

The background image shows the Chicago skyline across the Chicago River. The Willis Tower (formerly Sears Tower) is the central, tallest building. Other recognizable buildings include the John Hancock Center, the Aon Center, and various modern skyscrapers. In the foreground, a blue and white boat is on the river, and a red brick building is visible on the far right.

AMERICAN SOCIETY OF NEPHROLOGY

# KIDNEYWEEK<sup>2016</sup>

Chicago, IL • Nov 15 -20

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## Chicago

The city of Chicago is located in northern Illinois, United States, at the south western tip of Lake Michigan. It covers an area of 60,000 hectares and sits 176 meters (578 feet) above sea level. With a population hovering near three million, Chicago is the state's largest and the country's third most populous city. It is the 5<sup>th</sup> largest body of fresh water in the world. Chicago's has wide parklands; including 3,000 hectares of city parks attracting an estimated 86 million visitors annually. It is a multicultural city with the values of America's heartland-integrity. Across the United States, it is recognized as a very passionate sports town. It is the leading city of the United States in reforming public schools, enhancing public safety and security initiatives, providing affordable housing in attractive and economically sound communities, ensuring accessibility for all and fostering, social, economic and environmental sustainability.





## Foreword

American Society of Nephrology (ASN) is working relentlessly towards the prevention, treatment, and cure of kidney diseases throughout the world. Its motive is to provide knowledge to the healthcare professional and educate them about the advancing researches and innovations in the field of renal diseases, by communicating new strategies in order to provide the quality care to patients with renal diseases.

Kidney Week of the American Society of Nephrology (ASN) is organized by American Society of Nephrology (ASN). In 2016, it was held during November 15 - 20, 2016 at McCormick Place, Chicago, Illinois, United States of America. The audiences in focus for this nephrology meeting were nephrologists, physicians, researchers, medical and other trainees—including, medical students, residents, graduate, students, post-docs, and fellows, thereby, providing its participants the exciting and challenging opportunities to communicate their knowledge, learn the latest scientific and medical advances, and engage in discussions with leading pioneers and stalwarts in this field.

The major objectives of this nephrology meeting were:

- To put forward the recent discoveries in basic, translational, and clinical research in nephrology
- Formulation of the novel research questions based on updated scientific and clinical advances in nephrology-related disciplines
- Devising new standards and approaches to clinical care of patients with kidney diseases and related disorders based on the recent advances in the areas of general nephrology, dialysis, transplantation, and hypertension.

In line with the provided information based on the abstracts and topic discussed, the ASN Kidney Week 2016 abstract compendium is our sincere work to present the clinically updated, relevant and latest information on various fields related to nephrology to the healthcare professionals. Each page comprises the highlighted key information for quick view of the page content.

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# KIDNEY WEEK<sup>2016</sup>

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A photograph of the Chicago skyline featuring the Willis Tower (formerly Sears Tower) and other skyscrapers against a blue sky with white clouds. The buildings are reflected in the water in the foreground.

# THURSDAY

17<sup>th</sup> November, 2016

## 1. Impact of L-carnitine treatment on intravenous iron administration induced oxidative stress and inflammatory response in patients with chronic kidney disease

Armaly Z, Hassan K, Habbashe N M, Ramadan R, Naser G, Farah R, Abassi Z.

Decreased erythropoietin (EPO) production, low iron stores, chronic inflammation and anemia is commonly witnessed in patients with chronic kidney disease (CKD). Therefore, treatment modalities should include iron supplements in combination with EPO. However, investigators have found that the iron treatment cause oxidative stress and inflammation in these individuals. It has been proposed by the investigators that L-carnitine supplementation in such cases might reduce the episodes of oxidative stress and inflammation. The present study was conducted to examine the long term L-carnitine therapy effects in prevention of intravenous iron administration (IVIR)-induced oxidative stress in patients with CKD.

*Combination therapy with carnitine and intravenous iron reduces the adverse consequences of intravenous iron administration induced oxidative stress in patients with chronic kidney disease*

The study included 32 patients with CKD and anemia. Patients were divided into 2 groups; Group 1 (n= 16) were given a weekly IVIR [Sodium ferric gluconate (125 mg/100 ml)] for 12 weeks and Group 2 (n=16) received the IVIR regimen with carnitine (20 mg/kg, IV) weekly. Weekly blood samples were drawn before and after each IVIR. Parameters like C-reactive protein (CRP), advanced oxidative protein products (AOPP), thiobarbituric acid reactive substances (TBARS), fibrinogen, neutrophil gelatinase-associated lipocalin (NGAL), in addition to routine complete blood count and biochemical were analyzed.

The results of the study declared that the combined administration of IVIR and carnitine increased hemoglobin (Hb) more profoundly (8%) than those treated with IVIR alone (13%). It was also noted that IVIR alone induced oxidative and inflammatory responses but the patients who received carnitine did not exhibit these effects. IVIR-induced elevation in CRP, NGAL, AOPP, TBARS and Fibronectin was noticed.

Thus, it can be concluded that combination therapy with carnitine and intravenous iron reduces the adverse consequences of intravenous iron administration induced oxidative stress in patients with chronic kidney disease.

## 2. Effects of erythropoiesis-stimulating agents in the treatment of deformed erythrocyte associated with chronic kidney disease

Aizawa K, Kawasaki R, Tashiro Y, Kondoh K, Shimonaka Y, Hirata M, Yasuno H.

Erythropoiesis-stimulating agents (ESAs) are commonly used in patients with anemia associated with chronic kidney disease (CKD) as they contribute to increase the number of erythrocytes. However, there are evidences which show that the use of ESAs leads to qualitative changes in erythrocytes such as deterioration in deformability and stability and shortened erythrocyte lifespan in patients with CKD resulting in poor prognosis. Thus, for the treatment of CKD ensuring hemoglobin (Hb) levels may not be sufficient for formulating an effective intervention.

The current study was executed on experimental models that were given anti-Thy1.1 antibody injection plus uninephrectomy was done at week 0. After the operation, uninephrectomy models were injected with Continuous Erythropoietin Receptor Activator – Methoxy Polyethylene Glycol-Epoetin  $\beta$  (C.E.R.A, 0.6  $\mu\text{g}/\text{kg}$ ) intravenously for every 2 weeks from week 4 to 16. Until week 18, blood and urine from the models were collected. Hb levels were assessed for therapeutic control of anemia. Laser diffraction ektacytometry and hemolysis test were used to quantify deformability and stability of erythrocytes respectively. Total urinary protein (uTP) and heart weight/body weight (HW/BW) were utilized to assess the kidney and cardiovascular status, respectively.

The results of the study declared that the experimental models demonstrated anemia and impaired erythrocyte deformability and stability. C.E.R.A. treatment significantly improved deformability and stability of the erythrocytes. But in the sham-operated group, C.E.R.A. treatment for improving erythrocyte deformability and stability did not show any change. Also, C.E.R.A. treatment did not alter the increased uTP and HW/BW in the CKD models.

Thus, it can be inferred that therapeutic administration of continuous erythropoietin receptor activator – methoxy polyethylene glycol-epoetin  $\beta$  ameliorated Hb levels and improved deformability and stability of erythrocytes in patients with anemia associated with chronic kidney disease.

### **3. Long-term safety and efficacy of multiple doses of continuous erythropoietin receptor activator – methoxy polyethylene glycol-epoetin $\beta$ in pediatric patients with chronic kidney disease**

Fischbach M, Wuehl E, Reigner S, Morgan Z, Schaefer F.

An open-label multicenter study was conducted to determine the long-term safety and efficacy of C.E.R.A. (Continuous Erythropoietin Receptor Activator – Methoxy Polyethylene Glycol-Epoetin  $\beta$ ) administration in pediatric patients affected with anemia related to chronic kidney disease.

The study recruited 64 patients; of them 47 finished the core phase. A total of 37 patients entered the safety extension and 17 completed 73 weeks of treatment. The study included a 2-week screening period, 16-week dose-titration period and 4-week evaluation period. Stable patients with Hb within  $\pm 1$  g/dL of baseline and between 10 and 12 g/dL were allowed to enter a 1-year optional safety extension. C.E.R.A was given to patients of age 6–17 years with history of hemodialysis and stable chronic renal anemia for every 4 weeks at a starting dose determined by previous epoetin alfa/beta or darbepoetin dosing. Two conversion factors were tested sequentially. In the optimum dose group ( $n=48$ ), the starting dose was 4  $\mu\text{g}$  for each weekly dose of 125 IU epoetin alfa/beta or 0.55  $\mu\text{g}$  darbepoetin.

From the results of the study, it was observed that most withdrawals cases were due to renal transplantation. In the optimum dose group, the median doses at the beginning of the study were 2.51 and 2.36  $\mu\text{g}/\text{kg}/4$  weeks for 6–11 and 12–17 year olds, respectively. Stability in the Hb

*With use of continuous erythropoietin receptor activator – methoxy polyethylene glycol-epoetin  $\beta$ , stable hemoglobin levels can be maintained effectively in the pediatric patients affected with anemia associated with chronic kidney disease*

concentration in response to the adjusted doses of C.E.R.A. was observed. Hb values of 70% of patients were within 10–12 g/dL at the end of study and 62% were within  $\pm 1$  g/ dL of baseline.

Thus, it can be concluded that with the use of continuous erythropoietin receptor activator – methoxy polyethylene glycol-epoetin  $\beta$ , stable Hb levels can be maintained effectively in the pediatric patients affected with anemia associated with chronic kidney disease.

#### **4. Benefits of physical activity during dialysis: Protective measure against cardiovascular diseases**

*Isnard MR, Coutard C.*

Physical activity during chronic illness has been observed to be beneficial. A study was conducted to assess the effectiveness of physical activity (PA) during dialysis as a protective measure against cardiovascular (CV) diseases. The multicentric prospective study recruited a group of 80 patients on dialysis and randomized them into two groups; the exercise group (EX) and the control group (CON) consisting of 40 patients each. The patients in both the groups were kept on a follow-up for a period of 2 years. The following parameters were measured to assess for CV risk; total cholesterol, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), triglycerides (TG) and hemoglobin (Hb) levels. All the parameters were checked before and after the 2 year follow-up (at month 0 and at month 24). The study also analyzed the number of antihypertensive treatments and collected the Erythropoiesis-Stimulating Agent (ESA) required doses. Hospitalizations with their etiologies were also noted for each group during the 2 year follow-up.

Results of the study were as follows:

- Of the 40 patients initially recruited in each group, a total of 35 patients were left in the CON group after 24 months due to the occurrence of 4 deaths and 1 renal transplantation, while the EX group comprised of 31 patients owing to 7 deaths and 2 transplantations
- The EX group demonstrated significant decrease in various parameters tested in the study (Table 1).
- Significant decrease in total cholesterol level was observed after 24 months in comparison to the level at the baseline

**Table 1: Alteration in various parameters used to assess cardiovascular risk in patients of the exercise group after 24 months**

Parameters	Baseline value	Value after 24 months
Total Cholesterol	$1.82 \pm 0.47$ g/l	$1.6 \pm 0.26$ g/l
Triglycerides	$1.63 \pm 0.9$ g/l	$1.44 \pm 0.74$ g/l
Erythropoiesis-Stimulating Agent (ESA) dose required	$110.83 \pm 70.8$ $\mu$ g/month	$75.7 \pm 69.7$ $\mu$ g/month
Number of antihypertensive drugs per patient	$1.85 \pm 1.08$	$0.75 \pm 0.84$

- The TG level also showed reduction after 24 months in this group
- The levels of HDL, LDL cholesterol and Hb did not show any significant variation in both the groups. However, the requisite Erythropoiesis-Stimulating Agent (ESA) doses were observed to be decreased after 24 months
- Appreciable fall in the number of antihypertensive drugs per patient was observed in the EX group in which the frequency of hospitalization of the patients was also less compared to the CON group.

The beneficial effects of intra-dialytic exercise program in cardiovascular protection were thus evident in the study. In addition to this, cardiovascular events are also reduced as observed in the two year follow-up.

## 5. Association of incident chronic kidney disease and reduced lung function

Sumida K, Kwak L, Grams M, Yamagata K, Kovacs J, Coresh J, Matsushita K.

Progressive reduction in lung functioning can have detrimental impact on the health of an individual. The cardiovascular deterioration associated with progressive decline in lung activity has been established. However, its effect relating to the incident end stage renal disease (ESRD) and chronic kidney disease (CKD) remains unclear. In this context, a study, Atherosclerosis Risk in Communities (ARIC) Study, evaluated the association of race- and sex-specific quartiles of percent-predicted forced vital capacity (FVC) and the proportion of forced expiratory volume in 1 second in FVC (FEV1/FVC) with subsequent risk of ESRD and CKD. The study recruiting a total of 14,946 candidates (age: 45-64 years) comprised of a 25 year long follow-up of the candidates. Methods used in the study included Kaplan-Meier method and Cox proportional hazards models with adjustment for potential confounders.

Incidence of ESRD and CKD was observed in 526 and 3,704 cases, respectively during the 25 years of follow-up. Patients with relatively lower percent-predicted FVC and FEV1/FVC demonstrated higher incidence of ESRD. The adjusted hazard ratio of incident ESRD for percent-predicted FVC in the lowest quartile was 1.72, and for FEV1/FVC was 1.33. Compared to the normal lung function pattern, highest adjusted HR of ESRD was observed in the mixed pattern, followed by restrictive and then obstructive pattern. Patients with CKD also demonstrated similar associations.

On the basis of the above findings, it can be inferred that reduced lung function, especially lower percent-predicted FVC independently correlates with CKD progression.

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*Reduced lung function  
independently  
correlates with  
chronic kidney disease  
progression*

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## 6. Healthcare management in late stage chronic kidney disease

Halinski C, Agoritsas S, Sakhya V, Balsam L, Fishbane S.

A healthcare management and informatics program named healthy transitions (HT) is established to improve late stage (stage 4/5) chronic kidney disease (CKD) care. The program

comprises of partnership of nurses with nephrologists guided by a clinical informatics system. It principally aims to improve the education/preparation for end stage kidney disease (ESKD). The impact of the program on ESKD was evaluated in the current analysis.

The analysis enrolled patients with stage 4/5 CKD and categorized them into HT intervention group and usual care (UC) group at four clinical sites. The patients in both the groups were followed up for a period of 18 months. The primary outcome was the percentage of patients who developed ESKD after treatment with home dialysis or kidney transplantation while the secondary outcome included those who were started on hemodialysis (HD) without hospitalization and access type for HD.

Both the groups consisted of 65 patients each. The baseline characteristics of patients in both the groups did not demonstrate significant variation. The mean estimated glomerular filtration rate (eGFR) at baseline of the patients in HT and UC group was  $18.5 \pm 6.4$  ml/min and  $19.9 \pm 6.7$  ml/min, respectively. A total of 25 and 23 patients were initiated with the renal replacement therapy (RRT) in HT and UT group, respectively. Out of the 25 patients in the HT group, 10 patients achieved the primary outcome while this count was 3 in the UC group. A non-hospital outpatient start was observed in 53.3% (8/15) and 15% (3/20) of the patients on HD in the HT and UC groups, respectively. Catheter was observed to be the sole access in 20% and 40% of the patients in HT and UC group, respectively. About 52.3% of the HT patients and 30% of the UC patients had a working arteriovenous fistula or graft (AVF or AVG).

In comparison with the UC, HT intervention seems to considerably increase the utilization of home dialysis and kidney transplantation and outpatient, nonhospital starts. Further studies are therefore required to test various other domains (cost effectiveness and scalability) of HT approach.

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*Healthy transitions intervention compared to the usual care seems to considerably increase the utilization of home dialysis and kidney transplantation and outpatient, nonhospital starts*

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## 7. Assessment of gender differences in progression of chronic kidney disease

Ricardo AC, Yang W, Appel LJ, Cedillo-Couvert EA, Chen J, Krousel-Wood M, Rahman M, Rosas SE, Saunders MR, Sha D, Sharma K, Steigerwalt SP, Wright JT, Daviglus ML, Lash JP. CRIC Study Group.

Male population in various parts of the world is associated with higher (1.5 times) incidence of end-stage renal disease (ESRD) compared to female population though the prevalence of chronic kidney disease (CKD) has been observed to be lower in this population compared with the female population. Rapid progression of CKD in males has been observed in earlier studies. However, this has not been a consistent finding. A study was conducted to evaluate the association of gender differences with CKD progression.

The prospective, longitudinal study recruited 1778 females and 2161 males. The association of gender with incident ESRD (dialysis or transplantation) was investigated

using Cox-proportional hazards models and the gender differences in estimated glomerular filtration rate (eGFR) slope were evaluated using linear mixed effects models.

The mean age of the recruited participants was 58 years. Initially at the time of recruitment, females, in comparison with males, were observed to have higher body mass index, lower eGFR, lower proteinuria and were physically inactive with lesser probability of having a smoking history. A total of 844 participants developed ESRD after an average follow-up time period of 6.9 years. On the basis of the fully-adjusted mixed effects models, the difference between eGFR slope of females and males was -0.17 ml/min/1.73m<sup>2</sup>/year.

It can be inferred that females are at lower risk of developing ESRD compared to males among the patients with CKD.

## 8. Association of fibroblast growth factor 23 with erythropoiesis-stimulating agent resistance in hemodialysis

Hamano N, Komaba H, Wada T, Kakuta T, Fukagawa M.

Fibroblast growth factor 23 (FGF23) has been observed to exert an inhibitory effect on erythropoiesis via suppression of erythropoietin production and downregulation of its receptor. Its effect on renal anemia when administered in high levels to patients on hemodialysis remains to be established. A study assessed the association of resistance to erythropoiesis stimulating agents (ESA) and FGF23 levels in hemodialysis patients. The study used baseline data from the Tokai Dialysis Cohort Study conducted on 654 hemodialysis patients. The index of resistance to ESA used in the study was erythropoietin resistance index (ERI), calculated as the weight-adjusted dose of ESA divided by the hemoglobin level. The authors defined top quartile of ERI as the ESA resistant group. Levels of serum FGF23 were calculated using chemiluminescence immunoassay which exclusively perceives the full length FGF23 peptide.

Following results were obtained in the study:

- The observed number of recruited patients receiving ESA at baseline was 458. The median ERI and FGF23 were 6.9 IU/kg/wk/g/dl and 1.955 pg/ml, respectively
- The independent risk factors for ESA resistance were mass body index, serum albumin, transferrin saturation, and FGF23 as identified by the multivariate logistic regression analysis.

*Elevated levels of fibroblast growth factor 23 contributes to erythropoiesis stimulating agents resistance in patients undergoing hemodialysis*

The contribution of elevated FGF23 levels to ESA resistance in patients undergoing hemodialysis is thus evident in the above findings. Further research is therefore required on FGF23-lowering treatment in improvement of renal anemia control in end-stage renal disease.

## **9. Assessing the association of body mass and response to erythropoiesis-stimulating agents in hemodialysis**

*Vecchio LD, Aicardi V, Longhi S, La Milia V, Pontoriero G.*

The association between erythropoiesis-stimulating agents (ESA) in high levels and malnutrition and inflammation among patients undergoing hemodialysis, is recognized. However, the response of ESA in patients with lean and fat body composition remains to be established.

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**Erythropoiesis-  
Stimulating agents  
hypo-response in  
patients undergoing  
hemodialysis is  
principally associated  
with decreased fat body  
mass**

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A group of 90 patients (mean age  $68.88 \pm 14.01$  years) receiving ESA therapy during hemodialysis were recruited in a study for nutritional assessment using body composition monitoring. Out of the total recruited patients, 53 were males. Reduced response to ESA was defined as ERI $>14.8$ . On the basis of the lean tissue index (LTI) and fat tissue index (FTI), percentiles relative to age- and sex-matched healthy population were calculated considering the variation in values of both the indices according to age and gender.

According to the results:

- The values of LTI and FTI were observed to be lower than the 10th percentile in 22% and 21% of the patients, respectively
- No significant difference was observed in the ferritin levels and TSAT
- An inverse relation was observed between the FTI values in ERI
- Higher levels of ERI were observed in patients with FTI values below the 10th percentile compared to those with 10-90th and  $>$  90th percentile (19.23 18.05,  $11.6 \pm 9.84$  and  $7.44 \pm 7.69$ , respectively;  $p= 0.025$ )
- Among the LTI percentile categories, an opposite trend was noted in the difference in mean ERI.

The above findings suggest that ESA hypo-response in patients undergoing hemodialysis is principally associated with decreased fat body mass.

## 10. High dose erythropoiesis-stimulating agents in patients with end-stage kidney disease and risk of mortality, cardiovascular events, and health-related quality of life

Valeria M, Palmer S, Ruospo M, Williams GJ, Craig JC, Hegbrant JBA, Giovanni FM.

It has been established that erythropoiesis-stimulating agent (ESA) therapy intends to increase the hemoglobin level in patients with end-stage kidney disease (ESKD). As a consequence however, this effect may increase risks of mortality while leading to poor cardiovascular events. However, it is still doubtful, that whether fixed treatment dose approach of ESA can mitigate this unfavorable effect and provide benefits to quality of life.

A study was conducted including 656 hemodialysis patients with anemia. Per week, these patients were made to receive ESA either at the high dose or low dose. High dose ESA contained epoetin alfa/epoetin beta (18,000 IU) or darbepoetin alfa (90 mcg), whereas low dose contained 4000 IU epoetin alfa or epoetin beta or 20 mcg darbepoetin alfa. The primary outcome was composite of death or a cardiovascular (CV) event such as non-fatal myocardial infarction, non-fatal stroke, or hospitalization for acute coronary syndrome, transient ischemic attack, unplanned percutaneous coronary intervention or peripheral revascularization. The result revealed that high-dose ESA strategy showed no increase in mortality, cardiovascular events (CVEs), and health-related quality of life.

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*Erythropoiesis-stimulating agent therapy increases the hemoglobin level in patients with end-stage kidney disease*

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## 11. Residual kidney function and its association with mortality in hemodialysis patients

Wang M, Chen J, Obi Y, Streja E, Csaba P, Kovesdy, Mehrotra R, Zadeh KK.

Residual kidney function (RKF) in hemodialysis patients and its relationship to mineral and bone disorders (MBD) and the possibility of survival is still not clear because of lack of documented studies. It has been hypothesized that RKF enhances the association between MBD parameters and death.

A study was conducted, wherein 35,114 incident hemodialysis patients treated in the year 2007 to 2011 were investigated across three strata of baseline residual renal urea clearance (CLurea). Cox models with adjustment for clinical characteristics and laboratory measurements were used for the analysis. The main aim of the study was to find out all-cause death rate association with serum phosphorus, uncorrected and albumin-corrected calcium, intact parathyroid hormone (PTH) and alkaline phosphatase (ALP).

The results revealed the following:

- Patients with higher CLurea who also had higher serum phosphorus concentrations were associated with incremental mortality risk, whereas patients with low CLurea and low intact PTH were associated with higher mortality risk.
- In addition to this, patients with high CLurea and high concentrations also showed a trend toward higher mortality risk.
- CLurea neither showed any alteration nor any associations of all-cause death with uncorrected total calcium, corrected total calcium, and ALP.
- Furthermore, it was also noted that across all CLurea strata, higher concentrations of these markers were straightaway associated with higher mortality risk. The authors concluded that RKF should be well accounted as it modifies its association with serum phosphorus and intact PTH. This relationship may provide clue to evaluate risk assessment of serum phosphorus and intact PTH.

*Acute kidney injury shows well preservation of secretory function and this secreted solutes can be used to evaluate renal function in acute kidney injury and establish commencement timing of dialysis*

## 12. Role of secretory function in acute kidney injury

Brien F, Sutherland SM, Plummer N, Meyer TW, Sirich TL.

Measurement of Urea Nitrogen (UN) and Creatinine (Cr) helps in routine evaluation of impairment of renal function in acute kidney injury (AKI). UN and Cr are the markers of tubular reabsorption and glomerular filtration. However, very few studies explaining tubular secretory function in AKI have been documented.

A study enrolling a total of 40 subjects aimed to evaluate plasma levels of the normally secreted solutes indoxyl sulfate (IS) and phenylacetylglutamine (PAG). The study was also aimed at measuring UN and Cr level. All these parameters were evaluated in 6 subjects with AKI and 25 subjects on maintenance hemodialysis (HD). In addition to this, solute clearances was also measured in 9 normal (NL) and same AKI group of individuals.

It was found that:

- Clearances relative to the Cr clearance were conserved for the secreted solutes in AKI
- On the other hand, a significant reduction was observed in fractional clearance of UN
- The UN level in AKI was seen to be raised to a similar degree as in HD
- However, in comparison to AKI subjects, the secreted solutes levels in HD individuals were found to be significantly higher.

The authors concluded that AKI shows well preservation of secretory function. These secreted solutes can be used for further studies, so as to evaluate renal function in AKI and establish commencement timing of dialysis.

### 13. Association of incomplete acute kidney injury with chronic kidney disease and sepsis survivors

Neyra JA, Xilong Li, HueBA, Yee J, Moe OW, Toto RD.

Sepsis is a condition where Acute Kidney Injury (AKI) is seen as its frequent complication followed by greater risk for Chronic Kidney Disease (CKD). The main aim of this study was to find out chances of increase in the risk of CKD in sepsis survivors patients after incomplete AKI recovery at 90 days post-discharge. The study included adults admitted to the intensive care unit (ICU) with a finding of severe sepsis/septic shock. Diagnosis of AKI at the time of ICU stay was based on Kidney Disease, Improving Global Outcomes (KDIGO) serum creatinine (SCr)-criteria referring baseline SCr within 3 months prior to admission. On the other hand, AKI recovery was decided by evaluating the ratio of 90-day in renal replacement therapy (RRT) free survivors, which was as follows

- SCr/baseline SCr <1.1 indicated complete recovery
- SCr/baseline SCr ≥1.1 to <1.5 indicated incomplete (mild) recovery
- SCr/baseline SCr ≥1.5 indicated incomplete (severe) recovery

Relative and/or absolute eGFR changes during the follow-up period were judged on the basis of incident or progressive CKD post-AKI.

The result revealed that out of 6290 patients included in the study, 3642 individuals had AKI, whereas, 741 needed acute RRT and 90-day death rate was observed in 26% of subjects. It was further found that among survivors, 1249 patients who suffered from AKI were RRT-free and these individuals had available follow-up data. Further, median follow-up of 319 patients with CKD was made for 2.5 years, which suggested that 54%, 29% and 13% had incomplete severe, incomplete mild and complete recovery, respectively. The authors concluded that following hospital discharge, incomplete AKI recovery within 90 days strongly predicts CKD in sepsis survivors. Thus, a well-timed assessment of AKI recovery can successfully help to find out risk associated to sepsis survivors.

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*Following hospital discharge, incomplete acute kidney injury recovery within 90 days strongly predicts chronic kidney disease in sepsis survivors*

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### 14. Assessment of nutritional factors as mortality predictors in hemodialysis patients

Kanno Y, Kanda E.

Nutritional status of the patients receiving hemodialysis (HD) is an important consideration. Regularly deliberated pre-HD laboratory data are widely used to evaluate the nutritional status of patients receiving HD. However, the pre-HD data always included a problem whether the most diluted value would be appropriate to assess. A study was conducted to compare the pre-and post HD laboratory data to investigate their value to predict mortality. A total of 104289 maintenance HD patients (males 61.2%) were included in the study and one- and five- year mortality were the measured outcome events. Mean age±standard deviation was  $65.47 \pm 12.18$  years and vintage was  $8.62 \pm 7.05$  years. The data to be assessed

were pre- and post- HD values of nutritional factors including body mass index (BMI), serum albumin, creatinine and urea nitrogen levels. The accuracy between pre- and post-HD values for the prediction of one- or five-year mortality was compared with the help of receiver operating characteristic (ROC) curves by the bootstrap resampling method.

Results of the study reported that the total number of patients who died in 1 year was 6868 (6.6%) and in 5 years was 3318 (31.8%). Post-HD serum albumin level [0.733 (95% CI 0.720, 0.746)] and pre-HD serum creatinine level [0.702 (95% CI 0.699, 0.706)] covered the highest area under ROC curve (AUCs) for the prediction of 1-year and 5-year mortality respectively. The AUCs depicted that the pre-HD values of BMI, serum creatinine and urea nitrogen levels were more exact in comparison to post-HD values. Similar trends were observed in the stratification analysis based on gender, age and diabetes mellitus as a cause of end-stage renal disease. Besides, the post-HD serum albumin level was more accurate for predicting 5-year mortality than the pre-HD level.

It was thus concluded that the pre-HD values of nutritional factors, apart from serum albumin levels, were more precise in comparison to post-HD values for anticipating mortality in patients undergoing hemodialysis.

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*Pre-hemodialysis values of nutritional factors, apart from serum albumin levels, were more precise in comparison to post-hemodialysis values for anticipating mortality in patients undergoing hemodialysis*

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## **15. Serum uric acid level: A marker of mortality risk in hemodialysis patients**

*Park C, Obi Y, Streja E, Soohoo M, Kalantar-Zadeh K.*

There is an increased risk of cardiovascular events and mortality with raised uric acid concentrations in the blood. Nevertheless, the risk of mortality associated with hyperuricemia in the hemodialysis (HD) patients population is a matter of debate. A retrospective study was conducted to evaluate the effects of increased serum uric acid on mortality risk in hemodialysis patients. The study examined a subcohort of 4,298 hemodialysis patients, the first serum uric acid measurements of which were obtained during treatment in a large dialysis organization from the year 2007-2011. The mean age of the patients was  $63 \pm 15$  years (39% of them were women) and mean uric acid level was  $6.6 \pm 1.8$  mg/dL. All the patients were randomized into 5 uric acid categories. The relation between serum uric acid levels and time to all-cause death from first uric acid measurements was measured with the help of Cox proportional hazards model. Results reported that there was reduced mortality risk among patients with high uric acid levels. The highest category ( $\geq 8.0$  mg/dL) showed non-significant reduced mortality risk, regardless of the adjustment models; while the lowest category ( $< 5.0$  mg/dL) depicted higher mortality in comparison to middle category (6.0- $< 7.0$  mg/dL). These reports were uniform among the subgroups of age, gender, race, diabetes, albumin and body mass index. Additionally, the low uric acid level associated mortality risk was noteworthy in patients with low nPCR ( $< 0.9$  g/kg/day).

The authors thus concluded that hyperuricemia appears to be marker of better nutritional status and reduces the all- cause mortality risk in hemodialysis patients.

## 16. Association of dietary protein intake with mortality in incident hemodialysis patients: Using normalized protein catabolic rate accounting for residual kidney function

Eriguchi R, Obi Y, Streja E, Rhee C, Soohoo M, Kalantar-Zadeh K.

Normalized protein catabolic rate (nPCR) is a significant index of dietary protein intake. Recent reports have suggested its association with mortality among hemodialysis patients. The reason behind this may be the non-accounting of residual renal urea clearance (CLurea) among hemodialysis patients during evaluation of nPCR. To evaluate this association, a study enrolled 36,713 incident hemodialysis patients in a dialysis organization from 1/2007 to 12/2011 and evaluated their nPCR at baseline or 6 months after dialysis. The mean age of the patients was  $62 \pm 15$  years, 37% of which were females, 28% were African-American, and 47% were diabetics. The association of nPCR with markers of mortality was examined using the Cox proportional hazard models. Results reported that at baseline, the median (IQR) of nPCR with CLurea was 0.94 (0.77, 1.14) g/kg/day. Higher mortality was reported in patients with nPCR value of < 0.7 g/kg/day, whereas a PCR value of > 1.1 g/kg/day was associated with better survival in comparison to reference (0.8-0.9 g/kg/day). Eventually, a reduction in nPCR value of < 0.1 g/kg/day was related to higher mortality and an increase in nPCR value of > 0.5 g/kg/day was associated with better survival.

To conclude, higher risk of death was reported in patients with low nPCR accounting for CLurea, and in those with decreased nPCR over the first 6 months of hemodialysis.

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*Normalized protein catabolic rate is a significant index of dietary protein intake. Recent reports have suggested its association with mortality among hemodialysis patients*

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## 17. Impact of dialysis session time on long term survival of maintenance hemodialysis patients

Kuragano T, Nakanishi T.

Super flux dialysis membrane is shown to improve the efficiency of dialysis in many patients nowadays. However, the relationship between the time of treatment and adverse events or survival in maintenance hemodialysis patients (MHD), with the use of high flux membrane has not been established yet. To establish this association a prospective multi-center study was carried out. A total number of 805 patients undergoing MHD were included in the study. The study was conducted for a total period of 3 years and serum levels of urea nitrogen (UN), creatinine (Cr),  $\beta$ 2microglobulin (MG), total protein, albumin, prealbumin, high sensitive C reactive protein (hCRP) were measured every 3 month. In addition to this, body mass index (BMI), and Kt/V were also assessed. Cox proportional hazards model for time-dependent variables were used to examine the links between dialysis intensity and adverse events or death. Results of the study divulged that no significant correlation was observed between pre-dialysis levels of  $\beta$ 2MG or UN. Besides, adverse event or survival, high pre-dialysis Cr level was related to the lower risk of hospitalization and death. Furthermore, low risk of cerebrovascular and cardiovascular disease (CCVD) and hospitalization was associated with high Kt/V.

No considerable amount of difference was observed among 3 groups of treatment time (<4 hours, 4-5 hours, >5 hours) with respect to serum levels of prealbumin, albumin, Cr, Kt/V and hCRP levels. Besides, it was observed that the BMI values were higher in the patients treated with >5 hours, in comparison to patients treated with <4 hours. Time dependent cox hazard model revealed that risk of hospitalization and death was comparatively lower in patients treated with 4-5 hours than those treated with <4 hours.

Given the results of the study it was concluded that higher Kt/V was associated with lower risk of CCVD and hospitalization of MHD patients, but not pre-dialysis level of  $\beta$ 2MG levels. Risk of hospitalization and death was more in patients kept on shorter dialysis session time (<4 hours).

## **18. Serum adiponectin level and peripheral artery disease: A pessimistic association among hemodialysis patients**

*Lai YH, Hsu BG.*

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*Nowadays super flux dialysis membrane has shown to improve the efficiency of dialysis in many patients*

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Peripheral arterial disease is known to be associated with high mortality rate in hemodialysis patients. Adipocytes secrete an anti-atherosclerotic fat-derived hormone which is thought to be involved in the pathogenic process of peripheral arterial disease in hemodialysis patients. The present study evaluated the association of serum adiponectin levels and peripheral artery disease by ankle-brachial index (ABI) in hemodialysis patients. A total number of 100 blood samples from 100 HD patients were included in the study. The values of ABI were measured by an ABI-form device (VaSera VS-1000) and a commercial enzyme-linked immunosorbent assay kit was used to measure serum adiponectin levels. The patients were divided 2 groups namely low and normal ABI groups. The patients with ABI values of < 0.9 were included in the low ABI group, which were reported to be 18% of the total number of patients.

Results reported that patients in the low ABI group had higher prevalence of diabetes, older age, and lower serum adiponectin level, in comparison to normal ABI group. Hemodialysis patients with diabetes mellitus had lower serum adiponectin level than non-DM HD patients. According to multivariable forward stepwise linear regression analysis the waist circumference, log transformed triglyceride (log-TG), and log transformed C-reactive protein (log-CRP) were the independent predictors of adiponectin levels in hemodialysis patients. Besides, multivariate logistic regression analysis, adiponectin levels and age were the independent predictors of peripheral arterial disease in hemodialysis patients. The values of sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver-operating characteristic (ROC) curve predicting peripheral arterial disease in hemodialysis patients were 72.22%, 64.63%, 36.68%, 99.92%, and 0.691 and the adiponectin cut-off value was 43.27  $\mu$ g/mL.

The results therefore were suggestive of positive association of serum adiponectin level with the pathogenetic process of peripheral arterial disease in hemodialysis patients.

## 19. Effects of gut microbiome and p-inulin on the progression of end stage renal disease in hemodialysis patients

Raj DS, Ramezani A, Li H, Landis JR, Charytan DM, Ikizler TA, Himmelfarb J, Kliger AS, Kimmel PL, Kusek JW, Dember LM.

End stage renal disease (ESRD)-associated inflammation and cardiovascular disease are the end results of alterations in the gut microbiome. Various studies have provided evidences in favor of this notion. It is therefore mandatory to characterize the composition, function, and stability of the gut microbiome in ESRD patients, prior to the initiation of clinical trials of interventions, including pre- or pro-biotics, to restore microbial symbiosis. A non-randomized, open label, crossover study is being planned by the NIDDK HDNT Consortium including a minimum of 10 patients receiving maintenance hemodialysis at 4 centers. The study protocol needs an intensive sampling of stool (1-2X/week) and blood(1X/week) during 3 phases including pre-treatment-8 weeks; treatment with p-inulin pre-biotic, 8 g 2X/day-12 weeks; and post-treatment-8 weeks. Besides, the composition of microbiome will be evaluated at the overall microbial diversity and individual taxon levels, and microbiome function will be assessed with metabolomic profiling and targeted metabolite measurements.

Additionally, a 16S rRNA gene sequencing, metabolomic studies, and analytical approaches are being piloted in a sub-set of samples collected at weeks 2 and 8 (phase 1) and weeks 14 and 20 (phase 2). Out of 10 patients followed for 143 pt-weeks thus far, have provided 152 of 154 (99%) blood samples and 157 of 161 (98%) stool samples, and have processed their stool samples generating 1564 of 1594 (98%) aliquots. The analytical approaches to high-dimensional, repeated measures data have been developed to assess within-person variability of microbiome composition and function, and effects of p-inulin on both parameters and the adherence to p-inulin as assessed by packet counts is reported to be 74% of the recommended dose.

It can be thus concluded that the feasibility of intensive stool and blood sample acquisition and the tolerability of p-inulin both seems to be adequate to generate data required to draw future clinical trials targeting the gut microbiome in ESRD.

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*End stage renal disease-associated inflammation and cardiovascular disease are the end results of alterations in the gut microbiome*

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## 20. Serum soluble α-klotho levels in maintenance of hemodialysis patients: Its clinical significance

Nakatani S, Ishimura E, Sakura M, Tateishi Y, Uedono H, Tsuda A, Usui N, Inaba M.

Patients with chronic kidney disease (CKD) have significantly reduced serum levels of soluble alpha-klotho (saKl). As renal functions deteriorate, its levels tend to decline progressively. The role of saKl in pathogenesis of cardiovascular diseases (CVD), diabetes mellitus (DM) and chronic kidney disease- mineral and bone disorder (CKD-MBD) in end-stage renal disease is not completely elucidated. In order to validate its role in pathogenesis of the above mentioned diseases, a study was conducted involving stable maintenance hemodialysis (HD) patients (n=188, 114 men and 74 women,  $66.5 \pm 11.1$  years, HD duration,  $101 \pm 90$  months).

The recently developed ELISA methods were used to measure the serum saKl levels.

The outcomes of the study were:

- The serum saKl levels in HD patients were  $445 \pm 158$  pg/ml, which was found to be lower than those of healthy Japanese subjects (740 pg/ml)
- Unlike some previously conducted studies that showed significantly correlations between saKl and CKD-BMD parameters, in present study the serum saKl levels did not show any significant correlations between any of these markers such as FGF23, intact PTH, phosphorus, calcium
- A comparison involving DM vs. non-DM, and with CVD histories vs. without CVD histories, serum saKl levels were not found to be significantly different (DM;  $447 \pm 170$  vs.  $444 \pm 148$  pg/ml,  $p=0.75$ , CVD;  $436 \pm 135$  vs.  $490 \pm 174$  pg/ml,  $p=0.61$ , respectively)
- However, in HD patients with DM and CVD histories ( $n=38$ ), a significant correlations between serum saKl and glycated albumin, a useful marker of glycemic control, plasma glucose, calcium and alkaline phosphatase were found
- The multiple regression analysis revealed that serum saKl levels showed significant, independent associations with glycated albumin ( $\beta=0.40$ ) and calcium ( $\beta=0.30$ ).

The study results unveiled the clinical significance of the measurement of serum saKl in HD patients with DM and CVD histories, that tend to reflect its parameters having anti-aging and/or anti-cachectic effects. saKl clinical significance on CKD-MBD may be smaller than its of anti-aging and/or anti-cachectic effects.

## **21. Worsening of the echocardiographic left atrial volume index in hemodialysis patients due to high ultrafiltration rate**

*Kim J, Choi S, Lee J, Kim S.*

Optimal fluid management is a prerequisite for hemodialysis patient. However, quick fluid removal and the resultant higher ultrafiltration rate (UFR) have adverse effects that lead to hemodynamic instability and cardiac injury. A study was conducted to evaluate the effects of the rapid UFR on the changes of echocardiographic left atrial volume index (LAVI) with time. The study comprised 124 patients who recently started hemodialysis. Echocardiography was performed at baseline and repeated 19.7 (11.3-23.1) months apart. Changes in LAVI per year ( $\Delta$ LAVI/yr, mL/m<sup>2</sup>/year) were calculated arithmetically, and the 75<sup>th</sup> percentile of the  $\Delta$ LAVI/yr distribution was regarded as a "significant" increment. UFR was expressed in terms of mL/hr/kg, and was used as a mean UFR over 30 days (approximately 12-13 treatment).

The outcomes of the study were:

- The study reported the mean inter-dialytic weight gain in study participants were  $1.88 \pm 0.94$  kg, and the UFR were  $8.01 \pm 3.87$  mL/h/kg
- The significant pathological increment point in  $\Delta$ LAVI/yr was 4.87 mL/1.73m<sup>2</sup>/yr. Correlation analysis revealed that  $\Delta$ LAVI/yr was closely associated with the baseline blood pressure (BP), hemoglobin level, residual renal function and UFR

- According to the ROC curve, the best cut-off of value of UFR for predicting the pathological increment was 10 mL/h/kg, with the area under the curve of 0.712
- According to the multivariate analysis, systolic BP, a history of coronary artery disease, hemoglobin <10 g/dL, and high UFR were significant predictors
- An increase of 1 mL/h/kg in the UFR was associated with 22% higher risk of deteriorating of the LAVI (odds ratio, 1.22; 95% confidence interval, 1.05–1.41)

Hence, in patient recently started on hemodialysis, a rapid UFR over 10 mL/h/kg may lead to maladaptive deterioration of the LAVI, a crucial predictor of long-term adverse outcomes.

## 22. Rectification of metabolic acidosis improves insulin resistance in chronic kidney disease

Bellasi A, Micco L, Lullo L, Cozzolino M, Di Iorio B, Landolfi P, Delfino O.

In chronic kidney disease patients, nutritional therapy or bicarbonate administration is widely used to correct metabolic acidosis (MA). However, it is still unclear that whether these interventions reduce insulin resistance (IR) in diabetic patients with CKD. A study was conducted to evaluate the effect of MA correction on endogenous insulin action in diabetic type 2 (DM2) CKD patients. The study comprised 145 CKD subjects (83 men and 62 women) with DM2 treated with oral antidiabetic drugs and completed 12 months follow up. All patients were randomly assigned 1:1 to either open-label as treatment group who were given oral bicarbonate to achieve serum bicarbonate levels of 24-28 mmol/L and as control group with no treatment. The Homeostatic model assessment (HOMA) index was employed to evaluate IR at study inception and conclusion. Parametric and non-parametric tests as well as linear regression were used.

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*In patients with chronic kidney disease, bicarbonate administration is widely used to correct metabolic acidosis*

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The outcomes of the study were:

- No differences in demographic and clinical characteristics between the 2 groups were observed at the baseline
- In treatment group, the average dose of bicarbonate was  $0.7 \pm 0.2$  mmol/kg
- Patients in the treatment group showed a better metabolic control as confirmed by lower insulin levels (13.4+5.2 vs 19.9+6.3; for treated and control subjects respectively), Homa-IR (5.9[5.0-7.0] vs 6.3[5.3-8.2]) and need for oral antidiabetic drugs
- The serum bicarbonate and HOMA-IR relationship was non-linear and the largest HOMA-IR reduction was noted for serum bicarbonate levels between 24-28 mmol/l
- After the adjustment for confounders, it was reported that serum bicarbonate rather than treatment has effect on HOMA-IR.

Serum bicarbonate is associated to IR and the greatest reduction in HOMA-IR is noted when serum bicarbonate is between 24-28 mmol/l. Bicarbonate treatment influences IR. However, alteration in the serum bicarbonate levels explains the effect of treatment on HOMA index. Future studies and clinical trials are warranted to validate these results in diabetic and non-diabetic CKD patients.

## Notes



AMERICAN SOCIETY OF NEPHROLOGY

# KIDNEY WEEK<sup>2016</sup>

Chicago, IL • Nov 15 - 20

A photograph of the Chicago skyline featuring the Willis Tower (formerly Sears Tower) and other skyscrapers, set against a blue sky with white clouds. The image is partially obscured by a large blue geometric shape in the foreground.

# FRIDAY

18<sup>th</sup> November, 2016

## 1. Aldosterone and vasopressin: Erythropoietic hormones

*Nonoguchi H, Izumi Y, Yasuoka Y, Nakayama Y, Nagai T, Nanami M, Nakanishi T, Mukoyama M, Kawahara K.*

Renal tubules produce erythropoietin (Epo) in response to hypoxia and/or anemia. A study was orchestrated to assess the effects of aldosterone and vasopressin on mRNA expression of Epo in distal nephron segments. The study involved 5-7 week-old experimental models whose tubule suspensions (TS) of cortex (CX), outer medulla (OM) and inner medulla (IM) were prepared. After the incubation of kidney slices in solution containing collagenase and vanilloid receptor (VR), microdissection of the nephron segments were done. Incubation of the TS or nephron segments with 109 M and 106 M aldosterone, vasopressin or vehicle for 2 hours at 37°C were also conducted. After the RNA extraction, real time polymerase chain reaction (PCR) was used to examine the expressions of GAPDH, Epo, EpoR, HIF2a, HIF1a, PHD2, mineralocorticoid receptor (MR), glucocorticoid receptor, EGFR, vasopressin V2 and V1a receptors (V2R and V1aR, respectively), GATA2 and GATA3 mRNAs.

The study results revealed that:

- Epo mRNA expression was discovered in TS of CX, OM and IM (CX=OM>IM) and was time-dependently decreased
- Aldosterone and vasopressin enhanced Epo mRNA expression in TS of CX and OM and vasopressin increased Epo mRNA in TS of IM
- In microdissected nephron segments, Epo mRNA was decreased with time. After 2-hour incubation with vehicle, Epo mRNA expression was not observed in CAL and MAL, while its expression was found at detectable level in the collecting ducts
- Aldosterone and vasopressin stimulated the expression of Epo mRNA in CAL, MAL, CCD, OMCD and IMCD
- Aldosterone and vasopressin stimulated mRNA expression of MR and V2R/V1aR, respectively
- Aldosterone and vasopressin stimulated the expression of Epo mRNA along with the increase of HIF2a, GATA 2 and GATA 3 mRNAs but not with HIF1a
- Aldosterone and vasopressin also stimulated EpoR mRNA expression.

In normal condition, distal nephron produces Epo. Aldosterone and vasopressin are erythropoietic hormones that are thought to be under the control of HIF2a and GATA2/3 pathways in the distal nephrons.

## 2. Decreasing CD127 expression on circulating CD8+T cells in patients with end-stage renal disease and its relation with resistance to erythropoiesis-stimulating agents

*Lio K, Ando Y.*

Interleukin 7(IL-7) is crucial for T cell homeostasis. In case of infection, IL-7 enhances CD8+T cell proliferation and cytolytic activity. Decreased CD127 (IL-7alphaR) expression on CD8+T

cells may cause loss of CD8+cytotoxic T lymphocyte activity and thereby cause increased susceptibility to infection. Resistance to erythropoiesis stimulating agents (ESAs) is linked increased incidence of with cardiovascular disease and mortality in end-stage renal disease (ESRD) patients. Immune disorders such as chronic inflammation are also involved. The given study compared the T cell phenotypes between 53 patients with stage 5 or 5D chronic kidney disease (CKD) and 16 control patients with stage 1 to 3A CKD. Furthermore, multivariate regression analysis was executed to detect the association between T cell phenotypes and the erythropoietin resistance index (ERI; mg/kg/Hb/week). Flow cytometric analysis was conducted to detect CD127- expressing CD8+T cells, CD3+T cells, CD4+ T cells, and CD8+T cells among the peripheral blood mononuclear cells.

The study reported decreased proportion of CD127-expressing CD8+ cells and the numbers of CD3+T cells and CD4+T cells in ESRD patients than in the controls. Based on multivariate linear regression analysis, the proportion of CD127hi CD8+ cells, but not the numbers of CD3+ cells or CD4+ cells, was associated with the ERI ( $\beta = -0.0006$ ).

A decreased proportion of CD127-expressing CD8+T cells and decreased numbers of CD3+T cells and CD4+T cells can be assumed as indicators of an ESRD-related immunological abnormality. Moreover, CD127 expression on CD8+T cells is associated with resistance to ESAs. Immunological alterations that increase susceptibility to infection can be due to the underlying resistance to ESAs.

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*Resistance to erythropoiesis-stimulating agents is linked with increased incidence of cardiovascular disease and mortality in patients with end-stage renal disease*

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### **3. Serum level of soluble Fas: An important predictor for the need of red blood cells transfusion in patients with chronic kidney disease**

Wallbach K, Silva L, Meniconi M, Dalboni M, Canziani M, Goes M.

Anemia in chronic kidney disease (CKD) cause inflammation, impaired erythropoietin (Epo) production, iron status, soluble Fas (sFas) and PTH levels. In cases of severe anemia, red blood cells (RBCs) transfusion might be harmful, and predicting it is often difficult. A prospective study involving 56 pre-dialysis patients for 144 months (Jan/2004-Dec/2015) was conducted. At the baseline, need for RBCs transfusion was the primary outcome. Serum sFas, IL-6, PTH, Epo level, EPI-CKD, Hb, Hct, iron status and use of rHuEPO were analyzed. Correlation between the variables and multivariate regression with Hb-dependent variable were executed on admission and binary logistic regression for RBCs transfusion was performed at the end of 144 months with sFas, EPI-CKD, transferrin saturation (Trs), IL-6 and Epo.

The outcomes of the study were:

- The population at baseline was 56+13 years, 65.5% (35) males; diabetes and hypertension were the important causes of kidney failure; Hb 12.5+2.3g/dL, Hct 37+7%, Trs 23+ 14%, ferritin 123+110ng/ml, EPI-CKD 34+14mL/min, sFas 3121+1249pg/ml, Epo 11+10pg/ml, IL-6 7.0 ± 6.4pg/mL, PTH 200 + 178pg/ml
- A positive correlation was found between Hb and EPI-CKD ( $r=0.35$ ;  $p=0.009$ ), Hb and Trs ( $r=0.14$ ;  $p=0.09$ ) and a negative correlation between Hb and sFas ( $r=-0.35$ ;  $p=0.008$ )

and Hb and PTH ( $r=-0.32$ ;  $p=0.03$ ). Independent association between Hb and sFas ( $b=-0.378$ ,  $p=0.02$ ) was found

- Four patients (7%) used rHuEPO and 8 (14%) required RBCs transfusion (3+1,5 units)
- RBCs transfusion group exhibit lower IL-6 (4.3+1.8, 7.4+6.8), EPI-CKD (22+9, 36+13) and Trs (18+7, 23+14;  $p=0.09$ ) but higher sFas (5067+1015,2797+960), Epo (15.8+13.4, 10.6+9.7) and PTH (313+277,189+170) levels
- After binary logistic regression it was reported that sFas levels were independently associated to RBC transfusion ( $b=1.001$  95% CI 1.000-1.001)

Serum sFas level is associated with anemia and is an independent predictor for the need of RBC transfusion in patients with CKD.

#### **4. Prevalence of anemia and treatment modalities used in patients with non-dialysis-dependent chronic kidney disease**

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*Serum sFas level is associated with anemia and is an independent predictor for the need of red blood cell transfusion in patients with chronic kidney disease*

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*St. Peter W, Guo H, Kabadi S, Zhao S, Gilbertson D, Heuer L, Peng Y, Pendergraft T, Li S.*

There is limited data available on the burden of anemia in stage 3-5 nondialysis-dependent chronic kidney disease (NDD-CKD) patients. A study was conducted to evaluated anemia prevalence, treatment patterns, and cardiovascular (CV) outcomes in adults with stage 3-5 NDD-CKD. The study procured the data from the Medicare and MarketScan® (commercial) claims records (10/1/2011 to 9/30/2012) to identify "older" (65+ yrs) and "younger" (18-64 yrs) CKD-NDD patients, respectively. In total, 148,550 (52%) older and 15,716 (28%) younger patients with anemia among stage 3-5 NDD-CKD patients in Medicare and MarketScan databases, respectively were identified. During the baseline year from 10/1/2011-09/30/2012, anemia status (defined by diagnosis codes), patient demographics, and comorbidities were ascertained. Anemia treatment patterns [erythropoiesis-stimulating agents (ESAs), intravenous (IV) iron, and red blood cell (RBC) transfusions] after baseline anemia diagnosis were assessed. CV outcomes were identified during the 1-yr follow-up period.

The study reported increased prevalence in anemia when CKD stage and age increased and was generally higher among women. The form of treatment (at least 1 administration) mostly used for anemia was RBC transfusions (22.2% older, 11.7% younger) followed by ESA (12.7% older, 10.8% younger) and IV iron (6.7% older, 9.4% younger). Increase in treatment across all modalities was seen with advancing CKD stage and age. Comorbidity burden and inflammatory conditions were more common in older patients relative to younger patients. As the stages of CKD increased, major adverse cardiac events and thromboembolic events (unadjusted) also showed a proportional rise and were more in patients with anemia compared to those without anemia.

The study concluded that approximately half of Medicare stage 3-5 NDD-CKD patients had anemia; RBC transfusion was a common resort used to treat anemia. Anemia treatment patterns varied in different age groups; older patients received twice as many RBC

transfusions as younger patients and were also more likely to receive treatment with ESAs. Moreover, investigation to assess the effects of anemia treatment patterns on CV outcomes is essential in this population.

## 5. Association between levels of phosphorus and hemoglobin in advanced stages of chronic kidney disease

Pecoits-Filho R, Tu C, Zepel L, Wong MMY, Pisoni RL, Port FK, Robinson BM, Massy Z, Tentori F.

Patients with advanced stages of chronic kidney disease (CKD) usually have high phosphorus (P) and low vitamin D levels, which are the characteristic presentations of mineral and bone disorder (MBD). Further, MBD is found to be associated with increased inflammation that may affect normal erythropoiesis. In this context, a study was conducted to better elucidate the relation between phosphorus and hemoglobin (Hb) levels using preliminary findings from the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps). In this prospective study, early data from CKDopps of CKD patients with eGFR <60 mL/min/1.73m<sup>2</sup> from national samples of nephrology clinics in Brazil, France, Germany, and US was evaluated. Linear mixed models were used to assess the effect of P on Hb, with different levels of adjustment for potential confounders and mechanistic variables.

Data of 5040 patients with mean age 69 years and median eGFR 28.8 mL/min/1.73m<sup>2</sup> was evaluated; 40% of them were female. The results revealed a positive association between eGFR and Hb, whereas an inverse association was found between eGFR and P. Further, higher levels of serum P exhibited a robust association with lower Hb even after adjustment for demographics, comorbidities, eGFR, labs, and vitamin D therapy. Findings from this multinational CKD cohort helped the researchers conclude that higher P was associated with lower Hb, independent of kidney function and other MBD markers/treatments. Further studies are warranted to explore the probable mechanisms for this association and may engender remarkable advances in the management of both anemia and MBD.

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*Higher phosphorus level was associated with lower hemoglobin level among patients with advanced stages of chronic kidney disease*

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## 6. Peroxisome proliferator-activated receptor signaling regulates nephrogenesis: A novel finding

Chambers JM, Poureetazadi SJ, Donahue E, Wingert RA.

The genetic and molecular mechanisms that regulate nephron segmentation during kidney development remain to be expounded. Embryonic zebrafish possess a primitive kidney, the pronephros, which contains proximal and distal segments, thus exhibiting conservation with mammalian nephrons, including humans. Using a novel chemical genetic screen, Chambers and colleagues discovered that peroxisome proliferator-activated receptor (PPAR) signaling is crucial for normal nephron segment development. PPARs are a group of nuclear receptor proteins that get activated by agonists such as fatty acids. PPARs undergo heterodimerization with retinoid X receptor (RXR) and act as transcription factors to regulate cell differentiation. In addition, these have various roles in metabolism. The

researchers observed that treatment with the PPAR agonist bezafibrate during nephrogenesis led to a reduced length of the distal tubule, whereas the proximal straight tubule domain increased. Importantly, the co-activator, ppargc1a, which binds to activated PPARs to regulate transcription of target genes, is expressed particularly in renal progenitors. The researchers, in an attempt to ascertain the functional role of this co-activator during nephron segmentation, knocked down ppargc1a and observed that deficiency reduced distal tubule formation. Further, it was observed during nephron development in ppargc1a<sup>-/-</sup> mutant experimental model that the distal tubule was similarly abrogated. Altogether, the present study reveals for the first time that PPAR activity is necessary for nephrogenesis. Further, PPARs have been shown to have renoprotective properties. Therefore, the findings of the present study may help in better acknowledgement of the therapeutic value of PPARs for the human kidney.

## **7. Appraising the effect of acute kidney injury on chronic kidney disease progression and proteinuria**

*Selby NM, Horne KL, Packington RA, Lee C, Reilly TT, Monaghan J, Kolhe NV, Fluck RJ, Taal MW.*

*Non-recovery of renal function is frequently observed at three months after acute kidney injury, even in a general hospital cohort with mostly AKI stage 1*

Studies are increasingly acknowledging the long-term sequelae of acute kidney injury (AKI) on renal function and mortality. However, prospective studies need to be conducted among common patient groups. In this context, Selby et al evaluated baseline data from a large case-control study of AKI in an undifferentiated hospitalized population; patients were selected using a hospital-wide electronic AKI detection system. Hospitalized patients who sustained AKI (cases) were matched 1:1 with hospitalized patients without AKI (controls) for age, baseline eGFR stage and diabetes. A total of 1125 patients were recruited; of them, 878 were successfully matched. Biochemical parameters including renal function and proteinuria were assessed three months post-AKI. CKD progression is defined as  $\geq 25\%$  reduction in eGFR with decline in eGFR stage.

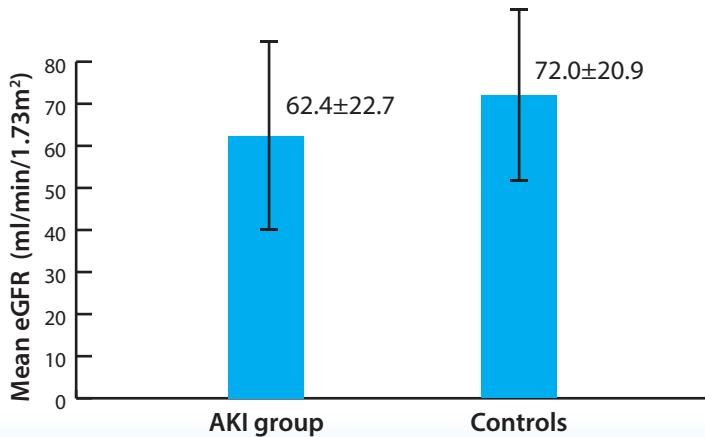
The results divulged the following:

- Cases and controls had no difference in age [70 yrs (interquartile range; IQR 14) versus 72 yrs (IQR 13),  $p=0.1$ ] or baseline CKD-EPI eGFR ( $69.0 \pm 21.6$  versus  $69.0 \pm 21.2$  ml/min/1.73m<sup>2</sup>,  $p=1.0$ ).
- AKI episodes were mostly stage 1 with median duration 3 days (IQR 2.5).
- Mean eGFR at three months was lower in the AKI group than controls:  $62.4 \pm 22.7$  versus  $72.0 \pm 20.9$  ml/min/1.73m<sup>2</sup>,  $p<0.001$  (Figure 1).
- CKD progression was observed in 84 cases (19%), compared to only 15 controls (3%).
- Albuminuria (albumin-to-creatinine ratio; ACR $\geq 3$  mg/mmol) was more frequent in the AKI group; 184 (42%) cases had albuminuria compared to 109 (25%) controls,  $p<0.001$ .
- Median ACR in the AKI group and the controls were 1.9 (IQR 10.3) mg/mmol and 0.9 (IQR 3.0) mg/mmol, respectively.

The researchers concluded that non-recovery of renal function is frequently observed at three months post-AKI, even in a general hospital cohort with mostly AKI stage 1. Albuminuria

is also a common observation after AKI; however, it is presently uncertain whether this suggests renal parenchymal injury at time of AKI or a pre-existing risk factor. Therefore, long-term follow-up is warranted that aim to develop strategies to better stratify individual risk.

**Figure 1: Lower value of mean eGFR at three months in acute kidney injury (AKI) group compared to controls**



## 8. Appraising the prevalence of hyponatremia in patients on hemodialysis and its association with mortality

Brenneis RA, Visscher DR, Braam B.

Hyponatremia is frequently observed in many patient groups and has been associated with increased mortality and adverse outcomes. Studies, although very few, suggest a high prevalence of hyponatremia in patients on hemodialysis (HD); however, information regarding the outcomes is scarce. Brenneis and colleagues conducted a study based on the premise that both persistent and episodic hyponatremia in patients on HD is prevalent and associated with increased mortality. A total of 2473 patients on in-center HD were evaluated for hyponatremia ( $\text{Na} < 135 \text{ mmol/L}$ ) using monthly plasma Na over a median of 4.6 years. Prevalence of 10 patterns was assessed: persistent hyponatremia, and combining episodic low (1-3 episodes), medium (4-7 episodes) or high ( $\geq 8$  episodes) frequency with short (1-2 months), medium ( $>2\text{-}\leq 4$  months) and long duration ( $>4$  months). Mortality was evaluated for persistent and episodic hyponatremia compared to normonatremia. Thirty-four percent of the patients had normal sodium (no hyponatremia), 1% had stable hyponatremia and 65% had an episodic sodium pattern. It was observed that both persistent hyponatremia, and average and long duration, low and medium frequency were associated with reduced survival compared to patients without hyponatremia. Further, high frequency hyponatremia episodes were not predictive of mortality compared to normonatremia. Findings in the present cohort of patients on HD are suggestive of a high prevalence of episodic hyponatremia. This indicates that a cross-sectional analysis of hyponatremia underestimates the prevalence. In addition, average and long duration with low and medium frequency hyponatremia is associated with increased mortality rate.

*Episodic hyponatremia is highly prevalent among patients on hemodialysis. Average and long duration with low and medium frequency hyponatremia is associated with increased mortality rate*

## 9. Effect of the long interdialytic interval on serum potassium and clinical outcomes among patients on hemodialysis

Brunelli SM, Du Mond C, Oestreicher N, Rakov V, Spiegel DM.

Hyperkalemia among patients on hemodialysis (HD) is found to be associated with morbidity and mortality. Patients who undergo HD thrice-weekly experience increased adverse outcomes after the 2-day interdialytic interval. In this context, a study was conducted to appraise the independent association between serum potassium (K) level and outcomes among patients on HD. It also aimed to evaluate how these associations were affected by day of week.

This retrospective study included patient-interval data, defined as a routine K measurement made among adult patients receiving in-center HD on Monday/Wednesday/Friday (Mon/Wed/Fri) at a US dialysis centre. Hospitalizations, deaths, and emergency department (ED) visits were the outcomes considered over the day of K measurement and the next 3 days. The results revealed an association between high serum K and hospitalization risk on all days. However, the association was the most remarkable on Fri ( $P$ -interaction=0.008). Adjusted odds ratios (OR) for serum K level,  $K5.5 < 6$ ,  $6 < 6.5$ ,  $6.5 < 7$ ,  $\geq 7$  (reference range:  $4 < 4.5$  mEq/L) were respectively: 1.68, 1.63, 2.19 and 3.51 on Fri; 1.04 ( $P=0.43$ ), 1.37, 1.91 and 2.09 on Wed; and 1.12, 1.22, 1.70, 2.78 on Mon. Further, high serum K level was remarkably associated with death and ED visit, although it did not differ by day of week. Adjusted ORs for K  $6 < 6.5$ ,  $6.5 < 7$ ,  $\geq 7$  were 1.52, 2.42, 3.37 for death, and 1.19, 1.48, 2.62 for visits to the ED. It was concluded that higher serum level of potassium is associated with increased risk of hospitalization, death, and ED visit. The finding that effect on hospitalization is altered by day of week, suggests an increased burden of high K over the long interdialytic interval. Further studies are warranted to ascertain whether directed intervention assuages this risk.

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**Higher serum level of potassium is associated with increased risk of hospitalization, death, and emergency department visit**

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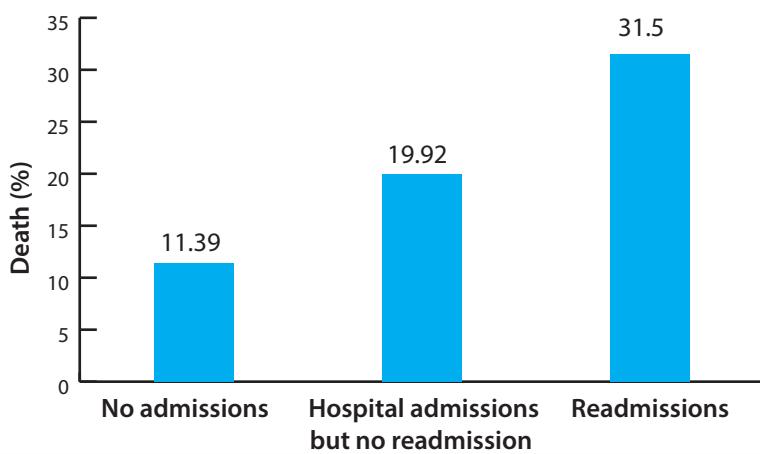
## 10. Association between readmission in the first year of dialysis and long-term outcomes among patients on hemodialysis

Jaar BG, Patzer RE, Lea JP, Plantinga L.

Patients on hemodialysis (HD) are frequently readmitted, that may be predictive of poor outcomes. Jaar and colleagues assessed long-term outcomes among patients on in-center HD readmitted in their first year of treatment. A total of 275,475 incident patients who were initiated on HD between September 2005 and September 2009 and remained on HD alive for at least 12 months were categorized as having no admissions, admissions but no readmission (within 30 days), and 30-day readmissions in the 90-365 days after HD initiation. Outcomes (mortality, transplantation, and hospitalizations) were evaluated between 366 and 730 days. Hazard ratios (HRs) and incidence rate ratios (IRRs) were estimated by multivariable Cox proportional hazards and Poisson models. The results divulged the following:

- In the first 90-365 days of HD, a total of 15.8%, 25.0%, and 59.1% of patients had readmissions, hospital admissions but no readmission, and no admissions, respectively.
- Patients with readmissions in year one had increased odds of death and hospitalization, and a lower probability of transplantation in their year two of HD, compared to their counterparts with no readmission or no admission (Figure 1).
- Further, adjusting for age, sex, race/ethnicity and comorbid conditions, it was found that the likelihood of poor outcomes in year two was more among patients with readmissions and with admissions but no readmission, compared to those without admission in year one: mortality, HR=2.84 (95% CI, 2.77-2.90) and 1.61 (95% CI, 1.51-1.65); and hospital admissions, IRR=5.02 (95% CI, 4.97-5.06) and 2.66 (95% CI, 2.64-2.68), respectively.

**Figure 1: Increased probability of death in 2<sup>nd</sup> year of hemodialysis among patients with readmissions in year 1**



*The likelihood of poor outcomes in year 2 was more among patients with readmissions and those with admissions but no readmission, compared to those without admission in year 1*

The researchers concluded that having hospital readmissions (within 30 days) early in the course of HD, even beyond having hospital admissions alone, is highly indicative of poor long-term subsequent outcomes, including death, not being transplanted, and further hospitalizations.

## 11. Impact of hemoglobin level on outcomes in advanced chronic kidney disease: A transition care analysis

Soohoo M, Streja E, Sim JJ, Rhee C, Nguyen DV, Kovesdy CP, Kalantar-Zadeh K.

Anemia is frequently encountered in patients with advanced chronic kidney disease (CKD). Several studies have confirmed a detrimental impact of high and low hemoglobin levels in dialysis and non-dialysis dependent CKD patients. The association between hemoglobin levels in predialysis period and early post-dialysis hospitalization periods is uncertain.

The study initially scanned the information of 85,505 US veterans with CKD who progressed to receive dialysis between 2007 and 2014. A total of 31,303 individuals with record of prior to transition hemoglobin levels (6 months) were enrolled in the study. Poisson models adjusted for demographics, comorbidities and laboratory covariate was used to evaluate the potential of hemoglobin as a categorical predictor of hospitalization within the first 6 months after shift to dialysis.

The mean age of the recruited group was 68 years. Among those enrolled, 30% were African-American and 8% were Hispanic. Diabetes was presumed to be the primary cause of end-stage renal disease in 48% of patients. The mean $\pm$ SD hemoglobin level was recorded to be  $10.7\pm1.6$  g/dL. A higher rate of hospitalization subsequent to transition was observed in patients with hemoglobin  $\leq 10$  g/dL compared to patients with hemoglobin 11 to  $<12$  g/dL, after post-adjustments across all levels.

Based on the above mentioned findings, it may be inferred that among individuals transitioning to dialysis, low hemoglobin levels prior to ESRD may be related with high rate of hospitalization.

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*Low hemoglobin  
level prior to end-  
stage renal disease is  
associated with high  
hospitalization rate  
post-transition to  
dialysis*

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AMERICAN SOCIETY OF NEPHROLOGY

# KIDNEY WEEK<sup>2016</sup>

Chicago, IL • Nov 15 - 20

A photograph of the Chicago skyline featuring the Willis Tower (formerly Sears Tower) and other skyscrapers against a blue sky with white clouds. The image is partially obscured by a large blue geometric shape in the foreground.

# SATURDAY

19<sup>th</sup> November, 2016

## **1. Anemia management in CKD: A comparison of subcutaneous and intravenous erythropoietin**

*Gul A, Schrader R, Miskulin D, Paine S, Harford A, Zager P.*

Erythropoietin (EPO) is commonly used for anemia management in end-stage renal disease. Numerous healthcare providers switched their patients from intravenous to subcutaneous EPO in due course of time. This may be attributable to high risk of composite death or cardiovascular disease hospitalization and need for high therapeutic doses with intravenous EPO. The study compared the potential advantages of subcutaneous EPO over intravenous EPO.

This retrospective study enrolled 24,957 hemodialysis patients treated from 2011 to 2014. Subcutaneous EPO was administered once whereas intravenous EPO was administered thrice weekly. Mean weekly EPO doses and related hemoglobin levels were derived using linear mixed model. Cox models with time varying covariates to adjust for age, vintage, race, sex, BMI, albumin and hemoglobin was used to evaluate the association of intravenous and subcutaneous EPO with hospitalization and mortality.

It was noted, that from 2011 to 2014, there was an increasing trend towards use of subcutaneous EPO (41% in 2011 to 69% in 2014). For set target hemoglobin, SC and IV mean weekly EPO doses did not differ significantly. Regardless of the route of EPO administration, high doses were associated with increased risk of hospitalization and mortality.

It was thus concluded that mean weekly doses, and the risks for hospitalization and mortality were similar for intravenous and subcutaneous EPO administration.

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*The risks for hospitalization and mortality were similar for intravenous and subcutaneous erythropoietin*

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## **2. Renoprotection with erythropoiesis-stimulating agents in chronic glomerulonephritis: Role of hemoglobin levels**

*Kawasaki R, Tashiro Y, Aizawa K, Shimonaka Y, Hirata M.*

Renoprotective properties of erythropoiesis-stimulating agents (ESAs) have been highlighted in several kidney disease models. Previous studies have shown that in chronic glomerulonephritis, a single injection of epoetin beta pegol (continuous erythropoietin receptor activator; C.E.R.A.) may offer profound renoprotection compared to single injection of epoetin beta (EPO). The findings also reflected that hemoglobin levels attained with C.E.R.A were higher than those achieved with EPO. The present study examined the role of increasing hemoglobin levels due to ESA in ameliorating renal injury in models of chronic glomerulonephritis. Renal function was determined by measuring 24-hour urinary total protein (uTP) and 24-hour liver-fatty acid-binding protein (L-FABP) levels at day 67. Hemoglobin levels and EPO levels in blood were measured at day 9.

It was observed that hemoglobin levels at day 9 were appreciably higher in the group treated with EPO compared to control;  $15.5 \pm 0.1$  vs.  $12.9 \pm 0.1$  g/dL, respectively. However, plasma EPO was not detected in either of the groups at that time. On day 67, the uTP and L-FABP levels were remarkably lower in EPO-treated chronic glomerulonephritis group compared to control group.

Based on the findings of the study, it was inferred that increase in hemoglobin levels due to ESA could arrest the progression of renal injury in chronic glomerulonephritis.

### **3. Pharmacological assessment of C.E.R.A in adults and children with chronic kidney disease**

*Chanu P, Frey N.*

The pharmacological properties of therapeutic agents may differ according to age. In this context, a study was conducted to evaluate the population pharmacokinetic/pharmacodynamic (PK/PD) properties of Continuous Erythropoietin Receptor Activator - Methoxy Polyethylene Glycol-Epoetin Beta (C.E.R.A) in adults and children with anemia of chronic kidney disease (CKD) and on hemodialysis.

From a 20-week open-label Phase II study of intravenous (IV) C.E.R.A. in patients aged 6–17 years on HD with stable chronic renal anemia, serum C.E.R.A. concentrations and hemoglobin (Hb) levels were collected. In addition, information collected during the clinical development of C.E.R.A. in adult patients with CKD was also pooled. PK/PD structural models previously developed for adults were used in the analyses.

The information for pediatric PK/PD characteristics was derived from 63 patients with 676 C.E.R.A. serum values and 1580 hemoglobin levels. The information for adult PK/PD characteristics was obtained from 524 patients with 5883 C.E.R.A. serum values and 12786 hemoglobin levels. The data in children was adequately described by the adult model used. As predetermined in adults, C.E.R.A clearance increased with body weight and the volume of distribution also increase with weight and age. After adjusting for these covariates, no PK variations were observed in adults and children.

The drug dependent parameters were equivalent in children and adults implying that the C.E.R.A. exposure-response relationship is alike in adults and children. In absence of erythropoietin-stimulating agent, the baseline hemoglobin increased with increasing body weight. The results co-related with those observed in adults. Intravenous and subcutaneous formulations had similar PK/PD characteristics. The PK/PD parameters showed no difference in different types of dialysis.

It was concluded that there are no differences in PK/PD characteristics of C.E.R.A. in adults and children with CKD.

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*The pharmacokinetic/pharmacodynamic characteristics of continuous erythropoietin receptor activator are similar in adults and children with chronic kidney disease*

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#### **4. Effectiveness of C.E.R.A in management of renal anemia before and after initiation of peritoneal dialysis**

*Fujimoto D, Adachi M, Nakayama Y, Inoue H, Kakizoe Y, Kuwabara T, Izumi Y, Mizumoto T, Mukoyama M.*

Information pertaining to management of renal anemia with Continuous Erythropoietin Receptor Activator (C.E.R.A) during pre- and post- peritoneal dialysis (PD) period is scarce. The present study evaluated the efficacy and dosage of C.E.R.A in ESRD patients before and after the initiation of PD.

A group of 16 patients initiated with PD were recruited in the study. The following parameters were measured: hemoglobin (Hb) levels, iron parameters (transferrin saturation and ferritin), C.E.R.A dosage, and erythropoietin resistance index (ERI) (C.E.R.A amount  $\mu\text{g}/\text{body weight kg/Hb (g/dL)/4}$ ) for 24 weeks before and after initiation of PD.

The outcomes of the study were:

- The Hb levels increased remarkable after initiation of PD; mean Hb levels 24 weeks before PD: 10.4 g/dL, at PD initiation: 10.2 g/dL, and 4 weeks after PD initiation: 11.7 g/dL
- After PD initiation the rate of patients with Hb  $\geq 11$  g/dL increased from 40% to 81.2%
- The mean C.E.R.A dosages were 73.3  $\mu\text{g}/\text{month}$ , 87.5  $\mu\text{g}/\text{month}$  and, 71.9  $\mu\text{g}/\text{month}$  at 24 weeks prior to PD initiation, at initiation, and at 4 weeks after PD, respectively. These results reflected that C.E.R.A dosage increased just before PD initiation and decreased subsequent to PD.
- In patients without diabetes, C.E.R.A dosage to maintain Hb levels decreased subsequent to PD initiation by almost 25% in comparison to prior to PD initiation. Conversely, the dosage did not alter after PD initiation in individuals with diabetes.
- ERI was 0.027, 0.036 and 0.026 at 8 weeks prior to PD initiation, at initiation, and at 8 weeks after PD, respectively. The results showed that ERI had the tendency to increase just before initiation and decreased significantly after PD.
- No significant changes in TSAT or ferritin levels were observed implying relatively stable iron metabolism with CERA treatment during PD initiation.

It was thus concluded that C.E.R.A prior to PD initiation was effective for management of renal anemia in patients with or without diabetes. Moreover, the C.E.R.A dosage may be reduced after initiation of PD in patients without diabetes.

#### **5. Novel biomarkers of iron metabolism in hemodialysis: A focus on non-transferrin bound iron**

*Saito N, Miyazaki S, Saito K, Morioka T, Shimada H, Ikarashi K, Tsubata Y, Yoshita K, Kohgo Y.*

Non-transferrin bound iron (NTBI) is related with organ damage due to its oxidative potential. It appears in the serum under iron overload. It is also noteworthy that intravenous

(IV) iron administration which is a common treatment for management of renal anemia in hemodialysis patients promotes the production of NTBI.

A group of 44 hemodialysis patient who did not receive iron or Erythropoiesis-Stimulating agents (ESA) for at least 2 months and 30 healthy volunteers were recruited in the study. The following parameters were observed; NTBI, Hepcidin25, soluble Tf receptor (sTfR), 8-oxo-2'-dehydroguanosine, high sensitive CRP, serum iron, TSAT and ferritin. Of the patients recruited, 23 patients in the hemodialysis group without iron load for 2 weeks were administered saccharated ferric oxide (Fe 40 mg) intravenously after hemodialysis session. A total of 19 patients received ESA. The NTBI and all other parameters were measured before and at 0.5, 1, 2, 4, 6, 20, 44 hours after IV iron administration.

The results showed that NTBI levels were higher in hemodialysis patients compared to controls. In hemodialysis group, NTBI correlated with TfT. Before IV iron administration, TSAT was 20% which increased to 81% at 0.5 hours. It gradually decreased to baseline levels after 44 hours of intravenous iron administration. The NTBI was 1.5 mg/dL before intravenous iron administration; it increased to 2.2 mg/dL at 4 hours and decreased to 1.8 mg/dL at 44 hours. The stepwise analysis showed that sTfR before IV iron administration was a negative predictor for NTBI.

It was thus inferred that there is an increase in NTBI levels in hemodialysis patients. These levels correlate with Tf and consistently increase after IV iron administration. Furthermore, sTfR was predictor of NTBI maximum increase rate. Therefore, iron metabolism in hemodialysis could be effectively predicted with NTBI, and NTBI could be a potential biomarker in this context.

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*Non-transferrin bound  
iron could be a novel  
marker to assess  
iron metabolism in  
hemodialysis patients*

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## 6. Ultrapure dialysate: Potential predictor of erythropoietin response in hemodialysis patients

Low CL, Yon CK, Chang M.

Chronic inflammation is an important contributor to erythropoietin (EPO) resistance in hemodialysis patients. In this regards, cytokines such as IL-6 and TNF- $\alpha$  have been shown to inhibit response to EPO. The proinflammatory milieu may be triggered due to endotoxins present in the dialysate. The AAMI recommends that endotoxin levels should not exceed 0.50 unit/ml in the dialysate. Consistently, preliminary examination has revealed that ultrapure dialysate may be associated with less resistance to EPO and decreased EPO requirement in hemodialysis patients owing to low endotoxin content, usually <0.03 unit/ml. The present study was conducted to analyze the impact of ultrapure dialysate on EPO response in hemodialysis patients. The study recruited at least 18 years old clinically stable individuals undergoing hemodialysis and receiving standard end stage renal disease care for minimum 3 months before enrollment. Patients with acute or chronic infections, chronic inflammatory disease, bleeding disorders and newly diagnosed malignancies were not included in the trial. Intra- and inter-individual changes in EPO response were estimated with Erythropoietin Resistance Index (ERI). Changes in CRP levels, EPO dose, and ERI were measured.

It was shown that there was no remarkable variation in all outcomes after installation of ultrafilters with ultrapure dialysate compared to baseline. The CRP levels estimated were  $1.57 \pm 2.56$  mg/L at baseline and  $1.68 \pm 2.05$  mg/L after installation. The weekly EPO dose and ERI remained almost similar after installation of ultrafilter.

The findings of this study thus show that reducing endotoxin levels beyond 0.01 unit/ml may not affect EPO responsiveness in hemodialysis patients.

## 7. Effect of dialysis adherence on anemia treatment

Nayak VS, Hamiduzzaman K, Gaweda AE, Brier ME.

A dearth of recent evidence exists on the impact of patient's dialysis adherence on the management of anemia. It was hypothesized by the researchers that nonadherence to dialysis can result in a significant reduction in the levels of hemoglobin (Hb) achieved. A retrospective analysis was performed by collecting data from the University of Louisville dialysis facility for the years 2004 to 2015. A total of 516 patients were analyzed, with a minimum of 90 schedule treatments during the calendar year. Patient adherence was recorded and treatment was marked as complete if erythropoietin and/or iron was given. The percentage of completed treatments, total Erythropoiesis-Stimulating Agent (ESA) and iron administered, the yearly mean run time, ultrafiltration, Hb, T sat, and ferritin achieved were evaluated. The doses of ESA and iron were adjusted by dry weight and reported as weekly dose. Decision tree classification technique was used for statistical analysis and the results are shown in table 1. The analysis resulted in 26 decision points (nodes), with 7 nodes related to ESA dose and mean Hb for that node. In nodes 1,4,5,6, and 7 ferritin significantly added 11 further nodes and is shown as a single break point or range with the corresponding mean Hb for that node. In nodes 4 and 6 adherence significantly added 8 additional nodes. All p values were  $< 0.012$ . It was concluded by the analysts that an adherence of less than 92% to 95% resulted in a remarkable decrease in Hb ranging from 0.4 to 0.6 mg/dl and higher ferritin resulted in lower Hb ranging from 0.5 to 1.1 mg/dl.

*An adherence of less than 92% to 95% resulted in a remarkable decrease in hemoglobin ranging from 0.4 to 0.6 mg/dl*

**Table 1: Results of the decision tree analysis**

Nodes	Population mean hemoglobin $11.4 \pm 1.3$						
	1	2	3	4	5	6	7
ESA U/ week/kg	0	0 to 1.5	1.5 to 3.3	3.3 to 11.3	11.3 to 15.3	15.3 to 35.1	$>35.1$
Hb g/dl	13.1	11.5	10.9	11.0	11.2	11.4	11.0
Ferritin ng/ ml (nodes 8-18)	$<523, >523$			$<737, 737-1149, >1149$	$<977, >977$	$<1148, >1148$	$<849, >849$
Hb g/dl	13.6, 12.5			11.4, 10.9, 10.6	11.4, 10.8	11.6, 10.7	11.2, 10.7
% Adherance (nodes 19-26)				( $<737$ ) 95%   ( $737-1149$ ) 96%   ( $>1149$ ) 95%		( $<1148$ ) 92%	
Hb g/dl				11.2, 11.6   10.6, 11.2   10.3, 10.9		11.3, 11.8	

## 8. Effectiveness of biosimilar ESA: Outcomes of monitor-CKD 5 study

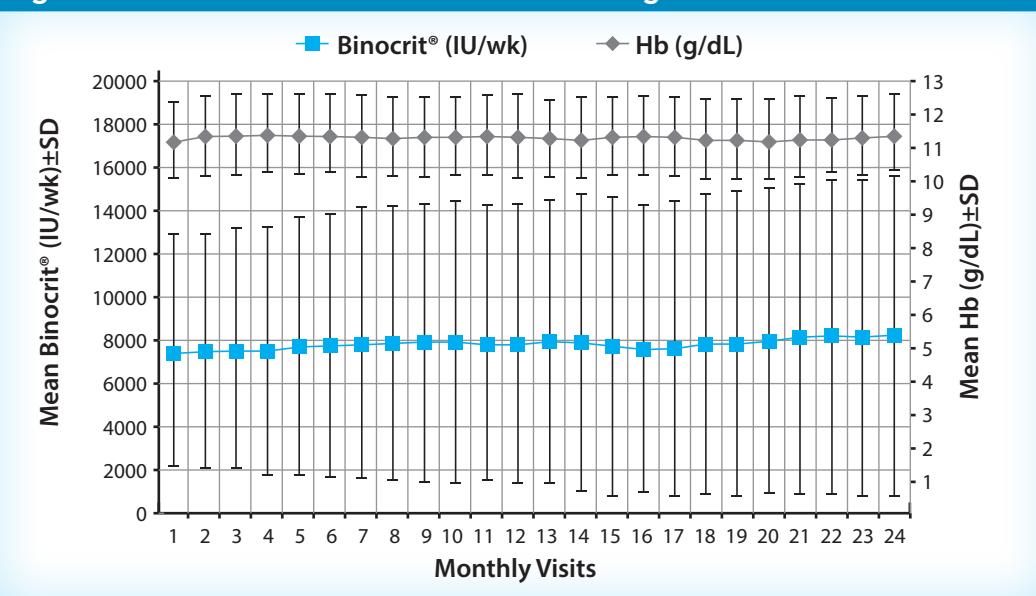
Mann JF, Gerard M, Combe C, Goldsmith D, Zaoui P, Dellanna F, Gorray M, Hoebel N, Macdonald K, Abraham I, Alexander F.

Longitudinal evidence on the use of biosimilar erythropoiesis-stimulating agents (ESAs) on real-world is growing. A European study; MONITOR-CKD 5 evaluated long-term safety and effectiveness of biosimilar epoetin α (Binocrit®) on hemodialysis (HD) patients. The 2-year long prospective study enrolled 2023 patients from 10 European countries, with renal anemia on HD. Patients were treated with Binocrit® and its dosing and hemoglobin (Hb) outcomes were evaluated. The key points of the study were:

- The mean $\pm$ SD age was  $64.8\pm14.95$ y; 59.3% were male, mean time on HD was  $3.8\pm4.6$ y, and nearly 82.5% patients had received ESA previously
- The cause of CKD among the study group was; diabetic nephropathy (25.4%), chronic glomerulonephritis (20.4%), renal vascular disease (16.4%)
- Initially 73.0% had adequate iron stores while 22.2% had functional and 4.8% absolute deficiency
- The mean serum ferritin ranged from  $466\pm320$  to  $581\pm434$ ng/mL, over 2 years
- Supplemental iron was administered to 59.7-67.5% of patients and transfusion to 0.3-1.2% of patients
- Baseline Hb was  $11.1\pm1.1$ g/dL, with 68% between 10-12g/dL
- Mean weekly Binocrit® dose at baseline was  $106.5\pm78.7$  IU/kg
- Mean Hb and Binocrit® dose remained stable over 24 months (Figure 1).

*Biosimilar epoetin α (Binocrit®) maintains stable hemoglobin over 24 months in patients on hemodialysis*

Figure 1: Mean Binocrit® doses with mean hemoglobin outcomes in 24 months



The study presents first 24 months outcomes of the effectiveness of Binocrit® on HD patients. It was inferred from the study that Binocrit® maintains stable Hb over 24 months, consistent with originator.

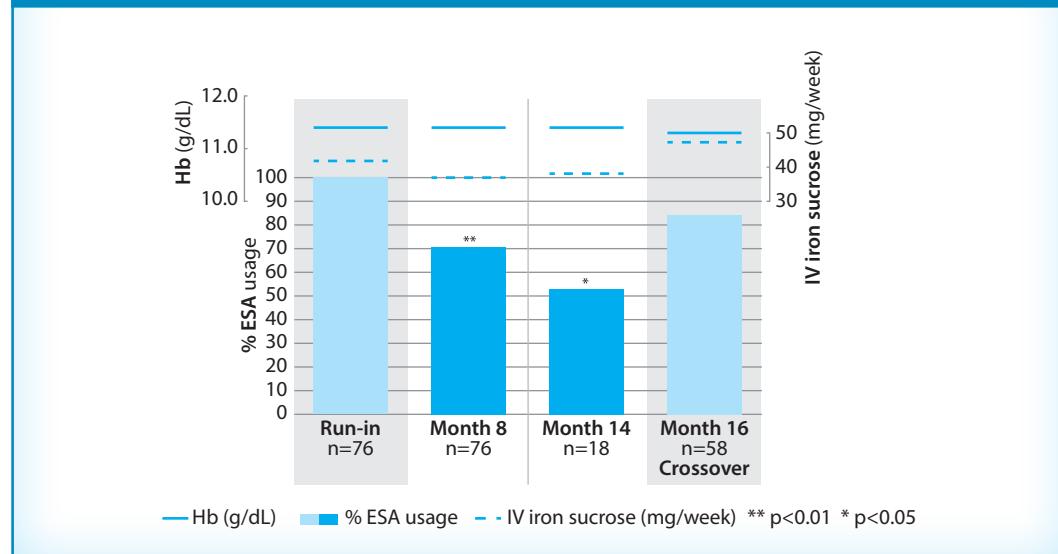
## **9. Novel bloodline technique for improving anemia therapy in hemodialysis patients**

*Macdougall IC, Sousa A, Ryzlewicz T, Becker FF, Beech AF, Kilgallon W.*

A reduced red blood cell survival is seen in the patient on hemodialysis (HD) that can be due to hemolysis associated with uremia and due the HD procedure itself. The blood-air contact in the extra-corporeal circuit adds to the same. Oxyless is a novel bloodline that can reduce blood-air contact by 99.1%, which may further reduce the dose of Erythropoiesis-Stimulating Agent (ESA) in HD patients. In an open label prospective analysis following a 3 month run-in period, 142 patients; aged >18 years, HD > 3 months via an A-V fistula were selected for treatment with Oxyless bloodlines, in two cohorts. After 8 months, cohort 1 (109 patients) was returned to the control bloodlines in the crossover phase for a further 8 months. Cohort 2 (33 patients) continued with Oxyless bloodlines for 14 months without crossover.

**Study supports the validity of oxyless bloodline in optimizing anemia management, the mean ESA dose reduced by 34% after 8 months and by 14 months it further reduced to 53%**

**Figure 1: Variation in ESA usage, IV iron dose and hemoglobin levels with time in HD patients on oxyless bloodline**



The study divulged the following:

- The mean ESA dose reduced by 34% after 8 months and by 14 months it further reduced to 53%
- The IV iron dose reduced by 12% after 8 months and by 14 months it fell by 25%, compared to baseline

- The hemoglobin (Hb) levels remained stable throughout at 11.5 g/dL
- For cohort 1 ESA doses increased to 82% of their baseline levels, Hb levels were 11.3 g/dL, while the iron dose returned to 120% of pre-treatment level after 16 months (Figure 1)
- At Month 8, patients of shorter dialysis period showed a greater reduction in ESA usage (n=45, <4 years, -47%) compared with patients of longer period (n=31, 4-17 years, -16%), irrespective of their diabetic status.

Above results support the validity of oxyless bloodline in optimizing anemia management, and suggests clinical and economic advantage of this technology.

## 10. Effect of altitude on continuous erythropoietin receptor activator (C.E.R.A.) dose in chronic kidney disease patients

Suarez MG, Wong AC, Aviles RA, Buenrostro LEM, Quintana FE, Pardo SA, Garcia MA, Anaya OC.

Anemia is a common complication of chronic kidney disease (CKD) and is associated with increased mortality worldwide. Iron and erythropoiesis-stimulating agents (ESAs) are frequently used for these patients on Hemodialysis (HD). It has been observed that HD patients living at higher altitudes have higher Hb levels and lower ESA requirements than others. The long half-life, low binding affinity, and low systemic clearance of Continuous Erythropoietin Receptor Activator (C.E.R.A.) permit once a month dose. The multicenter Phase IV ALTITUDE trial was performed to determine the required C.E.R.A. dose to achieve hemoglobin (Hb) level of 11–12 g/dL in ESA-inexperienced, CKD patients living at either <50m above sea level (masl) or ≥1800masl. C.E.R.A. was administered to 86 patients with stage III–V CKD divided in two groups (29 patients with altitude <50masl and 57 ≥1800masl). Among these 86 patients, 34 were pre-dialysis and 52 on HD. The mean age of the patients was 56 yrs; 44% were male, and etiology of CKD was diabetes in 57 pts and hypertension in 28. The iron profile was normal in all the patients. For the two groups; <50masl and ≥1800masl, the mean Hb values were 9.4 and 9.0 g/dL and mean C.E.R.A. doses were 71 and 52.2 µg, at the baseline, respectively. Out of the total 86 patients, 66 successfully completed the study and 64 reached the target Hb level, with mean C.E.R.A. doses of 160.5 and 70.0 µg in the <50 and ≥1800 masl groups, respectively (Table 1). The significant difference between groups was majorly affected by the HD population. Thereby, it can be concluded that lower C.E.R.A. doses are needed to normalize the Hb levels in CKD patients living at higher altitudes than those at sea level.

*Lower continuous erythropoietin receptor activator doses are needed to normalize the hemoglobin levels in patients with chronic kidney disease living at higher altitudes than those living at sea level*

**Table 1: Comparison of required C.E.R.A. dose in two groups showing effect of altitude**

		C.E.R.A. dose required (µg)			
Altitude	Patients	Mean	SD	Median	Range
<50masl	22	160.5	107.7	150	50-442
≥1800masl	42	70.0	33.9	59	30-175

## 11. Study on prevalence and dosing patterns of erythropoiesis stimulating agents: DOPPS- 5

Fuller DS, Robinson BM, Bikbov B, Locatelli F, Pisoni RL.

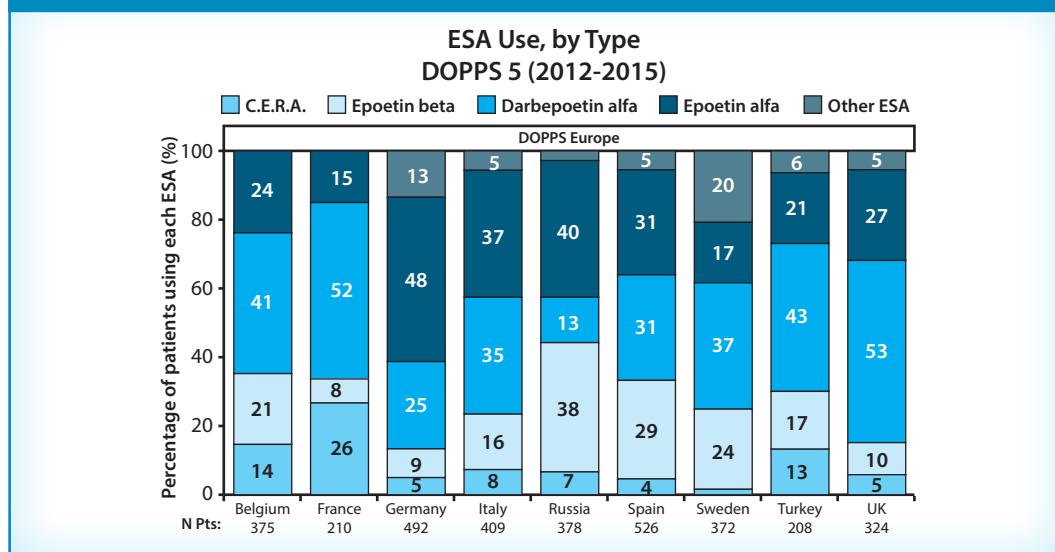
Erythropoiesis stimulating agent (ESA) alternatives to epoetin alfa (EA), which are in use in different countries, are methoxy polyethylene glycol-epoetin beta [continuous erythropoietin receptor activator (C.E.R.A.)], darbepoetin alfa (DA), and epoetin beta (EB). Dialysis Outcomes and Practice Patterns Study (DOPPS) phase 5 conducted on 4230 patients in 167 facilities from 9 countries (Belgium, France, Germany, Italy, Russia, Spain, Sweden, Turkey, and UK) between the years 2012 and 2015. The prevalence and dosing patterns for C.E.R.A., DA, EB, and EA were evaluated, using weighted analyses.

Results obtained from the study were:

- The overall prevalence was 8%, 35%, 19%, and 31% for C.E.R.A., DA, EB, and EA, respectively
- The percentage of facilities using C.E.R.A. ranged from 20% (UK) to 58% (France); for DA: 30% (Russia) to 87% (Turkey) for EB: 15% (UK) to 53% (Italy/Turkey); for EA: 17% (France) to 86% (Ger) [Figure 1]
- In facilities using C.E.R.A., median % ESA-treated patients using C.E.R.A. was 13% [IQR=6-38%, mean=28%]; for DA: 43% [IQR=17-85%, mean=49%]; for EB: 33% [IQR=15-90%, mean=47%]; for EA: 48% [IQR=26-89%, mean=54%]
- Frequencies for C.E.R.A. dosing were: 1x/mo (81%) and 2x/mo (12%); for DA: 1x/wk (66%) and 2x/mo (22%); for EB/EA: 3x/wk (39%), 2x/wk (27%), and 1x/wk (30%)
- Median dose for C.E.R.A. was 109 mcg/mo [IQR=69-162, mean=157]; for DA: 121 mcg/mo [IQR=64-211, mean=171]; for EB: 5.6 ku/wk (IV, 57%) and 5.1 ku/wk (SC); for EA: 5.8 ku/wk (IV, 81%) and 4.2 ku/wk (SC)

*The overall prevalence was 8%, 35%, 19%, and 31% for continuous erythropoietin receptor activator, darbepoetin alfa, epoetin beta, and epoetin alfa, respectively*

**Figure 1: Percentage of patients using different ESAs**



- The mean hemoglobin (Hb) levels achieved were similar (11.1-11.2 g/dl) in the patients on C.E.R.A., DA, EB, or EA.

ESAs including C.E.R.A., DA, EB, and EA are in use in different countries to maintain Hb at desired levels. The obtained results can provide beneficial insights for the clinicians looking forward to these agents.

## 12. Effect of calcium on hematopoiesis in hemodialysis patients

Ito K.

Effective hematopoiesis is important for the patients on hemodialysis. In a retrospective study the effect of calcium on hemoglobin (Hb) level was assessed. A total of 106 patients on maintenance hemodialysis were studied. The doses of intravenous (IV) erythropoiesis stimulating agents (ESAs) and saccharated ferric oxide were regulated to correct Hb level. Additionally, the doses of oral calcium carbonate, cinacalcet, and IV maxacalcitol were modified to maintain serum albumin-corrected calcium concentration (C-Ca) in the desired range. After 6 months, 98 patients were evaluated; aged  $63.5 \pm 10.9$  y; 59 males; 21 diabetics, and dialysis period 13.0 y. Due to insufficient blood analysis or patient loss, 8 patients were excluded from the study.

Results obtained from the study can be summarized as:

- Decrease in calcium carbonate and/or increase in cinacalcet lowered C-Ca ( $P=0.0010$  and  $P=0.0007$ , respectively). While, changes in maxacalcitol did not significantly modified C-Ca
- Intact parathyroid hormone (PTH) levels raised from  $204.3 \pm 127.7$  to  $251.3 \pm 143.2$  ( $P=0.0042$ )
- Hemoglobin and transferrin saturation changed from  $10.78 \pm 1.34$  g/dL and  $32.0 \pm 13.1\%$  to  $11.1 \pm 1.31$  and  $28.2 \pm 13.0$ , respectively ( $P=0.0319$  and  $0.0128$ )
- In univariate analysis, Hb at baseline, C-reactive protein (CRP) at baseline, increment of serum albumin concentration in 6 months ( $\Delta$ Alb), and increment of C-Ca ( $\Delta$ C-Ca,  $-0.02 \pm 0.87$  mg/dL) were associated with  $\Delta$ Hb ( $0.37 \pm 1.84$  g/dL)
- In multivariate analysis, with  $\Delta$ Hb as the dependent variable showed that lowering C-Ca, but not CRP or  $\Delta$ Alb, was associated with the increase of Hb. Nearly same results were observed in 54 patients (subset) on stable or reduced doses of ESA and ferric oxide in 6 months (Table1).

*Calcium level may effect hematopoiesis or red blood cell survival, irrespective of erythropoiesis stimulating agents or ferric oxide*

The author concluded that calcium level may effect hematopoiesis or red blood cell survival, irrespective of ESAs or ferric oxide.

**Table 1: Serum albumin-corrected calcium concentration and hemoglobin levels in the study population**

	R2	Independent Variable	Standard β	95% Confidential Interval
All Patients (N=98)	0.509	Hb at Baseline	-0.668	-1.128 — -0.730
		ΔC-Ca	-0.274	-0.881 — -0.277
Subset (N=54)	0.533	Hb at Baseline	-0.621	-1.171 — -0.616
			-0.338	-1.138 — -0.312

Subset: In these 54 patients, doses of ESA and ferric oxide remained unchanged or decreased during the study period.

### 13. Plasma concentration of trace metals in hemodialysis patients is associated with burden of dialysis and response to ESA

**Plasma trace metal concentrations associate with dialysis vintage, gender, and erythropoiesis stimulating agents' response**

*Merchant M, Brier ME, Gooding J, Sumner S, Mcritchie S, Harrington JM, Burgess JP, Rovin BH, Klein JB, Himmelfarb J.*

It has been observed that uremic toxins can form blood metal binding protein-adducts that are associated with erythropoiesis stimulating agents (ESAs). Therefore, knowledge of trace metal levels associating with hemodialysis patient response to ESAs dosing might improve the management of anemia in these patients. In the current work, Merchant et al tested the hypothesis that plasma trace metal concentrations correlate with the markers of anemia and response to ESAs treatment. The investigators analyzed EDTA-Plasma from 110 hemodialysis patients (77 prevalent, 33 incident) participating in a NIDDK funded study, using ICP-MS for plasma concentration of various metals, including As, Cd, Co, Cr, Cu, Mn, Mo, Ni, Pb, Sb, Se, Sn, V, and Zn. Subsequently, associations were determined between trace metals and gender, race, hemodialysis status, monthly hemoglobin values, total ESA dose for the month the sample was collected, erythropoietin response index (ERI), transferrin percent saturation, iron, ferritin, hepcidin and C-reactive protein (CRP). The results showed that the concentrations of Cd, Sn, Ni, and Mo were significantly higher in prevalent patients, as was detection of V. In contrast, concentrations of Mn were lower in the prevalent patients. Furthermore, Spearman correlations of the trace metals in prevalent plasma samples revealed that Cd concentrations were inversely correlated with hemoglobin levels, and positively correlated with EPO and ERI. In addition, Sn was positively correlated with the EPO, and Zn was negatively correlated with ERI. Cd concentrations were found to be significantly higher in the females compared to males. On multivariable regression, Cu and Se were positively and Mo was negatively correlated to CRP. V was found to exhibit negative correlation with hepcidin. In all, the authors concluded that plasma trace metal concentrations associate with dialysis vintage, gender, correlate with ESA response, and may be useful in guiding hemodialysis patient specific approaches to anemia management. According to the hypothesis, specific trace metals may play a causal role in the ESA resistance.

## 14. Survival and outcomes in advanced age with renal insufficiency

Xue H, Henry SL, Chen Q, Chang M, Mihara N, Rutkowski MP.

Elderly are the fastest growing segment of individuals with end-stage renal disease (ESRD). However, there is limited evidence for an overall survival or quality adjusted life advantages of renal replacement therapy (RRT) compared to conservative approaches in this population subgroup. In the current study, investigators aimed to illuminate the outcomes and survival of elderly patients with advanced renal failure relating to RRT choice, and to identify factors associated with disease progression and worse outcomes. Per protocol, a total of 2,062 adults, with mean age  $81.1 \pm 4.7$  years (49.5% female), who initiated RRT or maintained eGFR  $\leq 20$  for at least three consecutive months were followed for five years (from 2003 to 2008) with censoring at December 31, 2013. Subjects who did not initiate RRT were observed until death or the censor date. Furthermore, risk of transition to ESRD vs. death was stratified into five year age groups, and healthcare utilization was assessed based on the use of RRT. The results of the study revealed that the risk of progression to ESRD was higher than death up to the age of 90 years. Median survival was 33 and 20 months for RRT and non-RRT groups, respectively. Similarly, quality-adjusted survival was 21 and 14 months for RRT and no RRT groups, respectively. Peritoneal dialysis was found to offer the greatest survival benefit compared to hemodialysis or no RRT. Initial results seem to suggest that age is a better predictor of death than baseline eGFR, with age and survival inversely related, and those patients initiating RRT at the older ages (90+ years) experiencing the most limited survival. Nevertheless, RRT *per se* was associated with greater healthcare utilization, including more hospitalizations. In conclusion, RRT appears to afford a survival advantage over conservative non-RRT approaches amongst older adults with ESRD, though decrements in quality-of-life (QOL) may still limit its utility among the elderly. The finding may help in decision support for initiating or forgoing RRT in the elderly patients with ESRD.

*Renal replacement therapy per se was associated with greater healthcare utilization, including more hospitalizations. In conclusion, renal replacement therapy appears to afford a survival advantage over conservative non-renal replacement therapy approaches amongst older adults with end-stage renal disease, though decrements in quality-of-life may still limit its utility among the elderly*

## 15. Mortality and hospitalizations in intensive dialysis

Mathew A, McLeggon JA, Mehta NR.

Most end-stage renal disease (ESRD) patients are treated with three times per week hemodialysis, while some receive intensive hemodialysis as short or nocturnal regimens. Seeing that existing data on mortality and hospitalization in intensive compared to conventional hemodialysis is conflicting, authors in the current systematic review and meta-analysis reviewed the available evidence on intensive compared to conventional hemodialysis to evaluate outcomes of mortality and hospitalization. Various databases, including the Cochrane Central Register, MEDLINE, EMBASE and Web of Science, were searched until March 15, 2016, and observational studies and randomized controlled trials (RCTs) comparing intensive hemodialysis (>4 times/week or >5.5 hours/ hemodialysis) with conventional hemodialysis ( $\leq 4$  hemodialysis/week and  $\leq 5.5$  hours/ hemodialysis) that reported mortality and/or hospitalization were included. Risk of bias was evaluated

using standard tools, and meta-analyses were conducted using random effects models. When reported, investigators analyzed home vs. in-center, and nocturnal vs. short daily hemodialysis, separately in order to reduce heterogeneity. Overall, the systematic review included 23 studies (2 RCTs and 21 observational) with 48,018 reported patients (38,300 on conventional hemodialysis and 9,718 on intensive hemodialysis). Due to incomplete data reporting, eight studies were included in the meta-analysis. The results showed that compared with conventional hemodialysis, home nocturnal, home short daily and in-center nocturnal hemodialysis had significantly lower mortality. Compared to conventional hemodialysis, hospitalization rate/year and hospitalization days were significantly lower in nocturnal hemodialysis. Selection bias, lack of data, and limited number of RCTs precluded some data pooling and comparisons between important subgroups. Overall, the authors concluded that intensive hemodialysis may be associated with reduced mortality and hospitalization compared to conventional hemodialysis. Nonetheless, confounding by indication and the lack of multiple RCTs limits the preferential use of intensive hemodialysis. Further research is needed on identifying specific patient subgroups that would benefit from intensive hemodialysis.

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*Outpatient vascular access care may have the potential to reduce mortality rates in patients on hemodialysis when compared to patients receiving vascular access care in other settings or no care at all*

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## **16. Associations between vascular access care and mortality rates in hemodialysis patients**

*Han H, Reviriego-Mendoza M, Chaudhuri S, Butler KG, Rosen S, Brzozowski J, Larkin JW, Latif W, Koh E, Usvyat LA, Miller G, Rosenblatt M, Sor M, Maddux FW.*

Fresenius vascular care offers outpatient vascular access care for Fresenius medical care North America hemodialysis patients. In the current study, Han et al evaluated the associations in mortality rates for Fresenius vascular care outpatient vascular access care vs. other vascular access providers that are mostly in a hospital setting or no vascular access care received at all. The authors analyzed data from 4,691 hemodialysis patients who visited Fresenius vascular care at any time during 2014. Control patients were selected by 1:1 matching exactly for the concurrent year of Fresenius vascular care, state of residence, race, gender, and access type, in addition to, nearest neighbor matching on the logit of the propensity score for age, dialysis vintage, albumin, body mass index (BMI), and Kt/v. Further analysis was performed for 4,376 Fresenius vascular care patients with a pre-existing arteriovenous fistula or graft (AVF/AVG). Six month mortality rates/100 patient years were compared between the study groups after January 1, 2015. Overall, data from 9,382 hemodialysis patients was analyzed for this study. The results showed that compared to matched control patients, mortality rates in Fresenius vascular care patients were decreased by 33%. Similarly, patients enrolled in Fresenius vascular care with a preexisting AVF/AVG showed a 28% reduction in mortality when compared to controls. In conclusion, the study suggested that outpatient vascular access care may have the potential to reduce mortality rates in hemodialysis patients when compared to patients receiving vascular access care in other settings or no care at all. More studies are required to determine the long-term mortality outcomes associated with Fresenius vascular care vascular access care.

## Notes



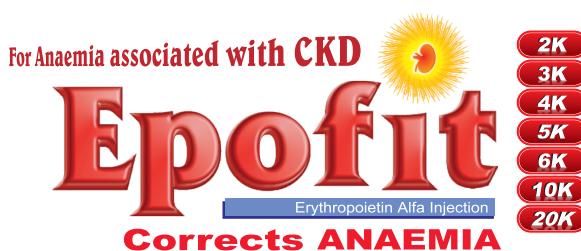
## Notes



In Anemia associated with CKD



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