



Congress Service

42nd Annual Meeting of the American Society of Nephrology

October 27 – November 1, 2009
San Diego, California, USA



Fresenius Medical Care



Cardioprotective Haemodialysis

**There's more to dialysis
than dialysis**

Fresenius Medical Care is aware of the significance of the excessive cardiovascular risk in dialysis patients. That's why our dialysis therapy systems are specifically designed to minimize additional, treatment-related risk factors. What can we achieve? Improved blood pressure and anaemia control with less medication, fewer hypotensive episodes during treatment, reduced inflammatory stimuli and response, and reduced oxidative stress.



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Selected Abstracts of the
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1. Mineral Metabolism and Bone Diseases

Nutritional Vitamin D Deficiency in Hemodialysis Patients with Secondary Hyperparathyroidism

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Purpose: Assess nutritional vitamin D deficiency (ND-def) in EVOLVE (Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events) study participants.

Methods: Serum calcidiol (25D) levels were measured in participants in EVOLVE, a global clinical trial that enrolled 3883 hemodialysis patients with secondary hyperparathyroidism (sHPT).

Results: Nutritional vitamin D deficiency (serum 25D level <30 ng/mL) was present in 79.8%, although 61.5% were already receiving various vitamin D sterols used commonly to treat sHPT. More pronounced nutritional vitamin D deficiency with values <15 or <5 ng/mL was found in 39.0% and 1.3%, respectively. Excluding <3% of subjects given ergo- or cholecalciferol, 85.0% of those treated with vitamin D sterols

vs 73.8% of untreated subjects had 25D levels <30 ng/mL, and the mean (SD) 25D level was lower in those receiving D sterols, 18.8±11.0 ng/mL, than in untreated subjects, 22.1±12.9 ng/mL (P<0.0001). For those not treated with D sterols, the proportion of subjects with nutritional vitamin D deficiency, as defined by 3 different threshold levels of 25D, did not differ by severity of sHPT as judged by baseline parathyroid hormone (PTH) (Table); there was no correlation between 25D and PTH levels.

Conclusions: Nutritional vitamin D deficiency is widespread among HD patients with sHPT, but its presence does not affect the severity of sHPT. Nutritional vitamin D deficiency is more common among those who are managed with vitamin D sterols.

Serum 25D (ng/mL)	Plasma PTH (pg/mL)			
	300-600	601-900	901-1200	>1201
<30 ng/mL	77.4	73.7	70.0	71.9
<15 ng/mL	36.6	34.5	33.6	32.7
<5 ng/mL	1.4	1.6	2.3	1.5

Values represent % of subjects in each category

Targeting of PTH and Timing and Frequency of Blood Collection, Significantly Influence CKD-MBD Biochemical Results

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² COSMOS Group (Current Management of Secondary Hyperparathyroidism – A Multicenter Observational Study)

COSMOS is a 3-year, multicentre, prospective, observational cohort study collecting data from 4500 patients at 227 facilities across 20 European countries. Facilities and patients were identified using a stratified, random selection methodology. Each centre completed a questionnaire including facility practices, and timing and frequency of laboratory data collection. Patient data included demographics, medical history, laboratory parameters and therapy. In this report, we analysed in 4195 patients from 214 facilities the likely influence of the time and frequency of blood collection on each dialysis site on the main CKD-MBD surrogate markers.

Measurement of the biochemical parameters post-weekend (long interdialytic period) (N=2274) was associated with higher levels of serum phosphorous and lower levels of PTH than measurements

in the mid-week (short interdialytic) period (N=1921) (5.5 ± 1.5 vs 5.2 ± 1.5 mg/dL, $p < 0.0001$ and 294 ± 308 vs 369 ± 545 pg/mL, $p < 0.0001$, respectively). The measurement of Ca and P monthly or more often than monthly (N=3837) was associated with lower levels of PTH (323 ± 437 vs 385 ± 405 pg/mL, $p = 0.013$). The achieved serum PTH was directly proportional to the PTH levels selected by each facility as the target for initiation of active suppression of PTH. These results indicate that simple and routine practices such as time and frequency of blood testing and predefined targets can have important impact in the CKD-MBD results.

Magnesium and Mortality Risk in Hemodialysis Patients

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Introduction: Few studies have examined the relationship between serum magnesium (Mg) levels and outcomes in hemodialysis patients.

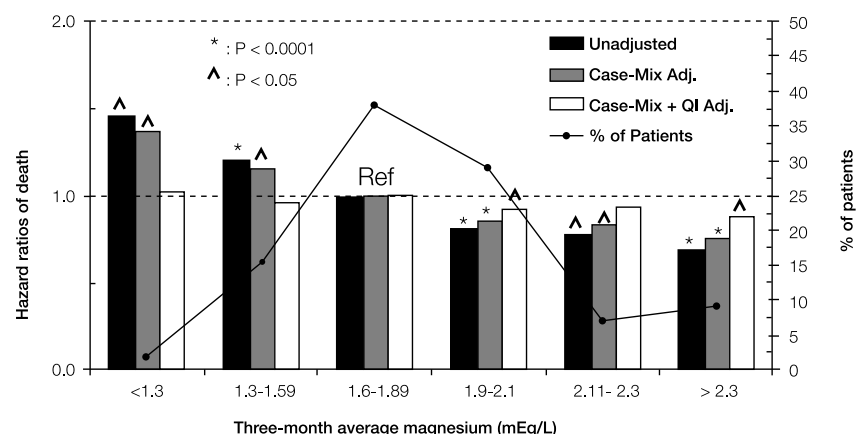
Methods: All chronic hemodialysis patients treated at Fresenius Medical Care North America facilities with at least one serum Mg result between 10/1-12/31, 2007 (baseline) and who survived into 1/1/08, were included. Case-mix (age, gender, race, diabetes mellitus, body surface area, and vintage) and vascular access were identified as of 1/1/08 and mortality was followed until 12/31/08. Cox models were constructed, including one with adjustment for case-mix and 5 quality indicators (QI) at baseline: albumin, hemoglobin, phosphorus, eKt/V, and vascular access.

Results: From 110,271 patients as of 1/1/07, 27,544 (25%) had Mg drawn. Demographic characteristics were similar between patients with and without Mg results,

with mean age of 61.8 ± 14.8 years, 53.7% males, 48.6% white, 43.8% black and 7.5% other races, 53.6% with diabetes, body surface area of 1.84 ± 0.28 m² and vintage of 3.5 ± 3.6 years. Patients had 44.1% fistulas, 24.3% grafts, and 30.9% catheters. The mean serum Mg was 1.85 ± 0.31 (normal: 1.3-2.1 mEq/L). Compared to Mg = 1.6-1.89 mEq/L (mid-normal), the unadjusted hazard ratio (HR) decreases significantly beginning at Mg ≥ 1.9 , to as low as 0.68 for Mg > 2.3 ($p < 0.0001$), with case mix + QI adjusted HR=0.87 ($p = 0.03$) as shown below.

Conclusion: In this observational retrospective analysis, high normal and elevated serum Mg levels were associated with lower risk of mortality in prevalent hemodialysis patients. Cause and effect were not established. Further study is required to evaluate clinical implications of this finding.

Relative risk of mortality: magnesium



Efficacy of CALcium Acetate/MAGnesium Carbonate (OsvaRen®) Versus Sevelamer-HCl (Renagel®) in Hemodialysis Patients (CALMAG Study)

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Phosphate binders are needed to control serum phosphorus (sP) in patients on dialysis. One possibility is to use a combination of calcium with magnesium, but studies in a larger population are missing.

Methods: The following controlled randomized, investigator masked, multicentre trial investigates the effect of calcium acetate (450 mg, i.e. 110 mg Ca), magnesium carbonate (235 mg, i.e. 60 mg Mg) [CaMg] on sP-lowering in a European population for a period of 24 weeks in comparison to Sevelamer-HCl (800 mg) with the aim to lower sP below the K/DOQI target. Patients underwent a 2-3 week p-binder washout period before randomization.

Results: 326 patients in 5 European countries (D, ES, P, RO and

PL) were included, 71 patients dropped out during screening and wash-out. 255 patients were randomized 1:1. Drop outs: n=34 (Sevelamer), n=18 patients (CaMg); safety set=252; FAS=244 (Full Analysis Set). PPS=204 (Per-Patient Set). Mean age was 57 years, M/F 54/45%.

No drug-related serious adverse events occurred.

In conclusion: OsvaRen achieves a significantly better overall sP and Ca x P product control (AUC) compared to Sevelamer-HCl. Thus, it is a logical cost-effective, first-line treatment of hyperphosphatemia with a favourable safety and tolerability profile.

	Study results				Significance
	CaMg		Sevelamer		
	Baseline*	Week 25*	Baseline*	Week 25*	
sP (mmol/L)	2.46±0.49	1.70±0.48	2.48±0.47	1.77±0.61	n.a.**
sCa (mmol/L)	2.15±0.23	2.22±0.16	2.19±0.18	2.19±0.16	0.0032
sMg (mmol/L)	0.99±0.15	1.30±0.25	1.00±0.16	1.04±0.19	<0.0001
AUC*** sP (mmol/L)		299±72		324±81	0.0042
AUC Ca x P (mmol ² /L ²)		664±176		712±187	0.0534
AE****: Gastrointestinal		9.7%		17.3%	
AE: Cardiac		2.4%		3.2%	

*(mean±SD); **Confirmation of study hypothesis, not analyzed, ***Area under the curve, ****Adverse events

2. Anaemia Therapy

Center Effects on Anemia Management of Patients with CKD-Related Anemia

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Purpose: Transfusions (packed red blood cells, PRBC) are reserved for acute treatment of severe anemia in CKD patients. Chronic PRBC expose patients to significant adverse effects, including the development of antibodies directed against human leukocyte antigens, which makes it difficult to find a match for kidney transplantation. This may delay the time to transplantation. We evaluated determinants of the decision to initiate anemia treatment and the choice of treatment [PRBC versus erythropoiesis stimulating agents (ESA)] in patients with non-dialysis CKD-related anemia.

Methods: Incident CKD patients (eGFR < 60 cc/min/1.73m²), receiving outpatient care in the Veterans Health Administration, with incident anemia were identified (n=145,173). Records included monthly hemoglobin values, presence or absence of anemia treatment, and treatment with 1 PRBC or ESA administrations for the month. Pooled logistic regression was used to determine factors associated with: 1) decision to initiate anemia treatment and, 2) among those treated, the choice of treatment (PRBC vs. ESA). Covariates used in the model included patient demographics,

clinical characteristics (Hb, eGFR, etc.), treatment location, and center tendency to use either ESA or PRBC. Adjusted odds-ratios were calculated per one standard deviation change in aggregate center treatment rates.

Results: Compared to patient demographics and clinical characteristics, center tendency was the strongest predictor of future treatment initiation and choice (p < 0.001). Greater center use of either ESA (OR=1.15, p < 0.001) or PRBC (OR=1.08, p < 0.001) was highly predictive of initiation of anemia management in CKD patients. Centers with greater utilization of ESA were less likely to treat with PRBC (OR=0.76, p < 0.001). Centers with greater utilization of PRBC were more likely to treat anemia with PRBC (OR=1.38, p < 0.001).

Conclusion: Center practice patterns appear to be more influential than patient clinical characteristics in determining the anemia management of non-dialysis CKD patients in this cohort. This may have important clinical consequences for patients likely to receive kidney transplants.

Patients with Heart Failure and Diabetes Mellitus Have Differential Outcomes with Treatment for Anemia: A Secondary Analysis of the CHOIR Trial

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Background: Trials testing anemia management strategies in CKD patients have demonstrated risk associated with hemoglobin targets of 13 g/dL or greater. This analysis was undertaken to examine subgroups based on the presence of heart failure and diabetes mellitus.

Methods: CHOIR was a randomized trial comparing the effect of treatment with epoetin-alfa to two hemoglobin targets on the endpoint of death, heart failure hospitalization, stroke, and myocardial infarction in patients with CKD and anemia. Prior heart failure was defined as the presence of heart failure, cardiomyopathy, and left/right ventricular dysfunction. Diabetes mellitus was defined as either the presence of a history of or etiology of renal failure by type 1 or 2 diabetes mellitus. Kaplan-Meier curves were constructed as descriptive statistics and Cox hazards regression was utilized to estimate the hazard ratio (HR) of the predictors of the primary composite endpoint. Subgroup comparisons are carried out by forming contrasts based on the models with interactions.

Results: Heart failure interacted significantly with hemoglobin target ($p=0.028$) after adjusting for

baseline covariates. Among subjects with heart failure in the multivariable model, there was no increased risk associated with the higher target hemoglobin ($HR=0.99$, $p\geq 0.99$). Among subjects without heart failure, the risk associated with the higher target hemoglobin was significant ($HR=1.86$, $p=0.004$). Comparing Kaplan-Meier curves, subjects with diabetes mellitus did not have an increased risk associated with the higher hemoglobin target ($p=0.249$ based on unadjusted Cox model with interaction) while subjects without diabetes mellitus demonstrated a better survival in the low as compared to high hemoglobin target ($p=0.04$). The interaction between diabetes mellitus and treatment arm did not however reach statistical significance ($p=0.559$) in the multivariable model.

Conclusions: These results suggest that the presence of comorbidities such as diabetes mellitus or heart failure makes the hazard associated with a higher hemoglobin target in anemia correction clinically not detectable.

Limits of an Optimal Correction of Renal Anaemia in Haemodialysis Patients

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Background: Appropriate management of anaemia is an important aspect of dialysis patient care. Governmental regulations as well as some medical guidelines suggest that correction of renal anaemia in dialysis patients to a haemoglobin level of 10-13 g/dl is optimal. However, little is known about the normal intra-individual variation of haemoglobin over time to predict whether this optimal haemoglobin corridor can be reached in a normal dialysis population.

Methods: The stable haemodialysis population of a large provider was screened for patients with at least 10 monthly haemoglobin values over one year (n=7780). Intra-individual variation of haemoglobin was defined as the standard deviation (ISD) of the individual's haemoglobin measurements. Effects of dialysis time, Kt/V, blood pressure, Ca x P, dialysis vintage, or type of erythropoiesis stimulating factors (ESF) were analyzed.

Results: Mean haemoglobin was 11.8±0.91 mg/dL. ISD was lowest in patients who required no or very little ESF. Haemoglobin-variation was larger in women than in men and increased with age, higher CRP, number of hospital admissions, increased doses of ESF, number of ESF dosage changes, and frequency of ESF applications per week. ISD was not influenced by dialysis time, Kt/V, blood pressure, Ca x P, dialysis vintage, or type of ESF.

Conclusion: Even in stable patients who require no or very low amounts of ESF haemoglobin values scattered between 10.68 and 13.72 mg/dL. This range increased with factors such as age or sex, which cannot be therapeutically influenced. When considering upper limits of a target range for anaemia management these normal variations should be taken into account.

Introduction of an ESA Dose Adjustment Algorithm Designed to Reduce Hemoglobin Cycling

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Hemoglobin cycling has been associated with increased mortality in hemodialysis patients. Cycling can occur if the ESA dose is increased (or decreased) repeatedly without allowing the hemoglobin to reach steady state. In a stable patient, an increase in ESA should lead to a gradual rise in hemoglobin over approximately 3 months. Making a second increase during this period can cause the hemoglobin to overshoot, initiating a cycle, especially if the target range is very narrow.

ESA dose adjustments for centre-based HD patients in our unit are made using a computerised decision support system (DSS). Until Dec-2008, the DSS used a 'reactive' algorithm based on current hemoglobin, recent rise/fall and a target range of 11 to 12 g/dl. This often led to hemoglobin cycling as described above. In Jan-2009, the DSS switched to an algorithm that recommends dose adjustments only if the predicted steady state hemoglobin is outside the wider target range of 10.5 to 12.5 g/dl. Patients who were at the minimum or maximum point of an hemoglobin cycle at conversion were reviewed manually and in most cases prescribed the ESA dose received before the last change. Hemoglobin, ferritin and doses of ESA and IV iron were compared for the four months before and after conversion.

259 ESA-dependent patients who had been on hemodialysis for at least 9 months were converted from the reactive to the predictive algorithm. Fewer than 10% of patients required manual review. The frequency of ESA (darbepoetin) dose changes dropped from 1 per 2.6 months to 1 per 4.2 months ($p < 0.0001$). The mean hemoglobin and the proportion of patients with hemoglobin outside the desired target range was unchanged (11.6 ± 1.4 g/dl and 42% in May-2009 compared to 11.7 ± 1.4 g/l and 44% in Jan-2009), despite a gradual decrease in mean darbepoetin dose from 30.8 to 28.7 mcg/week ($p = 0.02$). There were no significant changes in iron requirements (mean 37 ± 32 mg/week) or serum ferritin levels (mean 520 ± 210 g/l) during the conversion period.

Although it is too early to assess the effect of converting to a predictive algorithm on hemoglobin cycling, the change in algorithm has led to significant decreases in both the frequency of ESA dose changes and the mean ESA dose with no detrimental effect on hemoglobin levels.

The Impact of Ferritin Cycling on Stable Hemoglobin Levels in Hemodialysis Patients

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It had been reported that anemia and hemoglobin (Hb) variability are associated with mortality in hemodialysis patients who are treated with erythropoiesis-stimulating agents (ESA). We hypothesized that the iron store of hemodialysis patients is an important factor, which is associated with hemoglobin variability. We evaluated the relationship between ferritin variability and hemoglobin stability.

Method: 168 hemodialysis patients, who were treated with ESA were defined on the basis of patterns of hemoglobin and ferritin during the 12-month (from Jun 2007). Low Hb (L-Hb): consistently low (<10 g/dl), Low ferritin (L-ferritin): consistently low (<50ng/dL). Target Hb (T-Hb): consistently target (10-11g/dL), Target ferritin (T-ferritin): consistently target (50-300ng/dL). Low-amplitude fluctuation with low Hb (LAL-Hb) and ferritin (LAL-ferritin), low-amplitude fluctuation with high Hb (LAH-Hb) and ferritin (LAH-ferritin) levels, and high-amplitude fluctuation (HA-Hb and HA-ferritin). High Hb (H-Hb): consistently high (>11g/dL), High ferritin (H-ferritin): consistently high (>300ng/dL).

Result: Common patterns of hemoglobin cycling in our study were HA-Hb (36%), LAL-Hb (41%), while those of ferritin cycling were HA-ferritin (45%) and LAL-ferritin (21%). Number of ferritin cycling was significantly ($p<0.0001$) correlated with number of hemoglobin excursion (decrease), which could be associated with cardiovascular event. T-ferritin (H-Hb: 9.8% and T-Hb: 21.2%) and LAH-ferritin (T-Hb: 12.8% and LAL-Hb: 18.6%) were favorable for maintaining stable hemoglobin. In contrast, HA-ferritin (H-Hb: 0%, T-Hb: 0%, and LAL: 18.8%) and LAH-ferritin (H-Hb: 0%, T-Hb: 2.8%, and LAL-Hb: 3.2%) seldom attained T-Hb.

Conclusion: Greater ferritin variability is associated with unstable hemoglobin levels in hemodialysis patients. The estimation of ferritin variability in patients with renal anemia could be better estimate for hemoglobin stability, and indicator for dose of ESA and iron.

Plasma Hepcidin Predicts Haemoglobin Response to Intravenous Iron in Haemodialysis Patients

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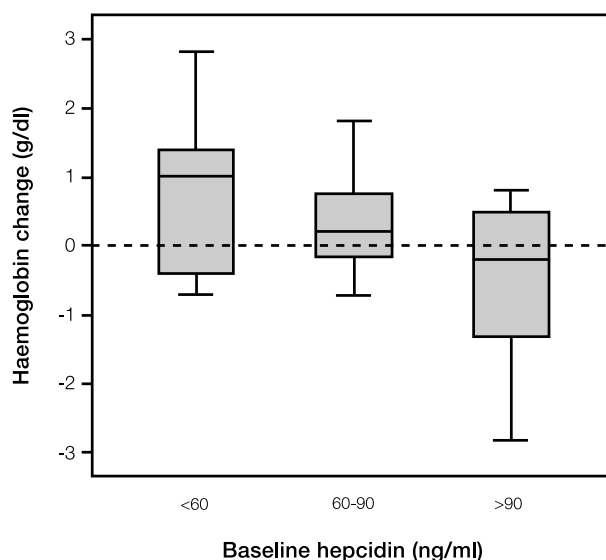
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Correct use of intravenous iron is crucial in overcoming the morbidity associated with erythropoietin resistance, but current measures of iron status are unreliable in renal failure. The hepatic peptide hepcidin is the master regulator of iron absorption and transport. Circulating hepcidin levels reflect both iron availability and iron demand in renal failure.

Using a competitive radioimmunoassay, plasma hepcidin was measured in a group of stable haemodialysis patients prior to therapy with intravenous iron. Baseline parameters predictive of the change in haemoglobin over the following month were identified.

In 67 patients (44 male, aged 22-92) mean hepcidin was 72.5 ± 3.4 ng/ml (mean \pm SE), and levels were correlated with ferritin and erythro-

poietin dose ($R=0.394$, $p<0.001$ and $R=-0.285$, $p=0.019$). Change in haemoglobin after iron therapy was correlated with baseline haemoglobin and hepcidin ($R=-0.343$, $p=0.005$ and $R=-0.322$, $p=0.008$), and not related to other baseline parameters, including ferritin and transferrin saturation. Haemoglobin change is shown in the figure according to baseline hepcidin category: a positive response to iron (increase in haemoglobin or stable haemoglobin with reduction in erythropoietin dose) was seen in 86.4%, 68.8% and 30.8% of patients in the low, medium and high hepcidin groups ($p=0.003$). Plasma hepcidin is predictive of the haemoglobin response to intravenous iron. Hepcidin measurement may be useful as a guide to the therapy of anaemia in haemodialysis patients.



Long-Term Survival on Hemodialysis: Adverse Effects of Large Doses of IV Iron

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Iron insufficiency has adverse effects on chronic HD patient survival (KalantarZadeh, JASN 2005, 16:3070; Pollak, BMC Nephrology 2009, 10:6). In 1774 patients treated by chronic maintenance hemodialysis from January 1998 to June 2007, we reported that each of patient lifetime mean low serum iron, low transferrin saturation (TSAT), and low serum ferritin was associated with adverse survival effects. Repletion with moderate IV iron doses had favorable effects, but large doses had adverse survival effects (Pollak, op cit). We analyzed data on the 1565 patients who had received IV iron, with available lifetime TSAT and serum ferritin data. We divided them into 3 groups: 1428 with lifetime TSAT >20% (mean age 58.6 years, 28% with ≥ 2 co-morbid conditions); 47 with lifetime TSAT $\leq 20\%$, serum ferritin $\leq 200 \mu\text{g/L}$ (mean age 59.3 years, 36% with ≥ 2 co-morbid conditions); 90 with lifetime TSAT $\leq 20\%$, serum ferritin $>200 \mu\text{g/L}$ (mean age 67.5 years, 52% with ≥ 2 co-morbid condi-

tions). Each was further divided into two subgroups: lifetime IV iron doses of 1-455 mg/month or >455 mg/month. Age and proportion with ≥ 2 co-morbid conditions were identical in both subgroups, but mortality expressed as deaths per 1000 patient years was 2.1 to 3 times higher in the subgroup IV iron >455 mg/month.

It is unclear whether IV iron doses >455 mg/month are inherently toxic or rather identify patients who lose substantially greater amounts of iron, and whose mortality is increased as a result of continuing iron deficiency, the underlying cause of the iron loss, or both.

We conclude that IV iron doses >455 mg/month identify patients at high risk for death irrespective of their TSAT, and who require close follow-up. This adverse effect on survival is not consequent on differences in population characteristics, nor as shown previously (Pollak op cit) is it associated with major infections including pneumonia, cellulitis, and skin ulceration.

Lifetime IV Iron	TSAT >20%	TSAT $\leq 20\%$ Ferritin $\leq 200 \mu\text{g/L}$	TSAT $\leq 20\%$ Ferritin $>200 \mu\text{g/L}$
1-455 mg/month	103.6	223.9	220.9
>455 mg/month	224.2	669.4	517.1

3. Cardiovascular Diseases

Toward Target Blood Pressure in Hemodialysis: Findings from the DOPPS

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The paradoxical association of blood pressure and mortality among hemodialysis (HD) patients presents a conundrum in clinical practice.

Using data from 24,775 patients (504 facilities) in the Dialysis Outcomes and Practice Patterns Study (DOPPS, an HD cohort study in 12 countries), we studied associations with mortality of (i) baseline pre-dialysis systolic blood pressure (SBP), (ii) change in SBP over time (by linear regression) and (iii) among those where initial SBP was >160 mm Hg. (iv) We also compared the relationship of SBP and mortality between strata of ‘healthier’ vs. ‘sicker’ patients defined by dichotomizing the pop-

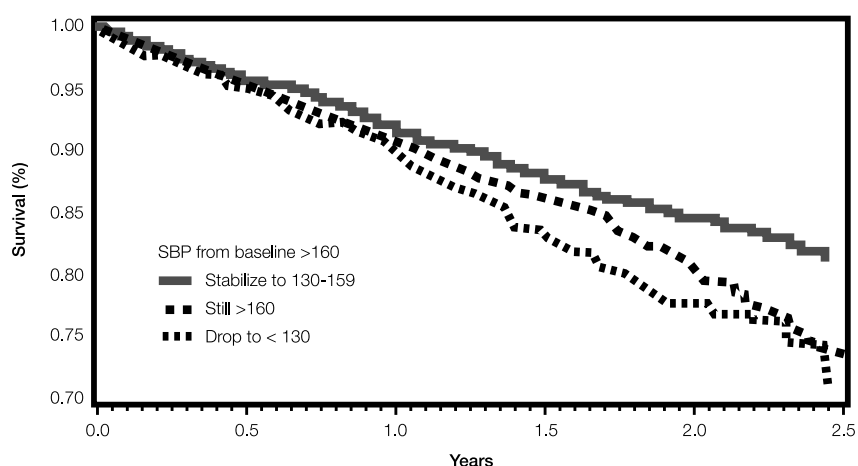
ulation at the median baseline risk for death based on demographics, comorbidities, nutritional and laboratory measures. Cox regression models were adjusted for case-mix and stratified by country and DOPPS phase.

The lowest risk of mortality was observed in patients with SBP 130-160 mm Hg. The highest risk was seen for patients where initial SBP was in the <130 mm Hg category, and patients with SBP falling by >15 mm Hg/year (Table). ‘Healthier’ HD patients showed higher risk at SBP ≥ 160 mm Hg, whereas ‘sicker’ patients had low-

er risk at SBP ≥ 160 mm Hg. Baseline SBP ≥ 160 mm Hg (Figure) patients whose SBP dropped over time to 130-160 mm Hg had the lowest mortality risk.

Among healthier HD patients, SBP 130-160 mm Hg is associated with longer survival. Falling SBP over time to <130 mm Hg predicts higher mortality. The paradoxical relationship of SBP and mortality in hemodialysis is partially explained by patient health status. These findings are consistent with target SBP ~ 130-160 mm Hg, and can inform practice and design of future trials.

Adjusted^a Kaplan-Meier survival for patients with initial with initial SBP >160 mm HG



Adjusted^a HR of mortality by slope in SBP v. mean SBP categories

Slope (mm Hg/year)	Mean SBP (mm Hg)			Overall
	<130	130-160	160+	
<-15	1.74 ^{**}	1.35 [*]	1.25 [*]	1.26^{***}
-15 to +15	1.33 [*]	1 (ref)	1.13	1 (ref)
>+15	1.32 [*]	0.92	1.11	0.96
Overall	1.33^{***}	1 (ref)	1.07	

* P<0.5 from 9 cell reference of mean SBP130-160 and slope -15 to +15

** p<0.5 from 9 cell reference and from 3 cell column reference slope of -15 to +15

*** p<0.5 from marginal overall references of mean SBP of 130-160 or slope of -15 to +15

^a Adjusted for age, gender, race, BMI, 13 summary comorbidities, dialysis duration, Kt/V, protein catabolic rate, vintage and s.albumin, PTH, ferritin, phosphorous, creatinine, and haemoglobin, stratified by country and phase

Evolution of Systolic Blood Pressure in the First Year of Hemodialysis: A Comparison between Tassin, France, and Renal Research Institute, USA

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Systolic blood pressure (SBP) is a major determinant of morbidity and mortality in hemodialysis patients. In the general population SBP is influenced by genetic and environmental factors, but in hemodialysis patients SBP may be related to treatment practices.

We studied temporal evolution of average weekly pre-HD SBP in 1st year of hemodialysis in 2 cohorts of incident hemodialysis patients from US and France. US patients started HD between 1/1/2001 and 8/31/2008, French patients between 1/1/2000 and 1/1/2009. Only patients who survived >90 days from start of hemodialysis were included. Cohorts were compared by t-test.

3,517 US patients (age 61±15 years [mean±SD], 58% males, 47% blacks, 43% whites, 51% diabetes) and 212 French patients (age 63±16 years, 63% males, 2% blacks, 96% whites, 30% diabetes) were studied. Temporal evolution of SBP differed significantly (Fig 1a). SBP was higher in US patients compared to Tassin patients at hemodialysis initiation (150.6 vs 143.3 mmHg, P<0.0001)

and at the end of 1st year (151 vs 131 mmHg, P<0.0001). Treatment time in US patients was 210±23 min, in Tassin 382±77 min (P<0.0001). Dialysate sodium in US was 140±1.5 and in Tassin 138 mmol/L. Post-HD weight declined initially in both cohorts (Fig 1b).

This study reveals a sharp contrast in temporal evolution of SBP between incident US and Tassin hemodialysis patients. In Tassin patients SBP steadily declined during 1st year of hemodialysis,

whereas US patients experienced a rise of SBP until week 12 followed by a plateau.

We hypothesize that in addition to blood pressure management (drug prescription patterns, SBP targets, and dietary salt intake) lower dialysate sodium and therefore lower sodium gradient between dialysate and blood, and longer treatment time in Tassin contribute significantly to lower SBP by permitting reduction in body sodium content.

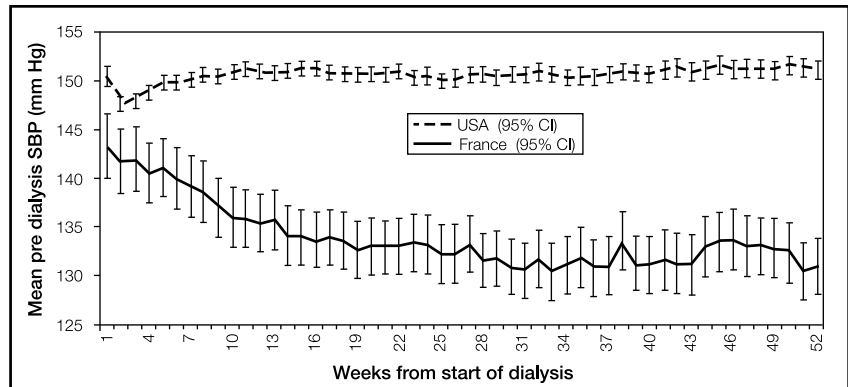


Figure 1a: Evolution of SBP

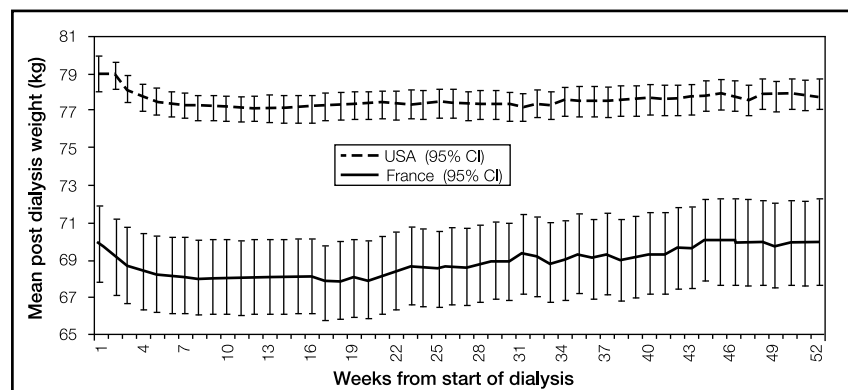


Figure 1b: Evolution of post-HD weight

Interdialytic Weight Gain or Chronic Fluid Overload. Which is More Dangerous for Chronic HD Patients?

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Introduction: In a recent publication (Circulation 2009), Kalantar-Zadeh analysed the mortality risk induced by the interdialytic weight gain (IWG) in 34.000 hemodialysis patients over a 2-year follow-up. A hazard ratio (HR) of 1.25 in patients with an IWG >2.5 L was found after adjusting with a multivariate Cox Model. This publication highlights the lack of objective methods to assess the fluid overload (FO) as a limitation of the study. By contrast, Wizemann (NDT 2009) analysed a cohort of 256 patients with objective methods to assess fluid overload using bioimpedance spectroscopy (BIS) and found a HR=2.1 (Cox Model) in patients presenting FO/ECW (Fluid overload normalised to extracellular water, ECW) of more than 15% in a 3.5 year follow-up. The question remains which of

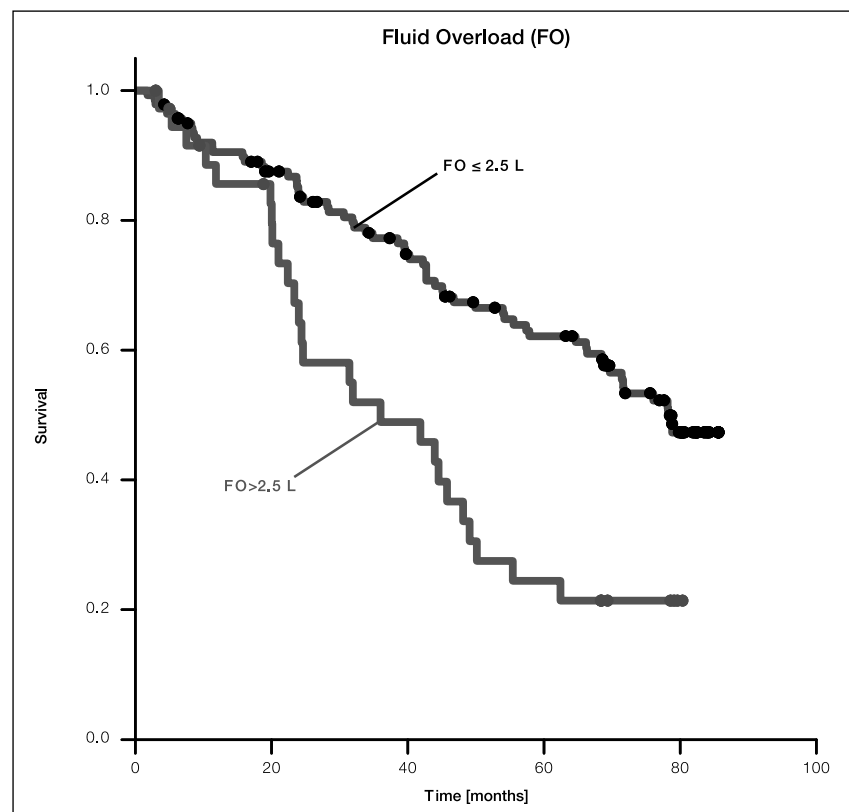
chronic fluid overload or IWG represents the higher mortality risk for hemodialysis patients.

Methods: We analysed 180 hemodialysis patients over a follow-up period of 6.5 years. Fluid overload was measured objectively with BIS (BCM-Body Composition Monitor). Patients were defined as being fluid overloaded when presenting FO/ECW >15% and separated into two groups accordingly.

IWG was analysed as the difference between pre- and post-weight. Two patient groups were defined, those with an IWG above 2.5 L and those below 2.5 L.

Results: 63 patients survived the 6.5-year follow-up, 28 patients were censored due to transplantation or centre change, 88 patients died in the phase of the 6.5 year follow-up resulting in an overall annual mortality of 8.9%. An IWG > 2.5 L was not linked to a significant overall mortality risk. In contrast, chronic fluid overload (FO/ECW>15%) was associated with a significant increased mortality risk ($p<0.0001$) in the Kaplan-Meier analysis.

Discussion: Objective measures of fluid overload are essential to reduce the cardiovascular risk of HD patients.



Cycling of Plasma Bicarbonate Levels by Hemodialysis Significantly Affects the Coronary Artery Calcification in Hemodialysis Patients

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Background: Acidosis is known to promote bone resorption, while constant acidic conditions do not contribute to vascular calcification. In patients on hemodialysis, cyclic changes of acid-base balance occur at each hemodialysis session. Pre-dialysis acidic state usually improves by the end of hemodialysis. The purpose of this study is to clarify the effect of acid-base status of pre-dialysis, post-dialysis, and their cycling by hemodialysis on coronary artery calcification (CAC) in prevalent hemodialysis patients.

Patients and Methods: We evaluated 88 prevalent hemodialysis patients (31 women, 57 men; age 66 ± 11 years; hemodialysis duration 89 ± 69 months). CAC scores (CACS) were measured by multi-detector-row computed tomography according to Agatston Score. Blood gas samples were taken before and after the first hemodialysis session of the week. We evaluated the association between CACS and several parameters including age, sex, hemodialysis duration, albumin, Ca, Pi, CaPi, i-PTH, high-sensitive C-reactive protein, comorbid condition including hypertension and diabetes mellitus, and bicarbonate levels before and after hemodialysis.

Results: CACS was 2044 ± 4118 (0~30676). Plasma bicarbonate levels before and after hemodialysis session was 17.8 ± 1.7 and 20.5 ± 2.5 mmol/l, respectively. Corrected bicarbonate levels by single hemodialysis (Δ bicarbonate) were 2.70 ± 2.48 mmol/l. In univariate analysis, CACS was negatively correlated with predialysis bicarbonate levels ($r=0.334$, $p=0.001$), and positively correlated with bicarbonate ($r=0.245$, $p=0.021$), hemodialysis duration ($r=0.403$, $p=0.001$). Mineral abnormalities or micro-inflammation were not correlated with CACS. Multivariate analysis showed longer hemodialysis duration and lower predialysis bicarbonate levels were the independent contributing factors for CACS. Furthermore, bicarbonate had a negative correlation with predialysis bicarbonate levels ($r= -0.509$, $p<0.0001$).

Conclusion: The cycling of bicarbonate levels by hemodialysis (i. e. predialysis acidic state and its postdialysis neutralization) significantly affected more on CAC in hemodialysis patients with longer hemodialysis duration.

Dialysate Potassium Concentration and Risk of Peridialytic Cardiac Arrest among Hyperkalemic Hemodialysis Patients

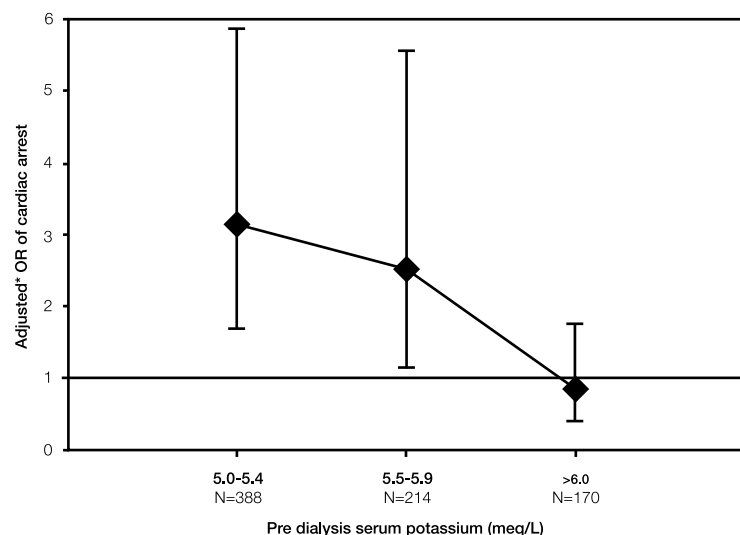
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Hyperkalemia may contribute to excess cardiac arrhythmias and subsequent mortality among hemodialysis patients, but previous studies have also shown a consistent association between the use of low potassium (K) dialysate and increased risk of cardiac arrest. We sought to examine the influence of low K dialysate on the risk of peridialytic cardiac arrest among hyperkalemic hemodialysis patients. We previously designed a case control study from among

43,200 US Davita (formerly Gambro) hemodialysis patients between 2002-2005. Using this resource, we identified 182 subjects who experienced a witnessed peridialytic cardiac arrest and had a last re-corded pre-dialysis serum K of 5.0 meq/L, and we compared them with 590 hyperkalemic ($K \geq 5$ meq/L) controls. We examined the unadjusted and adjusted odds of cardiac arrest based on last known dialysate K concentration using logistic regression techniques. 29% of cardiac arrest patients were using low (<2 meq/L) K dialysate at the time of the arrest compared to 17% of controls. There were no differences in age or dialysis vintage between the two groups, but the cardiac arrest group had a higher mean predial-

ysis serum K (5.7 vs. 5.6, $p=0.03$) and a greater prevalence of congestive heart failure (41% vs. 29%, $p<0.01$). After accounting for differences in demographic factors, cardiac comorbidities, and predialysis serum K, use of low K dialysate was associated with an increased risk of cardiac arrest (adjusted OR 1.9, 95% CI 1.3-2.8). Subgroup analysis revealed that the increased risk associated with low K dialysate was observed primarily among patients with predialysis serum K between 5.0-6.0. We conclude that the use of low K dialysate < 2 meq/L to manage patients with moderate hyperkalemia ($K<6$ meq/L) may be associated with an increased risk of cardiac arrest, and alternate dialysis strategies for managing hyperkalemia should be investigated.

Risk associated with low potassium dialysate in hyperkalemic patients



*OR adjusted for age, serum potassium level and history of CHF. Error bars depict 95% CI.

4. Elderly Patients with Chronic Kidney Disease

Prevalence of Chronic Kidney Disease in an Elderly Population: Impact of the Choice of the Equation Used for Estimating GFR

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Background: We have compared the prevalence of stage 3 CKD in an elderly population using either the creatinine- or the cystatin C-based equations.

Methods: On a voluntary way, all the patients aged at least 45 years and living in the Province of Liège (Belgium) were invited to be screened for CKD. This province has an area of 3862 km and its population reaches 1.037.161 inhabitants. Serum creatinine has been measured with an IDMS traceable method (compensated Jaffé, Roche). Cystatin C was measured with the nephelometric method (Siemens). The study period was between June 2008 and April 2009. GFR was estimated by creatinine-based equations (MDRD and CKD-EPI equations) and by three cystatin C-based equations published by the Levey's group (Levey 1 is based on cystatin C, Levey 2 on cystatin C, age, sex and ethnicity, Levey 3 combined age, sex, ethnicity, cystatin C and creatinine).

Results: 1992 subjects were screened (47% men, mean age of 62 ± 8 years). Mean serum creatinine and plasma cystatin C were

0.86 ± 0.20 mg/dL and 0.76 ± 0.16 mg/L. The prevalence of stage 3 CKD in this population using the MDRD or the CKD-EPI equations was 11.04 and 7.98%. If the three cystatin C equations are used, the prevalence would be 1.10, 2.11 and 3.82%.

Conclusion: In our population, we describe large discrepancies in the CKD prevalence according to the equations used for estimating GFR. The classical MDRD study equation gives the greater prevalence, notably comparing to the new CKD-EPI equation. This last equation is thought to be more accurate in normal creatinine ranges. Discrepancies are still more impressive when cystatin C and creatinine-based equations are compared. The choice of the equation used for estimating GFR has thus a true and great impact on the prevalence of CKD in epidemiological studies.

Our work confirms the urgent need of studies with GFR measured by a reference method.

36 Months Follow-Up of Renal Function in Elderly with CKD

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Introduction and aim: CKD is a global public health problem. Prevalence of low estimated glomerular filtration (eGFR) increases with age. We followed-up for 36 months the renal function of elderly with CKD.

Patients and methods: 80 clinically stable patients, with a median age of 83 years; women: 68.8%; diabetics: 35%; randomly recruited in the Departments of Geriatric and Nephrology, within January-April 2006, were followed-up for 36 months. We separated them in two groups based on their serum creatinine (sCr) baseline: Group 1: 38 patients with sCr \leq 1.1 mg/dl (range: 0,7-1,1); and Group 2: 42 patients with sCr $>$ 1.1 mg/dl (range: 1,2-3). We measured creatinine, urea in serum; and estimated GFR at baseline and 36 months, using abbreviated MDRD. Statistical comparisons using repeated measures, SPSS 11.0 program.

Results: 30% of patients died. 70% were followed-up for 36 months: global evolution (baseline/36 months): sCr (mg/dl): 1.25 \pm 0.47/1.36 \pm 0.61 p=0.020; urea (mg/dl): 57.92 \pm 30 / 66.75 \pm 40 p=0.006; MDRD (ml/min): 53.33 \pm 16/50.23 \pm 17, p=0.032). Data of both groups are shown in the table. Deterioration of sCr was higher in those with/without proteinuria: 1.85 \pm 0.68/2.15 \pm 0.85 vs 1.10 \pm 0.25/1.16 \pm 0.32 (mg/dl), p=0.032.

Conclusions: We confirm a slow deterioration of renal function on time in our CKD elderly, but this deterioration was not worse in patients with worst baseline renal function. Only proteinuria determined worse follow-up of renal function. Therefore, elderly patients with low eGFR and without proteinuria have a more optimistic prognosis.

	GROUP 1 (*) N=30	GROUP 2 (*) N=26	p (1)	p (2)
sCr baseline/36 months (mg/dl)	0.94 \pm 0.1/1.0 \pm 0.1	1.55 \pm 0.5/1.71 \pm 0.6	0.022	NS
Urea baseline/36 months (mg/dl)	40.63 \pm 10/45.97 \pm 13	75.21 \pm 34/87.52 \pm 47	0.006	NS
MDRD baseline/36 months (ml/min)	64.55 \pm 11/60.75 \pm 13	42.54 \pm 13/40.11 \pm 14	0.033	NS

(*): both groups were different at baseline (P=0.000)

p (1): changes with time of follow-up

p (2): differences in change between both groups after follow-up

Mortality in Elderly Dialysis Patients: The Association with Demographic, Patient and Practice Variables

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Introduction: People aged 75 or older account for over one fifth of prevalent dialysis patients in Australasia and the US. The mortality rate on dialysis of this group is high, giving rise to questions about the utility of dialysis in the aged population.

Methods: A retrospective analysis of patients aged 75 years or older starting dialysis between 2002-2005 was conducted using the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry. The association of demographic, comorbid and practice variables with the primary endpoint of mortality was assessed with univariate and multivariate proportional hazards models.

Results: A total of 1781 patients aged 75 or older were included with median follow-up of 2.3 years. Overall 1141 patients (64%) died with 1 and 2 year survival rates of 76.8% and 59.1% respectively. All the following variables were independent predictors of mortality in the multivariate model: Age (1 year increment, hazard ratio (HR) 1.05, 95% confidence interval (CI) 1.03-1.07), underweight

status (BMI<18.5, HR 1.71, 95% CI 1.28-2.29), late presentation (HR 1.22, 95% CI 1.05-1.42), and lack of permanent dialysis access at first dialysis (HR 1.35, 95% CI 1.17-1.56) while haemodialysis as the dialysis modality at 3 months was associated with reduced mortality (HR 0.77, 95% CI 0.66-0.90). The number of comorbidities was also associated with a graduated increase in mortality (1 comorbidity: HR 1.36, 95% CI 1.11-1.66, 2 comorbidities: HR 1.54, 95% CI 1.26-1.88, 3 or more comorbidities: HR 1.85, 95% CI 1.51-2.26). **Conclusion:** We have identified some potentially modifiable factors for the high mortality in patients aged 75 or older at dialysis initiation. The extent to which residual confounding and patient selection affect these results is unknown, however, decisions regarding commencement of treatment for elderly dialysis patients should be informed by the best available evidence about potential gains in quality and quantity of life.

The Competing Risk of Cardiovascular-Related Death and Progression to End-Stage Renal Disease among Older Chronic Kidney Disease Patients

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Background: Among older adults with moderate chronic kidney disease, the competing risk of progression to end-stage renal disease (ESRD) and death, in particular, cardiovascular-related death is unknown. We compared the rates of ESRD, cardiovascular disease death (CVD death) and non-cardiovascular death (non-CV death) in participants of the Cardiovascular Health Study (CHS), a longitudinal cohort study of community-dwelling adults 65 years of age and older.

Methods: 1,268 CHS participants with an eGFR <60 ml/min per 1.73 m² at study entry were followed until the time of first event (ESRD, CVD death, or non-CV death) or until study end on March 31, 2003. ESRD was ascertained through linkage to the United States Renal Data System and chart review. Rates of each event of interest were calculated and a Cox Proportional Hazards Model with a competing risk framework was used to examine risk factors for development of ESRD.

Results: The mean age of the cohort was 75 years of age and the mean and median eGFR at study entry were 51 and 53 ml/min per 1.73m², respectively. During a mean follow-up of 9 years, 5% of the cohort progressed to ESRD and 61% of the cohort died. The rate (per 100 person-years) was 0.5 for ESRD, 3.0 for CVD death, and 3.8 for non-CV death. Lower eGFR (HR 3.8 per 10 ml/min/1.73 m² decrease, 95% CI 3.0,4.8), male gender (HR 3.9, 95% CI 2.2,7.0), African-American race (HR 2.2, 95% CI 1.1,4.2), and diabetes (HR 2.3, 95% CI 1.2,4.1) were associated with an increased risk of ESRD.

Conclusions: Based on the observed event rates, older persons with moderate CKD are nearly thirteen-fold more likely to die from any cause than to progress to ESRD, and are six-fold more likely to die from cardiovascular-related causes than develop ESRD.

5. Epidemiology of Renal Replacement Therapy

Towards Understanding the Worldwide Variation in Renal Replacement Therapy Incidence: The EVEREST* Study

*Explaining the Variation in Epidemiology of RRT through Expert opinion, Secondary data sources and Trends over time

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Purpose: To examine the association between renal replacement therapy (RRT) incidence per million population (pmp) and general population age-health indicators, macroeconomic indices and renal service factors in 46 countries worldwide.

Methods: Numbers of patients commencing RRT in 2003-5 were collected for each country stratified by age and gender. General population age-health and macroeconomic data were collected from secondary sources. National experts provided primary data on renal service funding, resources and organisation. Countries were stratified into low or high Human Development Index (HDI) groups.

Results: Life expectancy at 60 was positively associated with RRT incidence ($R^2=0.14$, $p=0.02$) but only in low HDI countries ($R^2=0.52$, $p=0.002$). No association was observed between RRT incidence and general population diabetes prevalence or cardiovascular mortality. Of the macroeconomic factors, only % gross

domestic product (GDP) spent on healthcare ($R^2=0.29$, $p<0.0001$) and WHO Responsiveness Index ($R^2=0.21$, $p=0.001$) were positively associated with RRT incidence, though GDP per capita and public as % total expenditure on healthcare were associated with RRT incidence in the low and high HDI groups, respectively. Of the renal service indicators, there was a positive correlation between RRT incidence and the number of main dialysis facilities pmp ($R^2=0.44$, $p=0.001$ and $R^2=0.18$, $p=0.04$ in the low and high HDI groups, respectively) and the % facilities in the private-for-profit sector, although only in the high HDI group ($R^2=0.54$, $p<0.0001$).

Conclusions: Macroeconomic and healthcare organisational indices show stronger associations with national RRT incidence rates than general population age-health indicators. Patterns vary according to HDI category.

An Update on Renal Replacement Therapy in Europe: ERA-EDTA Registry Data from 1997 to 2006

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Diseases

Recent studies indicate a stabilization in the incidence rates of renal replacement therapy (RRT) in a number of European countries. The aim of this study was to provide an update on the incidence, prevalence and outcomes of RRT in Europe over the past decade.

Twenty-two European national or regional renal registries participating in the ERA-EDTA Registry from 1997 to 2006, participated in the study. Incidence and prevalence trends were analysed with Poisson and Joinpoint regression. Adjusted Cox regression was used to examine patient survival.

The total adjusted incidence rate of RRT in the 22 participating registries increased from 110.4 pmp in 1997 to 119.8 pmp in 2000, i.e. an average annual percentage change (AAPC) of +2.6% (95% CI: +1.5 to +3.7%) per year. Thereafter, the incidence increased more slowly to 126.2 pmp in 2004 (AAPC: +1.0% (95% CI: +0.0 to +2.0%)). Between 2004 and 2006 the incidence rate of RRT remained stable (AAPC: -0.0%

(95% CI: -2.2 to +2.4)). This stabilization in the incidence of RRT is largely due to a decrease among patients aged 65-85 years and those with RRT for ESRD due to diabetes mellitus and hypertension/renal vascular disease. However, the incidence still increased in patients above 85 years with 6.5% per year. The overall adjusted prevalence in Europe continued to increase linearly with 2.7% per year.

The risk of death decreased for all treatment modalities, with the most substantial improvement in peritoneal dialysis patients (-17% (95% CI: -13 to -21%)) and in kidney transplant recipients (-16% (95% CI: -10 to -22)).

This European study shows that in recent years on average the overall incidence rate of RRT has stabilized. The survival of patients on dialysis, and even more, after kidney transplantation has continued to improve.

Dialysis Modality Choice in Patients with Diabetes Mellitus, Cardio- or Cerebrovascular Disease, or Malignancy in Europe

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Background: The prevalence of comorbidities at the onset of end-stage renal disease is rising. We aimed to assess dialysis modality choice in patients with diabetes mellitus, cerebrovascular disease (CD), peripheral vascular disease (PVD), ischemic heart disease (IHD), or malignancy (MAL).

Methods: ERA-EDTA Registry data from 18,503 incident dialysis patients (1998-2006) with data on comorbidity at the start of dialysis from Austria, Belgium (French-speaking), Catalonia (Spain), Finland, Greece, Norway, Sweden, and the UK were included. Day 91 on dialysis was considered as start of treatment. We performed multivariate logistic regression analyses stratified for gender to assess the risk of receiving treatment with peritoneal dialysis compared to hemodialysis.

Results: Of the participating patients, mean (SD) age was 63 (15) years, 62% were male, and 82% were on hemodialysis. The risk of receiving peritoneal dialysis significantly decreased with increasing age; we found an odds ratio (OR) of 0.53 (95% CI: 0.45-0.63) for males 70 years, and of 0.30 (95% CI: 0.25-0.37) for females 70 years (reference group:

20-44 years). Patients with PVD, CD, and MAL were significantly less likely to receive peritoneal dialysis when compared to patients without those conditions (ORs between 0.65 [95% CI: 0.56-0.76] and 0.72 [95% CI: 0.64-0.81]). In diabetics, the risk of receiving peritoneal dialysis compared to hemodialysis was only higher in men (OR: 1.19, 95% CI: 1.07-1.33). The presence of IHD had no significant influence on modality choice. Finally, the presence of multiple comorbidities was negatively associated with the risk of receiving peritoneal dialysis; patients with 3-5 comorbidities had a 16% lower risk of receiving peritoneal dialysis compared to those without reported comorbidities (OR: 0.84, 95% CI: 0.72-0.97).

Conclusion: Based on data from 8 European renal registries, we conclude that incident patients with higher age, PVD, CVD, MAL, and multiple comorbidities are less likely to receive peritoneal dialysis as dialysis treatment. Contrasting, the presence of IHD does not influence the risk of receiving either peritoneal dialysis or hemodialysis.

6. Haemodialysis Therapy

Switch from Low-Flux Haemodialysis to Post-Dilutional On-Line Haemodiafiltration: Effects on Inflammation and Recombinant Human Erythropoietin Dose in Uraemic Patients

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Background: Chronic inflammation is a common feature in haemodialysis patients and it is associated with poor anaemia control.

Purpose: To evaluate the effect of the switch from standard hemodialysis (HD) to post-dilution ol-HDF on serum C-reactive protein (hsCRP), serum beta-2-microglobulin (B2m), and recombinant human erythropoietin dose (EPO dose) levels.

Protocol: Prospective comparison of 6 months conventional HD (period 1) and 6 months ol-HDF (Period 2) on: hsCRP, B2m, EPO dose (U/Kg/week) in 30 patients (26 men, 4 women, mean age 57 ± 13 years) in chronic HD treatment for 12-108 months. Other variables included: body weight (BW), serum albumin (sAlb), Hemoglobin (Hb), TSAT, serum ferritin (F), serum sodium (Na), serum potassium (K), pre-dialysis systolic (PAS) and diastolic (PAD) blood pressure. Iron supple-

ments and EPO were managed according to the K/DOQI guidelines recommendations. Blood flow rate, dialysis time, dialysate flow, were kept constant. Post-dilution replacement fluid in ol-HDF amounted to 19.9 ± 2.1 l/session.

Results: Comparison of serum hsCRP, B2m, EPO dose, and Hb concentrations between the two periods of observation is shown in the table.

No significant variations of BW, PAS, PAD, Na, K, sAlb, F, TSAT, were observed.

Conclusion: The change from conventional low-flux HD to ol-HDF resulted in a significant reduction of hsCRP and B2m concentrations, associated with a significant reduction in EPO dose in the presence of stable Hb concentrations. This suggests better control of inflammatory status by ol-HDF compared to standard HD.

	Period 1: HD			Period 2: ol-HDF		
	Start	End	p	Start	End	p
hsCRP (mg/dl)	6.6±8.4	5.3±7.5	NS	5.3±7.5	2.0±2.7	<0.01
B2M (mg/dl)	29.5±14.8	29.0±14.4	NS	29.0±14.4	21.3±12.3	<0.0001
EPO dose (U/K/week)	104±69	92±61	NS	92±61	57±35	<0.008
Hb (g/dl)	11.6±0.5	11.6±0.7	NS	11.6±0.7	11.7±0.6	NS

Long-Term Patient Survival on Haemodialysis: Association with Treatment Time

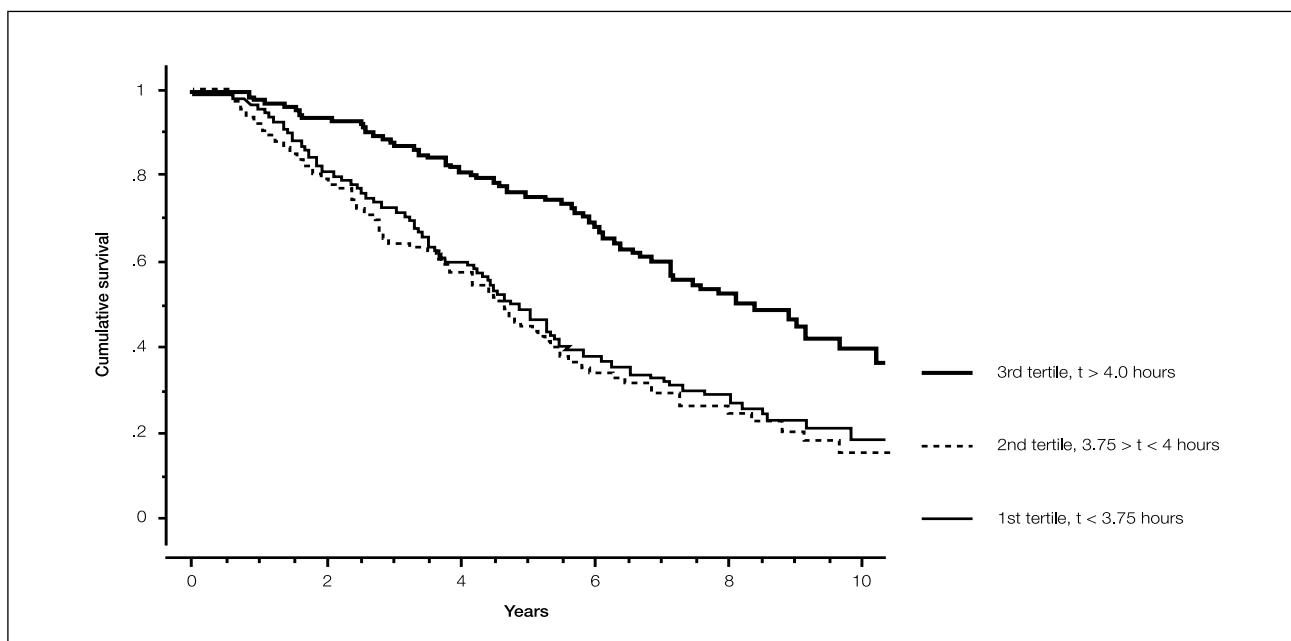
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Economic constraints of limited supply and high demand have driven treatment time on haemodialysis down. Although the HEMO study suggests that there is a ceiling to the survival advantage accrued by increasing Kt/V, centres demonstrating higher cumulative patient survival, such as Tassin, report the longest treatment times. Our large

single centre has consistently achieved high targets for Kt/V coupled with relatively long treatment times. Our policy is not to penalise small patients by reducing treatment time when they have achieved high Kt/V largely by virtue of their size. We analysed the impact on 10 year patient survival of higher Kt/V > 1.6 with longer treatment times. Four hundred and fifty-one incident patients commenced on haemodialysis between 1st Jan 1996 and 31st Dec 2001 were prospectively followed to end Nov 2008. Dialysis adequacy was measured monthly. Patient survival for those on third tertile for time on dialysis, $t > 4.0$ hours, was significantly higher, 39.7% than for those on first, and second tertiles, 15.4% and 18.9% at 10 years ($p < 0.0001$).

Within dialysis dose categories of Kt/V, extended treatment times ($t > 4$ hours) were predictive of improved survival. Kt/V > 1.6 and $t > 4.0$ hours resulted in significantly higher cumulative patient survival of 54.3% v 38.9% in those with Kt/V > 1.6 but $t < 4$ hours ($p < 0.04$). Similarly Kt/V < 1.6 and $t > 4.0$ hours resulted in significantly higher cumulative patient survival of 17.9% v 3.1% in those with Kt/V < 1.6 but $t < 4$ hours ($p < 0.0001$). Time on dialysis was an independent predictor of survival, each hour increment decreased the relative risk of death by 63%, [CI: 0.25-0.54]. We conclude higher treatment times result in higher cumulative patient survival and is irrespective of dialysis dose.



Seasonal Variation in Death among Patients Established on Haemodialysis

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Aim: Cardiovascular disease is the main cause of death in patients on haemodialysis. The expected rate of attrition is expected to be uni-

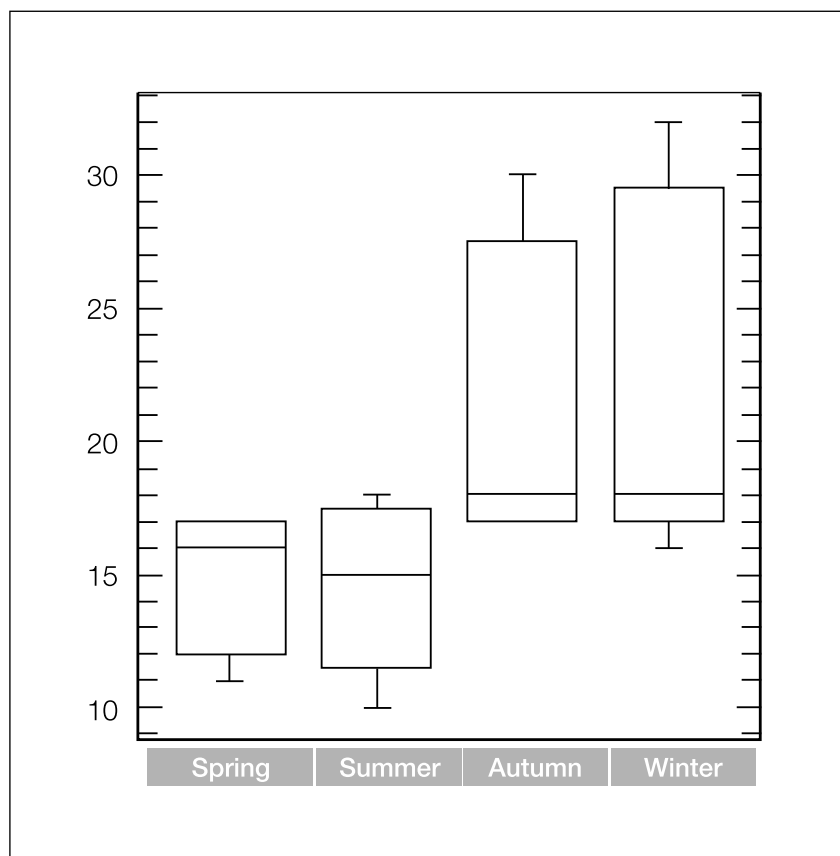
form throughout the year. We analysed seasonal variation in death rate among the prevalent dialysis patients in a large single center.

Methods: We investigated number of deaths in established (>90 days) dialysis patients between 1/3/2004 to 28/02/2009. Date of death was collected for all pa-

tients. Seasons were defined by months as follows: spring (Mar-May), summer (Jun-Aug), autumn (Sep-Nov), and winter (Dec-Feb). The data was analysed for variance using ANOVA.

Results: 576 patients on haemodialysis died during this period. Of these 365 were in established patients. Average duration for which these patients were on dialysis was 920 days. There was a significant variance in number of deaths by season which were 74, 73, 107 and 111 during spring, summer, autumn and winter respectively ($p=0.003$).

Conclusion: This study indicates disproportionate number of deaths in established dialysis patients during autumn and winter months. Some studies indicate higher cardiovascular mortality in non-dialysis population in winter months, attributing that to low vitamin D levels and increased blood pressure. This study has stimulated further analysis to investigate cause of death, co-morbidities, blood pressure control and PTH levels. This might help us to identify a vulnerable sub-population and to increase surveillance during these months.



Number of deaths in established patients on haemodialysis by season for years 2004 to 2008

	2004-5	2005-6	2006-7	2007-8	2008-9	Total
Prevalent patients	360	399	454	523	594	
Spring	16	13	11	17	17	74
Summer	10	13	15	17	18	73
Autumn	17	17	18	25	30	107
Winter	18	16	27	18	32	111
Total Deaths (%)	61 (16.9)	59 (14.8)	71 (15.6)	77 (14.7)	97 (16.3)	365

7. Miscellaneous

Risk of Inappropriate Dosing of Select Medications: An Analysis of MDRD Use Instead of Cockcroft-Gault for Estimation of Glomerular Filtration Rate

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This study analyzed the percentage of inpatient medication orders which would result in a different suggested dosing regimen when estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) equation instead of the Cockcroft-Gault (CG) equation.

A convenience sample of patients >60 years of age, admitted to a tertiary care teaching hospital and initiated on at least 1 of 19 specified medications were prospectively identified. Patients with acute renal failure, renal replacement therapy, or those with <2 measures of serum creatinine within 72 hours of medication initiation were excluded. eGFR was calculated by both the MDRD and CG equations for each patient.

Over a 9-month period, 1069 patients with 1570 orders were included for analysis. The mean eGFR as calculated by the MDRD vs CG was [(77.1±28.8 ml/min) vs (61.6±24.9 ml/min, p<0.001)] respectively. Two hundred seventeen (13.8%) medication orders had conflicting dosing regimens when calculating eGFR using MDRD vs CG. Of these orders, 18 (8.3%) were appropriate using CG, with

the MDRD recommending a higher dose in 215 (99.1%) cases. Discordant dosing regimens occurred most commonly with nitrofurantoin (10/14, 71%), gabapentin (37/104, 35%), and glyburide (13/54, 24%). In a population of hospitalized patients >60 years of age, eGFR estimates using MDRD vs. CG vary widely and result in conflicting dosing recommendations in 13.8% of specified medication orders. These results are concerning since clinical laboratories, including our institution, have begun the automatic reporting of eGFR as calculated by the 4-variable MDRD equation. This practice conflicts with FDA-approved dosing regimens that are determined based upon eGFR utilizing the CG equation, and with recommendations discouraging use of the MDRD for purposes of medication dosing. Clinicians unaware of this distinction may use inappropriate information when developing medication regimens, potentially resulting in excessive drug exposure, expense, and adverse reactions.

International Variation in C-Reactive Protein (CRP) Levels and Associations with Outcomes: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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KDOQI has identified “finding the optimal ‘cut-off’ point at which elevated CRP predicts outcomes,” as a research priority. The purpose of this study was to describe international variation in CRP levels among dialysis patients, and to evaluate the relationship between CRP levels and mortality.

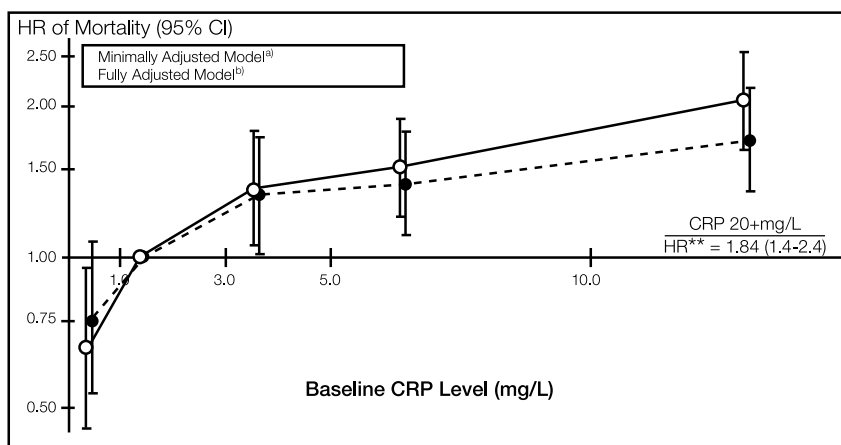
We analyzed 4,461 prevalent HD patients from 2005-08 in 10 countries in the DOPPS, a prospective cohort study (Canada and the US were excluded due to infrequent CRP measurement.) Cox regression was used to estimate the hazard ratio (HR) of mortality by category of CRP level.

66% of facilities (N=135/204) measured CRP \geq 3 months in \geq 75% of patients. Among these facilities, the CRP levels were

much lower in Japan (median 1.0 mg/L, interquartile range [IQR] 0.5-3.3) than Europe (EU)/Australia-New Zealand (ANZ) (median 7.0 mg/L, IQR 3.2-14.5). Other inflammatory markers (e.g. albumin, WBC) did not differ by region. CRP was positively associated with all-cause mortality (Figure). The magnitude of the association did not differ appreciably in Japan vs. EU/ANZ (p-value for testing homogeneity of all RRs = 0.57 in multivariable model).

CRP levels in HD patients were much lower overall in Japan than EU/ANZ, as in the general population. The positive association of CRP with mortality showed a monotonic trend, even at low CRP levels and despite limitations of some CRP assays at low levels.

Figure: Hazard Ratio (HR) of Mortality by Baseline CRP Category*



^{a)} Cox model adjusted for demographics (age, sex, vintage) and accounting for facility, clustering and stratified by country

^{b)} Additionally adjusted for demographics, 12 summary comorbid conditions, baseline lab values and catheter use n=4222 patients on dialysis for 90 days <1 mg/l (n=525), 1-<3mg/l (Ref) (n=843); 3-<5 mg/l (n=660) 5-<10mg/l (n=884); 10-<20mg/l (n=534) >20 mg/l (n=576); median follow-up time was 2.3 years

* CRP categories are plotted at the median value for each category [0.4; 1.4; 3.5; 6.4 and 13 mg/l]. The median value of the 20+ mg/l category was 34 mg/l

** The p-value for testing the difference in hazard ratios for the effects of CRP level between Japan and Europe/ANZ (the CRP region interaction) was 0.57 for log(CRP)

Aspirin Resistance in Hemodialysis Patients

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Background: Aspirin resistance is a new concern with a prevalence of 28% in the population with cardiovascular diseases. An association between aspirin resistance and chronic kidney disease was described in 2 studies with a predominant Asian population. According to our knowledge, the incidence of aspirin resistance in the hemodialysis population was not studied before.

Purpose of study: We tried to study the incidence of aspirin resistance in patient on hemodialysis along with their clinical and biological profile.

Methodology: We collected the blood of 66 hemodialysis patients taking different doses of aspirin (81 mg and 325 mg) just prior to their dialysis session. We excluded all patients taking clopidogrel, coumadin or NSAIDs, and patients with thrombocytopenia, bleeding disorder or liver failure. Aspirin resistance was tested using the rapid platelet function assay VerifyNow Aspirin.

Results: We found that 34.8% of hemodialysis patients were aspirin resistant. There was no difference between the aspirin sensitive and the aspirin resistant groups as far as ethnicity, sex or platelets count. There was a higher incidence of aspirin resistance (46.2%) in the diabetic population undergoing hemodialysis ($p=0.034$). This resistance was not dose-dependant (31.6% versus 36.2% ($p=0.78$) for the 325 mg and 81 mg respectively)

Conclusion: Although patients on hemodialysis tend to have higher incidence of bleeding, we found a high percentage of aspirin resistance. A possible explanation is the inability of aspirin to inhibit thromboxane A2 biosynthesis. Patients who are resistant to aspirin have a greater risk of cardiovascular morbidity than patients who are sensitive to aspirin. Further studies are needed to evaluate the clinical translation of these results.

Holiday Travel in Haemodialysis Patients is Associated with Increased Infection, Loss of Vascular Access and Anaemia

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Travel in our haemodialysis patients is associated with some risk. The risk of Hepatitis C infection has been reported in the literature, but otherwise data is scant in order for patients to make an informed choice.

We prospectively collected data on outcomes following holiday travel from Apr 08-Mar 09, at 2 satellite units at our centre. 69 patients travelled, aged 63.6 ± 12.9 years, of diverse ethnic background 28/69 South Asian, 30/69 Caucasian, 7/69 Black, 4 Other. 34 had a long-term cuffed central venous catheters [CVC], 24 arterio-venous fistulae [AVF] and 2 arterio-venous graft [AVG]. 84 holidays were taken, 45 to Europe, 12 to Middle East, 17 to India, 4 to USA, 4 to Africa, and 2 to Pacific Rim. The incidence of travel of 0.83/1000 patient months.

One patient died during travel. One patient had revision of his AVF whilst away necessitating a temporary CVC, one patient required ligation of an infected ulcerated AVF on return. The blood stream infection [BSI] rate for travellers

with CVC was 0.25 vs 0.99/1000 access days in the 3 months pre and post travel [$p < 0.05$]. The BSI rate for patients with AVF was 0 vs 0.91/1000 access days in the same period [$p < 0.05$]. In patients returning with BSI: 2 had travelled to India and 3 to the Middle East, one patient had 2 organisms, the remainder had 1, there were equal numbers of gram-positive and negative organisms. There were no viral Hepatitis or HIV seroconversions.

There was a significant decrease in mean haemoglobin from 12.3 ± 0.9 to 11.9 ± 1.0 g/dl [$p < 0.05$]. A total of 14 units of blood were transfused <1 week of return in 7 patients. There were no significant changes in erythropoietin dose, C-reactive protein or albumin.

We conclude holiday travel is associated with significantly increased infection rates, loss of vascular access and anaemia.

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