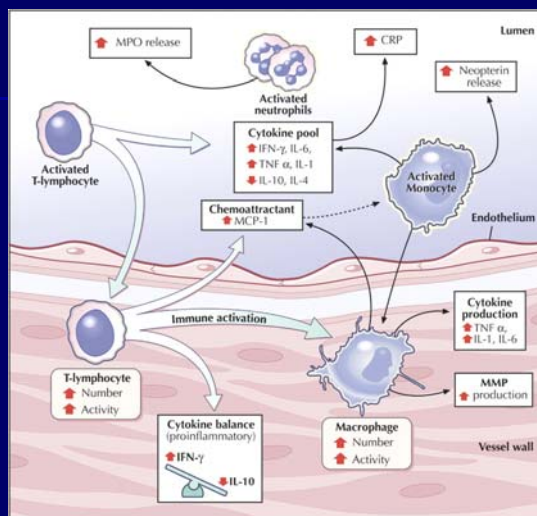
Copyright © American Heart Association



CRP or hs-CRP

- CRP is an inflammatory biomarker
- It is predominantly secreted by the liver and adipose tissues in response to inflammatory stress
- CRP is regulated by interleukin-6

Inflammatory changes in acute coronary syndrome



Ray, K. K. et al. J Am Coll Cardiol 2005;46:1425-1433

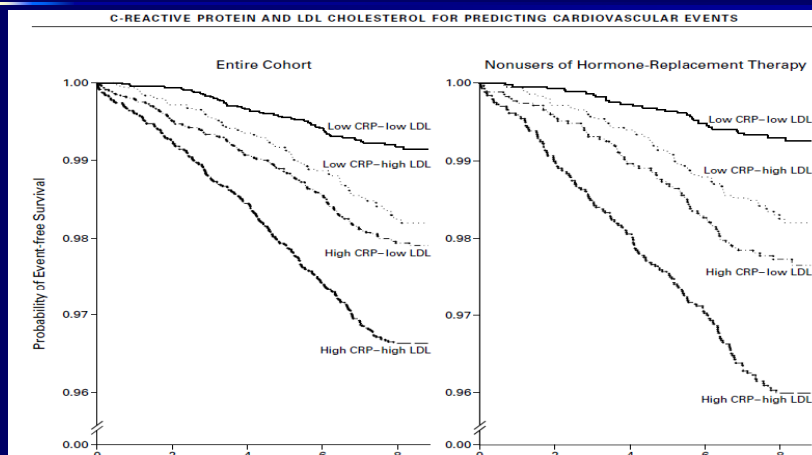


The CRP story

- 2002 Ridker published C-reactive protein level is a stronger predictor of cardiovascular events than the LDL cholesterol level and adds prognostic information to that conveyed by the Framingham risk score
- Studied >28,000 women for >8 yrs

Ridker PM, Rifai N, Rose L, Buring JE, Cook NR.
N Engl J Med. 2002 Nov 14;347(20):1557-65

Event free survival 8 years



Background

- Statins were demonstrated to lower CRP in addition to LDL cholesterol
- Benefits of statins were better when both CRP and LDL were lowered
- Healthy subjects with elevated CRP and normal LDL could benefit from statin therapy

Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein

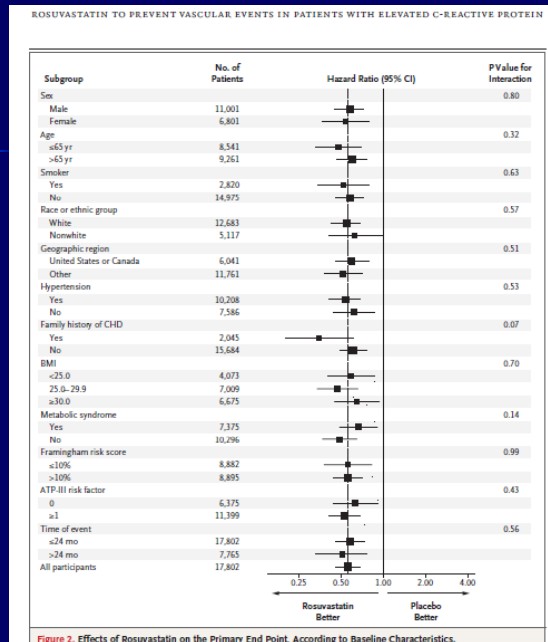
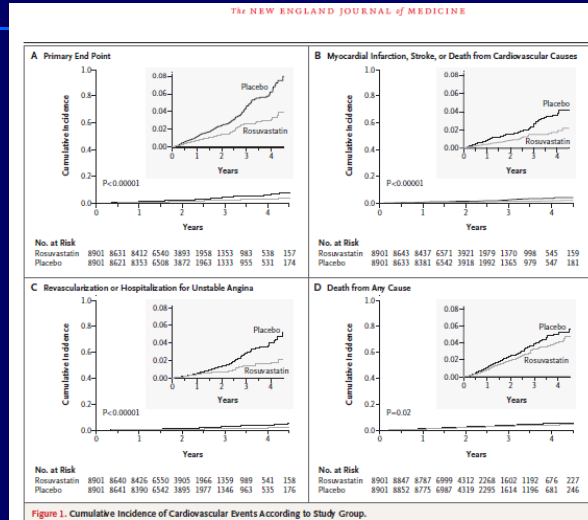
- 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to rosuvastatin, 20 mg daily, or placebo
- Combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular cause

Ridker P, New Eng J Med 2008; 359:2195-2207

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

- Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%
- Consistent reduction in all outcomes were observed in all subgroups evaluated
- The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes

JUPITER endpoints



JUPITER and AFib

- **17,120 participants without prior history of arrhythmia were included in this analysis.**
- **Characteristics**
 - Age median 66 years
 - 38% were women
 - Hypertension, overweight
 - median hs-CRP was 4.3 mg/L.
- **Each increasing tercile of baseline hs-CRP was associated with a 36% increase in the risk of developing AF**
- **The group randomized to rosuvastatin had a 27% lower risk of developing AF during the trial period compared to those randomized to placebo**

Pena JM, Eur Heart J. 2011 Dec 20

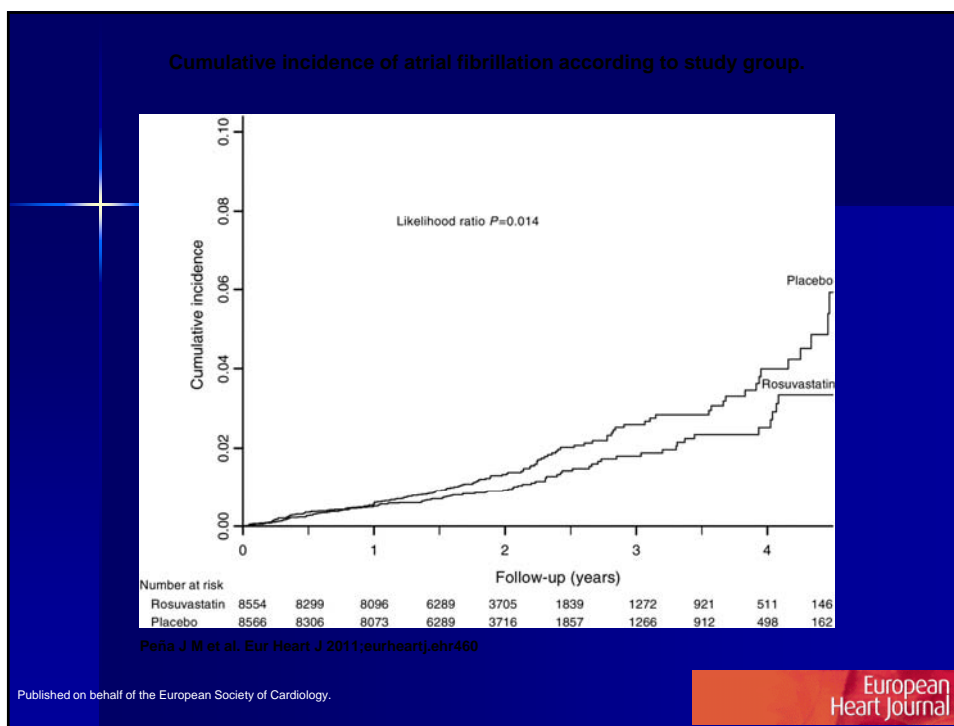
High-sensitivity C-reactive protein, statin therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial

Table 2

Relationship between baseline high-sensitivity C-reactive protein in tertiles and risk of atrial fibrillation

| Tertile | High-sensitivity C-reactive protein (mg/L) | Patients (n) | Incidence rate (per 100 person-years) | HR ^a | 95% CI | P-value |
|--------------|--|--------------|---------------------------------------|-----------------|-----------|---------|
| Total cohort | | | | | | |
| Highest | ≥5.8 | 5862 | 0.83 | 1.96 | 1.38–2.78 | 0.0002 |
| Middle | 3.2–5.8 | 5696 | 0.75 | 1.70 | 1.20–2.41 | 0.003 |
| Lowest | <3.2 | 5562 | 0.43 | Ref. | Ref. | Ref. |
| P-trend | | | | | | 0.0002 |
| Placebo | | | | | | |
| Highest | ≥5.8 | 2719 | 1.00 | 2.26 | 1.42–3.60 | 0.0005 |
| Middle | 3.2–5.8 | 2878 | 0.85 | 1.74 | 1.08–2.80 | 0.02 |
| Lowest | <3.2 | 2969 | 0.47 | Ref. | Ref. | Ref. |
| P-trend | | | | | | 0.0005 |
| Rosuvastatin | | | | | | |
| Highest | ≥5.8 | 2843 | 0.66 | 1.62 | 0.95–2.76 | 0.01 |
| Middle | 3.2–5.8 | 2818 | 0.65 | 1.63 | 0.95–2.74 | 0.08 |
| Lowest | <3.2 | 2893 | 0.38 | Ref. | Ref. | Ref. |
| P-trend | | | | | | 0.08 |

^aHazard ratio adjusted for age (continuous), sex, blood pressure ≥140/90 mmHg or taking antihypertensive medications (yes/no), body mass index (categories: <22, 22–25, 25–30, ≥30 kg/m²), HbA1c (quartiles: <5.5, 5.5–5.7, 5.7–5.9, ≥5.9%), metabolic syndrome (yes/no), race, exercise (less than once/week vs. ≥1/week), drug assignment (in total cohort), current smoking (yes/no), and alcohol use (categories: <1–3/month, 1–6/week, daily).



2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults: Executive Summary

- A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

J Am Coll Cardiol. 2010;56(25):2182-2199

Class 1:

- **Global risk scores (such as the Framingham Risk Score) that use multiple traditional cardiovascular risk factors should be obtained for risk assessment in all asymptomatic adults without a clinical history of CHD.**
- **These scores are useful for combining individual risk factor measurements into a single quantitative estimate of risk that can be used to target preventive interventions**
- ***(Level of Evidence: B)***

J Am Coll Cardiol. 2010;56(25):2182-2199

Table 2. Comparison of a Sample of Global Coronary and Cardiovascular Risk Scores

| | Framingham | SCORE |
|-------------------------|--|---|
| Sample size | 5,345 | 205,178 |
| Age (y) | 30 to 74; M: 49 | 19 to 80; M: 46 |
| Mean follow-up (y) | 12 | 13 |
| Risk factors considered | Age, sex, total cholesterol, HDL cholesterol, smoking, systolic blood pressure, antihypertensive medications | Age, sex, total-HDL cholesterol ratio, smoking, systolic blood pressure |
| Endpoints | CHD (MI and CHD death) | Fatal CHD |

Framingham Risk Score Calculator

NATIONAL CHOLESTEROL EDUCATION PROGRAM
Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The [risk assessment tool](#) below uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age: years

Gender: ☐ Female ☐ Male

[Total Cholesterol:](#) mg/dL

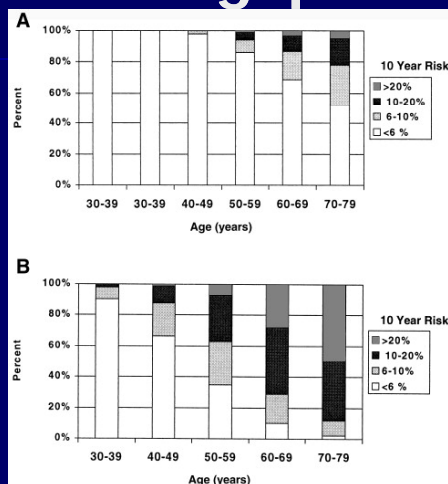
[HDL Cholesterol:](#) mg/dL

[Smoker:](#) ☐ No ☐ Yes

[Systolic Blood Pressure:](#) mm/Hg

Currently on any medication to treat high blood pressure. ☐ No ☐ Yes

Detection gap?



Pasternak RC, Abrams J, Greenland P, et al. 34th Bethesda Conference: task force #1—identification of coronary heart disease risk: is there a detection gap? J Am Coll Cardiol 2003;41:1863–74

748 *Circulation* February 12, 2008

Table 5. CVD Points for Women

| Points | Age, y | HDL | Total Cholesterol | SBP Not Treated | SBP Treated | Smoker | Diabetic |
|--------|--------|-------|-------------------|-----------------|-------------|--------|----------|
| -3 | | | | <120 | | | |
| -2 | | 60+ | | | | | |
| -1 | | 50-59 | | | <120 | | |
| 0 | 30-34 | 45-49 | <160 | 120-129 | | No | No |
| 1 | | 35-44 | 160-199 | 130-139 | | | |
| 2 | 35-39 | <35 | | 140-149 | 120-129 | | |
| 3 | | | 200-239 | | 130-139 | Yes | |
| 4 | 40-44 | | 240-279 | 150-159 | | | Yes |
| 5 | 45-49 | | 280+ | 160+ | 140-149 | | |
| 6 | | | | | 150-159 | | |
| 7 | 50-54 | | | | 160+ | | |
| 8 | 55-59 | | | | | | |
| 9 | 60-64 | | | | | | |
| 10 | 65-69 | | | | | | |
| 11 | 70-74 | | | | | | |
| 12 | 75+ | | | | | | |

Points allotted Total

D'Agostino RB et al, *Circulation* 2008;117, 743-753

Family history: Class 1

- Family history of atherothrombotic CVD should be obtained for cardiovascular risk assessment in all asymptomatic adults
- *Level of Evidence: B*

J Am Coll Cardiol. 2010;56(25):2182-2199

Reynolds Risk Score

| Reynolds (Women) | Reynolds (Men) |
|---|--|
| 24,558 | 10,724 |
| >45; M: 52 | >50; M: 63 |
| 10.2 | 10.8 |
| Age, HbA1C (with diabetes), smoking, systolic blood pressure, total cholesterol, HDL cholesterol, hsCRP, parental history of MI at <60 y of age | Age, systolic blood pressure, total cholesterol, HDL cholesterol, smoking, hsCRP, parental history of MI at <60 y of age |
| MI, ischemic stroke, coronary revascularization, cardiovascular death (CHD and CVD combined) | MI, stroke, coronary revascularization, cardiovascular death (CHD and CVD combined) |

Gender ☐ Male ☐ Female

Age Years (Maximum age must be 80)

Do you currently smoke? ☐ Yes ☐ No

Systolic Blood Pressure (SBP) mm/Hg

Total Cholesterol mg/DL (or) mmol/L

HDL or "Good" Cholesterol mg/DL (or) mmol/L

High Sensitivity C-Reactive Protein (hsCRP) mg/L

Did your Mother or Father have a heart attack before age 60 ? ☐ Yes ☐ No

Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score JAMA 2007;297:611–19.

CRP: Class 2

■ Class 2A

- In men 50 years of age or older or women 60 years of age or older with low-density lipoprotein cholesterol less than 130 mg/dL; not on lipid-lowering, hormone replacement, or immunosuppressant therapy; without clinical CHD, diabetes, chronic kidney disease, severe inflammatory conditions, or contraindications to statins, measurement of CRP can be useful in the selection of patients for statin therapy
- *Level of Evidence: B*

■ Class 2B

- In asymptomatic intermediate-risk men 50 years of age or younger or women 60 years of age or younger, measurement of CRP may be reasonable for cardiovascular risk assessment
- *Level of Evidence: B*

J Am Coll Cardiol. 2010;56(25):2182-2199

CRP: Class 3

- In asymptomatic high-risk adults, measurement of CRP is not recommended for cardiovascular risk assessment
 - *Level of Evidence: B*
- In low-risk men younger than 50 years of age or women 60 years of age or younger, measurement of CRP is not recommended for cardiovascular risk assessment
 - *Level of Evidence: B*

J Am Coll Cardiol. 2010;56(25):2182-2199

Natriuretic Peptides Class 3

- **Measurement of natriuretic peptides is not recommended for CHD risk assessment in asymptomatic adults**
- **Level of Evidence: B**

J Am Coll Cardiol. 2010;56(25):2182-2199

Statins for primary prevention of cardiovascular events in women

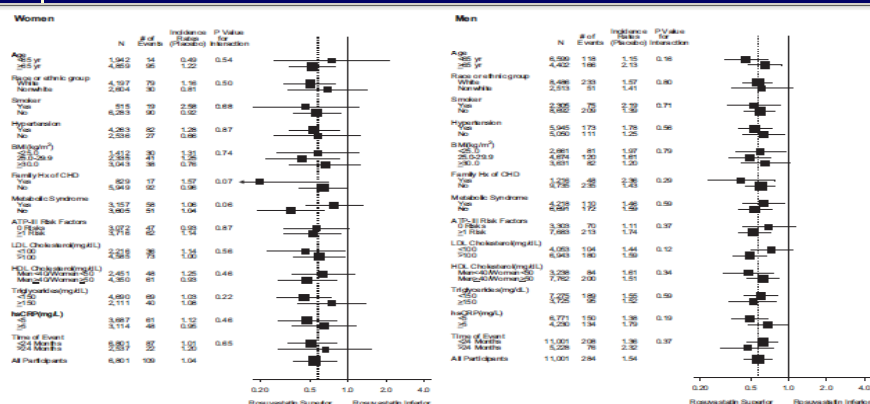


Figure 1. Effects of rosuvastatin on the primary composite end point according to baseline characteristics. The dashed overall line indicates the overall HR for the entire cohort (men and women combined). Hx indicates history; CHD, coronary heart disease; and BMI, body mass index.

Mora S et al, *Circulation* 2010, 121:1069-1077

Meta-analysis of primary prevention in women

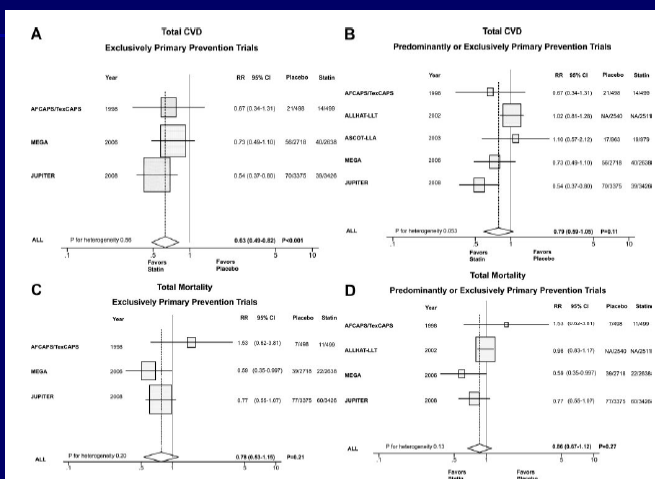


Figure 2. RR of allocation to statin vs placebo in women in relation to CVD in exclusively primary prevention trials (A) and predominantly or exclusively primary prevention trials (B) and of total mortality (C and D). The size of the squares is proportional to the number of events. Mean age, percent diabetic, and statin dose were as follows: AFCAPS/TexCAPS: 63 years, 9%, and lovastatin 20 to 40 mg/d, respectively; ALLHAT-LLA: 66 years, 35%, and pravastatin 20 to 40 mg/d; ASCOT-LLA: 63 years, 24%, and atorvastatin 10 mg/d; WESA: 60 years, 18%, and pravastatin 10 to 20 mg/d; and JUPITER: 66 years, 0%, and rosuvastatin 20 mg/d.

Effectiveness-based guidelines for the prevention of cardiovascular disease in women: 2011 Update

- Task force considers either FRS or Reynolds score are appropriate for use
- Do not endorse using CRP as no data supports that CRP reduction improves clinical outcome
- Current recommendations are to use new cut point of $\geq 10\%$ 10 year risk all CVD not just CHD

Mosca L et al, Circulation 2011;123:1243-1262

Class 3 recommendations

- **Menopausal therapy**
 - Hormone therapy and selective estrogen-receptor modulators (SERMs) should not be used for the primary or secondary prevention of CVD
 - (*Class III, Level of Evidence A*).
- **Antioxidant Supplements**
 - Antioxidant vitamin supplements (eg, vitamin E, C, and beta carotene) should not be used for the primary or secondary prevention of CVD
 - (*Class III, Level of Evidence A*).
- **Folic Acid**
 - Folic Acid, with or without B6 and B12 supplementation, should not be used for the primary or secondary prevention of CVD
 - (*Class III, Level of Evidence A*).
- **Aspirin for MI in women <65 years of age**
 - Routine use of aspirin in healthy women < 65 years of age is not recommended to prevent MI
 - (*Class III, Level of Evidence B*).

Clinical implications

- Patients are broadly categorized into low-, intermediate-, and high-risk subsets, and level of intensity and type of treatments are based on these differing assessments of risk
- Global risk score and family history are inexpensive, cost-efficient screening tools that determine management strategies

J Am Coll Cardiol. 2010;56(25):2182-2199

Clinical implications

- Persons at low risk do not require further testing for risk assessment, as more intensive interventions are considered unwarranted
- Those already documented to be at high risk (established CHD or coronary risk equivalents) are already candidates for intensive preventive interventions, so that added testing will not provide incremental benefit

High-Value Testing Begins With a Few Simple Questions

- Did the patient have this test previously?
- Will the test result change my care of the patient?
- What are the probability and potential adverse consequences of a false positive result?
- Is the patient in potential danger over the short term if I do not perform this test?
- Am I ordering the test primarily because the patient wants it or to reassure the patient?
 - If so, have I discussed the above issues with the patient?
 - Are there other strategies to reassure the patient?

Ann Int Med 2012; 156:162-163 (www.annals.org)

Value of biomarkers for early detection of cardiovascular disease

- CRP measurements can be used in patients with intermediate FHR or Reynolds score when considering the use of statin therapy
- BNP is not recommended for early detection of CVD
- TnI is a marker of myocardial necrosis and not early detection of CVD
- Other markers under investigation but no role for routine use at this time
- Adult Treatment Panel III ('02, updated '04) will be replaced by ATP IV spring 2012

Questions