High-Sensitivity C-Reactive Protein as a Predictor of All-Cause Mortality: Implications for Research and Patient Care

Based on more than a decade of evidence, high-sensitivity C-reactive protein (hsCRP) is in clinical use as an inexpensive adjunct to global cardiovascular risk prediction, as a tool to determine risk of future diabetes and metabolic syndrome, and as a method for monitoring efficacy of statin therapy. In the last decade, more than 20 prospective cohort studies have indicated that hsCRP concentrations independently associate with future risk of myocardial infarction, stroke, metabolic syndrome, and type 2 diabetes, and most studies of adequate sample size have found that hsCRP adds prognostic information to global risk prediction scores. On this basis, guidelines for use of hsCRP in clinical practice have been issued by the Centers for Disease Control and Prevention, and novel algorithms for risk prediction that incorporate hsCRP, such as the Reynolds Risk Score (www.reynoldsriskscore.com), have been shown to improve risk classification, particularly for “intermediate risk” patients who account for more than 70% of all vascular events. Further, as statins lower hsCRP in an LDL cholesterol–independent manner and as best clinical outcomes occur among statin-treated patients who not only reduce LDL cholesterol below 70 mg/L (70 mg/dL) but also reduce hsCRP below 2 mg/L, the concept of “dual goals” has been introduced into cardiovascular clinical practice. Because of its relationships with insulin resistance, leptin, and cytokine function, as well as its role in endothelial dysfunction and inhibition of fibrinolysis, CRP has also been of pathophysiologic interest as an intellectual bridge linking low-grade systemic inflammation to both diabetogenesis and atherogenesis.

Given the consistency and generalizability of these data, it is not surprising that clinical investigators might also seek evidence regarding CRP as a potential determinant of all-cause mortality. After all, coronary heart disease, cerebrovascular disease, and diabetes together account for >60% of adult deaths in the United States and Europe. In this issue of Clinical Chemistry, two reports address this research question from different perspectives, one evaluating CRP measurement among hospitalized patients and one evaluating hsCRP in a general outpatient community.

In the first report, Marsik et al. (8) report that patients with CRP concentrations >5 mg/L at the time of hospital admission had a 50% to 330% increase in risk of death from any cause. This increase in risk was present in both short-term and long-term follow-up, rose in magnitude as concentrations of CRP increased >10 mg/L, and was associated with not only cardiovascular mortality but also mortality from cancer. Importantly, the mortality risk associated with increased CRP concentrations was independent of underlying disease status or reason for initial hospitalization. Characterizing CRP as a unique “triage marker for future death,” Marsik et al. argue that evaluation of inflammatory risk in the hospital setting should be routinely performed to identify very-high-risk patients in need of additional close monitoring. While provocative, this conclusion is consistent with data from prior investigations that have reported hsCRP to predict total mortality among patients hospitalized for acute ischemia, patients in general intensive care units, those undergoing bypass surgery, or in clinics limited to patients with diabetes, end-stage renal failure, chronic obstructive pulmonary disease, or cancer (9–11).

The second report, from Koenig et al. (12), deals with the issue of hsCRP as a predictor of death in the Monitoring of trends and determinants in Cardiovascular Disease (MONICA)/KORA (Cooperative Health Research in the Region of Augsburg) Augsburg general population cohort in Southern Germany. In this prospective evaluation of 3620 initially healthy men followed over a 7.1-year period, 408 deaths occurred. After adjustment for age, smoking, hypertension, hyperlipidemia, diabetes, obesity, and socioeconomic markers, those with baseline hsCRP concentrations >3 mg/L had a 2-fold increase in risk of total mortality [hazard ratio (HR) 1.9, 95% CI 1.4–2.5]. Consistent with data from the hospitalized patients, risks in the MONICA/KORA Augsburg cohort associated with hsCRP were most prominent for vascular mortality (HR 2.2, 95% CI 1.4–3.3), but were also present for

1 Nonstandard abbreviations: hsCRP, high-sensitivity C-reactive protein; MONICA, Monitoring Cardiovascular Disease; HR, hazard ratio.
cancer mortality at a lower magnitude of effect (HR 1.7, 95% CI 1.0–2.7).

Data from both of these studies confirm prior work in this field. As shown in Table 1, 13 prospective cohort studies involving nearly 63 000 initially healthy individuals report that hsCRP concentrations are a potent predictor of short- and long-term risk of death (12–24).

Notably, higher risks are reported in studies of the elderly; among elderly participants in the Cardiovascular Health Study, risks of near-term death (within 3 years) increased 4-fold among men with hsCRP in the highest compared with the lowest quartile (HR 4.1, 95% CI 2.7–6.3) (24).

In this analysis, risks were even higher for near-term death when a second inflammatory biomarker, fibrinogen, was also increased. Specifically, for those with both hsCRP and fibrinogen concentrations in the highest quartile at baseline, a 9.6-fold increase in near-term death was observed (95% CI 4.3–12.1), whereas cardiovascular mortality increased more than 13-fold (HR 13.5, 95% CI 3.2–56.5) (24).

Thus, individuals with the highest inflammatory biomarker concentrations were not “false-positives,” but rather were the patient group at highest absolute risk.

Beyond confirming prior work, the current data from the MONICA-Augsburg cohort also provide a direct screening comparison of hsCRP to hyperlipidemia and obesity as determinants of mortality. In this regard, the MONICA data are of considerable pathophysiologic interest. Whereas hsCRP concentrations were associated with a more than doubling of mortality risk, concentrations of total cholesterol (2436 vs 2436 mg/L [243.6 vs 243.6 mg/dL], P = 0.99), HDL cholesterol (499 vs 502 mg/L [49.9 vs 50.2 mg/dL], P = 0.8), total:HDL cholesterol ratio (5.0 vs 5.0, P = 0.9), and

### Table 1. hsCRP in the prediction of total and cardiovascular mortality in prospective cohorts of apparently healthy men and women.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Age, years</th>
<th>End point</th>
<th>Sex</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris et al. (1999) (13)</td>
<td>Iowa 65+ Rural Heart Study</td>
<td>1293</td>
<td>&gt; 65</td>
<td>Total mortality</td>
<td>M, W</td>
<td>1.6 (1.0–2.6)*</td>
</tr>
<tr>
<td>Jager et al. (1999) (14)</td>
<td>Hoorn Study</td>
<td>610</td>
<td>&gt; 50</td>
<td>CV mortality</td>
<td>M, W</td>
<td>2.2 (1.0–5.3)*</td>
</tr>
<tr>
<td>Ridker et al. (2000) (15)</td>
<td>Women’s Health Study</td>
<td>27 939</td>
<td>&gt; 44</td>
<td>CV mortality</td>
<td>W</td>
<td>2.0 (1.4–3.0)*</td>
</tr>
<tr>
<td>Mendall et al. (2000) (16)</td>
<td>Caerphilly Prospective Heart Disease Study</td>
<td>2512</td>
<td>&gt; 45</td>
<td>CV mortality</td>
<td>M</td>
<td>2.4 (1.3–4.4)*</td>
</tr>
<tr>
<td>Strandberg and Tilvis (2000) (17)</td>
<td>Helsinki Ageing Study</td>
<td>455</td>
<td>&gt; 75</td>
<td>Total mortality</td>
<td>M, W</td>
<td>1.2 (1.1–1.4)*</td>
</tr>
<tr>
<td>Albert et al. (2002) (18)</td>
<td>Physician’s Health Study</td>
<td>299</td>
<td>&gt; 40</td>
<td>Sudden death</td>
<td>M</td>
<td>2.7 (0.9–8.8)*</td>
</tr>
<tr>
<td>Tice et al. (2003) (19)</td>
<td>Study of Osteoporotic Fractures</td>
<td>9704</td>
<td>&gt; 65</td>
<td>CV mortality</td>
<td>W</td>
<td>8.0 (2.2–29.0)*</td>
</tr>
<tr>
<td>Boekholdt et al. (2006) (20)</td>
<td>EPIC-Norfolk</td>
<td>987</td>
<td>&gt; 45</td>
<td>CV mortality</td>
<td>M, W</td>
<td>2.9 (1.8–4.7)*</td>
</tr>
<tr>
<td>Laaksonen et al. (2005) (21)</td>
<td>Kuopio Heart Study</td>
<td>1476</td>
<td>&gt; 50</td>
<td>CV mortality</td>
<td>M</td>
<td>2.9 (1.5–5.9)*</td>
</tr>
<tr>
<td>Okin et al. (2005) (22)</td>
<td>Strong Heart Study</td>
<td>2155</td>
<td>&gt; 50</td>
<td>CV mortality</td>
<td>M, W</td>
<td>2.1 (1.3–3.3)*</td>
</tr>
<tr>
<td>Tuomisto et al. (2006) (23)</td>
<td>FINRISK Study</td>
<td>6051</td>
<td>&gt; 25</td>
<td>Total mortality</td>
<td>M</td>
<td>2.4 (1.4–4.1)*</td>
</tr>
<tr>
<td>Jenny et al. (2007) (24)</td>
<td>Cardiovascular Health Study</td>
<td>2480</td>
<td>&gt; 65</td>
<td>CV mortality</td>
<td>M</td>
<td>4.3 (2.2–8.4)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3348</td>
<td>&gt; 65</td>
<td>CV mortality</td>
<td>W</td>
<td>2.3 (1.0–4.9)*</td>
</tr>
<tr>
<td>Koenig et al. (2008) (12)</td>
<td>MONICA-Augsburg Cohort Study</td>
<td>3620</td>
<td>&gt; 45</td>
<td>CV mortality</td>
<td>M</td>
<td>2.2 (1.4–3.3)*</td>
</tr>
</tbody>
</table>

HR calculated as a comparison of those with hsCRP: a > 3 mg/L vs < 1 mg/L, b per 10 mg/L change, c those in the top vs bottom quartile, or d top vs bottom quintile. All HRs, except those from Mendall et al. (16), are adjusted for available traditional risk factors.
body mass index (27.8 vs 27.9 kg/m², P = 0.8) were virtually identical at baseline in comparisons of survivors and nonsurvivors. Explanations for this apparent paradox are not clear, yet almost identical comparative data have been reported by Boekholdt et al. in the European Prospective Investigation of Cancer (EPIC)-Norfolk prospective study (20), where hsCRP was a stronger predictor of coronary artery disease incidence and cardiovascular mortality than blood pressure, obesity, HDL cholesterol, or LDL cholesterol. In both the MONICA/KORA and EPIC-Norfolk data, only diabetics and smoking carried greater prognostic weight for mortality than increased hsCRP.

What is not clear from any available data is how the knowledge that increased hsCRP concentrations predict mortality would alter therapy or improve outcomes. Although Marsik et al. (8) suggest that those with high CRP concentrations at hospital admission should be “targeted for intervention,” it is uncertain what such interventions could be that would go beyond standard of care. This is particularly true of cancer mortality, where increased CRP concentrations are largely a result of prevalent disease, rather than a marker of future risk (25). In the setting of cardiovascular disease, the primary role of hsCRP screening remains in global risk prediction where better estimates of risk can be used to better target proven preventive therapies. Even in this setting, it should be remembered that we remain without definitive data that CRP reductions per se will reduce vascular event rates, although initial vascular-protective data for direct CRP inhibitors is promising (26). Thus, although observations that increased hsCRP concentrations strongly relate to near-term mortality are robust, much research needs to be done to address how this prognostic information can be garnered to improve patient care. Ultimately, hard end-point studies will be needed to discern whether hsCRP is more than a screening tool, but a potential target for therapy.

Financial Disclosures: Dr. Ridker is listed as a co-inventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes.

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References


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