

Predictors of Cardiovascular Death in ESRD

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End stage renal disease (ESRD) is a situation with a cardiovascular risk profile of almost unique severity. While traditional risk factors dominate the scene in the general population, non traditional risk factors like inflammation (high C Reactive Protein, CRP), high brain natriuretic peptide, as an expression of left ventricular hypertrophy and left ventricular dysfunction, and accumulation of the endogenous inhibitor of the NO synthase, asymmetric dimethyl arginine are all markers of high CV risk of ESRD patients. To obtain a quantitative insight on the predictive power of traditional and emerging risk factors in ESRD, we performed a detailed multivariate survival analysis in the cardiovascular risk extended evaluation (CREED) cohort database. As expected, traditional risk factors (ie, age, sex, smoking, diabetes, and risk factors peculiar to the uremic state such as low serum albumin level) and treatment modality contributed to explain the all-cause mortality (37%) and cardiovascular variation mortality (24%) variation as well. When cardiovascular comorbidities were considered in this analysis, the explained variation in mortality increased to 45.4% and 36.4%, respectively. Furthermore, a combined score based on 2 biomarkers (brain natriuretic peptide and C-reactive protein levels) increased the explanatory power of these models by about 10%. In conclusion, traditional risk factors explain about half of all-cause and cardiovascular mortality variation in the ESRD population. The combined use of 2 biomarkers reflecting inflammation and left ventricular mass and function increases by about one fifth the explained mortality variation in this population. Biomarkers give information beyond that provided by traditional risk factors and therefore represent an useful adjunct for the definition of the risk profile of ESRD patients.

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According to the classic definition introduced by Kannel et al,¹ risk factors are markers that are related statistically to the risk for morbid events. The association between these factors and outcomes may be either causal or noncausal. Causal risk factors are of major relevance because they both signal the presence and the severity of the disease and because often they also may be used as a guide to treatment (eg, serum cholesterol). Noncausal risk factors (eg, creatinine) are useful for monitoring the evolution of a given disease or for prognostic purposes. The time dimension is fundamental for the interpretation of the association between a purported risk

factor and a given event. Indeed, synchronous observations (surveys) in general are far more prone to bias than prospective observations (cohort studies). Furthermore, because the link between risk factors and clinical outcomes may vary in different populations and disease states, validation of prognostic factors demands that they are tested specifically in the particular population in which they are planned to be applied in clinical practice, a concept that is true particularly in end-stage renal disease (ESRD) in which reverse epidemiology is pervasive.²

In this review we perform a prognostic exercise by estimating the variation in all-cause and cardiovascular (CV) mortality explained by classic and emerging risk factors in the dialysis population. The specific question posed here is whether the combined use of 3 solid biomarkers of high risk, namely serum C-reactive protein (CRP) levels,³⁻⁶ plasma B-type natriuretic peptide (BNP) levels,^{7,8} and asymmetric dimethyl arginine (ADMA) levels⁹ add significant information to prognostic models based on classic risk factors and on risk factors peculiar to ESRD.

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The study basis was the CREED cohort, a dialysis population that we described in detail elsewhere.¹⁰ In the present analysis we included 246 patients with ESRD (138 men and 108 women) 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 greater than 35%, without history of clinical evidence of circulatory congestion,¹¹ and without intercurrent acute coronary syndromes at the time of the study. A total of 117 patients had at least 1 CV event. The prevalence of diabetes mellitus in this cohort was 15% (ie, 37 of 246 patients). A total of 104 patients were habitual smokers. The follow-up period lasted 34 ± 16 months (range, 0.8-52.0 mo).

Definitions and Analytical Approach

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

We estimated the explained variation in incident all-cause and CV death (multivariate Cox's models) following the approach proposed by Hosmer and Lemeshow.¹² To construct multivariate Cox models, we considered a series of traditional risk factors (age, sex, smoking, diabetes, serum cholesterol level, systolic pressure, and antihypertensive therapy) and factors peculiar to ESRD (treatment modality [hemodialysis/CAPD], duration of regular dialysis treatment, hemoglobin level, serum albumin level, serum calcium and phosphate levels, and plasma total homocysteine level). In the first step we identified covariates that were associated with all-cause and CV mortality with a *P* value less than .10 at univariate Cox regression analysis. These variables were then jointly included into multivariate models to construct basic models for all cause and CV death. After the definition of basic models, we added the comorbidity score (model 1) to establish whether this score adds significant prognostic information. Following the same analytical approach we then tested, one by one, the predictive value of the 3 biomarkers (BNP, ADMA, and CRP). Furthermore, to compare directly the relative risk associated with high BNP, ADMA, and CRP levels, we categorized these variables as tertiles and calculated their associated relative risks.

Predicting Mortality and Cardiovascular Events in the Dialysis Population

The all-cause annual mortality rate in this cohort was approximately 15%. As expected, traditional (Framingham) risk factors (ie, age, sex, smoking, diabetes) and risk factors peculiar to the uremic state such as low serum albumin level and

Relative Risk for incident CV events (adjusted)

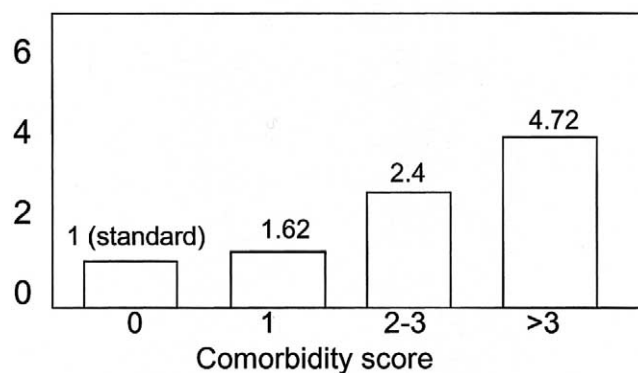


Figure 1 Risk associated with increasing levels of the comorbidity score.

treatment modality (hemodialysis or peritoneal dialysis) all contributed to such a high mortality rate. The (all-cause) mortality variation explained by these factors was 37% whereas the corresponding figure for CV mortality was 24%. Therefore, 63% and 76% of all-cause and cardiovascular mortality, respectively, remained unexplained by risk models based on the aforementioned variables. It is well known that previous CV events are strong predictors of incident CV events, a phenomenon that is captured by clinical scores that sum the number of adverse events on an individual basis. Following this approach we constructed a CV comorbidity score based on past cardiac ischemic events (electrocardiogram-documented anginal episodes and myocardial infarction), arrhythmia, heart failure, cerebrovascular events (transient ischemic attack (TIA) or stroke), and evidence of peripheral vascular disease (Fig 1). We divided patients into 4 groups: the first group comprised CV event-free patients (standard group), the second group comprised patients with just 1 CV event, the third group comprised patients with 2 or 3 CV events, and the fourth group comprised patients with more than 3 CV events. As expected, the (adjusted) risk for incident CV events increased in parallel with the comorbidity score, again further documenting the prognostic implication of previous CV events. Yet, when the CV comorbidity score was added to the basic model, the explained variation in mortality for all-cause mortality increased to only 45.4% (from 37%) and CV mortality increased to 36.4% (from 24%). Thus, even after considering background CV events, a substantial proportion of CV risk excess remains unexplained in the dialysis population.

Several risk markers have been reported to be associated with CV damage in uremic patients on dialysis. For the present analysis we considered 3 biomarkers: (1) CRP level, a globular protein that circulates in pentameric form (a pentraxin) that is a reliable marker of the inflammatory process and a predictor of death and adverse CV outcomes in the dialysis population⁶; (2) BNP level, a 32 amino acid peptide that is produced mainly in the left ventricle and has been shown to be associated with left ventricular hypertrophy (LVH) and left ventricular dysfunction as well as with all-cause and CV mortality in the same popula-

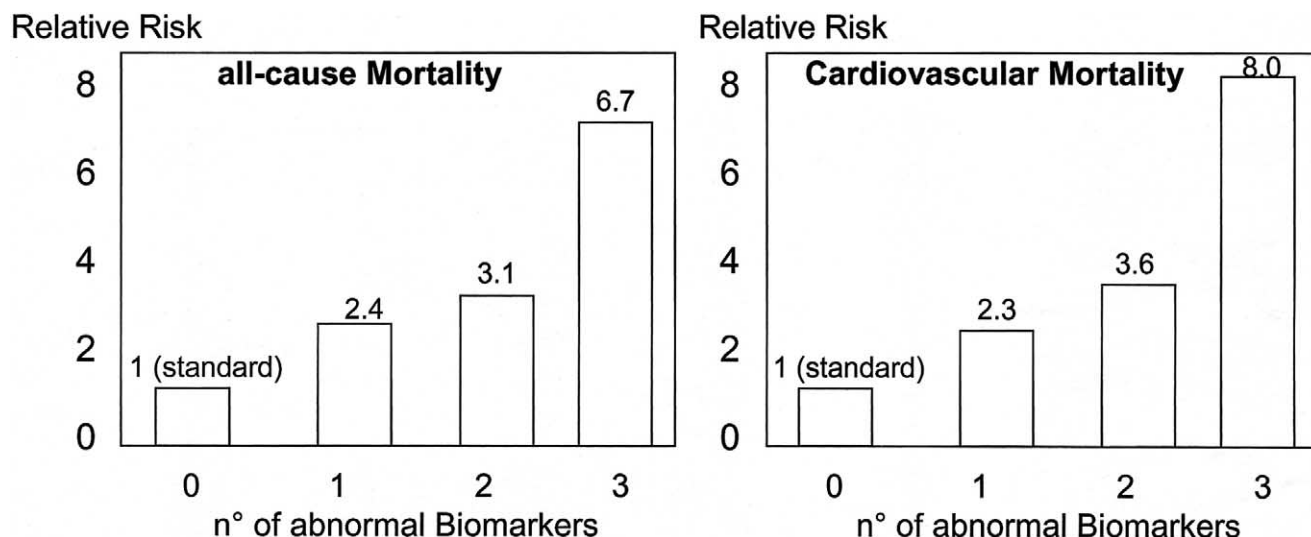


Figure 2 All cause and cardiovascular mortality risk associated with abnormal biomarkers. Data are adjusted for age, sex, smoking, diabetes, albumin, treatment modality and comorbidity score.

tion¹⁰; and (3) ADMA, an endogenous inhibitor of nitric oxide synthase that may trigger platelet and leukocyte aggregation, vasoconstriction, and cardiovascular complications in ESRD patients.⁹ Thus, high levels of these 3 biomarkers either are involved causally in inflammation, vasculotoxicity, and cardiovascular remodeling of ESRD patients (CRP and ADMA levels) or reliably reflect alterations in left ventricular mass and function in this condition (BNP level). Yet we should bear in mind that the observation that a given biomarker is associated with structural indicators of cardiovascular damage and even the fact that it predicts CV events does not guarantee that the biomarker in question is useful for risk stratification in clinical practice. Only if the biomarker adds significant prognostic information to that provided by established risk factors in the target population can we affirm that it may be useful in clinical practice. In other words, to test the usefulness of biomarkers we should test them in prognostic models including classic risk factors, and only if the explained variation of the outcome measure (all-cause and CV death) is increased materially by the inclusion of the biomarker can we conclude that the same biomarker conveys significant clinical information.

In the models shown in Figure 2, the explained variation in mortality was 45.4% (all-cause death) and 36.4% (CV death). When we added plasma BNP concentration to these models, we registered a 5.7% and 4.9% increase in all-cause and CV mortality explained variation, respectively. A similar gain in explanatory power was registered (in separate models) by adding serum CRP (all-cause mortality, 3.8%; CV mortality, 5.4%) or plasma ADMA (5.6% and 3.3%, respectively). Thus, biomarkers of left ventricular mass and function, inflammation, and endothelial dysfunction add significant prognostic information to statistical models aimed at estimating mortality and CV risk in ESRD patients. These explanatory gains ($\approx 5\%$), although not trivial if one considers that the combined use of classic risk factors and of comorbidities explains just 45% of the mortality variance in ESRD patients, are not substantial. A complementary, important question is

whether the combined use of biomarkers may increase further the predictive power of prognostic models. To test this hypothesis we categorized patients in terms of tertiles of BNP, CRP, and ADMA levels (ie, classified them as having 0, 1, 2, or 3 biomarkers in the third tertile of relative data distributions). We looked first at the relative risk for all-cause mortality associated with the number of abnormal biomarkers adjusted for age, sex, smoking, diabetes, albumin, treatment modality, and comorbidity score. The standard risk group included patients who had no biomarker in the third tertile. As shown in Figure 2, patients who had all 3 biomarkers in the highest tertile had a relative risk that was 6.7 times (all-cause mortality) and 8 times (CV mortality) higher than those in the standard risk group. Thus, the death risk in ESRD patients increases in a dose-response fashion according to the number of deranged biomarkers. To estimate the gain in prognostic power allowed by the combined use of the 3 biomarkers we added CRP, BNP, and ADMA to the statistical model shown in Figure 2 (model 1). When the three biomarkers were used jointly, the explained mortality variation increased to 57.0%, an 11.6% gain. By the same token, explained variation in CV mortality increased to 46.9%, a 10.5% gain. Importantly, this explanatory gain was similar to that achievable by the joint use of 2 biomarkers (CRP and BNP, all-cause death, 9.9%; CV death, 10.5%; CRP and ADMA, 9.0% and 8.4%, respectively). Thus, the joint use of just 2 well-standardized, widely available biomarkers increased by about one fifth the explained variance in all-cause and cardiovascular mortality in ESRD, thereby allowing a better risk stratification in these patients.

Further Considerations on Prognostic Factors in ESRD

The limited prognostic value of traditional risk factors in ESRD constitutes an objective limitation for risk stratifica-

tion in the dialysis population. To improve the prediction of future events (ie, for refining prognosis) and to identify modifiable risk factors that can be targeted by specific treatments (ie, for prevention), increasing attention presently is paid to emerging risk factors. In this scenario CRP appears as a solid, independent predictor of death risk in the dialysis population. Although there is still no evidence either in the general population or in the dialysis population that decreasing CRP levels necessarily will decrease cardiovascular risk, this biomarker conveys important prognostic information beyond traditional risk factors and background cardiovascular events because it is related better to clinical events than actual disease burden.¹³ BNP is a sensitive guide to the presence of left ventricular dysfunction and left ventricular hypertrophy in asymptomatic patients¹⁴ in the general population, and such characteristics have been confirmed specifically in the ESRD population.⁸ ADMA mediates the effects of many risk factors and risk markers on the nitric oxide synthase pathway and it currently is considered an important biomarker reflecting the summative effect of various risk factors on endothelial function,¹⁵ a hypothesis specifically supported by the observation that this substance is associated independently with mortality and cardiovascular events in the dialysis population.⁹

We focused our attention on these biomarkers because they reflect a wide range of pathologic processes, namely atherosclerosis and the risk for thrombosis (CRP and ADMA) and left ventricular remodeling and function (BNP and ADMA). As expected, the plasma concentrations of these substances were interrelated in ESRD patients but the correlation coefficients indicated that they had, at most, a 16% (highest $r = 0.41$) common variance, a phenomenon also implying that their combined use may improve risk stratification. In fact, their combined use increased the explanatory power for mortality and CV 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,¹⁶⁻¹⁷ again an observation emphasizing the importance of nontraditional risk factors. In this regard, it is important to note that the combination of 2 biomarkers, CRP and BNP, was almost as informative as the combination of 3 biomarkers. This finding has biological plausibility because the third biomarker we considered (ie, ADMA) is a factor that is associated with both atherosclerosis and cardiovascular remodeling (ie, 2 pathologic process separately and perhaps more accurately reflected by CRP and BNP). This observation in no way detracts from ADMA being a risk factor of primary importance. In fact, the role of this factor in the high mortality of dialysis patients again is highlighted further by the present analysis.⁹ It is worth noting that the 2 biomarkers that formed the best prognostic combination, BNP and CRP, both possess the major characteristics required for a marker to be recommended for wide use in clinical practice, namely that the proposed biomarker should provide independent information in risk or prognosis beyond that available from global

assessment algorithms such as the Framingham risk score and that it should be easy to measure and cost effective in outpatient settings. The ideal biomarker also should have the characteristic that a reduction in its levels leads to reduced vascular risk, but this is not a critical issue for risk prediction.

Just completed¹⁸ and ongoing trials should 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 also may have other far-reaching implications because the measurement of circulating levels of these substances may be useful also for comparing the cardiovascular burden of diverse dialysis populations. The determination of cause of death by using death notifications notoriously is inaccurate,¹⁹ and a poor correlation between the type of cardiac death as determined by clinicians and as determined by an expert panel has been noted by comparing death notifications to the USRDS and the corresponding adjudicated deaths in the HEMO study.²⁰ On the other hand, registered comorbidities may not reflect accurately the actual severity of underlying organ damage. 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 that may result useful both for clinical research and for benchmarking.

In conclusion, traditional risk factors explain approximately half of the mortality variation in the ESRD population. The combined use of 2 biomarkers reflecting inflammation and left ventricular mass and function increases the explained variation in mortality in this population by about one fifth. These findings identify a potential role for these biomarkers to be incorporated into diagnostic and therapeutic strategies aimed at the detection and treatment of atherosclerotic complications and heart failure prevention strategies.

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