Combined Effects of Inflammatory Status and Carotid Atherosclerosis
A 12-Year Follow-Up Study

Florian J. Mayer, MD; Christoph J. Binder, MD, PhD; Oswald F. Wagner, MD; Martin Schillinger, MD; Erich Minar, MD; Wolfgang Mlekusch, MD; Dimitris Tsiantoulas, PhD; Georg Goliasch, MD, PhD; Matthias Hoke, MD

Background and Purpose—Inflammatory responses play a key role in atherogenesis. The aim of this study was to assess the prognostic value of hsCRP (high-sensitivity C-reactive protein) and to evaluate whether degree of carotid stenosis and serum levels of hsCRP jointly predict long-term mortality in asymptomatic patients with carotid atherosclerosis.

Methods—One thousand sixty-five patients with neurological asymptomatic carotid atherosclerosis as evaluated by duplex sonography were prospectively followed for cause-specific mortality.

Results—During a median of 11.81 years, a total of 549 deaths, including 362 cardiovascular deaths, were recorded. The risk of all-cause and cardiovascular mortality significantly increased in patients with elevated serum levels of hsCRP (the adjusted hazard ratio for cardiovascular mortality per increase of 1 mg/dL of hsCRP levels was 1.47; \( P < 0.001 \)). Patients with a high degree of carotid stenosis and increased hsCRP levels were particularly at risk of adverse outcome. Patients with carotid narrowing over 50% and hsCRP levels >0.29 mg/dL (=median) had nearly twice as high a risk of cardiovascular mortality compared with patients with carotid stenosis of <50% and hsCRP levels <0.29 mg/dL (adjusted hazard ratio 1.89; \( P < 0.001 \)). Improvement in risk stratification with combined assessment of carotid stenosis and hsCRP was confirmed by an improvement of the continuous net reclassification improvement with 18% for all-cause mortality and 15% for cardiovascular mortality compared with the degree of carotid stenosis alone (\( P < 0.01 \)).

Conclusions—Measurement of hsCRP in combination with ultrasound investigations of the carotid arteries at a single time point provides additional prognostic information for patients with asymptomatic carotid atherosclerosis.

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Key Words: biomarker • carotid atherosclerosis • carotid stenosis • C-reactive protein • risk factor
prognostic value of hsCRP for cause-specific mortality in a large prospectively collected cohort of patients with asymptomatic carotid atherosclerosis. Given the importance of inflammatory processes in atherogenesis, we further hypothesized that the degree of carotid narrowing and levels of hsCRP jointly contribute to the cardiovascular risk in these patients.

**Patients and Methods**

In this single-center study, we prospectively enrolled 1363 consecutive patients who underwent ultrasound investigations of the extracranial carotid arteries between March 2002 and March 2003. Study design, inclusion, and exclusion criteria have been published previously. Patients with prevalent atherosclerotic carotid artery disease, defined by the presence of nonstenotic plaques or carotid stenosis of any degree, who were neurologically asymptomatic at the time of screening were enrolled. Patients underwent baseline ultrasound investigation and a second ultrasound examination after 6 to 9 months. The main indications for performing ultrasound investigation were carotid bruits, prevalence of cardiovascular risk factors, and known atherosclerotic diseases in other vessel areas. Patients with current infectious, inflammatory diseases or active malignancies, symptomatic of carotid artery disease that necessitated revascularization therapy, patients having undergone bilateral carotid occlusions, bilateral stent implantation, or bilateral carotid endarterectomy, as well as patients with a myocardial infarction, stroke, coronary revascularization, or peripheral vascular surgery during the preceding 6 months, were excluded from the study. The rationale behind this was the assumption that acute cardiovascular events may affect laboratory measurements and reflect the severity of an acute situation more strongly than chronic atherosclerotic disease of the carotid artery. Cardiovascular and all-cause mortality were assessed by searching the national death register for the specific cause of death (according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision). Only the specific cause of death (eg, acute myocardial infarction) was used to categorize death as either all-cause, cardiovascular, or noncardiovascular death (Table I in the online-only Data Supplement). In 43% of deaths, the underlying cause was assessed by autopsy. The study protocol was in line with the Declaration of Helsinki and was approved by the institutional review board of the Medical University of Vienna. All patients gave their written informed consent.

**Clinical and Laboratory Data**

Every enrolled patient completed a detailed study questionnaire that was reviewed by a physician assessing the patient’s medical history, current medication, biometric data, and family history. All clinical characteristics were ascertained by 2 independent observers. Antecubital venous blood samples were drawn and analyzed directly without freezing according to local laboratory standard procedures within 2 to 4 hours of sampling. Serum levels of hsCRP were determined at admission by a high-sensitivity assay (N Latex CRP Mono, DADE Behring, IL) with a detection limit of 0.03 mg/dL and a coefficient of variation of 4.6%. Treating an inflammatory disease (N Latex CRP Mono, DADE Behring, IL) with a detection limit of 0.03 mg/dL and a coefficient of variation of 4.6%.

Levels of hsCRP were categorized in tertiles to obtain clinically useful measures for the effect sizes. Continuous data are presented as median and interquartile range (range from the 25th to the 75th percentile). Discrete data are given as counts and percentages. Analysis of variance and the χ² test were used for comparisons between tertiles, as appropriate. The log-rank test was used for comparison between groups. Event-free survival probabilities were estimated using the Kaplan–Meier method. Univariable and multivariable Cox proportional hazards models were applied to assess the association between levels of hsCRP levels and the occurrence of either all-cause or cardiovascular death, including the following variables: age (years), sex (male/female), history of myocardial infarction (binary), history of stroke (binary), peripheral arterial disease (binary), body mass index (kg/m²), hypertension (binary), diabetes mellitus (binary), serum creatinine (mg/dL), glycohemoglobin A1c (%), levels of triglycerides (mg/dL), total cholesterol levels (mg/dL), low density lipoprotein cholesterol levels (mg/dL), and statin treatment (binary). The selection of the variables was defined a priori and is based on current guidelines for cardiovascular risk prediction. All of the variables listed above were included in every multivariable Cox proportional hazard model used for this study. Results of the Cox models are presented as hazard ratios (HR; 95% confidence interval [CI]). We assessed the overall model fit using Cox–Snell residuals. We also tested the proportional hazard assumption for all covariates using Schoenfeld residuals (overall test) and the scaled Schoenfeld residuals (variable-by-variable testing). The discriminatory power of the respective variables was assessed using Harrell’s C-statistic. An improvement in individual risk prediction was examined using the net reclassification improvement. Interactions between hsCRP and degree of carotid artery stenosis were tested by entering interaction terms in the Cox proportional hazard regression models. A 2-sided P value of <0.05 was considered significant. All calculations were performed with SPSS (version 20.0, SPSS Inc) and the STATA11 software package (StataCorp) for Windows.

**Results**

A total of 1363 patients were enrolled in the study. Ninety-five (7%) of these patients had missing duplex ultrasound follow-up data, and 203 patients (16%) were lost to clinical follow-up, leaving 1065 patients for the final analysis. The 298 patients who had to be excluded did not significantly differ from the patients who were included in terms of baseline and demographic parameters (age, sex, frequency of atherothrombotic risk factors, cardiovascular comorbidities, patients’ medical history, family history, results of health assessments and physical examinations, and degree of carotid stenosis; data not shown).

An overall survival rate of 48.5% was determined for the median follow-up of 11.81 years (interquartile range, 6.01–12.43 years), corresponding to 9871 overall person-years. A total of 549 (51.5%) deaths were recorded. Of these, 362 (34.0%) patients died of cardiovascular causes, 142 (13.3%) of malignant diseases, and 45 (4.2%) of other causes (Table I in the online-only Data Supplement). The patient population comprised 668 male patients (62.7%); the median age was 69.0 years (interquartile range, 61.2–76.2 years) at the time of inclusion. Demographic and clinical characteristics of the 1065 patients included are shown in Table. The median baseline hsCRP levels were 0.29 mg/dL (interquartile range, 0.14–0.64 mg/dL); 374 (36.7%) patients had unilateral or bilateral carotid artery narrowing of >50% at enrollment.
All-Cause Mortality

Elevated levels of hsCRP were significantly associated with increased risk of all-cause death. Patients who died within the period of follow-up had significantly higher mean baseline hsCRP levels than those who survived (0.4 mg/dL versus 0.61 mg/dL; P < 0.001). In the Cox proportional hazard regression analysis, increased levels of hsCRP were significantly associated with increased risk of all-cause mortality (crude HR for an increase of 1 mg/dL of hsCRP levels 1.45 [95% CI 1.31–1.61; P < 0.001]; adjusted HR for an increase of 1 mg/dL of hsCRP levels 1.46 [95% CI 1.31–1.63; P < 0.001]). Kaplan–Meier analysis for tertiles of hsCRP levels demonstrated a significant increase in all-cause mortality with increasing hsCRP levels. The cumulative 12-year survival rates for all-cause death were 72%, 65%, and 61% in the first, second, and third tertile of hsCRP levels, respectively (log-rank P < 0.001; Figure 1). For all-cause death, adjusted HRs for increasing tertiles of hsCRP were 1.28 (95% CI 0.97–1.68) and 1.75 (95% CI 1.34–2.29, P < 0.001) compared with the first tertile (Table II in the online-only Data Supplement).

Combined Effect of Degree of Carotid Stenosis and hsCRP Levels

To assess the combined effect of carotid stenosis and hsCRP levels on long-term outcome, the patient population was stratified into 4 subgroups according to their levels of hsCRP and degree of carotid narrowing. Group 1 was defined by carotid narrowing of <50% and levels of hsCRP <0.29 mg/dL (median). Group 2 included patients with carotid narrowing <50% and hsCRP levels >0.29 mg/dL. Group 3 represented patients with carotid narrowing >50% and hsCRP levels <0.29 mg/dL, and group 4 patients with both carotid stenosis >50% and hsCRP levels of >0.29 mg/dL. The rationale behind this was that, according to current guidelines and consensus statements, carotid narrowing (assessed by sonography) <50% is considered hemodynamically insignificant and is, therefore, often referred to as carotid plaque. In addition, large epidemiological studies suggest that CRP levels above 0.3 mg/dL indicate increased cardiovascular risk.

Cardiovascular Mortality

Patients who died of cardiovascular diseases had significantly higher baseline hsCRP levels than those who survived (0.40 mg/dL versus 0.60 mg/dL; P < 0.001). Increased levels of hsCRP were significantly associated with increased risk of cardiovascular death (crude HR for an increase of 1 mg/dL of hsCRP levels 1.43 [95% CI 1.26–1.63; P < 0.001]; adjusted HR for an increase of 1 mg/dL of hsCRP levels 1.47 [95% CI 1.29–1.68; P < 0.001]). The cumulative 12-year survival rates for cardiovascular death were 72%, 65%, and 61% in the first, second, and third tertile of hsCRP levels, respectively (log-rank P < 0.001; Figure 1). For cardiovascular death, adjusted HRs for increasing tertiles of hsCRP were 1.28 (95% CI 0.97–1.68) and 1.75 (95% CI 1.34–2.29, P < 0.001) compared with the first tertile (Table II in the online-only Data Supplement).
The cumulative 12-year survival rates for all-cause death were 60% in the first, 51% in the second, 39% in the third, and 32% in the fourth group (log-rank \( P < 0.001 \); Figure 2). Adjusted HRs for the risk of all-cause death in groups 2, 3, and 4 were 1.30 (95% CI 1.03–1.65), 1.41 (95% CI 1.01–1.82), and 1.75 (95% CI 1.37–2.50; \( P < 0.001 \)), respectively, compared with the first group. Furthermore, combined assessment of degree of carotid stenosis and continuous levels of hsCRP led to a substantial improvement of the discriminatory power measured by Harrell’s C statistic for all-cause mortality (carotid narrowing >50%: 0.55 versus carotid narrowing and hsCRP: 0.60; \( P < 0.001 \)). Furthermore, an improvement in individual risk stratification with combined assessment of degree of carotid stenosis and levels of hsCRP was confirmed by a significant improvement of the continuous net reclassification improvement, with 18% for all-cause mortality (\( P = 0.004 \)) compared with degree of carotid stenosis alone.

The cumulative 12-year survival rates for cardiovascular death were 73% in the first, 68% in the second, 62% in the third, and 53% in the fourth group (log-rank \( P < 0.001 \); Figure 1 in the online-only Data Supplement). Adjusted HRs for the risk of all-cause death in groups 2 to 4 were 1.36 (95% CI 1.02–1.81), 1.29 (95% CI 0.94–1.77), and 1.89 (95% CI 1.40–2.55; \( P < 0.001 \)) compared with group 1 (Figure 3). Combined assessment of degree of carotid stenosis and continuous levels of hsCRP displayed a significant improvement in the discriminatory power for cardiovascular mortality (carotid narrowing >50%: 0.56 versus carotid narrowing and hsCRP: 0.60; \( P < 0.001 \)). Improvement in individual risk stratification with combined assessment of degree of carotid stenosis and levels of hsCRP was confirmed by a significant improvement of the continuous net reclassification improvement, with 18% for cardiovascular mortality (\( P = 0.004 \)) compared with degree of carotid stenosis alone.

Figure 1. Kaplan–Meier estimates of all-cause and cardiovascular mortality during a median follow-up time of 11.81 years (IQR, 6.01–12.43) according to tertiles of hsCRP. The log-rank test was used for comparison between groups. A, Kaplan–Meier estimates of all-cause mortality. 549 (51.5%) all-cause deaths were recorded. B, Kaplan–Meier estimates of cardiovascular mortality. 367 (34%) cardiovascular deaths were recorded. hsCRP indicates high-sensitivity C-reactive protein; and IQR, interquartile range.

Figure 2. Kaplan–Meier estimates of all-cause and cardiovascular mortality during a median follow-up time of 11.81 years (IQR, 6.01–12.43) according to degree of carotid stenosis and levels of hsCRP. Group 1 was defined by carotid narrowing of <50% and levels of hsCRP <0.29 mg/dL (median). Group 2 included patients with carotid narrowing <50% and hsCRP levels >0.29 mg/dL. Group 3 represented patients with carotid narrowing >50% and hsCRP levels <0.29 mg/dL, and group 4 patients with both carotid stenosis >50% and hsCRP levels of >0.29 mg/dL. Log-rank test for the overall comparison among groups. A, Kaplan–Meier estimates of all-cause mortality. 549 (51.5%) all-cause deaths were recorded. B, Kaplan–Meier estimates of cardiovascular mortality. 367 (34%) cardiovascular deaths were recorded. CV indicates cardiovascular death; hsCRP, high-sensitivity C-reactive protein; and IQR, interquartile range.
of hsCRP was confirmed by a significant improvement in the continuous net reclassification improvement, with 15% for cardiovascular mortality (P=0.02) compared with degree of carotid stenosis alone.

We did not observe any significant interactions between hsCRP and degree of carotid artery stenosis in regard to all-cause mortality (P value for interaction =0.40) or cardiovascular mortality (P value for interaction =0.89).

No significant association was found between the risk of noncardiovascular mortality and combined groups (data not shown).

**Discussion**

In recent decades, many aspects of the processes leading to atherosclerosis have been unraveled. There is now general agreement that atherosclerosis is a chronic inflammatory disease, which subsequently triggers robust cellular and humoral reactions that promote plaque development.25 This prominent involvement of these inflammatory responses might support the idea of using circulatory inflammatory biomarkers for cardiovascular risk prediction. C-reactive protein is a highly sensitive marker of inflammation and tissue damage and one of the most frequently measured blood parameters in clinical medicine. In acute phase responses, such as in the case of infections, levels of CRP can rise ≤1000-fold within 6 hours, making it an essential biomarker for everyday clinical diagnostic procedures. HsCRP is more precise than standard measurement of CRP and enables measurement of low levels of CRP, which is commonly found in chronic inflammation. The analysis of hsCRP is—compared with other inflammatory biomarkers—simple, automated, and routinely available at relatively low cost. Several studies suggest that an elevated hsCRP is predictive of coronary heart disease. HsCRP has been shown to be predictive of cardiovascular outcome in various patient populations with coronary heart disease26 and peripheral arterial disease,27 but few studies have investigated the association between hsCRP and long-term mortality in a prospective manner. To the best of our knowledge, this is the first study investigating the relationship between hsCRP and mortality in patients with carotid atherosclerosis. We found a significant association between levels of hsCRP and mortality in neurologically asymptomatic patients with carotid narrowing after 12 years of follow-up. After adjustment for established cardiovascular risk factors, the hazard ratio for cardiovascular mortality almost doubled when we compared participants in the top third of the group with respect to baseline hsCRP values with those in the bottom third. These effect sizes are in line with previously published data about the predictive value of hsCRP in patients with stable coronary artery disease,28 suggesting that patients with asymptomatic carotid atherosclerosis with increased inflammatory responses need to be intensely monitored by the treating physician.

A plethora of evidence suggests that the degree of inflammation correlates with the severity and outcome of patients with atherosclerotic diseases,29 whereas subclinical markers of arterial dysfunction might not improve risk prediction in these patients. Lorenz et al showed in 2012 in a meta-analysis including >36000 participants from the general population that no association between carotid intima media thickness—a marker for arterial dysfunction—and cardiovascular risk can be found30; yet, they observed a highly significant association between carotid intima media thickness and hsCRP. These findings suggest that the individual inflammatory status might be the driving force behind the development and progression of atherosclerotic plaques in subjects with arterial dysfunction. In this context, we investigated whether the individual degree of atherosclerotic burden and inflammatory status jointly contribute to the cardiovascular risk. Indeed, our prospective cohort study revealed that patients with a high degree of carotid stenosis and increased hsCRP levels are at greater risk of adverse outcomes. Nearly half of the patients enrolled in this study with carotid narrowing over 50% and hsCRP levels over 0.29 mg/dL died after 12 years of follow-up compared with only 27% of patients with carotid stenosis under 50% and hsCRP levels <0.29 mg/dL. Our findings suggest that patients who undergo ultrasound examination of the external carotid arteries at a single time point profit from an additional assessment of serum levels of hsCRP.

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*Figure 3.* Risk of all-cause and cardiovascular mortality according to groups 1 to 4. Group 1 was defined by carotid narrowing of <50% and levels of hsCRP <0.29 mg/dL (=median). Group 2 included patients with carotid narrowing <50% and hsCRP levels >0.29 mg/dL. Group 3 represented patients with carotid narrowing >50% and hsCRP levels <0.29 mg/dL, and group 4 patients with both carotid stenosis >50% and hsCRP levels of >0.29 mg/dL. Log-rank test for the overall comparison among groups. Diamonds indicate HR. The first group serves as the reference category. CI indicates confidence interval; CV, cardiovascular death; HR, hazard ratio; and hsCRP, high-sensitivity C-reactive protein.
Evidence derived from genetic and some experimental studies suggests that CRP is not likely to be involved causally in atherogenesis. However, as discussed earlier, it has been proven to be a sensitive and independent marker of chronic inflammation in patients with cardiovascular diseases. Taken together, this would suggest that an inflammation-dependent increase of CRP levels—in contrast to genetically determined elevated levels of CRP—is a prognostic marker for cardiovascular disease risk. We consider this particularly important because it suggests a crucial role for immunity and inflammation in human atherosclerosis that has been demonstrated in numerous experimental studies using animal models of atherosclerosis. However, a contribution of plaque inflammation to elevate CRP levels cannot be excluded. Further research will be necessary to elucidate whether inflammation reflected by high CRP levels is causal in atherosclerosis or whether elevated CRP levels simply reflect inflamed plaques.

Inhibiting inflammatory responses might grant us novel pharmaceutical options for atherosclerosis. In this context, new therapeutic approaches testing the idea that targeting inflammation can reduce the risk of adverse cardiovascular outcome in patients with chronic atherosclerotic diseases have been initiated. The CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) evaluates whether inhibition of interleukin-1β (a potent inflammatory cytokine) reduces major cardiovascular events in patients with advanced coronary artery disease and serum levels of hsCRP >0.2 mg/dL. The CIRT (Cardiovascular Inflammation Reduction Trial) tests whether low-dose methotrexate (20 mg per week) can reduce rates of cardiovascular events among stable post-myocardial infarction patients with type 2 diabetes mellitus or metabolic syndrome, comorbidities by high CRP levels is causal in atherosclerosis. Inflammation in patients with cardiovascular diseases. Taken from the Atherosclerene study. Eur Heart J. 2006;27:150–156. doi: 10.1093/eurheartj/ehj582.


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/content/47/12/e280.full.pdf

Data Supplement (unedited) at:
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In the article by Mayer et al, “Combined Effects of Inflammatory Status and Carotid Atherosclerosis: A 12-Year Follow-Up Study,” which published online on November 1, 2016, and appeared in the December 2016 issue of the journal (Stroke. 2016;47:2952–2958. DOI: 10.1161/STROKEAHA.116.013647), a correction is needed.

On page 2952, in the author byline, “Goliasch Georg” is changed to read, “Georg Goliasch.”

This correction has been made to the current online version of the article, which is available at http://stroke.ahajournals.org/content/47/12/2952.
SUPPLEMENTAL MATERIAL

Combined Effects of Inflammatory Status and Carotid Atherosclerosis: A 12-Year Follow-Up Study.

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Table I. Cause of death of 1065 patients.

CV (cardiovascular) and all-cause mortality were assessed by searching the national death record for the specific cause of death (according to the “International Statistical Classification of Diseases and Related Health Problems, 10th Revision”). The specific cause of death was then used to categorize death as either all-cause, cardiovascular or non-cardiovascular death. In 43% of deaths the underlying cause was assessed by autopsy.

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<th>Cause of Death</th>
<th>Number</th>
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<td>Acute myocardial infarction</td>
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<tr>
<td>Coronary Heart Disease</td>
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<tr>
<td>Heart failure</td>
<td>92</td>
</tr>
<tr>
<td>Stroke / Intracranial bleeding</td>
<td>19</td>
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<td>Aortic aneurysm</td>
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<tr>
<td>Peripheral arterial disease</td>
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<td>Diabetes mellitus (with and without complications)</td>
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<tr>
<td>Injuries</td>
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<tr>
<td>Kidney disease</td>
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<tr>
<td>Diseases of the respiratory system</td>
<td>16</td>
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<tr>
<td>Alzheimer’s Disease</td>
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<tr>
<td>Chronic hepatitis C</td>
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<td>Leukemia/Lymphoma</td>
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<td>All-Cause</td>
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Table II. Results of univariate and multivariate Cox Regression analyses. Risk for all-cause and cardiovascular mortality according to tertiles of hsCRP and combined groups. 1<sup>st</sup> Tertile includes patients with hsCRP lower than 0.2 mg/dl, 2<sup>nd</sup> Tertile patients with hsCRP levels between 0.2 to 0.5 mg/dl and the 3<sup>rd</sup> Tertile patients with hsCRP above 0.5 mg/dl. Group one was defined by carotid narrowing of lower than 50% and levels of hsCRP lower than 0.29 mg/dL (=median). Group two included patients with carotid narrowing lower than 50% and hsCRP levels above 0.29 mg/dl. Group three represented patients with carotid narrowing above 50% and hsCRP levels lower than 0.29 mg/dl and group four patients with both carotid stenosis above 50% and hsCRP levels of more than 0.29 mg/dl. The first tertile and the first group serve as the reference category. CI=confidence interval; HR = hazard ratio; hsCRP = high sensitivity C-reactive protein.
Figure I. Combined effects of serum levels of hsCRP and degree of carotid stenosis on cardiovascular mortality during a median follow-up time of 11.81 years (IQR, 6.01–12.43). A total of 367 (34%) cardiovascular deaths were recorded. Bars indicate the frequency of cardiovascular deaths according to serum levels of hsCRP and degree of carotid stenosis. CV = cardiovascular, hsCRP = high sensitivity C-reactive protein.