C-Reactive Protein, Fatal and Nonfatal Coronary Artery Disease, Stroke, and Peripheral Artery Disease in the Prospective EPIC-Norfolk Cohort Study

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Objective—Circulating levels of C-reactive protein (CRP) are associated with an increased risk of coronary artery disease (CAD), stroke, and peripheral artery disease (PAD). Observational and experimental evidence suggest that CRP might differentially predict fatal and nonfatal cardiovascular events. Here, we sought to determine the predictive value of CRP for fatal and nonfatal CAD, stroke, or PAD.

Approach and Results—CRP levels were measured in 18,450 apparently healthy participants in the EPIC-Norfolk cohort. Cox proportional hazards models were used to quantify the association between CRP levels and fatal and nonfatal CAD events, strokes, and PAD events. Bootstrapping was applied to test for significant differences between the risk of fatal and nonfatal events. During 208,485 person-years at risk, 2915 CAD events, 361 strokes, and 657 PAD events occurred. CRP was associated with fatal and nonfatal CAD events and nonfatal PAD events. When adding CRP to predictive risk models for fatal and nonfatal events corrected for known cardiovascular risk factors, the net reclassification index was 2.1% for fatal and 1.9% for nonfatal events. Multivariate adjusted hazard ratios for fatal CAD events (hazard ratio, 1.36; 95% confidence interval, 1.27–1.46) differed significantly (mean difference, 13%; 95% confidence interval, 5.1%–21.9%; P<0.001) from the multivariate adjusted hazard ratio for nonfatal CAD events (hazard ratio, 1.21; 95% confidence interval, 1.15–1.26).

Conclusions—In the EPIC-Norfolk cohort, CRP was associated with fatal and nonfatal CAD events, as well as nonfatal PAD events. Adding CRP to risk stratification models resulted in a small improvement in classification for both fatal and nonfatal events. Importantly, CRP was significantly more strongly associated with fatal CAD events than with nonfatal CAD events. (Arterioscler Thromb Vasc Biol. 2013;33:00-00.)

Key Words: atherosclerosis ■ coronary artery disease ■ C-reactive protein ■ peripheral arterial disease ■ stroke

Atherosclerosis is a systemic, low-grade inflammatory disease34 that may result in a variety of clinical complications, including coronary artery disease (CAD), stroke, and peripheral artery disease (PAD). C-reactive protein (CRP) is an acute phase protein and a member of the family of pentaxins. It is predominantly produced in the liver, and its plasma concentration can rise up to 1000-fold during serious infections or major tissue damage.3 CRP is present in the atherosclerotic plaque,5 where it colocalizes with monocytes, monocyte-derived macrophages, and lipoproteins.6,7 The presence of CRP within the atherosclerotic plaque, combined with the proatherogenic effects attributed to CRP,8-10 has fueled the concept that CRP may be a causal factor in atherogenesis.12 However, others have refuted a causal relationship by observing that CRP polymorphisms associated with increased CRP levels were not proportionally associated with an increased risk of CAD.13,14 Nonetheless, the association between CRP levels and the risk of future myocardial infarction or ischemic stroke has been studied extensively. In a large meta-analysis of 54 long-term prospective studies with individual records of 160,309 people without a history of vascular disease, CRP was strongly associated with the risk of CAD and ischemic stroke.15 However, these studies usually examined associations between circulating CRP levels and the sum of both fatal and nonfatal cardiovascular events as a combined outcome. If CRP is differentially associated with fatal and nonfatal CAD, the associations between CRP and fatal cardiovascular events might have been underestimated. Recently, CRP was shown to have a stronger association with fatal than nonfatal vascular events in the Prospective Study of Pravastatin in the Elderly at
Risk (PROSPER) trial that enrolled elderly men and women with a mean age of 76 years. Both in vitro and in vivo data indicate that not only inflammation in general but also CRP itself can aggravate myocardial infarction promoting more severe cardiovascular events.

We therefore hypothesized that CRP is more strongly associated with fatal compared with nonfatal CAD events, strokes, and PAD events in the general population. We tested this hypothesis in the EPIC-Norfolk prospective population study. Here, we present our data.

Materials and Methods

Materials and methods are available in the online-only Supplement.

Results

CRP levels were available in 18,450 participants. In Table 1, baseline characteristics and the calculated FRS are listed for the study participants. The mean FRS was 12.8±10.8 indicating a 10-year average risk of 12.8% for a CAD event. Table 2 shows the association between CRP levels and traditional cardiovascular risk factors. As expected, CRP levels were associated with all major traditional risk factors for cardiovascular disease (CVD). Body mass index, waist circumference, age, and triglycerides had the strongest correlation with CRP serum concentrations. Hazard ratio (HRs) for all fatal cardiovascular events were higher compared with HRs for all nonfatal cardiovascular events, but none reached our predefined Bonferroni corrected P value (P<0.01) Table 3 shows the number and percentages of fatal and nonfatal CAD, stroke, and PAD-related events for each CRP quartile.

CRP Levels and CAD Events

The unadjusted HR for 1 mg/L CRP increment was 1.67 (95% confidence interval [CI], 1.57–1.77) for fatal CAD events and 1.42 (95% CI, 1.36–1.47) for nonfatal CAD events (Table 3). The multivariate adjusted HR for fatal CAD was 1.36 (95% CI, 1.27–1.46) and for nonfatal CAD was 1.21 (95% CI, 1.15–1.26). HRs for the risk of fatal and nonfatal CAD events according to CRP quartiles are displayed in Table 5. The multivariate adjusted HRs for fatal CAD events were significantly different from the multivariate adjusted HRs for nonfatal CAD events (mean difference, 13%; 95% CI, 5.1%–21.9%; P<0.001).

CRP Levels and Stroke

The unadjusted HR for 1 mg/L CRP increment was 1.59 (95% CI, 1.24–2.04) for fatal stroke and 1.38 (95% CI, 1.23–1.52) for nonfatal stroke. The multivariate adjusted HR for fatal stroke and nonfatal stroke did not reach our predefined multiple testing P value. HRs for the risk of fatal and nonfatal stroke according to CRP quartiles are displayed in Table 5. The multivariate adjusted HR for fatal stroke and nonfatal stroke did not differ significantly (mean difference, 21.0%; 95% CI, −11.5% to 62.6%; P=0.23).

CRP Levels and Peripheral Arterial Disease

The unadjusted HR for 1 mg/L CRP increment was 1.86 (95% CI, 1.49–2.92) for fatal PAD events and 1.59 (95% CI, 1.49–1.70) for nonfatal CAD events. The multivariate adjusted HR for nonfatal PAD events remained statistically significant (HR, 1.36; 95% CI, 1.26–1.48), whereas for fatal PAD events, the multivariate adjusted HR lost statistical significance. HRs for the risk of fatal and nonfatal PAD events according to CRP quartiles are displayed in Table 4. The multivariate adjusted HRs for fatal CAD did not differ significantly compared with that for nonfatal PAD events (mean difference, 6.6%; 95% CI, −42% to 74.9%; P=0.77). Figure 1 displays the event-free survival curves for stroke, CAD, and PAD according to CRP concentrations.

CRP and Fatal Versus Nonfatal Cardiovascular Prediction Performance

The C statistic for all combined fatal CAD, stroke, and PAD events was 0.82 (95% CI, 0.81–0.83; P<0.001), whereas the C statistic for nonfatal events was 0.76 (95% CI, 0.75–0.77; P<0.001). Figure 2 displays the receiver operating characteristic curve for fatal and nonfatal cardiovascular events. Table 5 presents the reclassification table for fatal and nonfatal cardiovascular events. The use of CRP in addition to
established CVD risk factors to predict fatal cardiovascular events resulted in 126 individuals being correctly reclassified into a higher risk category, as compared with the model without CRP. A total of 112 individuals were incorrectly reclassified into a lower risk category. Similarly, 1121 individuals who did not develop CVD during follow-up were correctly reclassified into a lower category, whereas 897 individuals were incorrectly reclassified into a higher category. The net effect was a correct reclassification in 224 fatal events. The net reclassification improvement was 2.1% (95% CI, 0.7%–3.5%; P <0.001).

The use of CRP in addition to established CVD risk factors to predict nonfatal cardiovascular events resulted in 111 individuals being correctly reclassified into a higher risk category, as compared with the model without CRP. A total of 98 individuals were incorrectly reclassified into a lower risk category.

Table 2. Association Between CRP and Cardiovascular Risk Factors

<table>
<thead>
<tr>
<th>CRP Serum Concentration Quartiles, mg/L</th>
<th>Participants, n</th>
<th>Age, y</th>
<th>Women, n (%)</th>
<th>Body mass index, kg/m²</th>
<th>Waist circumference, cm</th>
<th>Cigarette smoking, n (%)</th>
<th>Diabetes mellitus, n (%)</th>
<th>Myocardial infarction at baseline, n (%)</th>
<th>Hormone replacement therapy, n (%)</th>
<th>Systolic blood pressure, mm Hg</th>
<th>Diastolic blood pressure, mm Hg</th>
<th>Total cholesterol, mmol/L</th>
<th>LDL cholesterol, mmol/L</th>
<th>HDL cholesterol, mmol/L</th>
<th>Triglycerides, mmol/L</th>
<th>CRP, mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt;0.80 mg/L)</td>
<td>4461</td>
<td>55.8±8.8</td>
<td>2439 (55)</td>
<td>24.4±2.9</td>
<td>82.8±10.9</td>
<td>377 (8.5)</td>
<td>49(1.1)</td>
<td>62 (1.4)</td>
<td>338 (7.6)</td>
<td>130±17</td>
<td>80±11</td>
<td>5.93±1.08</td>
<td>3.77±0.97</td>
<td>1.5±0.43</td>
<td>1.2 (0.9–1.8)</td>
<td>0.5 (0.3–0.6)</td>
</tr>
<tr>
<td>2 (0.8–1.6 mg/L)</td>
<td>4702</td>
<td>58.8±9.1</td>
<td>2542 (54)</td>
<td>25.8±3.18</td>
<td>86.9±11.6</td>
<td>449 (9.6)</td>
<td>82 (1.7)</td>
<td>118 (2.5)</td>
<td>459 (9.8)</td>
<td>134±18</td>
<td>82±11</td>
<td>6.20±1.14</td>
<td>3.99±1.02</td>
<td>1.44±0.41</td>
<td>1.5 (1.0–2.1)</td>
<td>1.1 (0.9–1.3)</td>
</tr>
<tr>
<td>3 (1.6–3.3 mg/L)</td>
<td>4755</td>
<td>60.5±8.9</td>
<td>2573 (54)</td>
<td>26.9±3.55</td>
<td>89.8±11.7</td>
<td>552 (11.7)</td>
<td>116 (2.4)</td>
<td>195 (4.1)</td>
<td>566 (11.9)</td>
<td>137±18</td>
<td>83±11</td>
<td>6.32±1.17</td>
<td>4.08±1.04</td>
<td>1.39±0.45</td>
<td>1.7 (1.2–2.4)</td>
<td>2.2 (1.9–2.7)</td>
</tr>
<tr>
<td>4 (&gt;3.3 mg/L)</td>
<td>4532</td>
<td>61.6±8.8</td>
<td>2619 (58)</td>
<td>28.0±4.47</td>
<td>92.5±12.5</td>
<td>702 (15.6)</td>
<td>156 (3.4)</td>
<td>225 (5.0)</td>
<td>772 (17.0)</td>
<td>140±19</td>
<td>84±11</td>
<td>6.28±1.22</td>
<td>4.01±1.06</td>
<td>1.34±0.40</td>
<td>1.8 (1.2–2.5)</td>
<td>5.7 (4.2–8.8)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or number (percentage). Triglycerides and CRP are presented as median with the 25th to 75th percentile and log transformed before analysis. For triglycerides, the Spearman correlation between CRP serum concentration and triglycerides is presented. CRP indicates C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and R, Pearson correlation between log-transformed CRP serum concentration and risk factors.

*P value for linearity between CRP serum concentration quartiles and risk factor levels.
†P value corresponding to R.

Table 3. Coronary Artery Disease, Stroke, and Peripheral Artery Disease by CRP Quartiles

<table>
<thead>
<tr>
<th>CRP Serum Concentration Quartiles</th>
<th>Overall fatal events</th>
<th>Overall nonfatal events</th>
<th>Coronary artery disease</th>
<th>Overall</th>
<th>Follow-up, y</th>
<th>Patient years of follow-up</th>
<th>Overall fatal events</th>
<th>Overall nonfatal events</th>
<th>Coronary artery disease</th>
<th>Overall</th>
<th>Follow-up, y</th>
<th>Patient years of follow-up</th>
<th>Overall fatal events</th>
<th>Overall nonfatal events</th>
<th>Coronary artery disease</th>
<th>Overall</th>
<th>Follow-up, y</th>
<th>Patient years of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt;0.80 mg/L)</td>
<td>4461</td>
<td>12.0±1.89</td>
<td>53532</td>
<td>87 (8.7)</td>
<td>396 (13.0)</td>
<td>635 (20.9)</td>
<td>79 (9.5)</td>
<td>286 (13.7)</td>
<td>7 (14.3)</td>
<td>4461</td>
<td>12.0±1.89</td>
<td>53532</td>
<td>87 (8.7)</td>
<td>396 (13.0)</td>
<td>7 (14.3)</td>
<td>4461</td>
<td>12.0±1.89</td>
<td>53532</td>
</tr>
<tr>
<td>2 (0.8–1.6 mg/L)</td>
<td>4702</td>
<td>12.0±2.07</td>
<td>56424</td>
<td>148 (16.5)</td>
<td>635 (20.9)</td>
<td>259 (28.9)</td>
<td>139 (16.7)</td>
<td>456 (21.9)</td>
<td>7 (14.3)</td>
<td>4702</td>
<td>12.0±2.07</td>
<td>56424</td>
<td>148 (16.5)</td>
<td>635 (20.9)</td>
<td>259 (28.9)</td>
<td>4702</td>
<td>12.0±2.07</td>
<td>56424</td>
</tr>
<tr>
<td>3 (1.6–3.3 mg/L)</td>
<td>4755</td>
<td>11.8±2.48</td>
<td>56109</td>
<td>259 (28.9)</td>
<td>895 (29.5)</td>
<td>402 (44.9)</td>
<td>238 (28.6)</td>
<td>610 (29.3)</td>
<td>19 (38.8)</td>
<td>4755</td>
<td>11.8±2.48</td>
<td>56109</td>
<td>259 (28.9)</td>
<td>895 (29.5)</td>
<td>402 (44.9)</td>
<td>4755</td>
<td>11.8±2.48</td>
<td>56109</td>
</tr>
<tr>
<td>4 (&gt;3.3 mg/L)</td>
<td>4532</td>
<td>11.4±3.02</td>
<td>51665</td>
<td>259 (28.9)</td>
<td>1111 (36.6)</td>
<td>402 (44.9)</td>
<td>377 (45.3)</td>
<td>730 (35.1)</td>
<td>16 (32.7)</td>
<td>4532</td>
<td>11.4±3.02</td>
<td>51665</td>
<td>259 (28.9)</td>
<td>1111 (36.6)</td>
<td>402 (44.9)</td>
<td>4532</td>
<td>11.4±3.02</td>
<td>51665</td>
</tr>
</tbody>
</table>

Distribution of events (number and percentage) across CRP quartiles. Mean follow-up±SD is given in years and calculated for overall mortality. CRP indicates C-reactive protein.
Similarly, 911 individuals who did not develop CVD during follow-up were correctly reclassified into a lower category, whereas 703 individuals were incorrectly reclassified into a higher category. The net effect was a correct reclassification in 13 nonfatal events. The net reclassification improvement was 1.9% (95% CI, 0.6%–3.3%; \( P < 0.001 \)).

To further determine the addition of CRP to the model to predict CVD risk, the IDI was calculated. The IDI for fatal cardiovascular events was 0.008 (95% CI, 0.006–0.010; \( P < 0.001 \)), whereas the IDI for nonfatal cardiovascular events was 0.003 (95% CI, 0.002–0.004; \( P < 0.001 \)).

**Discussion**

We confirm the findings from previous studies that elevated CRP levels are associated with an increased risk of future CAD events in apparently healthy individuals. In addition, we show that CRP levels are also associated with PAD events. More importantly, we observed that the association with CRP levels is stronger for fatal CAD events compared with nonfatal CAD events. The latter may imply a pathological role for either CRP itself or inflammation in general in promoting more severe cardiovascular events, associated with an increased propensity of fatal events.

**Table 4.** Hazard Ratios for Cardiovascular Events According to CRP Concentrations

<table>
<thead>
<tr>
<th>CRP Quartiles</th>
<th>1 (&lt;0.80 mg/L)</th>
<th>2 (0.8–1.6 mg/L)</th>
<th>3 (1.6–3.3 mg/L)</th>
<th>4 (&gt;3.3 mg/L)</th>
<th>( P ) Value*</th>
<th>CRP†</th>
<th>( P ) Value ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Fatal events (n=833)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Unadjusted model</td>
<td>1.00</td>
<td>1.67 (1.27–2.11)</td>
<td>2.93 (2.27–3.77)</td>
<td>5.08 (3.99–6.48)</td>
<td>&lt;0.001</td>
<td>1.67 (1.57–1.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted model</td>
<td>1.00</td>
<td>1.04 (0.79–1.39)</td>
<td>1.41 (1.08–1.84)</td>
<td>2.16 (1.66–2.80)</td>
<td>&lt;0.001</td>
<td>1.36 (1.27–1.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonfatal events (n=2082)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted model</td>
<td>1.00</td>
<td>1.56 (1.35–1.81)</td>
<td>2.17 (1.88–2.49)</td>
<td>2.90 (2.53–3.33)</td>
<td>&lt;0.001</td>
<td>1.42 (1.36–1.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted model</td>
<td>1.00</td>
<td>1.12 (0.96–1.31)</td>
<td>1.31 (1.13–1.52)</td>
<td>1.61 (1.39–1.88)</td>
<td>&lt;0.001</td>
<td>1.21 (1.15–1.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Fatal events (n=49)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Unadjusted model</td>
<td>1.00</td>
<td>0.95 (0.33–2.70)</td>
<td>2.63 (1.10–6.25)</td>
<td>2.43 (1.00–5.91)</td>
<td>0.026</td>
<td>1.59 (1.24–2.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted model</td>
<td>1.00</td>
<td>0.65 (0.23–1.88)</td>
<td>1.54 (0.62–3.79)</td>
<td>1.24 (0.48–3.24)</td>
<td>0.277</td>
<td>1.34 (1.00–1.79)</td>
<td>0.048</td>
</tr>
<tr>
<td>Nonfatal events (n=312)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Unadjusted model</td>
<td>1.00</td>
<td>1.55 (1.06–2.27)</td>
<td>2.01 (1.39–2.89)</td>
<td>2.88 (2.03–4.10)</td>
<td>&lt;0.001</td>
<td>1.38 (1.23–1.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted model</td>
<td>1.00</td>
<td>1.01 (0.67–1.49)</td>
<td>1.06 (0.72–1.55)</td>
<td>1.32(0.98–1.94)</td>
<td>0.297</td>
<td>1.10 (0.98–1.25)</td>
<td>0.118</td>
</tr>
<tr>
<td><strong>Peripheral artery disease</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Fatal events (n=14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted model</td>
<td>1.00</td>
<td>1.91 (0.17–21.1)</td>
<td>1.96 (0.18–21.6)</td>
<td>9.72 (1.23–76.7)</td>
<td>0.017</td>
<td>1.86 (1.19–2.92)</td>
<td>0.007</td>
</tr>
<tr>
<td>Adjusted model</td>
<td>1.00</td>
<td>1.34 (0.12–15.0)</td>
<td>1.13 (0.10–13.1)</td>
<td>4.35 (0.49–33.5)</td>
<td>0.182</td>
<td>1.48 (0.86–2.53)</td>
<td>0.153</td>
</tr>
<tr>
<td>Nonfatal events (n=643)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted model</td>
<td>1.00</td>
<td>1.59 (1.17–2.15)</td>
<td>2.93 (2.22–3.87)</td>
<td>4.39 (3.36–5.74)</td>
<td>&lt;0.001</td>
<td>1.59 (1.49–1.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted model</td>
<td>1.00</td>
<td>1.21 (0.88–1.65)</td>
<td>1.82 (1.36–2.43)</td>
<td>2.48(1.85–3.32)</td>
<td>&lt;0.001</td>
<td>1.36 (1.26–1.48)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted model: Adjusted for age, sex, body mass index, smoking status, systolic blood pressure, LDL cholesterol, HDL cholesterol, diabetes mellitus, and hormone replacement therapy. CRP indicates C-reactive protein; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

* \( P \) value for linear trend across CRP quartiles.
†Hazard ratios and corresponding 95% confidence intervals per 1 mg/L CRP increase. CRP values were log transformed before analysis.
‡ \( P \) value corresponding to CRP as log-transformed continuous variable.

**Figure 1.** Event (fatal or nonfatal)-free survival curves for coronary artery disease (A), stroke (B), and peripheral artery disease (C) stratified by baseline C-reactive protein quartiles. In each panel, the inset shows the same data on an enlarged \( y \) axis. Displayed \( P \) values were calculated using a log-rank test.
Several publications have reported an association between CRP levels and major cardiovascular events in patients with PAD.22–24 However, data on the association between CRP levels and risk of future peripheral vascular disease are scarce. Only a few studies have reported data on this outcome with relatively few cases compared with similar studies reporting coronary and cerebrovascular endpoints. One nested case–control study reported a relative risk of PAD of 2.8 (95% CI, 1.3–5.9) for people in the highest CRP quartile compared with the lowest CRP quartile.25 Of the 1519 healthy individuals in the Edinburgh Artery Study, 208 subjects developed symptomatic PAD. CRP was significantly \( (P < 0.01) \) associated with PAD, with a corresponding HR of 1.30 (95% CI, 1.1–1.6). 26 Our finding of an association between CRP levels and fatal PAD events requires the following considerations. There were only few fatal PAD events, limiting the statistical power for such an analysis. Also, the combined group of PAD diseases was diagnosed on the basis of International Classification of Diseases, Tenth Revision codes I70 to I73, which may have included several cases of nonatherosclerotic diseases, such as Raynaud disease or vasculitis. Although we expect the number of such diagnoses to be low compared with atherosclerotic PAD, we cannot exclude the possibility that this may have confounded the PAD results.

Our observation that CRP levels are more strongly associated with fatal CAD events compared with nonfatal CAD events is underlined by the observation that CRP adds more discriminative power to the fatal compared with the nonfatal predictive risk model as demonstrated by the comparative predictive risk analyses. These findings may have different explanations. First, inflammation in general can promote more serious atherothrombotic reactions comprising thrombosis, endothelial dysfunction, and vasoconstriction, thereby increasing the likelihood of a fatal outcome following plaque rupture.27–30 In line, serum levels of inflammatory markers obtained during an acute setting are associated with an adverse outcome.30 These findings are corroborated by association studies showing that cardiovascular mortality is increased after an acute respiratory tract infection or urinary tract infections in the general population with odds ratios up to 4-fold in the first 2 weeks after the infective episode31 and data suggesting an activation of the coagulation system by inflammatory cytokines.32 Second, our findings are also compatible with the hypothesis that in the case of an acute coronary syndrome, CRP contributes to a more severe outcome by aggravating myocardial cell death and contributing to a wider area of tissue loss. This concept is supported by studies reporting that CRP as well as CRP-complement complexes accumulate in infarcted human myocardium.33,34 CRP bound to ischemic cardiomyocytes has been shown to recruit complement factor 1a and thereby activate the complement system,20 and injection of human CRP into rats after ligation of the coronary artery enhanced infarct size by \( \approx 40\% \). This concept is further corroborated by the observation that in vivo complement depletion markedly reduced infarct size, even when initiated up to 2 hours after coronary ligation.19

When interpreting the results of our study, several aspects need to be taken into account. An important strength of this study is the large number of cardiovascular outcomes, and PAD outcomes in particular. However, it must be noted that

### Table 5. Cardiovascular Risk Reclassification Table Comparing Model A and Model B for Fatal and Nonfatal Events

<table>
<thead>
<tr>
<th>Model A</th>
<th>Model B (Including CRP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For fatal events</td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>6456 (94)</td>
</tr>
<tr>
<td>5%–&lt;10%</td>
<td>461 (15)</td>
</tr>
<tr>
<td>10%–&lt;20%</td>
<td>0 (0)</td>
</tr>
<tr>
<td>≥20%</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

| For nonfatal events | | |
| <5% | 4280 (95) | 220 (5) | 0 (0) | 0 (0) | 4500 | 220 (5) |
| 5%–<10% | 358 (8) | 3609 (85) | 304 (7) | 0 (0) | 4271 | 662 (15) |
| 10%–<20% | 0 (0) | 361 (8) | 4094 (86) | 290 (6) | 4745 | 651 (14) |
| ≥20% | 0 (0) | 0 (0) | 290 (7) | 3605 (93) | 3895 | 290 (7) |

Model A: adjusted for age, sex, BMI, smoking status, systolic blood pressure, LDL cholesterol, HDL cholesterol, diabetes mellitus, and hormone replacement therapy. Model B: adjusted for age, sex, BMI, smoking status, systolic blood pressure, LDL cholesterol, HDL cholesterol, diabetes mellitus, hormone replacement therapy, and CRP. BMI indicates body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.
the defined outcomes of CAD, stroke, and PAD events may have included some nonatherosclerotic events, although the number of these events is only limited. Also, no changes in lipid-lowering therapy were recorded during follow-up. Statins decrease systemic CRP levels, and the use of such medication could have altered CRP levels and the inherent cardiovascular risk.34

In summary, we confirm a strong and independent association between elevated CRP levels and an increased risk of CAD and PAD outcomes. Importantly, CRP levels were more strongly associated with the risk of fatal CAD events compared with nonfatal CAD events. This study lends further support to investigate the efficacy and safety of targeting inflammation per se for the prevention of cardiovascular events.

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Disclosures

None.

References


C-reactive protein (CRP) has been widely acknowledged as an independent risk factor for cardiovascular disease. The association between circulating CRP levels and cardiovascular disease end points are most often based on composite end points including both fatal and nonfatal events. Here, we examined a possible differential association between CRP and fatal or nonfatal events. We demonstrate that elevated levels of CRP increase the risk of more severe cardiovascular events. These results suggest that elevated levels of CRP might contribute directly to a more severe outcome of cardiovascular events. These data lend further support to investigate the efficacy and safety of targeting inflammation to reduce the severity of cardiovascular events.
C-Reactive Protein, Fatal and Nonfatal Coronary Artery Disease, Stroke, and Peripheral Artery Disease in the Prospective EPIC-Norfolk Cohort Study
Diederik F. van Wijk, S. Matthijs Boekholdt, Nicholas J. Wareham, Sara Ahmadi-Abhari, John J.P. Kastelein, Erik S.G. Stroes and Kay-Tee Khaw

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Material and methods

Study design
EPIC-Norfolk is a prospective population study of 25,639 male and female inhabitants of Norfolk, United Kingdom, aged between 39 and 79 years old. Briefly, EPIC-Norfolk is part of the 10-country collaborative EPIC study designed to investigate determinants of cancer. Additional data were obtained to enable assessment of determinants of other diseases such as CAD. At the baseline survey between 1993 and 1997, participants completed a detailed health and lifestyle questionnaire with additional data collection performed by trained nurses at a clinic visit. The study cohort was similar to UK population samples with regard to many characteristics including anthropometry, blood pressure, and lipids, but with a lower proportion of smokers. Full details of the population have been reported elsewhere.

All individuals have been flagged for mortality at the UK Office of National Statistics, with vital status ascertained for the entire cohort. The death certificates were coded by trained nosologists according to the International Classification of Diseases (ICD) 10th revision. In addition, participants were identified by using unique National Health Service number through data linkage with the East Norfolk Health Authority (ENCORE) database, which identifies all hospital contacts throughout England and Wales for residents of Norfolk. Participants were identified as having a non-fatal or fatal cardiovascular event if the corresponding ICD-10 code was recorded as the underlying cause of that hospitalization (non-fatal event) or mortality (fatal event). For the purposes of this analysis, three discrete outcome measures were considered: CAD, stroke and PAD related events. CAD events were defined by ICD-10 codes I20-25 and stroke outcomes were defined by ICD-10 codes I63 and I65-66. PAD events were defined by ICD-10 codes I70-73. We report results for follow-up through March 31st 2008. The study complies with the Declaration of Helsinki. The Norwich District Health Authority Ethics Committee approved the study and all participants gave signed informed consent.

Laboratory measurements
Non-fasting blood samples were drawn into plain and citrate bottles. Blood samples were processed directly at the Department of Clinical Biochemistry, University of Cambridge, or stored at −80°C. Serum levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured in fresh samples with the RA 1000 (Bayer Diagnostics, Basingstoke, UK). LDL-C levels were calculated using the Friedewald formula. When additional funding became available in 2010, serum concentrations of CRP were measured in all participants with available frozen baseline serum samples using a full-range, high-sensitivity assay on an Olympus AU640 clinical chemistry analyzer (Olympus UK Ltd, Watford, United Kingdom).

Statistical analysis
Study participants with missing data for CRP Levels were excluded from the current analysis. Summary data are presented as mean ± standard deviation for continuous variables with a normal distribution, median and interquartile range for continuous variables with a non-normal distribution, and percentage (number) for categorical variables. Because triglycerides and CRP were not normally distributed, these parameters were log-transformed before analysis. The Framingham risk score (FRS) was calculated using a previously reported algorithm, which takes into account age, sex, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic and diastolic blood pressure, smoking and a history of diabetes mellitus. CRP serum levels were divided into quartiles. We assessed the C statistic for all combined coronary events (CAD), stroke and PAD fatal and non-fatal events. The C statistic represents the area under the receiver operating characteristic curve (for which larger values indicate better discrimination). To further compare the performance of the models for fatal and non-fatal events we calculated the proportion of participants in the test cohort who were reclassified into either higher- or lower-risk clinical risk categories using two models. Model A was corrected for sex, age, body mass index (BMI), smoking status, systolic blood pressure,
LDL-cholesterol, HDL-cholesterol, diabetes mellitus and hormone replacement therapy. Model B was corrected for all variables of Model A with the addition of CRP as additional variable. In addition to the reclassification table the net reclassification index (NRI) and the integrated discrimination improvement (IDI) were calculated.

A Cox proportional hazards model was used to define the associations between CRP, fatal and non-fatal CAD, stroke and PAD events. Associations were expressed as hazard ratios (HR) and corresponding 95% confidence intervals (95%CI) both by CRP quartile using the lowest quartile as reference category, and by 1 mg/L increment of CRP. Individuals were censored at the time of the first occurrence of the cardiovascular event analyzed, the time of death, or the end of follow-up which was March 31st 2008, whichever came first. Cox regression models were performed according to 2 different models. The first model was unadjusted. The second model adjusted for sex, age, body mass index (BMI), smoking status, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, diabetes mellitus and hormone replacement therapy. We present uncorrected probability values and consider a multiple testing Bonferroni corrected probability value of p<0.001 significant.

To determine statistical differences between the fatal and non-fatal HR's we applied the bootstrap method with Cox regression modeling estimating the HR for log-linear transformed CRP on fatal and non-fatal endpoints for the unadjusted model and for the multivariate adjusted model. After obtaining 10,000 HR's for fatal and non-fatal events, we subtracted the HR's to calculate the differences between the fatal and non-fatal HR's. These 10,000 differences were used to generate a mean and standard deviation. A 95%CI excluding unity was considered statistically significant. All statistical analyses were performed using R (R-Project for Statistical Computing, GNU project).
References
