Strong prognostic value of C-reactive protein and albuminuria for the risk of mortality in the general population.

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Abstract

Background. Both increased C-reactive protein (CRP) and albuminuria have been found associated with an increased risk of total and cardiovascular (CV) mortality in individual studies. It has not yet been investigated whether CRP and albuminuria add to the risk of total and CV mortality.
Methods and Results. We conducted a prospective study with a median follow-up of 1709 days in the city of Groningen, the Netherlands, comprising of 8,592 men and women, aged 28-75 years old. These subjects were identified in the Prevention of Renal and Vascular Endstage Disease (PREVEND) study during 1997-1998. CRP and albuminuria levels were measured at baseline using highly sensitive methods, in addition to conventional risk factors. Crude analyses showed that both CRP and albuminuria increased and added to the absolute and relative risk of total, CV and non-CV mortality. In multivariate analyses, both CRP and albuminuria levels increased the risk of both CV and non-CV mortality (CRP: hazard ratio for CV 1.19 (95%CI 1.01-1.41) and non-CV 1.30 (1.16-1.45); albuminuria: CV 1.23 (1.09-1.39) and non-CV 1.14 (1.03-1.26) per 2-fold increase of their levels, respectively). This increased risk appeared to be independent of classical risk factors and of each other. Diabetes, elevated blood pressure and total cholesterol did not add prognostic information to the multivariate model, whereas smoking and male gender increased the risk approximately 2-fold. For both CRP and albuminuria, the increase in mortality risk was not significantly higher for CV as compared to non-CV mortality.
Conclusions. CRP and albuminuria are independent, additive risk predictors of all-cause, CV and non-CV mortality among subjects in the general population. Both markers provide more information about CV risk than conventional risk factors alone.

Introduction

C-reactive protein (CRP), the prototypic acute-phase protein, predicts cardiovascular (CV) morbidity and mortality in high-risk patient groups,[1,2] type 2 diabetes mellitus[3] and the general population.[4-10] Increased levels of albuminuria have been shown to predict CV disease among subjects with either diabetes or hypertension, and in the elderly.[11-15] We showed that albuminuria is an independent predictor of mortality in the general population, which was more attributable to CV than to non-CV causes.[16] Both CRP and albuminuria may thus serve as a screening tool in the general population to improve the identification of subjects at increased risk of death.

It is widely assumed that CRP represents the inflammatory component of the process of atherosclerosis in the arterial vessel wall.[17] The commonly held view is that albuminuria reflects

generalized endothelial dysfunction along the vascular tree.[18] Since CRP and albuminuria represent closely related pathophysiological pathways of the same disease process, one might anticipate that the association of either marker with mortality is, more or less, explained by the other. Interestingly, in a cross-sectional study, we recently found that CRP and albuminuria are differently associated with manifestations of disease in various vascular beds, like the heart, the kidney, and peripheral arteries.[19] Prospective data concerning the relative contribution of CRP and albuminuria to the risk of CV versus non-CV mortality in the general population are yet not available.

Therefore, we questioned whether CRP and albuminuria independently add to the risk of all-cause, CV and non-CV mortality, and independently of classical risk factors. Second, we questioned whether these risk markers are more specifically related to CV than to non-CV mortality. Finally, we investigated possible effect-modification by albuminuria on the relation between CRP and mortality, and vice versa.

Methods

Population and design

PREVEND is the acronym of Prevention of REnal and Vascular ENd stage Disease study, which is designed to prospectively investigate the natural course of urinary albumin excretion and its relation to renal and CV disease in a large cohort drawn from the general population. Details of this study have been described elsewhere.[20,21] In short, in 1997-1998, all inhabitants of the city of Groningen were sent a short questionnaire on demographics and cardiovascular morbidity and a vial to collect an early morning urine sample. Altogether, 40,856 subjects responded (47.8%). Pregnant women and diabetic subjects using insulin were excluded. All participants with a urinary albumin concentration >10 mg/L (n=7,768) were invited to our outpatient clinic together with a random sample of subjects with a urinary albumin concentration <10 mg/L (n=3,395). The study population comprised of 8,592 subjects who completed the total screening program.

The screening program consisted of two visits. Shortly, the first visit comprised of anthropometric measurements (height, weight, waist circumference), blood pressure measure-ments each minute during 10 minutes in supine position, ankle pressure measurements and the evaluation of a self-administered questionnaire by a trained nurse. This questionnaire included renal, CV and oncological morbidity, and data on the use of anti-hypertensive, lipid lowering medication and anti-diabetic medication. The second visit comprised of electrocardiographic recordings, blood pressure measurements each minute during 8 minutes and fasting blood samples were drawn. Subjects were asked to collect two times 24 hours urine samples as described before.

All participants gave written informed consent. The PREVEND study was approved by the local medical ethics committee and was conducted in accordance with the guidelines of the Declaration of Helsinki.

Definitions, calculations and exclusion

Blood pressure data are based on the average of four blood pressure values: i.e. the last two blood pressure values of both visits. Body mass index (BMI) was calculated as the ratio of weight and height squared (kg/m^2). Type 2 diabetes was defined as a fasting glucose level of >7.0 mmol/L or a non-fasting glucose level >11.1 mmol/L or the use of anti-diabetic drugs. Smoking was defined as current smoking. Histories of myocardial infarction or cerebrovascular disease were considered present if a participant reported having been hospitalized for at least 3 days because of these conditions. Peripheral artery disease was defined as an ankle-brachial index <0.9 in at least one leg and/or prior arterial surgery of the lower limbs.

Creatinine clearance was calculated as the mean creatinine clearance of two urine collections with and without correction for body surface area as an estimate of glomerular filtration rate (GFR). We validated the relation between GFR and mortality with renal function equations commonly used in population-based studies: the Cockcroft-Gault and the simplified MDRD formula (Modification of Diet in Renal Disease). We used creatinine clearance per body surface area in the final analysis, since indexed or non-indexed GFR estimates yielded similar results.

Urinary albumin measurements were considered unreliable in 451 subjects with either leukocyturia or erythrocyturia (erythrocytes >50 cells mm^3 or leukocytes >75 cells mm^3, or leukocytes = 75 cells mm^3 and erythrocytes >5 cells mm^3). In 415 cases, CRP levels could not be measured. Thus, 7,726 subjects were eligible for analysis.

Laboratory methods

Urinary albumin concentrations were determined by nephelometry with a threshold of 2.3 mg/L and intra- and inter-assay coefficients of variation of less than 2.2% and 2.6%, respectively (Dade Behring Diagnostic, Marburg, Germany). High sensitive CRP was also determined by nephelometry with a threshold of 0.175 mg/L and intra- and inter-assay coefficients of less than 4.4% and 5.7%, respectively (BNII N, Dade Behring, Marburg, Germany). Plasma glucose and serum cholesterol were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, New York, U.S.A.). Urinary leukocyte and erythrocyte measurements were done by Nephur-test+leuco sticks (Boehringer Mannheim, Mannheim, Germany).

Mortality data

From the time of recruitment, the vital status of all participants was evaluated through the municipal register. The cause of death was obtained by linking the number of the death certificate to the primary cause of death as coded by a physician from the Central Bureau of Statistics. Causes of death were coded according to the 10th revision of the International Classification of Diseases (ICD-10). Cause-specific events used in the analysis were CV disorders (ICD-10 codes I01-I99), and the remaining codes were those from non-CV causes (malignancies: C00.0-D48.9, and the remainder categories).

Survival time for the participants was defined as the period from the date of the first screening in the outpatient clinic until the date of death or the 31st of December 2002. If a person had moved to an unknown destination, the person was censored on the last available date.

Statistical analysis

We fitted Cox proportional hazard models to evaluate the effect of albuminuria and CRP on mortality. The proportional hazard assumption was assessed for every predictor variable using graphical approaches. The log-log-survival curve was found constant over time for each parameter. Both CRP and albuminuria showed a log-linear functional shape with the response variable and were transformed to a 2-log scale. This means that risk estimates should be interpreted as the relative risk if values of CRP or albuminuria were doubled (e.g. 1 to 2 mg/L or 10 mg/24h to 20 mg/24h).

Our cohort consisted of a random sample of control subjects and a selected sample of subjects with <10 mg/L and >10 mg/L of albumin in their urine. Therefore, risk estimates were calculated by adding the selection parameter as a confounder in stratified analysis. The addition of this selection parameter did not influence the results essentially.

Two competing death causes were distinguished: CV and non-CV. We used competing risk analyses which allowed us to compare the effects of explanatory variables on either CV or non-CV death.[22] Models are presented as crude and age/gender adjusted risks of mortality. From the final multivariate model, we calculated relative hazards and cumulative incidences across continuous, and 25th and 75th percentile levels of CRP and albuminuria on CV mortality, respectively. Results are summarized by hazard (risk) ratios with 95% confidence intervals (95%CI). A value of $P<0.05$ (2-sided) was used as the nominal level of statistical significance. We used the statistical packages SPSS 10.0 (Chicago, IL, USA) and SAS 8.2 (Cary, NC, USA) for the analysis.

Results

Population characteristics

During a median follow-up of 1709 days (maximum 1933 days), 214 subjects died among a total of 7,726 subjects. As indicated by the death certificates, sixty-five subjects were classified as CV mortality cases and 149 as non-CV mortality cases.

Table 1 shows the baseline characteristics of all 7,726 participants according to their survival status. Compared to the subjects who survived, those who died had a higher baseline prevalence of an elevated CRP (>3 mg/L) as well as a higher prevalence of high-normal albuminuria (15-30 mg/24h), microalbuminuria (30-300 mg/24h) and macroalbuminuria (>300 mg/24h) (all $P<0.001$). Compared to non-CV mortality, those who died from CV causes had a higher baseline level of albuminuria and a higher prevalence of micro- and macroalbuminuria ($P<0.001$), whereas the baseline level and prevalence of an elevated CRP did not significantly differ between the two competing death causes.

Compared to the subjects who survived, those who died had a higher baseline prevalence of all CV risk factors. Compared to non-CV mortality, subjects who died from CV causes were older and more likely to be male. They had a higher mean BMI, waist circumference, systolic and diastolic blood pressure, a lower creatinine clearance per BSA and a higher prevalence of cerebrovascular disease (all $P<0.05$).

C-reactive protein, albuminuria and mortality

Table 2 shows the crude incidence rates per 1,000 persons-years for all-cause, CV and non-CV mortality stratified by categories of albuminuria and CRP. At every level of CRP, increasing levels of albuminuria contributed to an increased absolute risk of all-cause, CV and non-CV mortality, and vice versa. The rate ratios were found homogeneous across CRP and albuminuria groups (all P values>0.05). This observation suggests an additive relationship of CRP and albuminuria to the crude risk of mortality.

Table 3 summarizes the crude and age/gender adjusted results of the Cox proportional hazard model using competing risk analyses. When adjusted for age and gender, a doubling of CRP and albuminuria increased the odds of CV as well as non-CV mortality (CRP: CV 1.40 and non-CV 1.29; albuminuria: CV 1.38 and non-CV 1.13, respectively). CRP appeared equally predictive for CV as for non-CV mortality (P_{CV}=0.36), whereas albuminuria was more specifically related to CV death (P_{CV}=0.005). Inclusion of other risk parameters in the regression model slightly attenuated the relationship between CRP, albuminuria and the risk of mortality (Table 4). In this multivariate

Table 1. Population characteristics according to survival status.

	Overall	Alive	CV death	Non-CV death
Subjects, N	7,726	7,512	65	149
C-reactive protein, mg/L	1.3 (0.6-2.9)	1.2 (0.5-2.9)†	2.7 (1.8-6.6)	2.4 (1.2-7.1)
Elevated CRP, %[a]	24.1	23.9†	47.8	43.2
Albuminuria, mg/24h	9 (6-17)	9 (6-17)†	37 (11-77)‡	16 (9-40)
High-normal albuminuria, %[b]	14.7	14.6†	16.9	18.8
Microalbuminuria, %[b]	12.8	12.2†	42.3‡	31.0
Macroalbuminuria, %[b]	1.4	1.3†	11.3‡	3.3
Age, year	49 (13)	49 (12)†	65 (9)‡	62 (11)
Male gender, %	51.6	51.1†	80.3‡	63.5
Body mass index, kg/m^2	26.1 (4.2)	26.1 (4.3)†	27.6 (3.7)‡	26.3 (4.0)
Waist circumference, cm, M	94 (11)	94 (11)†	101 (10)‡	96 (11)
Waist circumference, cm, F	83 (13)	83 (13)†	94 (11)‡	86 (12)
Systolic BP, mmHg	129 (20)	129 (20)†	150 (24)‡	139 (25)
Diastolic BP, mmHg	74 (10)	74 (10)†	81 (10)‡	78 (10)
Anti-hypertensive use, %	11.9	11.5†	32.4	23.3
Cholesterol, mmol/L	5.6 (1.1)	5.6 (1.1)†	5.9 (1.2)	6.0 (1.2)
Lipid lowering therapy, %	4.5	4.3†	14.9	8.2
Glucose, mmol/L	4.9 (1.2)	4.9 (1.2)†	5.2 (1.1)	5.2 (1.2)
Diabetes, %	3.8	3.6†	9.9	9.0
Current smoking, %	34.2	33.9†	43.7	44.9
Creatinine clearance, ml/min/1.73m^2	103	103†	85‡	92
Myocardial infarction, %	3.1	2.9†	21.4	12.4
Peripheral artery disease, %	5.9	5.6†	22.2	17.1
Cerebrovascular disease, %	0.6	0.6†	8.7‡	1.3
Malignancy, %	1.5	1.4†	4.2	3.8

Means (standard deviation) and medians (interquartile range) are given for variables with Gaussian and non-Gaussian distributions, respectively. CV = cardiovascular. BP = blood pressure. M = Male. F = Female. a) An elevated CRP is defined as a CRP level >3 mg/L. b) High-normal albuminuria is defined as a urinary albumin excretion of 15-30 mg/24h, microalbuminuria 30-300 mg/24h and macroalbuminuria >300 mg/24h. † Alive versus CV death ($P<0.05$) ‡ CV versus non-CV death ($P<0.05$).

Table 2. Stratified crude incidence rates, defined as cases per 1,000 person-years, for all-cause, CV and non-CV mortality by albuminuria and C-reactive protein.

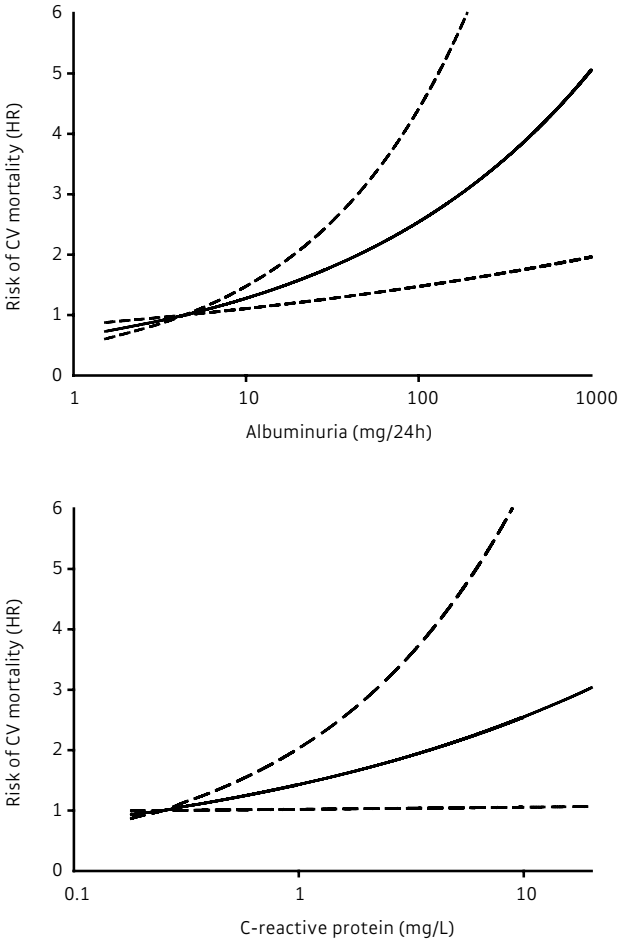
CRP	All-cause mortality		CV mortality		Non-CV mortality	
	UAE 0-30	*UAE >30*	*UAE 0-30*	*UAE >30*	*UAE 0-30*	*UAE >30 mg/24h*
0.2-0.6 mg/L	1.4 (0.7-3.3)	4.4 (1.8-10.6)	0.3 (0.1-1.1)	0.6 (0.1-4.4)	1.1 (0.6-2.2)	3.8 (1.7-8.4)
0.6-1.2 mg/L	2.8 (1.5-5.2)	9.3 (5.2-14.2)	0.5 (0.1-1.4)	3.1 (1.5-6.5)	2.3 (1.4-3.8)	6.2 (3.7-10.4)
1.2-2.7 mg/L	4.0 (2.5-7.0)	13.8 (8.9-21.4)	0.8 (0.4-2.0)	5.7 (3.5-9.2)	3.2 (2.1-5.0)	8.1 (5.4-12.2)
> 2.7 mg/L	6.9 (4.5-10.9)	17.8 (12.4-25.1)	1.5 (0.8-3.1)	7.0 (4.6-10.0)	5.4 (3.7-7.8)	10.8 (7.8-15.1)
MH	0.73		0.95		0.63	

CV = cardiovascular. UAE = urinary albumin excretion (albuminuria). MH = Mantel-Haenszl test of homogeneity (*P* value) Crude incidence rates (95% confidence interval) are stratified by different levels of albuminuria and CRP. A non-significant *P* value for the homogeneity test indicates that the relative increase of mortality rates (=rate ratio) with increasing CRP levels does not differ between the UAE 0-30 mg/24h and UAE 30+ mg/24h groups.

analysis, a doubling of CRP was associated with a 1.19 (1.01-1.41) higher risk of CV mortality, whereas a doubling of albuminuria was associated with a 1.23 (1.09-1.39) higher risk of CV mortality. The discriminative power of albuminuria to CV relative to non-CV mortality was lost in the multivariate model (P_{CV}=0.31), although the point estimate of CV mortality (HR 1.23) was higher than the risk of non-CV mortality (HR 1.14). A significant interaction between CRP and albuminuria with the risk of CV mortality could not be observed (*P*=0.28).

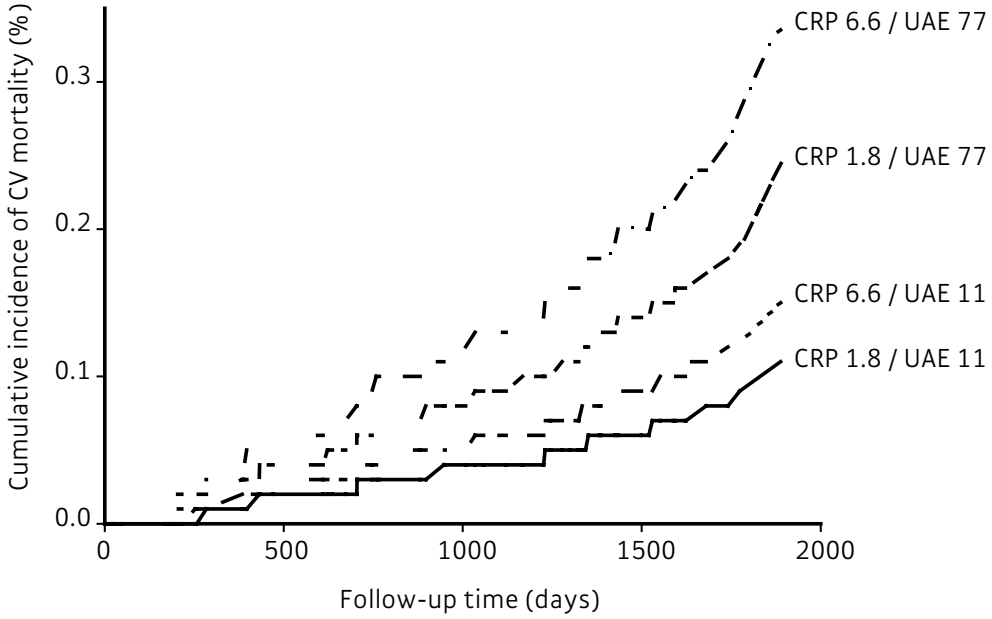
Table 3 and 4 show all risk factors, including CRP and albuminuria, in ranking order according the magnitude of the Wald statistic of CV death. In the multivariate model, albuminuria showed a higher Wald statistic than CRP (11.2 versus 3.8). Since the Wald is directly related to the precision of the regression coefficient, the effect of albuminuria on CV mortality is more precise than CRP which is expressed by the smaller confidence intervals. The estimated risks and Wald statistic of albuminuria were found equal if we either implemented the first or second sample or the mean of two urinary samples in the model. The calculated risks (95%CI) of CV mortality across levels of CRP and albuminuria are graphically depicted on a continuous scale in figures 1a and 1b. Among the conventional risk factors, diabetes, increased blood pressure, and cholesterol levels did not significantly add prognostic information to the risk of CV death, whereas smoking and male gender increased the risk of CV death approximately 2-fold. Also, baseline cerebrovascular disease, GFR and waist circumference added prognostic information to the risk of CV death. With respect to non-CV death, age, CRP, smoking, waist circumference (inversely), and albuminuria

Figure 1a, 1b. Relative hazards of cardiovascular mortality across continuous levels of albuminuria (1a) and C-reactive protein (1b).



Relative hazards of cardiovascular mortality across continuous levels of albuminuria (1a) and C-reactive protein (1b). The lines indicate the estimated hazard ratios (95%CI, dotted lines) according to the regression coefficients in table 4. The 95%CI's cross, since the reference value is set at the 10th percentile of the CRP as well as the albuminuria distribution

Figure 2. Cumulative incidence of cardiovascular mortality across percentile level of albuminuria and C-reactive protein.



This figure represents the cumulative incidence (%) of cardiovascular mortality across percentile values (25^{th}, 75^{th}) of both albuminuria and C-reactive protein for nondiabetic, nonhypertensive, nonhyperlipidemic, nonsmoking, 50-year old males with no history of myocardial infarction or stroke. In this figure, the 25^{th} and 75^{th} percentile values of CRP and albuminuria correspond to the CRP and albuminuria distribution of the subjects who died from CV causes. UAE = urinary albumin excretion (=albuminuria).

were identified as independent predictors (in ranking order: Wald 73.6, 21.8, 8.5, 7.2 and 6.5, respectively, not shown).

To show the additive effects of CRP and albuminuria within the currently used reference ranges, cumulative incidence functions using the multivariate Cox model were calculated for the combined 25^{th} and 75^{th} percentile CRP/albuminuria values of the mortality cases (Figure 2). The curves represent the cumulative incidence functions of CV mortality for a non-hypertensive, non-hyperlipidemic, non-diabetic, non-smoking 50-year-old male without a history of myocardial infarction or stroke. The 5-years cumulative incidence of CV mortality is estimated ~0.1% in subjects with low CRP/low albuminuria levels and ~0.35% in subjects with high CRP/high albuminuria levels.

Discussion

In this study, we have shown the independent, additive value of CRP and albuminuria with respect to the risk of all-cause, CV and non-CV mortality in the general population. The relative risks and cumulative incidences of CV death are comparable with increasing levels of both markers, although albuminuria provides a more accurate marker of CV death relative to CRP. The risks of death conveyed by elevated CRP and albuminuria levels were not significantly more attributable to death from CV causes than to death from non-CV causes. The data support earlier findings that CRP and albuminuria levels within clinically used reference limits already increase the risk of death.

This is the first study to show the independent contribution of CRP and albuminuria to the risk of CV death in the general population. Our results are in line with an earlier report, which described the independent relation of both markers with the risk of CV mortality in type 2 diabetes.[3] Our results clearly extend results from individual studies relating either CRP or albuminuria with CV mortality, which suggested independent contributions of both markers beyond conventional risk factors in types of populations.[1-11] We show that the risk conveyed by CRP and albuminuria goes beyond the risk held by conventional risk factors used in (absolute) risk scores: hypertension, hyperlipidemia, smoking and diabetes.[23] Regarding the strength of association of CRP and albuminuria with the short-term risk of mortality in our study, both markers may add prognostic information in risk scores in the primary prevention of CV death.

Ridker *et al* already proposed CRP as a potential adjunct in global risk assessment in the primary prevention of CV disease.[24] Regarding the strong and independent role of albuminuria in CV risk prediction, the same proposition can be made for albuminuria. Just recently, the JUPITER study group has initiated a clinical trial with a statin aimed at reducing CV endpoints in subjects with elevated CRP, but normal lipid levels.[25] Since pharmacological intervention in diabetic subjects with microalbuminuria has clearly shown renal and cardiovascular benefit,[26-28] such albuminuria-targeted intervention may also show benefit in primary prevention of CV disease and mortality. Recent data from the PREVEND-IT study show that such a protection may well apply to the general population as well (abstract: Asselbergs *et al*, Circulation 2004).

Only recently, a large case-control study by Danesh *et al* showed a significant, but moderate predictive performance of CRP to the risk of coronary heart disease.[29] In contrast to our study and studies performed by Ridker *et al*,[30] blood pressure and especially total cholesterol appeared better predictors of coronary heart disease than CRP. Reasons for these inconsistencies remain elusive.

Our results also add to our knowledge concerning the pathophysiological role of inflammation and endothelial dysfunction in CV disease progression. The precise mechanism by

Table 3. Cause-specific hazard ratios: crude, age and gender adjusted Cox regression models.

		Crude models			Age and gender adjusted models				
Risk factor	CV / non-CV	HR	95%CI	*P*	HR	95%CI	*P*	P_{cv}	Wald[a)]
Albuminuria (doubling)	CV	1.57	1.42-1.73	<0.001	1.38	1.23-1.54	<0.001	0.005	32.2
	Non-CV	1.33	1.22-1.44	<0.001	1.13	1.03-1.24	0.01		
C-reactive protein (doubling)	CV	1.54	1.33-1.77	<0.001	1.40	1.21-1.64	<0.001	NS	18.9
	Non-CV	1.43	1.30-1.57	<0.001	1.29	1.16-1.43	<0.001		
Cerebrovascular disease (yes)	CV	13.1	5.72-32.8	<0.001	9.73	3.99-24.3	<0.001	0.03	23.7
	Non-CV	2.09	0.52-8.45		1.52	0.38-6.16			
Systolic BP (per 5 mmHg)	CV	1.19	1.15-1.25	<0.001	1.10	1.04-1.15	<0.001	<0.001	13.3
	Non-CV	1.10	1.07-1.14	<0.001	0.99	0.95-1.02			
Myocardial infarction (yes)	CV	7.89	4.29-14.5	<0.001	2.94	1.58-5.46	<0.001	NS	11.7
	Non-CV	4.17	2.51-6.93	<0.001	1.56	0.93-2.62			
Peripheral artery disease (yes)	CV	4.56	2.46-8.45	<0.001	2.74	1.48-5.10	0.001	NS	10.2
	Non-CV	3.04	1.93-4.80	<0.001	1.84	1.16-2.91	0.01		
Waist circumference (per 5 cm)	CV	1.31	1.20-1.42	<0.001	1.18	1.07-1.31	0.001	<0.001	10.2
	Non-CV	1.10	1.04-1.16	0.001	0.92	0.86-0.99	0.04		
Smoking (yes)	CV	1.43	0.88-2.34		2.01	1.23-3.30	0.006	NS	7.7
	Non-CV	1.49	1.08-2.06	0.02	2.09	1.50-2.90	<0.001		
GFR (per 5 ml/min/1.73m^2)	CV	0.82	0.77-0.87	<0.001	0.89	0.83-0.94	<0.001	0.008	7.1
	Non-CV	0.89	0.86-0.93	<0.001	0.98	0.94-1.02			
Diastolic BP (per 5 mmHg)	CV	1.36	1.22-1.52	<0.001	1.17	1.03-1.32	0.01	0.01	6.3
	Non-CV	1.17	1.08-1.26	<0.001	0.97	0.89-1.06			

Risk factor	CV / non-CV	HR	95%CI	P	HR	95%CI	P	P_{CV}	Wald[a)]
Glucose (per 1 mmol/L)	CV	1.13	1.00-1.28	0.05	0.99	0.84-1.17		NS	0.9
	Non-CV	1.13	1.04-1.22	0.003	0.99	0.89-1.10			
Diabetes (yes)	CV	2.92	1.33-6.40	0.008	1.47	0.67-3.24		NS	0.3
	Non-CV	2.52	1.45-4.38	0.001	1.27	0.73-2.22			
Body mass index (per 5 kg/m^2)	CV	1.38	1.10-1.73	0.006	1.15	0.87-1.54		0.05	0.3
	Non-CV	1.08	0.90-1.30		0.80	0.65-1.00	0.05		
Anti-hypertensive use (yes)	CV	3.18	1.88-5.39	<0.001	1.42	0.84-2.42		NS	0.2
	Non-CV	2.27	1.56-3.30	<0.001	1.01	0.69-1.49			
Lipid lowering therapy (yes)	CV	3.11	1.48-6.54	0.003	1.61	0.77-3.40		NS	0.2
	Non-CV	1.61	0.85-3.07	0.15	0.84	0.44-1.61			
Cholesterol (per 1 mmol/L)	CV	1.22	1.00-1.48	0.05	1.01	0.81-1.26		NS	0.0
	Non-CV	1.27	1.12-1.44	<0.001	1.07	0.92-1.24			

P_{CV} = CV versus non-CV mortality. a) In ranking order, the Wald is the value of the Wald statistic of the age and gender adjusted risk of CV mortality.b) GFR is expressed as the mean of two creatinine clearances corrected for body surface area.

which CRP and albuminuria increase the risk is not clear. Since CRP and albuminuria have been suggested to reflect intimately related processes in atherosclerotic vascular disease, we had expected to find that the association between each marker and death would be attenuated by the other. However, each parameter explained only a minor part of variance of the other. How can we explain this relative independence of both markers? A few issues need to be addressed.

First, the general opinion that CRP reflects the low-grade inflammation indicative of atherosclerosis, which eventually leads to an acute coronary or cerebral event, warrants consideration for two reasons. Coa *et al* already showed that elevated CRP levels predicted the risk of stroke in the elderly independent from carotid atherosclerosis as assessed by intima-media thickness.[31] Further, our study indicates the non-specificity of CRP as a marker of inflammation. An equally strong relation was found between CRP and two competing death causes: CV and non-CV, though the risk estimate for non-CV death was, although not statistically significant, higher relative to CV death (1.30 versus 1.19). In a case-control study, Gussekloo *et al* earlier found equally strong associations between CRP and all-cause mortality as well as fatal stroke in the elderly (though not statistically assessed).[8] An equally strong relation was also found between albuminuria and CV and non-CV death, though the risk estimate for CV death was higher relative to non-CV death (1.23 versus 1.14). Higher levels of albuminuria may be more specific for CV involvement relative to higher levels of CRP. It may be hypothesized that higher levels of CRP may be less specific for atherosclerosis due to confounding from concurrent illnesses, whereas rising degrees of albuminuria may much more lack the influence of confounding factors.

Finally, CRP may reflect a different pathophysiological process in the general population as compared to other populations. The concept of CRP being a marker of inflammation in (vulnerable) coronary plaques or damaged myocardium comes from earlier studies, in which it was shown that elevated CRP levels at hospital admission for myocardial infarction strongly predicted CV outcome.[1] Subsequently, this inflammation hypothesis was extended to populations at lower risk for CV events. Although the association between CRP and mortality was also apparent in the majority of studies in low risk populations, the specificity of CRP as a marker of (unstable) atherosclerosis may be higher in high-risk populations.

A number of risk factors, which may themselves be linked to mortality, are related to CRP as well as albuminuria. These include diabetes, hyperglycemia, hypertension, (abdominal) obesity, insulin resistance, dyslipidemia, smoking, renal function, prevalent atherosclerosis as well as age or ageing [32,33]. Adjustment for these factors only slightly attenuated the relation between either CRP or albuminuria with the risk of death. Only adjustment for age weakened the associations markedly. Interestingly, diabetes, elevated blood pressure and total cholesterol were not retained in the multivariate model.

Table 4. Cause-specific hazard ratios: mutually adjusted Cox regression models.

Risk factor	CV / non-CV	HR	95%CI	*P*	P_{CV}	Wald[a)]
Albuminuria (doubling)	CV	1.23	1.09-1.39	<0.001	NS	11.2
	Non-CV	1.14	1.03-1.26	0.01		
C-reactive protein (doubling)	CV	1.19	1.01-1.41	0.04	NS	3.8
	Non-CV	1.30	1.16-1.45	<0.001		
Age (per 5 years)	CV	1.54	1.31-1.80	<0.001	NS	28.6
	Non-CV	1.49	1.36-1.63	<0.001		
Cerebrovascular disease (yes)	CV	6.53	2.56-16.7	<0.001	0.03	15.4
	Non-CV	0.57	0.08-4.10			
GFR (per 5 ml/min/1.73m^2)	CV	0.91	0.85-0.97	0.002	0.03	9.4
	Non-CV	0.99	0.95-1.03			
Smoking (yes)	CV	2.12	1.25-3.59	0.005	NS	7.8
	Non-CV	1.67	1.18-2.36	0.003		
Male gender	CV	2.06	1.07-3.95	0.03	NS	4.7
	Non-CV	1.42	0.97-2.07			
Waist circumference (per 5 cm)	CV	1.11	1.00-1.25	0.05	0.003	3.7
	Non-CV	0.89	0.82-0.97	0.007		

P_{CV} = CV versus non-CV mortality. a) In ranking order, the Wald is the value of the Wald statistic of the age and gender adjusted risk of CV mortality. The following variables were not retained in the model: BMI, systolic and diastolic blood pressure, anti-hypertensive medication, cholesterol, lipid-lowering medication, glucose, diabetes, myocardial infarction, peripheral artery disease and baseline malignancy.

CRP and albuminuria have been associated with dysfunction of the coagulation and fibrinolytic system as a proposed link between the two markers and CV death.[34,35] Further, markers of leukocyte adhesion, like levels of soluble vascular and intercellular adhesion molecule-1, have been related to the prevalence and the development of an albuminuria.[36] We were also unable to control for those factors, which could explain the relation between CRP, albuminuria and death, e.g. inflammatory processes equally related to premature CV death (arthritis, subclinical atherosclerosis, chronic pulmonary disease et cetera). It is apparent that mechanisms underlying the increased CV risk of an increased CRP as well as albuminuria require further elucidation.

The relation between CRP and non-CV mortality needs further exploration. In our earlier report we have already discussed the relation between albuminuria and non-CV death.[16] The incidence of non-CV death was mostly attributable to death from malignant neoplasms. Risk factors related to elevated levels of pro-inflammatory proteins, like obesity, increase the risk of cancer.[37] Further, the relation between CRP and non-CV death could be related to the presence of malignancy at baseline. However, adjustment for the presence of obesity, smoking or malignancies at baseline did not change the association between CRP and non-CV death.

We confirm the earlier finding of albuminuria being more related to CV as compared non-CV death, although this discrimination was found non-significant. It may be due to the smaller number of CV events relative to our previous report (65 in 7,726 subjects versus 178 cases in 40,856 subjects).[16] Further, the latter report included variables, which were obtained from questionnaires, except for albuminuria itself.[16] In the present study, we were able to adjust for measured blood pressure, total cholesterol and others. Further, we added other factors like waist circumference and renal function into our models, which were not included in our previous report. Most probably, these two factors attenuated the relation between albuminuria and CV death, resulting in a non-significant discrimination between CV and non-CV death.

The present study has a number of limitations. To appreciate our findings of the current study, some issues need to be addressed. First, our cohort consists of a selected sample of subjects with an elevated urinary albumin concentration (>10 mg/L) and a randomly selected sample of control subjects (<10 mg/L). This sampling procedure might have introduced a selection bias and, therefore, this bias might affect absolute values and point estimates. However, we added the variable 'selection' in our model, to control for the sampling procedure.

Biological variability in terms of within-subject variability of both CRP and albuminuria is also a main issue. This variation can be as high as 40-50 percent for both markers.[38,39] Misclassification due to variability may have caused underestimation of the observed association between CRP and albuminuria with mortality, since this variability is not related to the explanatory and outcome measures (i.e. non-differential misclassification). Serial measurements might have improved our ability to estimate the observed effects on mortality, as recently shown with respect to CRP and CV death.[40] If CRP and/or albuminuria should be used in primary prevention, repeated assessments of both markers will probably provide a more reliable risk calculation. On the other hand, Danesh *et al* clearly showed that the long-term variation of CRP, blood pressure and cholesterol were comparable.[29] Therefore, this variability may have underestimated our risk estimates, but comparisons between parameters and risk of mortality seems legitimate.

A strong point of our study is the detailed measurement of well-known CV risk factors and indicators, so that we could control our analysis for factors that might be regarded as important

confounders of the association of both CRP and albuminuria with mortality.

In conclusion, we show a strong and independent value of both CRP and albuminuria to risk of CV and non-CV mortality. Mechanisms underlying the increased CV and non-CV risk held by an increased CRP and urinary albumin excretion require further elucidation. There may be an important clinical role for both markers in CV risk assessment, which goes beyond blood pressure and lipid screening alone. Because both markers provide independent prognostic information, and because both markers are modifiable by different strategies, intervention studies may help to define optimal preventive treatment in subjects with both elevated CRP levels and albuminuria.

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