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Original communication

Interactions between C-reactive protein and traditional risk factors in predicting mortality of older adults

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Summary: *Background:* Elevated levels of C-reactive protein (CRP) are known to be associated with cardiovascular (CV) morbidity and mortality in older adults, however, there seems to be heterogeneity of this association across subsets of individuals. We aim to assess the effects of interactions between CRP and one of the following traditional CV risk factors regarding all-cause mortality in unselected elderly men and women: age, sex, body mass index, diabetes, and hypertension. *Patients and methods:* Three hundred and forty-four general practitioners all over Germany enrolled 6,817 unselected participants, aged 65 years or older, and performed thorough examinations, including CRP measurement at baseline (getABI study). All-cause mortality was determined in the following seven years. Cox regression analyses were done using uni- and multivariable models. *Results:* At baseline 4,172 participants of this cohort had a CRP value of ≤ 3 mg/L (low level CRP group), 2,645 participants had a CRP value of > 3 mg/L (high level CRP group). The unadjusted hazard ratio for all-cause death of the high level CRP group compared to the low level CRP group was 1.49 (95 % confidence interval [95 %CI] 1.34 to 1.66). After adjustment for sex, age, education, peripheral artery disease/media sclerosis, other prior vascular events, smoking status, diabetes, systolic blood pressure, antihypertensive medication, body mass index, cholesterol, and statin use, the hazard ratio was 1.34 (95 %CI 1.20 to 1.50). Significant interactions with CRP were found for sex (adjusted hazard ratio 1.38, 95 %CI 1.11 to 1.72), age (0.75, 95 %CI 0.60 to 0.94), and baseline systolic blood pressure (0.64, 95 % CI 0.51 to 0.81). The interactions of CRP with body mass index and of CRP with diabetes were not significant. *Conclusions:* In older German adults, there seem to be effect modifications by age, sex, and arterial hypertension regarding the effect of CRP in the prediction of all-cause mortality.

Keywords: Risk factors, CRP, interaction, mortality, older adults

Introduction

Elevated levels of C-reactive protein (CRP) are known to be associated with cardiovascular morbidity [1, 2] and mortality [3] in older adults. This association is thought to be caused by systemic inflammation leading to the initiation and progression of atherosclerosis [4]. This was most clearly seen with CRP levels of >3 mg/L [5]. However, there seems to be heterogeneity of this association across subsets of individuals raising the suspicion of interactions [6] between the effects of elevated CRP levels and other variables, such as age, sex, metabolic syndrome, diabetes, and arterial hypertension.

The effects of elevated CRP levels on cardiovascular diseases varied across different age groups [7]. The ten-year follow-up results of the Cardiovascular Health Study showed a different impact of elevated CRP levels on the incidence of coronary heart disease for men and women [8]. CRP enhanced the prognostic information of the metabolic syndrome for coronary heart disease in the West of Scotland Coronary Prevention Study [9]. CRP was a significant predictor of cardiovascular diseases in participants without diabetes, but not in patients with diabetes in the Strong Heart Study [10]. This finding was confirmed in two other studies [11, 12]. Higher CRP levels were associated with pre-clinical atherosclerosis in participants with normal blood pressure but not in those with arterial hypertension in a large Korean cohort [13].

Because study findings are heterogeneous and are still under debate, we performed a retrospective analysis of the seven-year data of the German epidemiological study on ankle brachial index (getABI), a prospective cohort study set up in October 2001 [14]. We focused on the question of interactions of elevated CRP levels with the above mentioned traditional risk factors regarding all-cause mortality in the elderly.

This study aims for assessing the impact of interactions between CRP and one of the following traditional cardio-

vascular risk factors regarding all-cause mortality in unselected elderly men and women: age, sex, body mass index (BMI), diabetes, and arterial hypertension.

Patients and methods

The getABI study is a prospective cohort study. Three hundred and forty-four general practitioners all over Germany enrolled 6,880 participants aged 65 years or older with a follow-up of seven years. A thorough physical examination including blood pressure measurement and blood sampling was performed at baseline and at the follow-up visits one, three, five, and seven years after baseline. High sensitive CRP measurements were made in a central laboratory. Details have been presented elsewhere [15].

Definition of risk factors

The diagnosis of diabetes was assumed if it was clinically diagnosed by the physician, if the HbA1c was ≥6.5% or if participants were receiving any type of oral anti-diabetic drug or insulin at baseline.

Systolic blood pressure measurements were usually obtained by a standardized Doppler ultrasonic device, preferably on the left arm. If ultrasound measurements were missing, results obtained by conventional blood pressure measurement were used. The intake of angiotensin-1 receptor antagonists, ACE inhibitors or diuretics at baseline was labelled as antihypertensive medication.

A pre-existing cardiovascular disease was assumed if there was a history of prior myocardial infarction, stroke, coronary revascularisation or revascularisation of the carotid arteries. Participants with an ankle brachial index (ABI) of >1.5 were labelled as having media sclerosis, those with an ABI of <0.9 as having peripheral artery disease (PAD). PAD was also assumed in participants with typical signs such as claudication, history of peripheral revascularisation, necrosis/gangrene, and/or limb amputation due to arterial occlusion.

A current smoker status was defined by currently smoking cigarettes with a history of one pack (20 cigarettes) per day for more than one year.

Statistical models

The characteristics of the participants with CRP values at baseline are presented descriptively.

Event rates are expressed per 1,000 person-years with corresponding 95% confidence interval (95%CI). Cox proportional hazards models are used to assess the association of risk factor interactions with all-cause mortality in the course of the seven-year follow-up. This was done for the interaction term of the CRP level (≤ 3 versus [vs] >3 mg/L) with one of the following risk factors: age (≤75 vs >75 years), sex, BMI (<30 vs ≥30 kg/m²), diabetes, and arterial hypertension (defined as systolic blood pressure at baseline ≥140 mm Hg).

Univariable as well as multivariable Cox regression analyses were used. The multivariable models comprised 13 parameters as covariates:

- sex,
- age (≤75 vs >75 years),
- education as classified by the International Standard Classification of Education (ISCED) (0–3: pre-primary up to upper secondary education vs 4–6: post-secondary, non-tertiary education up to second stage of tertiary education),
- smoking status (never or past vs currently smoking),
- BMI (<30 vs ≥30 kg/m²),
- diabetes,
- systolic blood pressure (<140 vs ≥140 mm Hg),
- antihypertensive medication,
- statin use,
- cholesterol (< 240 vs ≥240 mg/dl),
- PAD or media sclerosis (as defined above),
- pre-existing other cardiovascular conditions, and
- CRP (≤3 vs >3 mg/L).

All p-values are two-sided with a p-value of <0.05 labelled as statistically significant. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina, USA).

The getABI trial was approved by the institutional review board of the University of Heidelberg with an amendment for this post-hoc analysis by the ethics committee of the University of Bochum. The getABI trial was supported by an unrestricted educational grant from Sanofi-Aventis GmbH, Berlin, Germany (2001 to 2007) and the German Federal Ministry of Education and Research (2007 to 2010).

Results

Baseline characteristics

In the getABI study 6,880 participants were enrolled. Sixty-three of them had no (high sensitivity) CRP values determined at baseline. The remaining 6,817 participants made up the cohort for this post-hoc analysis. Of the cohort 4,172 participants (61.2%) had a CRP value of ≤3 mg/L, 2,645 participants (38.8%) had a CRP value of >3 mg/L. Baseline characteristics are shown in Table I.

CRP level and all-cause mortality

Before assessing the impact of the interactions of the CRP level (≤3 vs >3 mg/L) with other risk factors, we determined the association of CRP with overall mortality. The group of participants with a baseline CRP level of ≤3 mg/L showed 24 deaths in 1,000 patient-years compared to more than 35

deaths in the group with a CRP level of >3 mg/L (Table II). This corresponds with an unadjusted hazard ratio of elevated CRP levels for all-cause death of 1.49 (95%CI 1.34 to 1.66). After adjustment for sex, age, education (ISCED), PAD/media sclerosis, other prior vascular events, smoking status, diabetes, systolic blood pressure, antihypertensive medication, BMI, cholesterol, and statin use, the hazard ratio of elevated CRP levels (1.34, 95%CI 1.20 to 1.50) remained significant (p<0.001) (Table II).

Interactions of CRP level and traditional risk factors

Five possible CRP interactions were investigated. Significant interactions with CRP levels of >3 mg/L were found for sex, age, and baseline systolic blood pressure. The interaction term of CRP and diabetes as well as that of CRP and BMI showed no significant impact on all-cause mortality (Table III).

In the group with female participants with a baseline CRP level of ≤3 mg/L, there were 20 deaths in 1,000 patient-years compared to 25 deaths in the group with a CRP level of >3 mg/L (Table IV). By contrast, in the male participant group 29 deaths in 1,000 person-years occurred if the baseline CRP level was ≤3 mg/L compared to 53 deaths in 1,000 patient-years for those with a CRP level of >3 mg/L. This yielded an adjusted hazard ratio for the interaction term of 1.38 (95% CI 1.11 to 1.72) (Table III).

Participants younger than 75 years with a baseline CRP level of ≤3 mg/L had an event rate of 16 deaths in 1,000 patient-years compared to nearly 27 deaths in the group with a CRP level of >3 mg/L (Table V). Older participants with a CRP level of ≤3 mg/L showed a higher event rate of

Table I. Participant characteristics with CRP measures at baseline

	All participants (n=6,817)	CRP ≤3 mg/l (n=4,172)	CRP >3 mg/l (n=2645)
CRP, mean (SD)	4.5 (8.3)	1.6 (0.7)	9.2 (11.9)
Female sex, n (%)	3,945 (57.9)	2,353 (56.4)	1,592 (60.2)
Mean age, years (SD)	72.5 (5.3)	72.5 (5.3)	72.6 (5.3)
65–69 years, n (%)	2,348 (34.4)	1,433 (34.3)	915 (34.6)
70–74 years, n (%)	2,199 (32.3)	1,361 (34.3)	838 (31.7)
75+ years, n (%)	2,270 (33.3)	1,378 (33.0)	892 (33.7)
ISCED 0-3, n (%)	1,690 (24.8)	948 (22.8)	742 (28.0)
Peripheral artery diseases or mediasclerosis, n (%)	1,276 (18.7)	677 (16.2)	599 (22.6)
Other prior vascular event, n (%)	1,090 (16.0)	646 (15.5)	444 (16.8)
Current smoker, n (%)	631 (9.3)	317 (7.6)	314 (11.9)
Diabetes, n (%)	1,743 (25.6)	958 (23.0)	785 (29.7)
Systolic blood pressure ≥ 140 mm Hg (%)	4,374 (64.2)	2,603 (62.4)	1,771 (67.0)
Antihypertensive medication, n (%)	3,518 (51.6)	1,989 (47.7)	1,529 (57.8)
BMI ≥30 kg/m², n (%)	1,570 (23.0)	738 (17.7)	832 (31.5)
Cholesterol ≥ 240 mg/dl, n (%)	1,530 (22.4)	933 (22.4)	597 (22.6)
Statin use, n (%)	1,390 (20.4)	915 (21.9)	475 (18.0)

CRP: C-reactive protein; n: number; SD: standard deviation; ISCED: international standard classification of education (range 0-6); BMI: body mass index

Table II. Association between CRP and all-cause mortality

	Events n	Person-years n	Event rate per 1,000 person-years (95% CI)	Unadjusted hazard ratio (95% CI)	p-value	Adjusted* hazard ratio (95% CI)	p-value
Total	1,288	45,336	28.4 (26.9 to 30.0)	–	–	–	–
CRP ≤3 mg/l	675	28,120	24.0 (22.2 to 25.8)	Reference	–	Reference	–
CRP >3 mg/l	613	17,216	35.6 (32.8 to 38.4)	1.49 (1.34 to 1.66)	<0.001	1.34 (1.20 to 1.50)	<0.001

CRP: C-reactive protein; n: number; CI: confidence interval

* adjusted for sex, age, education (ISCED), peripheral artery disease/mediasclerosis, other prior vascular events, smoking status, diabetes, systolic blood pressure, antihypertensive medication, body mass index, cholesterol, statin use

42 deaths per 1,000 patient-years with only a slight increase of up to 54 deaths if the baseline CRP level was >3 mg/L. This corresponds to an adjusted hazard ratio of all-cause death for the interaction term of CRP and age of 0.75 (95% CI 0.60 to 0.94) (Table III). On the other hand, the absolute increase in event rates was almost the same in both age groups (11.3 vs 11.6 deaths in 1,000 person-years) (Table V).

In participants with a baseline systolic blood pressure of <140 mm Hg, a baseline CRP level of ≤3 mg/L was associated with a rate of nearly 21 deaths in 1,000 patient-years; the rate increased to more than 40 deaths in the group with a CRP level of >3 mg/L (Table VI). A baseline systolic blood pressure of ≥140 mm Hg was associated with a rate of 26 deaths per 1,000 patient-years if the CRP level was not above 3 mg/L and a relative small increase of up to 33 deaths per 1,000 patient-years if the baseline CRP level was >3 mg/L. This is in accordance with an adjusted hazard ratio of the interaction term of CRP and systolic blood pressure of 0.64 (95% CI 0.51 to 0.81) (Table III).

Table III. Interactions between CRP and one other variable (out of age, sex, diabetes, body mass index, systolic blood pressure) regarding all-cause mortality

	Adjusted* hazard ratio (95% CI)	p-value
CRP × age	0.75 (0.60 to 0.94)	0.011
CRP × sex	1.38 (1.11 to 1.72)	0.004
CRP × diabetes	1.04 (0.83 to 1.31)	0.727
CRP × body mass index	0.88 (0.68 to 1.16)	0.367
CRP × systolic blood pressure	0.64 (0.51 to 0.81)	<0.001

CRP: C-reactive protein; CI: confidence interval
* adjusted for sex, age, CRP, education (ISCED), peripheral artery disease/mediasclerosis, other prior vascular events, smoking status, diabetes, systolic blood pressure, antihypertensive medication, body mass index, cholesterol, statin use

Discussion

Over the past two decades, inflammation has proved to be a pivotal factor in the pathogenesis of atherosclerosis, especially in the initiation, growth, and complication of atherosclerotic plaques [5]. As CRP can be found in direct contact with activated complement fragments in atherosclerotic lesions and in vitro results point to a role of CRP in complement activation, CRP seems to be not only a marker of inflammation, but also an active component in human atherogenesis [16].

In this post-hoc analysis of a large German cohort with a follow-up of seven years, elevated CRP levels predicted increased all-cause mortality (adjusted hazard ratio 1.34, 95%CI 1.20 to 1.50) in older adults. Moreover, there is heterogeneity in the impact of elevated CRP levels on mortality, indicating interactions of CRP with age, sex, and elevated systolic blood pressure: elevated CRP levels had a relatively higher prognostic value in participants younger than 75 years, in males, and in participants without elevated systolic blood pressure at baseline. In general, there were effect modifications by the traditional risk factors sex, age, and systolic blood pressure. No significant heterogeneity was found for the impact of elevated CRP levels on mortality between participants with low or high BMI and between participants with or without diabetes.

The different prognostic impact of elevated CRP levels in various age groups was also reported in the Helsinki Ageing Study. In this study participants with a baseline CRP level lower or higher than 5 mg/L were compared. The prognostic value of the baseline CRP became weaker with increasing age and was only significant in the youngest group (75 years old) [3]. This result corresponds to our finding in which the relative increase in mortality rates in participants with elevated baseline CRP levels was higher in the younger subgroup. Nonetheless, the absolute increase was nearly identical in both age groups (11.3 vs 11.6 events in 1,000 person-years; Table V). This indicates that the age-related heterogeneity of the prognostic value of elevated baseline CRP is only due to the general increase of event rates in older groups and does not reflect a higher

Table IV. Impact of CRP level and gender on all-cause mortality

	Events n	Person-years n	Event rate per 1,000 person-years (95% CI)	Unadjusted hazard ratio (95% CI)	p-value	Adjusted* hazard ratio (95% CI)	p-value
Total (n = 6,817)	1,288	45,336	28.4 (26.9 to 30.0)	–	–	–	–
CRP ≤3 mg/dl and female sex (n = 2353)	327	16,121	20.3 (18.1 to 22.5)	Reference	–	Reference	–
CRP >3 mg/dl and female sex (n = 1592)	267	10,732	24.9 (21.9 to 27.9)	1.23 (1.04 to 1.44)	0.013	1.13 (0.96 to 1.33)	0.146
CRP ≤3 mg/dl and male sex (n = 1819)	348	11,999	29.0 (26.0 to 32.0)	1.45 (1.25 to 1.69)	<0.001	1.44 (1.23 to 1.68)	<0.001
CRP >3 mg/dl and male sex (n = 1053)	346	6,484	53.4 (47.7 to 59.0)	2.71 (2.33 to 3.16)	<0.001	2.25 (1.92 to 2.63)	<0.001

CRP: C-reactive protein; n: number; CI: confidence interval
* adjusted for age, education (ISCED), peripheral artery disease/mediasclerosis, other prior vascular events, smoking status, diabetes, systolic blood pressure, antihypertensive medication, body mass index, cholesterol, statin use

grade of the underlying inflammatory vascular process in younger persons. This is confirmed by results from the National Health and Nutrition Examination Survey in which no interaction between the CRP and leptin levels with age could be found [17].

Many studies have shown differences in men and women regarding the prognostic value of elevated CRP levels. In the National Health and Nutrition Examination Survey III, men with a CRP of >3.0 mg/L had increased all-cause mortality hazards compared to those with a CRP of ≤3.0 mg/L (hazard ratio 1.57, 95% CI 1.29–1.90). In women, elevated CRP values were not significantly associated with higher all-cause mortality hazards (HR 1.09, CI 0.93–1.29) [18]. Similar results were shown in the EPIC-Norfolk study in which the association between elevated CRP levels and all-cause mortality was apparent in all men, but only in those women with the highest levels of the CRP distribution [19]. Although CRP levels are lower in Japanese subjects compared with Western ones, CRP was an independent predictor of all-cause mortality in apparently healthy Japanese men but not women [20]. The reason for this gender difference needs to be elucidated.

It is well known that arterial hypertension is associated with elevated CRP levels [21]. In this cohort, a significant interaction between CRP and blood pressure values at baseline was found: an elevated CRP level nearly doubled the mortality rate in participants with normal blood pressure, whereas the mortality rate increased by less than one third in patients with high blood pressure. This result is comparable to the above mentioned finding in a large Korean cohort in which an association of a CRP level >2 mg/L with pre-clinical atherosclerosis was found in participants with normal blood pressure but not in those with arterial hypertension [13]. The pathophysiological background of this questionable association is not clearly understood.

Our results concerning the lack of an interaction between CRP levels and diabetes confirm the findings of a pooled analysis of 25,979 participants from four U.K. prospective cohort studies in which no significant interaction

Table V. Impact of CRP level and age on all-cause mortality

	Events n	Person-years n	Event rate per 1,000 person-years (95% CI)	Unadjusted hazard ratio (95% CI)	p-value	Adjusted* hazard ratio (95% CI)	p-value
Total (n = 6,817)	1,288	45,336	28.4 (26.9 to 30.0)	–	–	–	–
CRP ≤3 mg/dl and age <75 years (n = 2,794)	298	19,230	15.5 (13.7 to 17.3)	Reference	–	Reference	–
CRP >3 mg/dl and age <75 years (n = 1,753)	313	11,663	26.8 (23.9 to 29.8)	1.74 (1.49 to 2.04)	<0.001	1.56 (1.33 to 1.84)	<0.001
CRP ≤3 mg/dl and age ≥75 years (n = 1,378)	377	8,890	42.4 (38.1 to 46.7)	2.77 (2.38 to 3.23)	<0.001	2.71 (2.32 to 3.16)	<0.001
CRP >3 mg/dl and age ≥75 years (n = 892)	300	5,553	54.0 (47.9 to 60.1)	3.55 (3.03 to 4.17)	<0.001	3.18 (2.69 to 3.75)	<0.001

CRP: C-reactive protein; n: number; CI: confidence interval
* adjusted for sex, education (ISCED), peripheral artery disease/mediasclerosis, other prior vascular events, smoking status, diabetes, systolic blood pressure, antihypertensive medication, body mass index, cholesterol, statin use

Table VI. Impact of CRP level and systolic blood pressure on all-cause mortality

	Events n	Person-years n	Event rate per 1,000 person-years (95% CI)	Unadjusted hazard ratio (95% CI)	p-value	Adjusted* hazard ratio (95% CI)	p-value
Total (n = 6,817)	1,288	45,336	28.4 (26.9 to 30.0)	–	–	–	–
CRP ≤3 mg/dl and systolic blood pressure <140 mm Hg (n = 1,569)	221	10,598	20.9 (18.1 to 23.6)	Reference	–	Reference	–
CRP >3 mg/dl and systolic blood pressure <140 mm Hg (n = 874)	226	5,592	40.4 (35.1 to 45.7)	1.96 (1.63 to 2.36)	<0.001	1.79 (1.49 to 2.16)	<0.001
CRP ≤3 mg/dl and systolic blood pressure ≥140 mm Hg (n = 2,603)	454	17,522	25.9 (23.5 to 28.3)	1.25 (1.06 to 1.46)	0.007	1.12 (0.96 to 1.32)	0157
CRP >3 mg/dl and systolic blood pressure ≥140 mm Hg (n = 1,771)	387	11,624	33.3 (30.0 to 36.6)	1.60 (1.36 to 1.89)	<0.001	1.30 (1.10 to 1.54)	<0.001

CRP: C-reactive protein; n: number; CI: confidence interval
* adjusted for age, sex, education (ISCED), peripheral artery disease/mediasclerosis, other prior vascular events, smoking status, diabetes, antihypertensive medication, body mass index, cholesterol, statin use

between diabetes and CRP regarding all-cause mortality was found [22]. The same was deduced from data of the third National Health and Nutrition Examination Survey, where the interaction term for CRP and diabetes concerning all-cause mortality was not significant [17].

Finally, in this study as well as in the third National Health and Nutrition Examination Survey [17] interaction between BMI and CRP regarding all-cause mortality was not apparent. In our study the cut point was set at a BMI of 30 kg/m^2, whereas in the third National Health and Nutrition Examination Survey the cut point was 25 kg/m^2. Different results were seen in a Japanese study [23] that divided the cohort of 1,871 patients with coronary artery disease into three groups: BMI <24 kg/m^2, 24.0–27.9 kg/m^2 and ≥28 kg/m^2. Using the group with a BMI of 24.0–27.9 kg/m^2 and CRP <3 mg/L as reference, the hazard ratio was 1.16 for the group with the same BMI but with CRP values of ≥3 mg/L. The group with a BMI of <24 kg/m^2 had a hazard ratio of 0.93 if the CRP was <3 mg/L but 2.55 if the CRP was ≥3 mg/L. A similar difference was seen in patients with a BMI of ≥28 kg/m^2 who had a hazard ratio of 1.42 if the CRP was <3 mg/L compared to 3.41 if the CRP was ≥3 mg/L. Thus, a J-shaped heterogeneity could be seen that might have been missed by dichotomising the cohort as it was done in this study and in the third National Health and Nutrition Examination Survey.

The strengths of the getABI study lie in the large cohort in a primary care setting and in the effort to reduce selection bias. This was achieved by the setting the study over three pre-specified weeks, incorporating general practitioners from all parts of Germany, including about 20 primary care attendees. On the other hand, there are some limitations to the getABI study. Only persons of at least 65 years were recruited. Therefore, study results may only be applicable to this age group. The analyses of this study used single CRP measurements at baseline. Thus it is not possible to allow for regression dilution bias. However, CRP values have been shown to be fairly stable in individual patients [24] and are therefore considered suitable for long-term predictions.

Unanswered questions and future research

The most striking interaction in this analysis is seen between CRP and gender. The pathophysiological concept for this observation is still lacking. The interaction between CRP and blood pressure needs to be confirmed in further studies.

As vascular inflammation may cause plaques and promote their instability, the Cardiovascular Inflammation Reduction Trial (CIRT) investigates if low dose methotrexate, an anti-inflammatory agent which is widely used in rheumatic diseases, can reduce morbidity and mortality among patients with a coronary artery disease (NCT02576067) [25]. In case of positive results, the presence of CRP interactions might guide differential therapeutic decisions.

Conclusions

In elderly German adults, the effect of CRP in predicting all-cause mortality seems to be modified by age, gender, and arterial hypertension.

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