CENTER FOR MEDICAL STATISTICS,
INFORMATICS AND INTELLIGENT SYSTEMS
MEDICAL UNIVERSITY OF VIENNA
Institute of Clinical Biometrics

Epidemiological Publications

2020

1. Haller MC, Wallisch C, Mjoen G, Holdaas H, Dunkler D, Heinze G, Oberbauer R: Predicting donor, recipient and graft survival in living donor kidney transplantation to inform pretransplant counselling: the donor and recipient linked iPREDICTLIVING tool - a retrospective study. *Transpl Int* (2020) 33(7): 729-739; https://doi.org/10.1111/tri.13580

   Abstract: *Although separate prediction models for donors and recipients were previously published, we identified a need to predict outcomes of donor/recipient simultaneously, as they are clearly not independent of each other. We used characteristics from transplantations performed at the Oslo University Hospital from 1854 live donors and from 837 recipients of a live donor kidney transplant to derive Cox models for predicting donor mortality up to 20 years, and recipient death, and graft loss up to 10 years. The models were developed using the multivariable fractional polynomials algorithm optimizing Akaike's information criterion, and optimism-corrected performance was assessed. Age, year of donation, smoking status, cholesterol and creatinine were selected to predict donor mortality (C-statistic of 0.81). Linear predictors for donor mortality served as summary of donor prognosis in recipient models. Age, sex, year of transplantation, dialysis vintage, primary renal disease, cerebrovascular disease, peripheral vascular disease and HLA mismatch were selected to predict recipient mortality (C-statistic of 0.77). Age, dialysis vintage, linear predictor of donor mortality, HLA mismatch, peripheral vascular disease and heart disease were selected to predict graft loss (C-statistic of 0.66). Our prediction models inform decision-making at the time of transplant counselling and are implemented as online calculators.*

2. Sheikh Rezaei S, Gleiss A, Reichardt B, Wolzt M: Use of Clopidogrel, Prasugrel, or Ticagrelor and Patient Outcome after Acute Coronary Syndrome in Austria from 2015 to 2017. *J Clin Med* (2020) 9(11): 3398; https://doi.org/10.3390/jcm9113398

   Abstract: *BACKGROUND: Dual antiplatelet therapy improves patient outcome after acute coronary syndrome (ACS), but prescription differences of P2Y12 inhibitor treatments exist. The aim of the present investigation was to study the long-term utilization and patient outcomes of clopidogrel, prasugrel, and ticagrelor in patients with ACS from 2015 to 2017 in Austria. METHODS: Data from 13 Austrian health insurance funds of patients with a hospital discharge diagnosis of ACS for the years 2015 to 2017 were analyzed. The primary end point was to investigate the recurrence of ACS or death. RESULTS: Of 49,124 P2Y12 inhibitor-naive patients with a hospital discharge diagnosis of ACS, 25,147 subjects filled a P2Y12 inhibitor prescription within 30 days after the index event. Of these patients, 10,626 (42.9%) subjects had a prescription for clopidogrel, 4788 (19.3%) for prasugrel, and 9383 (37.8%) for ticagrelor. Ticagrelor was the most frequently prescribed P2Y12 inhibitor among patients below 70 years old, and clopidogrel in those aged >/=70 years. Occurrence of an endpoint was highest in elderly patients. After adjustment for age, sex, and pre-existing medication as proxy for comorbidity, the hazard ratio for ACS or death for prasugrel vs. clopidogrel of 0.70 (95% CI: 0.61; 0.79) was similar to that of ticagrelor vs. clopidogrel (0.70; 95% CI: 0.64; 0.77). CONCLUSION: Prescription of ticagrelor or prasugrel after ACS were associated with a lower risk of ACS recurrence or death compared to clopidogrel.*

3. Tian Y, Reichardt B, Dunkler D, Hronsky M, Winkelmayer WC, Bucsics A, Strohmaier S, Heinze G: Comparative effectiveness of branded vs. generic versions of antihypertensive, lipid-lowering and hypoglycemic substances: a population-wide cohort study. *Sci Rep* (2020) 10(1): 5964; https://doi.org/10.1038/s41598-020-62318-y

   Abstract: *Generic medications offer substantial potential cost savings to health systems compared to their branded counterparts. In Europe and the US, they are only approved if they are bioequivalent to the respective originator product. Nevertheless, the lack of clinical outcomes is sometimes used as the reason for hesitancy in prescribing generics. We performed an observational retrospective study on 17 branded vs. generic pharmaceutical substances for the treatment of hypertension/heart failure, hyperlipidemia, and diabetes mellitus in a dataset of 9,413,620 insured persons, representing nearly the full population of Austria, from 2007 to 2012. We compared generic vs. branded medications using hazard ratios for all-cause death and major adverse cardiac and cardiovascular events (MACCE) as outcomes of interest. Using patient demographics, health characteristics from hospitalization records, and pharmacy*

records as covariates, we controlled for confounding in Cox models through inverse probability of treatment weighting (IPTW) using high-dimensional propensity scores. We observed that the unadjusted hazard ratios strongly favor generic drugs for all three pooled treatment indications (hypertension/heart failure, hyperlipidemia, diabetes mellitus), but were attenuated towards unity with increasingly larger covariate sets used for confounding control. We found that after IPTW adjustment the generic formulation was associated with significantly fewer deaths in 10 of 17 investigated drugs, and with fewer MACCE in 11 of 17 investigated drugs. This result favoring generic drugs was also present in a number of sub-analyses based on gender, prior disease status, and treatment discontinuation. E-value sensitivity analyses suggested that only strong unmeasured confounding could fully explain away the observed results. In conclusion, generic medications were at least similar, and in some cases superior, to their branded counterparts regarding mortality and major cardiovascular events.

4. Umek W, Gleiss A, Bodner-Adler B, Reichardt B, Rinner C, Heinze G: The role of prescription drugs in female overactive bladder syndrome-A population-wide cohort study. *Pharmacoepidemiol Drug Saf* (2020) 29(2): 189-198; https://doi.org/10.1002/pds.4920

   Abstract: *PURPOSE: Overactive bladder (OAB) syndrome has severe effects on quality of life. Certain drugs are known risk factors for OAB but have not been investigated in a population-wide cohort. The objective of this study was to investigate the role of prescription drugs in the etiology of the OAB. METHODS: Retrospective cohort study using a population-wide database of 4 185 098 OAB-naive women followed Strengthening the Reporting of Observational Studies in Epidemiology guidelines. We investigated the subscription use of anticholinergic medication and 188 chemical substances, which are suspected triggers for OAB (trigger medications [TMs]). We hypothesized a relationship between the prescription for one or more TM and the prescription for anticholinergic medication against OAB (marker medication [MM]). RESULTS: The use of MM in Austria increased from 2009 to 2012 on average by 0.025 percentage points per year (95% confidence interval [CI]: 0.015-0.036). In December 2012, 1 in 123 women filled a prescription for any MM, equaling an average utilization of 0.84%. The relative risk of filling a prescription for a MM 6 months after filling a prescription for a TM was 2.70 (95% CI: 2.64-2.77). All investigated medication classes showed a higher risk for the prescription for MM. Medication from classes "genitourinary system and sex hormones" and "systemic anti-infectives" caused the highest increase in risk (109% and 89%, respectively). Prescriptions for class "cardiovascular system" caused the lowest increase in the risk (15%). CONCLUSION: Certain prescription medications are a significant risk factor for the need to take anticholinergic medication as a consequence.*

5. Wallisch C, Heinze G, Rinner C, Mundigler G, Winkelmayer WC, Dunkler D: Re-estimation improved the performance of two Framingham cardiovascular risk equations and the Pooled Cohort equations: A nationwide registry analysis. *Sci Rep* (2020) 10(1): 8140; https://doi.org/10.1038/s41598-020-64629-6

   Abstract: *Equations predicting the risk of occurrence of cardiovascular disease (CVD) are used in primary care to identify high-risk individuals among the general population. To improve the predictive performance of such equations, we updated the Framingham general CVD 1991 and 2008 equations and the Pooled Cohort equations for atherosclerotic CVD within five years in a contemporary cohort of individuals who participated in the Austrian health-screening program from 2009-2014. The cohort comprised 1.7 M individuals aged 30-79 without documented CVD history. CVD was defined by hospitalization or death from cardiovascular cause. Using baseline and follow-up data, we recalibrated and re-estimated the equations. We evaluated the gain in discrimination and calibration and assessed explained variation. A five-year general CVD risk of 4.61% was observed. As expected, discrimination c-statistics increased only slightly and ranged from 0.73-0.79. The two original Framingham equations overestimated the CVD risk, whereas the original Pooled Cohort equations underestimated it. Re-estimation improved calibration of all equations adequately, especially for high-risk individuals. Half of the individuals were reclassified into another risk category using the re-estimated equations. Predictors in the re-estimated Framingham equations explained 7.37% of the variation, whereas the Pooled Cohort equations explained 5.81%. Age was the most important predictor.*

6. Wallisch C, Heinze G, Rinner C, Mundigler G, Winkelmayer WC, Dunkler D: Publisher Correction: Re-estimation improved the performance of two Framingham cardiovascular risk equations and the Pooled Cohort equations: A nationwide registry analysis. *Sci Rep* (2020) 10(1): 10778; https://doi.org/10.1038/s41598-020-67920-8

   Abstract: *An amendment to this paper has been published and can be accessed via a link at the top of the paper.*

2019

1. Bekos C, Muqaku B, Dekan S, Horvat R, Polterauer S, Gerner C, Aust S, Pils D: NECTIN4 (PVRL4) as Putative Therapeutic Target for a Specific Subtype of High Grade Serous Ovarian Cancer-An Integrative Multi-Omics Approach. *Cancers (Basel)* (2019) 11(5): 698; https://doi.org/10.3390/cancers11050698

   Abstract: *In high grade serous ovarian cancer patients with peritoneal involvement and unfavorable outcome would benefit from targeted therapies. The aim of this study was to find a druggable target against peritoneal metastasis. We constructed a planar-scale free small world-co-association gene expression network and searched for clusters with hub-genes associated to peritoneal spread. Protein expression and impact was validated via immunohistochemistry and correlations of deregulated pathways with comprehensive omics data were used for biological interpretation. A cluster up-regulated in miliary tumors with NECTIN4 as hub-gene was identified and impact on survival validated. High Nectin 4 protein expression was associated with unfavorable survival and (i) reduced expression of HLA genes (mainly MHC I); (ii) with reduced expression of genes from chromosome 22q11/12; (iii) higher BCAM in ascites and in a high-scoring expression cluster; (iv) higher Kallikrein gene and protein expressions; and (v) substantial immunologic differences; locally and systemically; e.g., reduced CD14 positive cells and reduction of different natural killer cell populations. Each three cell lines with high (miliary) or low NECTIN4 expression (non-miliary) were identified. An anti-Nectin 4 antibody with a linked antineoplastic drug-already under clinical investigation-could be a candidate for a targeted therapy in patients with extensive peritoneal involvement.*

2. Duftschmid G, Rinner C, Sauter SK, Endel G, Klimek P, Mitsch C, Heinzl H: Patient-Sharing Relations in the Treatment of Diabetes and Their Implications for Health Information Exchange: Claims-Based Analysis. *JMIR Med Inform* (2019) 7(2): e12172; https://doi.org/10.2196/12172

   Abstract: *BACKGROUND: Health information exchange (HIE) among care providers who cooperate in the treatment of patients with diabetes mellitus (DM) has been rated as an important aspect of successful care. Patient-sharing relations among care providers permit inferences about corresponding information-sharing relations. OBJECTIVES: This study aimed to obtain information for an effective HIE platform design to be used in DM care by analyzing patient-sharing relations among various types of care providers (ToCPs), such as hospitals, pharmacies, and different outpatient specialists, within a nationwide claims dataset of Austrian DM patients. We focus on 2 parameters derived from patient-sharing networks: (1) the principal HIE partners of the different ToCPs involved in the treatment of DM and (2) the required participation rate of ToCPs in HIE platforms for the purpose of effective communication. METHODS: The claims data of 7.9 million Austrian patients from 2006 to 2007 served as our data source. DM patients were identified by their medication. We established metrics for the quantification of our 2 parameters of interest. The principal HIE partners were derived from the portions of a care provider's patient-sharing relations with different ToCPs. For the required participation rate of ToCPs in an HIE platform, we determine the concentration of patient-sharing relations among ToCPs. Our corresponding metrics are derived in analogy from existing work for the quantification of the continuity of care. RESULTS: We identified 324,703 DM patients treated by 12,226 care providers; the latter were members of 16 ToCPs. On the basis of their score for 2 of our parameters, we categorized the ToCPs into low, medium, and high. For the most important HIE partner parameter, pharmacies, general practitioners (GPs), and laboratories were the representatives of the top group, that is, our care providers shared the highest numbers of DM patients with these ToCPs. For the required participation rate of type of care provide (ToCP) in HIE platform parameter, the concentration of DM patient-sharing relations with a ToCP tended to be inversely related to the ToCPs member count. CONCLUSIONS: We conclude that GPs, pharmacies, and laboratories should be core members of any HIE platform that supports DM care, as they are the most important DM patient-sharing partners. We further conclude that, for implementing HIE with ToCPs who have many members (in Austria, particularly GPs and pharmacies), an HIE solution with high participation rates from these ToCPs (ideally a nationwide HIE platform with obligatory participation of the concerned ToCPs) seems essential. This will raise the probability of HIE being achieved with any care provider of these ToCPs. As chronic diseases are rising because of aging societies, we believe that our quantification of HIE requirements in the treatment of DM can provide valuable insights for many industrial countries.*

3. Hutter HP, Waldhoer T, Muller K, Hackl M, Weitensfelder L, Heinzl H: Cancer incidence in an Austrian alpine valley 1983-2012 : A descriptive study. *Wien Klin Wochenschr* (2019) 131(9-10): 200-204; https://doi.org/10.1007/s00508-019-1476-7

Abstract: *After one of Austria's largest environmental scandals in 2014, which involved the release of hexachlorobenzene (HCB) in the Carinthian valley Gortschitztal, concerns about increased cancer rates have arisen in the affected local population. A descriptive study was conducted to examine the cancer incidence rates between 1983 and 2012. Data from the affected area (Gortschitztal, district St. Veit) were compared to data from the neighboring area within the same district and Carinthia excluding St. Veit, considering incidence rates of liver, lung, kidney, thyroid cancer and mesothelioma. Prostate cancer and carcinoma in situ were both included and excluded from overall cancer incidents in order to prevent potential bias due to screening programs. Considering the observed variability at an overall level, no conspicuous differences in cancer incidences could be found (Carinthia: 495, St. Veit West: 408, St. Veit East: 572 cases per 100,000 person-years in 2012). For some cancer types, e.g. liver, thyroid cancer and mesothelioma, the affected region showed a higher increase in rates than the neighboring area or Carinthia overall; however, these increased rates date back to a time prior to the HCB exposure, suggesting other carcinogenic influences, such as asbestos exposure from antecedent years.*

4. Kammer M, Heinzel A, Willency JA, Duffin KL, Mayer G, Simons K, Gerl MJ, Klose C, Heinze G, Reindl-Schwaighofer R, Hu K, Perco P, Eder S, Rosivall L, Mark PB, Ju W, Kretzler M, McCarthy MI, Heerspink HL, Wiecek A, Gomez MF, Oberbauer R, Consortium BE-D: Integrative analysis of prognostic biomarkers derived from multiomics panels helps discrimination of chronic kidney disease trajectories in people with type 2 diabetes. *Kidney Int* (2019) 96(6): 1381-1388; https://doi.org/10.1016/j.kint.2019.07.025

Abstract: *Clinical risk factors explain only a fraction of the variability of estimated glomerular filtration rate (eGFR) decline in people with type 2 diabetes. Cross-omics technologies by virtue of a wide spectrum screening of plasma samples have the potential to identify biomarkers for the refinement of prognosis in addition to clinical variables. Here we utilized proteomics, metabolomics and lipidomics panel assay measurements in baseline plasma samples from the multinational PROVALID study (PROspective cohort study in patients with type 2 diabetes mellitus for VALIDation of biomarkers) of patients with incident or early chronic kidney disease (median follow-up 35 months, median baseline eGFR 84 mL/min/1.73 m(2), urine albumin-to-creatinine ratio 8.1 mg/g). In an accelerated case-control study, 258 individuals with a stable eGFR course (median eGFR change 0.1 mL/min/year) were compared to 223 individuals with a rapid eGFR decline (median eGFR decline -6.75 mL/min/year) using Bayesian multivariable logistic regression models to assess the discrimination of eGFR trajectories. The analysis included 402 candidate predictors and showed two protein markers (KIM-1, NTproBNP) to be relevant predictors of the eGFR trajectory with baseline eGFR being an important clinical covariate. The inclusion of metabolomic and lipidomic platforms did not improve discrimination substantially. Predictions using all available variables were statistically indistinguishable from predictions using only KIM-1 and baseline eGFR (area under the receiver operating characteristic curve 0.63). Thus, the discrimination of eGFR trajectories in patients with incident or early diabetic kidney disease and maintained baseline eGFR was modest and the protein marker KIM-1 was the most important predictor.*

5. Kossmeier M, Heinze G: Predicting future citation counts of scientific manuscripts submitted for publication: a cohort study in transplantology. *Transpl Int* (2019) 32(1): 6-15; https://doi.org/10.1111/tri.13292

Abstract: *Citations are widely used for measuring scientific impact. The goal of the present study was to predict citation counts of manuscripts submitted to Transplant International (TI) in the two calendar years following publication. We considered a comprehensive set of 21 manuscript, author, and peer-review-related predictor variables available early in the peer-review process. We also evaluated how successfully the peer-review process at TI identified and accepted the most promising manuscripts for publication. A developed predictive model with nine selected variables showed acceptable test performance to identify often cited articles (AUROC = 0.685). Particularly important predictors were the number of pages, month of publication, publication type (review versus other), and study on humans (yes versus no). Accepted manuscripts at TI were cited more often than rejected but elsewhere published manuscripts (median 4 vs. 2 citations). The predictive model did not outperform the actual editorial decision. Both findings suggest that the peer-review process at TI, in its current form, was successful in selecting submitted manuscripts with a high scientific impact in the future. Predictive models might have the potential to support the review process when decisions are made under great uncertainty.*

6. Wallisch C, Heinze G, Rinner C, Mundigler G, Winkelmayer WC, Dunkler D: External validation of two Framingham cardiovascular risk equations and the Pooled Cohort equations: A nationwide registry analysis. *Int J Cardiol* (2019) 283:165-170; https://doi.org/10.1016/j.ijcard.2018.11.001

Abstract: *BACKGROUND: Cardiovascular prevention guidelines advocate the use of statistical risk equations to predict individual cardiovascular risk. However, predictive accuracy and clinical value of existing equations may differ in populations other than the one used for their development. Using baseline and follow-up data of the Austrian health-screening program, we assessed discrimination, calibration, and clinical utility of three widely recommended equations-the Framingham 1991 and 2008 general cardiovascular disease (CVD) equations, and the Pooled Cohort equations predicting atherosclerotic CVD. METHODS: The validation cohort comprised 1.7M individuals aged 30-79, without documented CVD history who participated in the program from 2009 to 2014. CVD events were defined by a cardiovascular cause of hospitalization or death. RESULTS: The observed five-year general CVD risk was 4.66%. Discrimination c-indices (0.72-0.78) were slightly lower than those reported for the development cohorts. C-indices for women were always higher than for men. CVD risk was overestimated by the Framingham 2008 equation, but underestimated by the Pooled Cohort equations. The Framingham 1991 equation was well-calibrated, especially for individuals up to 64years. If applied to recommend health interventions at a predicted five-year risk between 5 and 10%, the equations were clinically useful with their net benefits, weighting true positives against false positives, ranging from 0.13 to 3.43%. CONCLUSION: The equations can discriminate high-risk from low-risk individuals, but predictive accuracy (especially for high-risk individuals) might be improved by recalibration. The Framingham 1991 equation yielded the most accurate predictions.*

2018

1. Geroldinger A, Sauter SK, Heinze G, Endel G, Dorda W, Duftschmid G: Mortality and continuity of care - Definitions matter! A cohort study in diabetics. *PLoS ONE* (2018) 13(1): e0191386; https://doi.org/10.1371/journal.pone.0191386

   Abstract: *OBJECTIVE: To demonstrate that when investigating the relevance of continuity of care for patient outcomes, different definitions can lead to contradicting results. METHODS: We used claims data from the regional public health insurer of Lower Austria covering the period from 2008 to 2011. The study sample included subjects with repeated dispensings of anti-diabetic drugs. The continuity of care index was calculated firstly based on a patient's contacts with general practitioners (primary COCI) and secondly based on contacts at all medical disciplines (total COCI). The association of the two continuity of care measures with mortality was assessed in separate univariable and multivariable Cox regression models. RESULTS: Our study sample consisted of 51,717 patients with a median observation time of 3.65 years. The data showed that a high total COCI was associated with increased mortality, while there was no association between primary COCI and mortality. CONCLUSIONS: Measures of continuity of care are highly sensitive to the type of medical disciplines taken into account. The continuity of care index calculated from contacts at all medical disciplines might measure diversity rather than continuity of care.*

2. Heinzel A, Kammer M, Mayer G, Reindl-Schwaighofer R, Hu K, Perco P, Eder S, Rosivall L, Mark PB, Ju W, Kretzler M, Gilmour P, Wilson JM, Duffin KL, Abdalla M, McCarthy MI, Heinze G, Heerspink HL, Wiecek A, Gomez MF, Oberbauer R, Consortium BE-D: Validation of Plasma Biomarker Candidates for the Prediction of eGFR Decline in Patients With Type 2 Diabetes. *Diabetes Care* (2018) 41(9): 1947-1954; https://doi.org/10.2337/dc18-0532

   Abstract: *OBJECTIVE: The decline of estimated glomerular filtration rate (eGFR) in patients with type 2 diabetes is variable, and early interventions would likely be cost-effective. We elucidated the contribution of 17 plasma biomarkers to the prediction of eGFR loss on top of clinical risk factors. RESEARCH DESIGN AND METHODS: We studied participants in PROVALID (PROspective cohort study in patients with type 2 diabetes mellitus for VALIDation of biomarkers), a prospective multinational cohort study of patients with type 2 diabetes and a follow-up of more than 24 months (n = 2,560; baseline median eGFR, 84 mL/min/1.73 m(2); urine albumin-to-creatinine ratio, 8.1 mg/g). The 17 biomarkers were measured at baseline in 481 samples using Luminex and ELISA. The prediction of eGFR decline was evaluated by linear mixed modeling. RESULTS: In univariable analyses, 9 of the 17 markers showed significant differences in median concentration between stable and fast-progressing patients. A linear mixed model for eGFR obtained by variable selection exhibited an adjusted R(2) of 62%. A panel of 12 biomarkers was selected by the procedure and accounted for 34% of the total explained variability, of which 32% was due to 5 markers. The individual contribution of each biomarker to the prediction of eGFR decline on top of clinical predictors was generally low. When included into the model, baseline eGFR exhibited the largest explained variability of eGFR decline (R(2) of 79%), and the contribution of each biomarker dropped below 1%. CONCLUSIONS: In this longitudinal study of patients with type 2 diabetes and maintained eGFR at baseline, 12 of the 17 candidate biomarkers were associated with eGFR decline, but their predictive power was low.*

3. Nagler EV, Haller MC, Van Biesen W, Vanholder R, Craig JC, Webster AC: Interventions for chronic non-hypovolaemic hypotonic hyponatraemia. *Cochrane Database Syst Rev* (2018) 6:CD010965; https://doi.org/10.1002/14651858.CD010965.pub2

   Abstract: *BACKGROUND: Chronic (present > 48 hours) non-hypovolaemic hyponatraemia occurs frequently, can be caused by various conditions, and is associated with shorter survival and longer hospital stays. Many treatments, such as fluid restriction or vasopressin receptor antagonists can be used to improve the hyponatraemia, but whether that translates into improved patient-important outcomes is less certain. OBJECTIVES: This review aimed to 1) look at the benefits and harms of interventions for chronic non-hypovolaemic hypotonic hyponatraemia when compared with placebo, no treatment or head-to-head; and 2) determine if benefits and harms vary in absolute or relative terms dependent on the specific compound within a drug class, on the dosage used, or the underlying disorder causing the hyponatraemia. SEARCH METHODS: We searched the Cochrane Kidney and Transplant Register of Studies up to 1 December 2017 through contact with the Information Specialist using search terms relevant to this review. Studies in*

the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov. We also screened the reference lists of potentially relevant studies, contacted authors, and screened the websites of regulatory agencies. SELECTION CRITERIA: We included randomised controlled trials (RCTs) and quasi-RCTs that compared the effects of any intervention with placebo, no treatment, standard care, or any other intervention in patients with chronic non-hypovolaemic hypotonic hyponatraemia. We also included subgroups with hyponatraemia from studies with broader inclusion criteria (e.g. people with chronic heart failure or people with cirrhosis with or without hyponatraemia), provided we could obtain outcomes for participants with hyponatraemia from the report or the study authors. DATA COLLECTION AND ANALYSIS: Two authors independently extracted data and assessed risk of bias. We expressed treatment effects as mean difference (MD) for continuous outcomes (health-related quality of life, length of hospital stay, change from baseline in serum sodium concentration, cognitive function), and risk ratio (RR) for dichotomous outcomes (death, response and rapid increase in serum sodium concentration, hypernatraemia, polyuria, hypotension, acute kidney injury, liver function abnormalities) together with 95% confidence intervals (CI). MAIN RESULTS: We identified 35 studies, enrolling 3429 participants. Twenty-eight studies (3189 participants) compared a vasopressin receptor antagonist versus placebo, usual care, no treatment, or fluid restriction. In adults with chronic, non-hypovolaemic hypotonic hyponatraemia, vasopressin receptor antagonists have uncertain effects on death at six months (15 studies, 2330 participants: RR 1.11, 95% CI 0.92 to 1.33) due to risk of selective reporting and serious imprecision; and on health-related quality of life because results are at serious risk of performance, selective reporting and attrition bias, and suffer from indirectness related to the validity of the Short Form Health Survey (SF-12) in the setting of hyponatraemia. Vasopressin receptor antagonists may reduce hospital stay (low certainty evidence due to risk of performance bias and imprecision) (3 studies, 610 participants: MD -1.63 days, 95% CI -2.96 to -0.30), and may make little or no difference to cognitive function (low certainty evidence due to indirectness and imprecision). Vasopressin receptor antagonists probably increase the intermediate outcome of serum sodium concentration (21 studies, 2641 participants: MD 4.17 mmol/L, 95% CI 3.18 to 5.16), corresponding to two and a half as many people having a 5 to 6 mmol/L increase in sodium concentration compared with placebo at 4 to 180 days (moderate certainty evidence due to risk of attrition bias) (18 studies, 2014 participants: RR 2.49, 95% CI 1.95 to 3.18). But they probably also increase the risk of rapid serum sodium correction - most commonly defined as > 12 mmol/L/d (moderate certainty evidence due to indirectness) (14 studies, 2058 participants: RR 1.67, 95% CI 1.16 to 2.40) and commonly cause side-effects such as thirst (13 studies, 1666 participants: OR 2.77, 95% CI 1.80 to 4.27) and polyuria (6 studies, 1272 participants): RR 4.69, 95% CI 1.59 to 13.85) (high certainty evidence). The potential for liver toxicity remains uncertain due to large imprecision. Effects were generally consistent across the different agents, suggesting class effect.Data for other interventions such as fluid restriction, urea, mannitol, loop diuretics, corticosteroids, demeclocycline, lithium and phenytoin were largely absent. AUTHORS' CONCLUSIONS: In people with chronic hyponatraemia, vasopressin receptor antagonists modestly raise serum sodium concentration at the cost of a 3% increased risk of it being rapid. To date there is very low certainty evidence for patient-important outcomes; the effects on mortality and health-related quality of life are unclear and do not rule out appreciable benefit or harm; there does not appear to be an important effect on cognitive function, but hospital stay may be slightly shorter, although available data are limited. Treatment decisions must weigh the value of an increase in serum sodium concentration against its short-term risks and unknown effects on patient-important outcomes. Evidence for other treatments is largely absent.Further studies assessing standard treatments such as fluid restriction or urea against placebo and one-another would inform practice and are warranted. Given the limited available evidence for patient-important outcomes, any study should include these outcomes in a standardised manner.

4. Svoboda M, Mungenast F, Gleiss A, Vergote I, Vanderstichele A, Sehouli J, Braicu E, Mahner S, Jager W, Mechtcheriakova D, Cacsire-Tong D, Zeillinger R, Thalhammer T, Pils D: Clinical Significance of Organic Anion Transporting Polypeptide Gene Expression in High-Grade Serous Ovarian Cancer. *Front Pharmacol* (2018) 9:842; https://doi.org/10.3389/fphar.2018.00842

Abstract: *High-grade serous ovarian cancer (HGSOC) is considered the most deadly and frequently occurring type of ovarian cancer and is associated with various molecular compositions and growth patterns. Evaluating the mRNA expression pattern of the organic anion transporters (OATPs) encoded by SLCO genes may allow for improved stratification of HGSOC patients for targeted invention. The expression of SLCO mRNA and genes coding for putative functionally related ABC-efflux pumps, enzymes, pregnane-X-receptor, ESR1 and ESR2 (coding for estrogen receptors ERalpha and ERss) and HER-2 were assessed using RT-qPCR. The expression levels were assessed in a cohort of 135 HGSOC patients to elucidate the independent impact of the expression pattern on the overall survival (OS). For identification of putative regulatory networks, Graphical Gaussian Models were constructed from the expression data*

with a tuning parameter K varying between meaningful borders (Pils et al., 2012; Auer et al., 2015, 2017; Kurman and Shih Ie, 2016; Karam et al., 2017; Labidi-Galy et al., 2017; Salomon-Perzynski et al., 2017; Sukhbaatar et al., 2017). The final value used (K = 4) was determined by maximizing the proportion of explained variation of the corresponding LASSO Cox regression model for OS. The following two networks of directly correlated genes were identified: (i) SLCO2B1 with ABCC3 implicated in estrogen homeostasis; and (ii) two ABC-efflux pumps in the immune regulation (ABCB2/ABCB3) with ABCC3 and HER-2. Combining LASSO Cox regression and univariate Cox regression analyses, SLCO5A1 coding for OATP5A1, an estrogen metabolite transporter located in the cytoplasm and plasma membranes of ovarian cancer cells, was identified as significant and independent prognostic factor for OS (HR = 0.68, CI 0.49-0.93; p = 0.031). Furthermore, results indicated the benefits of patients with high expression by adding 5.1% to the 12.8% of the proportion of explained variation (PEV) for clinicopathological parameters known for prognostic significance (FIGO stage, age and residual tumor after debulking). Additionally, overlap with previously described signatures that indicated a more favorable prognosis for ovarian cancer patients was shown for SLCO5A1, the network ABCB2/ABCB3/ABCC4/HER2 as well as ESR1. Furthermore, expression of SLCO2A1 and PGDH, which are important for PGE2 degradation, was associated with the non-miliary peritoneal tumor spreading. In conclusion, the present findings suggested that SLCOs and the related molecules identified as potential biomarkers in HGSOC may be useful for the development of novel therapeutic strategies.

2017

1. Auer K, Bachmayr-Heyda A, Aust S, Grunt TW, Pils D: Comparative transcriptome analysis links distinct peritoneal tumor spread types, miliary and non-miliary, with putative origin, tubes and ovaries, in high grade serous ovarian cancer. *Cancer Lett* (2017) 388:158-166; https://doi.org/10.1016/j.canlet.2016.11.034

   Abstract: *High grade serous ovarian cancer (HGSOC) is characterized by extensive local, i.e. peritoneal, tumor spread, manifested in two different clinical presentations, miliary (many millet sized peritoneal implants) and non-miliary (few large exophytically growing peritoneal nodes), and an overall unfavorable outcome. HGSOC is thought to arise from fallopian tube secretory epithelial cells, via so called serous tubal intraepithelial carcinomas (STICs) but an ovarian origin was never ruled out for at least some cases. Comparative transcriptome analyses of isolated tumor cells from fresh HGSOC tissues and (immortalized) ovarian surface epithelial and fallopian tube secretory epithelial cell lines revealed a close relation between putative origin and tumor spread characteristic, i.e. miliary from tubes and non-miliary from ovaries. The latter were characterized by more mesenchymal cell characteristics, more adaptive tumor immune infiltration, and a favorable overall survival. Several molecular sub-classification systems (Crijns' overall survival signature, Yoshihara's subclasses, and a collagen-remodeling signature) seem to already indicate origin. Putative origin alone is a significant independent predictor for HGSOC outcome, validated in independent patient cohorts. Characteristics of both spread types could guide development of new targeted therapeutics, which are urgently needed.*

2. Aust S, Felix S, Auer K, Bachmayr-Heyda A, Kenner L, Dekan S, Meier SM, Gerner C, Grimm C, Pils D: Absence of PD-L1 on tumor cells is associated with reduced MHC I expression and PD-L1 expression increases in recurrent serous ovarian cancer. *Sci Rep* (2017) 7:42929; https://doi.org/10.1038/srep42929

   Abstract: *Immune-evasion and immune checkpoints are promising new therapeutic targets for several cancer entities. In ovarian cancer, the clinical role of programmed cell death receptor ligand 1 (PD-L1) expression as mechanism to escape immune recognition has not been clarified yet. We analyzed PD-L1 expression of primary ovarian and peritoneal tumor tissues together with several other parameters (whole transcriptomes of isolated tumor cells, local and systemic immune cells, systemic cytokines and metabolites) and compared PD-L1 expression between primary tumor and tumor recurrences. All expressed major histocompatibility complex (MHC) I genes were negatively correlated to PD-L1 abundances on tumor tissues, indicating two mutually exclusive immune-evasion mechanisms in ovarian cancer: either down-regulation of T-cell mediated immunity by PD-L1 expression or silencing of self-antigen presentation by down-regulation of the MHC I complex. In our cohort and in most of published evidences in ovarian cancer, low PD-L1 expression is associated with unfavorable outcome. Differences in immune cell populations, cytokines, and metabolites strengthen this picture and suggest the existence of concurrent pathways for progression of this disease. Furthermore, recurrences showed significantly increased PD-L1 expression compared to the primary tumors, supporting trials of checkpoint inhibition in the recurrent setting.*

3. Bachmayr-Heyda A, Aust S, Auer K, Meier SM, Schmetterer KG, Dekan S, Gerner C, Pils D: Integrative Systemic and Local Metabolomics with Impact on Survival in High-Grade Serous Ovarian Cancer. *Clin Cancer Res* (2017) 23(8): 2081-2092; https://doi.org/10.1158/1078-0432.CCR-16-1647

   Abstract: *Purpose: Cancer metabolism is characterized by alterations including aerobic glycolysis, oxidative phosphorylation, and need of fuels and building blocks.Experimental Design: Targeted metabolomics of preoperative and follow-up sera, ascites, and tumor tissues, RNA sequencing of isolated tumor cells, local and systemic chemokine, and local immune cell infiltration data from up to 65 high-grade serous ovarian cancer patients and 62 healthy controls were correlated to overall survival and integrated in a Systems Medicine manner.Results: Forty-three mainly (poly)unsaturated glycerophospholipids and four essential amino acids (citrulline) were significantly reduced in patients with short compared with long survival and healthy controls. The glycerophospholipid fingerprint is identical to the fingerprint from isolated (very) low-density lipoproteins (vLDL), indicating that the source of glycerophospholipids consumed by tumors is (v)LDL. A glycerophospholipid-score (HR, 0.46; P = 0.007) and a 100-gene signature (HR, 0.65; P = 0.004) confirmed the independent impact on survival in training (n = 65) and validation (n = 165) cohorts. High concentrations of LDLs and glycerophospholipids were independently predictors for favorable survival. Patients with low glycerophospholipids presented with more systemic inflammation (C-reactive protein and*

fibrinogen negatively and albumin positively correlated) but less adaptive immune cell tumor infiltration (lower tumor and immune cell PD-L1 expression), less oxygenic respiration and increased triglyceride biosynthesis in tumor cells, and lower histone expressions, correlating with higher numbers of expressed genes and more transcriptional noise, a putative neo-pluripotent tumor cell phenotype.Conclusions: Low serum phospholipids and essential amino acids are correlated with worse outcome in ovarian cancer, accompanied by a specific tumor cell phenotype. Clin Cancer Res; 23(8); 2081-92. (c)2016 AACR.

4. Haller MC, Kainz A, Baer H, Oberbauer R: Dialysis Vintage and Outcomes after Kidney Transplantation: A Retrospective Cohort Study. *Clin J Am Soc Nephrol* (2017) 12(1): 122-130; https://doi.org/10.2215/CJN.04120416

Abstract: *BACKGROUND AND OBJECTIVES: Historically, length of pretransplant dialysis was associated with premature graft loss and mortality after kidney transplantation, but with recent advancements in RRT it is unclear whether this negative association still exists. DESIGN, SETTING, PARTICIPANTS, &MEASUREMENTS: This is a retrospective cohort study evaluating 6979 first kidney allograft recipients from the Austrian Registry transplanted between 1990 and 2013. Duration of pretransplant dialysis treatment was used as categoric predictor classified by tertiles of the distribution of time on dialysis. A separate category for pre-emptive transplantation was added and defined as kidney transplantation without any dialysis preceding the transplant. Outcomes were death-censored graft loss, all-cause mortality, and the composite of both. RESULTS: Median duration of follow-up was 8.2 years, and 1866 graft losses and 2407 deaths occurred during the study period. Pre-emptive transplantation was associated with a lower risk of graft loss (hazard ratio, 0.76; 95% confidence interval, 0.59 to 0.98), but not in subgroup analyses excluding living transplants and transplants performed since 2000. The association between dialysis duration and graft loss did not depend on the year of transplantation (P=0.40) or donor source (P=0.92). Longer waiting time on dialysis was not associated with a higher rate of graft loss, but the rate of death was higher in patients on pretransplant dialysis for >1.5 years (hazard ratio, 1.62; 95% confidence interval, 1.43 to 1.83) compared with pretransplant dialysis for <1.5 years. CONCLUSIONS: Our findings support the evidence that pre-emptive transplantation is associated with superior graft survival compared with pretransplant dialysis, although this association was weaker in transplants performed since 2000. However, our analysis shows that length of dialysis was no longer associated with a higher rate of graft loss, although longer waiting times on dialysis were still associated with a higher rate of death.*

5. Haller MC, Kammer M, Kainz A, Baer HJ, Heinze G, Oberbauer R: Steroid withdrawal after renal transplantation: a retrospective cohort study. *BMC Med* (2017) 15(1): 8; https://doi.org/10.1186/s12916-016-0772-6

Abstract: *BACKGROUND: Immunosuppressive regimens in renal transplantation frequently contain corticosteroids, but many centers withdraw steroids as a consequence of unwanted side effects of steroids. The optimal timing to withdraw steroids after transplantation, however, remains unclear. The aim of this study was to determine an optimal time point following kidney transplantation that is associated with reduced mortality without jeopardizing the allograft to allow safe discontinuation of steroids. METHODS: We conducted a retrospective cohort study and computed a concatenated landmark-stratified Cox supermodel to estimate hazard ratios and 95% confidence intervals for mortality and graft loss using dynamic propensity score matching to adjust for confounding by indication. RESULTS: A total of 6070 first kidney transplant recipients in the Austrian Dialysis and Transplant Registry who were transplanted between 1990 and 2012 were evaluated and classified according to steroid treatment status throughout follow-up after kidney transplantation; 2142 patients were withdrawn from steroids during the study period. Overall, 1131 patients lost their graft and 821 patients in the study cohort died. Steroid withdrawal within 18 months after transplantation was associated with an increased rate of graft loss compared to steroid maintenance during that time (6 months after transplantation: HR = 1.8; 95% CI, 1.3 to 2.6; 18 months after transplantation: HR = 1.3; 95% CI, 1.1 to 1.6; 24 months after transplantation: HR = 1.2; 95% CI, 0.9 to 1.5), while mortality was not different between groups. CONCLUSIONS: Our findings suggest that steroid withdrawal after anti-IL-2 induction in the first 18 months after transplantation is associated with an increased risk of allograft loss.*

6. Nistor I, Bolignano D, Haller MC, Nagler E, van der Veer SN, Jager K, Covic A, Webster A, Van Biesen W: Why creating standardized core outcome sets for chronic kidney disease will improve clinical practice. *Nephrol Dial Transplant* (2017) 32(8): 1268-1273; https://doi.org/10.1093/ndt/gfv365

Abstract: *Chronic kidney disease (CKD) is common and is associated with increased mortality, morbidity and cost. However, insufficient high-quality trial data are available to answer many relevant clinical questions in this field. In addition, a wide range of variable outcomes are used in studies, and often they are incompletely reported.*

Furthermore, there is a lack of patient-relevant outcomes, such as mortality, morbidity, quality of life, pain, need for dialysis or costs. Common problems with outcome reporting are as follows: choosing the wrong domains to measure; within domains, choosing the wrong measures (invalid surrogates, composite, non-patient relevant); within measures, choosing the wrong/variable metrics; and within metrics, choosing variable presentation methods. With this article, we aim to underline why standardized outcome reporting is key to achieving evidence-based guidance and improving clinical care for patients; highlight the frameworks available for achieving core outcome sets; and starting from these frameworks, we propose steps needed to develop a core outcome set in the field of CKD. We hope that standardized core outcome sets for nephrology will lead to the most important outcome of guideline production, improving outcomes for our patients.

7. Pichler G, Haller MC, Kainz A, Wolf M, Redon J, Oberbauer R: Prognostic value of bone- and vascular-derived molecular biomarkers in hemodialysis and renal transplant patients: a systematic review and meta-analysis. *Nephrol Dial Transplant* (2017) 32(9): 1566-1578; https://doi.org/10.1093/ndt/gfw387

Abstract: *Background: Patients undergoing hemodialysis and kidney graft recipients are high-risk populations for cardiovascular and all-cause mortality. Fibroblast growth factor 23 (FGF23), osteoprotegerin (OPG), RANK ligand, osteopontin (OPN), Klotho protein and bone morphogenetic protein-7 (BMP-7) are bone- and vascular-derived molecular biomarkers that have been shown to be associated with cardiovascular surrogate end points; however, currently available data on the prognostic value of these biomarkers is inconsistent. The aim of the present study was to conduct a systematic review and meta-analysis in order to summarize the available evidence on the association of molecular biomarkers with mortality in individuals undergoing hemodialysis and renal transplant patients. Methods: Two databases (MEDLINE and Embase) were systematically searched. Studies were eligible if the association of biomarker and mortality was reported as time-to-event data [hazard Ratio (HR)] or as effect size with a fixed time of follow-up [odds Ratio (OR)]. Abstracted HRs were converted onto a standard scale of effect and combined using a random effects model. Results: From a total of 1170 studies identified in initial searches, 21 met the inclusion criteria. In hemodialysis patients, comparing the lower third with the upper third of baseline FGF23 distribution, pooled HRs (95% confidence intervals) were 1.94 (1.47, 2.56) for all-cause mortality and 2.4 (1.64, 3.51) for cardiovascular mortality. For the same comparison of baseline OPG distribution, pooled HRs were 1.8 (0.95, 3.39) for all-cause mortality and 2.53 (1.29, 4.94) for cardiovascular mortality. Reported risk estimates of RANK ligand, OPN, Klotho protein and BMP-7 were not suitable for pooling; however, only Klotho protein was significantly related to mortality. For kidney graft recipients, four studies that investigated the relationship of FGF23 and OPG with mortality were identified, all of which reported a significant association. Conclusions: In hemodialysis patients, FGF23 is a predictor of all-cause and cardiovascular mortality, whereas the predictive value of OPG is restricted to cardiovascular mortality. Further studies are needed in order to gain insight into the prognostic value of these biomarkers in renal transplant recipients.*

8. Schalling M, Gleiss A, Gisslinger B, Wolfler A, Buxhofer-Ausch V, Jeryczynski G, Krauth MT, Simonitsch-Klupp I, Beham-Schmid C, Thiele J, Gisslinger H: Essential thrombocythemia vs. pre-fibrotic/early primary myelofibrosis: discrimination by laboratory and clinical data. *Blood Cancer J* (2017) 7(12): 643; https://doi.org/10.1038/s41408-017-0006-y

9. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, van Biesen W, Nagler E, Gonzalez-Espinoza L, Ortiz A, Hyponatraemia Guideline Development G: Hyponatraemia diagnosis and treatment clinical practice guidelines. *Nefrologia* (2017) 37(4): 370-380; https://doi.org/10.1016/j.nefro.2017.03.021

Abstract: *Hyponatremia, defined as a serum sodium concentration <135mmol/l, is the most common water-electrolyte imbalance encountered in clinical practice. It can lead to a wide spectrum of clinical symptoms, from mild to severe or even life threatening, and is associated with increased mortality, morbidity and length of hospital stay. Despite this, the management of hyponatremia patients remains problematic. The prevalence of hyponatremia in a wide variety of conditions and the fact that hyponatremia is managed by clinicians with a broad variety of backgrounds have fostered diverse institution- and specialty-based approaches to diagnosis and treatment. To obtain a common and holistic view, the European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), represented by European Renal Best Practice (ERBP), have developed clinical practice guidelines on the diagnostic approach and treatment of hyponatremia as a joint venture of 3societies representing specialists with a natural*

interest in hyponatremia. In addition to a rigorous approach to the methodology and evaluation of the evidence, the document focuses on patient-positive outcomes and on providing a useful tool for clinicians involved in everyday practice. In this article, we present an abridged version of the recommendations and suggestions for the diagnosis and treatment of hyponatremia extracted from the full guide.

10. Sukhbaatar N, Bachmayr-Heyda A, Auer K, Aust S, Deycmar S, Horvat R, Pils D: Two different, mutually exclusively distributed, TP53 mutations in ovarian and peritoneal tumor tissues of a serous ovarian cancer patient: indicative for tumor origin? *Cold Spring Harb Mol Case Stud* (2017) 3(4): 1-15; https://doi.org/10.1101/mcs.a001461

Abstract: *High-grade serous ovarian cancer (HGSOC) is characterized by a TP53 mutation rate of up to 96.7% and associated with a more aggressive tumor biology. The origin of HGSOC is thought to arise either from fallopian tube secretory cells or the ovarian surface epithelium/inclusion cysts, the former with more evidence. Peritoneal tumor spread is heterogeneous, either excessive in the peritoneum (with miliary appearance) or more confined to the ovaries with only few (bigger and exophytically growing) peritoneal implants. Using RNA sequencing and DNA digital droplet polymerase chain reaction (PCR), we identified two different functional TP53 mutations in one HGSOC patient: one exclusively in the ovarian tumor mass and the other exclusively in ascites tumor cells, peritoneal tumor masses, and a lymph node metastasis. In blood, both mutations could be detected, the one from the peritoneal tumors with much higher frequency, presumably because of the higher tumor load. We conclude that this mutually exclusive distribution of two different TP53 mutations in different tumor tissues indicates the development of two independent carcinomas in the peritoneal cavity, probably one originating from a precancerous lesion in the fallopian tube and the other from the ovaries. In addition, in the patient's ascites CD45 and EpCAM, double-positive cells were found-proliferating but testing negative for the above-mentioned TP53 mutations. This mutually exclusive distribution of two TP53 mutations is probably further evidence that HGSOC can originate either from the fallopian tube or (more seldom) the ovaries, the former more prone for excessive peritoneal tumor spread.*

11. Waldhoer T, Heinzl H: Exploring the possible relationship between ambient heat and sudden infant death with data from Vienna, Austria. *PLoS ONE* (2017) 12(9): e0184312; https://doi.org/10.1371/journal.pone.0184312

Abstract: *A non-linear relationship between maximum ambient temperature and number of sudden infant death syndrome (SIDS) cases had been reported for Montreal, Canada, for the warm season. In particular, high maximum ambient temperatures were found to be extra-hazardous for infants. The study was replicated with data from Vienna, Austria, applying the same statistical approach. Vienna is roughly comparable to Montreal with regard to temperatures in the warm season, size of population, and number of SIDS cases. Although the Viennese study was powerful enough to detect even smaller effects, the Montrealean results could not be confirmed. The Viennese results do not support the hypothesis of a strong effect of maximum ambient temperature on the risk of SIDS during the warm season.*

2016

1. Abramowicz D, Hazzan M, Maggiore U, Peruzzi L, Cochat P, Oberbauer R, Haller MC, Van Biesen W, Descartes Working G, the European Renal Best Practice Advisory B: Does pre-emptive transplantation versus post start of dialysis transplantation with a kidney from a living donor improve outcomes after transplantation? A systematic literature review and position statement by the Descartes Working Group and ERBP. *Nephrol Dial Transplant* (2016) 31(5): 691-697; https://doi.org/10.1093/ndt/gfv378

   Abstract: *This position statement brings up guidance on pre-emptive kidney transplantation from living donors. The provided guidance is based on a systematic review of the literature.*

2. Dunkler D, Kohl M, Teo KK, Heinze G, Dehghan M, Clase CM, Gao P, Yusuf S, Mann JF, Oberbauer R, Investigators O: Population-Attributable Fractions of Modifiable Lifestyle Factors for CKD and Mortality in Individuals With Type 2 Diabetes: A Cohort Study. *Am J Kidney Dis* (2016) 68(1): 29-40; https://doi.org/10.1053/j.ajkd.2015.12.019

   Abstract: *BACKGROUND: We quantified the impact of lifestyle and dietary modifications on chronic kidney disease (CKD) by estimating population-attributable fractions (PAFs). STUDY DESIGN: Observational cohort study. SETTING & PARTICIPANTS: Middle-aged adults with type 2 diabetes but without severe albuminuria from the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET; n=6,916). FACTORS: Modifiable lifestyle/dietary risk factors, such as physical activity, size of social network, alcohol intake, tobacco use, diet, and intake of various food items. OUTCOMES: The primary outcome was CKD, ascertained as moderate to severe albuminuria or >/=5% annual decline in estimated glomerular filtration rate (eGFR) after 5.5 years. The competing risk for death was considered. PAF was defined as the proportional reduction in CKD or mortality (within 5.5 years) that would occur if exposure to a risk factor was changed to an optimal level. RESULTS: At baseline, median urinary albumin-creatinine ratio and eGFR were 6.6 (IQR, 2.9-25.0) mg/mmol and 71.5 (IQR, 58.1-85.9) mL/min/1.73m(2), respectively. After 5.5 years, 704 (32.5%) participants developed albuminuria, 1,194 (55.2%) had a >/=5% annual eGFR decline, 267 (12.3%) had both, and 1,022 (14.8%) had died. Being physically active every day has PAFs of 5.1% (95% CI, 0.5%-9.6%) for CKD and 12.3% (95% CI, 4.9%-19.1%) for death. Among food items, increasing vegetable intake would have the largest impact on population health. Considering diet, weight, physical activity, tobacco use, and size of social network, exposure to less than optimum levels gives PAFs of 13.3% (95% CI, 5.5%-20.9%) for CKD and 37.5% (95% CI, 27.8%-46.7%) for death. For the 17.8 million middle-aged Americans with diabetes, improving 1 of these lifestyle behaviors to the optimal range could reduce the incidence or progression of CKD after 5.5 years by 274,000 and the number of deaths within 5.5 years by 405,000. LIMITATIONS: Ascertainment of changes in kidney measures does not precisely match the definitions for incidence or progression of CKD. CONCLUSIONS: Healthy lifestyle and diet are associated with less CKD and mortality and may have a substantial impact on population kidney health.*

3. Gleiss A, Frass M, Gaertner K: Re-analysis of survival data of cancer patients utilizing additive homeopathy. *Complement Ther Med* (2016) 27:65-67; https://doi.org/10.1016/j.ctim.2016.06.001

   Abstract: *In this short communication we present a re-analysis of homeopathic patient data in comparison to control patient data from the same Outpatient s Unit "Homeopathy in malignant diseases" of the Medical University of Vienna. In this analysis we took account of a probable immortal time bias. For patients suffering from advanced stages of cancer and surviving the first 6 or 12 months after diagnosis, respectively, the results show that utilizing homeopathy gives a statistically significant (p<0.001) advantage over control patients regarding survival time. In conclusion, bearing in mind all limitations, the results of this retrospective study suggest that patients with advanced stages of cancer might benefit from additional homeopathic treatment until a survival time of up to 12 months after diagnosis.*

4. Haller MC, Royuela A, Nagler EV, Pascual J, Webster AC: Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev* (2016) 8: CD005632; https://doi.org/10.1002/14651858.CD005632.pub3

   Abstract: *BACKGROUND: Steroid-sparing strategies have been attempted in recent decades to avoid morbidity from long-term steroid intake among kidney transplant recipients. Previous systematic reviews of steroid withdrawal after*

kidney transplantation have shown a significant increase in acute rejection. There are various protocols to withdraw steroids after kidney transplantation and their possible benefits or harms are subject to systematic review. This is an update of a review first published in 2009. OBJECTIVES: To evaluate the benefits and harms of steroid withdrawal or avoidance for kidney transplant recipients. SEARCH METHODS: We searched the Cochrane Kidney and Transplant Specialised Register to 15 February 2016 through contact with the Information Specialist using search terms relevant to this review. SELECTION CRITERIA: All randomised and quasi-randomised controlled trials (RCTs) in which steroids were avoided or withdrawn at any time point after kidney transplantation were included. DATA COLLECTION AND ANALYSIS: Assessment of risk of bias and data extraction was performed by two authors independently and disagreement resolved by discussion. Statistical analyses were performed using the random-effects model and dichotomous outcomes were reported as relative risk (RR) and continuous outcomes as mean difference (MD) with 95% confidence intervals. MAIN RESULTS: We included 48 studies (224 reports) that involved 7803 randomised participants. Of these, three studies were conducted in children (346 participants). The 2009 review included 30 studies (94 reports, 5949 participants). Risk of bias was assessed as low for sequence generation in 19 studies and allocation concealment in 14 studies. Incomplete outcome data were adequately addressed in 22 studies and 37 were free of selective reporting.The 48 included studies evaluated three different comparisons: steroid avoidance or withdrawal compared with steroid maintenance, and steroid avoidance compared with steroid withdrawal. For the adult studies there was no significant difference in patient mortality either in studies comparing steroid withdrawal versus steroid maintenance (10 studies, 1913 participants, death at one year post transplantation: RR 0.68, 95% CI 0.36 to 1.30) or in studies comparing steroid avoidance versus steroid maintenance (10 studies, 1462 participants, death at one year after transplantation: RR 0.96, 95% CI 0.52 to 1.80). Similarly no significant difference in graft loss was found comparing steroid withdrawal versus steroid maintenance (8 studies, 1817 participants, graft loss excluding death with functioning graft at one year after transplantation: RR 1.17, 95% CI 0.72 to 1.92) and comparing steroid avoidance versus steroid maintenance (7 studies, 1211 participants, graft loss excluding death with functioning graft at one year after transplantation: RR 1.09, 95% CI 0.64 to 1.86). The risk of acute rejection significantly increased in patients treated with steroids for less than 14 days after transplantation (7 studies, 835 participants: RR 1.58, 95% CI 1.08 to 2.30) and in patients who were withdrawn from steroids at a later time point after transplantation (10 studies, 1913 participants, RR 1.77, 95% CI 1.20 to 2.61). There was no evidence to suggest a difference in harmful events, such as infection and malignancy, in adult kidney transplant recipients. The effect of steroid withdrawal in children is unclear. AUTHORS' CONCLUSIONS: This updated review increases the evidence that steroid avoidance and withdrawal after kidney transplantation significantly increase the risk of acute rejection. There was no evidence to suggest a difference in patient mortality or graft loss up to five year after transplantation, but long-term consequences of steroid avoidance and withdrawal remain unclear until today, because prospective long-term studies have not been conducted.

5. Heinze G, Jandeck LM, Hronsky M, Reichardt B, Baumgartel C, Bucsics A, Mullner M, Winkelmayer WC: Prevalence and determinants of unintended double medication of antihypertensive, lipid-lowering, and hypoglycemic drugs in Austria: a nationwide cohort study. *Pharmacoepidemiol Drug Saf* (2016) 25(1): 90-99; https://doi.org/10.1002/pds.3898

Abstract: *PURPOSE: Double medication is defined as the unintended overlapping prescription of two identical substances with the same route of administration by two different prescribers to the same patient. Consequences of double medication are reduced patient safety and excess healthcare costs. Based on nationwide prescription data from 2011 covering 97% of Austria's population, we estimated double medication prevalences for treatment of hypertension, hyperlipidemia, and diabetes mellitus. METHODS: We investigated prescriptions of 88 antihypertensive, 16 lipid-lowering and 29 hypoglycemic substances in 7,971,323 persons in 2011. Prevalence of double medication was calculated patientwise (prevalence by patients) and timewise (prevalence by patient-years). Risk factors for double medication were identified by logistic regression. RESULTS: For antihypertensive, lipid-lowering, and hypoglycemic subtances, overall 15.0% (men: 15.1%, women: 15.0%), 13.1% (13.7%, 12.5%), and 13.0% (13.0%, 13.4%) of patients were doubly medicated, respectively. Corresponding prevalences by patient-years were 1.6%, 2.0%, and 1.2%. Logistic regression confirmed lower age and copayment waiver as independent risk factors of double medication. Furthermore, double medication occurred more often with prescriptions from hospitals or internal medicine specialists compared with general practitioners, as well as in August compared with earlier or later in the calendar year. CONCLUSION: While appropriate care or comanagement of patients by internal medicine specialists and general practitioners may explain some of the double prescriptions, our data indicate that unintended double medication is frequent. In Austria, lack of financial incentives of patients to avoid filling duplicate prescriptions explains a considerable fraction of double medication occurrences.*

2015

1. Dunkler D, Gao P, Lee SF, Heinze G, Clase CM, Tobe S, Teo KK, Gerstein H, Mann JF, Oberbauer R, Ontarget, Investigators O: Risk Prediction for Early CKD in Type 2 Diabetes. *Clin J Am Soc Nephrol* (2015) 10(8): 1371-1379; https://doi.org/10.2215/CJN.10321014

   Abstract: *BACKGROUND AND OBJECTIVES: Quantitative data for prediction of incidence and progression of early CKD are scarce in individuals with type 2 diabetes. Therefore, two risk prediction models were developed for incidence and progression of CKD after 5.5 years and the relative effect of predictors were ascertained. DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: Baseline and prospective follow-up data of two randomized clinical trials, ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and Outcome Reduction with Initial Glargine Intervention (ORIGIN), were used as development and independent validation cohorts, respectively. Individuals aged >/=55 years with type 2 diabetes and normo- or microalbuminuria at baseline were included. Incidence or progression of CKD after 5.5 years was defined as new micro- or macroalbuminuria, doubling of creatinine, or ESRD. The competing risk of death was considered as an additional outcome state in the multinomial logistic models. RESULTS: Of the 6766 ONTARGET participants with diabetes, 1079 (15.9%) experienced incidence or progression of CKD, and 1032 (15.3%) died. The well calibrated, parsimonious laboratory prediction model incorporating only baseline albuminuria, eGFR, sex, and age exhibited an externally validated c-statistic of 0.68 and an R(2) value of 10.6%. Albuminuria, modeled to depict the difference between baseline urinary albumin/creatinine ratio and the threshold for micro- or macroalbuminuria, was mostly responsible for the predictive performance. Inclusion of clinical predictors, such as glucose control, diabetes duration, number of prescribed antihypertensive drugs, previous vascular events, or vascular comorbidities, increased the externally validated c-statistic and R(2) value only to 0.69 and 12.1%, respectively. Explained variation was largely driven by renal and not clinical predictors. CONCLUSIONS: Albuminuria and eGFR were the most important factors to predict onset and progression of early CKD in individuals with type 2 diabetes. However, their predictive ability is modest. Inclusion of demographic, clinical, and other laboratory predictors barely improved predictive performance.*

2. Dunkler D, Kohl M, Heinze G, Teo KK, Rosengren A, Pogue J, Gao P, Gerstein H, Yusuf S, Oberbauer R, Mann JF, Investigators O: Modifiable lifestyle and social factors affect chronic kidney disease in high-risk individuals with type 2 diabetes mellitus. *Kidney Int* (2015) 87(4): 784-791; https://doi.org/10.1038/ki.2014.370

   Abstract: *This observational study examined the association between modifiable lifestyle and social factors on the incidence and progression of early chronic kidney disease (CKD) among those with type 2 diabetes. All 6972 people from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) with diabetes but without macroalbuminuria were studied. CKD progression was defined as decline in GFR of more than 5% per year, progression to end-stage renal disease, microalbuminuria, or macroalbuminuria at 5.5 years. Lifestyle/social factors included tobacco and alcohol use, physical activity, stress, financial worries, the size of the social network and education. Adjustments were made for known risks such as age, diabetes duration, GFR, albuminuria, gender, body mass index, blood pressure, fasting plasma glucose, and angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers use. Competing risk of death was considered. At study end, 31% developed CKD and 15% had died. The social network score (SNS) was a significant independent risk factor of CKD and death, reducing the risk by 11 and 22% when comparing the third to the first tertile of the SNS (odds ratios of CKD 0.89 and death 0.78). Education showed a significant association with CKD but stress and financial worries did not. Those with moderate alcohol consumption had a significantly decreased CKD risk compared with nonusers. Regular physical activity significantly decreased the risk of CKD. Thus, lifestyle is a determinant of kidney health in people at high cardiovascular risk with diabetes.*

3. Dunkler D, Kohl M, Teo KK, Heinze G, Dehghan M, Clase CM, Gao P, Yusuf S, Mann JF, Oberbauer R: Dietary risk factors for incidence or progression of chronic kidney disease in individuals with type 2 diabetes in the European Union. *Nephrol Dial Transplant* (2015) 30 Suppl 4:iv76-85; https://doi.org/10.1093/ndt/gfv086

   Abstract: *BACKGROUND: Although the prevalence of chronic kidney disease (CKD) is approximately 30% in the group of people with diabetes, data on interventions in the very early stage of the disease are still missing. Furthermore, the effects of modifiable lifestyle factors such as nutrition on incidence and progression of CKD in patients with diabetes in*

Europe remain elusive. METHODS: We analyzed whether diet quality and adherence to dietary guidelines using the modified Alternate Healthy Eating Index (mAHEI) score was associated with CKD incidence or progression after 5.5 years in 3088 European participants of the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) with type 2 diabetes and baseline normo- or micro-albuminuria. Death was considered as a competing risk in the multinomial logit regression models, which were adjusted for age, gender, duration of diabetes, ONTARGET randomization, baseline albuminuria and glomerular filtration rate (GFR). We also estimated the potential impact on population health of improvement in diet quality. RESULTS: At study end, 450 (14.6%) participants had died and 926 (30%) had experienced the renal endpoint of incidence or progression of CKD, of which 422 (13.7%) participants had progressed to micro- or macro-albuminuria, 596 (19.3%) had a GFR-decline of >5% per year and 18 (0.6%) had developed end-stage renal disease. Participants in the healthiest tertile of the mAHEI score had a decreased risk of incidence or progression of CKD (odds ratio 0.8, 95% confidence interval 0.68-0.94) and death (0.65, 0.52-0.81) compared with participants in the least healthy tertile. If individuals with a suboptimal dietary quality (e.g. mAHEI < 28) were able to improve their diet to an mAHEI of 28, 3.2% of CKD incidence or progression and 10.0% of deaths might be avoided in 5.5 years. CONCLUSIONS: If the association between diet and these endpoints is causal, then optimizing diet quality in individuals with diabetes who have no CKD or very early CKD would have substantial population benefits in terms of prevention of CKD incidence or progression and mortality in this high-risk population.

4. Haller MC, van der Veer SN, Nagler EV, Tomson C, Lewington A, Hemmelgarn BR, Gallagher M, Rocco M, Obrador G, Vanholder R, Craig JC, van Biesen W: A survey on the methodological processes and policies of renal guideline groups as a first step to harmonize renal guidelines. *Nephrol Dial Transplant* (2015) 30(7): 1066-1074; https://doi.org/10.1093/ndt/gfu288

Abstract: *BACKGROUND: Worldwide, several bodies produce renal guidelines, potentially leading to duplication of effort while other topics may remain uncovered. A collaborative work plan could improve efficiency and impact, but requires a common approved methodology. The aim of this study was to identify organizational and methodological similarities and differences among seven major renal guideline bodies to identify methodological barriers to a collaborative effort. METHODS: An electronic 62-item survey with questions based on the Institute of Medicine standards for guidelines was completed by representatives of seven major organizations producing renal guidelines: the Canadian Society of Nephrology (CSN), European Renal Best Practice (ERBP), Kidney Disease Improving Global Outcome (KDIGO), Kidney Health Australia-Caring for Australians with Renal Insufficiency (KHA-CARI), Kidney Disease Outcome Quality Initiative (KDOQI), Sociedad Latino-Americano de Nefrologia e Hipertension (SLANH) and United Kingdom Renal Association (UK-RA). RESULTS: Five of the seven groups conduct systematic searches for evidence, two include detailed critical appraisal and all use the GRADE framework. Five have public review of the guideline draft. Guidelines are updated as new evidence comes up in all, and/or after a specified time frame has passed (N = 3). Commentaries or position statements on guidelines published by other groups are produced by five, with the ADAPTE framework (N = 1) and the AGREEII (N = 2) used by some. Funding is from their parent organizations (N = 5) or directly from industry (N = 2). None allow funders to influence topic selection or guideline content. The budgets to develop a full guideline vary from $2000 to $500 000. Guideline development groups vary in size from <5 (N = 1) to 13-20 persons (N = 3). Three explicitly seek patient perspectives, for example, by involving patients in the scoping process, and four incorporate health economic considerations. All provide training in methodology for guideline development groups and six make their methods public. All try to avoid overlapping topics already planned or published by others. There is no common conflict of interest policy. CONCLUSIONS: Overall, there is considerable commonality in methods and approaches in renal guideline development by the different organizations, although some procedural differences remain. As the financial and human resource costs of guideline production are high, a collaborative approach is required to maximize impact and develop a sustainable work plan. Coming to consensus on methods and procedures is the first step and appears feasible.*

5. Heinze G, Hronsky M, Reichardt B, Baumgartel C, Mullner M, Bucsics A, Winkelmayer WC: Potential savings in prescription drug costs for hypertension, hyperlipidemia, and diabetes mellitus by equivalent drug substitution in Austria: a nationwide cohort study. *Appl Health Econ Health Policy* (2015) 13(2): 193-205; https://doi.org/10.1007/s40258-014-0143-4

Abstract: *BACKGROUND: Healthcare systems spend considerable proportions of their budgets on pharmaceutical treatment of hypertension, hyperlipidemia, and diabetes mellitus. From data on almost all residents of Austria, a country with mandatory health insurance and universal health coverage, we estimated potential cost savings by substituting prescribed medicines with the cheapest medicines that were of the same chemical substance and strength,*

and available during the same time. METHODS: Data from 8.3 million persons (98.5 % of the total Austrian insured population) from 2009-2012 were analyzed. Real prescription costs for antihypertensive, lipid-lowering, and hypoglycemic medicines achievable by same-substance, same-strength drug substitution were computed for each active ingredient, and per gender and 1-year age category of patients. RESULTS: In 2012, health insurance providers spent <euro>231.3 million, <euro>77.8 million, and <euro>91.9 million for antihypertensive, lipid-lowering, and diabetes medications, of which <euro>52.2 million (22.6 %), <euro>15.9 million (20.5 %), and <euro>4.1 million (4.5 %), respectively, could have been saved by same-substance drug substitution. Highest potential savings were calculated for amlodipine (<euro>8.0 million, 65.4 %), simvastatin (<euro>12.2 million, 59.3 %), and metformin (<euro>2.4 million, 54.6 %), respectively. Higher savings for men than for women resulted from differing prescribed cumulative dosages and proportions of patients with co-payment waiver. Potential cost savings in antihypertensive and lipid-lowering drugs increased from 2009-2012. CONCLUSION: Our study highlights the cost-savings potential from arguably the most acceptable of interventions, simply switching to the cheapest available same-substance, same-strength product. In 2012, this strategy could have reduced costs for antihypertensive, lipid-lowering, and hypoglycemic treatment by up to 18.0 %.

6. Heinze G, Wallisch C, Kainz A, Hronsky M, Leffondre K, Oberbauer R, Mayer G: Chances and challenges of using routine data collections for renal health care research. *Nephrol Dial Transplant* (2015) 30 Suppl 4:iv68-75; https://doi.org/10.1093/ndt/gfv110

Abstract: *BACKGROUND: Collections of electronic medical records (EMRs) can provide a rich source of information for renal health care research. However, their use in statistical analyses requires many preparatory steps, including coding of freetext entries and clear definitions of time windows for harvesting prognostic factors and outcomes. We analyse a large collection of EMRs to identify prognostic factors of adequate health care in diabetic patients at risk for chronic kidney disease, and discuss benefits and risks of such re-use of routine data. METHODS: In a representative sample of 695 068 patient records collected in 58 Austrian general practitioners' offices, we could identify 31 374 patients with diabetes mellitus. As outcomes, we investigated whether a patient received a serum creatinine measurement, and the time elapsing between two consecutive serum creatinine measurements. Prognostic factors were defined by extracting previous diagnoses, laboratory measurements, drug prescriptions and demographic characteristics from the records. RESULTS: Serum creatinine was measured annually in 44.4% of diabetic patients with previous signs of reduced kidney function and in 20.5% of the patients without such signs. Within 1 year after the first measurement, a follow-up measurement was made in 79.4 and 68.4% of the patients, respectively. Previous diagnoses, laboratory measurements, drug prescriptions and demographic characteristics explained 41% of the observed variance of kidney function monitoring. With 24% explained variance, previous referrals to laboratories were identified as the most important prognostic factor group. CONCLUSIONS: The analysis of large routine data collections poses various challenges, among which the need for coding free text into variables and various sources of biases are most demanding. However, routine data collections represent the daily practice of health care and offer many chances for renal health services and outcomes research.*

7. Kainz A, Hronsky M, Stel VS, Jager KJ, Geroldinger A, Dunkler D, Heinze G, Tripepi G, Oberbauer R: Prediction of prevalence of chronic kidney disease in diabetic patients in countries of the European Union up to 2025. *Nephrol Dial Transplant* (2015) 30 Suppl 4:iv113-118; https://doi.org/10.1093/ndt/gfv073

Abstract: *BACKGROUND: Diabetes and chronic kidney disease (CKD) are a growing burden for health-care systems. The prevalence of diabetes has increased constantly during the last decade, although a slight flattening of end-stage renal disease as a result of diabetes has been observed recently in some European countries. In this study, we project the prevalence of CKD in patients with diabetes in European countries up to the year 2025. METHODS: We analysed the population with diabetes and development of nephropathy in 12 European countries, which we computed from models published previously and on data from the annual reports of the European Renal Association (1998-2011). The prevalence of CKD stage 5 in patients with diabetes up to the year 2025 was projected by the Lee-Carter algorithm. Those for stage 3 and 4 were then estimated by applying the same ratios of CKD prevalences as estimated in the Austrian population with diabetic nephropathy. RESULTS: The estimated prevalence of CKD in patients with diabetes is expected to increase in all 12 countries up to the year 2025. For CKD stage 3, we estimate for Austria in 2025 a prevalence of 215 000 per million diabetic population (p.m.p.) (95% confidence interval 169 000, 275 000), for CKD4 18 600 p.m.p. (14 500, 23 700) and for CKD5 6900 p.m.p. (5400, 8900). The median prevalence in the considered countries is 132 900 p.m.p. (IQR: 118 500, 195 800), 11 500 (10 200, 16 900) and 4300 (3800, 6300) for CKD stages 3, 4 and 5, respectively. Altogether, these data predict in the years 2012-25 an annual increase of 3.2% in the prevalence*

of diabetic CKD stage 5. CONCLUSIONS: Due to the increase in prevalence of diabetes and CKD5, the costs of renal therapy are expected to rise. We believe that these data may help health-care policy makers to make informed decisions.

8. Mayer M, Gleiss A, Hausler G, Borkenstein M, Kapelari K, Kostl G, Lassi M, Schemper M, Schmitt K, Blumel P: Weight and body mass index (BMI): current data for Austrian boys and girls aged 4 to under 19 years. *Ann Hum Biol* (2015) 42(1): 45-55; https://doi.org/10.3109/03014460.2014.907444

Abstract: *BACKGROUND: BMI reference charts are widely used to diagnose overweight, obesity and underweight in children and adolescents. AIM: To provide up-to-date national reference values for Austria. METHODS: A cross-sectional sample of over 14 500 children and adolescents (4-19 years) stratified by provinces according to age- and sex-specific population proportions was drawn via schooling institutions (kindergartens, schools and vocational colleges). The generalized additive models for location, scale and shape were used for a flexible estimation of percentile curves. RESULTS: Austrian boys and girls have higher average weight compared with previous prevalence data. BMI centiles matching BMI values at age 18 years, which are used for defining thinness, overweight and obesity in adults, were calculated. In Austria, using reference values as thresholds, approximately 18% of boys and 12% of girls are overweight (with thresholds passing through BMI 25.00-29.99 kg/m(2) in adults) and 5% of boys and 3% of girls are obese (with thresholds passing through BMI >/=30.00 kg/m(2) in adults). CONCLUSION: Overweight and obesity are common in Austria and their prevalence is increasing (using the same IOTF reference for international comparison). Up-to-date national BMI reference values are provided to classify children and adolescents according to the proposed overweight and obesity thresholds.*

9. Mayer M, Gleiss A, Häusler G, Borkenstein M, Kapelari K, Köstl G, Lassi M, Schemper M, Schmitt K, Blümel P: BMI-Referenzwerte für österreichische Knaben und Mädchen. *J KLIN ENDORKINOL STOFFW* (2015) 8(2): 38-40;

10. van der Veer SN, Haller MC, Pittens CA, Broerse J, Castledine C, Gallieni M, Inston N, Marti Monros A, Peek N, van Biesen W: Setting Priorities for Optimizing Vascular Access Decision Making--An International Survey of Patients and Clinicians. *PLoS ONE* (2015) 10(7): e0128228; https://doi.org/10.1371/journal.pone.0128228

Abstract: *BACKGROUND: Many decisions around vascular access for haemodialysis warrant a collaborative treatment decision-making process, involving both clinician and patient. Yet, patients' experiences in this regard have been suboptimal. Although clinical practice guidelines could facilitate collaborative decision making, they often focus on the clinicians' side of the process, while failing to address the patients' perspective. The objective of this study was to explore and compare kidney patients' and clinicians' views on what vascular access-related decisions deserved priority for developing guidelines that will contribute to optimizing collaborative decision making. METHODS: In the context of updating their vascular access guideline, European Renal Best Practice surveyed an international panel of 85 kidney patients, 687 nephrologists, 194 nurses, and 140 surgeons/radiologists. In an electronic questionnaire, respondents rated 42 vascular access-related topics on a 5-point Likert scale. Based on mean standardized ratings, we compared priority ratings between patients and each clinician group. RESULTS: Selection of access type and site, as well as prevention of access infections received top priority across all respondent groups. Patients generally assigned higher priority to decisions regarding managing adverse effects of arteriovenous access and patient involvement in care, while clinicians more often prioritized decisions around sustaining patients' access options, technical aspects of access creation, and optimizing fistula maturation and patency. CONCLUSION: Apart from identifying the most pressing knowledge gaps, our study provides pointers for developing guidelines that may improve healthcare professionals' understanding of when to involve patients along the vascular access pathway.*

2014

1. Eichinger S, Heinze G, Kyrle PA: D-dimer levels over time and the risk of recurrent venous thromboembolism: an update of the Vienna prediction model. *J Am Heart Assoc* (2014) 3(1): e000467; https://doi.org/10.1161/JAHA.113.000467

   Abstract: *BACKGROUND: Patients with unprovoked venous thromboembolism (VTE) can be stratified according to their recurrence risk based on their sex, the VTE location, and D-dimer measured 3 weeks after anticoagulation by the Vienna Prediction Model. We aimed to expand the model to also assess the recurrence risk from later points on. METHODS AND RESULTS: Five hundred and fifty-three patients with a first VTE were followed for a median of 68 months. We excluded patients with VTE provoked by a transient risk factor or female hormone intake, with a natural inhibitor deficiency, the lupus anticoagulant, or cancer. The study end point was recurrent VTE, which occurred in 150 patients. D-dimer levels did not substantially increase over time. Subdistribution hazard ratios (95% confidence intervals) dynamically changed from 2.43 (1.57 to 3.77) at 3 weeks to 2.27 (1.48 to 3.48), 1.98 (1.30 to 3.02) , and 1.73 (1.11 to 2.69) at 3, 9, and 15 months in men versus women, from 1.84 (1.00 to 3.43) to 1.68 (0.91 to 3.10), 1.49 (0.79 to 2.81) , and 1.44 (0.76 to 2.72) in patients with proximal deep vein thrombosis or pulmonary embolism compared with calf vein thrombosis, and from 1.30 (1.07 to 1.58) to 1.27 (1.06 to 1.51), 1.20 (1.02 to 1.41), and 1.13 (0.95 to 1.36) per doubling D-dimer. Using a dynamic landmark competing risks regression approach, we generated nomograms and a web-based calculator to calculate risk scores and recurrence rates from multiple times after anticoagulation. CONCLUSIONS: Risk of recurrent VTE after discontinuation of anticoagulation can be predicted from multiple random time points by integrating the patient's sex, location of first VTE, and serial D-dimer measurements.*

2. Haller MC, Vanholder R, Oberbauer R, Zoccali C, Van Biesen W: Health economics and European Renal Best Practice--is it time to bring health economics into evidence-based guideline production in Europe? *Nephrol Dial Transplant* (2014) 29(11): 1994-1997; https://doi.org/10.1093/ndt/gft369

   Abstract: *Medical management of patients with kidney disease is complex and resource intensive. In times of limited health care budgets, economic evaluations have become more important over the past few years in identifying interventions with a beneficial cost-effectiveness to maximize the benefits served from the available resources. However, integrating evidence from health-economic evaluations into clinical practice guidelines remains a challenge. European Renal Best Practice (ERBP), the official guideline body of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) herewith presents some lines of thought that need consideration in the discussion on incorporating health-economic considerations into clinical guideline development.*

2013

1. Dunkler D, Dehghan M, Teo KK, Heinze G, Gao P, Kohl M, Clase CM, Mann JF, Yusuf S, Oberbauer R, Investigators O: Diet and kidney disease in high-risk individuals with type 2 diabetes mellitus. *JAMA Intern Med* (2013) 173(18): 1682-1692; https://doi.org/10.1001/jamainternmed.2013.9051

   Abstract: *IMPORTANCE: Type 2 diabetes mellitus and associated chronic kidney disease (CKD) have become major public health problems. Little is known about the influence of diet on the incidence or progression of CKD among individuals with type 2 diabetes. OBJECTIVE: To examine the association between (healthy) diet, alcohol, protein, and sodium intake, and incidence or progression of CKD among individuals with type 2 diabetes. DESIGN, SETTING, AND PARTICIPANTS: All 6213 individuals with type 2 diabetes without macroalbuminuria from the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) were included in this observational study. Recruitment spanned from January 2002 to July 2003, with prospective follow-up through January 2008. MAIN OUTCOMES AND MEASURES: Chronic kidney disease was defined as new microalbuminuria or macroalbuminuria or glomerular filtration rate decline of more than 5% per year at 5.5 years of follow-up. We assessed diet using the modified Alternate Healthy Eating Index (mAHEI). The analyses were adjusted for known risk factors, and competing risk of death was considered. RESULTS: After 5.5 years of follow-up, 31.7% of participants had developed CKD and 8.3% had died. Compared with participants in the least healthy tertile of mAHEI score, participants in the healthiest tertile had a lower risk of CKD (adjusted odds ratio [OR], 0.74; 95% CI, 0.64-0.84) and lower risk of mortality (OR, 0.61; 95% CI, 0.48-0.78). Participants consuming more than 3 servings of fruits per week had a lower risk of CKD compared with participants consuming these food items less frequently. Participants in the lowest tertile of total and animal protein intake had an increased risk of CKD compared with participants in the highest tertile (total protein OR, 1.16; 95% CI, 1.05-1.30). Sodium intake was not associated with CKD. Moderate alcohol intake reduced the risk of CKD (OR, 0.75; 95% CI, 0.65-0.87) and mortality (OR, 0.69; 95% CI, 0.53-0.89). CONCLUSIONS AND RELEVANCE: A healthy diet and moderate intake of alcohol may decrease the incidence or progression of CKD among individuals with type 2 diabetes. Sodium intake, within a wide range, and normal protein intake are not associated with CKD. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00153101.*

2. Gleiss A, Lassi M, Blumel P, Borkenstein M, Kapelari K, Mayer M, Schemper M, Hausler G: Austrian height and body proportion references for children aged 4 to under 19 years. *Ann Hum Biol* (2013) 40(4): 324-332; https://doi.org/10.3109/03014460.2013.776110

   Abstract: *BACKGROUND: Previous studies have demonstrated differences between national and the WHO reference curves in children older than 5 years. Moreover, reference curves for body proportions (sitting height, subischial leg length and their ratio) based on state-of-the-art statistics are not available. AIM: To develop reference curves for height and body proportions for use in Austria and compare the curves with WHO reference curves. To estimate and statistically investigate extreme percentiles. SUBJECTS AND METHODS: A sample of approximately 14 500 children between 4-19 years of age was drawn via schooling institutions, stratified by provinces according to age- and sex-specific population proportions. GAMLSS models were used for a flexible estimation of percentile curves. RESULTS AND CONCLUSIONS: After the age of 5 years national reference curves are more suitable than the WHO reference curves for clinical use in Austria. These height curves are very similar to the German reference curves published recently. Therefore, these reference curves for criteria of body proportions are recommended for use in other populations. Further validation studies are needed to establish whether the recently recommended -2.5 and -3.0 SD for height are a sensitive and specific cut-off in the diagnostic work-up for children with a suspected growth disorder using this new Austrian height chart.*

3. Pils D, Horak P, Vanhara P, Anees M, Petz M, Alfanz A, Gugerell A, Wittinger M, Gleiss A, Auner V, Tong D, Zeillinger R, Braicu EI, Sehouli J, Krainer M: Methylation status of TUSC3 is a prognostic factor in ovarian cancer. *Cancer* (2013) 119(5): 946-954; https://doi.org/10.1002/cncr.27850

   Abstract: *BACKGROUND: Current prognostic information in ovarian cancer is based on tumor stage, tumor grade, and postoperative tumor size. Reliable molecular prognostic markers are scarce. In this article, the authors describe epigenetic events in a frequently deleted region on chromosome 8p22 that influence the expression of tumor suppressor candidate 3 (TUSC3), a putative tumor suppressor gene in ovarian cancer. METHODS: Messenger RNA*

expression and promoter hypermethylation of TUSC3 were studied in ovarian cancer cell lines and in tumor samples from 2 large, independent ovarian cancer cohorts using polymerase chain reaction-based methods. RESULTS: The results indicated that TUSC3 expression is decreased significantly because of promoter methylation in malignant ovarian tumors compared with benign controls. Almost 33% of ovarian cancer samples had detectable TUSC3 promoter methylation. Furthermore, methylation status of the TUSC3 promoter had a significant and independent influence on progression-free and overall survival. CONCLUSIONS: TUSC3 hypermethylation predicted progression-free and overall survival in ovarian cancer. The current observations suggested a role for N-glycosylating events in ovarian cancer pathogenesis in general and identified the epigenetic silencing of TUSC3 as a prognostic factor in this disease.

2012

1. Polterauer S, Grimm C, Hofstetter G, Concin N, Natter C, Sturdza A, Potter R, Marth C, Reinthaller A, Heinze G: Nomogram prediction for overall survival of patients diagnosed with cervical cancer. *Br J Cancer* (2012) 107(6): 918-924; https://doi.org/10.1038/bjc.2012.340

   Abstract: *BACKGROUND: Nomograms are predictive tools that are widely used for estimating cancer prognosis. The aim of this study was to develop a nomogram for the prediction of overall survival (OS) in patients diagnosed with cervical cancer. METHODS: Cervical cancer databases of two large institutions were analysed. Overall survival was defined as the clinical endpoint and OS probabilities were estimated using the Kaplan-Meier method. Based on the results of survival analyses and previous studies, relevant covariates were identified, a nomogram was constructed and validated using bootstrap cross-validation. Discrimination of the nomogram was quantified with the concordance probability. RESULTS: In total, 528 consecutive patients with invasive cervical cancer, who had all nomogram variables available, were identified. Mean 5-year OS rates for patients with International Federation of Gynecologists and Obstetricians (FIGO) stage IA, IB, II, III, and IV were 99.0%, 88.6%, 65.8%, 58.7%, and 41.5%, respectively. Seventy-six cancer-related deaths were observed during the follow-up period. FIGO stage, tumour size, age, histologic subtype, lymph node ratio, and parametrial involvement were selected as nomogram covariates. The prognostic performance of the model exceeded that of FIGO stage alone and the model's estimated optimism-corrected concordance probability was 0.723, indicating accurate prediction of OS. We present the prediction model as nomogram and provide a web-based risk calculator (http://www.ccc.ac.at/gcu). CONCLUSION: Based on six easily available parameters, a novel statistical model to predict OS of patients diagnosed with cervical cancer was constructed and validated. The model was implemented in a nomogram and provides accurate prediction of individual patients' prognosis useful for patient counselling and deciding on follow-up strategies.*

2. Puchhammer-Stockl E, Aberle SW, Heinzl H: Association of age and gender with alphaherpesvirus infections of the central nervous system in the immunocompetent host. *J Clin Virol* (2012) 53(4): 356-359; https://doi.org/10.1016/j.jcv.2011.12.015

   Abstract: *BACKGROUND: The alphaherpesviruses Varicella-zoster virus (VZV) and human herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) can cause severe infections of the central nervous system (CNS). OBJECTIVES: To analyze whether age and gender of immunocompetent individuals are associated with the incidence of herpesvirus CNS diseases. STUDY DESIGN: A total of 241 patients with virologically confirmed HSV-1, HSV-2 or VZV-infection of the CNS (excluding neonatal infection and varicella), diagnosed at the Department of Virology, Medical University Vienna, from 2001 to 2009 were analyzed retrospectively. The relative incidence of disease was evaluated statistically with respect to gender and age. RESULTS: The relative incidence of VZV CNS disease increased with age ($p<0.0001$), and nonlinear age dependences were observed for HSV-1 ($p=0.005$) and HSV-2 disease ($p=0.002$). These effects were influenced significantly by the patient's gender in VZV ($p=0.0003$) and HSV-1 disease ($p=0.008$). Overall, 50.7% of VZV infections in males, but only 23.5% of those in females, occurred before age 45, and 28.9% of HSV-1 infections in males and 8.8% of those in females occurred before age 30. Women represented 71.9% of HSV-2 CNS infections ($p=0.02$). CONCLUSIONS: The patient's gender is clearly associated with the incidence of CNS disease caused by VZV, HSV-1 and HSV-2, and its influence varies over one's lifetime.*

2010

1. Eichinger S, Heinze G, Jandeck LM, Kyrle PA: Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. *Circulation* (2010) 121(14): 1630-1636; https://doi.org/10.1161/CIRCULATIONAHA.109.925214

Abstract: *BACKGROUND: Predicting the risk of recurrent venous thromboembolism (VTE) in an individual patient is often not feasible. We aimed to develop a simple risk assessment model that improves prediction of the recurrence risk. METHODS AND RESULTS: In a prospective cohort study, 929 patients with a first unprovoked VTE were followed up for a median of 43.3 months after discontinuation of anticoagulation. We excluded patients with a strong thrombophilic defect such as a natural inhibitor deficiency, the lupus anticoagulant, and homozygous or combined defects. A total of 176 patients (18.9%) had recurrent VTE. Preselected clinical and laboratory variables (age, sex, location of VTE, body mass index, factor V Leiden, prothrombin G20210A mutation, D-dimer, and in vitro thrombin generation) were analyzed in a Cox proportional hazards model, and those variables that were significantly associated with recurrence were used to compute risk scores. Male sex (hazard ratio versus female sex 1.90, 95% confidence interval 1.31 to 2.75), proximal deep vein thrombosis (hazard ratio versus distal 2.08, 95% confidence interval 1.16 to 3.74), pulmonary embolism (hazard ratio versus distal thrombosis 2.60, 95% confidence interval 1.49 to 4.53), and elevated levels of D-dimer (hazard ratio per doubling 1.27, 95% confidence interval 1.08 to 1.51) were related to a higher recurrence risk. Using these variables, we developed a nomogram that can be used to calculate risk scores and to estimate the cumulative probability of recurrence in an individual patient. The model was cross validated, and patients were assigned to different risk categories based on their risk score. Recurrence rates corresponded well with the different risk categories. CONCLUSIONS: By use of a simple scoring system, the assessment of the recurrence risk in patients with a first unprovoked VTE and without strong thrombophilic defects can be improved.*

2009

1. Heinze G, Kainz A, Horl WH, Oberbauer R: Mortality in renal transplant recipients given erythropoietins to increase haemoglobin concentration: cohort study. *BMJ* (2009) 339:b4018; https://doi.org/10.1136/bmj.b4018

   Abstract: *OBJECTIVE: To determine the optimal range of increase in haemoglobin concentration with treatment with erythropoietins that is safe and is not associated with mortality. DESIGN: Retrospective cohort study. The analysis was adjusted for several covariables with Cox regression analysis with spline functions. Use of erythropoietins, haemoglobin concentration, and covariables were included in a time varying manner; variable selection was based on the purposeful selection algorithm. SETTING: Transplantation centres in Austria. PARTICIPANTS: 1794 renal transplant recipients recorded in the Austrian Dialysis and Transplant Registry who received a transplant between 1 January 1992 and 31 December 2004 and survived at least three months. MAIN OUTCOME MEASURES: Survival time and haemoglobin concentration after treatment with erythropoietins. RESULTS: The prevalence of use of erythropoietins has increased over the past 15 years to 25%. Unadjusted extended Kaplan-Meier analysis suggests higher mortality in patients treated with erythropoietins, in whom 10 year survival was 57% compared with 78% in those not treated with erythropoietins (P<0.001). In the treated patients there were 5.4 events/100 person years, compared with 2.6 events/100 person years in those not treated (P<0.001). After adjustment for confounding by indication, comorbidities, comedication, and laboratory readings, haemoglobin concentrations >125 g/l were associated with increased mortality in treated patients (hazard ratio 2.8 (95% confidence interval 1.0 to 7.9) for haemoglobin concentration 140 g/l v 125 g/l), but not in those not treated (0.7, 0.4 to 1.5). When haemoglobin concentrations were 147 g/l or above, patients treated with erythropoietins showed significantly higher mortality than those who were not treated (3.0, 1.0 to 9.4). CONCLUSION: Increasing haemoglobin concentrations to above 125 g/l with erythropoietins in renal transplant recipients is associated with an increase in mortality. This increase was significant at concentrations above 140 g/l.*

2. Heinze G, Oberbauer R, Kainz A, Mitterbauer C, Koppelstaetter C, Horl WH, Mayer G: Calcineurin inhibitor-based immunosuppressive therapy, donor age, and long-term outcome after kidney transplantation. *Transplantation* (2009) 87(12): 1821-1829; https://doi.org/10.1097/TP.0b013e3181a66cfc

   Abstract: *BACKGROUND: It is unclear whether the choice of maintenance immunosuppression modulates the negative effect of advanced donor age on outcome after renal transplantation. METHODS: All 1829 patients who received their first transplant between 1990 and 2003 at the Vienna Medical Centre and had a functioning graft after 90 days were studied. At this time point, 1587 received calcineurin inhibitors (CNI+), 242 did not (CNI-). Actual and functional graft survival was analyzed in subgroups based on donor age (<36, 36-49, 50-64, and >64 years) and immunosuppressive therapy. RESULTS: The median follow-up time was 7 years. In total, we observed 312 deaths and 275 graft losses. After adjusting for several variables considered as potential confounders, actual graft survival was better in CNI+ patients compared with CNI- patients only if donor age was less than 36 years (adjusted hazard ratio 0.25, 95% confidence interval 0.17-0.38) or 36 to 49 years (0.43, 95% confidence interval 0.29-0.62). Similar results were obtained for functional graft survival. Patient survival was significantly better in CNI+ subjects irrespective of donor age (0.41, 95% confidence interval 0.30-0.57). DISCUSSION: Use of CNI 90 days after transplantation is associated with improved patient survival even after adjustment for confounders, but its beneficial association with actual and functional graft survival is lost or at least reduced if kidneys from donors older than 50 years are used.*

3. Wohrer A, Waldhor T, Heinzl H, Hackl M, Feichtinger J, Gruber-Mosenbacher U, Kiefer A, Maier H, Motz R, Reiner-Concin A, Richling B, Idriceanu C, Scarpatetti M, Sedivy R, Bankl HC, Stiglbauer W, Preusser M, Rossler K, Hainfellner JA: The Austrian Brain Tumour Registry: a cooperative way to establish a population-based brain tumour registry. *J Neurooncol* (2009) 95(3): 401-411; https://doi.org/10.1007/s11060-009-9938-9

   Abstract: *In Austria, registration of malignant brain tumours is legally mandatory, whereas benign and borderline tumours are not reported. The Austrian Brain Tumour Registry (ABTR) was initiated under the auspices of the Austrian Society of Neuropathology for the registration of malignant and non-malignant brain tumours. All Austrian neuropathology units involved in brain tumour diagnostics contribute data on primary brain tumours. Non-microscopically verified cases are added by the Austrian National Cancer Registry to ensure a population-based dataset. In 2005, we registered a total of 1,688 newly diagnosed primary brain tumours in a population of 8.2 million inhabitants with an overall age-adjusted incidence rate of 18.1/100,000 person-years. Non-malignant cases*

constituted 866 cases (51.3%). The incidence rate was higher in females (18.6/100,000) as compared to males (17.8/100,000), while 95/1,688 (5.6%) cases were diagnosed in children (<18 years). The most common histology was meningioma (n = 504, 29.9%) followed by glioblastoma (n = 340, 20.1%) and pituitary adenoma (n = 151, 8.9%). Comparison with the Central Brain Tumor Registry of the United States (CBTRUS) database showed high congruency of findings. The ABTR model led by neuropathologists in collaboration with epidemiologists and the Austrian National Cancer Registry presents a cooperative way to establish a population-based brain tumour registry with high quality data. This setting links cancer registration to the mission of medical practice and research as defined by the World Medical Association in the Declaration of Helsinki. The continued operation of ABTR will aid in monitoring changes in incidence and in identifying regional disease clusters or geographic variations in brain tumour morbidity/mortality.

2008

1. Waldhoer T, Wald M, Heinzl H: Analysis of the spatial distribution of infant mortality by cause of death in Austria in 1984 to 2006. *Int J Health Geogr* (2008) 7(21): 21; https://doi.org/10.1186/1476-072X-7-21

Abstract: *BACKGROUND: In Austria, over the last 20 years infant mortality declined from 11.2 per 1,000 life births (1985) to 4.7 per 1,000 in1997 but remained rather constant since then. In addition to this time trend we already reported a non-random spatial distribution of infant mortality rates in a recent study covering the time period 1984 to 2002. This present study includes four additional years and now covers about 1.9 million individual birth certificates. It aimes to elucidate the observed non-random spatial distribution in more detail. We split up infant mortality into six groups according to the underlying cause of death. The underlying spatial distribution of standardized mortality ratios (SMR) is estimated by univariate models as well as by two models incorporating all six groups simultaneously. RESULTS: We observe strong correlations between the individual spatial patterns of SMR's except for "Sudden Infant Death Syndrome" and to some extent for "Peripartal Problems". The spatial distribution of SMR's is non-random with an area of decreased risk in the South-East of Austria. The group "Sudden Infant Death Syndrome" clearly and the group "Peripartal Problems" slightly show deviations from the common pattern. When comparing univariate and multivariate SMR estimates we observe that the resulting spatial distributions are very similar. CONCLUSION: We observe different non-random spatial distributions of infant mortality rates when grouped by cause of death. The models applied were based on individual data thereby avoiding ecological regression bias. The estimated spatial distributions do not substantially depend on the employed estimation method. The observed non-random spatial patterns of Austrian infant mortality remain to appear ambiguous.*

2007

1. Heinze G, Oberbauer R: Does size matter? *Nephrol Dial Transplant* (2007) 22(9): 2725-2726; https://doi.org/10.1093/ndt/gfm310

2006

1. Heinze G, Collins S, Benedict MA, Nguyen LL, Kramar R, Winkelmayer WC, Haas M, Kainz A, Oberbauer R: The association between angiotensin converting enzyme inhibitor or angiotensin receptor blocker use during postischemic acute transplant failure and renal allograft survival. *Transplantation* (2006) 82(11): 1441-1448; https://doi.org/10.1097/01.tp.0000244587.74768.f7

   Abstract: *BACKGROUND: Postischemic acute renal transplant failure occurs in approximately one fourth of all dead donor transplantations. Uncertainty exists regarding the putative association between the use of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II AT1 receptor blockers (ARBs) and kidney transplant graft survival in patients with delayed allograft function. METHODS: We conducted an open cohort study of all 436 patients who experienced an acute renal transplant failure out of all 2,031 subjects who received their first kidney transplant at the Medical University of Vienna between 1990 and 2003. Actual and functional graft survival was compared between users and nonusers of ACEI/ARB using exposure propensity score models and time-dependent Cox regression models. RESULTS: Ten-year actual graft survival averaged 44% in the ACEI/ARB group, but only 32% in patients without ACEI/ARB (P=0.002). The hazard ratio of actual graft failure was 0.58 (95% confidence interval: 0.35-0.80, P=0.002) for ACEI/ARB users compared with nonconsumers. Seventy-one percent of subjects with ACEI/ARB had a functional graft at 10 years versus 64% of ACEI/ARB nonusers (P=0.027). The hazard ratio of functional graft loss was 0.48 (95% confidence interval: 0.24-0.91, P=0.025). CONCLUSIONS: Use of ACEI/ARB in patients experiencing delayed allograft function was associated with longer actual and functional transplant survival.*

2. Heinze G, Mitterbauer C, Regele H, Kramar R, Winkelmayer WC, Curhan GC, Oberbauer R: Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *J Am Soc Nephrol* (2006) 17(3): 889-899; https://doi.org/10.1681/ASN.2005090955

   Abstract: *Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II type 1 receptor blockers (ARB) reduce cardiovascular death in the general population, but data for renal transplant recipients remain elusive. Similarly, ACEI/ARB have been shown to reduce proteinuria, but data on graft survival are lacking. Therefore a retrospective open cohort study was conducted of 2031 patients who received their first renal allograft at the Medical University of Vienna between 1990 and 2003 and survived at least 3 mo. Patient and graft survival was compared between patients with versus without ACEI and/or ARB therapy. Data were analyzed with and without propensity score models for ACEI/ARB therapy. Medication and comorbidities were analyzed as time-dependent variables in the Cox regression analyses. Ten-year survival rates were 74% in the ACEI/ARB group but only 53% in the noACEI/ARB group (P<0.001). The hazard ratio (HR) of ACEI/ARB use for mortality was 0.57 (95% confidence interval [CI] 0.40 to 0.81) compared with nonuse. Ten-year actual graft survival rate was 59% in ACEI/ARB patients but only 41% in nonusers (P=0.002). The HR of actual graft failure for ACEI/ARB recipients was 0.55 (95% CI 0.43 to 0.70) compared with nonusers; the HR of functional graft survival was 0.56 (95% CI 0.40 to 0.78). Ten-year unadjusted functional graft survival rates were 76% among ACEI/ARB patients and 71% in noACEI/ARB recipients (P=0.57). In summary, the use of ACEI/ARB therapy was associated with longer patient and graft survival after renal transplantation. More frequent use of these medications may reduce the high incidence of death and renal allograft failure in these patients.*

3. Waldhoer T, Haidinger G, Wald M, Heinzl H: Non-random geographical distribution of infant mortality in Austria 1984-2002. *Wien Klin Wochenschr* (2006) 118(11-12): 341-347; https://doi.org/10.1007/s00508-006-0610-5

   Abstract: *Over the last 20 years in Austria infant mortality has declined from 11.2/1,000 life births (1985) to 4.7/100,000 (1997) but has remained constant since then. This stagnation is in contrast to the trend in Finland, where the infant mortality rate is both lower than in Austria and continues to decline. In attempting to understand this difference we concentrated on the spatial distribution of infant mortality in Austria in addition to the trend over time. We describe the regional distribution of infant mortality adjusted by risk factors over the period from 1984 to 2002 based on data from 1.6 million birth certificates. All variables we examined were significant due to the large number of observations. We calculated an R-squared measure to assess the ability of our regression model to predict the survival status of newborns. Only the variables birth weight, gestational age, infant's length at birth and to a lesser extent year of birth had relevant impacts in terms of predictive ability. All remaining variables did not notably contribute to the*

prediction of survival status of the newborn despite their significance. In the greater area of Styria, infant mortality is significantly lower than in the rest of Austria even when the mortality rates are adjusted for variables such as birth weight, gestational age, sex of the newborn and sociodemographic status of the mother. In the period from 1984 to 2002 about 1500 more infants would have survived the first year of life if the mortality rate in the rest of Austria had been the same as in this area. In our regression model many important risk factors were included. Nevertheless, we can not explain the observed spatial pattern in infant morality. Further analytic studies are needed to explore the impact of variables other than those contained in the birth certificates.

2005

1. Pils D, Horak P, Gleiss A, Sax C, Fabjani G, Moebus VJ, Zielinski C, Reinthaller A, Zeillinger R, Krainer M: Five genes from chromosomal band 8p22 are significantly down-regulated in ovarian carcinoma: N33 and EFA6R have a potential impact on overall survival. *Cancer* (2005) 104(11): 2417-2429; https://doi.org/10.1002/cncr.21538

   Abstract: *BACKGROUND: Loss of heterozygosity on chromosomal band 8p22 is a common event in several epithelial tumors including ovarian carcinoma. So far, no clear evidence for a tumor suppressor gene (TSG) in this region has been found. METHODS: On the basis of publicly available expression data in ovarian tissues, the authors selected the eight most noteworthy genes from 8p22 (DLC1, N33, ZDHHC2, FLJ32642, PDGFRL, MTSG1, PCM1, and EFA6R) for a detailed expression analysis in 58 primary ovarian carcinoma tissues and in 38 ovarian cancer cell lines by using quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR). Expression data were correlated to various clinicopathologic characteristics and survival. RESULTS: Two genes showed a significantly (P< 0.05) lower expression in grade 3 tumors compared with tumors of lower grade (N33) or compared with normal controls and tumors with lower grade (EFA6R). Expression of N33 and EFA6R seems to have an impact on survival, in particular when the combined expression of both genes was used as predictive factor (P< 0.003). In addition, N33 and EFA6R showed a complete loss of expression in several ovarian cancer cell lines. Three genes (FLJ32642, MTSG1, and PCM1) had a significantly (P< 0.001, P< 0.004, and P< 0.001) lower expression in primary ovarian carcinoma compared with controls (ovarian tissues and cysts). CONCLUSIONS: Two to five new potential tumor suppressor or antagonizing gene candidates (N33 and EFA6R with impact on survival, and potentially FLJ32642, MTSG1, and PCM1) for ovarian carcinoma, were identified from the chromosomal band 8p22 and are promising candidates for further functional analysis in ovarian carcinoma.*

2. Waldhor T, Vutuc C, Haidinger G, Mittlbock M, Kirchner L, Wald M: Trends in infant mortality in Austria between 1984 and 2002. *Wien Klin Wochenschr* (2005) 117(15-16): 548-553; https://doi.org/10.1007/s00508-005-0401-4

   Abstract: *Infant mortality rate is an important medical indicator and is often used for comparing countries with respect to welfare and public health. Among other factors, effective medical technology, better access to pre- and postnatal care for all socioeconomic groups and better nutrition have decreased infant mortality in Austria from about 200 deaths per 1000 live births at the beginning of the 20th century to about 5 deaths per 1000 live births at the end. In this study we present the trends in infant mortality, based on 1,654,519 individual birth records, in Austria since 1984. The infant mortality rate dropped rapidly from about 12 per 1000 live births in 1985 to 4.6 per 1000 live births during the last two years of our study (2001/02). Infant mortality rates stratified by cause of death show somewhat differing trends. In particular, the number of deaths due to peripartal problems decreased as the result of improvements in obstetrics and neonatology, but in 1995 a change in the definition of live birth led to a rise of about 20% in the stillbirth rate. At present, Austria has one of the lowest infant mortality rates of all European countries; however, between 1999 and 2002 the mortality rate has been fairly static. A further reduction in mortality clearly cannot be achieved by advances in medicine alone. It remains a challenge for health politicians, physicians and society at large to reduce the prevalence of well-known risk factors such as alcohol abuse, heavy overweight and smoking during pregnancy.*

2002

1. Edler L, Heinzl H: Exploring the Relationships Between Exposure to PCDDS/FS and Neurological Health Effects in Humans. *Organohalogen Compounds* (2002) 57:415-418;

2000

1. Heinzl H, Muttray A, Jung D, Hergert A, Rose DM, Konietzko J, Hofmann HC, Portier C, Edler L: Exploring possible dose-response relationships between 2,3,7,8-tetrachlorodibenzo-p-dioxin concentration and heart rate variability in humans. Organohalogen Compounds. *Organohalogen Compounds* (2000) 48:195-198;