Diabetes – clinical research

OM001 NON-ALBUMINURIC RENAL IMPAIRMENT IN TYPE 2 DIABETIC PATIENTS – THE SWEDISH NATIONAL DIABETES REGISTER (NDR)

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Introduction and Aims: Type 2 diabetes (T2D) is one of the leading causes of end stage renal disease (ESRD) but not all patients with T2D develop renal dysfunction (albuminuria and/or renal impairment). Albuminuria and renal impairment are the two main manifestations of renal disease in T2D, but not entirely linked in patients with T2D. Recent data suggest that there are distinct pathways to development of non-albuminuric or albuminuric renal impairment. The aim of this study was to identify clinical characteristics associated with non-albuminuric renal impairment in type 2 diabetic patients in a large nation-wide population-based diabetes register.

Methods: 62 661 patients with T2D aged 30-80 years with complete datasets reported on albumin excretion, renal function (serum creatinine) and clinical characteristics to the Swedish National Diabetes register; NDR in 2008 were included in the study. Complete datasets were found in 63% of all patients reported to NDR this year. Albuminuria was defined as urinary albumin excretion rate > 20 μg/min and renal impairment as estimated glomerular filtration rate; eGFR < 60 ml/min/1.73 m² according to MDRD. Logistic regression analyses for clinical and biochemical variables with renal impairment with or without albuminuria as dependent variable were preformed. Adjusted odds ratios were calculated and continuous variables were increased per one standard deviation; SD.

Results: 24% of all patients had albuminuria (n=15 039) (68% micro- and 32% macroalbuminuria) and 15% renal impairment (n=9 308). Among patients with renal impairment 56% had non-albuminuric and 42% albuminuric renal impairment. In a multivariate analyses patients with non-albuminuric renal impairment had significantly and independently shorter diabetes duration (adj OR 0.73; 95%CI 0.70-0.76), higher total cholesterol (1.05; 1.01-1.10), lower levels of triglycerides (0.83; 0.80-0.87), lower systolic blood pressure (0.81; 0.78-0.84), better glycemic control (HbA1c%) (0.86; 0.82-0.91), lower BMI (0.88; 0.84-0.93) and were more often female and non-smokers as compared with patients with albuminuric renal impairment.

Conclusion: In this population-based nationwide study the majority of patients with type 2 diabetes and renal impairment were non-albuminuric. Distinct sets of risk factors were associated with the presence or absence of albuminuria, patients with non-albuminuric renal impairment having less prominent features of the "metabolic syndrome". This finding could partly be explained by the use of renin angiotensin system inhibitors among non-albuminuric patients but also support the concept of different underlying pathophysiology mechanisms. Development of markers and methods for a more accurate estimation of renal function in T2D patients without albuminuria is important for screening and future treatment of these patients.

Fig. 1. ROC analysis of detection of DN progression. Bars indicate areas under the ROC curve obtained for CKD273 model (CKD273, dark blue), the albumin excretion rate (AER, white), and the serum creatinine level (S-crea, light blue), analyzed for correct classification of normo- or microalbuminuric subjects, we could demonstrate that an AUC of 0.85 (p=0.0001) for a period 3-4 years (see figure 1). One of the hallmarks of diabetes and associated complications appears to be the increase in extracellular matrix (ECM) and the release of its components, most notably collagen. This process appears to be in part due to reduced proteolysis and is reflected at a very early stage by the decrease in urinary collagen fragments. Assessment of these seems to result in a much higher accuracy of predicting DN than urinary albumin or serum creatinine.

OM003 TRANSPLANTATION OF THE TYPE 1 DIABETIC PATIENT: THE LONG-TERM BENEFIT OF A FUNCTIONING PANCREAS ALLOGRAFT

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Introduction and Aims: We recently demonstrated that a functioning pancreas independently contributes to improved kidney graft and patient survival in type 1 diabetes who receive a simultaneous pancreas kidney transplant (SPK; J Am Soc Nephrol 19: 1557, 2008).

Methods: Using the data of the Collaborative Transplant Study (CTS), we now analyzed data up to year 20 after transplantation. We studied type 1 diabetic recipients of deceased donor kidneys (DDK), living donor kidneys (LDK), or SPK performed during three time periods: 1984 to 1990, 1991 to 2000, and 2001 to 2007.

Results: DDK recipients showed inferior graft and patient survival as compared to LDK and SPK recipients starting from year 6 after transplantation. LDK recipients had a superior graft survival rate initially, but the survival rates of kidneys in SPK recipients merged with those of LDK after the first decade of follow up. The results of patient survival paralleled those
of kidney graft survival: an early advantage of LDK as compared to SPK faded away during prolonged follow up. Multivariate analysis showed that graft and patient survival of SPK recipients was superior to that of LDK recipients after the tenth posttransplant year for transplants performed between 1984 to 1990 (patient survival: hazard ratio HR = 0.52, p<0.0001; graft survival: HR = 0.63, p=0.048).

Conclusions: We conclude that the early survival benefit of LDK as compared to SPK is lost during long-term follow up, probably due to improved glycomic control.

OM004 VASOCONSTRICTOR EFFECTS OF INSULIN IN THE HUMAN MICROCIRCULATION ARE MEDIATED VIA ENDOTHELIN-1-TYPE-B-RECEPTORS
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Introduction and Aims: In the vasculature insulin activates two distinct signaling pathways that result in secretion of nitric oxide (NO) and endothelin (ET-1), respectively. NO, stimulated by higher insulin doses, is thought to be the underlying agent in insulin-mediated, endothelium-dependent vasodilation. However, we have shown that at low doses insulin causes vasoconstriction in the human microcirculation. We postulated that ET-1 stimulated by insulin could be responsible for this vasoconstriction.

In an earlier study we found, that insulin at a dose, that by itself caused vasoconstriction, inhibited vasodilation to an ET-1-type-A-receptor (ET-A)-antagonist, suggesting increased insulin-mediated ET-1-activity. The role of ET-1-type-B (ET-B)-receptors in this setting remained to be identified and ET-B-type-B-receptors (ET-B) in combination. Effects of BQ123 10^-8mol and BQ788 (10^-8 and 10^-10mol) were used a Laser-Doppler-Imager (moor LDI-V5.0, Axminister,UK) to measure changes in skin blood flow. 10^7 IU insulin (Insuhuman Rapid, Sanofi,Germany) were injected intradermally alone or following injection of the ET-A-antagonist BQ123 10^-7mol, the ET-B-antagonist BQ788 10^-8mol in combination. Effects of BQ123 10^-7mol and BQ788 10^-8mol in combination were also recorded. Recordings of BQ123 10^-7mol and BQ788 were also recorded. Data are presented as arbitrary perfusion units (PU) and are given as mean ±SD. Two-way ANOVA was used to analyze time-effect responses.

Results: Again insulin led to mild but significant vasoconstriction (P<0.0001 vs. baseline) and reduced BQ123-mediated vasodilation (BQ123 vs. BQ123+insulin: +177±60 vs. +87±39PU, P<0.0001). ET-B-blockade with BQ788 at the lower dose (10^-7mol) produced vasocostriction (-24±8PU, P<0.0001 vs. baseline), which at the higher dose (10^-6mol) was no longer present. In the presence of ET-B-blockade (BQ788 10^-7mol insulin-induced vasodilation (+104±32PU, P<0.0001 vs. baseline). Blockade of both ET-A and ET-B-receptors induced pronounced vasodilation that was not different from vasodilation to ET-A-blockade alone. However, in the presence of BQ788 insulin no longer affected vasodilation induced by BQ123.

Conclusions: Vasoconstrictor effects of low insulin doses in the peripheral microcirculation of healthy humans seem to be mediated via ET-B-receptors.

OM005 PREVENTION OF MICROALBUMINURIA IN TYPE 2 DIABETES (ROADMAP TRIAL)
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Introduction and Aims: Microalbuminuria is an early sign of diabetic nephropathy and increased cardiovascular risk. We investigated whether early treatment with an angiotensin receptor blocker (ARB) in diabetic subjects with normal albumin excretion delays the occurrence of microalbuminuria and concomitantly recorded cardiovascular and renal events.

Methods: We studied 4,447 patients with type 2 diabetes and at least one additional cardiovascular risk factor in a randomized, double-blind, multicentre, controlled, and event-driven (onset of microalbuminuria) trial. They received either 40 mg olmesartan or placebo once daily for a median duration of 3.2 years. In both groups, additional antihypertensive drug treatment (except ACE inhibitors or ARBs) was used to reach the target blood pressure of <130/80 mmHg.

Results: Baseline eGFR, blood pressure and cardiovascular disease (CVD) risk profiles were comparable in both groups. Nearly 80% of the subjects in the olmesartan group and 71% in the placebo group achieved target blood pressure at month 48. Kaplan-Meier analysis showed a cumulative incidence of microalbuminuria of 8.2% (n=178) with olmesartan and 9.8% (n=210) with placebo which represents a risk reduction of 23% (HR: 0.77; 95.1% CI: 0.63 to 0.94; p=0.01) in favour of subjects receiving olmesartan.

At study end eGFR was lower in the olmesartan-treated subjects (80.1 vs. 83.7 mL/min/1.73 m², p<0.001). In both groups 23 subjects had a doubling of the baseline serum creatinine. Overall cardiovascular morbidity and mortality rate was low and similar between groups with cardiovascular morbidity events in 81 (3.6%) and 91 (4.1%) patients, and total mortality in 26 (1.2%) and 15 (1.7%) on olmesartan and placebo, respectively (p>0.1). Cardiovascular mortality however was higher (15 (0.7%) vs. 3 (0.1%); p=0.01) in the olmesartan group, possibly due to hypotensive episodes in subjects with pre-existing CVD.

Conclusions: In subjects with type 2 diabetes and excellent blood pressure control early treatment with the ARB olmesartan showed a significant risk reduction regarding the ‘time to onset of microalbuminuria’.

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and a minority of CD8+ T cells. OX40L, also a member of the tumor necrosis factor superfamily, is present on antigen presenting cells. Signaling through OX40/OX40L promotes T cell division and survival. They also suppress Treg activity. In murine cardiac allograft model OX40/OX40L signaling induces early allograft rejection (Burrell et al. Journal of Immunology 2009). Herein we examined the role of OX40/OX40L in acute cellular rejection (ACR) of human renal allografts by studying their expression pattern in urinary cells.

Methods: We obtained urine samples at the kidney biopsy from 57 human kidney transplant recipients; 27 samples were obtained from 27 transplant recipients with biopsy confirmed acute cellular rejection and 30 samples were obtained from 30 transplant recipients with stable renal allograft function and normal protocol biopsies. Total RNA was isolated from urinary cells, reverse transcribed to cDNA, preamplified with gene specific oligonucleotide primers, and absolute mRNA copy numbers were quantified using real time quantitative PCR assays by the standard curve method developed and validated in our laboratory.

Results: The log-transformed mean (±SE) ratio of OX40 mRNA to 18S rRNA copies was higher in the urine of ACR patients compared to stable, 6.73±0.41 versus 3.87±0.45 (P<0.0001). The log-transformed mean (±SE) ratio of OX40L mRNA copies to 18S RNA copies was also higher in the urine of ACR patients compared to stable 2.59±0.58 versus 0.78±0.37 (P=0.01). Analysis of ROC curves demonstrated that ACR can be predicted with 90% sensitivity and 74% specificity using 6.01 as cutoff for OX40 mRNA (AUC: 0.82; P<0.0001) and 74% sensitivity and 80% specificity using 2.56 as cutoff for OX40L mRNA (AUC: 0.70, P=0.01). Spearman’s coefficient (r_s) data revealed a significant inverse relationship between log-transformed ratios of OX40 mRNA to 18S RNA copies and the time from transplantation to biopsy proven ACR (r_s=-0.41; P=0.03). The patients with early (within 3 months of transplantation) ACR had higher mRNA levels of OX40, as compared to patients with late ACR (mean ±SE, 7.55±0.39 vs. 6.25±0.59; P=0.05).

Conclusions: OX40 and OX40L expression is upregulated during an episode of ACR in human kidney transplant recipients. Our data shows that the OX40/OX40L costimulatory pathway plays a pivotal role during the development of ACR in human renal allografts. In addition, measurement of urinary cell mRNA levels of OX40 and OX40L can noninvasively diagnose the presence of acute cellular rejection in human kidney transplant recipients.

OM007 IMPROVED RENAL FUNCTION OF AN EVEROLUSIM/ENTERIC-COATED MYCOPHENOLATE SODIUM REGIMEN AFTER CALCINEURIN INHIBITOR WITHDRAWAL IN DE NOVO RENAL TRANSPLANT PATIENTS: 2 YEARS FOLLOW-UP OF THE ZEUS-TRIAL

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Introduction and Aims: To follow-up on renal function, efficacy and safety after a conversion to an everolimus/enteric-coated mycophenolate sodium (EC-MPS) regimen after Cyclosporine (CsA) withdrawal in de novo kidney allograft recipients at month (Mo) 24 post transplantation.

Methods: In this prospective, open-label, controlled, multi-center study renal allograft recipients were randomized to an immunosuppressive regimen consisting of either Everolimus/EC-MPS or CsA/EC-MPS at Mo 4.5 after transplantation. After completion of the core study at Mo 12, patients were included in an observational 12-Mo follow up study.

Results: 300 pts were randomized to either Everolimus/EC-MPS (n=155) or CsA/EC-MPS (n=145). 244 (81.3%) pts completed the 24 month visit. Renal function expressed as calculated GFR (Nankivell method) was similar in both groups at baseline (randomization 4.5 Mo post tx) with an improvement by 7.16 mL/min/1.73m2 in favor of the Everolimus/EC-MPS regimen (p=0.017) at Mo 24 (61.7±17.1 vs. 68.2±19.4 mL/min/1.73m2). The observed GFR slope from randomization to Mo 24 was +6.7±[+3.2,+10.2] mL/min/1.73m2 for Everolimus/EC-MPS and -0.8±[-4.5,+2.9] mL/min/1.73m2 for CsA/EC-MPS pts. Fewer pts in the everolimus group had a decline of GFR compared to renal function at randomization (Nankivell: 24.7% vs 41.4%; p=0.0034) compared with cyclosporine. BPAR was reported in 17 (11.0%) Everolimus/EC-MPS treated vs. 7 (4.8%) CsA/EC-MPS treated patients between randomization and Mo 24. After 12 months two additional BPAR occurred in each group. Three death and one graft loss was observed in the CsA/EC-MPS group none in the Everolimus group. The number of patients with infections (35 pts (22.6%) in the Everolimus vs. 30 pts (20.7%) in the CsA group) and hospitalization (43 pts (27.7%) in the Everolimus vs. 51 pts (35.2%) in the CsA group) in the follow-up period (Mo 12 to Mo 24) was comparable in both groups.

Conclusions: The conversion to Everolimus/EC-MPS in de novo renal transplant patients after CNI withdrawal early after transplantation reflects a novel therapeutic approach which significantly maintains renal function over a period of 24 months without compromising efficacy and safety.

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at >5 years post-graft failure. For the first 2 years following graft failure, patients commencing on PD have a lower adjusted mortality than those on HD (HR 0.75, p=0.02).

Conclusions: In keeping with previous work, the initiation of dialysis following transplant loss is associated with significant mortality, most pronounced in the 1st year after graft failure. Patients commencing dialysis after graft failure do significantly worse than “fit” (i.e. suitable for transplantation) patients initiating RRT. Patients starting on PD have better outcomes; probably reflecting patient selection bias with fetter patients (fewer co-morbidities) opting for PD. The observation that the period of highest mortality risk is around the time of transplant failure suggests the cause is directly related to complications of graft failure and its management, rather than to underlying comorbidity causing both graft loss and mortality. Further analyses of the patient- and centre-level causes of this increased mortality risk are required, to inform the future development of risk-reduction strategies.

**OM009 DECOY OR NOT DECOY IN DIAGNOSTIC ALGORITHMS FOR BK POLYOMAVIRUS (BKV) INFECTION IN KIDNEY TRANSPLANTATION?**

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**Introduction and Aims:** BK Polyomavirus nephropathy (BKVAN) occurs in 3% to 4% of kidney transplant recipients, causing graft loss in 50% of cases. Early identification of BKV infection may allow prevention of BKVAN, but the diagnostic algorithm for screening the disease is controversial. The aim of the study is a retrospective evaluation of prevalence, risk factors and outcome of BKV infection among 636 patients who underwent kidney transplantation at our Center from 1998 to 2008, with the aim of evaluating the appropriateness of our diagnostic algorithm.

**Methods:** Our algorithm included detection of Decoy cells in urinary cytology as the first step of screening (I) at 1, 3, 6, 9, 12, 18, 24 months after transplantation, followed by qualitative PCR in urine (viruria) and blood cytology as the first step of screening (II) at 1, 3, 6, 9, 12, 18, 24 months after transplantation, and increased serum creatinine level or proteinuria.

**Results:** Among the 462 patients who completed the diagnostic algorithm, Decoy cells were found in 92 (20%) and had a negative impact on kidney survival (loss of the kidney in 6/92=7% vs 9/370=2%, p=0.045). This effect was present not only at the early stages of follow-up (97.8% vs 99.1% after 3 years), but also in the long-term (84% vs 94.7% after 9 years, p=0.045). Among the 92 patients with Decoy positive results, while viruria was present in 75 (81.5%), viremia was only demonstrated in 23 (25%) and a diagnosis of BKVAN was biopathically performed in 992 (10%) of these patients. Immunosuppressive protocol based on steroid, mycophenolate and tacrolimus had been adopted in all these patients, and immunosuppression was reduced in all patients, in association with antiviral treatment in 4/9. Viremia neutralized in all patients (9/9) but in 2/9 graft loss occurred, one patient died 2 years after viremia neutralization due to hepato-renal syndrome, and BKV inclusions were demonstrated in hepatocytes at autopsy.

**Conclusions:** In conclusion, BKVAN was diagnosed in 2% of our kidney transplant recipients, and caused graft loss in 22% of cases. Although decoy cell positivity had a high predictive value for the presence of viruria and resulted to be a risk factor for kidney survival, significant viremia was demonstrated only in a minority of cases, and the lag-time occurring before a biopsy confirmation of infection was unacceptably long eventually leading to misdiagnosis. Our experience suggests the opportunity of discussing whether different diagnostic algorithm constituted by BKV quantitative viremia as I step instead of III step would be more cost/benefit advantageous to achieve earlier diagnosis of BKVAN.
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Results: Preoperative serum P, iCa, iCa, iPTH, ALP were comparable. Subtotal parathyroidectomy (n=27) and total parathyroidectomy with autotransplantation (n=15) were performed. Mean iPTH15 value and iPTH% rates were 145.9±12.3 pg/ml and 76.91±0.7 and 522.5±5.4 pg/ml and 35% 75.1±2.0 (p=0.001) in Group 1 and 2 respectively. Mean serum iCa and iCa at POD1 in Group 1 and 2 were 7.6±0.1 mg/dl, iCa 0.91±0.4 mmol/L and 8.3±0.3 mg/dl, 1.05±0.4 mmol/L (p<0.05), respectively. ALP levels were similar. However serum ALP levels regressed compared to preoperative baseline postoperatively at 1 month demonstrated higher decrease in group 1 (42.7%) compared to Group 2 (21.9%).

Conclusions: iPTH15 value and iPTH% rate is a helpful method of predicting successive surgical resection in patients undergoing parathyroidectomy because of secondary hyperparathyroidism. The rate of decrease in iPTH detected intraoperatively compared to baseline levels exceeding 90% successfully reflects successive surgery. Postoperative normocalcemia without calcium replacement treatment would also raise a suspicion about completeness of surgical resection.

OM013  PLASMIN ACTIVATION IS PROTECTIVE IN HYPERTENSION INDUCED KIDNEY INJURY IN MICE

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Introduction and Aims: Plasmin can exert beneficial as well as deleterious effects on chronic kidney injury, at least in part via activation of matrix metalloproteinases (MMP). We studied the role of plasmin for hypertension-induced kidney damage in plasminogen activator inhibitor-1 (PAI-1) deficient mice with increased plasmin generation, and in tissue-type plasminogen activator (t-PA) deficient mice with deficient plasmin generation. We hypothesized that increased plasmin generation is protective against kidney injury in mice, whereas a lower plasmin generation is harmful.

Methods: Hypertensive nephropathy was induced by continuous angiotensin II (Ang II) infusion via osmotic minipumps. The effect of Ang II infusion was determined in wild-type (WT, n=9), PAI-1 deficient (PAI-1 (-/-), n=13) and t-PA deficient (t-PA (-/-), n=16) mice, and normotensive control animals of the respective genotype. Blood pressure was detected by continuous radiotelemetric intra-arterial measurement in 5-6 animals per genotype. After four weeks of Ang II infusion mice were sacrificed. Albuminuria and aldosterone plasma levels were evaluated. Immunostaining and computer-aided quantitative evaluation were performed for collagen 1 and nphrin. Gene expression of collagen 1, transforming-growth-factor-beta (TGF-b), MMP-2, and MMP-9 were investigated by real-time PCR.

Results: Aldosterone plasma levels were elevated by Ang II (p<0.01) to an identical degree in all genotypes. Blood pressure was increased in all genotypes by Ang II (p<0.01). Albuminuria was significantly reduced in Ang II treated PAI-1 (-/-) mice compared to Ang II treated t-PA (-/-) mice (203±111 vs. 709±150 microg/24h, p<0.01). Ang II treated PAI-1 (-/-) exhibited higher Nephrin immunostaining than t-PA (-/-) mice (p<0.05). Interstitial collagen 1 accumulation was induced by Ang II in all genotypes. Compared to WT (19±2), t-PA (-/-) mice had a higher (25±2, p<0.05) and PAI-1 (-/-) mice had a lower (14±1, p<0.05) collagen 1 accumulation. Collagen 1 and TGF-b gene expression was increased by Ang II in WT and PAI-1 (-/-) mice (p<0.05) but not in t-PA (-/-) mice, compared to normotensive controls. MMP-2 and MMP-9 expression was increased by Ang II in WT and PAI-1 (-/-) (p<0.05) but not in t-PA (-/-) mice. Preliminary results from zymograms indicate that MMP activity in kidney tissue was reduced in Ang II treated t-PA (-/-) mice.

Conclusions: Lack of PAI-1 protects mice with Ang II induced hypertension from podocyte damage and interstitial fibrosis. In contrast, lack of t-PA aggravates interstitial fibrosis, and this effect appears to be due to decreased degradation of collagen 1. Our findings support the notion that plasmin protects from podocyte damage and interstitial fibrosis in hypertensive kidney injury.
CILIARY NEUROTROPHIC FACTOR DEFICIENCY PROTECTS AGAINST ANGIOTENSIN II INDUCED HYPERTENSION

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Introduction and Aims: Ciliary Neurotrophic factor (CNTF) is an interleukin-6-like (IL-6) cytokine which plays a distinct role in survival and differentiation of neuronal cells. Through binding to its own receptor and activation of the Jak2/STAT3-signaling cascade, CNTF mediates anti-inflammatory effects and reduces apoptosis. CNTF deficient mice show a detrimental progression of autoimmuno encephalomyelitis. Despite the well examined role of CNTF in the central nervous system, its role in other tissues is poorly understood. Angiotensin II induces the expression of IL-6 mainly by increased production of reactive oxygen species. Activation of the renin angiotensin system is a typical finding in chronic kidney disease. Due to the nature of CNTF and its receptor as an IL-6-like ligand and receptor, this study focuses on the role of CNTF in angiotensin II (angII) induced hypertension in uninephrectomized mice.

Methods: One week after uninephrectomy, angII osmotic minipumps (1000ng/min/kgBW) were implanted in CNTF-KO (C57/Bl6j background) and matched C57/Bl6j male mice (WT) (n=19). Blood pressure was measured via tail cuff for 2 weeks. In addition, kidneys from WT- and CNTF-KO-mice were isolated perfused and a dose-response relationship to ang II was measured.

Results: WT- and CNTF-KO-mice developed hypertension within the first two days after surgery. Both groups showed an increase in systolic blood pressure (BP) over time. Comparison between the WT and CNTF-KO group revealed that at any time point BP was significantly lower in the CNTF-KO-group compared to the WT-group (WT vs. CNTF-KO week1: 153±3 vs. 139±3 mmHg; week 2: 168±4 mmHg vs. 151±5 mmHg). Heart hypertrophy was significantly less in the CNTF-KO (6.5±0.4 g/mg BW) compared to the WT-group (8.2±0.6 mg/g BW). In the isolated perfused kidney, angII dependent response pressure was significantly lower in the CNTF-KO-group compared to the WT-group.

Conclusions: This study shows that CNTF plays an important role in BP response to angII. However, at present, it cannot be distinguished whether intra- or extracellular actions of CNTF are responsible for the differences in blood pressure regulation. Future studies are needed to elucidate the underlying mechanisms.

Results: Before L-NNAME application, the basal MBP was 99.1±6.9 mmHg in TLR4-/- and 101.1±2.9 mmHg in WT (pns). At the end of L-NNAME application (mean of 3 days), the MBP was significantly increased in the WT (112.0±2.9 mmHg, p < 0.05) but not in the TLR4-/- group (102.0±3.7 mmHg; WTL-name vs. TLR4-/- L-name: p < 0.05).

HW/BW was lower in TLR4-/- compared to WT (TLR4-/-: 4.1±0.3 g/kg versus WT: 4.6±0.2 g/kg; p < 0.05) and cardiomyocytes were smaller in the knockout (TLR4-/-: 396.8±65.5 μm² units versus WT: 469.2±78.6 μm² units; p < 0.05).

Nordradrenaline- and calcium-dependent constriction was significantly reduced in the resistance arteries of TLR4-/- (NEmax.TLR4-/-: 16.1±4.3 mN/mm vs. NEmax.WT: 22.2±4.8 mN/mm; Ca2+max.TLR4-/-: 20.9±4.1 mN/mm vs. Ca2+max.WT: 26.1±4.3 mN/mm; p < 0.05).

Conclusions: In a model of L-NNAME-induced hypertension, TLR4-/- shows reduced blood pressure, lower HW/BW, smaller cardiomyocytes and decreased vasocconstriction. These results suggest that the cardiovascular phenotype of TLR4-/- shows advantageous characteristics which are of benefit in hypertension research. A constitutive down-regulation of the innate immune system may be speculated as an underlying mechanism. Moreover, our results strengthen the hypothesis that TLR4-/- is characterized by a decreased cardiovascular risk. This might help in the development of new therapies for cardiovascular diseases.

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### OM017 EXPRESSION OF SENESCENCE MARKERS IN ACCELERATED ATEROGENESIS OF UNINEPHRECTOMIZED APOE-/- MICE

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**Introduction and Aims:** The life expectancy of a 20 year old patient on hemodialysis is equivalent to that of an 80 year old individual without renal disease. Whether this is explained by the cumulation of classical and non-classical cardiovascular risk factors in uremia or whether uremia is a state of premature and accelerated aging is unclear. We compared cardiovascular alterations by “young” (16 weeks) and “young” (32 weeks) sham-op and uninephrectomized (UNX) ApoE-/- mice.

**Methods:** Sixty-four ApoE-/- mice receiving normocholesterol diet were divided into 4 groups: UNX and Sham-op, observation period of 16 or 32 weeks (wk) post-operative. UNX was performed at 8 weeks of age. Hearts and aortas were harvested for analysis through stereology and immunohistochemistry. Aortic expression of senescence-related markers p16, p21, and telomerase were accessed through RT-PCR.

**Results:** Compared to Sham-op (16 and 32wk) aorta and heart remodeling were more pronounced in UNX 32-wk animals, which presented a significant increase in wall to lumen ratio, plaque size and a reduced heart capillary length density despite no significant alterations in blood pressure. Plaque total collagen content was overall low and similar between groups. However, collagen I and libronectin expression in plaques were significantly higher by UNX 32-wk animals compared to Sham-op and UNX 16 wk. RT-PCR of aortic material showed a higher expression of p21 in the UNX 32wk animals compared to all other groups (10.4±4.6 vs. 3.1±0.43, 4.5±3 and 6.2±2.3 ratios/HFRT, p<0.05) and a lower telomerase expression compared to Sham-op 16 and 32wk.

**Conclusions:** UNX promoted significant aortic and cardiac remodelling, which was paralleled by increased expression of p21 and reduced telomerase activity after a 32 week observation period.

**Disclosure:** This work was supported by the Genzyme Renal Innovations Program (GRIP).

### OM018 COEXISTENCE OF IMPAIRED MYOCARDIAL FATTY ACID METABOLISM AND INSULIN RESISTANCE PREDICTS CARDIAC DEATH OF HEMODIALYSIS PATIENTS WITH NORMAL CORONARY ARTERIES

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**Introduction and Aims:** We evaluated the predictive value of impaired myocardial fatty acid metabolism or insulin resistance for cardiac death of chronic hemodialysis patients with normal coronary arteries.

**Methods:** We prospectively enrolled 155 hemodialysis patients (89 men and 66 women, 64±11 years), who had undergone single-photon emission computed tomography (SPECT) using the iodinated fatty acid analogue, iodine-123-b-ethyl iodophenylpentadecanoic acid (BMIPP), and had normal coronary arteries identified by coronary angiography. Uptake on SPECT images was graded in 17 segments on a five-point scale (0, normal; 4, absent) and assessed as summed BMIPP score. Insulin resistance was determined using the homeostasis model assessment index of insulin resistance (HOMA-IR). Patients who had clinical histories of myocardial infarction and/or coronary revascularization were excluded from the study.

**Results:** During a 5.1±2.0-year follow-up, 42 died of cardiac events (acute myocardial infarction, 7; congestive heart failure, 18; sudden cardiac death, 17). Stepwise Cox hazard analysis associated cardiac death with reduced myocardial uptake of BMIPP (BMIPP summed score ≥ 1: hazard ratio 1.069, P<0.0001) and increase in insulin resistance (HOMA-IR, 1 mg/dl×U/ml: hazard ratio 1.262, 95% CI, 1.004). When the study participants were divided into 4 subgroups depending on the cut-off values for cardiac death in BMIPP summed score (12) and HOMA-IR (5.1) determined by receiver operating characteristic analysis, Kaplan-Meier survival estimates revealed that the event-free rates of cardiac death at 5 years were 98.7% in subgroup I (BMIPP summed score <12 and HOMA-IR <5.1, n = 81), 88.2% in subgroup 2 (BMIPP summed score ≥12 and HOMA-IR ≥5.1, n = 18), 52.9% in subgroup 3 (BMIPP summed score ≥12 and HOMA-IR <5.1, n = 16), and 32.2% in subgroup 4 (BMIPP summed score ≥12 more and HOMA-IR ≥5.1, n = 40), respectively (Figure 1). BMIPP summed score significantly correlated with HOMA-IR, and patients who had caused cardiac death were intensively distributed in the area of BMIPP summed score ≥12 and HOMA-IR ≥5.1 (Figure 2).

**Conclusions:** Coexistence of insulin resistance and impaired myocardial fatty acid metabolism evaluated by HOMA-IR and BMIPP SPECT may indicate a strong risk for cardiac death in hemodialysis patients who have normal coronary arteries.

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coronary heart disease, heart failure, stroke, chronic obstructive pulmonary disease, neoplasm) and Model 4: Model 3 + weight + six main baseline laboratory values (hemoglobin, calcium, phosphorous, K/Na, C reactive protein, albumin). In every model AVF was used as reference for RR.

**Results:** According to selection criteria, 13,014 incident patients were included and 43,438 VA were created on these patients. Mean age was 58±6±16.4 years, 52.2% male, 30.1% diabetics. Mean survival time according to VA type was 5.75 years for AVF, 5.72 years for grafts and 4.38 years for permanent catheter (PC) (p<0.0001). RR for mortality and VA type is shown in table 1.

**Conclusions:** Permanent catheter showed an independent effect on patient survival that remains after adjusting for case mix, comorbidities, weight and main baseline laboratory values. The impact of graft in survival fades out after adjustment in our population. Given that this is an observational study, prospective, controlled clinical trials are needed to support our findings.

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**OM020 BEDSIDE STENOSIS SURVEILLANCE PROGRAM IN ARTERIOVENOUS FISTULA (AVF) MAY BE GUIDED BY THE ANATOMIC SITE**

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**Introduction and Aims:** Due to the different stenosis location and access blood flow (Qa) levels, it has been postulated that the diagnostic criteria for stenosis in AVF may vary according to the anatomic site.

**Methods:** To test this hypothesis, we evaluated the diagnostic accuracy of physical exam (PE). Qa and access recirculation (by ultrasonod dilution technique), Qb/NAP (the ratio of dialysis blood pump flow to negative arterial pre-pump pressure), and derived static venous pressure (V APR, according to Frinak et al.) in detecting angiographically-proven stenosis in 100 hemodialysis patients (pts) (70 males, 30 females, aged 67±6±16 y) with mature AVF.

**Results:** The arteriovenous anastomosis was located in the lower third of the forearm (dA VF) in 36 pts, and more proximally in the remaining 64 pts (pA VF), either in the mid-third of the forearm (n=31) or in the elbow region (n=33). Fistulography identified 15 stenoses in dA VF, all located upstream to the venous needle (mflow stenosis, STin) and 13 downstream to the venous needle (outflow stenosis, STout). The combination of the two slightly improved AC (82% [95% CI 60-92], sensitivity (SE) 79% [49-95], specificity (SP) 85% [62-97] for PE). The combination of the two tests using PE as a triage followed by Qa measurement in the event of a negative PE, improved AC (82% [95% CI 60-92], SE 86% [58-94], SP 85% [62-97] for PE). Qa was only documented in 16 y) with stenosis in AVF may vary according to the anatomic site.

**Primary patency (months)** 36.3 (24.7-48.0) 36.9 (31.8-42.0) 0.93

**V A thrombosis (%)** 7.7 17.6 0.37

**Ratio number VA/patient** 1.5±1.48 1.9±1.59 0.92

**Baseline Qa (ml/min)** 887.4±407.1 1142±492.3 0.006

**Overall Qa (ml/min)** 921.2±405.3 1230±471.4 0.002

**VA with PE (%)** 53.8 27.7 0.010

**VA with stenosis ≥50% (%)** 50 21.8 0.003

**Effective VA intervention (%)** 26.9 12.6 0.076

**Qa, after elective intervention (ml/min)** 314.3±91.2 477.6±349.2 0.28

**VA thrombosis (%)** 7.7 17.6 0.37

**Thrombosis rate (episodes/VA/year)** 0.047 0.128 0.063

**Primary patency (months)** 36.3 (24.7-48.0) 36.9 (31.8-42.0) 0.93

**Secondary patency (months)** 47.9 (38.8-57.1) 43.5 (38.2-48.7) 0.35

*Ischemic cardiomyopathy or cerebrovascular disease or peripheral arteriopathy.**Results are expressed as mean and 95% confidence intervals.

**Conclusions:** 1) The functional VA profile is worse in pts with DN. 2) The prevalence of significant VA stenosis is higher in pts with DN. 3) The surveillance program applied can explain the similar VA thrombosis and patency rates obtained during the study period.
COST ANALYSIS OF ONGOING CARE OF FISTULAE THROMBOSIS IN DIALYSIS PATIENTS: THE IMPACT OF ANGIOPLASTY PERFORMED BY NEPHROLOGISTS

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Introduction and Aims: Functional AVF is a prerequisite for adequate dialysis treatment. Previous studies that have examined the procedure of choice for AVF thrombectomy have focused exclusively on clinical outcomes. Providing that the cost of these procedures may be very significant, we performed the first economic analysis among dialysis patients with AVF thrombosis to determine the cost-effectiveness of percutaneous transluminal angioplasty (PTA).

Methods: This is a controlled cohort study from patients referred to our centre with clotted AVF during the year 2008. From January to August 2008, PTA was performed in our centre 3x/week. From September to December 2008 the endovascular unit was unavailable due to facility renewal. Therefore, these accesses were consequently abandoned and patients were given a tunneled cuffed catheter placement (TCC) to bridge the interval until a new AVF was created. Patients treated with PTA formed the case group (Group A) and those with TCC the control group (Group B). Patient follow-up started on the day the vascular access intervention was first performed and continued for 6 months. Fifty nine prevalent dialysis patients (n = 59) were included in the study; Group A included 35 patients and Group B 24 patients, respectively. Clinical and demographic data were collected from both hospital and satellite unit records. A direct access care-related cost was estimated for each procedure. Costs are reported in 2009 Euro (€). Rehospitalisation and death were accounted for.

Results: Demographic and clinical features were similar between study groups (M/F: 39/20; P=0.4; median age 65±13 years; P=0.07; Charlson comorbidity index=5±2; P=0.4). Angioplasty and TCC were both technically successful in the majority of the cases (97% and 83%, respectively). Nevertheless, at 6 months, the primary patency of AVFs submitted to PTA was better than TCC.

In fact, 2 Group B patients died due to catheter-related bacteraemia. The use of access-related procedures and hospitalizations were significantly higher in Group B patients (mean 0.16 vs. 0.02 event/patient-month; P = 0.002). Furthermore, a higher proportion of Group A patients had functioning AVF as a permanent vascular access at the end of follow-up (90.9% vs. 36.4%, P = 0.0001). The cost of vascular access care was substantial, with a mean cost of €1537 at 6 months. Cost analysis showed that performing PTA for AVF thrombosis led to a 2-fold reduction in access-related expenses per patient-month (€206 vs. €504; P = 0.017).

Conclusions: This controlled cohort study shows that performing PTA on clotted fistulae rather than TCC placement as a bridge for a new AVF, reduces the total access-related costs and comorbidity, and improves access patency in the first 6 months after AVF thrombosis.

OM023 BASIC VEIN TRANSPOSITION (BVT): SINGLE CENTRE EXPERIENCE DURING FIVE YEARS

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Introduction and Aims: With the increasing number and co-morbidities of patients in maintenance hemodialysis, there is a growing problem of how to achieve a durable autogenous angioaccess. In patients in whom a radiocephalic or brachiocephalic arteriovenous fistula (AVF) failed or cannot be fashioned, the brachio basilic AVF with BVT is an alternative to prosthetic grafts and central venous catheters (CVCs). We reviewed the outcomes of BVT to clarify current maturation, patency rates and risk factors for AVF failure.

Methods: We undertook a single centre retrospective review of all patients submitted to BVT in our institution, between November 2005 and September 2009. We analyzed maturation time, complications, primary and secondary patency and risk factors for AVF failure. Primary patency was defined as the interval from the time of surgery until any intervention; secondary patency was the interval from the time of any intervention until failure.

Results: Basilic vein transposition was performed in 84 patients (82 two time procedures), in 52 men (62%), with mean age of 62.6±16 years; 18% were diabetic. The mean number of previous autogenous angio accesses was 2.1±1.5. Perioperative complications occurred in 18 patients (21%), including hemotoma (n=6), infection (n=5), primary failure (n=4), venous hypertension (n=2) and steal syndrome (n=1). Time of maturation before venepuncture was 66±48 days. Mean follow-up time was 13.7±12.5 months. Primary patency rates were 85.5%, 69.5% and 57.7%, compared with secondary patency rates of 91.3%, 75.4% and 68% at 3, 6 and 12 months, respectively.

Patients with primary AVF failure had higher body mass index (29.8±2.0 kg/m² versus 24.2±3.1 kg/m²; P=0.013). Previous renal replacement therapy time, age, gender, diabetes mellitus, vascular disease, use of antiplatelet drugs, statins and calcium channel blockers didn't have statistically significant differences in primary or secondary patency at 3, 6 or 12 months.

Conclusions: Basilic vein transposition is a surgical procedure that permits optimization of venous capital for the creation of autogenous angioaccess. In our study, there weren't any major complications; antibiotic prophylaxis may reduce perioperative infections. Obesity was a risk factor for primary failure; in our population, we didn't identify any other demographic, clinical or pharmacological factors associated with BVT failure. In selected patients, BVT may offer an efficacious alternative to prosthetic grafts and CVCs.

OM024 CHRONIC KIDNEY DISEASE STAGES 1-3 INCREASE RISK FOR VENOUS THROMBOSIS

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Introduction and Aims: Chronic kidney disease (CKD) stages 4-5 as well as micro-albuminuria have been associated with venous thrombosis. However, the risk for venous thrombosis in CKD stages 1-3 has not yet been investigated, nor differences in the risk for venous thrombosis between decreased estimated glomerular filtration rate (eGFR) and elevated albuminuria. Therefore, we investigated whether CKD patients with stage 1-3, according to the Kidney Disease Outcomes Quality Initiative guidelines, had an increased risk for venous thrombosis, and whether the risk for venous thrombosis was different for decreased eGFR as compared to elevated albuminuria.

Methods: Data were used of subjects participating in the Prevention of Renal
and Vascular End-stage Disease (PREVEND) study of whom data were available on albuminuria and serum creatinine. Our main study outcome was symmetric and objectively verified venous thrombosis. Hazard ratios (HRs) with 95% confidence intervals (CI) for venous thrombosis were calculated for CKD stages 1, 2, and 3 and for decreased eGFR (60-90 ml/min, 30-60 ml/min) in the absence and in the presence of albuminuria (albuminuria >30 mg per day) as compared to subjects with an eGFR >90 ml/min without albuminuria.

**Results:** Of the 8495 subjects, 243, 856, and 491 subjects had CKD stage 1, 2, and 3, respectively. During a mean follow-up period of 8.6 years, 128 subjects developed venous thrombosis. The age- and sex-adjusted HRs for CKD stage 1, 2, 3 with and without albuminuria were respectively 3.7, 2.7, 3.8, and 1.5 as compared to subjects with eGFR >90 and no albuminuria (Table 1). In the overall group of subjects without albuminuria, no association was found between eGFR and incident venous thrombosis after adjustment for age and sex. However, subjects with albuminuria were at increased risk for venous thrombosis independent of impaired eGFR. Additional adjustment for BMI, hypertension, high-sensitivity C-reactive protein, and diabetes did not result in large differences for none of the analyses.

**Table 1. CKD stages and venous thrombosis**

| Characteristic | Albuminuria | CKD stage | Crude HR (95% CI) | Adj HR (95% CI) |
|---------------|-------------|-----------|-------------------|-----------------|
| Reference eGFR>90 | No | 1.0 | 1.0 |
| Decreased eGFR | 60-90 | No | 2.2 (1.2-4.1) | 1.5 (0.8-2.9) |
| 30-60 | 3** | 3.6 (1.4-9.3) | 1.5 (0.6-4.2) |
| Elevated albuminuria eGFR>90 | Yes | 1 | 4.8 (1.9-12.4) | 3.7 (1.4-9.5) |
| Elevated albuminuria | 60-90 | Yes | 2 | 5.2 (2.6-10.5) | 2.7 (1.3-5.7) |
| Elevated albuminuria | 30-60 | Yes | 3*** | 10.3 (4.2-24.7) | 3.8 (1.3-9.7) |

**Conclusions:** CKD stages 1 and 2 were associated with venous thrombosis. CKD stage 3 however, was only associated with venous thrombosis in the absence of albuminuria. In the general population the risk for venous thrombosis associated with CKD seems more related to albuminuria than to impaired eGFR.

**OM025 INTERVENTIONS FOR REGRESSION OF LEFT VENTRICULAR HYPERTROPHY IN PATIENTS WITH CHRONIC KIDNEY DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS**

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**Introduction and Aims:** Left ventricular hypertrophy (LVH) is extremely common in patients with chronic kidney disease (CKD) and is associated with poor survival. The purpose of this systematic review was to study benefits and harms of all interventions used for regression of LVH in CKD patients.

**Methods:** The Cochrane Controlled Trial Registry, MEDLINE and EMBASE were searched for randomised controlled trials (RCT) studying any intervention for regression of LVH in CKD patients. Trials with follow up of less than 3 months, or less than 10 patients in one or both arms, involving kidney transplant patients were excluded. Summary estimates were obtained by using a random effects model and heterogeneity measured using I².

**Results:** Thirty-one trials involving 2,876 patients (mean age 53 years, men 60%, mean LV mass index (LVMI) 118 g/m²) and 9 types of interventions met the inclusion criteria. Inhibition of renin angiotensin aldosterone system (RAAS) (10 trials, 475 patients) was associated with reduction in LVMI (weighted mean difference [WMD] -13.7 g/m², 95% confidence interval [CI]-19.9, -7.6, P<0.001). Anemia correction with erythropoiesis stimulating agents (ESA) (7 trials, 1,647 patients) had no effect on LVMI (WMD -1.52 g/m², 95%CI -5.75, 2.71, P=0.481). Use of icodextrin in 2 trials in 99 peritoneal dialysis (PD) patients did not show any effect on LV mass (WMD -7, 95%CI -20.9, 34.9 g, P=0.623). Meta-analysis was not possible for other trials due to either single studies for other interventions or statistical heterogeneity or clinical diversity.

**Conclusions:** RAAS inhibition was associated with regression of LVH. Icodextrin in PD patients and anemia correction with ESA had no beneficial effect on regression of LVH. More data are required to assess the validity of LVH as a surrogate marker in CKD patients.

**Disclosure:** DJ has received consultancy fees, speaker’s honoraria and travel sponsorship from Roche, Amgen and Janssen-Cilag.

**OM026 MAGNESIUM AND MORTALITY RISK IN HAEMODIALYSIS PATIENTS**

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**Introduction and Aims:** From small studies, higher serum magnesium (Mg) levels may be cardio-protective in hemodialysis (HD) patients. We evaluated the association between Mg levels and mortality risk in a large national sample of HD patients in the United States.

**Methods:** All chronic HD patients treated at Fresenius Medical Care North America facilities on January 1, 2008 with serum Mg results from the prior baseline quarter (October 1st to December 31, 2007) formed the study cohort. Case-mix (age, gender, race, diabetes mellitus, and vintage) were recorded and mortality outcome was tracked until December 31, 2008. Cox models were constructed to evaluate the association of mortality risk with Mg:

- Unadjusted (Mg categories: <1.3, 1.3-1.59, 1.6-1.89, 1.9-2.1, 2.1-2.3, 2.3-2.4, 2.41-2.5, 2.51-2.6 and >2.6 mg/L) dose-response.
- Case-mix adjusted (age, gender, race, presence of diabetes mellitus, body surface area, and dialysis vintage).

**Results:** A quarter (27,544 of 110,271) of active prevalent patients had Mg levels. Demographic characteristics were similar between patients with and without Mg results as shown in Table 1.

**Table 1. Baseline patients characteristics**

| Characteristics | Mg Measured at Baseline | All patients |
|-----------------|-------------------------|--------------|
| N               | 27,544                  | 110,271      |
| Age (years)     | 61.8 (14.8)             | 61.69 (15.0) |
| Male Sex (%)    | 53.7                    | 54.5         |
| Race (%)        | 48.6                    | 51.4         |
| White           | 48.6                    | 51.4         |
| Black           | 43.8                    | 40.5         |
| Other           | 7.6                     | 8.1          |
| Diabetes (%)    | 53.6                    | 53.8         |
| Vascular Access (%) | 44.1                | 45.3         |
| Fistula        | 44.1                    | 45.3         |
| Graft            | 24.3                    | 24.2         |
| Catheter        | 30.9                    | 30.0         |
| Unknown         | 0.6                     | 0.5          |
| Vintage (years) | 3.5 (3.6)               | 3.6 (3.7)    |
| Albumin (g/dL)  | 3.80 (4.0)              | 3.81 (0.39)  |
| Phosphorous (mg/dL) | 11.88 (1.14) | 11.88 (1.12) |
| eKt/V           | 1.48 (0.29)             | 1.48 (0.29)  |

The average Mg was 1.85±0.31 meq/L (normal range: 1.3-2.1 meq/L). There were 10,466 patients in the magnesium reference group (1.6-1.89 meq/L).
meq/L). The Mg category with the fewest patients was 2.51-2.6 meq/L with N=261 patients. Figure 1 shows a linear trend with lower mortality risk associated with increasing Mg levels. The survival benefit was not significant at levels beyond 2.6 meq/L. Compared to mid-normal values (Mg =1.6–1.89 meq/L), the unadjusted hazard ratio (HR) drops significantly to as low as 0.54 for Mg 2.51-2.6 meq/L, remaining significantly at HR=0.58 after adjustment for case mix.

**Conclusions:** Preliminary analyses reveal that high normal and elevated serum Mg levels were associated with lower risk of mortality in prevalent HD patients. Considering an elevated cardiovascular disease burden in this population, the pathobiology may be similar to the cardio-protective effects of higher Mg levels observed in patients with heart failure. We recommend further study to evaluate the potential mechanism(s) and clinical implication(s) of this finding in patients with end-stage renal disease treated by hemodialysis.

**Disclosure:** The presenting author is employee of Fresenius Medical Care.