56th ERA-EDTA Congress 2019 Conference Review™

Making Education Easy | June 13–16, 2019; Budapest, Hungary

In this review:

Abbreviations used in this review:

ACE = angiotensin converting enzyme
aHUS = atypical haemolytic uraemic syndrome
ARB = angiotensin-2 receptor blocker
BMI = body mass index
BP = blood pressure
CKD = chronic kidney disease
CV = cardiovascular
GFR = glomerular filtration rate
HbA_{1c} = glycosylated haemoglobin
RAAS = renin-angiotensin-aldosterone system
SGLT = sodium glucose cotransporter

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Welcome to this review of the recent 56th Congress of the ERA-EDTA (European Renal Association – European Dialysis and Transplant Association), organised in conjunction with the Hungarian Society of Nephrology.

The key theme for this Congress was 'precision nephrology', with presentations summarising what is known and what still needs to be elucidated so the best care can be provided to patients. The main programme included three plenary lectures given by outstanding scientists and excellent speakers, complemented by various interesting industry symposia. The selection of presentations and commentary for this review has been carried out by Paul J. Champion de Crespigny from the Royal Melbourne Hospital who attended the Congress.

We always like to hear what you think of our reviews, so please send us any comments and feedback you have.

Kind Regards,

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Sleep disordered breathing: a pervasive problem in CKD

Presenter: Mallamaci F, Reggio Calabria, Italy

Summary: Sleep apnoea is a modifiable CV risk factor for the general population, including patients with CKD and dialysis patients. Although renal transplant patients have a similar prevalence of sleep apnoea to the general population, it is their main determinant of nocturnal hypertension. Renal transplantation is associated with an early improvement in sleep-disordered breathing, but stabilisation is not seen and re-emergence occurs over longitudinal observations. BMI appears to be an important determinant of the re-emergence of sleep-disordered breathing after renal transplantation.

Comment: Sleep apnoea has been recognised for two decades and is associated with increased activation of the sympathetic nervous system, including during the day. Studies comparing GFR and the incidence of sleep apnoea have not demonstrated an increased frequency of overall sleep apnoea as renal function declines (Canales *et al.* NDT 2008; stage 3 CKD versus higher GFR levels). Fleshman (NDT 2010) showed that whilst obstructive sleep apnoea was not increased in incidence, central sleep apnoea was increased in patients with lower GFRs. Other studies showed that sleep apnoea increases in severity as patients approach end-stage renal failure (Markou *et al.* Lung 2006).

Mallamaci reported she has a publication in preparation showing a direct relationship between hypertension and nocturnal hypoxaemia, and also a correlation between SaO_2 and arterial intimal medial thickness. Unselected dialysis patients had a 15% incidence of sleep apnoea but there was a 75% incidence in patients with symptoms of sleep disturbance. Zoccali *et al.* found (J Am Soc Nephrol 2002) that lower oxygen saturations are associated with an increase in vascular events in association with sleep apnoea and a poorer survival.

Renal transplantation results in improved sleep apnoea, but on return to dialysis, apnoea/hypopnoea worsens. Post-renal transplant polysomnography has shown in 221 transplant patients that apnoea/hypopnoea was increased in association with oxygen desaturations, and whilst it improves initially following renal transplant, it worsens with time. BMI, male gender, increased C-reactive protein level, phosphate level, CV comorbidities, age and diabetes were all linked to an increased risk of sleep apnoea. Sleep apnoea is the most powerful functional correlate of nocturnal hypertension in renal transplant patients. Sleep apnoea improves post-transplant, but later emerges. In essence, central sleep apnoea is an issue in patients with renal disease.

Symposium 04

Independent commentary by Paul Champion de Crespigny, who is a nephrologist at The Royal Melbourne Hospital and obstetric physician at the Royal Women's hospital. He has a longstanding interest in general nephrology, dialysis, renal transplantation and clinical trials in nephrology. He has an interest in women's health and in particular the effect of renal disease on women's reproductive function and pregnancy outcomes.

Intradialytic hypoxia

Presenter: Kotanko P, New York, NY, USA

Summary: Patients undergoing haemodialysis have impaired oxygen supply to their tissues and organs. Tissue hypoxia is the terminal pathway of several pathologies, and the heart, gut and brain are particularly susceptible organs. Fluid management and ways of increasing intradialytic haemodynamic stability are important for improving oxygen supply to organs and tissues. There are a number of interventions that can be 'tissue protective', but noninvasive and continuous means of assessing tissue oxygen content are urgently needed.

Comment: This presentation discussed issues related to tissue oxygen delivery and fluid status. Peter Kotanko discussed that oxygen is delivered to tissues and the rate is defined by the cardiac output × haemoglobin × an adjustment for the dissolved oxygen. Oxygen transfer has both diffusive and convective components with a diffusion pattern dependent on the distance between the tissue and the capillaries. Increased lung water is associated with impaired pulmonary oxygen uptake and in particular impaired oxygen diffusion with interstitial fluid overload. Pulmonary ultrasound images can identify B lines as described by Zoccali C *et al.* in J Am Soc Nephrol in 2013; pulmonary congestion is associated with an increased all-cause mortality and cardiac events. Convective oxygen transport is affected by cardiac dysfunction, anaemia and reduced arterial oxygen saturations. Patients with average nocturnal oxygen saturations ≤95% have worse outcomes compared with those with average nocturnal oxygen saturations >95%. Intradialytic oxygen saturations can be measured 150 times per second or 9000 times per minute. Oxygen saturations have been shown to be variable during dialysis and there were noted to be improved oxygen saturations in association with fluid removal during dialysis. It was noted that one patient's oxygen saturation fell to 63.7% on dialysis who was noted by the caring nurse to be 'sleeping'.

A study over 3 years (Meyring-Wösten A *et al.* Clin J Am Soc Nephrol 2016) found a link between the more time a patient has oxygen ≤90% and all-cause mortality. The concept of hypoxaemic burden was discussed and 10% of patients who had an oxygen concentration <90% for one third of dialysis were shown to have an increased rate of hospitalisation and a doubling of mortality rate. Mt Sinai hospital is considering studying if intradialytic oxygen administration versus air (given as placebo) alters outcomes in dialysis patients. Interstitial oedema is described in the heart, gut and brain in association with fluid overload. Appropriate management of fluids is essential to ensure adequate tissue oxygenation.

Symposium 04

Chronic interstitial nephritis of unknown etiology is a toxic tubular nephropathy

Presenter: de Broe M, Antwerp, Belgium

Summary/comment: Regional increases in incidence of interstitial nephritis of unknown aetiology was discussed. It has been noted in a patchy distribution in multiple countries including Sri Lanka, El Salvador, Peru, Egypt, Cameroon, France, Portugal and other countries. A hypothesis has been raised that the interstitial nephritis could be related to heat and dehydration; however, there are soft data to suggest it is related to chemicals and mechanisation. Interstitial nephritis is common in Honduras in sugar cane growing areas, but not in Cuba where similar climates and crops are found, but Cuba has banned the introduction of chemicals/herbicides. In Sri Lanka there appears to be a correlation between interstitial nephritis and shallow wells and absent where the water supply is plentiful. The possibility of herbicide contamination of shallow water supplies was proposed as a possible cause.

There are studies that suggest the death rate in Nicaragua and El Salvador relate to pesticides and end-stage renal failure, with the suggestion that the source of the problem is contaminated water. A US study by Sandler *et al.* in Occup Environ Med 2016 suggested an association between the use of agricultural chemicals and the incidence of end-stage renal disease. There is certainly no evidence that heat and volume depletion is associated with chronic interstitial nephritis. Histological studies in Sri Lanka and El Salvador have suggested the interstitial nephritis is associated with tubular basement membrane thickening and the presence of irregular shaped structures on electron microscopy measuring 4–5 microns in the proximal tubular cells, which stain with Jones strain. The structures in the proximal convoluted tubules have positive staining for γ-glutamyl transpeptidases with lysosomes positive for cathepsin B, and the distal tubules were found to be full of PCNA (proliferating cell nuclear antigen) activity, whereas there is usually none. It is unclear what the Jones positive staining structures are but they are not autophagosomes or lipids. There are also high concentrations of chronic interstitial nephritis of unknown aetiology in wine growing areas in Europe, where it is known there is extensive use of herbicides. Dr de Broe's group intend to survey the wine growing areas of Europe for renal disease.

Interstitial nephritis of unknown aetiology is associated with a reduction in renal size and tubular proteinuria without macroproteinuria.

Symposium 04

Outcomes of SGLT2i in diabetic kidney disease: is it all diabetes?

Presenter: Agarwal R, Indianapolis, IN, USA

Summary: Previous trials investigating the use of SGLT-2 inhibitors to reduce CKD progression in type 2 diabetes have not prespecified renal protection as a primary endpoint. The CREDENCE trial has reported that canagliflozin reduced the relative risk of CKD progression to end-stage renal disease by around one third in patients with an estimated GFR down to 30 mL/min/1.73m^2, but with only a small effect on glycaemic control and a systolic BP reduction equivalent to low-dose thiazide therapy.

Comment: The CREDENCE trial studied the risk of progression of CKD to end-stage renal failure in patients treated with canagliflozin. The study included patients with moderate albuminuria and mild-to-moderate renal impairment. The relative risk was reduced by one third when canagliflozin was given to patients with an estimated GFR as low as 30 mL/min/1.73m^2. The effect of canagliflozin on glycaemic control and the reduction in systolic BP were both small and the study suggested that the renal protection was greater than would be explained by the glycaemic control and the reduction in BP.

The CREDENCE study was terminated early because the interim analysis suggested the superiority of canagliflozin compared with placebo. Other studies have also suggested a reduction in progression to end-stage renal failure in patients with renal impairment treated with SGLT-2 inhibitors, but the studies did not have renal protection as a prespecified primary endpoint. This was one of several studies presented suggesting that the SGLT-2 inhibitors will have an important role in preventing not only the progression of patients with underlying renal disease to renal failure but also in reducing CV endpoints, including death in patients treated with SGLT-2 inhibitors.

Industry Sponsored Symposium

The knowns and unknowns of SGLT2 inhibition in CKD

Presenter: Fioretto P, Padua, Italy

Summary/comment: SGLT-2 inhibitors have been shown consistently to be nephroprotective in a number of long-term trials. There are nonglycaemic control effects of SGLT-2 inhibitors, which include natriuresis, a reduction in BP, weight loss and reduction in serum uric acid level. As a result of inhibiting the resorption of glucose, SGLT-2 inhibitors cause glycosuria and a natriuresis with an associated reduction in bodyweight and increased uric acid excretion. A reduction in BP and plasma volume is associated with their use. The SGLT-2 inhibitors have renal haemodynamic effects, including decreasing intraglomerular pressure. It is postulated that reducing glomerular hyperfiltration and intraglomerular pressure through tubuloglomerular feedback may be the reason for nephroprotection related to SGLT-2 inhibition.

Studies have suggested that RAAS inhibition results in a synergistic and additive reduction in intraglomerular pressure due to arteriolar effects. SGLT-2 inhibitors also have anti-inflammatory and antioxidative stress effects. There are currently two studies being undertaken studying the effects of SGLT-2 inhibitors in slowing the progression of renal disease in patients without diabetes. Experimental studies have suggested that dapagliflozin has an effect on some cytokines and increases renal oxygenation. Studies have also suggested that SGLT-2 inhibitors reduce energy demands in tubules. The increase in haematocrit in association with the use of SGLT-2 inhibitors improves oxygen delivery to the kidney. Animal models have shown that SGLT-2 inhibitors reduce renal ischaemia-reperfusion injuries in those models.

Industry Sponsored Symposium

The clinical landscape of managing patients with CKD: where are we now and what can we expect?

Presenter: Herrington W, Oxford, UK

Summary: Several large ongoing placebo-controlled trials in patients with renal and heart failure are expected to provide data on the effects of SGLT-2 inhibitor use on kidney disease progression, CV disease and safety outcomes across a wide range of different, as-yet unstudied patient types. Two such trials (DAPA-CKD and EMPA·KIDNEY), are particularly relevant to nephrology practice. This presentation on these ongoing trials covered some of the rationale for their designs and how they will add to the currently available data.

Comment: SGLT-2 studies have demonstrated beneficial effects in slowing the decline in renal function in patients with progressive declines in renal function and in treating heart failure. Long-term follow-up has not been undertaken. The CANVAS and DECLARE-TIMI58 trials showed large reductions in disease progression. Aggregating previous studies suggests an approximate 25% reduction in acute kidney injury in patients taking SGLT-2 inhibitors. It should be noted that the studies have looked at specific subgroups of patients, but the benefits have been shown across multiple studies with differing populations studied. Studies will hopefully be undertaken in patients with lower levels of proteinuria and lower levels of renal function. It is likely that the use of SGLT-2 inhibitors will become the 'standard of care', probably in combination with renin-angiotensin inhibition in proteinuric diabetic disease. Investigation in nondiabetic renal disease needs to be undertaken. The beneficial effects demonstrated appear greater than the benefits of renin-angiotensin blockade alone.

Industry Sponsored Symposium

Effects of linagliptin on kidney outcomes in patients with nephrotic range proteinuria: insights from CARMELINA

Presenter: Wanner C, Würzburg, Germany

Summary: This presentation reported on one of the largest cohorts of patients with type 2 diabetes and proteinuria in the nephrotic range treated with linagliptin. Over a median of 2.2 years of follow-up, linagliptin treatment did not impact the risks of CV events, heart failure events, all-cause hospitalisations, all-cause mortality or a series of composite renal outcomes. There was a modest reduction in the burden of albuminuria, and HbA_{1c} levels were reduced without affecting the risk of hypoglycaemia.

Comment: This was a review of the CARMELINA study, which investigated the role of the dipeptidyl peptidase-4 inhibitor, linagliptin, versus placebo. Linagliptin or placebo was added to 'standard of care'. CV risk factors were treated according to local guidelines. Inclusion criteria were documented type 2 diabetes on stable glucose-lowering drugs, ≥18 years of age, HbA_{1c} level 6.5–10.0%, BMI ≤45 kg/m^2, ≥1 of confirmed history of ischaemic heart disease, stroke or peripheral vascular disease, and an estimated GFR of 15–<45 mL/min/1.73m^2 or estimated GFR ≥45–75 mL/min/1.73m^2 with an albumin-creatinine ratio of >200 mg/mmol. Primary outcomes were 3P-MACE, being CV-related death, nonfatal myocardial infarction and nonfatal stroke, and secondary outcomes were end-stage kidney disease, estimated GFR decrease ≥40% from baseline or death due to kidney disease. There were no differences in adverse events. The results showed that there was a modest reduction in albuminuria but no effect on CV or renal endpoint outcomes.

Symposium 05: Late Breaking Clinical Trials

Pregnancy outcomes in patients enrolled in the global aHUS registry

Authors: Cummings L et al.

Summary: Patient characteristic and outcome data from the Global aHUS Registry on 37 patients with aHUS (atypical haemolytic uraemic syndrome) who had 40 pregnancies recorded were presented; outcomes were not reported for seven cases and there were two ongoing pregnancies at data cutoff. For the 31 pregnancies with known outcomes, 22 included eculizumab exposure. Compared with eculizumab-nonexposure, pregnancies with eculizumab exposure resulted in fewer live births (55% vs. 78%) and more elective terminations (36% vs. 11%) but a lower relapse rate (5% vs. 22%). There were no neonatal malformations reported. Among tested patients, 55% had complement mutations detected.

Comment: This poster is of interest in that the registry documents significant numbers of patients exposed to eculizumab in pregnancy. Whilst not showing that eculizumab is safe in pregnancy, it does support other publications that have supported that there is no current evidence of adverse outcomes related to the use of eculizumab in pregnancy when clinically indicated. As is frequently the case with the use of pharmacological agents in pregnancy, there are no totally convincing data to support safety from a pharmacological perspective in terms of foetal exposure to eculizumab; however, it is thought to be safe. Proof of safety is unlikely to be possible in the foreseeable future given such a trial would be difficult to undertake. The risk-benefit ratio needs to be considered in all patients. This registry will continue to provide valuable data relating to this uncommon condition in which there are relatively few reported pregnancies. In the future, given the greater awareness of aHUS, increasing numbers of women with aHUS are likely to embark on pregnancies whilst undergoing therapy with eculizumab.

Clinical nephrology 2: Poster SP075
Abstract

When to start dialysis: the final answer?

Presenter: Maizel J, Amiens, France

Summary/comment: Disappointingly, Dr Maizel presented data and a review of trials showing that the appropriate time to commence renal replacement therapy with dialysis in acute renal failure has not been established for either patient or renal survival. Dialysis is typically commenced for conditions including life-threatening hyperkalaemia, acidaemia, pulmonary oedema and uraemic complications, but the trials have failed to elucidate clear indications for the initiation of renal replacement therapy. In patients with slowly declining renal function, clinicians typically consider both results of laboratory tests including urea, potassium, acidosis and fluids, and the progression/decline in tests.

Symposium 18: Treatment of AKI: next generations therapies and renal replacement therapy in the Intensive Care Unit

Addressing the risk of hyperkalaemia: is there a sweet spot for potassium binding?

Presenter: van der Meer P, Groningen, The Netherlands

Summary/comment: The use of RAAS inhibitors in renal disease and cardiac failure is well established. Nephroprotective and cardioprotective therapeutics can pose difficulties with hyperkalaemia, resulting in cessation of ACE inhibitors/ARBs and spironolactone. There is a 'U'-shaped curve when plotting the serum potassium level against all-cause mortality. Studies of prescribing habits have shown that patient's RAAS inhibitors are often reduced in dosage because of hyperkalaemia, in particular when spironolactone is added to an ACE inhibitor or ARB combination. Studies have shown that the new potassium-binding resins can effectively lower potassium levels allowing the safe prescription of RAAS inhibitors in terms of serum potassium levels and the use of RAAS inhibitors in higher doses, but studies showing an improvement in outcomes in terms of progression of renal disease, cardiac events and death have not yet been completed and are being planned, including the DIAMOND-HF study.

Industry Sponsored Symposium: RAASi and Hyperkalaemia in Cardiorenal Disease: Opportunities for optimizing outcomes

Are frailty and sarcopenia definitions precise enough to establish a clinical diagnosis in the patient with chronic disease?

Presenter: Carrero JJ, Stockholm, Sweden

Summary: There are varying definitions for sarcopenia and frailty, which limits measuring their extent in patients with CKD. However, they do help identify patients at risk and improve care, so should be applied in clinical practice. Physical frailty scores are screening tools that provide a first step to identify problems. Treatment of frailty requires a multidisciplinary approach that is not well defined. In contrast, sarcopenia scores are assessment tools that allow treatment plans to be formulated. Sarcopenia can be formally diagnosed, and its treatment focusses on improving muscle strength and quality.

Comment: Frailty of patients as assessed by frailty scores varies significantly between countries. There are many frailty scores or frailty indices (more than 70) that can be used, and different categories derived including, for example, the categories or classifications of robust, prefrail and frail. Some assessments have multiple questions and some are short and relatively simple to administer. Frailty can also be divided into the nonphysical (cognitive, social and psychological) and the physical (unintentional weight loss, exhaustion, muscle weakness, slowness and physical function). Sarcopenia-associated complications and loss of muscle strength is associated with an increased risk of mortality. Muscle function is affected by a combination of muscle mass, use/disuse, muscle fibre composition, inflammation/disease and neurological aspects. Muscle quality is often impaired in CKD, even if there is no loss of muscle mass. Exercise has been shown to have an anti-inflammatory effect and exercise in patients on dialysis is associated with improved physical performance and exercise capacity. Frailty is a complex issue, and its role in evaluating patients for their suitability for dialysis and transplantation is evolving.

Symposium 33: Overcoming age with frailty evaluation in the kidney transplant recipient

