

Congress Service

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November 4-9, 2008, Philadelphia, PA, USA



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1. Anemia

Relationship between Haemoglobin, EPO Dose, and Mortality in a Cohort of 649 HD Patients from the UK, Spain, and Sweden: High EPO Doses are Associated with Reduced Survival

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Much discussion has focused in recent times on the relationship between haemoglobin and mortality, and the importance of EPO dose and sensitivity is increasingly recognised. Using the same protocol in all three centres, we retrospectively collected data from the databases of three renal units to examine survival in a cohort of HD patients in relation to achieved haemoglobin and EPO dose (U/kg/wk). A total of 649 prevalent patients (55% males; median age 67 [20-92] years) receiving regular HD and ESA therapy were included.

The median Hb for the entire cohort was 12 g/dl, and the median epoetin dose was 128.6 U/kg/wk. Patients were divided into 4 groups according to whether the Hb and EPO dose were above or

below the median, as follows: (1) High Hb, Low EPO; (2) High Hb, High EPO; (3) Low Hb, Low EPO; (4) Low Hb; High EPO, and the survival of each group over the subsequent 27 months was analysed using Kaplan-Meier plots (log rank χ^2 10.95; $p=0.01$).

Survival was best in the High Hb, Low EPO cohort (reference HR=1.0) and worst in the Low Hb, High EPO cohort (adjusted HR=2.04), and there was a 60% increased risk of death in patients receiving high doses of EPO despite good haemoglobin levels (HR=1.60 [1.02-2.51]).

This analysis has the usual limitations of an observational study, but it is nevertheless a concern that the patients on the highest doses of EPO had the greatest mortality, independent of their achieved Hb.

Cox proportional hazard ratios of Hb/EPO dose in relation to mortality

	Crude	Adjusted for age, sex and diabetes
High Hb, Low EPO	1.00	1.00
High Hb, High EPO	1.39 (0.89-2.17)	1.60 (1.02-2.51)
Low Hb, Low EPO	1.36 (0.87-2.13)	1.33 (0.85-2.07)
Low Hb, High EPO	1.90 (1.28-2.81)	2.04 (1.37-3.02)

Hemoglobin Variability and Its Association with Erythropoiesis Stimulating Agent (ESA) Use and Mortality in a Chronic Kidney Disease (CKD) Population: An International, Multicenter Study

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Aim: To describe hemoglobin variability in a pre-dialysis population and examine its association with ESA use and mortality.

Methods: This cohort study involved 22 centers in 7 countries. An individual patient hemoglobin variability was defined using 6 month baseline data between 1st January 2003 and 31st October 2005. A variety of definitions were examined: the residual standard deviation (SD) of Hb, change in consecutive hemoglobin levels, hemoglobin amplitude and categorisation of hemoglobin values. Patients were followed until 30th April 2007 for the primary outcome of mortality.

Results: In total 6165 CKD patients were followed for a mean of 34 ± 15.8 months. 49% were prescribed an ESA. The residual SD of hemoglobin was 4.9 ± 4.4 g/L in those patients not taking ESA

throughout the baseline period, compared to 6.8 ± 4.8 g/L for those on ESA, $p < 0.0001$. With any definition of hemoglobin variability, there was a statistically greater degree of variability in patients prescribed ESA ($p < 0.0001$ for all). The residual SD of hemoglobin was associated with a significantly increased risk of death, $HR = 1.03$ (95%CI 1.02-1.04) per g/L and this was independent of ESA use.

Conclusions: Hemoglobin variability is increased in CKD patients prescribed ESA, however its association with an increased risk of death holds true even in those not on ESA. Hemoglobin variability may well be another more sensitive marker of associated comorbidities. Targeting hemoglobin variability with specific agents may not be warranted until further studies have been conducted.

Dialysis Modality and Inflammatory State are the Principal Determinants of Hemoglobin Variability in Stable ESA Treated CKD Patients

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There is emerging evidence to suggest that hemoglobin variability is associated with poor outcomes in ESA treated patients. The commonest cause of hemoglobin variability is frequent dose changes and poor compliance. Contribution of co-morbidity associated factors in the causation of hemoglobin variability remains unclear. We conducted this study in stable ESA treated patients with no dose changes to determine the contribution of prescribing pattern independent factors in the causation of hemoglobin variability.

All nephrology patients starting an ESA from 2004 to 2006 in a single centre were retrospectively analysed. Stable dose of ESA was defined as no dose change over a one year period. We also excluded all patients who had hospital admissions.

A linear regression of hemoglobin over time for each patient was performed and residuals about the linear regression line were determined. Hemoglobin variability was assessed by determining the standard deviation of the residuals for each patient.

Our study group was divided into tertiles (n= 62) of high, medium and low hemoglobin variability.

These results show that inflammatory state as determined by CRP and ferritin and dialysis modality of CAPD was associated with increased hemoglobin variability.

These data will be useful in the design of future RCT where hemoglobin variability is the primary outcome measure.

	Low HbV (n=62)	Medium HbV (n=61)	High HbV (n=62)	p value
% of patients who had Hb >11.5 at any time	56.0	50.0	81.0	0.01
Number of excursion of >1.5g/Hb per test	0.094 (0.125)	0.282 (0.16)	0.401 (0.17)	<0.0001
CRP (mg/L)	10.8 (8.2)	13.9 (11.4)	21.6 (30.0)	0.05
Ferritin (µg/L)	287 (195)	334 (220)	429 (330)	0.01
Hb (g/dL)	12.15 (1.29)	11.84 (1.19)	11.50 (1.53)	0.02
Modality (CKD/PD/HD)	39/16/45	31/36/33	34/42/24	0.02

CRP = C-reactive Protein, Hb = hemoglobin, HbV = hemoglobin variability

Hemoglobin Variability Does Not Change with the Introduction of Erythropoietin Stimulating Agents during the First 20 Weeks in Chronic Kidney Disease Patients

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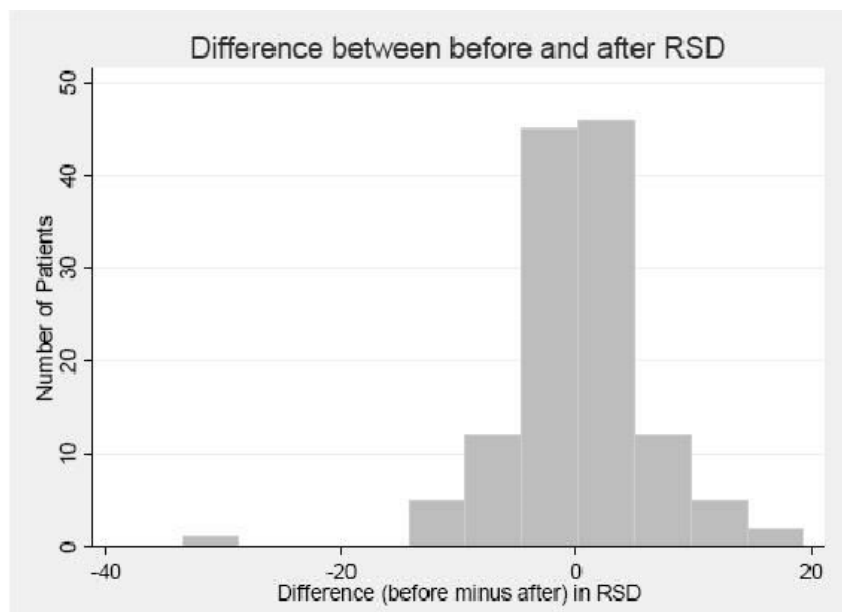
Background: Tighter control of hemoglobin with erythropoietin stimulating agonists (ESA) to recommended levels between 100-120g/L has become an important consideration. Studies indicate that greater than 90% of patients experience hemoglobin cycling while on ESA therapy with few patients remaining consistently within the target range. We are unaware of data that characterizes the hemoglobin variability in both the presence and absence of ESA therapy.

Methods: Retrospective data was obtained from the Southern Alberta Renal Program kidney disease database (PARIS) over a 24 month duration in chronic kidney disease

patients (CKD) being initiated ESA therapy (n=128). Residual standard deviation (RSD) was calculated for 20 weeks pre- and 20 weeks post-ESA therapy initiation.

Results: There was no significant difference in within patient RSD of hemoglobin levels before ESA therapy compared to after. Difference = 0.31 ± 6.18 (mean \pm SD), 95% CI of difference: 0.77 to 1.39; $p=0.57$).

Conclusions: Physiologic hemoglobin variability occurs in CKD patients regardless of ESA initiation. More studies are needed to explore the factors associated with hemoglobin variability in CKD patients during the maintenance phase.



RSD = Residual standard deviation

Association of Low Serum Calcium with ESA Hypo-Responsiveness in Hemodialysis Patients

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Background: Both hypercalcemia and high ESA dose requirements are each associated with increased morbidity and mortality in maintenance hemodialysis (MHD) patients. We hypothesized that serum calcium level may be associated with ESA responsiveness.

Methods: To determine the relationship between calcium levels and ESA dose requirements, we examined hemoglobin response to ESA treatment in a 12-month (7/2001-6/2002) cohort of 38,328 prevalent DaVita MHD patients who received ESA for at least 3 consecutive calendar quarters. Using repeated measure models, we distinguished the ESA response coefficient at the patient level from that of the population. We calculated the odds ratio and 95% confidence interval (CI) of upper vs. lower quartile of ESA response coefficient at patient level.

Results: In a logistic regression model case-mix-adjusted for age, gender, race, comorbidity, vintage, and dialysis dose, the odds ratio of achieving the highest quartile in ESA responsiveness (versus the lowest quartile) increased progressively with increasing serum calcium level. For each 1 mg/dL increase in 3-month averaged serum calcium, odds ratio increased by 1.27 (95% CI: 1.22-1.32, $p < 0.001$). Hypocalcemia (Ca < 8.4 mg/dL) was associated with an adjusted odds ratio of 0.61 (95% CI: 0.55-0.68, $p < 0.001$).

Conclusion: In this retrospective cohort analysis, hypocalcemia, but not hypercalcemia, was associated with ESA hypo-responsiveness in MHD patients. Limitations of observational data should be considered in interpreting these findings.

Vitamin D Deficiency and Anemia in Chronic Kidney Disease (CKD)

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Background: Vitamin D deficiency and anemia are common in CKD, yet few studies examined their relationship in patients with CKD. In vitro studies of red cell precursor cells show that calcitriol (1,25D) increases EPO receptor expression and stimulates proliferation with EPO. Thus, we hypothesized that vitamin D deficiency is associated with anemia in CKD.

Methods: We examined levels of hemoglobin (Hb), calcidiol (25D), and 1,25D in a cross-sectional study of 1,661 untreated subjects in the SEEK study, a multi-center U.S. cohort of patients with early CKD. 25D and 1,25D were examined on a continuous scale and categorically in tertiles. Anemia was defined as Hb<13.5 g/dl for men and <12 for women.

Results: The mean age of the study sample was 70±11 years, mean eGFR was 47±18 ml/min/1.73m², and mean Hb was 13±2 g/dl. 41% of study participants were anemic. Mean Hb levels decreased with decreasing tertiles of 25D and

1,25D (Table). In linear regression adjusted for age, sex, race, eGFR, diabetes, and PTH, there was a step-wise decrease in Hb with decreasing tertiles of 25D (25D>30 ng/ml ref; 25D 10-30, 2% lower Hb; 25D<10, 6% lower Hb, p<0.01) and 1,25D (1,25D>45 pg/ml ref; 1,25D 30-45, 2% lower Hb; 1,25D<30, 3% lower Hb, p<0.01). In logistic regression adjusted for the same covariates, the lowest tertile of 25D was associated with 2.8-fold increased risk of anemia (95%CI 1.5-5.1) compared to the highest tertile; the lowest tertile of 1,25D was associated with two-fold increased risk of anemia (95%CI 1.5-2.9) compared to the highest tertile.

Conclusion: 25D and 1,25D deficiency are independently associated with anemia in patients with CKD. The possibility that vitamin D may be useful in the direct or indirect treatment of anemia is intriguing and needs to be further explored.

Table: Mean Hemoglobin levels in tertiles of 25D and 1,25 D

	25D<10 ng/ml	25D = 10-30 ng/ml	25D>30 ng/ml	P
n	52	911	708	
Hemoglobin (g/dl)	11.7 ± 2	12.8 ± 2	13.5 ± 2	<0.001
	1,25D<30 pg/ml	1,25D = 30-45 pg/ml	1,25D>45 pg/ml	
n	897	456	308	
Hemoglobin (g/dl)	12.7 ± 2	13.3 ± 2	13.7 ± 2	<0.001

2. Mineral and Bone Disorders

Treatment of Secondary Hyperparathyroidism and K-DOQI Guidelines Achievement. COSMOS, a European Observational Study

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COSMOS is a multicentre, open prospective cohort study collecting clinical parameters and outcome data from a representative sample of 4500 hemodialysis patients from 227 medium-large facilities in 20 European countries. The objective of this analysis was to summarise baseline treatment of secondary hyperparathyroidism (SHPT) in these patients and the impact on bone biochemical parameters.

At enrollment, site investigators entered selected facility and patient information into a web-based data entry system, including demographics, medical history, routinely collected laboratory parameters during the previous six months and concomitant treatments. Fac-

ilities and patients were identified using a stratified, random selection methodology to include 20 patients from each active facility. Despite the wide use of drugs for the treatment of SHPT, only 22.3% [95%CI: 20.9 - 23.6] of patients are within K/DOQI guidelines targets for PTH and Ca x P. Moreover, only 9.0% of patients are within these targets for Ca, P, Ca x P and PTH simultaneously [95%CI: 8.1 - 9.9].

The study demonstrates the achievement of K/DOQI targets is low addressing the difficulties of achievement of these targets in the current clinical practice.

Table: Percentage of patients being treated with different drugs

	% of patients	95% CI
Phosphate binders	86.4	85.4 - 87.4
Calcium-containing phosphate binders	63.4	62.0 - 64.9
Aluminium-containing phosphate binders	12.5	11.5 - 13.5
More than 1 phosphate binder	23.4	22.2 - 24.7
Vitamin D or 25(OH)D	30.6	29.3 - 32.0
Vitamin D metabolites/analogues	48.0	46.5 - 49.5
Calcitriol	21.2	20.0 - 22.4
Alpha-calcidol	23.6	22.4 - 24.9
Paricalcitol	3.2	2.8 - 3.8
Calcimimetics	6.3	5.6 - 7.0

Serum PTH and Mortality Risk in a Large Cohort of European Hemodialysis (HD) Patients: 2-Year ARO Results

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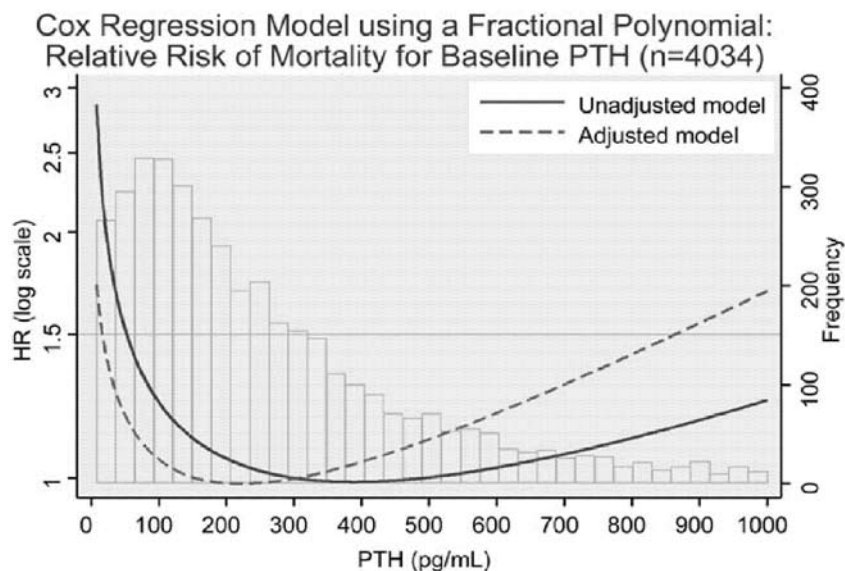
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The KDOQI guidelines for bone and mineral disorders recommend PTH 150-300 pg/mL. Few studies have examined the relation between PTH and mortality in European HD patients. This was explored in the ARO research initiative.

Data were collected from the EU Fresenius Medical Care HD network (172 centers) from Jan 2005 to Dec 2006 (n=11,122). Patients post-parathyroidectomy, cinacalcet treated, and incident patients (HD for <3 months) were excluded (n=1848). Second generation PTH assays were used. The relation between baseline PTH and mortality was evaluated with Cox regression using PTH as a categorical variable and also as a continuous variable with fractional polynomials. Analysis adjusted for demographics, medical history, dialysis parameters, serum laboratory values and concomitant medications. Missing PTH data were included in the categorical model, but excluded from the continuous Cox model. Patients were followed for a median of 1.9 years. 17% (1617/9274)

of patients died during follow-up. Patients in the lowest and highest PTH categories had the greatest risk of mortality (adjusted data only): PTH <75 pg/mL [HR 1.50 (95% CI: 1.21-1.86)], 75-150 pg/mL [1.30 (1.05-1.62)], 150-300 pg/mL [1], 300-600 pg/mL [1.33 (1.06-1.67)], 600-800 pg/mL [1.76 (1.23-2.51)], >800 pg/mL [2.09 (1.55-2.81)], missing PTH [1.19 (0.97-1.47)]. The fractional polynomials analysis was consistent with the above data (Figure).

Our findings show that patients with PTH levels within the recommended KDOQI target range have the lowest risk of mortality and suggest that extremes of PTH should be avoided.



Vitamin D Deficiency and Cardiac Mortality in Patients on Renal Replacement Therapy (RRT)

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Objective: Vitamin D deficiency is associated with hypertension and with cardiac and coronary morbidity. The aim of this study was to investigate the relation between serum levels of 25-hydroxy-vitamin D (25-OH-D) and cardiac mortality in the German RRT population.

Methods: A representative sub-cohort of 25,506 RRT patients had a total of 118,394 analyses of 25-OH-D between 1995 and 2006. During this period 38 % of all deaths resulted from cardiovascular diseases. Repeated measurements of 25-OH-D were summarized by calculating median, minimum und maximum for each patient over time. Low vitamin D status was defined for each patient by using her/his median 25-OH-D serum levels over time and applying cut-off levels of <20 g/l and <30 g/l, resp.

Results: From the 3976 cardiac deaths 36 % died due to myocardial infarction, 30 % due to sud-

den death, and 34 % due to other heart failures. The cohort's median of 25-OH-D of the patients' medians over time is 12.0 g/l 25-OH-D (median of the minima over time is 6.0 g/L, and median of the maxima over time is 18.7 g/l). Associated with low 25-OH-vitamin D levels the risk of death due to cardiac reason increased highly significant (< 20 g/l: adj. OR 1.78 (95% CI [1.55, 2.04], p = 0.000; ≥ 20 - <30 g/l: adj. OR 1.35 (95% CI [1.12, 1.55], p = 0.001).

Conclusion: Vitamin D deficiency is wide-spread in RRT patients. In spite of recommended target ranges only 11 % of this representative German RRT patient cohort have reached the target. Vitamin D deficiency (OR 1.78) and insufficiency (OR 1.38) are highly significant correlated with higher risk for cardiac death. D deficiency seems to be an important and independent risk factor of cardiac mortality in this population on RRT.

3. Cardiovascular Issues

ONTARGET: Cardiovascular Outcome in Patients at High Cardiovascular Risk and with Chronic Kidney Disease (CKD)

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In ONTARGET the effect of the angiotensin converting enzyme (ACE) inhibitor ramipril, the angiotensin receptor blocker (ARB) telmisartan, and the combination of the two drugs on cardiovascular morbidity and mortality has been examined during the follow-up of 56 months. The current prespecified analysis focuses on patients at high cardiovascular risk and with CKD stage 3-4, i.e. eGFR <60 ml/min/1.73m². Of the 6,249 subjects in ONTARGET with an eGFR <60 ml/min/1.73m² 2,039 patients were treated with ramipril 10 mg/day, 2,134 with telmisartan 80 mg/day and 2,076 with both drugs (combination therapy).

The primary composite endpoint (death from cardiovascular causes, myocardial infarction, stroke, hospitalisation for heart failure) increased progressively with severity of CKD (p<0.0001). Event rate per 1,000 patient years was 30.3 with eGFR>90 [in ml/min/1.73m²] (n=4505), 31.9 with eGFR 90-60 (n=14866), 45.5 with eGFR 59-45 (n=4755), 70.1 with eGFR 44-30 (n=1231) and 79.8 with eGFR <30

(n=263). The primary composite endpoint occurred in 458 patients in the ramipril group (22.5%), as compared with 493 patients in the telmisartan group (23.1%; relative risk 1.04; 95% CI, 0.91-1.18) and, as compared to 469 patients in the combination therapy (22.6%; relative risk 1.01; 95% CI; 0.89-1.15). Similar results were found for all cause mortality. As compared with the ramipril group, telmisartan group had lower rates of cough (relative risk 0.22, p<0.0001) and a higher rate of hypotension (relative risk 1.47, p=0.036) but the rate of syncope was the same in the two groups. The impact of albuminuria on cardiovascular outcome is currently analyzed.

We conclude that with decreasing eGFR the primary cardiovascular outcome increased progressively. In patients at high cardiovascular risk with eGFR <60 ml/min/1.73m², telmisartan was equivalent to ramipril and associated with less cough. The combination of the two drugs did not reduce the cardiovascular outcome in this very high risk group.

Feasibility of Dual Blockade of the Renin-Angiotensin System (RAS) in Chronic Kidney Disease (CKD) Stage 3-5

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Objective: Dual blockade has been claimed to have a specific renal protective effect and the treatment has therefore been suggested in CKD. The present study reports on the tolerability of dual blockade in a consecutive group of patients with CKD stage 3-5.

Material: 47 CKD patients with a median GFR of 27.4 (range 13.1-49.4) ml/min/1.73m² were studied.

Methods: All had been randomised in a run-in period to basic treatment with 20 mg of enalapril (n=26) or 16 mg of candesartan (n=21) when candesartan or enalapril, respectively, was added in incremental doses aiming at combined enalapril 20 mg and candesartan 16 mg to be reached over a period of 5 weeks. Thereafter full dual blockade was to be given for 3 weeks. Blood pressure, renal function and proteinuria were controlled at start, and at week 3, 5 and 8. A 30% increase in plasma-creatinine during the study was permitted. Hyperkalemia was treated with diuretics and dietary restriction.

Results: 26 patients (55%) tolerated full dual blockade, 2 patients

were excluded due to increases in plasma-creatinine > 30%, and 19 patients tolerated dual blockade in reduced dosage. Hyperkalemia was seen in 30 patients (64%). Plasma-creatinine was increased from median 231 (range 148-414) to median 254 (range 129-415) µmol/l, P< 0.009 at week 8, and plasma-urea increased from median 13.3 (range 7.4-35.5) to median 17.1 (range 5.8-39.6) mmol/l, P<0.003. Potassium was unchanged median 4.7 (range 3.6-5.7) mmol/l, blood pressure decreased from systolic median 130 (range 100-186) to 120 (range 95-196) mmHg, P< 0.0002 and diastolic blood pressure from median 77 (range 58-114) to 72 (range 57-112) mmHg, P< 0.03. 24h urinary albumin excretion decreased from median 2.6 (range 0.1-44.7) to median 1.1 (range 0.1-41) µmol/24h, P<0.001.

Conclusion: Only 55 % of CKD stage 3-5 patients tolerated full dual RAS blockade. Hence, caution is recommended when giving this treatment to patients with moderate to severe renal failure.

Factors Associated with Sudden Cardiac Death in Hemodialysis Patients

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We retrospectively examined factors associated with sudden cardiac death (SCD) in chronic hemodialysis (CHD) patients.

Data from 5 CHD units were examined for causes of death for all CHD patients who died during January 1999 – July 2000. The causes of death were classified into two groups: Group 1, SCD (ESRD form CM-2746-U3 codes 28 and 29) vs Group 2, death from all other causes. Hospital dialysis records were then reviewed to extract full demographics, medication history dialysis-related factors at the time of death 13 months earlier to determine if changes in these parameters over time could be associated with death.

A total of 103 deaths occurred during the study period: 41 were SCD and 62 were deaths from other causes. There were no statistically significant differences in gender, dialysis schedule and dialysis dose as measured by Kt/V. There were no significant differences in potassium, bicarbonate and phosphorus between groups. Albumin level was low in both groups but there was no statistically significant difference (3.29 vs 2.92 gm/dl). Calcium level was

significantly higher in the SCD group than in patients dying from other causes (9.65 vs 8.94 mg/dl, $p=0.026$). Weight gain prior to the last dialysis was greater in the SCD group than in patients who died from other causes (2.24 kg vs 1.43 kg, $p<0.01$). The volume of fluid removed at the last dialysis treatment was significantly greater in the SCD group than in patients who died from other causes (1.98 liters vs 1.30 liters, $p<0.05$). Analysis of changes over time revealed that the decline in albumin levels among both groups over the 3 months preceding death was similar between the groups. Hematocrits were higher in the SCD vs group 2 (35 vs 33.3%, $p<0.05$). We conclude that increased interdialytic weight gain and volume of fluid removed at dialysis are associated with sudden cardiac death as are higher serum calcium hematocrit levels. Hypoalbuminemia and decline in serum albumin level over time are associated with SCD and death from other causes to a similar degree. Several factors associated with SCD in hemodialysis patients, if recognized can be modified or corrected.

Arterial Stiffness in Hemodialysis: Which Parameter to Measure for Predicting Cardiovascular Mortality?

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In previous separate studies different measures of arterial stiffness are related to cardiovascular mortality, but their relative prognostic value has not previously been evaluated in one cohort.

Carotid-femoral pulse wave velocity (PWV), carotid augmentation index (AI), carotid pulse pressure (CPP) and carotid-brachial pulse pressure amplification (AMP) were measured in 98 patients before and after hemodialysis. Patients were followed for a median of 29 (range 0-35) months and the association of these eight parameters with cardiovascular mortality was assessed using log-rank tests and Cox proportional-hazards regressions – adjusted for age, diabetes and established cardiovascular disease.

During follow-up 40 patients died (mortality rate 20.7/100 patient years) of which 25 were of cardiovascular causes. Increasing PWV tertiles measured either pre- or postdialysis and decreasing AMP

tertiles- measured pre- but not postdialysis – were significantly related to cardiovascular mortality (p-values 0.011, 0.011 for PWV, and <0.001, 0.321 for AMP). Neither AI nor CPP were related to cardiovascular mortality, irrespective of the timing of the measurement. The adjusted hazard ratios for 1m/s higher pre- and postdialysis PWV were 1.24 [1.07-1.44] and 1.17 [1.06-1.28], respectively. The hazard ratio for 10% lower AMP, measured prior to dialysis, was 1.41 [1.03-1.92]. When included in the same model, both predialysis PWV and AMP remained significantly associated with cardiovascular survival (hazard ratios: 1.23 [1.07-1.42] and 1.39 [1.02-1.89]). Among different measures of arterial stiffness PWV is consistently related to cardiovascular mortality, irrespective of the timing of the measurement. Predialysis AMP, however, seems to provide additional prognostic information.

4. Clinical Nephrology Practice

HbA1c is a Poor Indicator of Glycaemic Control in Diabetic Patients on Haemodialysis

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Objective: It is important that glycaemic control in patients with diabetes mellitus on maintenance haemodialysis programmes is adequately monitored. Glycosylated haemoglobin (HbA1c) is the current gold standard marker for glycaemic control, however, there have been concerns over its reliability in this population. The continuous glucose monitoring system (CGMS) provides a technique to measure ambient glucose concentrations in subcutaneous interstitial fluid every 3 minutes by means of an implantable probe linked to a biosensor.

Aims: to examine: 1. 48-hour glucose profiles including a day on and off haemodialysis, and 2. the relationship between HbA1c and 48-hour glycaemic control in these subjects.

Research Design Methods: Using CGMS (GlucoDay S, Menarini Diagnostics) 48-hour glucose monitoring was performed in 17 (14 male) diabetic haemodialysis patients (mean age 62 years). No subject had a haemoglobinopathy or had received a blood transfusion in the preceding 3 months. All

subjects had stable haemoglobin levels and a mean erythropoietin dose of 43 µg of Darbepoetin/week. The CGMS recorded data during a 48-hour period which included one day with a dialysis session, and was downloaded to a computer for analysis. The current HbA1c value was assessed against the mean glucose values obtained from the CGMS data for each subject.

Results: We observed HbA1c greatly underestimated blood glucose values in 10/17 subjects ($r = 0.088$). Also, that off-dialysis days showed greater glycaemic excursions (mean blood sugar \pm SD 9.3 ± 3.8 mmol/L vs. 11.5 ± 6.2 mmol/L).

Conclusions: 1. Hypoglycaemic management may need to be varied according to dialysis days due to variation in glycaemic profiles between different dialysis days.

2. HbA1c frequently underestimates glycaemic control in haemodialysed patients. CGMS provides important clinical information, and has the potential to improve the clinical management of diabetic patients on haemodialysis.

A Randomized Trial Evaluating Three Regimens of Diuretics in Stage 4 Chronic Kidney Disease with Hypertension

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The efficient dose of diuretics to increase the fractional excretions of Na (FE Na) and Cl (FE Cl) in hypertensive patients with stage 4 chronic kidney disease (CKD) is not determined. Furthermore the type of diuretic (thiazide, loop diuretics) that should be used in this population is still a matter of debate.

We compared the efficacy of hydrochlorothiazide (HCT, 25 mg/d), furosemide (FUR, 60 mg/d) and the combination of HCT and FUR (HCT/FUR, 25 and 60 mg/d) in a double-blind randomized cross-over trial in 23 patients with stage 4 CKD and hypertension. The primary end-point was the FE Na and FE Cl ($FE\ Na = UNa \times Vol/GFR \times natremia$) after 3 months of each diuretic and their combination. Periods of treatment were separated by a one month wash-out period. Glomerular filtration rate (GFR), renal plasma flow (RPF), and filtra-

tion fraction (FF) were measured by Cr51-EDTA and Hippuran clearances. During the trial, diet and other treatments were not modified.

FUR and HCT did not increase FE Na and FE Cl at usual posology. Conversely the combination of FUR and HCT did increase FE Na and FE Cl ($p < 0.01$). Mean blood pressure decreased with the 3 regimens but was even lower with FUR/HCT. GFR and RPF were stable with the 3 regimens except for a decrease of GFR in the FUR/HCT regimen. FF decreased markedly with the 3 regimens.

In patients with stage 4 CKD and hypertension, a higher than usual posology of FUR or HCT is necessary to increase FE Na and FE Cl significantly. The combination FUR/HCT is very efficient to increase NaCl excretion and to control high blood pressure.

	Basal	FUR	HCT	FUR/HCT
FE Na (%)	3.4 ± 1.8	4.4 ± 2.2	3.9 ± 2.4	4.9 ± 2.8 ^a
FE Cl (%)	3.8 ± 2.0	5.1 ± 2.9	4.6 ± 2.5	6.0 ± 3.1 ^a
GFR (ml/min)	25 ± 10	21 ± 10	22 ± 10	17 ± 11 ^a
RPF (ml/min)	94 ± 35	96 ± 31	97 ± 36	85 ± 41
FF (%)	27 ± 7	22 ± 6 ^a	22 ± 7 ^a	20 ± 6 ^a
Mean BP mmHg	101 ± 13	93 ± 9 ^b	95 ± 7 ^b	86 ± 23 ^a

^ap < 0.01 versus basal; ^bp < 0.05 versus basal

FUR = furosemide, HCT = hydrochlorothiazide, FE = fractional excretion, GFR = glomerular filtration rate, RPF = renal plasma flow, FF = filtration fraction

Calcium and Risk of Mortality in Chronic Kidney Disease

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Background: The KDOQI guidelines recommend target calcium (Ca) levels between 8.4-9.5 mg/dL for CKD stage 5 and normal levels for CKD stages 3-4. Large cohort retrospective studies in dialysis patients demonstrate an association between hypercalcemia and increased mortality and some studies have suggested a low Ca may confer a survival advantage. Very little information is available regarding CKD patients not undergoing dialysis, thus a historical cohort analysis was performed from a single CKD clinic population to evaluate the relationship between Ca and mortality and/or renal death.

Methods: Baseline demographic data and laboratory biomarkers were evaluated using an independent two sample t-test. Univariate COX proportional hazard (PH) regression models were built for potential predictors, using models that accounted for both fixed baseline measures and change of measures over time. Outcomes of death and renal death (OC) were combined when no survival difference was demonstrated between these outcomes by Kaplan-Meier with log rank test.

Results: A total of 208 patients with a MDRD eGFR of 28.6 ± 13.1 ml/min were followed for a median of 25.5 months (range 3.1- 35.9 months). Mean serum phosphorus (Pi) was 4.1 ± 0.8 mg/dl. COX PH with fixed covariate at the baseline found that higher Pi was associated with an increased risk of OC with a hazard ratio (HR) of 1.52 (95% confidence interval (CI): 1.03-2.23, $p=0.034$). Higher serum Ca was associated with a decreased risk HR 0.47 (95% CI: 0.27-0.82, $p=0.008$). COX PH with time varying covariates confirmed the same finding with statistical significance for Pi (HR: 2.14, 95% CI: 1.52-3.01, $p < 0.001$) and Ca (HR: 0.41, 95% CI: 0.25-0.69, $p < 0.001$)

Conclusion: Ca levels remained in the normal range in most of our CKD patients. When evaluating Ca as a fixed baseline variable or as a variable changing over time, high normal range Ca was associated with a decreased risk of OC. Targeting of low serum Ca in CKD patients may not confer a survival benefit as has been suggested in dialysis patients. Clearly, further prospective studies are required.

5. Dialysis Therapies

Pronounced Decrease of Beta-2-Microglobulin by Online Hemodiafiltration in Patients without Residual Renal Function

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High beta-2-microglobulin (β_2m) levels have been associated with mortality in hemodialysis (HD) patients. It has been shown that hemodiafiltration (HDF) can lower pre-dialysis β_2m levels substantially.

In the present study we analysed determinants of pre-dialysis β_2m levels in 443 patients on low-flux HD (mean age 64 ± 14 years [SD], 62% male) of the Convective Transport Study (CONTRAST) cohort at baseline. In a subset of 312 patients, we studied the change of β_2m after randomization for treatment with online HDF or continuation of low-flux HD from baseline to six months.

At baseline, mean β_2m level was 25.0 ± 10.1 mg/L (SD) in patients with a preserved residual renal function ($n=229$; defined as a urinary production >100 ml/24h) and 37.9 ± 11.5 mg/L in patients without residual renal function ($n=214$, $p<0.001$). In a multivariate regression model residual creatinine clearance was strongly associated with β_2m level (regression coefficient -1.9 ± 0.2 (SE) mg/L per ml/min increase of creatinine clearance,

$p<0.001$). In addition, β_2m levels increased with the total time on renal replacement therapy and were slightly lower in diabetics.

During follow-up, β_2m levels significantly decreased from 29.4 ± 11.2 mg/L (SD) at baseline to 24.3 ± 9.1 mg/L after 6 months in the HDF patients, whereas a non-significant increase from 30.8 ± 12.6 mg/L to 33.3 ± 13.3 mg/L was observed in HD patients. In the HDF patients, the mean decrease in β_2m from baseline to 6 months was 7.9 ± 1.5 mg/L (SE) in patients without and 2.9 ± 0.9 mg/L in patients with a preserved residual renal function. Decrease of β_2m was independently associated with creatinine clearance.

In conclusion, residual renal function was an important determinant of β_2m level. β_2m was effectively lowered after 6 months of HDF treatment. However, the effects of HDF were much more pronounced in patients without residual renal function. These results suggest that the addition of convective clearance to dialysis is especially relevant for patients without residual renal function.

Longer Dialysis Sessions Reduce the Frequency of Ventricular Arrhythmias

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Introduction: The objective of this prospective-controlled study was to investigate the effects of thrice weekly nocturnal center hemodialysis (NHD) on cardiac arrhythmias in HD patients.

Methods: 48-h Holter ECG was recorded at baseline and at 3rd month in 30 patients assigned to 8-h thrice weekly NHD and 30 age-, sex-, diabetic status-, HD vintage-matched patients assigned to conventional 4-h HD (CHD). Demographical, laboratory and baseline echocardiographical data were recorded. Dialysate contents were similar in the groups.

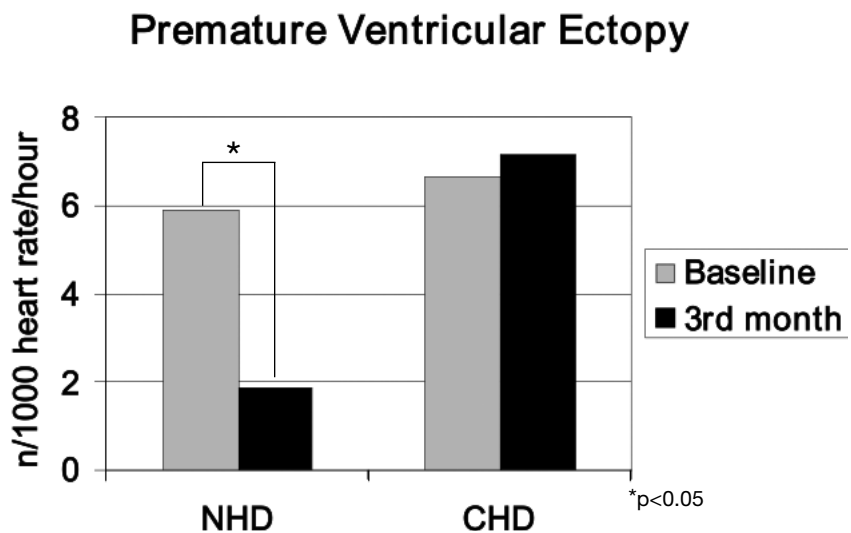
Results: Mean age was 47 ± 13 years, HD duration 62 ± 47 months, presence of cardiovascular disease history 12%. In study population, frequencies of premature ventricular (PVE) and supraventricular ectopy (PSE) were 63% and 91%, respectively. The number of PVE and PSE were 6.3 ± 16.5 vs 3.6 ± 7.0 per 1000 heart rate/hr and there was no difference between groups at base-

line. PVE was seen especially in patients with longer HD vintage, lower levels of serum albumin and hemoglobin. Baseline mean ejection fraction, left atrial volume and left ventricular mass index were not different between groups.

The number of PVE was significantly decreased in NHD group from 5.9 ± 1.4 to 1.5 ± 1.9 per 1000 heart rate/hour ($p < 0.05$), while no change was seen in CHD group (figure).

The number of PSE was slightly decreased in NHD group, despite a slight increase in CHD ($p > 0.05$). QTc interval remained stable in both groups.

Conclusion: Cardiac arrhythmias are more common in patients on CHD. NHD treatment is associated with lower frequency of ventricular arrhythmias.



NHD = Nocturnal Hemodialysis; CHD = Conventional Hemodialysis

Clinical Outcome of an In-Center Thrice Weekly Nocturnal Hemodialysis Program (3xNHDP)

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The mortality associated with conventional hemodialysis remains high. Recent studies have found that longer session times (4 to 4.5 hours) and lower ultrafiltration rates (less than 10 mL/h/kg) were both independently associated with a reduction in mortality.

We started an in-center 3xNHDP in May 2005 and have reported that serum phosphorus levels were significantly reduced (4.4 ± 1.1 vs 5.3 ± 1.3 mg/dL, $p=0.049$), the ultrafiltration rate (UFR) was decreased to 5.9 ± 1.7 mL/h/kg and there was no deterioration in a variety of psychosocial assessments after patients enrolled in the 3xNHDP (Adv Chronic Kid Dis 14:244, 2007). The long-term outcome from a 3xNHDP has not been described.

All patients starting the 3xNHDP in May 2005 to May 31, 2008 were included in the present analysis. The patients were dialyzed with the Fresenius NR Optiflux Dialyzer with blood flows of 400 cc/min and a dialysate flow of 750 cc/min for 8 hours. A total of 24 patients were enrolled for a total of 330 patient months of experience (range 1 to 36 months). The mean age was

47.7 ± 13.2 years. 21 (87.5%) of the patients were male. 13 (54%) were African American. The average Charlson comorbidity score was 4.7 ± 2.1 . The average UFR was 6.4 ± 2.7 mL/h/kg.

The average time to recovery for the patients to resume usual activities after 3xNHD was 2.5 ± 3.2 hours. 13 (54%) patients left the program. Seven (29.2%) patients transferred to conventional, thrice weekly HD after a mean of 14 ± 14 months (range 1 to 27 months); the primary reasons for these transfers involved problems with sleeping in the unit overnight. Four (16.7%) patients underwent renal transplantation after 8.5 months (range 1 to 16 months). One (4.2%) patient transferred to short, daily HD and 1 (4.2%) patient expired after 30 months on the 3xNHDP.

An in-center 3xNHD program is a successful alternative to conventional HD. Major benefits include low UFR, improved phosphate control and shorter time to recovery after dialysis. Multicentered long-term studies are necessary to determine the efficacy of 3xNHD as a long-term alternative HD therapy.

Risk Factors Associated with Low Weekly Haemodialysis Dose in 7 European Countries

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Aim: The purpose of this study, initiated by the QUality European STudies (QUEST) initiative Working Group on dialysis adequacy, was to investigate haemodialysis (HD) dose practice patterns and to study the association of patient characteristics and country with weekly HD duration.

Methods: A multivariate logistic regression was used to study factors associated with the probability of receiving HD for less than 12 hours/week in 26,136 patients on HD at 31 December 2005 and included in seven European registries.

Results: Eighty-three percent of the patients received HD for at least 12 hours per week as recommended by the European Best Practice Guidelines. Multivariate analysis showed significant differences across countries concern-

ing the risk of receiving less than 12 hours (OR ranged from 0.4 to 6.3). Other risk factors for shorter total HD duration included higher age (OR 1.3, 95%CI: 1.3-1.4, for each 10 years older), being female (OR 1.8, 95%CI: 1.6-1.9), low BMI (OR 0.92, 95%CI: 0.92-0.93) for each increase of 1 kg/m² of BMI) and being on RRT for a shorter time (OR 0.94, 95%CI: 0.93-0.95) for each increase of 1 year of RRT treatment). Diabetes was associated with longer total HD duration (OR 0.8, 95%CI: 0.8-0.9).

Conclusion: This study shows that 83% of the patients receive at least 12 hours HD per week as recommended by the EBPG but it also shows that there is great variability across countries and in patient subgroups concerning number and length of HD sessions.

The Association of Intradialytic Hypotension with Treatment Parameters and Correlation of 24-Hour Ambulatory Blood Pressure with Pre- Intra- and Post-Dialysis Blood Pressure Monitoring

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24-hour ambulatory blood pressure monitoring [ABPM] was made in 43 patients at a single dialysis centre. 27 male, 59.7 ± 13.8 years, 21 diabetic, mean intradialytic weight gain was 2.4 ± 0.9 kg. A median of 3 antihypertensive agents (range 0-5) were in use. 60% of patients were taking ACE inhibitors, 51% angiotensin receptor blockers, 47% calcium channel antagonists, 47% alpha blockers, 44% beta blockers and 7% nitrates.

ABPM was then correlated with average recordings from three contemporaneous dialysis sessions for: systolic and diastolic blood pressure pre-, intra- and post-dialysis; and intradialytic weight gain. There was a significant fall in systolic blood pressure and not diastolic blood pressure during haemodialysis, however this did not

correlate with intradialytic weight gain [$r=0.03$]. Neither was there an association with any particular class of antihypertensive or total number of antihypertensives.

Maximum systolic blood pressure on ABPM was most strongly correlated with post-dialysis systolic blood pressure [$R=0.73$]. Maximum diastolic blood pressure on ABPM was most strongly correlated with post-dialysis diastolic blood pressure [$R=0.66$].

Intradialytic fluid gains and antihypertensive agents do not determine intradialytic hypotension. Post-dialysis systolic blood pressure and diastolic blood pressure are most strongly predictive of maximum systolic blood pressure and diastolic blood pressure on ABPM.

Means \pm SD	Pre-dialysis	Intra-dialysis	Post-dialysis	ABPM Max Values
Systolic BP	$156 \pm 21^*$	$145 \pm 28^{**}$	$153 \pm 28^{**}$	182 ± 29
Diastolic BP	85 ± 13	84 ± 39	83 ± 14	102 ± 16

* $p=0.0005$, ** $p=0.0009$ paired t-test

Following the Target of Normohydration Provided by BIS Reduces Fluid Overload and Intradialytic Morbid Events

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Introduction: Assessment of hydration status in HD patients is a basic prerequisite for successful dialysis treatment. It was shown (Wabel et al NDT, 2008) that at least 25% of HD patients suffer from fluid overload $FO_{pre} > 2.5L$, which is associated with a significantly increased mortality (Wizemann et al. NDT Plus 2008). It is still a matter of debate if this FO can be removed without increasing intradialytic morbid events (IME). It was the aim of this trial to assess whether extreme $FO_{pre} > 3.5L$ can be corrected and whether this reduction has an effect on IMEs.

Methods: 529 BCM-Body Composition Monitor (Fresenius Medical Care) measurements were performed in 60 HD patients. Dry-weight (DW) was carefully adjusted over a period of one year following the normohydration target provided by the BCM as FO in liters: DW reduction in patients presenting $FO_{pre} > 3.5 L$; DW increase in patients with $FO_{pre} < -0.5 L$.

Results: 20% of all HD patients presented $FO_{pre} > 3.5 L$ at the start. The FO of these patients could be reduced by more than 2 L without the appearance of additional hypotensive episodes. Additionally 20% of HD patients were responsible for more than 85% of all IMEs in this center. Most of these patients were in a state of severe dehydration at the end of the HD session. Their dry weight was carefully increased by an average of 1.3 L and this resulted in a 4-fold reduction of IMEs.

Discussion: Our study demonstrated that achieving a state of normohydration and thus avoiding severe over- or dehydration helps to improve the treatment quality with less IMEs and an improved blood pressure control. The target provided by the BCM is of invaluable assistance to assess and achieve normohydration.

Table: Reaching normohydration in hyperhydrated patients

Hyperhydrated patients	First assessment	Last assessment	p-value
FO pre [L]	4.2 ± 0.6	2 ± 0.8	(p<0.001)
FO post [L]	2 ± 1.1	-0.7 ± 1.2	(p<0.001)
BP pre [mmHg] (mean of 6 treatments)	153 ± 17	133 ± 31	(p=0.042)
Antihypertensive medication	1.6 ± 1.5	1 ± 1.2	(p=0.031)
Hypotensive episodes & cramps (in previous 4 weeks)	0.7% ± 2.4%	0.7% ± 2.4%	

FO = Fluid Overload , BP = Blood Pressure

Bioimpedance Exhibits Significant Properties in Assessment of Hydration Status in Peritoneal Dialysis Patients

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Evaluation of correct fluid balance in chronic peritoneal dialysis (PD) patients is complex. Use of body weight, blood pressure, volume of ultrafiltration (UF) and peripheral

oedema has proven inaccurate. To overcome the problem, measurements with bioelectrical impedance analysis (BIA) technique with its ability to estimate body fluid compartments could be beneficial. Plasma B-type natriuretic peptide (BNP) reflects cardiac volume overload, and thus might assist in assessment of hydration status.

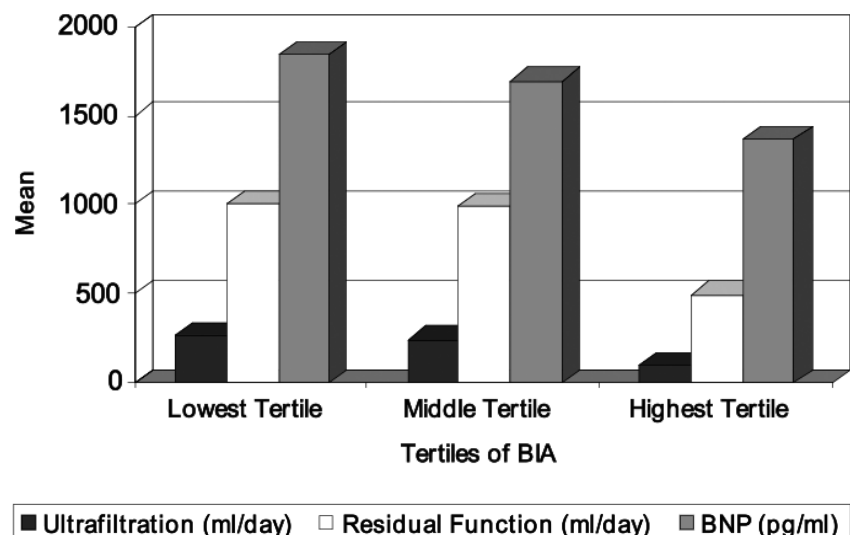
We performed a cross-sectional study of 63 out-patients in chronic peritoneal dialysis (45 in CAPD, 18 in APD).

Results of BIA measurements were divided into tertiles (using 253 Ω /m and 316 Ω /m as cut-off values for resistance/height) to define patients to groups 'wet' (<253 Ω /m), 'normal' (>253 Ω /m and <316 Ω /m) and 'dry'(>316 Ω /m).

BNP was markedly different between the groups, with the highest value in the wet group (BNP for wet 364pg/ml, normal 234pg/ml and dry 87pg/ml, p=0.044 for wet versus dry); residual renal function (RRF, diuresis) was significantly greater in the wet group (RRF for wet 1048ml, normal 974ml and dry 480ml, p=0.029 for normal versus dry, p=0.012 for wet versus dry); and UF was best preserved in the wet group (UF for wet 1.78l, normal 1.64l and dry 1.32l., p=0.011 for wet versus dry).

In this study, BIA tertiles were able to distinguish BNP, RRF and UF in a dose-dependent fashion, suggesting BIA to possess remarkable capability in assessment of fluid status in chronic peritoneal dialysis patients.

Mean BNP, RRF and UF vs. Tertiles of BIA



Effect of Low GDP Fluid Use on Residual Renal Function in Incident Peritoneal Dialysis Patients over 24-Month Period

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Background: In-vitro beneficial effect of low glucose degradation products (GDP) peritoneal dialysis (PD) fluid has been shown. Few clinical trials, however, demonstrated the benefit of low GDP PD fluid on residual renal function (RRF). We investigated whether low GDP fluid better preserves RRF in incident PD patients over 24 months.

Methods: We originally performed a randomized controlled trial with incident PD patients on either low GDP fluid (LF, Balance, Fresenius, n=48) or conventional fluid (CF, Stay safe, Fresenius, n=43), and 69 patients completed 1-year treatment. We extended our trial for up to 24 months. Among them, 41 patients completed the 24-month follow-up (LF, n=22; CF, n=19). RRF, peritoneal solute transport rate, and effluent levels of cancer antigen-125 (CA-125) and interleukin-6 were measured regularly.

Results: At baseline, LF and CF groups were not different in age, gender, comorbidity index and RRF. At 24 months, GFR of patients on LF was higher than

that of patients on CF (35.3 ± 6.86 vs 16.6 ± 4.33 L/week/1.73m², p=0.011). There was no difference of dialysate-to-plasma creatinine at 4 hr between the two groups after 24-month treatment period. Effluent levels of CA-125 increased in the LF group, compared with the CF group (p=0.042). Over 24-month follow-up, no differences between the two groups in the patient survival, and technique survival rate were observed. Number of peritonitis episodes, serum level of C-reactive protein, effluent level of interleukin-6, and dialysate glucose exposure were not different between the two groups.

Conclusion: Our study from the incident PD patients suggests that low GDP PD fluid use over 24-month treatment may preserve RRF better and may be beneficial for the mesothelial cell viability.

6. Vascular Access

Natural History of Blood Flow Rate of Vascular Access in Hemodialysis Patients

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Background: Adequacy of dialysis depends on a functional hemodialysis (HD) access with adequate blood flow (Qb). The aim of this study is to investigate the natural history of Qb of arteriovenous fistula (AVF) or arteriovenous graft (AVG).

Methods: This retrospective study was performed on HD patients treated at RRI units using AVF or AVG initially used for dialysis from 01/01/2000, followed up to 12/31/2007. Stated reasons for access failure were thrombosis, stenosis, inadequate flow, infection, aneurysm and inability to cannulate. Qb was reported as mean monthly values. Surviving accesses were categorized into three tertiles according to median Qb during the first three months and followed up to 2 years. Qb in the two years prior to access removal were analyzed.

Results: In 2173 surviving AVF and 763 surviving AVG enrolled in the study, Qb increased over the first 2 years in both groups. Slopes were dependent on initial Qb tertiles. Decreased Qb in both failure access groups (442 AVF and 244 AVG) occurred gradually over the period before failure occurred. Qb of AVF and AVG began to decrease from 8-10 months and 4-6 months respectively before removal.

Conclusion: This is the first substantial study of the natural history of Qb of vascular access. The increase over time both in AVF and surprisingly in AVG suggests the value of initial high flows. More importantly, decrease in both AVF and AVG much earlier than access failure occurred might suggest use of preventive measures in timely fashion.

Preservation of Arteriovenous Fistulae or Grafts (AVF/AVG): Use of Ionic Dialysance Based Access Flow Measurement with Timely Radiological Intervention

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Haemodialysis access dysfunction results in increased morbidity and mortality. However, the optimal surveillance and intervention strategy to maintain AVF/AVG remains unclear. The aim of this study was to evaluate the impact of regular access monitoring based on ionic dialysance derived measurement of access flow supported by radiological intervention.

In a single HD centre all HD patients with AVF or AVG (n=185) had monthly access flow measurement (Qa) assessed by ionic dialysance technique. Radiological study and potential intervention was triggered by a) a Qa < 600 ml/min, b) a fall of > 25% or c) clinical suspicion of stenosis. At each procedure the lesion types, site, severity, the intervention and the outcome were recorded. The Qa was repeated within 2 weeks. In one year 100 patients had 147 (132 AVF, 15 AVG) fistulograms performed. Of these, 129 had

significant lesions and angioplasty was attempted. The positive predictive value by Qa was 92%. Absolute Qa allowed differentiation between single venous stenosis, multiple venous stenosis and incipient thrombosis $p < 0.01$ between all groups).

Overall angioplasty success rate was 96%, with no complications. The mean Qa improvement post angioplasty was 452 ml/min (95% CI 142.2-761.5 ml/min). The overall mean access event-free survival post angioplasty was 16.2 months. Subgroup analysis found no recurrence during the 18 month study period when a cutting balloon had been utilised. Salvage of thrombosed access was successful in 88% (14/16).

The routine use of ionic dialysance to determine Qa as part of the dialysis treatment is a useful tool for the detection of access dysfunction allowing proactive radiological intervention.

Effect of Aspirin (ASA) on Primary Unassisted Graft Patency in the Dialysis Access Consortium (DAC) Graft Trial

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The effect of ASA on patency of arteriovenous grafts is uncertain. The DAC Graft Study reported that extended-release dipyridamole (ERDP) plus ASA produced an 18% reduction in the rate of loss of primary unassisted graft patency compared to placebo (HR=0.82, 95%CI 0.68-0.98, p=0.026). The trial permitted non-study related use of ASA, but excluded patients on other antiplatelet agents. In a post-hoc analysis, we examined the effect of ASA use at baseline on primary unassisted graft patency. 40% of 321 subjects assigned to ERDP/ASA and 44% of 328 assigned to placebo were taking ASA at baseline. Subjects on ASA were older (63 ± 12 vs 55 ± 15 yrs) and more often had diabetes (DM, 75% vs 54%), cardiovascular disease (CVD, 53% vs 32%), cerebrovascular disease (CeVD, 23% vs 11%) and used less tobacco (Tob, 11.8% vs 18.6%).

Subjects on ASA at baseline, continued on ASA throughout. A Cox regression model adjusted for age, DM, CVD, CeVD, Tob, ACEI/ARB use and albumin showed (Table) greater primary unassisted patency with assignment to ERDP/ASA, baseline ASA use and no current Tobacco use, but no significance for the 6 other covariates examined.

Neither the assigned treatment nor baseline ASA had a significant effect on the pre-specified secondary combined endpoint of cumulative graft patency or death. An interaction term between ERDP/ASA treatment and baseline ASA use was not significant (p=0.33) and not included in the final model.

The results raise the possibility that ASA alone may be effective at improving primary unassisted graft patency.

Table: Adjusted Cox regression model for primary unassisted graft patency

Variable	HR (95% CI)	P-value
ERDP/ASA	0.81 (0.67, 0.97)	0.02
Baseline ASA	0.81 (0.66, 0.99)	0.04
Tobacco use	1.43 (1.12, 1.82)	0.01

ERDP = extended-release dipyridamole, ASA = Aspirin

7. Outcome

High and Low Blood Pressure (BP) are Associated with Elevated Mortality in Hemodialysis (HD) Patients: Results from the DOPPS

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In observational studies of HD patients, elevated mortality is associated with low systolic BP (SBP) but not with SBP higher than

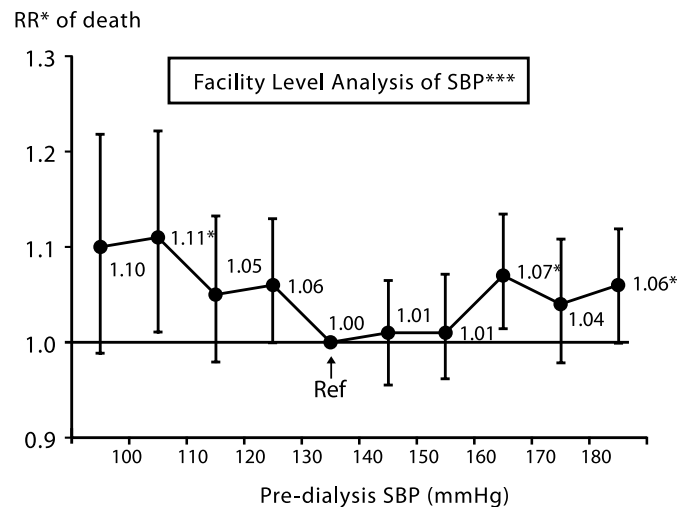
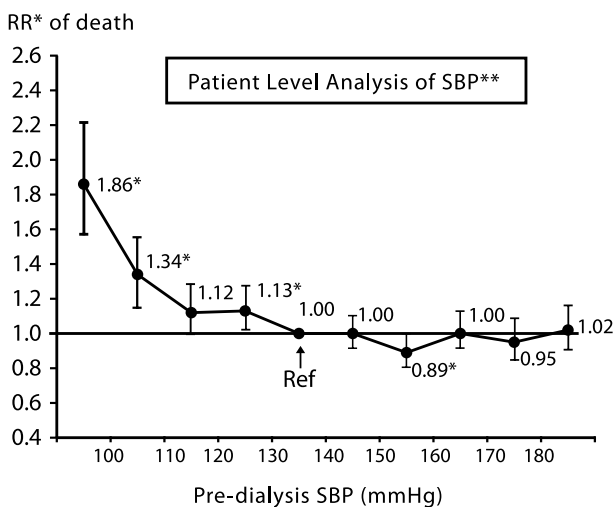
KDOQI and JNC VII target levels. Because these associations may be due in part to residual confounding, the optimal BP target remains unknown. To reduce this bias, we examined the relationship of the facility percentage of patients within BP categories to patient-level mortality among 22,942 prevalent HD patients in DOPPS I-III (1996 to 2008) using Cox models adjusted for patient factors.

Compared to other regions, SBP was higher in facilities in Japan than in North America. Overall, SBP varied markedly across facilities. Models based on patient-level SBP confirmed previous findings of a significantly elevated mortality risk for SBP <130 but not for high SBP (left figure). By contrast,

mortality was elevated for patients in facilities with greater proportions of either low or high SBP. Compared with SBP of 130 to <160, the HR for 10% more patients with SBP <130 = 1.06 (1.03-1.10, p<0.001) and for SBP >160 the HR = 1.06 (1.02-1.09, p<0.001). Details by 10 mmHg categories are provided (right figure).

The distribution of SBP varied substantially from facility to facility and is likely due in part to provider treatment preferences.

We have shown that facilities with more patients with either high SBP (≥160) or low SBP (<130) had higher mortality overall. Additional analyses are needed to identify facility practices that most clearly affect BP control.



* 22942 initial prevalent cross section patients with ESRD>180 days from 917 facilities in DOPPS I, II, III. Adjusted for age, gender, black race, BMI, vintage, study phase, serum albumin, creatinine, ferritin, PTH, hemoglobin, single pool Kt/V, phosphorus, catheter use, 13 comorbidities, stratified by country and accounted for facility clustering effects. In facility level model, instead of adjusting for patient level, hemoglobin, Kt/V, phosphate, and catheter use, adjusted for facility, % catheter use and % of hemoglobin, phosphate and Kt/V guidelines.

** Patient-level analysis of SBP. Mortality rate ratio (RR) for patients in each non-reference category of SBP vs patients in the reference category (130-140 mmHg)

*** Facility-level analysis of SBP. Mortality rate ratio (RR) for patients in facilities where 10% of patients are in non-reference category of SBP vs. patients in facilities where those 10% are in the reference category (130-140 mmHg).

High Body Mass Index (BMI) Does Not Improve Survival on Haemodialysis

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Purpose: To evaluate the impact of high body mass index (BMI) and change in BMI on survival in patients with established renal failure (ERF) incident to haemodialysis (HD). To facilitate the optimal management of overweight patients with chronic kidney disease approaching renal replacement therapy.

Methods: Retrospective review of electronic records of patients incident to HD at one centre between 1987 and 2006. All patients established on HD for over 90 days for whom a BMI result was calculable were included. Patients were categorized by BMI into 2 groups to represent under/normal weight (BMI<25) and overweight/obese (BMI>25). Patients who received a transplant were censored from the date of transplantation. The association between initial BMI, change in BMI in the first month of HD, age, comorbidity (by modified Charleston score) and survival up to 5 years were evaluated. Results were analysed using Kaplan-Meier, Log rank and Cox proportional hazard regression tests.

Results: 712 patients (419 male, 59%) commenced HD between 1987 and 2006 and had data available. 343 patients (48%) were overweight/obese, median

BMI was 28.5kg/m² (IQ range 5.6). The median survival in overweight patients (4.27 years) was not superior to normal/underweight patients (4.32 years, log rank 0.47). Weight loss within the first month of RRT was associated with shorter survival, 3.81 years, compared to 4.74 years in patients whose weight remained stable or increased (log rank 0.49). These effects of BMI on survival were relatively small compared to the effect of comorbidity and age, which remained significant in Cox regression analysis. The presence of cardiovascular comorbidity reduced median survival to 2.8 years (log rank <0.0001).

Conclusions: High BMI at initiation of HD is not associated with improved 5 year survival in our cohort with ERF. Stability of weight or even weight gain in the first month of HD is associated with improved 5 year survival, however this is not independent from age and comorbidity. Cardiovascular disease had the most deleterious effect on 5 year survival. We suggest that in ERF the management of obesity should target prevention and address it as a traditional cardiovascular risk factor.

Cumulative Difference in Mortality between Hemodialysis and Peritoneal Dialysis

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Background: Existing comparisons between hemodialysis (HD) and peritoneal dialysis (PD) have focused on mortality rates/hazards, which are point-in-time measures. Several studies have shown the initial mortality advantage of PD over HD diminishes and reverses as follow-up time increases. It is unclear whether the increase in early mortality on HD is offset by the subsequent decrease in mortality. Using national data, we compared PD and HD survival and restricted mean lifetime (area under the survival curve); i.e., focusing on cumulative mortality measures, as opposed to the less interpretable hazard/rate ratio.

Methods: Data from the Canadian Organ Replacement Register (CORR), the study population included 23,254 patients who initiated renal replacement therapy (RRT) on HD or PD between 1990 and 1998. An intent-to-treat analysis was performed, with covariate adjustment through inverse probability of treatment weighting. Survival probability and restricted

mean lifetime (area under the survival curve) on PD and HD were compared for the first 8 years post-RRT.

Results: Survival probability was significantly ($p < 0.05$) greater on PD for the first 31 months. Between months 32-44, there is no significant difference in survival. From month 45-96 survival was significantly higher on HD, although the relative difference was 9%. The area under the survival curve was significantly greater for PD up to month 65, with no significant difference thereafter. The area under the PD and HD survival curves is equal at month 86.

Conclusion: In terms of life expectancy, the mortality increase on HD early in the follow-up period is not offset by the mortality pattern later in the follow-up period. Although survival probability is ultimately significantly greater on HD, the area under the survival curves (reflecting life expectancy) is ultimately equal at least based on the first 90 months of dialysis.

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