C-reactive protein was a moderate predictor of coronary heart disease

Danesh J, Wheeler JG, Hirschfield GM, et al. **C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease.** N Engl J Med. 2004;350:1387-97.

QUESTION

How does C-reactive protein (CRP) compare with other circulating inflammatory markers in predicting the risk for coronary heart disease (CHD)?

METHODS

Design: Nested case–control study of participants in the Reykjavik Study.

Setting: Reykjavik, Iceland.

Patients: 2459 patients (mean age 56 y, 72% men) with major coronary events during mean 17.5-year follow-up were matched for year of recruitment, sex, and age with 3969 patients (mean age 56 y, 69% men) without a history of myocardial infarction (MI) (nested within the prospective cohort study).

Risk factors: CRP, erythrocyte sedimentation rate, and von Willebrand factor were prespecified to compare extreme thirds of patients and controls with respect to the distribution of values in the controls. Adjustment was done for age, sex, year of enrollment, smoking status, systolic blood pressure, total cholesterol level, triglyceride level, body mass index, FEV_1, presence or absence of diabetes, and socioeconomic status. Laboratory measurements were done blinded to participants' disease status.

Outcomes: Major CHD events, nonfatal MI, and CHD death.

RESULTS

Of the 2459 patients who had a major CHD event, 1458 (59%) died from CHD, and 1001 (41%) had a nonfatal MI. CRP was moderately associated with CHD (Table). The association with CHD for erythrocyte sedimentation rate and von Willebrand factor was weaker than CRP, but a stronger association was seen for such established risk factors as elevated total cholesterol level and smoking (Table).

CONCLUSION

C-reactive protein was a moderate predictor of coronary heart disease and added only marginally to the predictive value of established risk factors (elevated total cholesterol level and smoking).

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C-reactive protein (CRP) and other inflammatory markers associated with coronary heart disease (CHD) (comparison of extreme thirds of patients)*

Risk factors (cutoffs of values for the top and bottom thirds of the distribution of values in controls)	Odds ratio† (95% CI)
CRP level (2.0 and 0.78 mg/L)	1.45 (1.25 to 1.68)
Erythrocyte sedimentation rate (10 and 4 mm during first h)	1.30 (1.13 to 1.51)
von Willebrand factor level (124 and 88 IU/dL)	1.11 (0.97 to 1.27)
Total cholesterol level (6.80 and 5.85 mmol/L [263 and 226 mg/dL])	2.35 (2.03 to 2.74)
Smoking‡ (current vs never)	1.87 (1.62 to 2.16)

*CI defined in Glossary.
†Adjusted for age, sex, year of recruitment, CHD risk factors, and socioeconomic status.
‡Does not reflect thirds of a continuous distribution. Odds ratios compare current smokers with never smokers. Values distributed as current smokers = top; former smokers = middle; and nonsmokers = bottom.

COMMENTARY

The outstanding nested, case–control study by Danesh and colleagues investigated the relation between ultrasensitive CRP and CHD death and MI in an Icelandic population. The study confirmed the predictive value of CRP after adjusting for other CHD risk factors.

Previous recommendations from the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) in 2003 (1) indicated that CRP could be measured in persons at intermediate risk for CHD (a 10% to 20% 10-y risk for MI or CHD death), at the physician's discretion, or if the CRP level was > 3.0 mg/L (upper tertile of the population). Primary prevention efforts for CHD should be increased in these groups. Danesh and colleagues claim that this study lowers the strength of this association from the former relative odds of 2.0 to 1.45, which is substantially below that of total cholesterol (odds ratio [OR] 2.35) or current versus no smoking (OR 1.87).

Although these results suggest that the CDC/AHA recommendations should be reconsidered, this study does not diminish the recommendation. Within the first 10 years of the 17-year follow-up, the OR remained strong (1.84), weakened only for events in the years after the first decade (OR 1.26). This study also shows that CRP values taken 12 years apart remain as stable (correlation coefficient 0.59) as those for total cholesterol and systolic and diastolic blood pressures.

Although an ideal primary prevention recommendation for measuring CRP might be appropriate only for patients with intermediate CHD risk who have the average of 2 CRP values, it is practical to measure CRP at the same time as the initial lipid profile. CRP values 3.0 to 10.0 mg/L add information for determining CHD risk, whereas CRP values > 10 suggest inflammatory disease and cannot be used for CHD risk determination.

A primary prevention study has begun to test whether aggressive low-density lipoprotein (LDL) cholesterol lowering in patients with LDL cholesterol < 130 mg/dL but with an elevated CRP will be better than placebo for preventing a first CHD event. At this time, CRP should not be measured in patients with known CHD since aggressive preventive strategies for these patients should already have been instituted.

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Reference

1. **Pearson TA, Mensah GA, Alexander RW, et al.** Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003; 107:499-511.