**ACID BASE, ION DISORDERS, LITHISASIS**

**SP320**

**ACUTE-PHASE EFFICACY IN A PHASE 3 MULTICENTER, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF ZS-9 FOR HYPERKALAEMIA**

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**Introduction and Aims:** Hyperkalaemia is a risk factor for mortality in patients with cardiovascular disease and chronic kidney disease (CKD) (Goyal, 2012; Torlen, 2012) and limits use of renin-angiotensin-aldosterone system inhibitors (RAASi) in these patients. Sodium (or calcium) polystyrene sulfonate (SPS/CPS) has uncertain efficacy and has been associated with substantial adverse events, as well as poor gastrointestinal tolerability, and hence is suboptimal for acute use and unsuitable for chronic use (Harel, 2013; Sterns, 2010). Therefore, there is a need for a hyperkalaemia treatment that rapidly reduces serum potassium (K+) and is safe and well tolerated in these patients. ZS-9, a nonabsorbed cation exchanger designed to specifically entrap excess K+, significantly reduced K+ vs placebo over 48 hr with excellent tolerability in patients with CKD (Ash, 2013). We report acute-phase efficacy in a Phase 3 trial of ZS-9 in patients with hyperkalaemia.

**Methods:** Patients (N=753) with serum K+ 5.0-6.5 mmol/L were randomised (1:1:1:1:1) to ZS-9 (1.25g, 2.5g, 5g or 10g) or placebo given three times daily (TID) with meals for 48 hr (acute phase), after which those with K+ ≤ 5.9 mmol/L (n=542) were re-randomised to ZS-9 or placebo once daily for Day 3-15. Serum K+ was measured at baseline and at predefined intervals, including 1, 4, 24, and 48 hr after the first dose. The acute-phase primary efficacy endpoint was the rate of K+ change over the first 48 hr, using longitudinal modeling to account for all post-baseline data.

**Results:** Mean K+ at baseline was 5.3 mmol/L. Substantial percentages of patients had CKD (60%), a history of heart failure (40%), or diabetes (60%) or were on RAASi therapy (67%). ZS-9 demonstrated significant dose-dependent reductions in K+, the acute-phase primary efficacy endpoint was met for ZS-9 2.5g (p<0.0001), 5g (p=0.0001) and 10g TID (p=0.0001; Fig. 1).

There was a significant decrease in K+ by -0.11 mmol/L with ZS-9 10g vs an increase of +0.01 mmol/L with placebo (p=0.009) 1 hr after the first dose. At 48 hr K+ fell by -0.73 mmol/L with 10g TID vs -0.25 mmol/L with placebo (p=0.001); other significant reductions vs placebo are shown in Fig 2. Rates of all adverse events (AEs) and gastrointestinal AEs were not significantly different in the ZS-9 and placebo groups.

**Conclusions:** ZS-9 produced significant dose-dependent reductions in K+ when given TID for 48 hr, with an AE profile similar to placebo. The significant reduction in serum K+ 1 hr after the first ZS-9 10g dose further suggests that ZS-9 is effective in removing K+ from the small intestine fluid, where it is in equilibrium with blood levels. ZS-9 may address an important unmet clinical need by rapidly correcting hyperkalaemia in high-risk patients, many of whom require RAASi for end-organ protection.

**SP321**

**PHASE 3, MULTICENTER, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF ZS-9: SUBGROUP ANALYSIS STRATIFIED BY BASELINE SERUM POTASSIUM LEVELS**

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**Introduction and Aims:** Hyperkalaemia (potassium [K+] >5.0 mmol/L) is a common disorder in patients with chronic kidney disease (CKD), diabetes, and in those on renin-angiotensin-aldosterone inhibitor therapy. Polystyrene sulfonate (sodium or calcium) has limited efficacy and has been associated with substantial adverse events (AEs) and poor gastrointestinal (GI) tolerability. There is a need for a safe, fast-acting, effective treatment for sustained reduction of serum K+ in patients with hyperkalaemia, independent of its severity. ZS-9, a nonabsorbed cation exchanger designed to specifically entrap excess K+ in the GI tract, was shown to significantly reduce K+ (vs placebo) over 48 hr with excellent tolerability in patients with CKD and K+ >5.6 mmol/L. Here we report acute-phase efficacy stratified by baseline K+ in a large Phase 3 trial of ZS-9 in patients with relatively more severe, asymptomatic hyperkalaemia.

**Methods:** Patients (N=753) with K+ 5.0-6.5 mmol/L were randomised (1:1:1:1:1) to ZS-9 (1.25g, 2.5g, 5g or 10g) or placebo given three times daily (TID) with meals for 48 hr (acute phase), after which those with K+ ≤ 5.4 mmol/L (n=542) were re-randomized to ZS-9 or placebo once daily for Days 3-15. Changes in serum K+ over 48 hr (acute phase) were compared using unpaired t-test.

**Results:** Overall, baseline K+ was ≤5.3 mmol/L in 427 (56.7%), 4.4-5.5 mmol/L in 152 (20.2%) and >5.5 in 174 (23.1%) patients. Within these subgroups, mean K+ levels
were similar in the ZS-9 5g, ZS-9 10g and placebo groups at baseline (Table). At 48 hr, patients on ZS-9 5g or 10g TID had significantly greater decreases in K+ than did those on placebo, regardless of baseline K+ (Table, Figure). For those with starting K+ >5.5 mmol/L, the ZS-9 10g dose group achieved a mean K+ reduction of 1.1 mmol/L at 48 hr, ~14 hr after the last dose of ZS-9. Mean K+ levels for ZS-9 5g and 10g TID were within the normokalaemic range (3.5 to <5.0 mmol/L) at the end of the acute phase (Table), and there were no severe hypokalaemic episodes (<3.0 mmol/L). In the overall population, rates of AFs were not significantly different in the ZS-9 5g, 10g, and placebo groups.

**Conclusion:** Results of this subgroup analysis indicate that ZS-9 TID is effective in reducing K+ over 48 hr, regardless of baseline K+ concentration. Importantly, K+ reductions were largest in patients with the highest baseline K+ levels, suggesting that ZS-9 TID promotes a return to normokalaemia regardless of starting K+, with a low risk (0.3%) of mild hypokalaemia (3.0-3.5 mmol/L). ZS-9 is a novel therapy designed to specifically entrap excess K+ and may add an important unmet medical need by rapidly correcting various levels of hyperkalaemia.

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**SP322**

**DABIGATRAN VS WARFARIN TREATMENT: EFFECTS ON BONE VOLUME AND STRUCTURE IN RATS**

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**Introduction and Aims:** Warfarin acts as a vitamin K antagonist inhibiting the effects of Vitamin K-dependent Proteins (VKDPs): Bone Gla Protein (BGP or Osteocalcin) and Matrix Gla Protein (MGP) prevents vascular calcifications (VC). Dabigatran is a new oral anticoagulant not affecting vitamin K. We compared the impact of warfarin and dabigatran on bone and vascular calcifications, in rats with normal renal function.

**Methods:** Rats received for 6 weeks Dabigatran etexilate (0.6 mg/g of chow) or Warfarin (starting from 0.6 mg/kg and adjusted to achieve the desired INR between 2 and 3). Untreated Controls were fed a diet containing 8 mg of Vitamin K3 per gram of chow. Femur, tibia and vertebra were evaluated for immunohistochemical and morphometric analysis of bone remodelling. Samples of aorta and iliac arteries were preserved for histological examination (Von Kossa and Alizarin red staining) and 3). Untreated Controls were fed a diet containing 8 mg of Vitamin K3 per gram of chow. Femur, tibia and vertebra were evaluated for immunohistochemical and morphometric analysis of bone remodelling. Samples of aorta and iliac arteries were preserved for histological examination (Von Kossa and Alizarin red staining).

**Results:** Histomorphometric results of femur and vertebra analysis showed for parameters of structure a significantly decreased bone volume and increased trabecular separation in rats treated with warfarin with respect to controls and to rats treated with dabigatran (see table). In addition, in vertebra analysis we found that trabecular number differed significantly between the two treatment groups. In femur analysis warfarin was associated with significantly higher Activation Frequency (AfF) than in dabigatran treated and control rats, suggesting a significantly increased turnover. In vertebra analysis we found no significant differences in osteoblast activity and resorption parameters except for maximum erosion depth, which was higher in warfarin treated rats compared to dabigatran and control groups, suggesting a more pronounced osteoclastic activity. Furthermore in vertebra analysis we highlighted that warfarin treatment was associated to significantly higher Bone Formation Rate/Bone Surface (BFR/BS) and AfF than in dabigatran treated and control rats, suggesting that warfarin may cause an increased turnover characterized by increased remodeling cycles, with stronger osteoclastic activity with respect to other groups. There were no differences among the three groups of rats in arterial calcium deposition either in the aorta or in the iliac arteries.

**Conclusion:** Results observed in bone are remarkable, considering that, in our experimental setting, no vascular calcification were observed. This study demonstrates that treatment with warfarin was associated with significantly decreased bone volume, increased trabecular separation and higher turnover than in dabigatran treated and control rats. These findings suggest for the first time that dabigatran has a better bone safety profile than warfarin, as warfarin treatment affects bone by reducing trabecular size and structure, increasing turnover and reducing mineralization. These differences could translate into lower incidence of fractures in dabigatran treated patients both in the general population and in patients with chronic kidney disease.

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**SP323**

**FAT MALABSORPTION CONTRIBUTION TO HYPEROXALURIA AFTER ROUX-EN-Y GASTRIC BYPASS IN RATS**

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**Introduction and Aims:** Hyperoxaluria and a higher risk of nephrolithiasis is a common complication of bariatric surgery. We have previously shown that increased intestinal absorption of dietary oxalate is a predisposing mechanism for enteric hyperoxaluria among Roux-en-Y (RY) gastric bypass patients (CJASN 7: 2033-2040, 2012). The occurrence of fat intestinal malabsorption as a contributing factor for hyperoxaluria after RY remains controversial. Therefore, we aimed to investigate the presence of steatorrhea and its relation with urinary oxalate and other parameters in a RY gastric bypass model in rats.

**Methods:** Wistar male rats underwent RY or Sham surgeries. Two weeks after the procedures, animals received either a high oxalate (1% sodium oxalate) or fat (18% lipids) supplemented diet (RY-S and Sham-S) or a standard chow diet (RY and Sham) during 8 weeks. 24h urine collections and stool samples were obtained before the surgery (baseline) and at the end of study (final). Percent fecal fat was quantified by the

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<table>
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<th>Variable</th>
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<th>Dabigatran</th>
<th>Controls</th>
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Mean ± SD. Comparison between periods: (a) P < 0.05 vs baseline. Comparison between groups: (b) P < 0.05 vs Sham-S; (c) P < 0.05 vs Sham; (d) P < 0.05 vs RY.
Efficacy of ZS-9 in Patients Receiving RAAS Therapy: A Subgroup Analysis of a Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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Abstracts Nephrology Dialysis Transplantation

Introduction and Aims: Therapies that affect the renin-angiotensin-aldosterone system (RAAS) increase the risk of hyperkalaemia (potassium [K+] >5 mmol/L). Hyperkalaemia often prompts RAAS therapy discontinuation, despite its proven benefit in chronic kidney disease (CKD) and heart failure patients. There is an unmet need for safe, effective drugs that provide sustained K+ reduction. ZS-9 is a novel, nonabsorbed cation exchanger designed to specifically entrap excess K+. Here we report changes in serum K+ for the largest dose of ZS-9 (10g) vs placebo in patients stratified by baseline RAAS use (ie, RAAS vs non-RAAS) from a Phase 3 trial of ZS-9.

Methods: In the acute phase, 753 patients with K+ 5.0-6.5 mmol/L were randomised (1:1:1:1) to ZS-9 (1.25g, 2.5g, 5g or 10g) or placebo given three times daily (TID) with meals for 48 hours. In the extended efficacy phase, 542 patients who became normokalaemic (3.5-4.9 mmol/L) were re-randomised 1:1 to the same dose of ZS-9 received during the acute phase or placebo and treated once daily (QD) for 12 additional days. RAAS inhibitors were kept constant throughout the study.

Results: Overall, 67% of patients were receiving RAAS therapy at baseline, of whom 66%, 36%, and 9%, were on an ACE inhibitor, angiotensin receptor blocker, or spironolactone, respectively. At baseline mean K+ values were 5.3 mmol/L in all subgroups (Table 1). At the end of the acute phase (ie, 48 hours after the first dose), patients who received 10g ZS-9 had significantly greater decreases in K+ levels than did patients who received placebo, in both the RAAS (0.7 vs -0.2 mmol/L respectively; p<0.001) and non-RAAS (0.7 vs -0.3 mmol/L respectively; p=0.001) groups (Table 1). Extended efficacy phase baseline K+ values for ZS-9-treated and placebo-treated patients were similar in both the RAAS (4.5 vs 4.4 mmol/L, respectively) and non-RAAS groups (4.6 vs 4.4 mmol/L, respectively). On Day 15, change from extended phase baseline mean K+ levels were significantly smaller in ZS-9-treated patients than in placebo-treated patients, regardless of whether they were receiving RAAS or not (Table 2). In the overall population, rates of adverse events were not significantly different in the ZS-9 10g and placebo groups in both phases of the study.

Conclusions: These results show that ZS-9 was effective in decreasing K+ after 3 days of TID treatment and maintaining K+ levels with QD dosing in patients receiving RAAS therapy, results consistent with those in patients not on RAAS inhibitors. ZS-9 may become an important treatment for both correcting hyperkalaemia and, importantly, maintaining normokalaemia in a safe and well-tolerated manner. ZS-9 may enable optimal use of cardio- and renoprotective RAAS inhibitors in patients who may benefit from them.

Abstracts Nephrology Dialysis Transplantation

Vasopressin Receptor Antagonists for the Treatment of Heart Failure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Introduction and Aims: Heart failure (HF) and hyponatremia secondary to HF is associated with impaired quality of life, more frequent hospitalizations and with an overall annual mortality rate of 10%. In the modern therapy of both acute and chronic HF, arginine vasopressin secretion could be a potentially attractive goal. Elevated vasopressin secretion may contribute to the increase in systemic vascular resistance and pulmonary capillary wedge pressure followed by a decrease in stroke volume and cardiac output via V1a receptor stimulation. We aimed to assess benefits and harms of vasopressin receptor antagonists when compared with placebo in addition to standard care in adults with HF.

Methods: A systematic review and meta-analysis was conducted to identify randomized controlled trials without language restriction through comprehensive searches of CENTRAL and MEDLINE to January 2018. Trials independently abstracted all data and assessed methodological quality. Meta-analysis used a random effects model, with dichotomous outcomes expressed as risk ratios (RR) and continuous outcomes as mean differences (MD) with 95% confidence intervals (CI). All-cause and cardiovascular mortality, changes in clinical assessment of HF, serum sodium concentration (Na), kidney function and any treatment-specific side effects were the outcomes analyzed.

Results: We identified 13 trials, including 5525 participants. In 10 trials, all patients with cardiac failure received standard therapy for HF, consisting of diuretic treatment, vasodilators and beta-blockers. Two of these trials used furosemide therapy with doses higher than 40 mg daily. In low-quality evidence, vasopressor receptor antagonists in patients with heart failure had no effect on all-cause mortality (RR 0.98, CI 0.88-1.08), cardiovascular mortality (RR 1.03, CI 0.91-1.16) or change in creatinine (MD -0.01, CI -0.10-0.09 mg/dL), but reduced body weight by 0.8 kg from baseline (MD -0.83, CI -1.10 to -0.55 kg) and increased Na concentration (MD 2.61, 95% CI 1.88-3.35 mmol/L). Compared with placebo, vasopressin receptor antagonists increased the risk of adverse events by 14% (RR 1.14, CI 1.04-1.26). Studies were generally limited to short term follow-up with limited data available on patient important outcomes.

Conclusions: Vasopressin receptor antagonist may reduce body weight and increase serum sodium concentration but do not improve all-cause mortality, cardiovascular mortality or kidney function. In addition, acceptability of long-term treatment side effects and hospitalization appear problematic.
Introduction and Aims: Although cross-sectional studies suggested a relationship between proton-pump inhibitor (PPI) use and hypomagnesemia, no large-scale cohort study has been conducted thus far. Here, we examined the change in serum magnesium concentrations with (PPI group) or without the use of a PPI (control group) in a retrospective cohort of 1076 patients who underwent percutaneous coronary intervention (PCI) in a tertiary medical center.

Methods: Among 2892 patients hospitalized for PCI between January 2007 and May 2012, 1076 (60% who had baseline (1.6-2.5 mg/dL) and follow-up magnesium concentrations were enrolled in this study. Hypomagnesemia was defined as a serum magnesium concentration < 1.6 mg/dL. First, the patients were divided into two groups, namely the PPI and control groups. Second, the PPI group was further divided into a short-term PPI group (duration of use < 12 month) and a long-term PPI group (duration of use ≥12 months).

Results: The mean follow-up period was 19.2 ± 12 months. The incidence rate of hypomagnesemia during the follow-up period was 0.4% (85/336) in the control group and 0.9% (79/880) in the PPI group (P = 0.024). In the control group, the serum magnesium concentration < 1.6 mg/dL. First, the patients were divided into two groups, namely the PPI and control groups. Second, the PPI group was further divided into a short-term PPI group (duration of use < 12 month) and a long-term PPI group (duration of use ≥12 months).

Conclusions: Although hypomagnesemia could develop after PPI use, the change in magnesium serum level after PPI use was not significantly different from the normal baseline magnesium level.

SP327 CAFFEIN LEVELS ARE INVERSELY ASSOCIATED WITH KALIEMIA IN WOMEN: A POPULATION BASED STUDY

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1University Hospital of Geneva, Geneva, Switzerland, 2Institute of Social and Preventive Medicine, Lausanne, Switzerland, 3University Hospital of Lausanne, Social and Preventive Medicine, Lausanne, Switzerland, 4Hypertension Unit, University of Geneva, Geneva, Switzerland, 5Populational Epidemiology Unit, Geneva, Switzerland, 6Institute of Social and Preventive Medicine, Lausanne, Switzerland, 7Hypertension Unit, University Hospital of Geneva, Geneva, Switzerland

Introduction and Aims: Previous case reports have described the association between excessive caffeine consumption and hypokalemic. Population-based studies are however lacking and most studies do not measure blood caffeine levels. We examined the association of plasma caffeine levels with potassium in a population-based sample.

Methods: The Swiss Kidney Project on Genes in Hypertension is a family-based multi-centre (Lausanne, Bern, Geneva) population-based study that examines the genetic determinants of renal function and blood pressure. We measured plasma caffeine and potassium levels. Multilevel mixed-effect linear regression was used to examine the association of plasma caffeine tertiles with blood and 24-hour urinary potassium excretion, while taking familial correlations into account.

Results: The 536 men and 592 women included in this analysis had a median plasma caffeine level of 556.5 and 624.0 ng/ml, respectively, and a mean (±SD) plasma potassium level of 4.55 ± 0.48 mmol/L and 4.54 ± 0.49 mmol/L. There was a significant inverse association between plasma caffeine and potassium levels (β coefficient=-0.08 mmol/l; p=0.001). Moreover, the follow-up magnesium levels did not significantly differ between the two groups. After an analysis of covariate adjusting for age, sex, baseline GFR, baseline calcium level, use of diuretics, baseline potassium intensity, the follow-up magnesium levels did not significantly differ between the two groups (P = 0.381). Moreover, the follow-up magnesium levels did not significantly differ between the long-term (n = 76) and short-term PPI groups (n = 763), and the control group (n = 242; P = 0.620).

Conclusions: Although hypomagnesemia could develop after PPI use, the change in magnesium serum level after PPI use was not significantly different from the normal baseline magnesium level.

SP328 MAGNesium HOMEOSTASIS IN HEMODIALYSIS VERSUS PERITONEAL DIALYSIS PATIENTS: A PILOT STUDY

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Introduction and Aims: Serum magnesium (mG) levels are variable among end-stage renal disease (ESRD) patients on dialysis, determined by dietary intake, medications, residual renal clearance and dialysate Mg concentration. Furthermore, clinical studies have shown that lower mG is associated with vascular calcification and cardiovascular mortality in this patient group. However, limited data are available regarding mG metabolism under different dialysis modalities. The present study evaluated Mg homeostasis in hemodialysis (HD) versus peritoneal dialysis (PD) patients.

Methods: Thirty-four stable HD patients, (male/female: 24/10), aged 67 (25-89) years, dialyzed for 93 (6-373) months and 12 PD patients (male/female: 7/5), aged 63 (43-82) years, dialyzed for 44 (6-100) months were included in the study. In the HD group, 25 patients received conventional HD and 9 hemodialfiltration (HDF). Three weekly HD session length was 4.5 hours. In the PD group, 3 patients were on continuous ambulatory PD (CAPD) and 9 on automated PD (APD) plus one daily exchange.

Disalviate Mg concentration was 0.5 mmol/L for both HD and PD patients. Residual renal function was negligible (<100mL/24h) in both groups. Eighteen HD and 7 PD patients were on eneprome, at a dose of 20 mg once daily. Follow-up period was 3 months for both groups. No patient was receiving Mg-containing phosphate binders. Biochemistry measurements including mG, serum calcium (Ca), phosphorus (P), parathyroid hormone (PTH) and alkaline phosphatase (ALP) were performed monthly and dialysis adequacy was determined at the same intervals by single pool Kt/V (spKt/V) for HD and total weekly Kt/V urea for PD patients. Standardized Kt/V per week was calculated for HD patients to allow comparison with their PD counterparts. Mean values of the 3 measurements were compared for all the studied parameters.

Results: Main baseline demographics were similar between the two groups, with the exception of diabetes vintage that was significantly higher in HD group. Mean mG levels were found significantly higher in the HD group compared to PD group (2.27 ±0.21 vs 1.86±0.51 mg/dL, p<0.001). Mean PTH was also significantly higher in the HD group compared to PD group (707±718 vs 379±872 U/L, p<0.001). Dialysis adequacy was better in HD group (Kt/V 2.5±0.3 vs 2.2±0.5, p=0.01). No significant difference was found in the other studied parameters between the two groups (HD vs PD, mean: 9.09±0.54 vs 9.2±0.47 mg/dL, mean: 4.59±1.00 vs 4.00±0.73 mmol/L, mean: ALP 332.4±183.96 vs 265.27±133.16 U/L). Significantly lower mean mG levels were found in both HD and PD patients on PPI (2.03±0.39 vs 2.32 ±0.24 mg/dL, p=0.006), whereas no significant difference was found in the other studied parameters. Furthermore, no significant differences were noted in mG and the other studied parameters between men and women, CAPD/APD and HD/HDF patients.

Conclusions: HD patients showed higher mG and PTH levels compared to PD patients without significant differences in other parameters of bone metabolism. This difference in mG appeared to be independent of factors such as sex and HD or PD submodality. PPI use was associated with lower sMg levels in both dialysis diets. Dietary limitations in the PD group could explain lower sMg levels and would suggest oral supplementation or higher dialysate concentrations.

SP329 IS HYPONATREMIA RELATED TO THE SEASONS?

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Introduction and Aims: Hyponatremia is a common electrolyte disorder in in-patients and mortalyzed with morbidity and mortality. In this study we aimed to examine whether there is a relationship between in-patients with hyponatremia and seasonal change.

Methods: The patients who were in-patients in our service in 2012 were retrospectively analyzed. Sodium level <135 mEq/L was accepted as hyponatremia. Characteristics of the patients were collected from their files. Hyponatremia incidence was calculated as the proportion of in-patients with low sodium levels in a season to total number of in-patients in the same season.

Results: Of a total of 450 in-patients in our service in one year period, 318 were found to have hyponatremia (118/450). Of the patients with hyponatremia, 60 were male. Mean serum sodium level of the patients was 129.4±5.3 mEq/L. Hyponatremia incidence in autumn, winter, spring and summer were found to be (26/90) 28.8% (17/109) 15.6%, (21/103) 20.3% and (50/118) 41.9% respectively. There was no significant difference in distribution of hyponatremia patients according to seasons in terms of accompanying diseases, drug use, mortality and dialysis treatment. Comparison of hyponatremia incidence in in-patients in winter and summer revealed a significantly higher hyponatremia incidence in summer (p<0.001). We found a positive correlation between hyponatremia incidence and temperature (r=0.973, p=0.027).

However, there was a negative correlation between hyponatremia incidence and relative humidity (r =-0.915, p = 0.05).

Conclusions: The highest hyponatremia incidence was observed in summer in one-year period. Loss of sodium by perspiration along with increased temperature and/ or excessive hypotonic fluid intake might contribute to development of hyponatremia. Therefore, electrolyte-containing fluids can be consumed to reduce hyponatremia related morbidity and mortality in geographic regions with increased temperatures and decreased humidity ratios especially in summer season.

SP330 OXALATE NEPHROPATHY COMPLICATING TOTAL GASTRECTOMY - CLINICAL CASE OF END-STAGE RENAL DISEASE

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Introduction and Aims: Oxalate nephropathy is characterized by crystalline tubular deposits of calcium oxalate, with acute and chronic tubular injury, interstitial fibrosis and gradual renal insufficiency. Recognised causes of oxalate nephropathy include...
primary hyperoxaluria, ethylene glycol intoxication, entero hyperoxaluria, vitamin B6 deficiency and excessive ingestion of vitamin C or products rich in oxalic acid, such as cacao and nuts. Entero hyperoxaluria occurs in conditions associated with fat or bile acid malabsorption, such as inflammatory bowel disease, pancreatic insufficiency, biliary resection, blind loop syndrome and Roux-en-Y Gastric Bypass (RYGB).

**Methods:** We present clinical case of a male patient, 69 years of age, admitted for acute kidney injury, non-oliguric, characterized elevated levels of serum creatinine (10 mg/dL) and anemia (18.6 g/dL). Renal function was normal 8 months before. Patient was submitted to total gastrectomy due to gastric adenocarcinoma a year before this admission. Renal ultrasound showed left kidney with dimensions inferior to the limit of normality (right bipolal axis: 9.9 cm and left axis: 8.8 cm). Reasonable parenchyma thickness, however, with poor cortical-medullary differentiation in both the kidneys. Renal biopsy evidenced chronic interstitial nephritis with acute tubular necrosis due to calcium oxalate deposits.

**Results:** Patient was started on dialysis, which was suspended for a while, after an apparent partial recovery of renal function, with serum creatinine pre-dialysis of 4.9 mg/dL. However, due to new rise in serum creatinine, with hyperkalemia associated, patient restarted dialysis with the diagnosis of end-stage renal disease (ESRD) due to oxalate nephropathy.

**Conclusions:** Oxalate nephropathy is an under-recognized complication of RYGB, which typically results in rapid progression to ESRD. Although the main indication for this surgery is the treatment of obesity, this approach also constitutes the preferred mode of reconstruction after gastric carcinoma due to its ability to prevent reflux of biliary and pancreatic secretions. Causes of malabsorption in this patients include rapid intestinal transit, bacterial overgrowth and pancreatic undersecretion. Considering the rapid progression of oxalate nephropathy, patients who undergo RYGB should have regular follow-up of renal function and institute dietary modifications or even surgical reversal if necessary in order to reverse any decline in renal function, so early detection is important.

### EXTENDED EFFICACY OF ZS-9 ONCE-DAILY IN A PHASE 3 MULTICENTER, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF PATIENTS WITH HYPERKALEMIA

**Introduction and Aims:** Hyperkalemia predicts mortality in patients with cardiovascular disease and chronic kidney disease (CKD), and limits use of life-saving renin-angiotensin-aldosterone system inhibitors (RAASi). Sodium (or calcium) polystyrene sulfonate (SPS, CPS) has unreliable efficacy and has been associated with potentially serious adverse events. Due to poor gastrointestinal tolerability, SPS or CPS is not suitable for chronic use. ZS-9, a nonabsorbed cation exchanger designed to specifically entrap excess potassium (K+), significantly reduced serum K+ vs placebo over 48 hr with excellent tolerability in patients with hyperkalemia and CKD. Here we report the efficacy of ZS-9 during extended maintenance treatment in a Phase 3 trial in hyperkalaemic patients.

**Methods:** Patients (N=753) with serum K+ 5.0-6.5 mmol/L were randomised (1:1:1:1:1) to ZS-9 (1.25g, 2.5g, 5g or 10g) or placebo three times daily for 48 hr (acute phase), after which those with K+ ≤4.9 mmol/L were re-randomised 1:1 to the same dose of ZS-9 given during the acute phase or placebo once daily (QD) for Day 3-15 (extended phase). Serum K+ was measured at baseline and at predefined intervals, including on Days 4, 6, 9, 15 and 21 (7 days after the last dose of study drug). The primary efficacy endpoint for this phase was the rate of K+ change over Day 3-15, using

### SEVERE HYPOPHOSPHATEMIA IN A PATIENT WITH TYPE 1 NEUROFIBROMATOSIS: CASE REPORT

**Introduction and Aims:** Hypophosphatemia is a rare event in type 1 neurofibromatosis (NF1) with no clear pathophysiology. Here we present a case of a patient recently diagnosed with NF1 and hypophosphatemia that can be related to overproduction of FGF23.

**Results:** Case report: A 46 years old gentleman presented with cervical and left upper arm pain along with generalized fatigue. He had no significant past medical history but features compatible with NF1 i.e. café au lait spots and Lish nodules. A cervical MRI was performed and showed a neurofibroma along the cervical roots C3 and C4. The most striking blood chemistry abnormality was severe hypophosphatemia at 0.23 mmol/l (N=0.9-1.5). Of note, there were no deformities of the extremities and no past history of fractures. The bone mineral density measurement showed severe osteoporosis with a T score of -4 at the level of the wrist. The kidney function was normal and there was neither hypokalemia nor metabolic acidosis. There was also no glucosuria, no aminoaciduria and no uric acid loss (FE uric acid=2.57%), but the maximal reabsorptive capacity of the phosphorus (TRP) was relatively low at 89% (N=85-90%) and the TmPO4/GFR was inappropriate at 0.22 (N=0.89-1.34) denoting an isolated abnormality at the level of the phosphorus reabsorption in the proximal tubule. The PTH level was at 69 pg/ml (N=10-65) accompanied with a severe deficit in native vitamin D (vit D=5.7 ng/ml (N=30). FGF23 level was inappropriately high at 119 RU/ml (N=34-97) particularly in the setting of severe hypophosphatemia. After supplementation with native and active vit D the phosphorus level increased to 0.82 mmol/l but the TRP and TmPO4/GFR were still inappropriate at 77% and 0.65 respectively. The normalization of the 25(OH)D vitamin D translated into a normalization of the PTH level. The patient was operated of his neurofibroma in November and the active vit D was stopped one month later. The phosphorus level measured in January without any supplementation went down again to 0.77 mmol/l with a TRP and TmPO4/GFR at 83% and 0.64 respectively. FGF23 is secreted by osteocytes and acts on NPT2a and NPT2c transporters in the proximal tubule to inhibit the reabsorption of phosphorus. It has been implicated in urinary phosphorus loss in some mesenchymal tumors, resulting in oncogenic osteomalacia. In this case, the hypophosphatemia was due to urinary loss and was accompanied with inappropriately high levels of FGF23 with normal 1.25(SH) vit D. Our hypothesis is that FGF23 was secreted by mesenchymal neurofibroma cells. After surgery, the phosphorus loss persisted but to a much lesser extent, implicating again FGF23 in this case.
Conclusions: Hyponatremia is the most common electrolyte abnormality and the risk factor of mortality of hospitalized patients in western countries, but few data of large cohort study among Chinese patients. The gender difference of the prevalence and incidence in hypernatremia was still not well known.

Methods: To identify the prevalence and incidence among Chinese hospitalized hyponatremia patients between male and female, we conducted a cohort study of 200,037 patients hospitalized between 2008 and 2012 at a 1,800-bed university comprehensive hospital in Beijing, China. Demographic characteristics, laboratory data, clinical outcomes of all the patients, detailed medical conditions and Charlson comorbidity index of severe hyponatremia patients (Serum sodium <120 mEq/L, n=135) were collected. Multivariable analysis of risk factors was done by logistic regression. Multiple Cox hazard models were performed to observe the predictors of mortality of hyponatremia patients.

Results: Hyponatremia (serum sodium concentration <135 mEq/L) was observed in 19.6% of patients with much higher mortality than those normal serum sodium patients (4.53% vs 0.38%, p<0.001). Hyponatremia was proved as the independent risk factor of mortality (OR=1.083, 95% confidence interval [CI], 1.036-1.132, p<0.001). Both prevalence and mortality of hyponatremia among male patients was higher than female patients (25.98% vs 15.43%; 5.28% vs 3.94%, p<0.001). And the gender difference was not changed after age and degree of serum sodium stratification. But when adjusted by average death rate of different genders separately, the mortality due to hyponatremia for female was 2 to 3 times of male’s at the same age group.

Conclusions: Hyponatremia independently predict mortality of Chinese hospitalized patients. Male was prone to develop hyponatremia, but higher impact factor of hyponatremia contributing to mortality was observed in female. Hao J and Qiu L contributed equally to this work.
TREATMENT OF METABOLIC ACIDOSIS IN HEMODIALYSIS PATIENTS WITH REDUCED PILL BURDEN

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Introduction and Aims: Metabolic acidosis in hemodialysis patients is associated with increased mortality. Guidelines recommend treatment with oral NaHCO3 and/or individualized dialysate bicarbonate [HCO3-]d targeting a predialysis serum bicarbonate concentration ([HCO3-]s) of 20-22mmol/L. In our center, until recently, metabolic acidosis was corrected by oral supplementation and standard [HCO3-]d of 34mmol/L. To reduce the daily pill burden, we implemented a new protocol comprising discontinuation of oral NaHCO3 and upward adjustment of the [HCO3-]d. We evaluated efficacy and safety of this protocol.

Methods: All hemodialysis patients in our unit treated with oral NaHCO3 were studied (n=19). The new protocol involved two steps: 1) stopping NaHCO3 and increasing [HCO3-]d by 1-3mmol/L (depending on the NaHCO3 dose), and 2) weekly titration of [HCO3-]d targeting predialysis [HCO3-]s of 20-22mmol/L. Acid-base status, electrolytes and weight were monitored. Results before and after implementation of the protocol are shown (median and IQR).

Results: Daily number of NaHCO3 tablets (500mg/tablet) was 3.0Q(0.5-6) before implementation of the new protocol. After implementation [HCO3-]d was unchanged in 7 patients, increased by 1mmol/L in 4 patients and ≥2mmol/L in 8 patients. Target predialysis [HCO3-]s was equally achieved (38% before and 37% after) with a predialysis [HCO3-]s of 22.3(21.0-24.3) and 21.7mmol/L(20.1-23.0), respectively, p=0.21. Postdialysis pH7.50 was observed more frequently with the new protocol (21% versus 5% of the patients), however, not significant (p=0.34). The new protocol had no influence on postdialysis and intradialytic change in pCO2, [K+], [Ca2+] and [Na+], intradialytic weight loss and intradialytic weight gain. [HCO3-]d was positively related to predialysis [HCO3-]s (p=0.001) and intradialytic increase in [HCO3-] (p=0.004), but not to postdialysis levels or intradialytic change in pCO2, [K+] or [Na+]. [HCO3-]d was inversely related to postdialysis [Ca2+] (p=0.02), but not to intradialytic [Ca2+] decrease. The patient with the highest [HCO3-]d (40mmol/L) had the highest intradialytic increase in pCO2 and [Na+] (11mmHg and 9mmol, respectively), the lowest postdialysis [K+] (2.2mmol/L) and the highest intradialytic [Ca2+] decrease.

Conclusions: Replacing NaHCO3 by individualized increased [HCO3-]d is equally effective for achieving target predialysis [HCO3-]s. Risk profile appears acceptable since severe metabolic alkalosis with compensatory hypoventilation, amplified intradialytic [K+] and [Ca2+] decrease (due to respectively increased K+ shift into cells and calcium binding to albumin) or increased intradialytic weight gain (due to more intradialytic [Na+] loading) were not observed. However, larger randomized long-term studies with clinical endpoints comparing both treatments are warranted for proper safety assessment.

SAFETY AND TOLERABILITY OF ZS-9 IN A MULTICENTER, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL IN PATIENTS WITH HYPERKALAEMIA

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Introduction and Aims: Optimal use of cardio- and reno-protective renin-angiotensin-aldosterone system inhibitors (RAAs) is greatly limited by hyperkalaemia. Sodium (or calcium) polystyrene sulfonate (SPS/CPS) with or without sorbitol, has been used for controlling hyperkalaemia but its efficacy is uncertain and has been reportedly associated with potentially serious adverse events (AEs), including sodium loading and colonic necrosis (Harel 2013; Sterkn 2010). Thus, there is a need for a safe, well-tolerated and effective hyperkalaemia therapy. ZS-9, a nonabsorbed cation exchanger designed to specifically entrap excess potassium (K+), significantly reduced serum K+ vs placebo over 48 hr with excellent tolerability in patients with chronic kidney disease (CKD) and hyperkalaemia (Ash 2013). Here we report the safety of ZS-9 during a large, two-part Phase 3 hyperkalaemia trial.

Methods: Patients (N=753) with serum K+ 5.0-6.5 mmol/L were randomised (1:1:1:1) to ZS-9 (1.25g, 2.5g, 5g or 10g) or placebo thrice daily (TID) for 48 hr (acute phase), after which those with K+ ≤4.9 mmol/L (n=542) were either re-randomized 1:1 to the same dose of ZS-9 that was given during the acute phase or placebo once daily (QD), or (for placebo-treated patients) re-randomized to ZS-9 1.25g or 2.5g QD, for Day 3-15 (extended phase). AEs and serious AEs (SAEs) were recorded through study end.

Results: At baseline, mean age was 65 yr. CKD, heart failure, or diabetes was 60%, 40% and 60% respectively. Two-thirds of patients were on concomitant RAASi. The proportions of patients with ≥1 AE and ≥1 GI AE in the ZS-9 dose groups were not significantly different compared with placebo in either the acute or extended-treatment phases. In the acute phase, the proportion of patients with ≥1 AE (≥1 GI AE) with ZS-9 2.5g, 5g, 10g and placebo was 16.2% (4.5%), 9.2% (2.1%), 14.0% (3.8%), and 11.9% (3.5%), respectively, vs 10.8% (5.1%) with placebo. The most common (≥2%) SAEs in any treatment group (GI AEs in the acute phase were diarrhea and constipation. One SAE (placebo) was reported during the acute phase. The proportions of patients with ≥1 AE and ≥1 GI AE in the extended-treatment phase are shown in the Figure.

The number of patients with SAEs was low and similar for ZS-9 (3, 4, 3, and 0 patients each on ZS-9 1.25g, 2.5g, 5g and 10g, respectively) and placebo (5 patients) with extended treatment.

Conclusions: ZS-9 was well tolerated during 2 days of acute, thrice-daily treatment and 12 additional days of once-daily treatment. The incidence of GI AEs with ZS-9 was not significantly different from placebo in either phase, including at the highest doses of ZS-9. No SAEs were reported with ZS-9 in acute phase and the number of patients with ZS-9 vs placebo during extended treatment. Acute TID and extended QD dosing of ZS-9 was well tolerated and appeared to be safe in these high-risk patients with hyperkalaemia, potentially allowing optimal use of reno- and cardio-protective RAAs in patients who may benefit from such treatment.
fractional excretion of urea and hypouricemia. Hypothyroidism and hypocortisolism were excluded. Common etiologies of SIAD were also ruled out. The absence of enteropathic or extra-nodal lymphoma, was settled by PET-CT and total body CT scans, which also excluded other solid organ tumours.

**Results:** A therapy with low-dose vasopressin V2 receptor antagonist was started, allowing a rapid and sustained normalization of serum sodium levels.

**Conclusions:** We report the first evidence of association between SIAD and a type 2 RCD, possibly an early-stage malignant condition. Increasing salt intake and restricting water intake allowed to reach an unstable equilibrium, which was indeed poorly tolerated by the patient. Low-dose tolvaptan was safe and effective in restoring normal serum osmolarity and normal serum sodium concentrations, allowing more liberal water intake in a patient also on life-long GFD.