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# DIALYSIS MINERAL BONE DISEASE

## MO043 ADDITION OF SEVELAMER HYDROCHLORIDE ASSOCIATES WITH IMPROVED SURVIVAL ON HEMODIALYSIS: THE JAPAN DIALYSIS OUTCOMES AND PRACTICE PATTERNS STUDY (J-DOPPS)

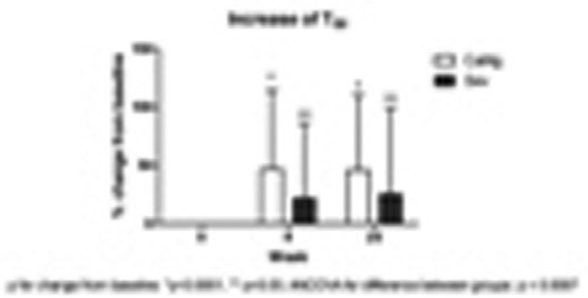
Hirotaka Komaba[1,2], Masatomo Taniguchi[3,4], Suguru Yamamoto[5], Takanobu Nomura[6] and Masafumi Fukagawa[1]
*[1]Tokai University School of Medicine, Isehara, Japan, [2]Harvard School of Dental Medicine, Boston, MA, [3]Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [4]University of Texas Southwestern Medical Center, Dallas, TX, [5]Niigata University Graduate School of Medical and Dental Science, Niigata, Japan, [6]Kyowa Hakko Kirin Co. Ltd, Tokyo, Japan*

**Introduction and Aims:** Previous studies suggested that sevelamer hydrochloride attenuates progression of arterial calcification and may reduce the risk of death in a head-to-head comparison with calcium-based phosphate binders. In the real world, however, sevelamer is often used as add-on or alternative therapy for patients with hyperphosphatemia when initiation or dose escalation of calcium-based phosphate binders is limited to avoid hypercalcemia. It is unknown whether the addition of sevelamer leads to improved survival in this situation.
**Methods:** We analysed the association between the addition of sevelamer and mortality among 2,453 haemodialysis patients participating in the Japan Dialysis Outcomes and Practice Patterns Study (J-DOPPS III, 2005-2008; J-DOPPS IV, 2009-2012). Mortality risk was assessed using standard baseline and time-dependent Cox regression models and inverse probability of treatment weighting (IPTW) using propensity score of initiating sevelamer.
**Results:** During a median follow-up of 24.2 months, 608 patients (24.8%) initiated sevelamer. Compared to untreated patients, patients who initiated sevelamer were younger with longer dialysis duration; were less likely to have diabetes and cardiovascular comorbidities; had higher serum calcium, phosphorus, and PTH levels; and were less likely to receive calcium carbonate and intravenous active vitamin D receptor activators. The incidence of mortality was 33.2/1000 person-years in the sevelamer group, compared with 73.1/1000 person-years in the non-sevelamer group (P <0.001). Addition of sevelamer was independently associated with decreased mortality in the standard baseline Cox regression (HR, 0.53; 95% CI, 0. 39 to 0.73), time-dependent Cox regression (HR, 0.46; 95% CI, 0.31 to 0.68), and IPTW method (baseline model: HR, 0.56; 95% CI, 0.47 to 0.66; time-dependent model: HR, 0.45; 95% CI, 0.30 to 0.68). Subgroup analysis suggested a more pronounced survival benefit associated with sevelamer in patients with higher serum phosphorus levels.
**Conclusions:** Addition of sevelamer is independently associated with decreased mortality. Our results suggest that additive therapy with sevelamer for treating hyperphosphatemia improves survival in maintenance haemodialysis patients.

## MO044 SERUM CALCIFICATION PROPENSITY OF HD PATIENTS IS THERAPEUTICALLY IMPROVED BY A CALCIUM ACETATE/ MAGNESIUM CARBONATE CONTAINING PHOSPHATE BINDER

Andreas Pasch[1], Angel LM De Francisco[2], Adrian Covic[3], Barbara Marzell[4], Hans J Arens[4], Jutta Passlick-Deetjen[5] and Wilhelm Jahnen-Dechent[6,7]
*[1]Inselspital, Bern, Switzerland, [2]Universidad de Cantabria, Santander, Spain, [3]C. I. Parhon University Hospital, Gr T. Popa, Iasi, Romania, [4]Fresenius Medical Care, Bad Homburg, Germany, [5]Heinrich-Heine University, Düsseldorf, Germany, [6]RWTH Aachen University, Aachen, Germany, [7]Helmholtz-Institute for Biomedical Engineering, Aachen, Germany*

**Introduction and Aims:** Magnesium has long been known as a potent calcification inhibitor. Addition of magnesium to human sera *in vitro* reduces the calcification propensity of these sera when measured with a newly developed *in vitro* calcification test (CALCISCO AG, Bern, Switzerland). This test measures the time which is needed for primary calcification particles to turn into secondary particles in serum. The longer the transformation time $T_{50}$, the lower the patient's propensity to calcify. The effect of therapeutic supplementation of magnesium, e.g. with a phosphate binder, on the calcification propensity in HD patients, has not been investigated yet.
**Methods:** The intrinsic calcification propensity of sera obtained from the CALMAG study was analysed with a novel *in vitro* calcification test. CALMAG was a controlled, randomized study, comparing the effect of Calcium acetate/Magnesium carbonate (CaMg) and sevelamer-HCl (Sev) on serum phosphorus. The analysis included 185 patients who completed the initial study per protocol (CaMg, n = 98; Sev, n = 87).
**Results:** Phosphate binder therapy reduced serum calcification propensity by delaying calciprotein particle- (CPP-) transformation time $T_{50}$ significantly over 25 weeks (CaMg: p < 0.0001, Sev: p=0.0083, Signed rank test); the reduction was significantly more pronounced with CaMg ( p=0.0022, Wilcoxon Mann-Whitney test). In the overall patient population, $T_{50}$ after 25 weeks showed a correlation with serum phosphorus (r = -0.29123, P < 0.0001), serum magnesium (r = 0.22890, P = 0.0018), iPTH (r = -0.19622, P = 0.0079), and b-CTX (r = -0.15809, P = 0.0316). There were no correlations with total or ionized calcium (r = 0.02747, P = 0.7113 and r = -0.02025, P = 0.7891, respectively).
**Conclusions:** Our data demonstrate for the first time that phosphate-binding therapy may positively affect serum calcification propensity of HD patients. The novel *in vitro* serum calcification test may identify therapies that are effective in protecting patients from future calcification. In this study, CaMg was more effective in decreasing calcification propensity than Sev. This difference is probably due to the anti-calcification properties of magnesium.



MO044

## MO045 CALCIUM MASS BALANCE IN HIGH EFFICIENCY ON-LINE CONVECTIVE THERAPIES WITH DIFFERENT INFUSION MODALITIES

Angelo Castellano[1], Pio Ruggiero[2] and Luciano Alberto Pedrini[3]
*[1]Nephrocare, Seriate, Italy, [2]Nephrology and Dialysis - Bolognini Hospital, Seriate, Italy, [3]Nephrology and Dialysis Nephrocare - Bolognini Hospital, Seriate, Italy*

**Introduction and Aims:** Calcium mass balance (CaMB) during haemodialysis contributes to overall calcium balance in patients on RRT and calcium overload may influence development and progression of vascular calcification. In order to better evaluate the clinical impact of high-efficiency convective treatments on the bone-vascular axis it is necessary to know how they influence CaMB during the dialysis session and if different infusion modes have different effects on it.
**Methods:** We compared three dialysis techniques: high-flux hemodialysis (HF-HD), on-line post-diluition HDF and on-line mixed HDF. Twelve chronic dialysis patients were enrolled. After a run-in period of 1 week, in which they underwent high-flux dialysis, patients were randomized to receive two alternate sequences of on-line HDF, one in post-diluition mode and the other in mixed-diluition mode. Each sequence was conducted for 2 weeks. Nominal ionized calcium dialysate concentration (CaD) was 1,5 mmol/l for all treatments. The other dialysis parameters (QB, time, etc) were kept constant in all sessions of the study. Total plasma (CaT) and ionized (Ca++) calcium was measured at the beginning and at the end of both mid-week sessions of each sequence , and CaMB was also evaluated from the dialysate side by collecting a representative sample of spent dialysate.
**Results:** The mean effective Qb was 372 ± 25 ml/min in HF-HD, 371 ± 26 ml/min in post-HDF and 372 ± 28 ml/min in mixed-HDF. Mean effective treatment duration was 242 ± 2 min in HF-HD and mixed-HDF, 245 ± 5 min in post-HDF. The mean convective volume was 26,2 ± 2,5 L in post-HDF and 39,2 ± 4,3 L in mixed HDF. We observed, in almost all treatments, an intradialytic gain of calcium: mean CaMB was 304 ± 263 mg in HF-HD, 401± 233 mg in post-diluition HDF and 288 ± 205 mg in mixed-diluition HDF. The difference in CaMB between mixed and post-HDF resulted statistically significant ( p= 0,047). The mean dialysate Ca++ concentration in the inlet dialysate was 1,39±0,03 mmol/L in mixed and post-HDF sessions and 1,38 ± 0,06 mmol/L in HF-HD sessions ( p=ns). The mean pre-dialysis plasma Ca++ was 1,18 ±0,06 mmol/L in post-HDF, 1,17±0,06 mmol/L in mixed HDF and 1,19 ± 0,07 mmol/L in HF-HD ( p=ns). The mean pre-dialysis Ca++ plasma/dialysate concentration gradient was 0,22±0,08 mmol/L in mixed and post HDF and 0, 21±0,07 mmol/L in

HF-HD (p=ns). Calcium gain during hemodialysis was correlated to the inlet dialysate calcium concentration (mean r 0,68; p < 0,05), and strongly correlated with its gradient across the membrane, especially for high-convective treatments (r=0,81; p<0,05). Mean pre- and post-dialysis plasma CaT concentrations were 8,96±0,45 and 10,2±0,5 mg/dl in HF-HD, 8,93±0,5 and 9,95±0,42 mg/dl in mixed-HDF, and 8,97±0,4 and 10,06±0,43 mg/dl in post-HDF (p < 0,05 for post-session values between HF-HD and mixed HDF).
**Conclusions:** The infusion modality in high-efficiency convective treatments appears to affect CaMB during the sessions. At similar operating conditions, mixed HDF promotes lower amount of calcium gain and less positive mass balance than post-HDF, probably due to the dilution effect of the pre-filter infusion rate (lower diffusion gradient to the patient). Lower than the usual CaD (1,5 mmol/l) should be set especially in post-HDF, in order to avoid large positive calcium mass balance, which may promote or worsen adynamic bone disease and vascular calcifications.

## MO046 VARIABILITY IN MINERAL METABOLISM PARAMETERS IS ASSOCIATED WITH AN INCREASED RISK FOR HOSPITALIZATIONS: RESULTS FROM THE MONDO CONSORTIUM

Fellype Barreto[1], Aileen Grassmann[2], Daniele Marcelli[2], Bernard Canaud[2], Peter Kotanko[3], Viviane C. Silva[1], Len Usvyat[4,3], Roberto Pecoits-Filho[1] and Mondo Consortium[5]
*[1]Pontifícia Universidade Católica do Paraná, Curitiba, Brazil, [2]Fresenius Medical Care, Bad Homburg, Germany, [3]Renal Research Institute, New York, NY, [4]Fresenius Medical Care North America, Waltham, MA, [5]Renal Research Institute, New York, NY*

**Introduction and Aims:** KDIGO guidelines on CKD-MBD suggest that therapeutic decisions should be based on trends rather than on single measurements of a laboratorial abnormality. However, studies showing the association between mineral metabolism disorders and morbidity and mortality are frequently based on single or very limited measurements of laboratory parameters. Data on calcium, phosphate and PTH variability in HD patients, and its association with hard outcomes, are still lacking in the literature. Our aim is to evaluate the associations between variability in mineral metabolism parameters and hospitalizations.
**Methods:** MONDO consists of hemodialysis (HD) databases from multiple dialysis providers [Usvyat, Blood Purif 2013; von Gersdorff, Blood Purif 2014]. We identified all patients in the Fresenius Medical Care Europe data base [17 countries] with in-center treatments between 1/2006 and 12/2012 who survived at least six months on HD. The mean and standard deviation of clinical and laboratory parameters were computed for the first 6 months (baseline) and all cause hospitalizations were observed in the following 12 months (follow up period). Poisson regression models were constructed to explore associations between baseline parameters and the number of hospitalizations in the follow up period.
**Results:** We studied 18955 patients (59% male, mean age=64.1 years). Phosphate and PTH variability were associated with higher number of hospitalizations, while calcium variability was associated with lower number of hospitalizations.
**Conclusions:** Phosphate variability was associated with higher number of hospitalizations while calcium variability was associated with lower number of hospitalizations. These studies may be helpful to identify trends that may identify HD patients at high risk for complications of mineral metabolism disorders.

Table 1. Poisson regression to predict number of hospitalizations in months 7 to 18 from the start of dialysis

| Parameter | Estimate | Wald 95% Confidence Limits | | p-value |
|---|---|---|---|---|
| **Intercept** | **0.589** | **0.359** | **0.819** | **<.0001** |
| **Age** | **0.003** | **0.002** | **0.005** | **<.0001** |
| **Gender = Male** | -0.027 | -0.061 | 0.007 | 0.114 |
| **Race = White** | **-0.326** | **-0.365** | **-0.287** | **<.0001** |
| **BMI (kg/m^2)** | **0.009** | **0.006** | **0.012** | **<.0001** |
| **Access = catheter** | **0.595** | **0.562** | **0.629** | **<.0001** |
| **Diabetic** | **0.322** | **0.287** | **0.356** | **<.0001** |
| **Treatment time (mins)** | **-0.007** | **-0.008** | **-0.006** | **<.0001** |
| **PreSBP<100** | **0.444** | **0.286** | **0.602** | **<.0001** |
| **PreSBP 100-140** | reference | | | |
| **PreSBP>140** | **0.074** | **0.039** | **0.109** | **<.0001** |
| **IDWG (%)** | **0.126** | **0.109** | **0.142** | **<.0001** |
| **Calcium 8.4-9.5 (mg/dL)** | -0.018 | -0.052 | 0.017 | 0.319 |
| **Calcium standard deviation** | **-0.180** | **-0.244** | **-0.116** | **<.0001** |
| **Phosphate 3.5-5.5 (mg/dL)** | 0.015 | -0.021 | 0.050 | 0.416 |
| **Phosphate standard deviation** | **0.164** | **0.131** | **0.196** | **<.0001** |
| **PTH 150-300(pg/mL)** | 0.034 | -0.001 | 0.069 | 0.058 |
| **PTH standard deviation** | **0.0003** | **0.000** | **0.000** | **<.0001** |

*Significant predictors are shown in bold*

MO046

## MO047 EFFECTS OF CINACALCET ON FRACTURE EVENTS IN PATIENTS RECEIVING HEMODIALYSIS: THE EVOLVE TRIAL

Tilman B Drueke[1], Sharon M Moe[2], Safa Abdalla[3], Patrick S. Parfrey[4] and Glenn M Chertow[5]
*[1]INSERM Unit 1088, Amiens, France, [2]Indiana Univ School of Medicine, Indianapolis, IN, [3]Stanford University, Palo Alto, CA, [4]Health Sciences Center, St. John's, NL, Canada, [5]Stanford University School of Medicine, Palo Alto, CA*

**Introduction and Aims:** Fractures are more frequent in patients receiving maintenance hemodialysis than in the general population; fractures are painful, impair quality of life and reduce life expectancy. The objectives of this analysis were to determine fracture sites, frequency of and risk factors for clinical fracture events, and the effect of cinacalcet on clinical fracture risk in patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism using data from the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial.
**Methods:** EVOLVE was a randomized, double-blind, placebo-controlled clinical trial that randomized 3883 hemodialysis patients with moderate to severe secondary hyperparathyroidism (median intact PTH, 693 pg/mL) to cinacalcet or placebo for treatment up to 64 months. For this analysis, we focused on clinical fracture events; the primary endpoint was first clinical fracture event in the defined risk period.
**Results:** Six hundred and twenty-two clinical fractures were observed in 493 patients - 255/1935 (13.2%) randomized to placebo and 238/1948 (12.2%) randomized to cinacalcet, with subsequent deaths at 30 days in 114 (44.7%) and 90 (37.8%) patients, respectively. The majority of clinical fractures involved cortical bone. In an unadjusted intention-to-treat analysis the relative hazard for fracture (cinacalcet versus placebo) was 0.89 (95% CI 0.75 to 1.07, p=0.22). After adjustment for baseline characteristics, the relative hazard was 0.84 (95% CI 0.69 to 1.01, p=0.066); accounting for multiple fractures, the relative hazard was 0.83 (95% CI 0.71 to 0.98). More than two-thirds of patients in both groups discontinued study drug for a variety of protocol-specified and non-specified reasons. Using a pre-specified lag censoring analysis (censoring data beyond 6 months after stopping study drug), the relative hazard for fracture was 0.72 (95% CI 0.58 to 0.90, p=0.003).
**Conclusions:** In an unadjusted intention-to-treat analysis, cinacalcet did not significantly reduce the risk of clinical fracture. However, when accounting for differences in baseline characteristics, multiple fractures, and/or events prompting discontinuation of study drug, cinacalcet reduced the risk of clinical fracture by 16 to 28%.