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Prognostic value of combined use of biomarkers of inflammation, endothelial dysfunction, and myocardiopathy in patients with ESRD

Francesca Mallamaci, Giovanni Tripepi, Sebastiano Cutrupi, Lorenzo S. Malatino, and Carmine Zoccali

CNR-IBIM, Institute of Biomedicine, Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension and Division of Nephrology, Reggio Calabria, Italy; and Department of Internal Medicine "L. Condorelli," University of Catania, Catania, Italy

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Background. Cardiovascular risk stratification is important in the clinical management of patients with end-stage renal diseases (ESRD) and biomarkers are increasingly used in these patients.

Methods. In a cohort of 246 dialysis patients without heart failure at baseline we tested the combined prognostic power of three well-established biomarkers: brain natriuretic peptide (BNP), C-reactive protein (CRP), and asymmetric dimethyl arginine (ADMA). The independent prognostic value of individual and combined biomarkers was estimated in separate Cox models, including standard risk factors in dialysis patients and comorbidities.

Results. When the prediction power of the three biomarkers was evaluated individually, BNP, ADMA, and CRP added significant predictive value ($P \leq 0.01$) to all-cause and cardiovascular mortality models and the explanatory gain attributable to these biomarkers were of similar degree (ranging from 3.3% to 5.7%). When the biomarkers were evaluated jointly, a score based on the BNP-CRP combination, increased by 9.9% (all-cause) and by 10.5% (cardiovascular) the explained mortality variance of standard Cox models and such gain in power was similar to that achieved by the CRP-ADMA combination (all-cause death 9.0% and cardiovascular death 8.4%). Of note, the explanatory gain derived by the simultaneous use of the three biomarkers was very similar (all-cause death 11.6% and cardiovascular death 10.5%) to that achieved by the use of two biomarkers.

Conclusion. These findings indicate a potential role for CRP, BNP, and ADMA to be incorporated into diagnostic and therapeutic strategies aimed at detection and treatment of atherosclerotic complications and at preventing heart failure in the dialysis population.

Key words: ADMA, BNP, CRP, cardiovascular risk, dialysis.

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Cardiovascular complications are the major cause of death in patients with end-stage renal disease (ESRD), accounting for approximately one half of all deaths and the mortality risk attributable to coronary heart disease in these patients is about 100 times higher than that in the general population [1]. Even though cardiovascular risk in patients with chronic kidney diseases now constitutes a major concern in the nephrology community, ESRD patients are treated much less intensively than needed [2]. Because of the daunting burden of cardiovascular disease and the still insufficient emphasis on appropriate treatment, cardiovascular risk stratification is a fundamental issue in strategies aimed at bettering clinical management of ESRD patients.

Inflammation, a critical element to the pathogenesis of atherosclerosis, is a pervasive phenomenon in ESRD and raised serum C-reactive protein (CRP), a reliable marker of this process, is demonstrable in up to 70% of patients on chronic dialysis [3–5]. Furthermore plasma B-type natriuretic peptide (BNP), a cardiac hormone reflecting left ventricular mass and function, is frankly elevated in about 80% of these patients [6, 7]. Likewise, asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of nitric oxide synthase (NOS) with potent vasoconstrictive and proatherogenic effects, is abnormally high in about 60% of the dialysis population [8, 9]. Observations associating the plasma concentration of these markers to cardiovascular damage [7, 10] are germane to prospective studies showing that elevated CRP [3–5], BNP [10], and ADMA [9] predict increased all-cause and cardiovascular death. Notwithstanding the association of each of these biomarkers with atherosclerotic disease and cardiomyopathy is fairly well established, the usefulness of their combined use has been scarcely investigated. The issue is relevant because a study examining the joint use of CRP and troponin T has convincingly demonstrated that high troponin T identifies inflamed patients at higher risk for cardiac death [11].

In the Cardiovascular Risk Extended Evaluation in Dialysis (CREED) study, a prospective cohort study in dialysis patients without heart failure at baseline, we measured CRP, BNP, and ADMA and reported their prognostic value for all-cause death and cardiovascular events as well as their relationship with structural surrogate markers of cardiovascular damage such as left ventricular hypertrophy (LVH) and carotid intima thickness. In the present study we tested the hypothesis that the combined measurement of these biomarkers may have a complementary role for the prognosis of dialysis patients. To this end we have performed new analyses to estimate the variance in all-cause and cardiovascular mortality explained by traditional and nontraditional risk factors and the additional explanatory power attributable to biomarkers used individually and combined.

Table 1. Demographic, anthropometric, clinical, and biochemical data of the study population

Age *years*	60.2 ± 15.3
Duration of regular dialysis treatment *months*	43(18–99)
Body mass index kg/m^2	24.9 ± 4.4
Number of males (%)	138 (56%)
Number of diabetics (%)	37 (15%)
Number of smokers (%)	104 (42%)
Number on antihypertensive therapy (%)	109 (44%)
Systolic pressure *mm Hg*	133.9 ± 22.4
Diastolic pressure *mm Hg*	75.3 ± 12.3
Heart rate *beats/min*	80.5 ± 12.0
Hemoglobin *g/L*	106.4 ± 19.0
Albumin *g/L*	40.1 ± 5.6
Cholesterol *mmol/L*	5.34 ± 1.41
Calcium * phosphate $mmol^2/L^2$	4.44 ± 1.17
Homocysteine μ*mol/L*	27.0 (19.6–40.2)
Brain natriuretic peptide *pmol/L*	24.4 (10.4–48.2)
Asymmetric dimethyl arginin μ*mol/L*	3.06 (1.77–4.33)
C-reactive protein *mg/L*	7.4 (3.4–16.4)

Data are reported as mean ± SD, median and interquartile range or as percent frequency, as appropriate.

METHODS

Protocol

The protocol was in conformity to the ethical guidelines of our institutions and informed consent was obtained from each participant.

Study cohort

Two hundred and forty six patients with ESRD (138 males and 108 females) who had been on regular dialysis treatment [196 on hemodialysis and 50 on chronic ambulatory peritoneal dialysis (CAPD)] for at least 6 months, with left ventricular ejection fraction >35% and without history of clinical evidence of circulatory congestion [12], were eligible for the study. No patient had inter-current acute coronary syndromes at the time of the study.

One hundred and seventeen patients had had at least one cardiovascular event. In particular, 62 patients had had one cardiovascular event (myocardial infarction in eight cases, ECG-documented anginal episodes in 28 cases, peripheral artery diseases in 11 cases, arrhythmia in 10 cases, transient ischemic attacks in four cases, and stroke in one case) and the remaining 55 patients had had two or three ($N = 46$) or more than three ($N = 9$) cardiovascular complications.

The main demographic, somatometric, clinical, and biochemical characteristics of patients included in the study are detailed in Table 1. Patients represented about the 70% of the dialysis population of two urban areas. The remaining 30% of patients were excluded because of the presence of circulatory congestion or major infections (20%) or because they were hospitalized for intercurrent illnesses or for logistic reasons/unwillingness to participate in the study (10%). The prevalence of diabetes mellitus in this cohort was 15% (i.e., 37 patients out of 246).

Hemodialysis patients were being treated three times a week with standard bicarbonate dialysis (sodium 138 mmol/L, HCO_3 35 mmol/L, potassium 1.5 mmol/L, calcium 1.25 mmol/L, and magnesium 0.75 mmol/L) by cuprophan or semisynthetic membranes (dialysis filters surface area 1.1 to 1.7 m^2). Dry weight was targeted in each case to achieve a normotensive edema-free state. The average urea Kt/V in these patients [13] was 1.22 ± 0.27. Patients on CAPD were all on four exchanges/day schedule with standard dialysis bags. The average weekly Kt/V in these patients [14] was 1.66 ± 0.32. One-hundred and four patients were habitual smokers (21 ± 17 cigarettes/day). One-hundred and thirty patients were on treatment with erythropoietin. One-hundred and nine patients were on antihypertensive treatment [76 on monotherapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 (AT1) antagonists, calcium channel blockers, alpha and beta blockers, and 33 on double or triple therapy with various combinations of these drugs].

Follow-up study

After the initial assessment patients were followed-up for an average time of 34 ± 16 months (range 0.8 to 52.0 months). During the follow-up period fatal cardiovascular events (myocardial and mesenteric infarction, heart failure, ECG-documented arrhythmia, pulmonary embolism, and stroke) and death were accurately recorded. Each death was reviewed and assigned an underlying cause by a panel of five physicians. As a part of the review process, all available medical information about each death was collected. This information always included study and hospitalization records. In the case of an out-of-hospital death family members were

interviewed by telephone to better ascertain the circumstances surrounding death.

Laboratory measurements

To minimize the effect of cyclic changes in extracellular volume all studies in hemodialysis patients were performed between 8.00 a.m. and 10.00 p.m. midweek, during the dialysis interval. Sampling was performed at empty abdomen in CAPD patients. After 20 to 30 minutes of quiet resting in semirecumbent position samples were taken into chilled ethylenediaminetetraacetic acid (EDTA) vacutainers, placed immediately on ice, centrifuged within 30 minutes at −4°C, and the plasma stored at−80°C before assay. Serum lipids, albumin, calcium and phosphate, and hemoglobin measurements were made by standard methods in the routine clinical laboratory. Methods of measurements of BNP [10], CRP [15], and ADMA [9] were detailed in previous papers.

Cardiovascular comorbidity score

This score was calculated on the basis of the presence/absence of background cardiovascular complications (previous myocardial infarction, stroke, transient ischemic attack, ECG-documented arrhythmia, anginal episodes, and peripheral artery disease). Patients were classified as having 0, 1, 2, or 3 and more than 3 previous cardiovascular complications.

Statistical analysis

Data are reported as mean SD, median and interquartile range or as percent frequency, as appropriate. To construct multivariate Cox models, we considered a series of traditional risk factors (age, gender, smoking, diabetes, serum cholesterol, systolic pressure, and antihypertensive therapy) and factors peculiar to ESRD [treatment modality (hemodialysis/CAPD), duration of regular dialysis treatment, hemoglobin, serum albumin, and serum calcium and phosphate] and plasma total homocysteine. In a first step we identified covariates that were associated to all-cause and cardiovascular mortality with $P < 0.10$ at univariate Cox regression analysis. These variables were then jointly included into multivariate Cox models ("basic models" both for all-cause and cardiovascular death). We then tested by the −2 log likelihood statistic [16] whether the sequential addition of the comorbidity score and of the three biomarkers (BNP, ADMA, and CRP considered individually and in various combinations) added significant prognostic information to basic models. Furthermore, to directly compare the relative risk associated with high BNP, ADMA, and CRP, we categorized these variables as tertiles and calculated their associated relative risks. The variance in incident all-cause and cardiovascular death explained by covariates in Cox models was estimated according to Hosmer and Lemeshow [17].

Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated with the use of the estimated regression coefficients and their standard errors in the Cox regression analysis. All calculations were done using a standard statistical package (SPSS for Windows version 9.0.1, March 11, 1999) (SPSS, Chicago, IL, USA).

RESULTS

The main demographic, somatometric, clinical, and biochemical data of the study population are reported in Table 1. Plasma BNP, plasma ADMA, and serum CRP were above the upper limits of the normal range in the majority of dialysis patients (i.e., 80%, 65%, and 54%, respectively).

Basic models of all-cause and cardiovascular mortality

During the follow-up period 97 patients died, 59 of them (i.e., 61% of total deaths) of cardiovascular causes. On univariate Cox regression analysis age, gender, smoking, diabetes, albumin, and treatment modality were all significantly associated to death and the multivariate Cox model based on these variables explained 37.2% of the variance in all-cause mortality (Fig. 1, upper panel). On the other hand age, gender, smoking, and diabetes were predictors of cardiovascular death and the corresponding multivariate Cox model explained 23.6% in cardiovascular mortality variance (Fig. 1, lower panel).

Prognostic impact of the cardiovascular comorbidity score

As expected, the incident risk of all-cause and cardiovascular mortality was strongly related with the number of previous cardiovascular complications (comorbidity score). Indeed (Table 2), the risk for all-cause and cardiovascular death increased in parallel with the number of previous cardiovascular complications so that patients with a comorbidity score >3 were those with the highest risk of death. When the comorbidity score was added to the basic models, the explained mortality variance reached 45.4% for all-cause death and 36.4% for cardiovascular death and the corresponding gains in predictive value were 8.2% and 12.8%, respectively (both $P < 0.001$) (Fig. 1).

Prognostic impact of high BNP, ADMA, and CRP

The additional independent prognostic value of plasma BNP, ADMA, and CRP was tested in separate Cox models (one model for each biomarker both for all-cause and cardiovascular death). These models included basic models variables plus the cardiovascular comorbidity score (the detailed models will be provided to interested

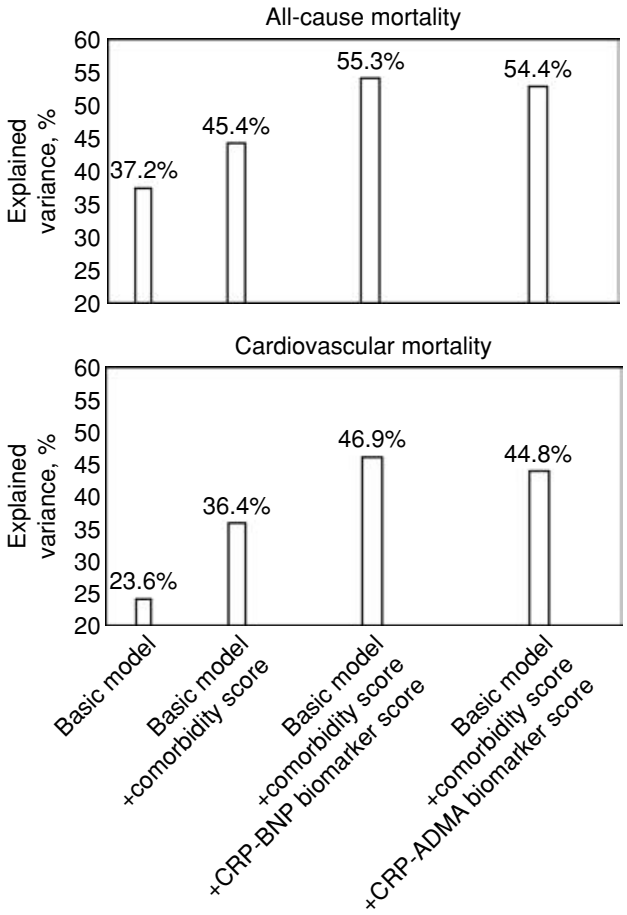

Fig. 1. Explained mortality variance (%). Besides C-reactive protein-brain natriuretic peptide (CRP-BNP) and CRP-asymmetric dimethyl arginine (ADMA) scores variables included in multivariate analyses of various complexity are age, gender, smoking, diabetes, albumin, treatment modality and comorbidity score for all-cause death and age, gender, smoking, diabetes, and comorbidity score for cardiovascular death. The statistical models are described in the **Results** section. A table with the detailed list of causes of death can be obtained from the authors.

readers on request). In these analyses BNP, ADMA, and CRP added significant predictive value (all $P \leq 0.01$) to all-cause (BNP +5.7%; ADMA +5.6%; and CRP +3.8%) and cardiovascular mortality (BNP +4.9%; ADMA +3.3%; and CRP +5.4%) models and the explanatory gain for these outcomes attributable to these biomarkers was of similar degree. Accordingly, the relative risks associated with high BNP, ADMA, and CRP (expressed as tertiles to allow direct comparison) were largely overlapping (Fig. 2). The survival curves by tertiles of BNP, ADMA, and CRP for all-cause and cardiovascular mortality are reported in Figure 3.

Combined prognostic power of BNP, ADMA, and CRP

The combined prognostic value of plasma BNP, ADMA, and CRP was evaluated by the "biomarker score" (i.e., the sum of these variables categorized in terms of tertiles). For the sake of parsimony, we first evaluated a biomarker score based on two biomarkers (CRP and BNP, CRP and ADMA, and ADMA and BNP). When the score derived from CRP and BNP was added to models incorporating the comorbidity score, the explained all-cause mortality variance rose from 45.4% to 55.3% (+9.9%) and the explained cardiovascular mortality variance from 36.4% to 46.9% (+10.5%) (Fig. 1). Such gain in power was similar to that achieved by the CRP and ADMA combination (all-cause death +9.0% and cardiovascular death +8.4%) (Fig. 1). The BNP and ADMA combination was less informative than the other two combinations (all-cause death +7.7% and cardiovascular death +5.6%). The explanatory gain derived by the simultaneous use of the three biomarkers (all-cause death +11.6% and cardiovascular death +10.5%) was almost identical to that obtained by the combination of just two biomarkers. Of note, both with the CRP-BNP and the CRP-ADMA combinations the risk increased in parallel with the plasma levels of corresponding biomarkers (biomarker score) (Fig. 4).

Table 2. Cox regression analysis for all-cause and cardiovascular mortality, including covariates of the basic models and the comorbidity score

	Units of increase	HR and 95% CI	*P* value
All-cause mortality			
Age	1 year	1.04 (1.02–1.06)	<0.001
Male gender		1.51 (0.89–2.55)	0.12
Smoking		1.22 (0.73–2.02)	0.45
Diabetes		1.61 (1.00–2.60)	0.05
Albumin	1 g/L	0.95 (0.91–0.99)	0.02
Treatment modality	0 hemodialysis; 1 CAPD	0.91 (0.52–1.61)	0.75
Comorbidity score	0	1[a]	
	1	1.62 (0.97–2.72)	0.06
	2–3	2.44 (1.44–2.14)	0.001
	>3	4.72 (2.09–10.65)	<0.001
Cardiovascular mortality			
Age	1 year	1.04 (1.02–1.06)	<0.001
Male gender		2.19 (1.11–4.31)	0.02
Smoking		1.15 (0.62–2.12)	0.66
Diabetes		1.40 (0.76–2.60)	0.28
Comorbidity score	0	1[a]	
	1	1.81 (0.89–3.68)	0.10
	2–3	3.36 (1.72–6.58)	<0.001
	>3	8.59 (3.41–21.61)	<0.001

CAPD is continuous ambulatory peritoneal dialysis. Factors which were not introduced into the two Cox models were those with $P > 0.10$ at univariate analysis. The list of these variables may be deduced from the description of the multivariable strategy adopted in this study (see **Methods** section).

[a]Reference group.

DISCUSSION

This study shows that in ESRD patients the combined use of biomarkers of inflammation, endothelial dysfunction, and myocardiopathy increases by about one fifth the explanatory power of all-cause and cardiovascular mortality models based on traditional risk factors, serum albumin, and comorbidities.

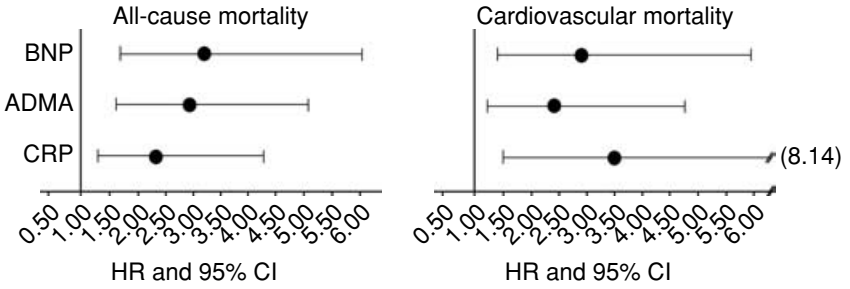

Fig. 2. HR and 95% CI for all-cause and cardiovascular mortality associated with brain natriuretic peptide (BNP), asymmetric dimethyl arginine (ADMA), and C-reactive protein (CRP) (third vs. first tertile). Data were appropriately adjusted for covariates included in the corresponding basic models of all-cause and cardiovascular death as well as for the comorbidity score. The categorization into tertiles was chosen because it produced a better data fitting than that into quartiles or quintiles. BNP in I tertile <14.3 pmol/L, II tertile ≥14.3 <36.1 pmol/L, and III tertile >36.1 pmol/L; ADMA I tertile <2.20 μmol/L, II tertile ≥2.20 <3.87 μmol/L, and III tertile >3.87 μmol/L; and CRP I tertile <3.4 mg/L, II tertile ≥3.4 <13.0 mg/L, and III tertile >13.0 mg/L. We divided the study population in tertiles because this categorization gave the best fitting with observed survival data.

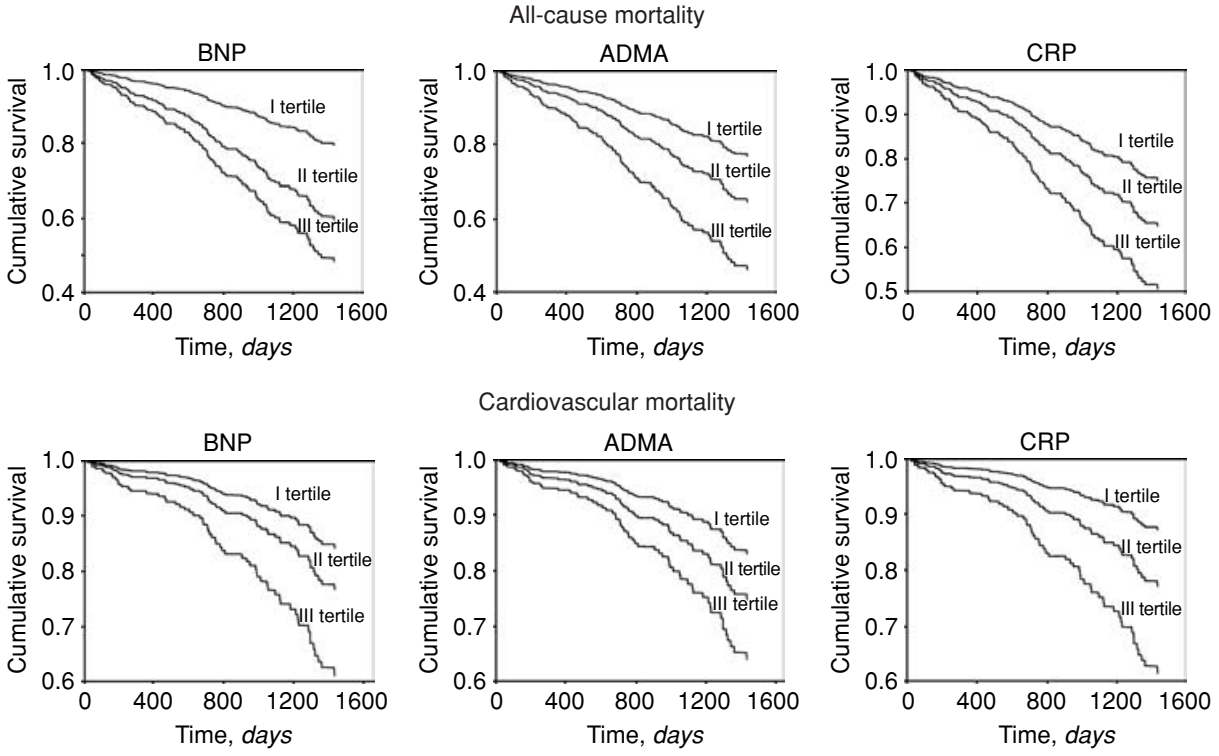

Fig. 3. Cox survival curves by tertiles of brain natriuretic peptide (BNP), asymmetric dimethyl arginine (ADMA), and C-reactive protein (CRP) for all0cause and cardiovascular mortality. Data were appropriately adjusted for covariates included in the corresponding basic models as well as for the comorbidity score.

The alarming rate of cardiovascular events in dialysis patients demands accurate risk profiling to identify individuals at greater risk and therefore needing intensive surveillance and treatment. Atherosclerosis is a risk factor both for renal disease and cardiovascular complications and undoubtedly the burden of cardiovascular events antedating ESRD in part explains why these patients are so predisposed to cardiovascular complications and death. As is commonly observed in American and in European dialysis populations, our cohort was relatively old and about one half of patients had evidence of cardiac ischemia, cerebrovascular or peripheral disease. It is well-known that background cardiovascular events constitute a strong predictor for future events, a notion further again confirmed by our prospective observations. In keeping with previous large-scale analyses in the ESRD population [18, 19] we found that age, gender, diabetes, smoking, and serum albumin were independent

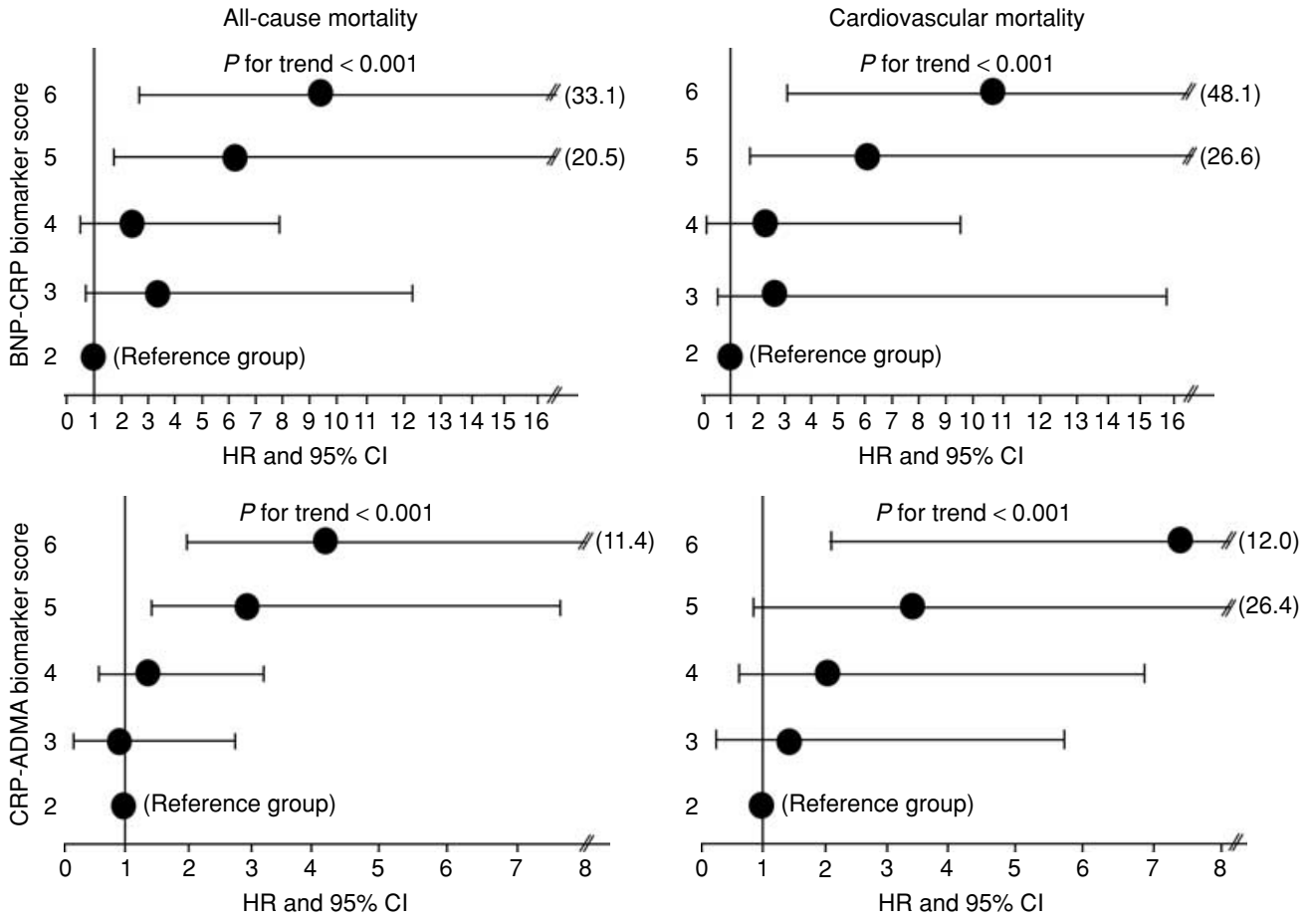

Fig. 4. HR and 95% CI for all-cause and cardiovascular mortality associated to the C-reactive protein-brain natriuretic peptide (CRP-BNP) and to CRP-asymmetric dimethyl arginine (ADMA) biomarker scores. Biomarker scores were calculated on individual basis by summing up the variables (CRP and BNP and CRP and ADMA) expressed as tertiles. Data were appropriately adjusted for covariates included in the corresponding basic model of all-cause and cardiovascular death as well as for the comorbidity score.

risk factors for death in the CREED cohort. However, the combined effect of these risk factors and of background cardiovascular complications explained only about 45% of mortality variance in these patients. Framingham risk factors account for more than the 80% of coronary events in individuals without cardiovascular events at baseline in the general population [20] but it is well documented that the explanatory power of traditional risk factors for cardiovascular events is much less in ESRD patients than in their age peers without renal diseases [21, 22]. The limited prognostic value of traditional risk factors in ESRD implies that attention should be focused also on other risk factors both to improve prediction of future events (i.e., for prognosis) and to identify modifiable risk factors which can be targeted by specific treatments (i.e., for prevention). In this regard CRP has now emerged as a solid, independent predictor of death risk in the dialysis population [3–5]. Although there is still no evidence either in the general population or in the dialysis population that lowering CRP will necessarily lower cardiovascular risk, this biomarker conveys important prognostic information beyond traditional risk factors and background cardiovascular events [3, 5]. BNP is a sensitive guide to the presence of LVH and left ventricular dysfunction in asymptomatic subjects [23], and such characteristics have been specifically confirmed in the ESRD population [6]. ADMA mediates the effects of many risk factors and risk markers on the NOS pathway and it is currently considered an important biomarker reflecting the summative effect of various risk factors on endothelial function [24], a hypothesis specifically supported by the observation that this substance is independently associated to mortality and cardiovascular events in the dialysis population [9]. We focused the attention on these biomarkers because they reflect a wide range of pathologic processes encompassing atherosclerosis and the risk for thrombosis. In fact their combined use increased the explanatory power for mortality and cardiovascular events of multivariate models based on standard risk factors and on comorbidities by about one fifth. Such an explanatory gain is important because the incidence of de novo cardiovascular disease in patients with ESRD is much higher

than predicted on the basis of traditional risk factors [21, 22]. In this regard it is important noting that the combination of two biomarkers, CRP and BNP or CRP and ADMA, was almost as informative as the combination of three biomarkers. This finding has biologic plausibility because, as previously noted, these biomarkers in part reflect overlapping pathologic processes [8, 25–28]. It is worth noting that the two biomarkers which formed the best prognostic combination, BNP and CRP, both possess the major characteristics required for a marker to be recommended for a wide use in clinical practice, namely, it should provide independent information in risk or prognosis beyond established risk factors and that it should be easy to measure and in a cost-effective manner. ADMA is a strong predictor of death and cardiovascular events but the measurement of plasma levels of this substance are still poorly standardized and performed only in few laboratories. The ideal biomarker should also have the characteristic that a reduction in its levels leads to reduced vascular risk but this is not a critical issue for risk prediction. Recently completed [29] and ongoing trials will provide specific answers to the hypothesis that CRP and BNP may be a guide to treatment in ESRD patients. If positive, these trials will constitute a definitive argument for the widespread use of these biomarkers in the dialysis population. In the specific case of ESRD, CRP and BNP may also have other practical implications because the measurement of circulating levels of these substances may be useful also for comparing the cardiovascular burden of diverse dialysis populations. Indeed comorbidities may not accurately reflect the actual severity of underlying organ damage. On the other hand, even comparisons based on fatal events may be imperfect because determination of cause of death using death notifications is notoriously inaccurate [30] and because a poor correlation exists between type of cardiac death as determined by clinicians and as adjudicated by expert panels [31]. Because CRP and BNP biologically reflect the burden of atherosclerosis and myocardial disease, their systematic use may allow more objective comparison of different dialysis units, an exercise which may result much useful both for research purposes as well as for benchmarking.

CONCLUSION

For steady-state patients with ESRD without intercurrent inflammatory processes or acute coronary syndromes and without heart failure, levels of CRP and BNP independently identify patients at risk of death and the combination of the two biomarkers identify patients at particularly high risk. In the aggregate, these findings identify a potential role for these biomarkers to be incorporated into diagnostic and therapeutic strategies aimed at detection and treatment of atherosclerotic complications and heart failure prevention strategies.

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Reprint requests to Professor Carmine Zoccali, CNR-IBIM, Istituto di Biomedicina, Epidemiologia Clinica e Fisiopatologia, delle Malattie Renali e dell'Ipertensione Arteriosa, c/o Ki Point-Gransial Srl Via Filippini, n. 85 89125 Reggio Calabria, Italy.
E-mail: carmine.zoccali@tin.it

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