Predictors of cardiovascular events in patients with end-stage renal disease: an analysis from the Fosinopril in Dialysis study

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Abstract

Background. Cardiovascular events (CVE) are a major cause of morbidity and mortality in end-stage renal disease (ESRD) patients. These patients are often excluded from CV clinical trials, and the prognostic factors associated with CVE in patients with ESRD have not been fully explored. A risk prediction model was created from the FOSIDIAL trial to identify factors predictive of CVE and to evaluate the relative strength of known predictors when considered together in a multivariate model.

Methods. FOSIDIAL was a prospective, randomized, double-blind study with 2-year follow-up and CVE adjudication. The study enrolled 397 patients with ESRD and left ventricular hypertrophy (LVH). CVE included cardiovascular death, non-fatal myocardial infarction, unstable angina, stroke, revascularization, heart failure hospitalization, resuscitated cardiac arrest and confirmed stroke. The model was built using a forward selection of all baseline variables. A structural equation model (SEM) was used to identify factors with an indirect association with CVE.

Results. CV history was the most important prognostic factor, followed by C-reactive protein (CRP), left ventricular mass index, diabetes and age. Smoking, low HDL, female gender and Kt/V were indirectly associated with CVE.

Conclusion. Prior CV disease, elevated CRP, LVH, diabetes or advanced age identifies patients at the highest risk for CVE. These data may be useful to detect high risk patients, to define potential targets for pharmacologic intervention, and to plan future studies in ESRD. Further research is needed to identify effective approaches that reduce the rate of CVE in these patients.

Keywords: cardiovascular disease; end-stage renal disease; morbidity; mortality

Introduction

Cardiovascular events (CVE) are a major cause of morbidity and mortality in patients with end-stage renal disease (ESRD). Based on data from the United States Renal Data System (USRDS), the 5-year survival rate for haemodialysis patients is only 34%, and CVE account for ~45% of all deaths [1]. An estimated 20% of cardiovascular deaths are attributed to myocardial infarction [1]. In France, the 3-year survival rate for incident patients starting renal replacement therapy from January 2002 to December 2004 was 62.1%. The 1-year survival rate in 2002–03 incident patients was 81% [2]. Survival is better in Europe as compared with the United States [3], but CVE still contribute importantly to morbidity and mortality.

Patients with ESRD are often excluded from cardiovascular clinical trials, despite the high prevalence of cardiovascular disease in the ESRD population [4]. As a result, little is known about the nature of CVE that occur in these patients. Several factors such as C-reactive protein (CRP) and left ventricular hypertrophy (LVH) have been shown in other studies to predict all-cause mortality, but factors that specifically predict CVE have been less widely evaluated [5–10]. Additionally, the strength of these
factors to specifically predict CVE when considered together in a multivariate model has not been fully explored.

The Fosinopril in Dialysis (FOSIDIAL) study was a 2-year, randomized, double-blind study of fosinopril (Fozitec® Merck Lipha, Lyon, France) or placebo in patients with ESRD and LVH [11]. The FOSIDIAL database was analysed to develop a multivariate predictive model for CVE in this high risk, ESRD population with LVH. The objective of this analysis was to comprehensively integrate known predictors in a simultaneous model to evaluate the association between these factors and CVE in high risk ESRD patients.

Subjects and methods

The FOSIDIAL study was conducted between October 1998 and December 2000. The study involved 47 centres in France, and it was approved by the local ethics committee at each centre. All patients provided written informed consent, and FOSIDIAL was conducted according to the principles outlined in the Declaration of Helsinki. The primary results of FOSIDIAL have been published [11]. All patients were undergoing haemodialysis for ESRD, and all had LVH, defined by a cardiac mass index >131 g/m² for men and >100 g/m² for women within 3 months of enrolment. Patients were randomized to fosinopril or placebo for 24 months. The primary endpoint was the occurrence of CVE, defined as the composite of cardiovascular death, non-fatal myocardial infarction, unstable angina, stroke, revascularization (percutaneous coronary intervention or coronary artery bypass grafting), hospitalization for heart failure, resuscitated cardiac arrest and confirmed stroke at 24 months. All CVE were adjudicated by a central event adjudication committee using prospectively defined criteria [11].

Statistical methods

A risk prediction model was created for the composite CVE endpoint described earlier. The variables for inclusion in the model were selected for the blinded cohort based on statistical and clinical considerations. Binary logistic regression was used as an appropriate analysis technique for dichotomous CVE occurrence. The analysis was conducted on the full set of randomized patients [intention to treat (ITT) sample]. The same analysis was repeated on the per protocol sample, which consisted of 380 patients [15 patients (8 placebo, 7 fosinopril) withdrew from the study early because of renal transplantation and 2 placebo patients represented protocol violations]. The analysis was also conducted in the ITT placebo sample (n = 201).

A total of 130 (32.7%) patients experienced a CVE during the 24-month study period. Baseline characteristics and potential individual predictors are displayed in Table 1.

Main model results

The final model results are shown in Table 2. The model findings were not different when the analysis was performed on the per protocol sample and the ITT placebo sample, except for P-values which were larger for the placebo sample since the population was smaller. A backward selection provided the same model. Three continuous covariates and three binary variables constitute the final model. The prevalence of each binary variable was considered as sufficient in the context of a prognostic model (diabetes 32.2%, CV history 29.3%, uncontrolled hypertension 60.7%). The overall predictive characteristics of the model are shown in Table 3.

CV history entered first in this model, followed by CRP, left ventricular mass index (LVMI), diabetes and age. The incidence of CVE was 54% in patients with a CV history and 24% in those without a CV history. CV history included a history of coronary artery disease (CAD), peripheral artery disease (PAD) or stroke.

CRP was also predictive of CVE. The relationship between CVE and CRP was not linear, and it was better described by a logistic curve. The CVE risk was small for low CRP values, but it significantly increased above 10 mg/l as determined by ROC. A higher CVE was observed in patients with CRP values >10 mg/l, particularly in patients without a CV history.

LVH had a linearly global negative association with CVE risk. The relative risk for CVE was 1.68 among patients with LVMI >180 as compared with patients with LVMI above 100 (women) or 131 (men) and less than 150. Patients with a CV history and LVMI >180 had a CVE RR of 2.66 as compared with patients with a CV history and LVMI above 100 (women) or 131 (men) and less than 150 (P = 0.18).
Diabetes mellitus constitutes the fourth strongest determinant baseline predictor of CVE incidence. The association was essentially only observed in patients with a history of CV disease. This observation was present for both SBP and DBP, although it was more pronounced for DBP. The relative risk associated with hypertension or hypotension (DBP < 70 mmHg and DBP < 120 mmHg) was 1.35, and it was slightly higher for patients without prior CVE. The lowest CVE rate was observed in normotensive patients, irrespective of their CV history. This observation was present for both SBP and DBP, although it was more pronounced for DBP. The relative risk associated with hypertension or hypotension (DBP) as compared with normotension was 1.35, and it was slightly higher for patients without a CV history ($RR = 1.48$).

### Structural equation modelling results

The SEM results are shown in Figure 1. The model provided evidence of goodness of fit with the studied sample [chi-square GF test, $P = 0.23$, Adjusted $R^2 = 0.392$.]
Goodness of Fit Index (AGFI) = 0.963. Factors that were not independent predictors in the prognostic model were found to be associated with CVE through the main predictors. HDL had an apparently important but indirect association with CVE through its association with decreasing LVH and CRP. Smoking habits were related to CVE, but through baseline CV history. Diabetes was also an important aggravating predictor of CV history, but it also had an additional association with CVE risk. Blood pressure control had a modest beneficial association with CVE.

The unexpectedly modest contribution of age in our predictive model may be due to the presence of CV history in the model. CV history takes into account age and many other indirect covariates. As a result, CV history constitutes an ideal covariate that summarizes baseline severity.

Diabetes, smoking and CRP were associated with CV history. Diabetes and CRP had an additional association with subsequent CVE beyond the baseline presence of CV history. This observation supports the interaction detected on the descriptive analysis between these variables and CV history. LVH was associated with an increased risk of CVE, and this relationship was aggravated by the patient’s CV history (Figure 1). This finding supports the observation of a suspected interaction between CV history and LVH.

Gender appears to be associated with multiple indirect relationships. Women had a higher HDL mean value, which was indirectly associated with CVE through CRP and LVH. Secondly, fewer women were smokers as compared with men, and this factor had a beneficial relationship with decreasing the baseline rate of CVE history in women. Finally, female patients tended to have higher Kt/V values, which in turn was positively associated with normotension, and a lower rate of CVE. BMI had multiple small indirect associations with increasing diabetes risk, decreasing HDL value and decreasing the Kt/V index. Kt/V had an indirect relationship with CVE. Higher values of Kt/V increased the probability of controlled DBP, which in turn, were associated with a lower CVE incidence (Figure 1).

Treatment and compliance effects were studied as additional variables within the frame of the model. Because compliance during the trial may be dependent on perceived efficacy, we used compliance during the first two months of the study. Treatment and compliance main effects and their first-order interaction entered the model, and only the interaction appeared to be significant ($P = 0.05$). The main effects of treatment and compliance considered separately were not significant. Thus, a modest beneficial association between fosinopril and CVE was detected only when compliance was considered. This observation supports the FOSIDIAL finding of a trend towards fewer CVE in patients randomized to fosinopril [11].

**Discussion**

Based on these data from the FOSIDIAL study, ESRD patients with pre-existing cardiovascular disease,
elevated CRP, LVH, diabetes and advanced age had the highest risk of CVE during 24 months of follow-up. These data present a unique opportunity to understand the prognostic strength of these variables when analysed together and to evaluate the direct and indirect associations between these predictors and clinical outcomes. This analysis provides a comprehensive evaluation of the factors that are related to CVE in high risk patients with ESRD.

The finding that prior CV disease was the main prognostic factor has important implications for clinical practice and research in ESRD patients. Efficacy of an investigational drug may depend in part on the presence or absence of CV disease at baseline. Consideration should be given to stratifying for prior CV disease or performing separate trials in patients with and without prior CV events.

These data suggest that classic CV risk factors differ among ESRD and non-ESRD patients. Diabetes was only relevant in patients with a history of CV disease. Smoking, LDL, HbA1C, BMI and gender were not directly associated with prognosis in the study population. It is possible that the dominant influence of CV history prevented the detection of factors that were of less prognostic importance. It is also plausible that the mechanism for CV events differs in ESRD patients. If the pathophysiology differs, then established treatments that are effective in non-ESRD populations may be ineffective in ESRD patients. Since neither LDL nor HbA1C were significantly related to CVE, LDL lowering therapies or treatments targeting glycaemic control may be ineffective in this patient group. For instance, the recent German Diabetes and Dialysis study of atorvastatin was conducted in patients with ESRD, but it did not show a reduction in cardiovascular morbidity or mortality [13]. More research is needed to identify effective therapeutic strategies in high risk patients with ESRD.

Importantly, this analysis identified a group of patients without a history of CV disease who were at high but modifiable risk. Patients with diabetes, elevated CRP and elevated LVH without a prior CV history have a high risk of CVE, and it may be possible to reduce this risk with targeted therapies. Pharmacologic agents that reduce inflammation and oxidative stress (i.e. antioxidants, folic acid or statins) or that promote LVH regression (i.e. renin angiotensin aldosterone system inhibitors or beta adrenergic antagonists) may be good candidates for future study in these patients. For example, the risk adjusted analysis of the FOSIDIAL study showed that fosinopril may reduce CVE in patients with ESRD and LVH [11]. Interventions targeting diabetes or inflammation may be most effective as primary rather than secondary prevention strategies since they were more powerful CVE predictors in patients with no history of CV disease. Recent secondary prevention studies of folic acid in non-ESRD patients with acute MI, stroke, known vascular disease or diabetes have failed to demonstrate a benefit in terms of CV risk [14,15], but it is possible that these findings may have been different in a primary prevention population.

Comparison of findings with other published reports

Elevated CRP is present in as many as 70% of patients with ESRD [5,9]. CRP was an independent predictor of mortality in a study of 224 haemodialysis patients after adjusting for age, race, diabetes, body surface area and cardiac troponin T, but the association was smaller than that detected in the FOSIDIAL model [5]. Tripepi et al. [9] have also shown that IL-6 and CRP were independent predictors of mortality. Although traditional risk factors were included in these models, LVH was not specifically listed among the considered variables. In our study, elevated CRP and LVH were both independently associated with CVE.

LVH has been associated with CVE in patients with ESRD [6,8]. These studies differ from FOSIDIAL in that the timing of LV mass measurement was remote from study enrolment (1 year) [6], whereas LV mass was measured within 3 months of randomization in the FOSIDIAL study. Other studies measured LVH by electrocardiogram [8]. These factors and other differences in study populations may account for the greater risk associated with LV mass in our study.

An interesting finding of our analysis was that LVH was an important predictor of CVE even though all patients had baseline LVH. In contrast, other studies that have reported LVH as a prognostic marker had a prevalence of LVH ranging from 65% to 75% [6–8,10]. The relative risk of CVE in this analysis was more than 60% higher for patients with the largest LVMI (>180) compared with those who had a lesser degree of LVH. The relative risk of CVE exceeded 2.5-fold for patients with the largest LVMI (>180) who also had a prior history of cardiovascular disease. Thus, this observation demonstrates that the adverse prognostic risk is associated with the degree of LVH, and not only the presence of LVH. This finding is hypothesis generating, and therapies that promote LVH regression may be associated with lower CVE risk even if they do not fully reverse the remodelling process.

The observation of the non-linear association between blood pressure and CVE is consistent with other studies evaluating the influence of blood pressure on mortality. Pre-haemodialysis SBP was associated with an increased relative risk of mortality over a mean follow-up of 2.6 years in an analysis of 5433 haemodialysis subjects [16]. A significantly higher mortality risk was also associated with post-dialysis SBP. In an analysis of 4499 US haemodialysis patients, the adjusted relative mortality risk was 1.86 for pre-dialysis SBP <110 mmHg [17]. Low DBP has also been associated with increased mortality [18,19].

Prognostic value of dialysis variables

Dialysis variables were not directly associated with CVE. Higher Kt/V was indirectly associated with
a lower rate of CVE, and this relationship appeared to be mediated through better blood pressure control. In a recent analysis of 22,000 patients enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS), higher Kt/V was independently associated with lower mortality [20]. In contrast, dialysis dose as measured by Kt/V was not associated with survival in a randomized trial of 1846 haemodialysis patients [21]. Blood pressure data were not reported in this study.

The finding that duration of dialysis was not directly associated with CVE in this analysis may be related to the characteristics of the study population. Patients in FOSIDIAL had been receiving dialysis for a mean of 2 years, and few patients with a recent onset of dialysis treatment were included. Patients who survive for this length of time after dialysis onset may be selected survivors. The results may have been different if patient’s recently beginning haemodialysis had been included. In addition, our endpoint of interest was CVE. Dialysis variables may have been predictive of other endpoints.

**Future ESRD clinical investigation**

For future ESRD trials, the patient population should exhibit risk factors that are modifiable by the pharmacologic intervention being studied. For example, investigations of agents that target CV remodelling, inflammation or oxidative stress should consider enrolling patients without a CV history, LV mass >131 g/m² (men) or >100 g/m² (women), CRP >10 mg/l and advanced age. Consideration should be given to stratifying for diabetes. Attention should also be placed on the degree of LVH, not only on the presence of LVH.

This analysis provides researchers with data that can be used to select a study population with high but still modifiable risk. Identifying a high risk group is useful to decrease sample size, but it is important to recognize that these patients may be too severely ill to benefit from certain therapies. A better understanding of the pathophysiology in these patients is needed to identify what aspects of disease are reversible and which are irreversible, so that targeted and effective therapeutic interventions can be developed.

The consideration of these predictors a priori may be useful in designing adequately powered studies in ESRD. A minimum sample size of 280 patients per group would be needed for an unadjusted analysis to detect a minimum risk difference of 10% in favour of the tested drug using a one-sided test at the 95% confidence level with 80% power, assuming a placebo CVE incidence of 30%. Only 220 patients per group would be needed in an adjusted analysis, based on our estimate of a determination coefficient. Although external validation of our findings would strengthen the application of these data for future study design, large data sets that fully capture the variables in our model are not immediately available to perform such an analysis. In the interim, the findings of our model may aid in performing initial sample size calculations. The best strategy is likely a self monitored trial, where the initial sample size is estimated based on these findings, and the exact sample size is modified as necessary by monitoring the estimated standard deviation and R-value, thus allowing the sample size to be determined with precision.

**Limitations**

This analysis was based on a reasonable, but not large, sample size. No a priori measures were taken to limit type I error accumulation. In addition, due to the well-known lack of power associated with interaction tests, some results were discussed that were associated with significance lower than the 95% confidence limit. The confidence levels were documented for each result. The consistency of results was tested by repeated analyses on different samples and by testing the reliability of our findings using an appropriate systemic structural approach.

This model originated from data collected in a prospective, randomized, controlled trial. Thus, we can ascertain associations based on these data, but we cannot determine causality. Although the data collection was comprehensive, other variables that were not collected in the database could be prognostically important. Due to the recruitment methods used to enrol patients into randomized, controlled trials (i.e. inclusion/exclusion criteria, informed consent requirements), our sample cannot a priori be considered as representative of ESRD, particularly because the centres were not randomly selected. However, several factors enhance the likelihood that these findings are generalizable to the broader ESRD population. The 47 study centres used were reasonably distributed throughout the country and the French health care environment. In addition, the eligibility criteria were not restrictive, and very few patients refused to provide informed consent. Finally, the main objective of the randomized, controlled trial was to study the effect of fosinopril on CVE. The model was well fitted on the placebo sample. In the overall data set, no treatment interaction was detected. The treatment effect was additive with the other main effects. In addition, there was no site effect interaction.

This analysis was strengthened by using a clinical trial data source in several important ways. First, FOSIDIAL obtained 2 year follow-up in all patients. This length and quality of follow-up may be difficult to achieve outside of a clinical trial. In addition, all CVE were adjudicated by a clinical events committee using pre-specified definitions. Thus, the determination of CVE was made using a consistent process with uniform criteria. Finally, few reasonably sized ESRD data sets are available from which to develop prognostic models specifically evaluating CVE. The FOSIDIAL database provided a unique opportunity to explore predictors of CVE among patients with ESRD. In the absence of a large observational database, the FOSIDIAL database provided an appropriate data source in which
to explore CVE predictors in ESRD patients. Larger studies are needed to confirm and extend our findings.

**Conclusion**

ESRD patients are at high risk of death and adverse cardiovascular outcomes. The presence of prior cardiovascular disease, elevated CRP, LVH, diabetes or advanced age identifies patients at the highest risk for CVE. Further research is needed to identify effective approaches that reduce the rate of CVE in these patients. Until evidence-based data are available to guide treatment, patients with these factors should be closely monitored and cardiovascular protection therapies should be optimized in an effort to reduce mortality and morbidity in this high risk population.

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**References**


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