



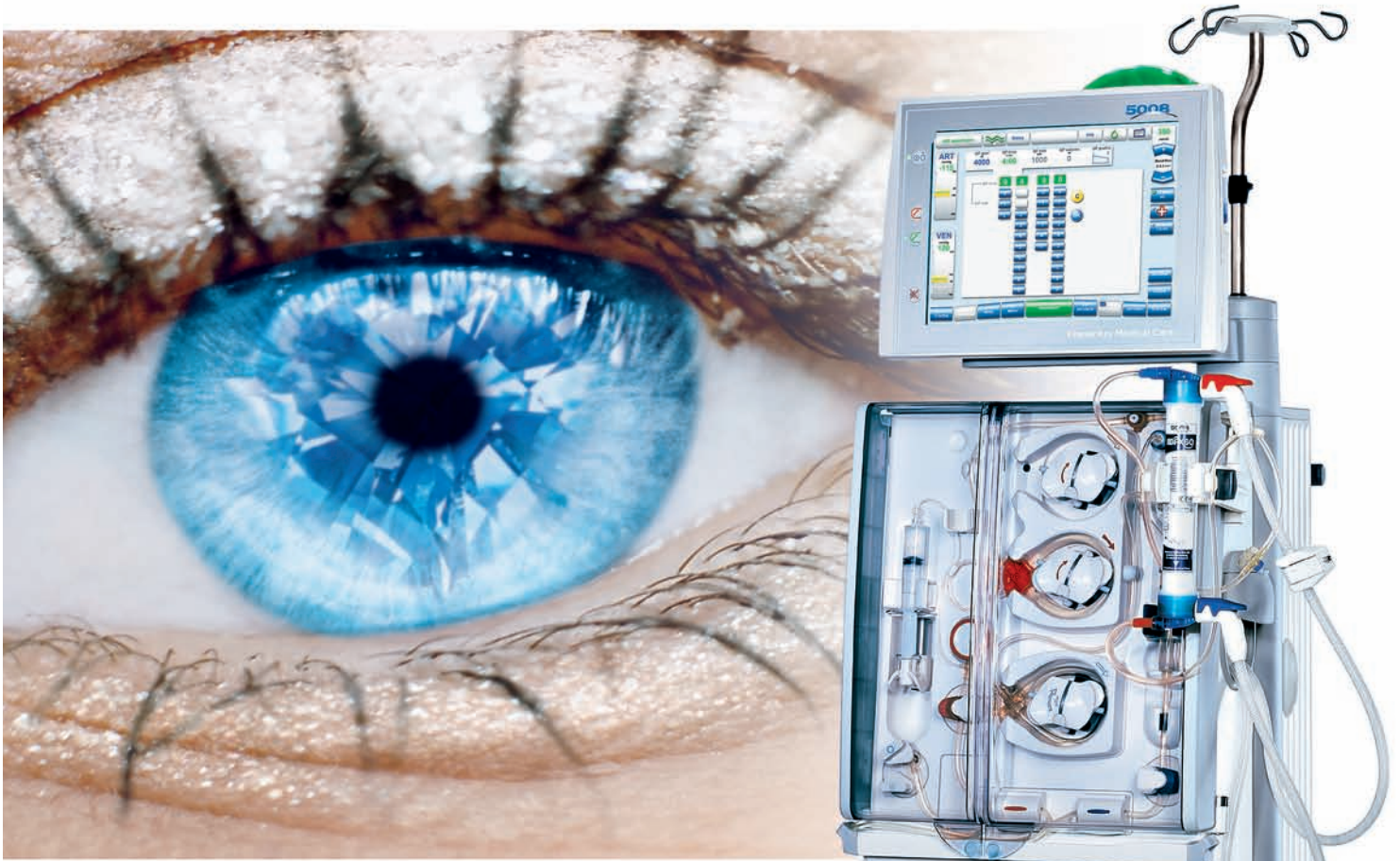
## **Congress Service**

40th Annual Meeting of the American Society of Nephrology  
October 31 – November 5, 2007, San Francisco, CA, USA



Fresenius Medical Care

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Selected Abstracts of the  
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# 1. New Insights in Kidney Disease

## Evidence for Association between a DNA Repair Gene and Albuminuria: The HyperGEN Study

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Podocyte injury manifests by increased albuminuria. Reactive oxygen species and DNA damage may influence podocyte apoptosis.

We tested if polymorphisms (SNPs) of the checkpoint 2 kinase gene (CHEK2), an important transducer in DNA damage signaling pathways, are associated with albuminuria in the Hypertension Genetic Epidemiology Network (HyperGEN). Hypertensive siblings and their offspring and/or parents were recruited from 5 field centers. We genotyped 1584 African American and 1531 Caucasian individuals for 5 CHEK2 tag-SNPs. Urine albumin-to-creatinine ratio (ACR), measured in timed, overnight samples, was rank-normalized. Hypertension was defined as blood pressure 140/90 or use of anti-hypertensive medications. Type 2 diabetes (T2DM) was defined as a fasting plasma glucose 126 mg/dL, or use of insulin/oral hypoglycemic agents. We

evaluated the additive genetic effect of CHEK2 SNPs on ACR using the measured genotype approach within the variance component analysis (SOLAR), which allows for family membership random effects and fixed effects of age, age<sup>2</sup>, sex, sex-by-age interaction, center, T2DM and hypertension treatment.

Approximately 75% of individuals had hypertension and 95% of hypertensive individuals were on medications. T2DM prevalence was 14% in Caucasians and 20% in African Americans. Two CHEK2 variants were independently associated with ACR in African Americans ( $P < 0.01$  rs2346397 and  $P = 0.06$  rs4035540). In addition, rs2346397 was significantly associated with ACR among non-diabetic African American individuals ( $P = 0.02$ ).

These results suggest that the pathogenesis of albuminuria in hypertensive individuals may involve DNA damage and apoptosis.

## Progression of Chronic Kidney Disease: Genetic Determinants of GFR Decline from the African American Study of Kidney Disease and Hypertension (AASK) Trial of Hypertensive Nephrosclerosis

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African Americans develop hypertensive nephrosclerosis with familial aggregation, prompting a search for genetic risk factors.

We used the AASK study to probe whether adrenergic pathway candidate genes predict GFR decline in 830 participants (501 male, 329 female). We scored 33 SNPs at 11 loci within the adrenergic pathway, and 14 SNPs at 10 loci associated with endothelial function or thrombosis/fibrosis. Loci contributing to GFR slope were analyzed in all individuals, and also by subgroup [baseline urinary protein/creatinine ratio >0.22 (n=250) or 0.22 (n=580)].

In the subgroup with greater proteinuria, no SNPs or haplotypes predicted GFR slope. Analysis was focused on the subgroup with less proteinuria. Polymorphisms at 5 of 11 adrenergic loci (2 SNPs at DBH and ADRB1; 8 haplotypes at CHGA, ADRB1, ADRB2, and GPRK2L) predicted chronic GFR decline rate, suggesting a global

effect (p=0.017). Multiple regression revealed that haplotypes at two key loci, ADRB2 (F=7.91, p=0.018, r<sup>2</sup>=0.386), or CHGA plus ADRB2 (F=4.86, p=0.037, r<sup>2</sup>=0.412), predicted 39–41% of variance in GFR decline rate. 8 of 11 pathway genes displayed gene-by-gene interactions on decline of GFR. Among these interactions, ADRB2 interacted with 4 other loci (TH, CHGA, SCG2 and GPRK2L). TNF interacted with 3 loci (ADRB2, GPRK2L and PDE4D). 12 SNPs and haplotypes at 4 candidate loci (TH, CHGA, CHGB, ADRB2) displayed gene-by-drug interaction on GFR decline. Population stratification did not contribute to this phenotype (p=0.45 by GAMOVA with IBS).

Our results document novel links between the adrenergic system and GFR decline rate, suggesting new strategies to probe the role and actions of the pathway within this setting.

## Telomere Attrition Is Associated to Inflammation and High Mortality in Prevalent Hemodialysis Patients. A Mechanism Mediated by Fetuin-A Levels?

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**Background:** Chronic kidney disease (CKD) predisposes to a 10-20 fold increased cardiovascular (CVD) risk. Patients are subjected to accelerated atherogenesis and vascular ageing. The length of the telomeres is a marker of cell senescence that has been related to CVD mortality in the general population. We investigated whether telomere attrition also contributes to increased mortality risk in CKD patients.

**Methods:** Cross-sectional study in prevalent patients undergoing hemodialysis (n=175; 98 males; average  $\pm$  SD age: 63  $\pm$  14 y). Biochemical markers of oxidative stress and inflammatory status were measured in relation to the patients leukocyte telomere length. Overall mortality was assessed after a median of 31 (range 2-42) months.

**Results:** Telomere length was shorter in the male HD patients, despite the women being older (6.31  $\pm$  1.05 vs 6.81  $\pm$  1.27 kb, p=0.002). Telomere length was associated to age (rho= -0.18,

p=0.01), fetuin-A (rho= 0.26; p=0.0004), hs-CRP (rho= -0.21; p=0.005) and IL-6 (rho= -0.17; p=0.02). In a multivariate logistic regression (pseudo  $r^2=0.14$ ), shorter telomere length was associated to age >65 y (odds ratio: 2.11; 95% CI: 1.10, 4.06), male sex (2.01; 1.05, 3.86), fetuin-A (1.85; 0.97, 3.50), and white blood cell count (2.04; 1.02, 4.09). Receiving operator characteristic curves identified a telomere length < 6.28 kb in this cohort as a fair predictor of mortality. Finally, reduced telomere length was associated to increased mortality independently of age, gender and inflammation (Likelihood Ratio 41.6; P <0.0001), but dependently of fetuin-A levels.

**Conclusion:** Age, male gender and inflammation were important contributors to reduced telomere length in these patients. Reduced telomere length contributes to increased mortality risk of HD patients through pathways that could involve circulating levels of fetuin-A.

# Endothelin-A Receptor Antagonism Improves Cardiovascular Function and Reduces Proteinuria in Patients with Chronic Kidney Disease

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**Introduction:** Endothelin-1 (ET-1) is implicated in the development and progression of CKD. We studied the effects of selective ETA receptor antagonism (BQ-123) on systemic and renal haemodynamics, arterial stiffness and endothelial dysfunction, and proteinuria in CKD.

**Methods:** We conducted a randomised, placebo-controlled, double-blind study comparing BQ123 with an open-label active control (nifedipine). These were acute studies using standard clearance techniques in 12 proteinuric CKD patients treated with ACE inhibitors and/or angiotensin receptor blockers.

**Results:** Both BQ123 and nifedipine reduced BP (mean arterial pressure: BQ123  $-11 \pm 2\%$ , nifedipine  $-16 \pm 2\%$ , both  $p < 0.01$  vs. placebo). Despite a significantly greater BP reduction seen with nifedipine, both BQ123 and nifedipine reduced arterial stiffness similarly (pulse wave velocity: BQ123  $-9 \pm 1\%$ , nifedipine  $-11 \pm 2\%$ , both  $p < 0.01$  vs. placebo). Whilst BQ123 had little effect on endothelial function measured by flow-mediated dilatation (FMD:  $1 \pm 1\%$ ), nifedipine worsened FMD ( $-3 \pm 1\%$ ,  $p < 0.05$  vs. placebo).

Despite the fall in BP, both BQ123 and nifedipine significantly increased renal blood flow (BQ123  $26 \pm 6\%$ , nifedipine  $25 \pm 10\%$ , both  $p < 0.01$  vs. placebo), and reduced renal vascular resistance (BQ123  $-30 \pm 7\%$ , nifedipine  $-38 \pm 9\%$ , both  $p < 0.01$  vs. placebo) similarly. BQ123 reduced proteinuria ( $-14 \pm 7\%$ ,  $p < 0.01$  vs. placebo), whereas nifedipine, by contrast, substantially increased proteinuria ( $41 \pm 7\%$ ,  $p < 0.01$  vs. placebo). Those with higher baseline proteinuria had a greater absolute reduction in proteinuria after BQ123, but the % reduction was similar. Neither drug caused sodium retention in these studies.

**Conclusion:** Selective ETA receptor antagonism is effective at reducing BP and arterial stiffness in patients with CKD currently treated for hypertension. Furthermore, these acute studies suggest a reduction in proteinuria independent of BP.

If maintained longer term, selective ETA receptor antagonism would confer both cardiovascular and renoprotective effects in patients with CKD.

## 2. Anemia

### The Prolylhydroxylase Inhibitor FG-2216 Stimulates EPO Production in Nephric and Anephric Dialysis Patients – Evidence for an Underutilized Production Capacity in Liver and Kidneys

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Inadequate serum EPO levels are considered the main cause of renal anemia, and the reasons are poorly understood. It is assumed that the EPO-producing peritubular fibroblasts lose endocrine function during the course of kidney injury and that the liver does not sufficiently compensate. Progress in understanding the molecular control of oxygen-dependent EPO production revealed an important role of hypoxia-inducible transcription factors (HIF) in the oxygen-dependent regulation of EPO. HIF degradation occurs through oxygen-dependent hydroxylation of prolyl residues by prolyl hydroxylases (PHD).

To test the ability of fibrotic kidneys to produce EPO and the ability of other organs to make EPO in anephric patients, we used FG-2216, a novel PHD inhibitor, which stabilizes HIF in an oxygen-independent fashion. A single dose Phase 1 study was performed in 12 hemodialysis (HD) patients, 6 of whom were anephric, and in 6 non-anemic volunteers. Recombinant EPO therapy

was discontinued one week before dosing in all HD patients. Day 1 hemoglobin levels were  $13.8 \pm 1.9$ ,  $14.2 \pm 1.2$ , and  $15.5 \pm 0.6$  g/dL for nephrics, anephrics and controls, respectively.

FG-2216 (20 mg/kg p.o.) resulted in a rise in EPO levels in all study subjects (T<sub>max</sub> was comparable for all groups). Median EPO levels increased from 17.4 to 240.6 (nephric), from 5.7 to 42.55 (anephric), and from 6.7 to 47.1 mU/ml in controls. Mean plasma half life of FG-2216 was similar in nephric and anephric patients, but twice as long as in controls. Dialysis clearance of FG-2216 was less than 2%, suggesting that timing of the dose of FG-2216 could be independent from HD.

In conclusion, endogenous EPO production can be stimulated by pharmacological manipulation of the HIF system. The response in nephric and anephric patients demonstrates that diseased kidneys retain a significant production capacity for EPO and that liver production of EPO may also be useful in a clinical setting.

## Hemoglobin Variability in Chronic Kidney Disease

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Anemia management in CKD is difficult. The ability to achieve desired hemoglobin targets in patients managed with erythropoiesis stimulating agents (ESAs) may be especially difficult as the process tries to mimic a biological system using intermittent exogenous dosing.

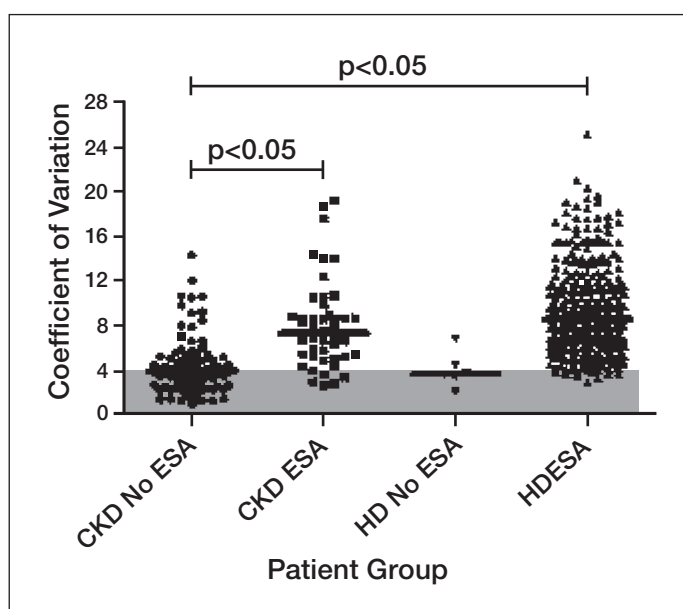
The purpose of this study is to determine the variability in hemoglobin values in patients at various stages of CKD.

**Methods:** The study design was a retrospective review of anemia management in CKD and HD patients. Patients with CKD had their hemoglobin variability analyzed by calendar year. Patients were grouped as either receiving or not receiving ESAs. CKD patients were excluded if they did not have at least 3 months of hemoglobin values during a calendar year. The first 3 months of HD hemoglobin values were also

excluded. One hundred thirty-seven CKD patient calendar years and 350 HD patient calendar years were available for analysis. Hemoglobin variability was defined as the individual patients coefficient of variability and calculated as the individual patients hemoglobin standard deviation divided by that patients mean hemoglobin x 100 ( $CV=SD/\text{mean hemoglobin} \times 100$ ). The coefficient of variability of hemoglobin values was compared between CKD patients receiving and not receiving ESAs. These two groups were also compared to HD patients receiving or not receiving ESAs.

**Results:** The coefficient of variability in hemoglobin values was significantly less for CKD patients not receiving ESAs than for CKD patients treated with ESAs whether they were not receiving HD (medians: 3.96 vs. 7.37,  $p<0.05$ ) or receiving HD (medians: 3.96 vs. 8.53,  $p<0.05$ ) (figure: shaded area represents normal range).

**Conclusions:** Patients with anemia receiving treatment with ESAs have significantly greater hemoglobin variability than CKD patients not receiving ESAs. This variability needs to be considered when hemoglobin targets and ranges are set by best practice guidelines.



## Identifying an Optimal Hematocrit Target To Minimize Mortality in Hemodialysis Patients

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Various studies of ESA treatment for anemia in CKD/ESRD patients suggest elevated mortality among patients with Hct >39 or <30. We aggregated Medicare claims from 2002–05 to the facility level (n=4,999 facilities) to study the relationship between facility mortality and hematocrit distributions across patient-months (PM) as facility-level analyses are often less prone to bias than patient-level analyses of observational data. Exclusion of facilities with <70% of patients on HD and small facilities resulted in n=15,961 facility-years and N=2,226,334 PM. For each facility-year, we calculated the percent of PM at each reported hematocrit level and the expected number of deaths based on patient age, race, ethnicity, sex, diabetes, years of ESRD, and comorbidities and BMI at incidence. Poisson models predicted facility deaths

based on the hematocrit distribution, adjusted for expected deaths. The table shows mortality relative risks (RR) at a facility per 10% more PM in a hematocrit category (reference category Hct=34–34.9). Mortality was lowest at facilities having more PM in the Hct range 33–35.9. Mortality was higher for facilities with more PM outside this range, although the RR pattern was somewhat non-monotonic on either side of this range. Smoothed results, not shown, suggest that the mortality RR declines gradually from 1.2 at Hct<29 down to 1.0 around Hct=33–35.9 and then increases to 1.1 at Hct ≥42. The roles of ESA dosing and hematocrit stability are not examined here. These analyses suggest facilities with more PM in the range Hct=33–35.9 have lower mortality than facilities with more PM outside of this range.

Table: Mortality Relative Risk

Hct	<20	20–26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43*
RR*	1.07	1.39	1.09	1.38	1.14	1.13	1.10	1.07	1.02	ref	1.02	1.08	1.06	1.02	1.07	1.06	1.08	1.11	1.11
% of PM	0.1	2.8	1.7	1.9	2.6	4.8	5.1	6.6	10.9	10.1	10.8	12.9	8.4	6.2	5.6	3.1	2.1	1.7	2.5

\* p<.01 except for Hct=33,35,38; PM = patient-months

## Impact of ESA Treatment Patterns and Dose Adjustments on Hb Variability in ESRD Patients – Results of a Large German Dialysis Cohort

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Hb variability is common in ESRD patients. The aim of this study was to assess the impact of dose adjustments and ESA treatment patterns on the ability of patients to achieve Hb targets in a large German dialysis patient cohort. We conducted a multicenter (n=17), retrospective, 6-months cohort study analyzing data from the AENEAS registry database. Inclusion criteria were at least one Hb value available per month, treatment with hemodialysis and ESAs (rhEpo/DA) started at least 3 months before observation period and no switch of ESA-type or blood transfusion recorded.

A total of 979 HD patients (age 66±14 years; m: 56.6%) could be analyzed. At baseline mean Hb was 11.6±1.2 g/L, 67.6% received rHuEPO, 32.4% Darbepoetin alfa (DA). Patients were divided into 4 groups: 0, 1–2, 3–5, ≥6 dose adaptations (weekly calculated dose). Hb stability was assessed by percentage of mean monthly Hb values between 11–13 g/dL within 6 months.

Main results are shown in the table. Only 6.2% of patients showed a

stable dosing, whereas 29.2% patients received on average more than one dose adaption every month. A high number of dose adaptations correlates with less patients continuously achieving Hb target (R –0.26). Patients with ≥6 dose adaptations showed a significantly higher (p <0.0001) ESA dose need, higher application frequency (p <0.0001) and a higher percentage of rHuEPO treated patients (p<0.001). No significant difference in CRP, Ferritin and TSAT could be observed between those groups.

Conclusion: Though dose adaptations usually intend to achieve Hb-targets, more dose adaptations correlated with lower Hb-target fulfillment. Less frequent dosing (typical for long acting ESA like DA) and lower ESA dose seem to increase the probability of achieving Hb targets.

dose adaption [n]	Patients [%]	Hb values in target [%]	ESA dose, median* [IE]	Applications/wk, median	DA [%]	rHuEPO [%]
0	6.2	81.9	4.000	1	5.5	6.5
1–2	25.6	70.7	4.923	1	27.3	24.8
3–5	38.9	60.8	5.538	1.2	43.9	36.4
≥6	29.2	55.2	7.077	1.9	23.3	32.2

\* DA dose was calculated in IE by using a equimolar conversion factor 1µg:200IE

### 3. Mineral Metabolism

#### Large International Initiative To Define Differences in PTH Assays Demonstrates K/DOQI Guideline Inappropriate for Use with Several Assays

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Plasma from 10,000 ESRD patient specimens was pooled to produce 3 levels of PTH corresponding to below the K/DOQI 150–300 pg/ml target, within the 150–300 pg/ml target and above the 150–300 pg/ml target. These 3 specimens were part of a larger panel of 10 specimens that included specimens containing synthetic 1–84 PTH and 7–84 PTH. The specimens were lyophilized and subjected to accelerated stability testing for a 10 year annual and bi-annual study of comparability and stability of PTH tests. The 2006 survey was completed with a distribution to over 400 clinical testing laboratories within Europe, USA, and Asia.

The K/DOQI guidelines were based on 73 articles that all referenced the Nichols Allegro IRMA iPTH assay. The K/DOQI guidelines are appropriate for use only

with the Nichols Allegro IRMA iPTH assay or a PTH assay that is aligned with the Nichols Allegro IRMA iPTH assay. The Scantibodies total IRMA PTH assay had been demonstrated and published to be aligned with the former Nichols Allegro IRMA iPTH assay. Therefore, the Scantibodies tPTH assay was used as the reference assay to which other PTH assays were compared.

Several PTH assays (including the Bayer Centaur DPC Immulite) were found to be inappropriate for use with the K/DOQI guidelines because of overestimation of PTH. Several assays (including the Diasorin IRMA iPTH) were found to be inappropriate for use with K/DOQI because of underestimation.

Overestimation or underestimation of PTH can lead to inappropriate treatments.

Table: Percent Recovery for iPTH Determinations in PTH Reference

Panel A-C (Pooled ESRD Patient Plasma) for the Major Manufacturer using Scantibodies tPTH IRMA as 100%

Manufacturer	Scantibodies	Abbott	Beckman	Bayer	Roche	UMCL	CisBio	DPC	Diasorin	AUHUZA	Alpco	Future	IDS	Torch
Mean %	100	155	108	126	108	55	94	165	75	53	124	133	51	118
± SD %	N/A	12.8	7.3	13.3	12.1	13.0	6.7	17.2	17.0	1.7	31.6	24.7	17.8	6.4
± CV	N/A	8.3	6.8	10.6	11.2	23.7	7.1	10.4	22.8	3.2	25.4	18.6	35.3	5.4

## Mortality and Hospitalization Rate in European Dialysis Patients Achieving the K/DOQI Targets. Preliminary Results from COSMOS

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K/DOQI guidelines recommend keeping the CKD5 patients in targets for Ca, P, Ca x P and PTH. In this work we present mortality (all-cause and cardiovascular-CV) and hospitalization rates in COSMOS patients within or outside these targets.

COSMOS is a three-year, multi-centre, open-label, prospective study surveying bone mineral disturbances in hemodialysis patients. The study includes data from approximately 5,700 dialysis patients at 285 centers in 21 European countries. Facilities and patients were randomly selected. Recruitment began in 2005.

In this analysis, we include data from the first 2,495 patients who completed an 18-months follow-up period. Mean values of bone biochemical parameters were calculated for the whole period and then the patients categorized as: below target, within target and above target. Mortality and hospitalization rate were calculated for each category.

Patients above target for Ca (N=851) showed a higher mortality rate than patients within target (N=1,255) and below target (N=293) (27.3%, 19.0% and 13.39%,  $p<0.001$ ). Cox's proportional hazards model adjusted for case mix indicated that patients with  $Ca>9.5$  mg/dL have a relative risk of death of 1.461 (95%CI, 1.178-1.812). CV mortality and hospitalization rate were also higher in patients above target for Ca (RR: 1.651, 95%CI:1.203-2.266, CV mortality and RR:1.255, 95%CI:1.103-1.428, hospitalizations). Levels of  $PTH<150$  pg/mL and Phosphate  $<3.5$  mg/dL were also associated with increased risk of death (RR:1.255, 95%CI:1.103-1.428 and RR:1.602, 95%CI:1.228-2.089; respectively). Reference groups were patients within targets in all cases.

In conclusion, CKD5 patients not achieving some of the classic bone and mineral K/DOQI targets show a higher risk of mortality and hospitalization.

## Effect of Atorvastatin on Progression of Heart Valve Calcification in Hemodialysis Patients Treated with Calcium Acetate or Sevelamer

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Heart valve calcification (HVC) is common in hemodialysis patients and may contribute to serious consequences. In the CARE-2 study, we compared the progression rate of HVC in HD patients treated with calcium acetate (CA) or sevelamer (SV) when LDL was lowered to < 70 mg/dL. HD patients with phosphorus (P) > 5.5 mg/dL, LDL > 80, and EBCT CAC scores 30 to 7000 were randomized to either CA or SV for 1 year. Atorvastatin was added to achieve above LDL goal in both groups. Primary endpoint: % change in CACS at 1 year analyzed by t-tests on Geometric Means (GM). Secondary endpoints: change in aorta, mitral, and aortic valve EBCT calcium scores, serum P, Ca, CaxP, PTH, HCO<sub>3</sub>, LDL. 203 patients were randomized: 103 CA, 100 SV. Achieved LDL levels: 68 and 62 mg/dl in CA and SV respectively. At baseline, calcification of mitral and aortic valves present in 54.7%, and 39.9%, respectively, 27% with both. For mitral and aortic valves, the table shows GM percent change from screening

values to Day 360. P and CaxP were similar. Adjusted Ca was higher in CA patients. Results unchanged including or excluding 0 scores at baseline or Day 360. HVC is common in HD patients. Its progression did not differ in CA and SV-treated HD patients following equivalent lipid control. Calcium load from use of calcium acetate does not contribute to progression of HVC in HDP. Uremia-related factors may contribute to progression of HVC.

Table. Comparisons of screening to Day 360 percent change in calcification scores

	Using log(Score)-transformation			Using log(Score+1)-transformation		
	Calcium Acetate	Sevelamer	P-value	Calcium Acetate	Sevelamer	P-value
Aortic Valve	61% (8,140)	43% (-4,114)	0.67	34% (-14,109)	36% (-6,95)	0.97
Mitral Valve	51% (9,110)	77% (31,140)	0.47	83% (19,182)	89% (32,169)	0.92

## 4. Cardiovascular Diseases

### Osteoprotegrin Predicts Cardiovascular Disease in Incident Dialysis Cohort

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Osteoprotegrin (OPG) is a potential regulator of calcification in vascular endothelium. Coronary calcification is common in ESRD, and OPG may accelerate atherosclerotic cardiovascular disease (ASCVD).

A prospective analysis of serum OPG and incident ASCVD was performed in a random sample of 199 participants chosen from 1,041 participants with serum available at baseline in Choices for Healthy Outcomes In Caring for ESRD (CHOICE) study enrolled from 10/95 to 6/98 among 81 U.S. dialysis clinics (with mean age, 56.4 yrs; 53.3% female; 62.8% White, 33.2% Black; 56.6% with baseline ASCVD; mean albumin 3.6 g/dL, mean calcium phosphate product 50.2 mg<sup>2</sup>/dL<sup>2</sup>). OPG was measured by enzyme immunoassay (ALPCO Diagnostics; CV 12%) and log-transformed for analyses. Incident ASCVD was defined as first hospitalization or mortality due to coronary artery,

cerebrovascular and peripheral vascular disease after start of dialysis. Participants were censored at transplant, non-ASCVD death, loss to follow-up or until 12/04. Median OPG was 12.6 pmol/L (IQR 9.2–16.8). By Cox regression analyses, greater OPG levels were associated with higher and graded risk of ASCVD (Table). OPG shows a strong association with ASCVD. Further studies are needed to explore the relationship of novel mineralization factors and ASCVD.

Table: Relative hazards (95% CI) for ASCVD associated with osteoprotegrin

	Unadjusted	Model 1*	Model 2*	Model 3*
Continuous, per log	2.48 (1.51–4.10)	2.21 (1.26–3.86)	2.19 (1.23–3.88)	1.75 (0.96–3.17)
By tertile (pmol/L):				
1 (3.0–10.2)	1.00	1.00	1.00	1.00
2 (10.2–15.4)	1.72 (0.95–3.11)	1.79 (0.97–3.30)	1.73 (0.94–3.18)	1.55 (0.83–2.87)
3 (15.4–31.5)	2.84 (1.62–4.99)	2.67 (1.40–5.09)	2.50 (1.31–4.79)	2.05 (1.04–4.03)
p for trend	<0.001	0.003	0.006	0.04

Model 1: Adjusted for age, sex, race

Model 2: Adjusted for model 1, corrected calcium-phosphorus product

Model 3: Adjusted for model 2, baseline ASCVD

## Serum Albumin, CRP, IL-6, and Fetuin-A as Predictors of Wasting, Cardiovascular Disease, and Mortality in Prevalent Hemodialysis Patients

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It is well established that low serum albumin, and high CRP and IL-6 levels predict protein-energy wasting (PEW), cardiovascular disease (CVD) and mortality in end-stage renal disease (ESRD) patients. Whereas a low serum fetuin-A level may predispose to vascular calcification and contribute to death in ESRD patients, its association to PEW is less clear. In this study, we compared the predictive power of serum fetuin-A in relation to that of serum albumin, CRP, and IL-6 as predictors for CVD and PEW, in 228 prevalent hemodialysis (HD) patients (age  $63 \pm 14$  years), who had been on dialysis for a median period of 36 months. Survival (42 months) was analyzed in relation to fetuin-A levels. PEW as evaluated by subjective global assessment was present in 48% of the patients. Sixtythree % of the patients had CVD. Accord-

ing to Receiver Operating Characteristic (ROC) analysis, IL-6 had the highest prediction for CVD (72%) and PEW (67%) followed by fetuin-A (68% and 64%, respectively). Fetuin-A levels were lower in patients with PEW as compared to well nourished patients ( $0.16 \pm 0.05$  vs  $0.19 \pm 0.07$  g/L ( $p < 0.01$ )). In unadjusted analysis, the lowest quartile of fetuin-A, against the other quartiles, was associated with all-cause mortality (Log Rank ( $\chi^2$ ) = 19.7;  $P < 0.0001$ ). After adjustment for age, sex, PEW and CRP, using the multivariate Cox regression analysis, death rate was still significantly higher in patients with low fetuin-A (HR, 23.7; CI, 1.10–3.48;  $P = 0.02$ ). In conclusion, a low circulating level of fetuin-A is associated with CVD and PEW, and independently predicts mortality in prevalent HD patients.

## Calcification Outcome in Renal Disease (CORD) – A Prospective Epidemiological Multinational Study: Importance of Changes in Aortic Stiffness on Outcome in Dialysis Patients

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**Purpose:** The present analysis evaluated the prognostic value of change in aortic stiffness over time on the occurrence of cardiovascular (CV) events and total mortality in dialysis patients.

**Patients and methods:** Stiffness was measured by carotid-femoral pulse wave velocity (PWV; SphygmoCor, AtCorMedical) at baseline and after 12 months. Of the original cohort of 1,093 patients 92% survived the first year; 432 had complete follow-up data up to 24 months by the time of this analysis.

**Results:** The average changes from baseline in PWV ( $\Delta$ PWV) and mean arterial pressure ( $\Delta$ MAP) were small but variable (mean $\pm$ SD):  $-0.09\pm 3.2$  m/s and  $-0.5\pm 16.8$  mmHg, respectively ( $P$ =NS) as expected in a heterogeneous cohort of dialysis patients. Major determinants of  $\Delta$ PWV were ( $\beta$ -coefficient [95%CI]),  $\Delta$ MAP ( $B=0.03$  [0.01;0.04],  $P=0.001$ ) and baseline PWV ( $B=-0.25$  [-0.32;-0.18],  $P<0.001$ ).

At two years, 172 patients (40%) had reached the composite endpoint all-cause mortality (74/432; 17%) or first CV event (98/432; 23%). After adjustment for baseline PWV (mean: 10.8m/s [10.4;11.1]) and  $\Delta$ MAP,  $\Delta$ PWV was 1.0m/s [0.5;1.6] higher in patients with an endpoint compared to those with a two-yr event-free survival ( $P<0.001$ ). In multiple logistic regression, each 1m/s  $\Delta$ PWV was associated with a 13% (OR: 1.13 [1.05;1.23] higher likelihood for occurrence of a CV event or death ( $P=0.001$ ), independently from the effect of baseline PWV (OR: 1.19 [1.12;1.28],  $P<0.001$ ) and history of CV disease (OR: 2.71 [1.76;4.17],  $P<0.001$ ).

**Conclusion:** The independent additional predictive value of changes in aortic stiffness on the occurrence of major CV events or death, supports the potential role of PWV in monitoring the progression of vascular damage.

## Inflammation Causes Abnormal Endothelial Function and Atherosclerosis (Intima-Media Thickness) in Chronic Kidney Disease

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Mortality in patients with Chronic Kidney Disease is high, predominantly cardiovascular and associated with inflammation. Abnormal endothelial function and IMT have been demonstrated in CKD but their relationship with inflammation is unknown. The study aimed to investigate the possible direct relationships of inflammation, endothelial dysfunction and atherosclerosis in CKD.

114 patients, 70 with CKD and 44 controls, were recruited. Endothelial function was measured with forearm ischemia and brachial artery ultrasound using our established protocols. CRP was measured using commercial assay. Atherosclerosis was estimated from carotid intima media thickness with ultrasound, using established protocols. All statistics were computed using SPSS 15.

The clinical characteristics of 114 cases were; age  $56 \pm 1$  years (Mean $\pm$ SEM), male 56%, diabetes 17%, smokers 10%, systolic BP  $135 \pm 2$  mmHg, diastolic BP  $79 \pm 1$  mmHg, cholesterol  $4.8 \pm 0.1$  mmol/L, HDL  $1.2 \pm 0.05$  mmol/L, LDL  $2.9 \pm 0.1$  mmol/L and TG  $1.4 \pm 0.08$  mmol/L. There CKD and controls were similar in age, gen-

der, diabetes, smoking, systolic and diastolic BP. Patients with CKD had lower total cholesterol ( $4.2 \pm 0.1$  vs.  $5.7 \pm 0.2$ ;  $p < 0.001$ ), lower LDL ( $2.4 \pm 0.1$  vs.  $3.7 \pm 0.1$ ;  $p < 0.001$ ), lower HDL ( $1.1 \pm 0.05$  vs.  $1.5 \pm 0.07$ ;  $p < 0.001$ ) and higher triglycerides ( $1.5 \pm 0.1$  vs.  $1.3 \pm 0.1$ ;  $p < 0.05$ ).

In CKD, FMD was lower ( $2.7 \pm 0.3$  vs.  $5.4 \pm 0.3$ ;  $p < 0.001$ ), IMT was higher ( $8.3 \pm 0.2$  vs  $6.3 \pm 0.2$ ;  $p < 0.001$ ) with a high CRP ( $4.8 \pm 0.5$  vs.  $1.7 \pm 0.2$ ;  $p < 0.001$ ). An increasing CRP was associated with decreasing FMD ( $R = 0.42$ ;  $p < 0.001$ ) and increasing IMT ( $R = 0.5$ ;  $p < 0.001$ ). Increasing CRP was an independent predictor of both FMD and IMT; adjusted for age, diabetes, smoking status, systolic BP, diastolic BP, cholesterol and LDL in patients with CKD.

The study demonstrated abnormal endothelial function and IMT associated with inflammation, in patients with CKD. We propose that high cardiovascular morbidity and mortality in patients with CKD result from inflammation mediated endothelial dysfunction which causes atherosclerosis.

## 5. Drug Therapy in Chronic Kidney Disease

### Best Option for Proteinuria Control: Angiotensin-Receptor Blockers – ACE-Inhibitors or Both? A Meta-Analysis

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**Purpose:** To compare the effectiveness of angiotensin-receptor blockers (ARB) vs. ACE-inhibitors (ACE-I) or the combination of both drugs on proteinuria

**Methods:** We searched for English language studies in MEDLINE and the Cochrane CENTRAL register (1990 to 9/2006). We selected randomised trials of ARB vs. ACE-I, ARB+ACE-I vs. ARB and ARB+ACE-I vs. ACE-I in diabetic and non-diabetic patients with microalbuminuria or proteinuria reporting proteinuria at baseline and after 1–12 months. Two investigators independently searched and abstracted the studies. We used ratio of means (RoM) as effect measure.

**Results:** 31 studies involving a total of 1882 patients reported the results of 56 short-term and 26 long-term comparisons. ARBs achieved a comparable short- and long-term reduction in proteinuria as did ACE-I (RoM: 0.99; 95% CI: 0.92 to 1.05 and RoM: 1.08; 95% CI: 0.96 to 1.22, respectively). The combination ARB+ACE-I further reduced proteinuria over either agent alone: combination vs. ARBs: RoM<sub>short-term</sub>: 0.76 [95%

CI: 0.68 to 0.85] RoM<sub>long-term</sub>: 0.75 [0.61 to 0.92]; combination vs. ACE-I: RoM 0.78 [95% CI: 0.72 to 0.84] RoM<sub>long-term</sub>: 0.82 [0.67 to 1.01]. All results revealed a high degree of homogeneity ( $I^2$ : 0% to 31%). Subgroup analyses on patient characteristics (microalbuminuria vs. proteinuria; diabetic vs. non-diabetic renal disease) or design characteristics (study quality; parallel design vs. cross-over design) confirmed consistency and homogeneity of the antiproteinuric effect. However, the small sample size of the majority of studies and their heterogeneous quality caution against far-reaching interpretations. Furthermore, proteinuria is a surrogate for patient-important progression of renal disease which weakens the consequences for treatment.

**Conclusions:** ARBs and ACE-Is are similarly effective in reducing proteinuria, independent of baseline proteinuria and type of renal disease. Combining both drugs can lower proteinuria by about 25% over and above what monotherapy with either drug can achieve.

## Rosiglitazone Is Associated with Increased Mortality among Diabetic HD Patients in the US DOPPS

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A recent meta-analysis reported an association between myocardial infarction and rosiglitazone (RGZ), a thiazolidinedione (TZD) oral hypoglycemic agent (OHA), among type 2 diabetics in the general population. The present study examines associations between mortality and prescription of RGZ among OHA-treated diabetic hemodialysis (HD) patients. Data were gathered as part of the Dialysis Outcomes and Practice Patterns Study (DOPPS), an international, observational study of HD patients in 12 countries. Current analyses examined the US sample of diabetics prescribed an OHA and enrolled in DOPPS between July 1999 and 2004 (n=2,393). Cox models assessed all-cause and CV mortality risk for (1) patient-level RGZ prescription vs. patients prescribed any other non-TZD OHA, and (2) the facility-level practice, as the percentage of facility patients prescribed RGZ. Adjustments included demographic factors, years with ESRD, coronary artery disease (CAD) and

11 other comorbid conditions, and insulin use. Results are expressed as adjusted hazard ratios (AHR).

The analyzed sample had a mean age of 63 years and 1.8 years on ESRD, were 50% male, and 32% were of black race. Median follow up time was 1.1 years. 7% of patients received RGZ. Patients prescribed RGZ were significantly ( $p<0.05$ ) more likely to be black, to have had more years with ESRD, or to have had CAD or hypertension, compared to non-RGZ patients on OHAs. Risk of myocardial infarction was also significantly higher in RGZ patients. The AHRs for mortality are shown below.

These results suggest that diabetic HD patients on RGZ have a greater mortality risk than those on a non-TZD OHA, even when analyzed at a facility level. Given the high prevalence of diabetes in HD patients and the elevated risk of CV disease, these findings warrant further study.

Treatment Measure	All-Cause Mortality		CV Mortality	
	AHR	95% CI	AHR	95% CI
Patient-level: RGZ, yes vs. no	1.34	1.01–1.77	1.50	1.06–2.12
Facility-level: 75th vs. 25th %ile of facility RGZ prescription	1.23	1.12–1.35	1.18	1.01–1.38

## A Pilot Trial of Antioxidant Therapy in Stage II-IV Chronic Kidney Disease

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**Purpose:** The purpose of this study was to investigate whether the combination of mixed tocopherols and alpha lipoic acid decreases oxidative stress and inflammation biomarkers in stage II-IV chronic kidney disease (CKD).

**Methods:** This was a prospective, randomized, double-blind, placebo-controlled pilot trial. Fifty-nine subjects with Stage II thru IV CKD (estimated GFR 15-70 ml/min per MDRD equation) were randomly assigned to receive either combination of mixed tocopherols (alpha, beta, delta, and gamma) 666 IU/day and alpha lipoic acid 600 mg/bid (n = 29) or matching placebos (n = 30) for a total of 2 months. Randomization assignments were stratified according to diabetic status. Plasma F<sub>2</sub>-isoprostanes, protein-reduced thiol content, interleukin 6 (IL-6), and serum CRP, were measured in all subjects at study initiation and completion.

**Results:** There were no significant differences in age (59.3±10.4 vs. 64.4±9.0 years), gender (%males: 52% vs. 53%), race (%white: 97%

vs. 93%), or diabetic status (55% vs. 53%) between study and placebo groups, respectively. Similarly, there were no differences in BMI (31.9±7.2 vs. 32.3±7.7 kg/m<sup>2</sup>) or eGFR (38.1±11.4 vs. 40.9±14.8 ml/min) between groups. After two months of treatment, there were no significant changes in F<sub>2</sub>-isoprostanes, protein-reduced thiol, CRP, and IL-6 concentrations with mixed tocopherols and alpha lipoic acid treatment compared to matching placebos (see Table). Diabetic status did not influence the results.

**Conclusions:** Mixed tocopherols and alpha lipoic acid treatment for 2 months did not significantly alter oxidative stress or inflammation biomarkers in subjects with Stage II-IV CKD.

	Tocopherols + ALA		Placebo	
	Baseline	Month 2	Baseline	Month 2
F <sub>2</sub> -Isoprostanes (ng/mL)	0.0657 ± 0.02	0.0729 ± 0.04	0.0753 ± 0.04	0.0693 ± 0.04
Thiols (μM)	314.4 ± 52.0	309.2 ± 46.6	324.4 ± 44.8	315.5 ± 39.9
CRP (mg/L)	13.9 ± 18.0	12.1 ± 12.5	14.2 ± 17.9	12.9 ± 15.7
IL-6 (pg/mL)	7.1 ± 7.1	7.7 ± 6.9	8.0 ± 7.0	9.9 ± 11.5

## Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID)

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**Background:** We evaluated the renoprotective effects as reflected by short-term changes in albuminuria of dual blockade of the renin-angiotensin system (RAAS) by adding Aliskiren, a novel oral direct renin inhibitor to treatment with maximal recommended dose of Losartan (100 mg OD) and optimal antihypertensive therapy in hypertensive type 2 diabetic patients with nephropathy.

**Design:** 599 patients were enrolled in this multi-national, randomized, double blind study. After a 3-months open-label run-in period on losartan 100 mg OD, patients were randomized to receive 6-month treatment with placebo or aliskiren (150 mg OD for 3 months followed by forced titration to 300 mg OD for another 3 months). The primary outcome was a reduction in early morning UACR from baseline to end of study.

**Results:** Baseline values for the aliskiren / placebo groups respectively were: UACR (mg/g) 750 (SD 687) / 778 (SD 676), overnight urinary albumin excretion rate UAER ( $\mu\text{g}/\text{min}$ ) 817 (SD 914)/ 763 (SD 736); mean eGFR ( $\text{ml}/\text{min}/1.73\text{m}^2$ )

69 (SD 26) / 67 (SD 25) and mean BP (mmHg) 135/78 (SD 12/8) / 134/77 (SD 12/9). Aliskiren reduced the mean UACR with 20% (95% CI: 9-30) ( $P \leq 0.0009$ ) and mean UAER with 18% (95% CI: 5-30) compared to placebo ( $P \leq 0.009$ ). The number of patients with  $\geq 50\%$  reduction in UACR at the end of the study was 24.7% versus 12.5% for aliskiren and placebo respectively ( $P < 0.0002$ ). eGFR remained unchanged and a small reduction in BP of 2/1 mmHg (SBP/DBP) occurred during aliskiren treatment ( $P=0.08$ ). Changes in albuminuria did not correlate to changes in BP. The total number of adverse events was similar in the 2 groups. Single-measurement serum-potassium  $\geq 6\text{mmol/l}$  occurred in 4.7% vs. 1.7% (NS) in the aliskiren and placebo groups respectively.

**Conclusion:** Aliskiren is renoprotective independently of its blood-pressure-lowering effect in hypertensive type 2 diabetic patients with nephropathy receiving recommended treatment with losartan and optimal antihypertensive therapy.

## Statins Do Not Increase Stroke Risk in Patients Initiating Dialysis: The Choices for Healthy Outcomes in Caring for End Stage Renal Disease (CHOICE) Study

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In the 4D trial, there was an unexpected higher rate of stroke among those treated with HMG-CoA reductase inhibitors (statins) than placebo among prevalent diabetic hemodialysis patients. It is not known if this was a type I error or a true association.

We investigated the association of statin use at baseline and cerebrovascular disease (CVA) among a national, incident dialysis cohort of 1,041 patients enrolled from 10/95 to 7/98. Incident CVA was defined as both non fatal (hospitalized stroke, carotid endarterectomy) and fatal (stroke death) events after dialysis initiation. Participants were censored for transplant, non-stroke death, lost to follow-up, or at 12/31/04. With Cox proportional hazards regression analysis, we assessed the independent risk of CVA associated with statin use after adjustment in separate models for a propensity to use statins score and for age, race, sex, history of CVA, smoking status, diabetes, hypertension, albumin, and cholesterol.

Mean age was 58 years with 54% male, 67% White, 74% on hemodialysis, and 16% taking statins. A total of 165 patients experienced a CVA; incidence rate was 5.2 per 100 person-years (95% CI [3.4–7.6]) for those taking statins and 4.8 per 100 person-years (95% CI [4.1–5.7]) for non-statin users. Statin use was not associated with increased hazard of CVA in univariate, propensity adjusted, or traditional multivariate analyses (Table).

We conclude that statin use among incident dialysis patients neither increases nor decreases the risk of CVA. Further studies are needed to understand the pathophysiology and prevention of stroke in patients with ESRD.

	Relative Hazard (95% CI) of CVA by Statin Use		
	Unadjusted	Model 1*	Model 2**
Statin Use	1.08 (0.73–1.61)	0.97 (0.62–1.51)	0.88 (0.56–1.38)

\* Model 1: Adjusted for deciles of propensity score

\*\* Model 2: Adjusted for age, race, sex, history of CVA, smoking status, diabetes, hypertension, albumin, cholesterol

## 6. Dialysis

### Nocturnal Hemodialysis Lowers Blood Pressure and Reduces Left Ventricular Mass: Results of a Randomized Controlled Trial

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Observational and case-control studies suggest that nocturnal hemodialysis (NHD) improves blood pressure (BP) and left ventricular (LV) mass. Prior to widespread uptake of this therapy, definitive evidence from randomized trials is required.

We performed a randomized trial in 52 HD patients, comparing NHD with conventional thrice weekly HD (CvHD) over 6 months. The primary outcome was a comparison between groups for the mean change in LV mass as measured by cardiac magnetic resonance. Change in systolic blood pressure (sBP) was specified a priori as a secondary outcome.

Results from 51 patients (mean age 54 years, 37% female) were available for analysis (one patient, randomized to NHD, dropped out of the study immediately and refused all study-related procedures). One death occurred (in the NHD group) and 2 patients were transplanted (both in the CvHD group). sBP, use of antihyperten-

sive medications, and LV mass were similar at baseline. At study exit, resting pre-dialysis sBP improved by 7 mmHg in the NHD group and worsened by 4 mmHg in the CvHD group (11 mmHg difference, 95% CI 2–24 mmHg), despite a decrease or discontinuation of antihypertensive medications in 16/26 patients assigned to NHD versus 3/25 patients assigned to CvHD ( $p < 0.001$ ). At study exit, using intent-to-treat analyses, NHD was associated with a reduction in LV mass when compared to CvHD (15.3 gram difference in change in LV mass, 95%CI 1.0–29.6 grams,  $p = 0.037$ ). In an analysis adjusting for baseline LV mass and sBP, the difference in change in LV mass persisted (19.7 gram difference, 95%CI 4.5–34.8 grams,  $p = 0.013$ ). Compared to thrice weekly CvHD, NHD improves BP, reduces antihypertensive medication drug use, and induces regression of LV mass.

## Evolution of Pre-Dialysis Protein Bound Uremic Solute Concentration with Post-Dilution On-Line Hemodiafiltration

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Although concentration of protein bound uremic compounds has been related to clinical outcome parameters in observational studies, few currently used dialysis strategies are known to remove those compounds more than standard hemodialysis to any significant extent. We previously demonstrated no superiority of high-flux hemodialysis over low-flux hemodialysis (Lesaffer et al., *NDT*, 15 (1):50-7).

In this study we evaluated the evolution of protein bound uremic solutes after a switch from high-flux hemodialysis to on-line post-dilution hemodiafiltration (Polyflux 170) in 10 stable patients. Net convective fluid exchange was  $22.8 \pm 1.7$  L. All other relevant parameters were kept stable. We compared pre-dialysis solute concentration at 4, 5 and 9 weeks vs baseline for the water soluble solutes (urea, creatinine), the protein bound compounds (hippuric acid, indole acetic acid, indoxylsulfate, p-cresylsulfate and CMPF), as well as for  $\beta$ 2-microglobulin.

Whereas no change of concentration was found for urea and creatinine, the concentration at 9 weeks of hippuric acid ( $4.92 \pm 2.16$  to  $3.84 \pm 2.22$  mg/dL, -22%,  $p < 0.01$ ), indoxylsulfate ( $1.67 \pm 0.55$  to  $1.33 \pm 0.59$  mg/dL, -20%,  $p < 0.05$ ), p-cresylsulfate ( $3.97 \pm 1.56$  to  $2.67 \pm 1.77$  mg/dL, -33%,  $p < 0.01$ ), CMPF ( $0.65 \pm 0.38$  to  $0.57 \pm 0.34$  mg/dL, -12%,  $p < 0.01$ ) and  $\beta$ 2-microglobulin ( $25.01 \pm 5.78$  to  $17.90 \pm 4.73$  mg/L, -28%,  $p < 0.01$ ) decreased consistently vs baseline. The decrease was progressive over the 9 weeks follow-up period. Indole acetic acid showed no significant changes. Data for the free active fraction of the protein bound compounds followed a similar evolution.

It is concluded that post-dilution hemodiafiltration adds to the removal of protein bound compounds and of  $\beta$ 2-microglobulin vs high-flux hemodialysis, resulting in a consistent decrease of their pre-dialysis concentration by -12 to -33% in 9 weeks.

## Evaluation of Clinical Dry Weight Assessment in Hemodialysis Patients by Bio-Impedance Spectroscopy: A Cross Sectional Study

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Modern concepts of dry weight assessment (DWA) in hemodialysis (HD) patients aim to avoid both overhydration (left ventricular hypertrophy) and underhydration (residual diuresis). Objective methods for DWA did not have the potential for routine use so far. Fluid management in HD is most often based on clinical criteria.

The aims of this study were 1) to define pre- and post-dialytic ranges of extracellular hydration in a cohort of HD patients in whom DWA was performed by clinical criteria 2) to reveal differences between diabetic and non-diabetic patients in this context and 3) to estimate the number of patients which could potentially benefit from correction of dry weight.

We used a new bioimpedance spectroscopy device (BCM, Fresenius) which implies a validated body composition model. For the first time this tool allows a quantification of extra-cellular fluid overload or deficiency ( $\pm$ EOH in L) in comparison to a healthy population. Normal EOH has been shown to range from  $-1.1$  to  $1.1$  L

(according to the 10th and 90th percentile of EOH measurements in 987 healthy subjects).

EOH was measured prior to a HD session in 370 stable HD patients (49.5% with diabetes). Weight and blood pressure were recorded pre- and post-treatment.

Pre-dialytic EOH ranged from  $-0.31$  to  $3.88$  while post-dialytic EOH was between  $-2.41$  and  $2.04$ L (10th and 90th percentile, respectively) showing that the EOH of healthy subjects is considered the optimal range for dry weight in a majority of HD patients. Comparison of diabetic vs. non-diabetic patients revealed no difference in this context. Based on the consideration that  $EOH < -1.1$ L before and  $>1.1$ L after HD indicates sub-optimal DWA we identified 106 (28.6%) patients in whom dry weight correction could prove beneficial.

We conclude that the BCM device is an interesting tool for DWA. Future studies should demonstrate the clinical benefit of such approach.

## Preserved Residual Renal Function in Incident Peritoneal Dialysis Patients Using Low Glucose Degradation Products Solutions

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There are few clinical trials on the long-term benefit of the biocompatible solution on residual renal function (RRF). We compared low glucose degradation products peritoneal dialysis fluid (LF) with conventional acidic, lactate-buffered fluid (CF) in a prospective randomized controlled trial.

After 1-month run-in period, 93 new PD patients were randomized for 12-month treatment with either LF (Balance<sup>®</sup>, Fresenius, n=48) or CF (Stay•safe<sup>®</sup>, Fresenius, n=45). RRF, acid-base balance, peritoneal equilibration test, adequacy of dialysis, and effluent levels of cancer antigen 125 (CA125) and interleukin-6 (IL-6) were measured every 6 months after run-in period.

Baseline parameters including demographic and laboratory profiles, RRF, dialysate-to-plasma ratio of creatinine at 4 hours (D/P Cr), and effluent CA125 and IL-6 were not different between the two treatment groups. At 12 months, glomerular filtration rate of patients using LF was higher, compared with patients on CF

( $33.7 \pm 40.2$  vs  $22.5 \pm 19.3$  L/1.73m<sup>2</sup>/week,  $p=0.039$  by ANCOVA). At 12 months, serum total CO<sub>2</sub> levels were higher and the serum anion gap was lower in LF group ( $p<0.01$ , respectively). D/P Cr was significantly higher and serum albumin levels were significantly lower in patients on LF ( $0.72 \pm 0.12$  vs  $0.65 \pm 0.09$ ,  $p=0.01$ ;  $3.47 \pm 0.43$  vs  $3.79 \pm 0.42$  g/dL,  $p=0.021$ , respectively). A strong negative correlation was found between D/P Cr and serum albumin ( $r=-0.386$ ,  $p=0.002$ ). No differences between groups were observed for C-reactive protein or normalized protein equivalent of nitrogen appearance. At 12 months, effluent CA-125 levels were significantly higher in patients on LF than patients on CF ( $p<0.05$ ), while levels of effluent IL-6 showed no difference.

In summary, LF better preserved RRF over 12-months treatment period. Additionally, pH-neutral PD fluid led to improved acid-base balance and effluent markers of mesothelial integrity, compared to conventional fluids.

# BIOKID: Randomized Controlled Trial Comparing Bicarbonate and Lactate Buffer in Biocompatible Peritoneal Dialysis Solutions in Children

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Double-chamber peritoneal dialysis fluids (PDFs) exert less local and systemic toxicity by their neutral pH and greatly reduced glucose degradation product (GDP) content. We previously demonstrated superior acidosis correction with bicarbonate-based biocompatible vs. lactate-buffered conventional PDF. Preliminary experimental comparisons of biocompatible PDFs suggest specific buffer-related differences regarding mesenteric perfusion and aquaporin expression in the peritoneal membrane.

In order to elucidate whether the buffer choice is of clinical relevance when using biocompatible PDFs, we performed a multi-center randomized controlled trial in 37 pediatric patients on automated PD. After a 2 months baseline period with conventional high-GDP PDF (CAPD, Fresenius), patients were randomized to neutral-pH, low-GDP PDFs which either contained 35 mM lactate (Balance Fresenius, LPDF) or 34 mM bicarbonate (BicaVera, BPDF). Clinical and biochemical follow-up was performed monthly, and peritoneal equilibra-

tion tests at 0, 3, 6 and 10 months.

Peritoneal equilibration rates, small solute and albumin clearances were similar in both groups at baseline and remained unchanged after 3, 6 and 10 months. No difference in blood pH or serum bicarbonate and oral buffer supply emerged during the study. Daily net ultrafiltration was  $5.6 \pm 2.6$  and  $4.9 \pm 1.9$  ml per gram glucose exposure at baseline in patients randomized for LPDF and BPDF respectively (n.s.). After 10 months ultrafiltration had decreased to  $4.2 \pm 1.2$  with LPDF and increased to  $5.2 \pm 1.7$  ml/g glucose with BPDF ( $p=0.06$  for slopes) at similar overall glucose exposure.

We conclude that when using biocompatible PDF, equally good acidosis control is achieved with lactate and bicarbonate buffer systems. While no differences in solute transport were apparent within 10 treatment months, ultrafiltration capacity tended to increase with bicarbonate based PDF.

## 7. Epidemiology and Outcome

### Lower Glomerular Filtration Rate in Adults with Low Birthweight: Results from the AusDiab Study

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**Aim:** To examine the association of birthweight with urine albumin/creatinine ratio (ACR) and glomerular filtration rate (GFR) in a representative sample of the adult Australian population.

**Methods:** 10,788 participants in the second wave of the AusDiab study were asked to complete a birthweight questionnaire. Urine albumin was measured by immunoassay and adjusted for urine creatinine. GFR was estimated using mean body mass (LBM-measured by bioimpedance) and serum creatinine (mg/dl): predicted GFR =  $(2.4 \times \text{LBM}) - (0.75 \times \text{LBM} \times \text{Scr})$  (Taylor et al, NDT, 2006). Low GFR was defined as values less than 10th percentile for each sex.

**Results:** Of 7,157 people who responded to the birthweight questionnaire, 4,502 (62.9%) reported their birthweights-range 0.4 to 7.0 kg, mean (SD) 3.4 (0.7) kg. Lean body mass was directly correlated with birthweight, while urine ACR and serum creatinine

levels were not. GFR was strongly and positively associated with birthweight, with a predicted increase of 2.6 ml/min (CI 2.1, 3.2) and 3.8 (3.0, 4.5) for each kg of birthweight for females and males, respectively. People in the lowest sex-specific birthweight quintile had the lowest mean GFR. This relationship persisted with adjustment for other measured factors. The OR (CI) for low GFR (<61.0 mls/min for females and < 87.4 males) in people of low birthweight (LBW, < 2.5 kg) compared with those of higher birthweight was 2.04 (1.45, 2.88) for females and 3.4 (2.11, 5.36) for males.

**Discussion:** In an affluent western country with a good adult health profile, birthweight had a positive relationship with GFR. Among possible explanations is the proven association of birthweight with nephron endowment. People of lower birthweight should take special care to avoid post-natal insults that further reduce nephron number.

## Projecting the ESRD Population to 2020

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While ESRD incidence rates have recently levelled off and prevalence rates continue to slow, ESRD incident and prevalent counts continue to increase. Using a Markov model, we previously showed projections of the US ESRD population to 2015, using data available through 2000. We have since updated our model using data through 2005, and present projections through 2020.

The non-stationary Markov model incorporates census projections, accounting for expected changes in demographics, and also incorporates expected changes in diabetes prevalence. USRDS data from 1978 through 2005 were used to obtain transition probabilities, as well as ESRD incidence and prevalence estimates, within categories of age, race, and cause of renal failure, over time.

The expected incident count by 2015 is 135,000, approximately 2,000 less than our prior results, and 150,000 per year by 2020.

The expected number of prevalent

patients in 2015 is 680,000, approximately 33,000 less than our prior results, and 785,000 by 2020.

ESRD incidence rates have levelled off overall, and have even started declining in certain subgroups, explaining part of the difference between our previous and current projections, which are particularly lower for prevalence. The USRDS recently began accounting for patients who recover renal function, further explaining the difference between previous and current projections. Death rates are also declining, which, combined with the aging baby boomer population, higher diabetes prevalence rates, better treatment of patients with CKD prior to dialysis (eventually allowing more individuals to survive to dialysis instead of dying), and better care of patients on dialysis, will lead to continued increases in overall counts of incident and prevalent ESRD patients.

	Incidence		Prevalence	
	Previous Projection	Current Projection*	Previous Projection	Current Projection*
2005	106,690	106,896	489,200	484,995
2010	120,061	120,253	593,953	579,105
2015	136,882	134,978	713,531	679,918
2020		150,772		784,613

\* Actual for 2005

## Dialysis Facility Hospitalization Rates Are Associated with Facility Practice Patterns

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KDOQI guidelines recommend hemodialysis (HD) patients have urea reduction ratio (URR) 65%, hematocrit (Hct) 33%, and arteriovenous fistulae (AVF) over grafts (AVG) or catheters for vascular access. We used national CMS ESRD data aggregated to the facility level to investigate whether facilities with more patients meeting KDOQI guidelines for dialysis dose, anemia management, and vascular access had lower hospitalization rates in 2005.

For each facility, we calculated the standardized total admission ratio (STAR); the % HD patients with URR $\geq$ 65; % HD patients using AVF, AVG, and catheters; and % dialysis patients with Hct <33, 33–35.9, 36–38.9, and 39+. The STAR compares the total number of hospital admissions in the facilities Medicare patients to the number that would be expected based on these patients age, race, sex, and ESRD cause. We studied the 3,509 facilities with at least 80% HD patients and  $\geq$ 5 patients in each measure listed above.

Poisson regression was used to model the number of admissions based on practice patterns adjusted for expected number of admissions and average facility patient demographics.

The table shows hospitalization risk associated with each practice pattern adjusted for the others as well as facility characteristics. For a given level of AVG use, having 10% more patients using catheters rather than AVF was associated with 9% higher STAR. Similarly, for a given level of catheter use, having 10% more patients using AVG rather than AVF was associated with 3% higher STAR. Facilities with more patients with URR 65+ or Hct 33+ had lower STAR (3% for URR and 4–6% for Hct). Facilities with 10% more patients with Hct 33–35.9 and 36+ rather than <33 had 6% and 4% lower STAR respectively.

Facilities with more patients meeting KDOQI guidelines for vascular access, anemia management, and dialysis dose had lower admission rates.

Table: Hospitalization Risk

Facility Practice Pattern	Relative Hospital Admission Rate**
AVG Use (vs. AVF)	1.03 *
Catheter Use (vs. AVF)	1.09 *
URR 65+ (vs. <65)	0.97 *
Hct 33–35.9 (vs. <33)	0.94 *
Hct 36–38.9 (vs. <33)	0.96 *
Hct 39+ (vs. <33)	0.96 *

\*\* per 10% more patients in category than ref group; \*p<0.0001

## Obesity Is a Risk Factor for Decline of Renal Function after the Start of Dialysis

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**Background:** In the general population, obesity is a risk factor for loss of renal function. The aim of this study was to assess the effect of obesity and underweight on decline of renal function after the start of dialysis.

**Methods:** Patients with residual renal function 3 months after the start of dialysis (baseline) and at least 2 additional GFR measurements during the subsequent 15 months, were selected from a prospective multicentre cohort study of incident dialysis patients in the Netherlands (NECOSAD). Patients were divided into 4 weight categories, based on their BMI at baseline: low (<20 kg/m<sup>2</sup>; n=74), normal (20–25 kg/m<sup>2</sup>; n=489), overweight (25–30 kg/m<sup>2</sup>; n=318) and obese (≥30 kg/m<sup>2</sup>; n=93). GFR was estimated as the mean of plasma and 24 h urine creatinine and urea clearances. Decline of GFR was estimated for all BMI categories by linear regression and linear mixed model analysis.

**Results:** A total of 974 patients were included (age: 58 ± 15 yr,

BMI: 24.9 ± 3.9 kg/m<sup>2</sup>, GFR: 4.4 ± 2.9 ml/min, 54% HD, 62% male). The mean decline of GFR per month was 0.09 ± 0.23 ml/min for low weight, 0.11 ± 0.22 ml/min for normal weight, 0.14 ± 0.20 ml/min for overweight and 0.19 ± 0.27 ml/min for obese patients. After adjustment for age, sex, primary kidney disease, dialysis modality, smoking, CVD and nPNA, the decline of GFR per month (95% CI) was 0.04 (0.01 to 0.08) ml/min higher for overweight and 0.10 (0.05 to 0.15) ml/min higher for obese patients, as compared to normal weight patients. In contrast, the monthly decline of GFR in underweight patients was 0.03 (–0.02 to 0.09) ml/min lower than in normal weight patients.

**Conclusion:** Obesity is an important risk factor for decline of renal function after the start of dialysis, while underweight does not accelerate decline of renal function. Possibilities to preserve renal function in dialysis patients should be investigated in further studies.

## Total Organ Mass Predicts Survival in Chronic Hemodialysis Patients

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Low BMI in maintenance hemodialysis (MHD) patients correlates with unfavorable clinical outcome. It has been proposed that uremic toxin generation occurs predominantly in visceral organs, and toxins distribute in body water and fat tissue. The generation relative to body water and the absolute concentration of uremic toxins may be relevant.

We investigated the relationship between total organ mass (TOM) and outcome in patients commencing HD between 1/1/2000 and 9/30/2005 and who survived the first 90 days. Patients were followed until death, transplantation, or unit transfer. The mean TOM was estimated by anthropometric regression models developed for healthy black and white males and females and expressed as percent of body weight (TOM%BW). Patients were stratified into tertiles of race- and gender-specific TOM%BW. Associations of TOM%BW and all-cause mortality were examined by Kaplan Meier and Cox regression analysis.

2,004 MHD patients (47% Blacks; 46% females; mean age±SD 65±15 years) were studied. Median observation time was 17 months (range: 5 to 63); 859 patients died (43 %). Overall mean TOM%BW was 4.54% (table).

TOM%BW was inversely related to postdialytic weight ( $R^2 = 0.68$ ,  $P < 0.0001$ ). Mean survival (months) in the lowest tertile was 34.4, in the middle tertile 31.2, and in the highest tertile 29.2 ( $P = 0.0001$ ; log rank test). In a Cox regression analysis with race, gender, age and serum albumin concentration as covariates, a high TOM%BW was associated with poor survival (RR 1.26 (95%CI: 1.13 to 1.40),  $P < 0.0001$ ).

The ratio of TOM to body weight (as a reflection of toxin diluting/metabolizing compartment) determines patient outcome, since small patients (high TOM%BW) generate uremic toxins at a higher rate relative to their toxin diluting/metabolizing volume (total body water and fat mass) compared to large patients.

Race	Sex	N	TOM%BW			
			Minimum	Maximum	Mean	SD
Black	F	468	2.25	7.00	4.19	0.66
	M	472	2.97	6.84	4.49	0.61
White	F	443	2.40	8.42	4.65	0.83
	M	621	3.05	7.43	4.75	0.64

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