DIALYSIS update

# Sudden cardiac death in dialysis patients

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## Contents



## Preface

Sudden cardiac death (SCD) is responsible for 25% of the mortality rate among dialysis patients. It highlights the burden of cardiovascular lesions associated with the chronic kidney disease (CKD). Many studies have tried to identify factors associated with this risk. As it is much higher in end-stage renal disease (ESRD) than in non-renal subjects with cardiovascular history, other risk factors than traditional ones are under the spotlight. Vitamin D deficiency is one of them. Bone mineral metabolism and vasculature keep up some “liaisons dangereuses” in CKD patients. Vitamin D findings are not a surprise even if the causality remains questionable. Besides exposition to hyperkalaemia and fluid overload after the weekly long dialysis-free interval, the potentially hazardous intradialytic ionic and fluid shifts question the adequacy of standard sequential dialysis prescription. However, the fact that SCD is as frequent in peritoneal dialysis as in haemodialysis patients suggests that factors shared by ESRD patients are probably as important as the specific ones related to dialysis mode.

Further prospective studies with close collaboration with cardiologists will allow designing adequate prevention, including cardioverter defibrillator needed in selected patients.

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## 1. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality

In dialysis patients ultrafiltration (UF) is of paramount importance to maintain volume control, but simultaneously it is associated with non-physiological fluid shifts and haemodynamic instability. Consequently, these factors may contribute to tissue ischaemia, maladaptive cardiac structural changes, arrhythmia, and sudden cardiac death. **Flythe JE et al.** thus investigated the associations between UF rate and both, all-cause and cardiovascular (CV) mortality in haemodialysis (HD) patients.

Study data originated from the HEMO study, a multicenter, randomised trial to investigate the effects of dialysis dose and membrane flux on clinical outcomes, with the primary outcome variable being mortality. The HEMO study patients were included between March 1995 and October 2000, had been on HD for at least three months and received HD three times per week. UF volume was measured as the change in weight over the course of dialysis (i.e. predialysis weight minus post-dialysis weight). UF rate was expressed in terms of ml/h/kg by dividing the UF volume by dialysis session length and target weight, and categorized as ≤10 ml/h/kg, 10–13 ml/h/kg, and >13 ml/h/kg based on precedent in the literature.

The mean UF rate for the total cohort (n=1846, mean age 57.6 ± 14 years) was 12.1 ± 4.6 ml/h/kg. 34.9%, 28.0%, and 37.1% of patients had UF rates ≤10, 10 - 13, and >13 ml/h/kg, respectively. High UF rate was statistically significantly associated with increased interdialytic weight gain and shorter HD session length. Compared to UF rates ≤10 ml/h/kg, UF rates >13 ml/h/kg were significantly associated with increased all-cause and CV mortality with adjusted hazard ratios (HR) of 1.59 and 1.71, respectively. UF rate between 10 and 13 ml/kg/h was not significantly associated with greater all-cause mortality and CV mortality. Only among patients with congestive heart failure there was a significant association between this UF rate category and all-cause mortality. To examine the thresholds at which UF rate may become harmful, the authors performed a secondary analysis. Thereby a cubic spline interpolation depicted that HRs for both, CV and all-cause mortality rose sharply at values between 10 and 14 ml/h/kg, and to a notably less extent at higher values (see **Figure 1**). Secondary analysis also showed that UF rate >13 ml/h/kg was significantly associated with a greater hazard for the composite outcome of CV hospitalization and CV mortality, whereas UF rate 10–13 ml/h/kg was not.

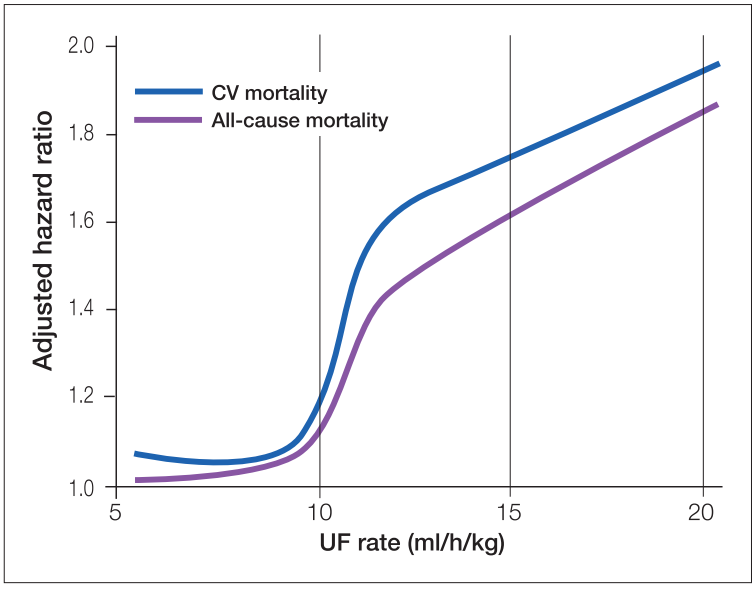


***Fig. 1:*** *Cubic spline analysis of the associations between UF rate and CV and all-cause mortality.*

According to the authors it was demonstrated for the first time that higher UF rates are associated with greater CV mortality. During dialysis, fluid is removed directly from the vascular space. When dialytic removal exceeds resorption from other compartments, circulating volume is reduced and transient myocardial ischaemia can result. This transient ischaemia could result in 'myocardial stunning', i.e. regional wall motion abnormalities. From animal studies, it is known that repeated myocardial stunning triggers a cascade of events, including fibrosis and remodeling, which predispose to ventricular dysfunction and arrhythmia.

Classifying high UF rate as a putative CV risk factor, Flythe et al discuss that there are two options to minimize UF rates in current clinical practice: first, restrict patients' fluid intake and secondly, allow more time for fluid removal.

*In conclusion, the present study reveals that among chronic HD patients, UF rates >13 ml/h/kg are associated with increased all-cause and CV mortality. CL*

Flythe JE, Kimmel SE, Brunelli SM: Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality; Kidney Int 79, 250 - 257, 2011

## 2. Modifiable risk factors associated with sudden cardiac arrest within haemodialysis clinics

Sudden cardiac arrest (SCA) is the most common cause of death among patients with end-stage renal disease maintained on HD. **Pun PH et al.** performed this study to better identify modifiable risk factors associated with the occurrence of HD-associated SCA. They were particularly interested in examining modifiable elements in the dialysis prescription that contribute to excess SCA risk.

43,200 patients on long-term HD treatment in 565 outpatient dialysis clinics of a large dialysis organization in the US were examined from 2002 - 2005. A case-control study design was used to compare in-clinic SCA patients (defined as patients who experienced an SCA within the facility of the outpatient HD clinic) with selected matched controls. 784 patients were identified who experienced a documented SCA within dialysis facilities which corresponds to an event rate of 4.5 events per 100,000 dialysis sessions or approximately 1 in 142 patient-years. After excluding patients with missing data and those with < 90 days of dialysis data, the clinical and dialysis-specific data of 502 patients who experienced an SCA were compared with 1632 age- and dialysis-vintage-matched controls.

The following results were found:

- The proportion of patients exposed to low potassium dialysate (< 2 meq/L) during the last recorded dialysis treatment was nearly double that of matched controls (17.7% vs. 9.3%, $p < 0.0001$) (see **Figure 2**). The relationship persisted even after adjusting for preexisting cardiac comorbidities and predialysis serum electrolyte levels. Even an increased risk of SCA with use of low potassium dialysate < 2 meq/L among patients with predialysis serum potassium levels above 5.0 meq/L was observed. Thus no advantage of using low potassium dialysate < 2 meq/L at any level of serum potassium was found.

- SCA subjects showed a significantly greater exposure to low calcium dialysate < 2.5 meq/L than the control group (11.8% vs 6.2%, $p < 0.0001$), which persisted in the adjusted model.

- Traditional cardiac risk factors including diabetes, congestive heart failure, coronary heart disease, a preexisting history of cardiac arrhythmia, and hyperlipidaemea were not significantly associated with an increased risk of SCA in the adjusted model.

- Prescription of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and activated vitamin D were independently associated with SCA, but there was no significant relationship between cardiovascular medications including aspirin, ß-blockers and statins and outcome in the adjusted model.

- Serum creatinine (7.0 vs 7.9 mg/dl, $p < 0.0001$), albumin (3.6 vs 3.7 mg/dl, $p = 0.005$), and haemoglobin (11.6 vs 11.8 g/dl, $p = 0.002$) were significantly lower among SCA patients, whereas serum bicarbonate levels were slightly higher among these patients (22.0 vs 21.0 meq/L, $p < 0.001$).

- SCA patients had a lower post-dialysis weight (67.1 vs 70.6 kg, p = 0.03) and a greater proportion of their post-dialysate weight removed through ultrafiltration (3.8% vs 3.5%, p < 0.001) expressed as an average over the 90-day study period leading up to the event.

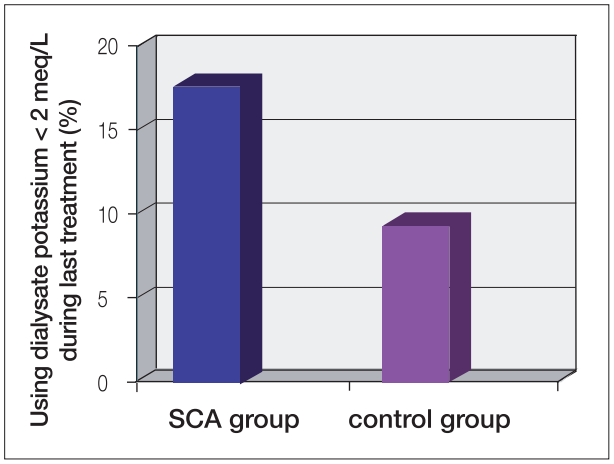


***Fig. 2:*** *Proportion of SCA and control cohorts who were prescribed dialysate potassium < 2 meq/L.*

*In summary, the authors found that modifiable elements of the HD prescription are crucial in determining peridialytic SCA risk and that these factors were more influential than traditional SCA risk factors. More focused attention to HD factors such as the management of dyskalaemia and volume homeostasis may significantly improve the risk profile of patients with end-stage renal disease.* *KB*

Pun PH, Lehrich RW, Honeycutt EF, Herzog CA, Middleton JP: Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics; Kidney Int 79, 218 – 227, 2011.

## 3. Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients

Vitamin D deficiency is observed in the vast majority of HD patients, and there is accumulating evidence that vitamin D, beyond its effects on bone and mineral metabolism, is also crucial for cardiovascular health and protection against infectious diseases. In view of the particularly high incidence of sudden cardiac death (SCD) in dialysis patients, accounting for one quarter of all deaths, **Drechsler C et al.** wanted to get a better understanding of the diagnostic and probably therapeutic implications of vitamin D in these patients. Therefore, they investigated the effect of 25-hydroxyvitamin D [25(OH)D] levels on SCD in relation to other cardiac, vascular, and infection-related outcomes in a large well-characterized cohort of HD patients (vitamin D is hydroxylated to 25(OH) D in the liver).

Between 1998 and 2002, a total of 1255 HD patients were included into the German Diabetes and Dialysis Study (4D study), of whom 1108 had a measurement of 25(OH)D at baseline. The mean follow-up period was 3.96 years on atorvastatin and 3.91 years on placebo. The primary analysis showed no significant effect of atorvastatin treatment on cardiovascular events (CVEs). In the patient group with a measurement of 25(OH)D at baseline, the mean age was 66 years, 54% were male and median 25(OH)D was 39 nmol/L (interquartile 28-55) at baseline. A total of 545 patients died, of whom 146 patients died of SCD. Furthermore, 37 patients died due to heart failure, and 111 patients due to infection. 174 patients experienced a myocardial infarction (MI) and 89 patients experienced a stroke.

Vitamin D status at baseline was strongly associated with the risk of SCD (see **Figure 3**). By Cox regression analysis, the unadjusted hazard to experience SCD was 3-fold higher in patients with severe vitamin D deficiency [25(OH)D of ≤ 25 nmol/L] as compared with those with sufficient 25(OH)D levels (>75 nmol/L) (HR: 2.99, 95%CI: 1.39 – 6.40). Patients with severe vitamin D deficiency had an adjusted 80% higher risk of experiencing a CVE and a 79% higher risk of all-cause mortality as compared with patients with sufficient vitamin D status. In categorical analysis, patients with severe vitamin D deficiency had a 2.8-fold increased risk of stroke compared with those with normal levels (adjusted HR: 2.58, 95%CI: 0.74-8.98). Deaths due to infection were almost 2-fold increased

in patients suffering from severe vitamin D deficiency (adjusted HR: 1.55, 95%CI: 0.64 - 3.73). In contrast, no association of vitamin D status with MI was found.

The authors point out that the associations of vitamin D deficiency with CV risk factors including type 2 diabetes, arterial hypertension, malnutrition, and inflammation may hypothetically explain the increased mortality risk in patients with low 25(OH)D levels. Moreover, the data from the Multi-Ethnic Study of Atherosclerosis suggest that vitamin D deficiency is prospectively associated with increased risk of coronary artery calcification. However, the strong association of vitamin D deficiency with SCD but not with MI might suggest that atherosclerosis related to vitamin D deficiency might not be the main pathophysiological link for the findings of the study. Direct vitamin D effects on the myocardium, which expresses the vitamin D receptor as well as 1α-hydroxylase, may therefore be of importance.

*In conclusion, the study results show that low 25(OH)D levels are associated with increased risks of SCD, CVE, and all-cause mortality, and there was a borderline non-significant association of vitamin D deficiency with increased risk of strokes and fatal infections. KB*

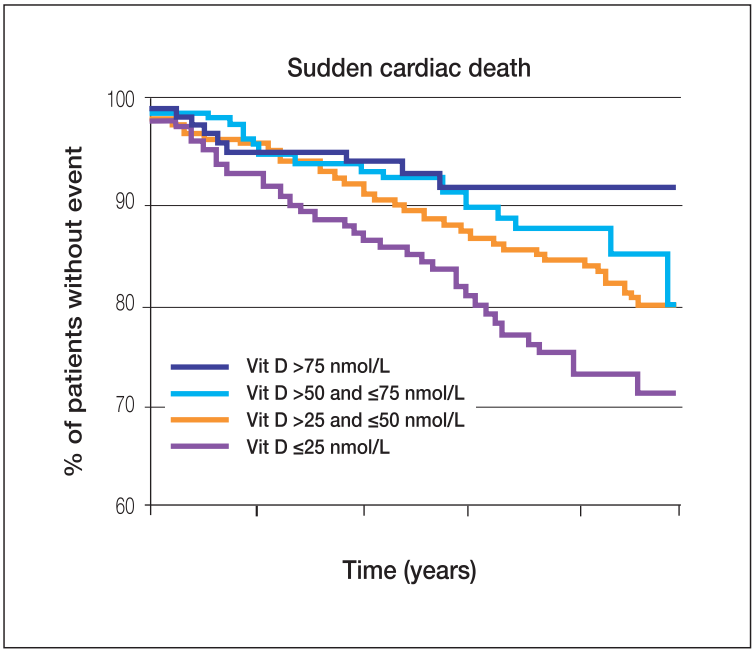


***Fig. 3:*** *Kaplan-Meier curves for the time to sudden cardiac death and different 25-hydroxyvitamin D levels at baseline.*

Drechsler C, Pilz S, Obermayer-Pietsch B, Verduijn M, Tomaschitz A, Krane V, Espe K, Dekker F, Brandenburg V, März W, Ritz E, Wanner C: Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients; Eur Heart J 31, 2253-2261, 2010.

## 4. Sudden cardiac death in end-stage renal disease patients: a 5-year prospective analysis

There exist few prospective data on risk factors associated with sudden cardiac death (SCD) in end-stage renal disease (ESRD) patients and practically none in long-term peritoneal dialysis (PD) patients. Thus, **Wang AY et al.** from Hong Kong tested in their prospective observational cohort study the role of clinical and echocardiographic parameters and serum biomarkers in predicting SCD in prevalent PD patients. This study was performed at a single dialysis centre between 1999 and 2005. 117 men and 113 women were recruited, representing 85% of the entire PD population in the centre. All of the patients were followed up for five years from the day of baseline assessment until death, or until they underwent kidney transplant. No patient was lost to follow-up, and all were treated with conventional lactate-buffered, glucose-based PD solutions. At study baseline, 2D-echocardiography was carried out and venous blood sample was collected for the measurement of albumin, fasting lipids, renal function, bone profile, intact parathyroid hormone, haemoglobin and the biomarkers cardiac troponin T (cTnT), N-terminal probrain natriuretic peptide (NT-pro-BNP), high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), fetuin-A, and myeloperoxidase (MPO).

Mean age of patients was 56 ± 11 years and their median dialysis duration was 26 months. During the 5-year follow-up 115 deaths occurred, of which 28 deaths were attributed to SCD. Of the biomarkers only cTNT and NT-pro-BNP were significantly as-

sociated with SCD in the univariate Cox regression analysis. A significant graded increase in the risk of developing SCD was found with increasing tertiles of cTNT and NT-pro-BNP (see **Figure 4a** and **4b**). In the multivariable Cox regression model considering clinical, biochemical, dialysis and echocardiographic parameters, left ventricular (LV) systolic dysfunction was the most significant predictor of SCD, followed by a high systolic and a low diastolic pressure. An ejection fraction ≤48% was the best cut off threshold in predicting an increased risk of SCD. The authors discuss that poor LV systolic function may predispose to heart failure and increase the risk of electric instability and ventricular arrhythmia. When not considering echocardiographic parameters in the Cox model, but instead the biomarkers cTNT, NT-pro-BNP and fetuin-A, NT-pro-BNP was independently predictive of SCD and more significant than cTNT in predicting risk of SCD. However, in the combined echocardiography and biomarker-based Cox model NT-pro-BNP did not retain independent significance, whereas LV systolic dysfunction and cTnT kept a significant independent association with SCD. Importantly, systolic hypertension and diastolic hypotension consistently remained independent significant risk factors in all of the 3 multivariable Cox regression models.

The findings on cTNT and NT-pro-BNP have several important clinical implications in ESRD patients. NT-pro-BNP may be used instead of echocardiography, but has no added value over this diagnostic method in predicting SCD risk. If echocardiography is not available, then NT-pro-BNP appears to be the most useful serum biomarker in predicting SCD compared with cTnT. On the other side, cTnT has an additional value because it gives independent predictive value for SCD beyond echocardiography.

*In conclusion, an even mild left ventricular systolic dysfunction (ejection fraction <48%) predicted an approximately threefold increased risk of SCD and measurement of cTnT, a highly sensitive marker of myocardial damage, gives additional prognostic value in ESRD patients.* *CL*

Wang AY, Lam CW, Chan IH, Wang M, Lui SF, Sanderson J: Sudden cardiac death in end-stage renal disease patients: a 5-year prospective analysis; Hypertension 56, 210 - 216, 2010

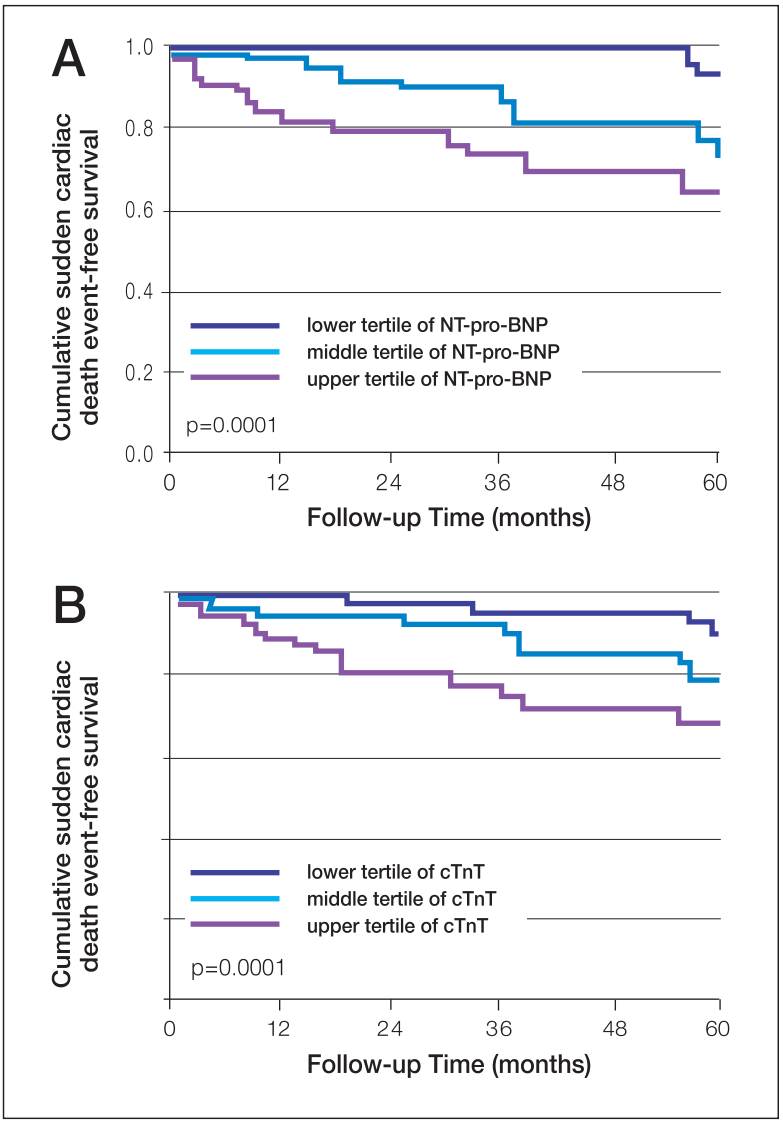


***Fig. 4a and 4b:*** *Cumulative SCD event-free survival probability of patients stratified by tertiles of NT-pro-BNP (Fig.* 4a) and cTNT (Fig. 4b).

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