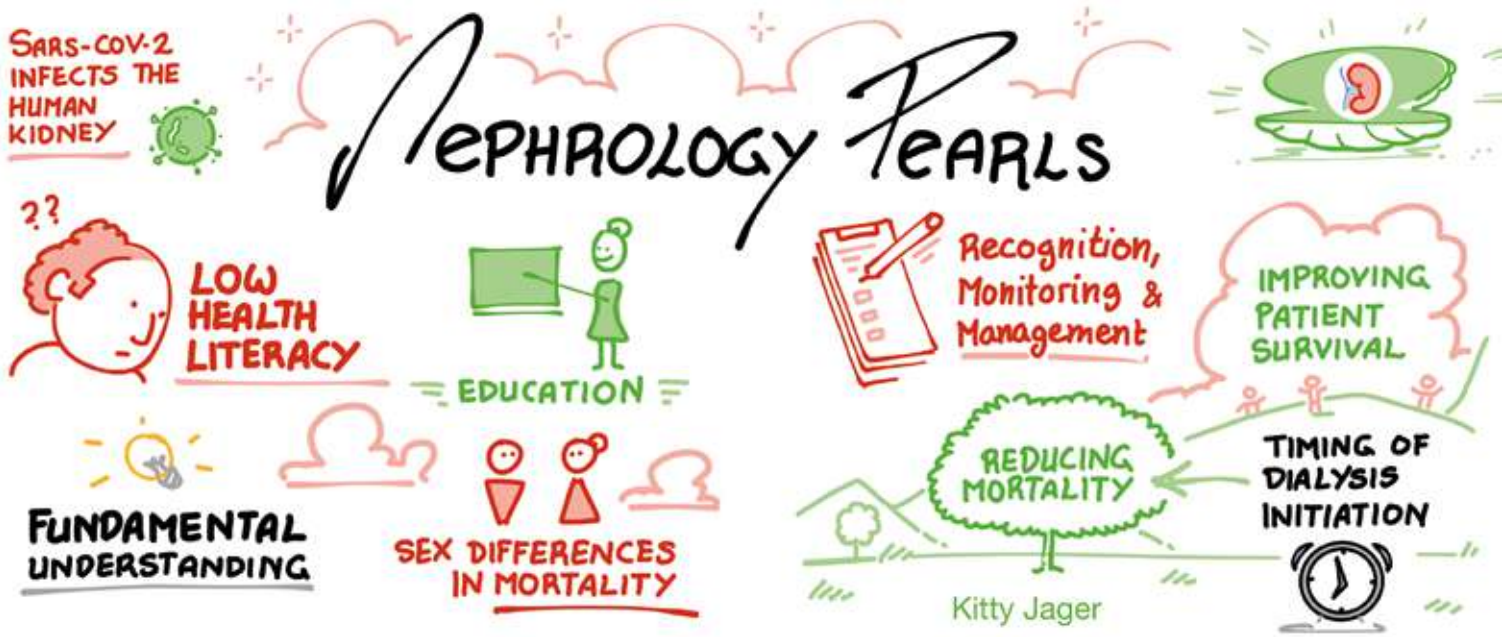
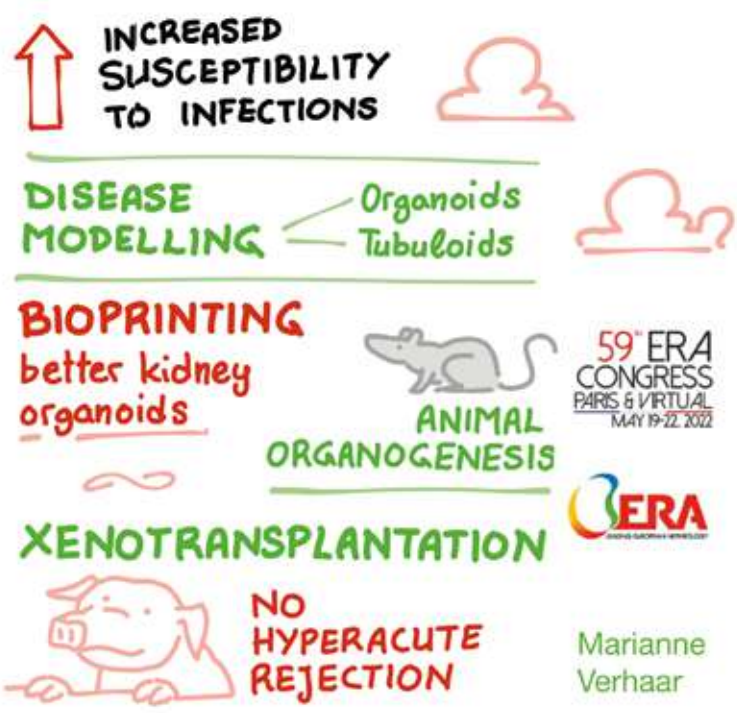
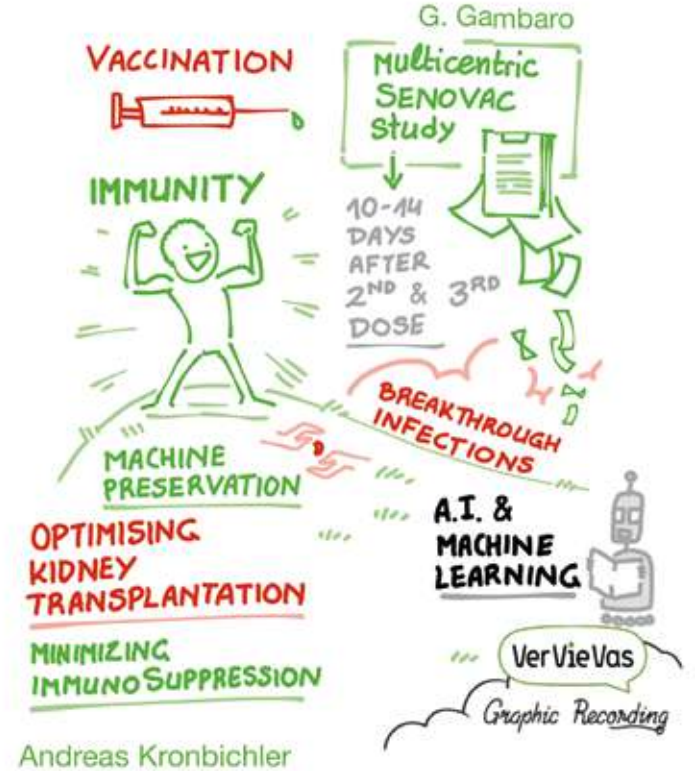
NEPHROLOGY EDUCATION PORTAL

59TH ERA CONGRESS
PARIS & VIRTUAL
MAY 19-22, 2022

Nep Special Edition – July 2022
Summary Reports







Letter from the Editor-in-Chief

Dear Colleagues, dear Friends,

I am very honoured to introduce, for the second consecutive year, the Nephrology Educational Portal special congress edition.

This edition will give you an overview of the 59th ERA Congress, that this year has been organized, after two years of pandemic, face to face in Paris. The congress has been a great success with more than 7,500 participants, in Paris and connected from home.

An important novelty of this edition is represented by the visual recording abstracts which have been realized by professional medical illustrators to providing a quick and useful idea of the session's content in a practical and funny way.

The summary contains, also, a link to the session original webcast.

Enjoy the summary reports.

Davide Bolignano

Nephrology Education Portal (NEP) Editor-in-Chief

NEP ERA NEPHROLOGY EDUCATION PORTAL

59TH ERA CONGRESS PARIS & VIRTUAL MAY 19-22, 2022

Table of Contents

SYMPOSIUM 0.7 - JOINT SYMPOSIA ERA-SFNDT ARTIFICIAL INTELLIGENCE IN NEPHROLOGY 5

Computer-assisted decision making in kidney care - *Alexandre Loupy, France*

From the database to the clinic - *Pierre-Antoine Gourraud, France*

Artificial intelligence in nephropathology - *Vincent Vuiblet, France*

Connected tools in nephrology - *Patrick Jourdain, France*

SYMPOSIUM 1.3 - TUBULAR TRANSPORT 9

Potassium channels controlling tubular functions - *Richard Warth, Germany*

Mitochondrial function and diversity along the nephron - *Andrew Hall, Switzerland*

Oxalate handling in health and disease-crosstalk gut and kidney - *Felix Knauf, Germany*

SYMPOSIUM 2.2 - CHALLENGES IN PEDIATRIC NEPHROLOGY 13

Impact of severe CKD on the developing brain and neurocognitive functioning - *Jaap Groothoff, Netherlands*

Transition of adolescents with CKD to adult clinics? - *Gema Ariceta, Spain*

Isotope diagnostics to improve CKD-MBD management -*Rukshana Shroff, United Kingdom*

SYMPOSIUM 2.5 - PREGNANCY AND THE KIDNEY 17

Renal and pregnancy outcomes in advanced CKD patients - *Liz Lightstone, United Kingdom*

Effect of pregnancy on eGFR slope and predictors of pregnancy outcomes in kidney transplantation - *Marleen C. van Buren, Netherlands*

Adverse pregnancy outcomes and long-term maternal kidney disease - *Peter Barrett, Ireland*

SYMPOSIUM 4.1 - RENAL AND CARDIAC PROTECTION IN DIABETIC AND NON-DIABETIC CKD 21

SGLT2 inhibitors: from bench to bedside for patients with cardiorenal disease - *Daniël van Raalte, Netherlands*

Novel mineralocorticoid receptors antagonists: an update of mechanisms and recent trials - *Frederik Persson, Sweden*

New kidney protective drugs: how do they impact the guidelines - *Paola Fioretto, Italy*

SYMPOSIUM 5.1 - CKD ARRHYTMIAS AND ANTICOAGULATION 25

Arrhythmias and heart failure in CKD and ESKD - *Karolina Szummer, Sweden*

Anticoagulation in patients with CKD and ESKD - *Marie Evans, Sweden*

Sudden death in patients with ESKD - *Nabuhiko Joki, Japan*

SYMPOSIUM 6.4 - HISTOPATHOLOGY AND BEYOND IN RENAL TRANSPLANTATION 29

Determination of early graft loss: what we learn from histopathological findings? - *Marlies Reinders, Netherlands*

The importance of electron microscopy in diagnosing renal transplant rejection - *Candice Roufosse, United Kingdom*

MicroRNA and chemokine profiles in urine to identify renal transplant rejection - *Michael Eikmans, Netherlands*

SYMPOSIUM 7.1 - HEART AND KIDNEY: AN INSIDIOUS RELATIONSHIP 33

Lung congestion in chronic kidney failure - *Carmine Zoccali, Italy*

The importance of screening and assessment of kidney function in patients with heart failure and DM2 - *Martin de Borst, Netherlands*

Uremic cardiomyopathy – is it truly reversible by transplantation? - *Charles Ferro, United Kingdom*

SYMPOSIUM 8.1 - UPCOMING INNOVATIONS IN ACUTE KIDNEY INJURY 37

Deciphering the molecular mechanisms of necroinflammation in acute tubular necrosis - *Wulf Tonnus, Germany*

What is to come in the next KDIGO AKI guideline? - *Marlies Ostermann, United Kingdom*

Identifying patients at risk of the AKI-to-CKD transition - *Morgan Grams, USA*

Table of Contents

SYMPOSIUM 8.3 - CLINICAL ASPECTS OF AKI PREVENTION AND TREATMENT **42**

The second hit hypothesis – What should we look for? - *Eric Hoste, Belgium*

Fluids in ICU – Which is the right one? - *Michael Joannidis, Austria*

Identifying patients at high risk of in-hospital AKI - *Catalina Martin, Spain*

MINI LECTURES **46**

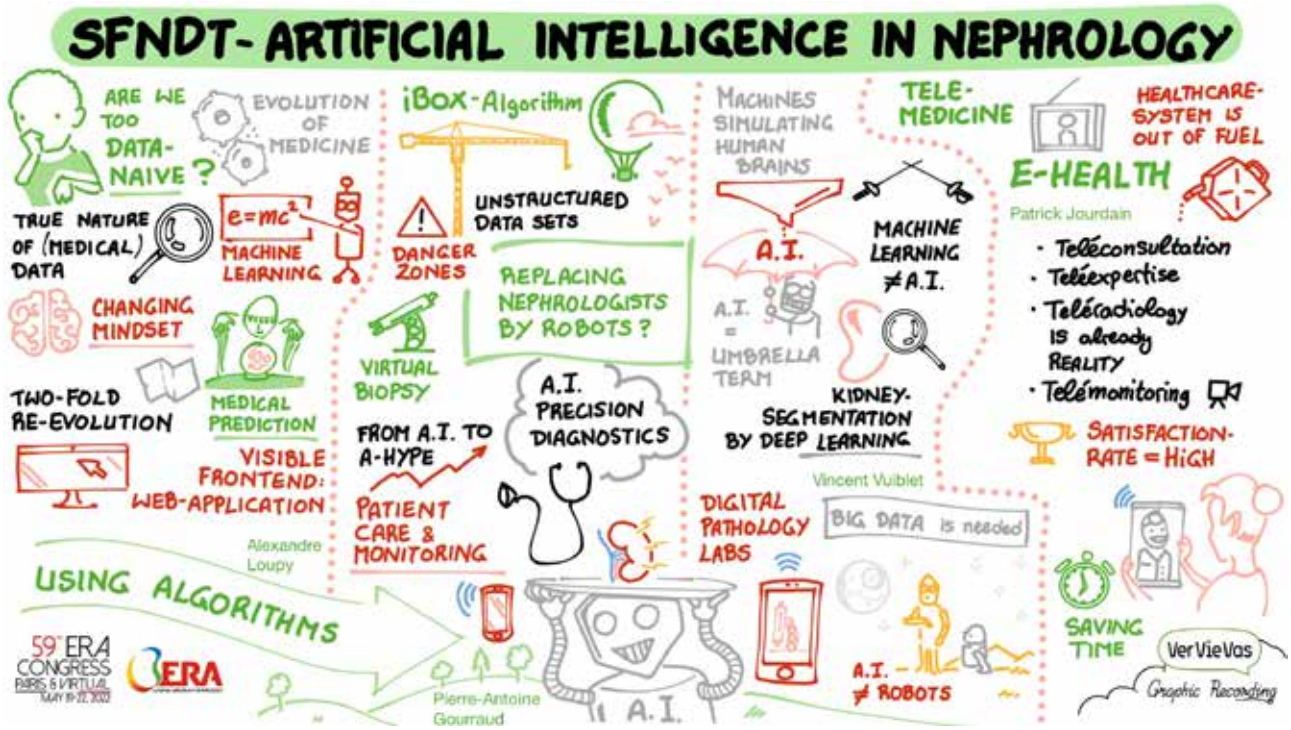
Zebrafish larvae to study and treat glomerular diseases - *Anna Iervolino, Italy*

The role of SGLT2 inhibition in heart failure: What can nephrologists learn from cardiologists? - *Nikolaus Marx, Germany*

Food as medicine – can it link the gut microbiota to an improved renal phenotype? - *Peter Stenvinkel, Sweden*

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) & Acute Kidney Injury (AKI) - *Mehmet Kanbay, Turkey*

Symposium 0.7
Joint symposia ERA-SFNDT Artificial Intelligence in nephrology



Computer-assisted decision making in kidney care

Alexandre Loupy, France

Physicians nowadays need to process large amounts of data to master the complexity of 21st-century patients, promptly establish the correct diagnosis, provide risk stratification and disease staging, and ensure an optimal response to therapy. In the niche specialty of kidney transplantation, integrative multi-modality strategies prove useful to this end.

Figure 1.
Features of the iBox algorithm (from ref. 1)

An international consortium, led by Professor Alexandre Loupy, head of the Paris Transplant Group, aimed to devise a universal digital biomarker tool to predict post-transplantation hard outcomes. The team developed the first universal algorithm for predicting the risk of kidney transplant loss - the Integrative Box (iBox) Scoring System and used it to study allocation and prognosis of allografts, as well as diagnosis and treatment efficacy. The group focused on proving that the iBox was generalizable to different transplant systems, database systems, and countries and that the parameters carried causality in the long-term allograft deterioration process, as well as on transportability. Another possible application of the iBox algorithm is patient monitoring and medical decision-making. It appears that iBox provides a reliable prediction of long-term graft survival and can be used as a contextualization tool in designing clinical trials and facilitating faster drug development.

Furthermore, iBox can be viewed as an emerging surrogate endpoint for future clinical trials.
The native kidney is one of the points of interest in kidney transplantation. It is therefore important to identify mechanistically informed biomarkers to frame the decision to perform a biopsy. This again calls for multi-modality. As opposed to testing cell-free DNA to obtain a positive or negative test, probabilistic assessment is used by embedding the test into different standard-of-care parameters, and measuring whether it brings an additional and in-depth value for predicting whether a kidney allograft is rejecting. Concerning precision diagnosis, an artificial intelligence (AI) tool needs to integrate diagnostic parameters. Thus, the group introduced the D6 approach, where D1 is standard pathology, D2 is immunohistochemistry, D3 is clinical context, D4 is mechanistically informed biomarkers, and D5 is the molecular dimension of diagnosis, and D6 is an integration of those. Three ongoing clinical trials are using the D6 approach in their standard diagnostic care, and clinicians are provided with molecular reports which are included in their assessment of how the patient should be treated. Another digital tool, the validated Virtual Biopsy system, predicts what a zero-time kidney biopsy would look like using parameters that are available at the time of transplant. It is currently in the pipeline for implementation in one of the Organ Procurement Organizations in the USA. Finally, AI-based simulation tools used for allograft allocation were monitored in the worldwide transplant activity during the COVID-19 crisis and different practice patterns were compared. By using such data the simulation algorithm can not only be descriptive but also generate policy changes.

From the database to the clinic

Pierre-Antoine Gourraud, France

The practice of medicine is ever-evolving and in the coming years it will not solely be based on the practitioner's experience and memory, but find leverage in the combined powers of on-demand data and real-time computation. Medical records are contributed by multiple sources – acquired from the patient, often written down by a caregiver, produced by medical devices, paid by insurance companies, stored by healthcare institutions, transformed by data scientists, etc., and must be observed as non-material goods, i.e. data.
The use of AI-processed data to make clinically valuable predictions is only one among the many possible AI applications, such as classification, transformation, image recognition, etc. Machine learning prediction has three stages: defining the problem, i.e. the hypothesis, the input of all available data, as the recording of data is no longer cost-limited to significant data, and finally the data prediction. The methodology for evaluating prediction is more important than the models/algorithms themselves. By using computation power, it is possible to employ multiple prediction methods, stress one or challenge another, operate with multiple classifiers, etc. Therefore, the focus is no longer on the model, but on the evaluation of the robustness of the prediction performance.

Figure 2.
Development of interfaces to manage and secure on-demand computation and aggregated statistics

In the context of the European project led by Professor Alexandre Loupy, a clinical decision support system is being built that combines integrative data and algorithm analytics principles into a platform, enabling the crunching of data from the database onto the bench, i.e. the clinic. The first key success factor of this platform is that the existing, validated and certified reference set databases come first. The application is therefore a window into the reference data, and the algorithm build comes on top of this data. The application uses distributed reference data, meaning that only the results of the computation travel, whereas the individual pieces of data used to make a decision remain in the database, which is the emerging principle of data governance. Also, the focus on the individual patient is the starting point of all computations supporting decision-making at the bedside. The user interface of the application provides graphical access to all data, lays out data of a single patient in an actionable way, and presents interactive results of analytics and prediction. The functionalities can trigger iterative enhancement of how to use the combined power of on-demand data access and computation.
Therefore, the road from database to clinic leads from creating value by combining data sources and data transformations via building clinical support with reference data, while looking at IA not as a revolution, but as a computational experiment.

Artificial intelligence in nephropathology

Vincent Vuiblet, France

Artificial Intelligence is an umbrella term for phrases such as data science, artificial intelligence, machine learning, and deep learning. There are certain misconceptions between deep learning and machine learning. The most common one is that deep learning is superior to machine learning, which is incorrect because the method's effectiveness is dependent on the issue at hand, as well as the quantity and type of data employed. Another misconception is that AI resembles C3PO, a human-like robot from Star Wars. The truth is that general AI or Super AI remains in the field of science fiction. However, narrow AI, which is suited for a specific task or an association of specific tasks, has been the focus of research ever since the middle of the 20th century.

From their first use in medicine in 1970, computers have made their way into the clinic, and nowadays AI is mentioned in 20,519 publications on PubMed, 82% of which have been published in the last 4 years. Three main fields of research of specific application of AI in nephropathology are segmentation, which involves identification inside the histologic component, classification, which is the foundation of the tool helping the pathologist to make a diagnosis, and quantification, which plays a vital role in prognosis. AI can aid nephropathologists by improving inter-pathologist reproducibility, time-saving, optimization of classification, accessing data otherwise invisible to pathologists, and finally, by integrating and compiling heterogeneous data from multiple sources (histology, electronic health records, biology).

To develop the use of AI in nephropathology, the following three elements are essential: data from Whole Slide Imaging (WSI), data-expert nephropathologist, and data scientist expert. Concretely, the prerequisites are digital pathology laboratories, 'dating sites' or locations where nephropathologists and data scientists would cooperate, and a network of nephropathologists who would collaboratively conduct research in multicentric studies. AI is an essential and strategic issue in nephropathology because it would facilitate the comprehension of pathology algorithms, enable nephropathology to be the lead field of AI-based tools development, maintain its digital sovereignty and ensure economic sustainability.

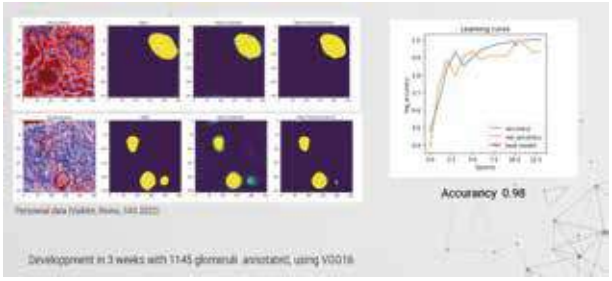


Figure 3.
Glomeruli detection by deep learning

Like the entire medical realm, nephropathology will be profoundly and positively transformed by AI, and medical professionals will inevitably be involved in the development and validation of their future AI-based tools. To keep up with imminent developments, pathology laboratories must quickly adapt to the needs of digital pathology, nephropathologists and data scientists have to work together, and big data needed to train AI models needs to rely heavily on multicenter collaboration.

Connected tools in nephrology

Patrick Jourdain, France

Telemedicine is very likely to become a significant part of chronic renal disease management as informatics and communication capabilities increase, such as the widespread availability of smartphones and the internet, as well as older patients' growing adoption of new communication technology. Another reason for promoting telemedicine development is the healthcare system's resource exhaustion, which is on the decline. Some of the drivers of a shift in viewpoint in favor of telemedicine include an increase in the number of elderly patients, a movement in the culture of senior health, an increase in the prevalence of hypertension, and an increase in the life expectancy of cardiovascular patients.

The umbrella term of e-health includes predictive medicine with a foundation in big data, health wellness with coaching, e-learning and connected medical tools, and telemedicine. Telemedicine covers different fields as well, such as teleconsultation, which used to involve the doctor, the patient, and the video link in between, but is now evolving to include connected devices. Tele-expertise, another aspect of telemedicine, is a discussion between different healthcare professionals and this kind of immediate cooperation saves valuable time for the patient, thereby amending therapy or providing treatment in the earlier disease stages. Tele-radiologic examination, especially echocardiography, is on expansion in France, where more than one hundred hospitals perform magnetic resonance imaging and tomodensitometry remotely, permitting highly specialized or training centers to interactively discuss the case. Tele-monitoring, with connected tools, focuses on structured telephone support to adapt care plans, and it can be complex or light, depending on factors such as the presence or absence of access to doctors,

Although benefits in terms of telemedicine include substantial time-saving and improved quality of care, telemedicine is not for all patients and under all circumstances. For instance, patients who find it difficult to use the application or patients with acute abdominal pain or with severe hypertension. Also, there are certain barriers for use of telemedicine in different countries, such as cost, legal grounding, culture, and infrastructure, and most importantly, in terms of chronic kidney disease has the strongest impact on the quality of life, and prioritization. Another challenge is how to combine single pathologies registered in the clinical information management system into polypathologies in an integrated data management system, to follow up with patients and monitor different contributing factors from different pathologies suffered by the individual patient. Nevertheless, telemedicine is a near-term reality that should be viewed as a continuous and integrated process in the life of the patient.

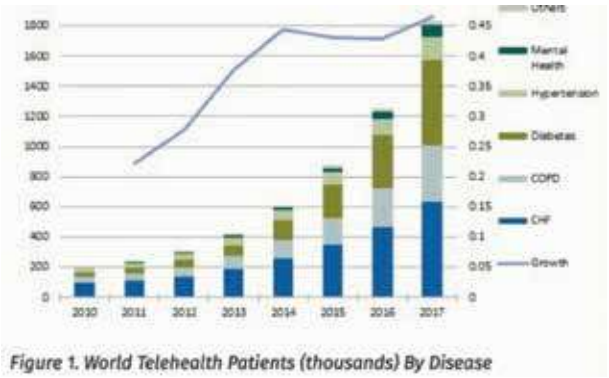


Figure 4.
The use of telemedicine in different specialties

Further readings

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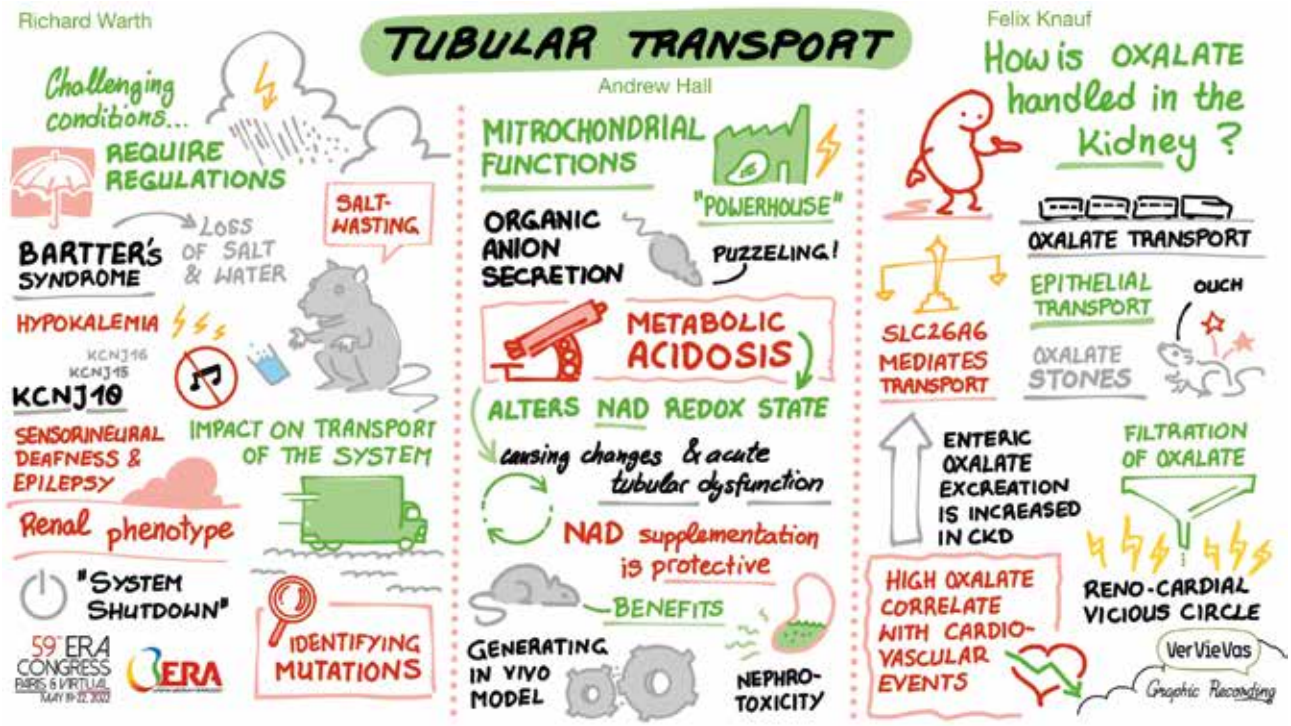
Written by Jasna Trbojevic-Stankovic.
All the speakers reviewed and approved the content.

Symposium 1.3
Tubular transport



Potassium channels controlling tubular functions

Richard Warth, Germany

Potassium channels are involved in a broad spectrum of functions in renal tubular cells. A multitude of potassium channel genes with variable expression has been identified recently, some of which are linked to diseases in humans. For example, Bartter syndrome is a rare inherited renal tubular disorder manifesting with polyuria, hypokalemic alkalosis, hyponatremia, hypercalciuria, and hypermagnesiuria. Types 1 and 2, caused by mutations in ROMK, NKCC2, and Barttin potassium channels, are very severe and manifest antenatally. Type 3, on the other hand, is caused by CLCKB/CLCKA mutations, and has a rather mild clinical picture. Bartter 4 has the added problem of deafness, and Bartter 6 is a transient antenatal condition caused by a mutation in factor MAGED2.

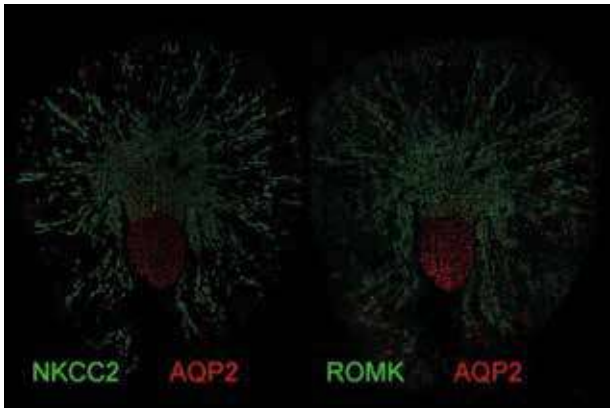


Figure 1.
ROMK, aquaporin 2 (AQP2), and the Na-K-2Cl cotransporter (NKCC2) expression in renal tubular cells

The renal outer medullary potassium channel (ROMK) is the most studied member of the family and with the highest degree of expression in the kidney. ROMK is involved in potassium transport out of the cells, playing an important role in potassium secretion in the cortical collecting duct and potassium recycling in the thick ascending limb of Henle's loop. By limiting the transmembrane transport in the thick ascending limb ROMK raises the sodium load in the distal portions of the nephron

where potassium is secreted in exchange for sodium. As a result, increased sodium reabsorption in the collecting system boosts potassium secretion.

KCNJ10 is a potassium channel with a much lower expression than ROMK, yet it plays a significant function in the kidney and other human organs. KCNJ10 is expressed on the basolateral membrane of the cortical thick ascending limb of Henle's loop where it inwardly rectifies potassium. Patients with epilepsy, sensorineural deafness, tubulopathy, and resulting ataxia, were found to have mutations in this potassium channel (EAST syndrome). Many other mutations have been discovered, most of which are linked to severe diseases. Still, not all patients with KCNJ10 mutation develop tubulopathy, indicating certain variability that is likely caused by the specific mutation and the context-dependence of its effects. This is supported by the fact that, in addition to the known symptoms, patients with this mutation also develop intellectual disabilities. KCNJ10 and its sub-unit, KCNJ16, are believed to mutually form channels for basolateral potassium recycling in distal tubules. A study in mice with a KCNJ16 mutation found that they had hyperkalemia as well, but strangely, they exhibited acidosis rather than alkalosis, indicating a different channel function in the distal nephron. Studies on KCNJ16 (Kir5.1) mutations revealed a common tubulopathy characterized by hypokalemia, salt wasting and acidosis, and sensorineural deafness.

Mitochondrial function and diversity along the nephron

Andrew Hall, Switzerland

In the kidney, there is a strong link between solute transport and aerobic metabolism. The transport demands are reflected in the density of mitochondria in different nephron segments. There are also certain adaptations of mitochondrial function to various transport tasks along the nephron. The in situ study with fluorescence microscopy of structure and function of mitochondria in the nephron and the effects of disease-causing insults reached interesting conclusions. Differences in the mitochondrial flavoprotein signal and the glutamate-glutamine pathway were found between segments s1 and s2 in the proximal tubule. Imaging of the collecting duct revealed heterogeneity in mitochondrial NADH signals and intercalated cells, as well as a very poor uptake of voltage-dependent dyes, implying that the mitochondria in this segment are not well energized. Therefore, other metabolic pathways are considered in intercalated cells in terms of glycolytic activity.

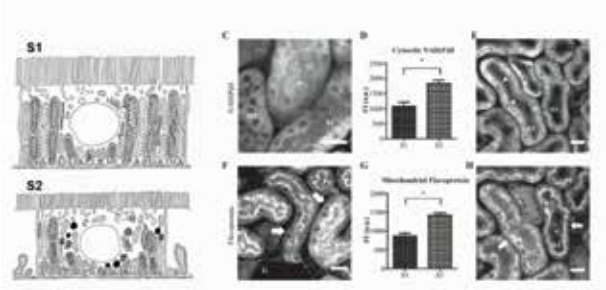


Figure 2.
Heterogeneity of mitochondrial function along the proximal tubule (from ref. 5)

Mitochondria in the proximal tubules are involved in the acidosis defense system of creating ammonia and bicarbonate via an NAD+-dependent process. The fact that treatment of severe metabolic acidosis with bicarbonate minimizes the risk of acute kidney injury (AKI) prompted an investigation of the effects of acidosis on mitochondrial function in the proximal tubule. Considering that NAD+ is critical for lipid metabolism in the proximal tubule, researchers studied the effects of acidosis on lipid metabolism in an in-vivo acidosis model in mice. The acidotic animals exhibited a significant increase in tubular lipid content, and the slice model revealed large vacuoles in the proximal tubules. Electron microscopy showed that these vacuoles were multi-lamellar bodies that operate as a lipid store within the cell, particularly in the s2 segment of the proximal tubule. The acidotic mice were then treated with bicarbonate, which significantly improved their tubular function. Thus it was established that NAD+ is primarily used for fatty acid metabolism in the proximal tubule, but it is also required for ammoniagenesis and is dramatically increased during acidosis, implying that these processes compete for NAD+. Treatment of increased intracellular NAD+ caused a significant improvement in tubular toxicity as well as favorable effects on lipids.

Another research focused on investigating the mechanism of toxicity of the antiviral medicine Tenofovir, which causes proximal tubulopathy and may induce Fanconi syndrome and AKI. Tubular cell exposure to increasing quantities of the drug enhanced the mitochondrial footprint, with characteristically large mitochondria and damaged cristae, as well as significant transport abnormalities. The results mirrorred the findings usually observed in the patients, pointing at high throughput imaging to generate more realistic in vitro models of tubular diseases.

Oxalate handling in health and disease-crosstalk gut and kidney

Felix Knauf, Germany

Oxalate enters the body through diet or is produced endogenously by the liver as a useless metabolic byproduct. It is predominantly excreted in the urine and, to a lesser extent, in the feces. It is also removed by microbial oxalate metabolism in the gut. The major insight into oxalate management in the proximal tubule was provided by the studies of chloride transport. The proximal tubule absorbs chloride primarily passively and paracellularly, but there is also a component of transcellular chloride absorption mediated by the SLC26A6 carrier, which is also involved in oxalate secretion, both in the kidneys and in the intestine. In the gut, oxalate predominantly binds with calcium to create a compound that is excreted in the feces. However, in physiological conditions there is never enough calcium present to combine with all the oxalate, thus some oxalate absorption occurs along with salt and water across the tight junction. In the intestine, the SLC26A6 transporter (A6) plays a key role in restricting the net absorption by back-secreting oxalate into the lumen.

Loss of kidney function leads to an increase in serum oxalate due to decreased clearance. Recent research on the oxalate handling processes in animal models of chronic kidney disease (CKD) observed an upregulation of the A6 oxalate transporter in the small intestine, but also in the colon which normally has a low A6 expression. Thus, in CKD oxalate removal through the stool increases, even eliminating the endogenously produced oxalate.

Recent research suggested oxalate was a novel risk factor for cardiovascular events. Its accumulation is associated with oxidative stress, inflammation, and elevated cardiovascular risk. Oxalate crystals can activate inflammatory cells, dendritic cells, macrophages, and monocytes by the toll-like receptor 4 inflammasome signaling that leads to cytokine release. It is believed that oxalate is pro-inflammatory, which may be the link to cardiovascular mortality. In a cohort of over one thousand hemodialyzed patients with diabetes, the risk for cardiovascular events and sudden cardiac death was significantly associated with elevated oxalate levels. Further research is expected to assess whether oxalate-lowering strategies could improve cardiovascular outcomes in dialysis patients.

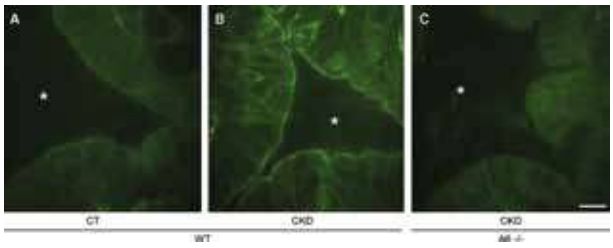


Figure 3.
The expression A6 oxalate transporter on the apical membrane of colon epithelium in mice with CKD (from ref. 11)

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Written by Jasna Trbojevic-Stankovic.
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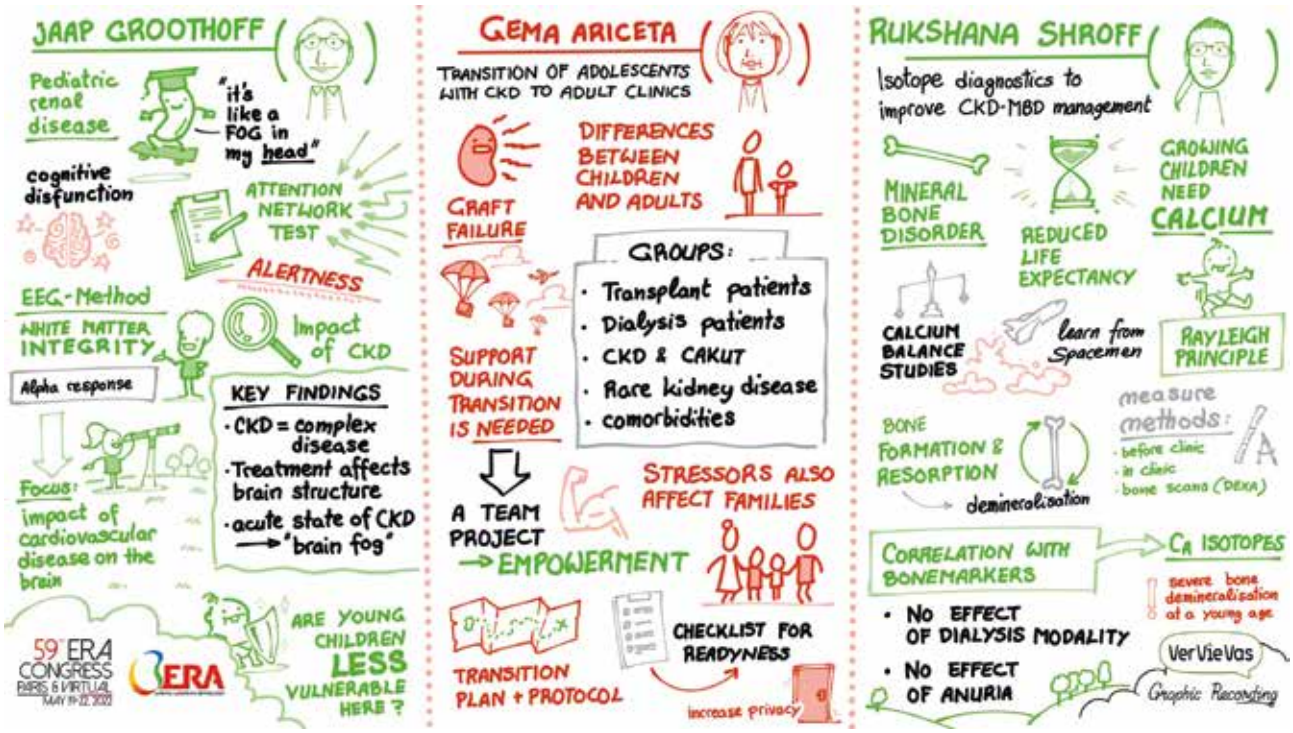
Symposium 2.2
Challenges in Pediatric Nephrology



Impact of severe CKD on the developing brain and neurocognitive functioning

Jaap Groothoff, Netherlands

The progression of chronic kidney disease (CKD) is associated with a myriad of systemic effects, including the impact on cognition. The research of the Amsterdam INPACT group, led by Sophie Lijdsman, found that children and young adults with CKD stage 4 and more are at risk for structural and functional brain abnormalities and neurocognitive dysfunctions. Especially in dialysis and transplant patients, there is impaired white matter integrity which is strongly associated with low full-scale IQ and basic speed and working memory performance. Impaired alertness and attention, as well as impaired alpha/theta EEG response, were found in patients with low current eGFR and longer exposure to low eGFR.

The reported cognitive problems include a lower full-scale IQ, attention deficit, impaired memory, and executive functioning, brain fog, as well as impaired memory function that may hamper the quality of life in adolescent kidney transplant recipients. To explore these issues, the group assessed structural abnormalities of the brain with magnetic resonance imaging (MRI) and diffusion tensor image

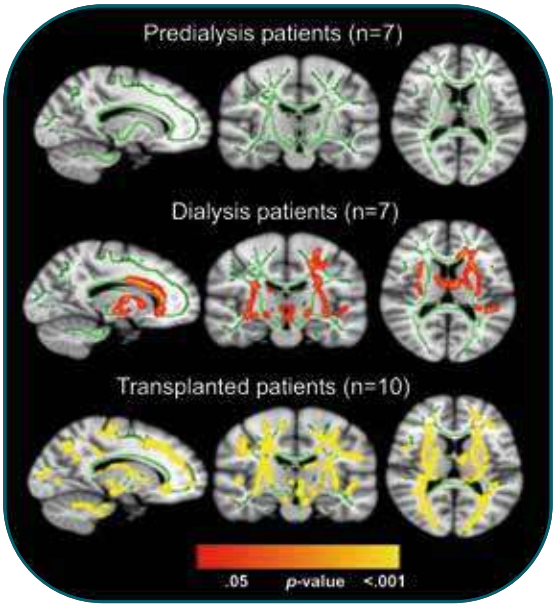


Figure 1.
Significantly lower white matter integrity in CKD, dialysis, and transplant patients compared to healthy controls on maps for fractional anisotropy (from ref. 1)

analysis (DTI) and evaluated brain function by electroencephalogram (EEG) temporal resolution. Cognitive functioning was analyzed using the comprehensive neurocognitive test battery. This included the estimated full-scale IQ and several neurocognitive components, among which a special test on alertness - the attention network test (ANT). The renal factors are taken into consideration as determinants were the eGFR, illness duration, and age at diagnosis, as well as the type of treatment (pre-dialysis, dialysis, and transplantation).

The research found a widespread disruption of white matter integrity throughout the group, with no significant differences between the dialysis and transplant groups. Older age at diagnosis and longer dialysis vintage at the time of transplantation negatively affected the neurocognition, including intelligence, basic speed, and working memory. On the other hand, no evidence was found to prove a difference between the predialysis group and healthy controls. To the surprise of the researchers, neurocognition was unaffected by eGFR and the duration of severe CKD. Concerning brain function and attention, the researchers concluded that problems in alertness and attention difficulties occur in patients with current low eGFR and longer exposure to low eGFR, and are most likely reversible after kidney transplantation. These functional abnormalities were reflected by altered EEG patterns. The conclusion is that the impact of severe CKD in children and young adults is complex. Severe CKD and its management may affect brain structure, , especially the white matter integrity, which may impact global cognition, memory and basic speed.

Also, CKD and exposure to uremic toxins impact brain function and provokes attention difficulties, but this issue is likely reversible after transplantation. Future research should focus on the impact of cardiovascular disease on the brain in young renal transplant patients, the impact of the CKD course and uremic toxins, as well as on exploring the aspect of physical exercise benefits for enhancing white matter function.

Transition of adolescents with CKD to adult clinics?

Gema Ariceta, Spain

The adolescent CKD group is characterized by the highest risk of poor self-management and unfavorable outcomes. Emerging adulthood has been recognized as a high-risk period for kidney transplant graph loss and recent evidence suggests that adolescents and young adults with CKD also have unfavorable prognoses in comparison with younger and older patients in a similar clinical setting. Therefore, novel research focuses on transitioning this vulnerable population to adult clinics.

Figure 2.
The transition process of CKD patients from pediatric to the adult clinic (from ref. 2)

Congenital anomalies of the kidney and urinary tract (CAKUT), glomerulonephritis, but also a substantial number of rare and genetic or inherited disorders are the most common causes of CKD. Therefore, the transition process must account for all these unique requirements. Although it has recently been reported that the incidence of children progressing to renal failure during their pediatric age has decreased in the CAKUT group, many of those patients continue to progress and reach renal failure in their 30s and 40s. This highlights the need to transition not only for patients with advanced CKD or post-transplant and dialysis patients but also for patients with milder CKD, to avoid a lack of adequate follow-up.

Transition needs to consider different patient profiles, such as patients with CAKUT who have associated uropathy and the associated need for lifelong urologic care. This indicates that the transition must not only include nephrology but urology as well. At the same time, there is a conflict between the need to provide independence to the patient in terms of self-management and the limitations that the patient may present, not only because of comorbidities but also due to the complexity of providing adequate care.

One of the main issues is that transition is not only a medical process. Instead, it is also influenced by many psychological and social factors, since it occurs when brain maturation is still incomplete. Adolescents with CKD face not only the typical challenges of emerging adulthood, but they must also learn to manage a lifelong condition on their own. Delicate peer interaction, extended school absence, strict immunosuppressant drug regimes, post-traumatic stress symptoms, and family instability owing to financial hardship may all worsen psychosocial challenges and lead to poor treatment adherence.

Successful transition lies in the individualized approach, identification of the most suitable specialists, and communication on all levels, as well as careful planning and adapting the existent protocols to the specific needs of the patient.

Isotope diagnostics to improve CKD-MBD management

Rukshana Shroff, United Kingdom

Chronic kidney disease in children is a substantial challenge and bone mineral disorders can be extremely difficult to manage in this population. Nearly 30% of children with CKD stage 2 and >90 % of children on dialysis have insufficient mineralization, which manifests with the occurrence of bone deformities and a much higher risk of fractures than in healthy age-matched children. The assessment of bone health poses a significant problem for physicians treating this vulnerable group.

Calcium is measured by imprecise and invasive methods such as serum calcium levels, bone biopsies, radiological changes, biomarkers, and parathyroid hormone (PTH). Calcium isotopes 42Ca and 44Ca, which are non-radioactive, are found in the human diet and are stored in bodily compartments via kinetic isotope fractionation principles. Isotopically light 42Ca is mostly absorbed into bone tissue, whereas heavier 44Ca is excreted in the urine and feces. When bone mineralization exceeds resorption, the 44/42Caserum ratio rises, indicating a positive calcium balance in the bones.

A recent study in a healthy population showed that children have the highest calcium isotope ratios due to rapid growth, followed by young adults and finally elderly subjects, with elderly osteoporotic women having the lowest calcium isotope ratio. In a further study in children with CKD and on dialysis, we using a somewhat different model that took into consideration the calcium loss through the kidneys in subjects with preserved diuresis, calcium exchange on dialysis, and possible extraosseous calcification. Compared to healthy age-matched children, subjects with CKD and those on dialysis have a significantly lower calcium isotope ratio. This points to substantial bone demineralization, similar to elderly osteoporotic subjects, signifying that children with CKD and and on dialysis are at the extreme of bone demineralization.

Therefore, the naturally occurring stable calcium isotope ratio in serum is a significant and independent predictor of bone calcium balance in children with CKD and on dialysis. It is more sensitive and accurate than the routinely measured biomarkers as well as bone mineral density measured by dual-energy x-ray absorptiometry (DXA) or peripheral quantitative computed tomography (pQCT). This isotope measurement can be used in many different groups, such as in children with inherited bone diseases, adults with CKD, and on dialysis, as a prognostic marker of fracture risk in older people and for sensitive monitoring of the effects of medications like steroids and anti-resorptive treatments that affect the bone.

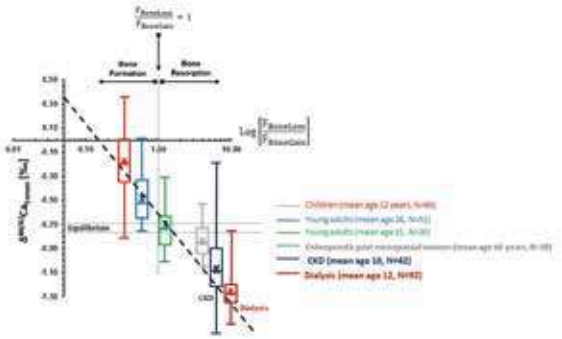


Figure 3.
Calcium isotope ratios and bone mineralization-demineralization status in different populations

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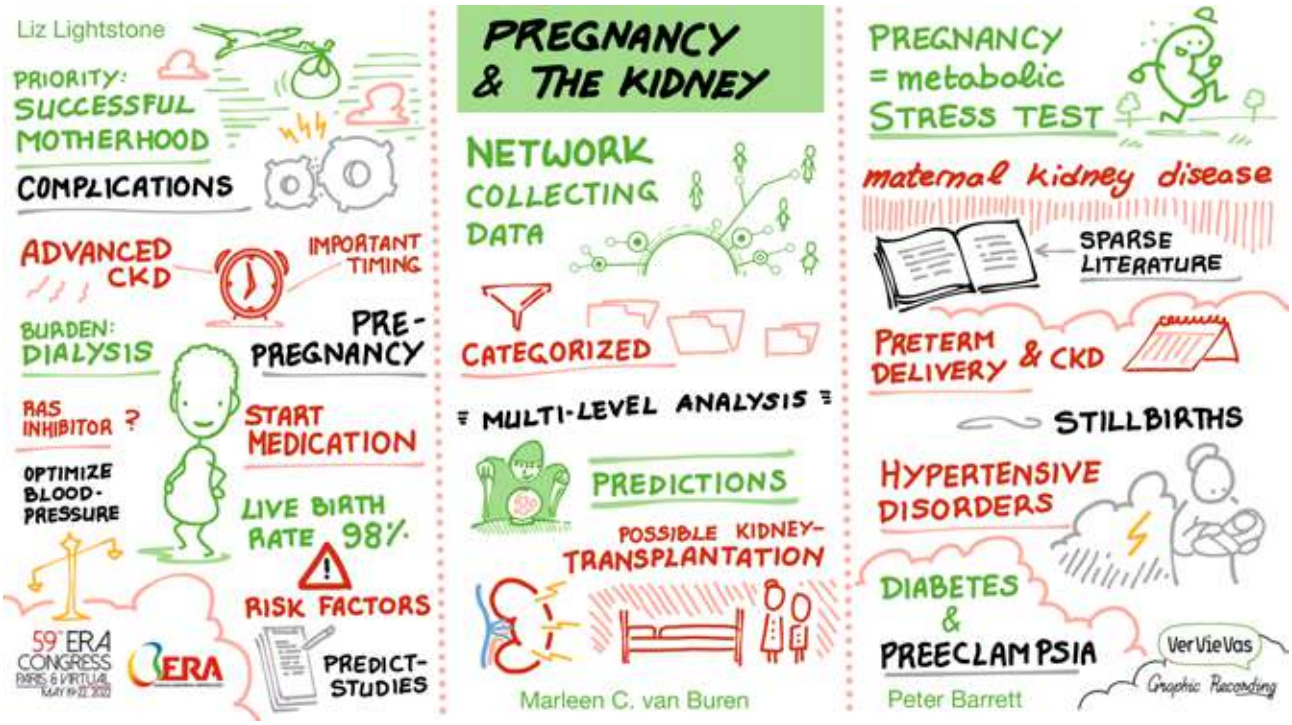
Symposium 2.5
Pregnancy and the kidney



Renal and pregnancy outcomes in advanced CKD patients

Liz Lightstone, United Kingdom

Chronic kidney disease (CKD) and other comorbidities in women of childbearing age are becoming more common, since the number of first-time births in women in their 30s and 40s has tripled and doubled, respectively. Fortunately, recent research enables medical professionals to provide better care for these patients before, during, and after pregnancy.

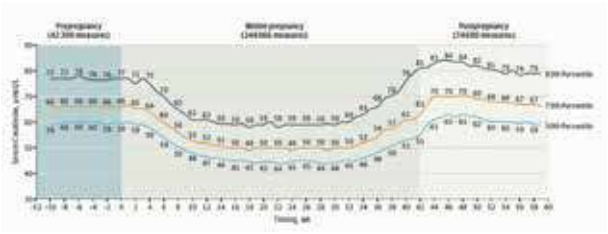


Figure 1.
Expected creatinine levels in pregnancy (from ref. 3)

Advanced CKD poses an increased risk of adverse outcomes, including, for the mother, preeclampsia, and possible accelerated loss of renal function, and for the fetus, fetal growth restriction and preterm delivery. Pre-pregnancy counseling should therefore include counseling on contraception, planning, and timing of pregnancy, review of current medications, and discussion about pregnancy and renal outcomes. Medications need to be reviewed carefully before pregnancy: some, such as those used in auto-immune medicine regimens, antihypertensives, and anti-diabetics, some should be discontinued even before planned conception (such as mycophenolate mofetil) or as soon as pregnancy is confirmed (such as ACE inhibitors), and alternative pregnancy safe medications started. In contrast, certain drugs should be introduced, such as hydroxychloroquine for patients with lupus nephritis and aspirin for all patients with CKD to reduce the risk of pre-eclampsia. During pregnancy, the dosage of some Immunosuppressants, most notably tacrolimus and cyclosporin, may also need to be revised due to altered handling of the drug during pregnancy. The retrospective and prospective cohort study led by Wiles and Webster followed 178 pregnancies in 159 women with CKD stages 3-5 – the live birth rate was high at 98% live birth rate but 56% of the babies were born pre-term. Early delivery

was more likely in women with hypertension and the risk doubled if they did not have a creatinine fall of at least 10% in early pregnancy. Proteinuria (urinary PCR) of more than 100mg/mmol was associated with an increased risk of having a baby with a lower than expected birthweight.

The fact that many women present to health professionals for the first time during pregnancy and that serum creatinine is not part of antenatal screening in most countries pose a considerable challenge to diagnosing kidney impairment in pregnant women. Therefore, it might be reasonable to include serum creatinine in routine prenatal testing and certainly in those women with known conditions that predispose to CKD such as diabetes or hypertension. Figure 1 highlights the range of creatinines to be seen in women of child bearing age pre, during and post partum. A creatinine of greater than 70, and certainly 77umol/l in pregnancy should raise concern about underlying kidney dysfunction. Multidisciplinary collaborative care during pregnancy is vital to ensure the mother's underlying disease, her blood pressure and proteinuria are adequately monitored and treated, and that the fetus is carefully reviewed to assessed fetal growth and development. Women with CKD are more likely to develop preeclampsia but it can be challenging to distinguish between worsening disease and superimposed pre eclampsia given both can present with hypertension and proteinuria. The recent advancement in measuring placental growth factor (PlGF), which is lower and declines precipitously in preeclampsia, has made this easier though the threshold at which PlGF is consider low may need to be higher in women with CKD. If kidney functioning is worsening due to underlying disease or the impact of pregnancy, but there is no preeclampsia and the fetus is not threatened, dialysis initiation can be considered when the urea is rising to 17mmol/l, rather than early delivery. If the woman is already on dialysis, the dialysis prescription should be increased at the onset of pregnancy, with previously optimized prescription pre-pregnancy. Decisions on delivery timing and mode should be guided by finding a balance between maternal health and the safety of the baby, the level of available neonatal care available, and avoiding acute kidney injury. Finally, post-partum care needs to take into consideration that pregnancy complications extend beyond the pregnancy, therefore proper follow-up must be conducted, not least to ensure that those women who presented for the first time in pregnancy, are fully diagnosed and have a proper treatment plan in place.

Effect of pregnancy on eGFR slope and predictors of pregnancy outcomes in kidney transplantation

Marleen C. van Buren, Netherlands

The nationwide cohort study from the PARTOUT (Pregnancy After Renal Transplantation OUTcomes) network from the Netherlands aimed to evaluate the pregnancy outcomes in kidney transplant recipients and to explore the effects of pregnancy on graft loss and eGFR after kidney transplantation. The study included 301 pregnancies in 202 patients, categorized by the value of pre-pregnancy eGFR.

First, the PARTOUT group looked at maternal outcomes per eGFR category and observed that the likelihood of development of gestational hypertension also rises with lower eGFR, while the probability of preeclampsia remains stable throughout the different eGFR groups, but rises to 100% at eGFR <30 mL/min. The combined adverse pregnancy outcomes (cAPO) were defined as low birth weight (<2500g), preterm birth (<37 weeks), severe hypertension in the 3rd trimester (>160mmHg systolic, >110mmHg diastolic blood pressure), and 3rd-trimester serum creatinine higher than preconception levels. The study concluded that overall pregnancy outcomes after kidney transplantation are positive, with a live birth rate of 93%, a mean gestational age of 35 + 4 weeks, and a mean birth weight of 2383 grams. The most important predictors of cAPO are high pre-pregnancy serum creatinine and the absence of a second-trimester decrease in serum creatinine or mean arterial pressure. Also, cAPO is a significant risk indicator for death-centered graft loss. (ref 4)

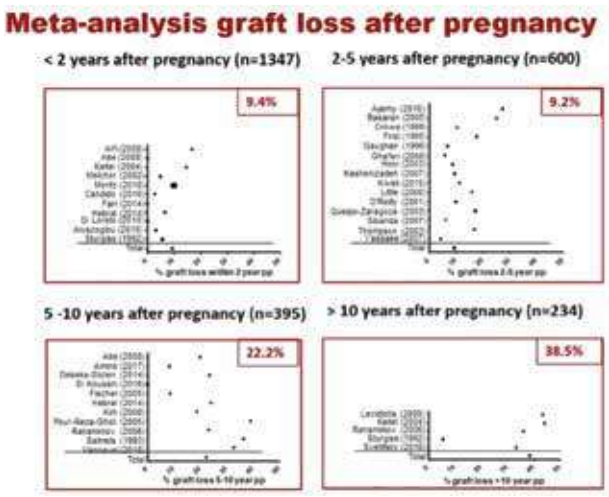


Figure 2.
Kidney graft loss after pregnancy

Furthermore, the PARTOUT group performed a meta-analysis on graft loss after pregnancy (ref 5 and figure 2). Ten of these studies used control groups to compare graft loss rates with women who did not get pregnant after kidney transplantation. The matched control groups

were heterogenic but most often for age and creatinine levels. No significant difference in graft loss was shown between the pregnant group and the control group. At last the PARTOUT group presented the multilevel analyses of pregnancy on eGFR slope. Results showed that pregnancy after kidney transplantation had no significant effect on eGFR, did not accelerate its slope, and did not amplify the negative effect of significant univariate predictors of worse eGFR. Also, multivariate generalized estimating equations analysis showed that transplant vintage, rejection before firs.t pregnancy, pre-pregnancy eGFR, and shorter transplant-to-conception interval are predictors of worse eGFR after kidney transplant, and not pregnancy itself. Graft survival after first delivery was significantly better in women with midterm hyperfiltration (>15% decrease in serum creatinine) during the first pregnancy (ref 6)

Adverse pregnancy outcomes and long-term maternal kidney disease

Peter Barrett, Ireland

There is increasing evidence that adverse pregnancy outcomes are associated with a higher risk of CKD later in life. Recent research by Peter Barrett aimed to assess whether post-pregnancy maternal CKD and end-stage kidney disease (ESKD) in previously healthy women may be associated with adverse pregnancy outcomes such as hypertensive disorders of pregnancy, preeclampsia and gestational hypertension, preterm delivery, delivery of a small for gestational age infant, gestational diabetes and pregnancy loss. Upon systematic review of the literature, research continued by conducting several original population-based cohort studies. The population of interest included women who had ever been pregnant and experienced at least one of the relevant adverse pregnancy outcomes. The control group included women who only had uncomplicated pregnancies. The data were obtained from the Swedish Medical Birth Register and included 1.9 million women and 3.8 million deliveries. The median follow-up period was 20.6 years and the outcomes observed were CKD and ESKD.

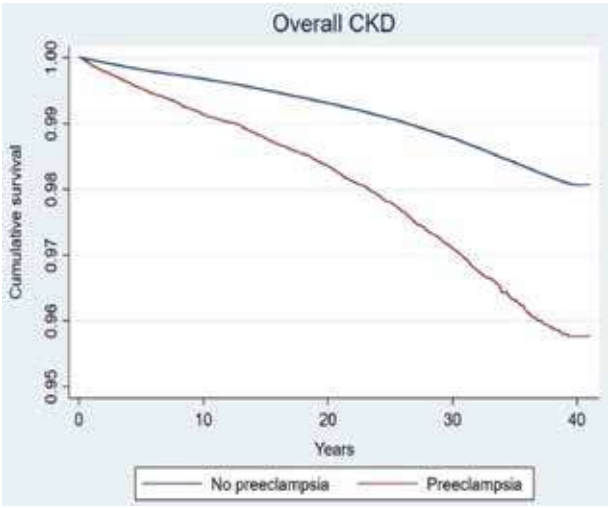


Figure 3.
The risk of developing CKD is related to the presence of preeclampsia during pregnancy

The first retrospective cohort study focused on pre-term delivery and found that women who had at least one preterm delivery before the 37th gestation week had a 39% higher risk of developing CKD during follow-up and more than double the risk of developing ESKD. These associations were stronger for women who had at least one extremely pre-term delivery (before 28 weeks gestation) or if they experienced pre-term preeclampsia. The next cohort study sought to measure whether women who experienced stillbirth have an increased risk for future kidney disease. The results showed that women who had at least one stillbirth had a modestly increased risk for CKD during follow-up and more than double the risk for ESKD over time. The third study investigated whether women who experienced hypertensive disorders during pregnancy have an increased risk of developing CKD, including subtypes of kidney disease. It concluded that women who had preeclampsia exhibited almost four times higher risk of developing diabetic or hypertensive CKD during follow-up compared to women who never had preeclampsia. More modest associations were observed for tubular interstitial disease and non-specific forms of CKD.

The most recent epidemiological study conducted by Barrett et al. focused on gestational diabetes and the long-term risk of CKD and ESKD, including subtypes of renal disease. It showed that subjects who had gestational diabetes alone and never developed type 2 diabetes had no significant risk of future kidney disease. On the other hand, women who went on to develop type 2 diabetes following pregnancy had a significantly higher risk of both CKD and ESKD, suggesting that gestational diabetes itself is not an independent risk factor.

Further research is needed to determine whether adverse pregnancy outcomes would add incremental value to existing clinical risk prediction tools. Also, some research gaps remain in terms of the risk profile of women who experience multiple adverse pregnancy outcomes concurrently. Finally, the effects of intermediate variables like post-pregnancy hypertension, hyperglycemia, or dyslipidemia need further consideration.

Further readings

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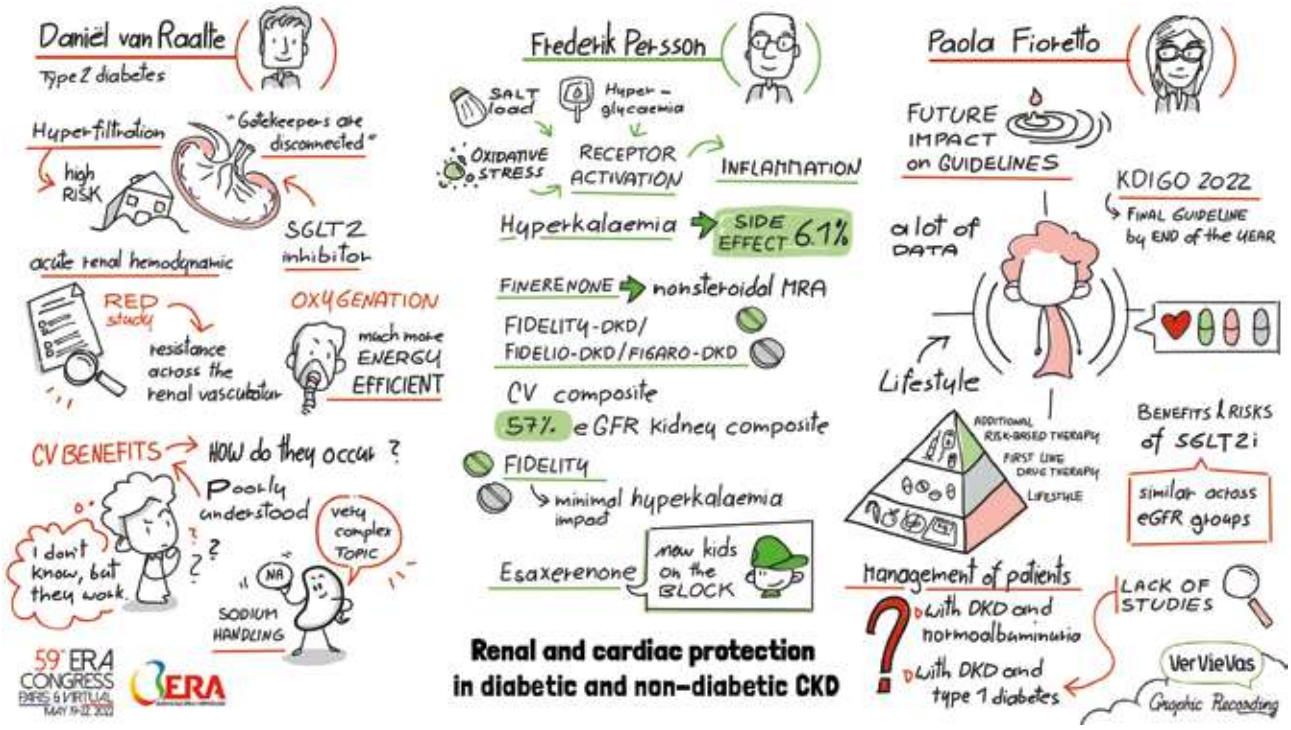
Written by Jasna Trbojevic-Stankovic.
All the speakers reviewed and approved the content.

Symposium 4.1
Renal and cardiac protection in diabetic and non-diabetic CKD



SGLT2 inhibitors: from bench to bedside for patients with cardiorenal disease

Daniël van Raalte, Netherlands

The strong connection between chronic kidney disease and cardiovascular disease poses a need for an approach that simultaneously addresses these issues. Sodium-glucose cotransporter-2 (SGLT2) inhibitors were initially introduced as glucose-lowering agents. Nevertheless, it was soon discovered that these drugs have immense kidney protective properties.

The renoprotective mechanism of SGLT2 inhibitors is still not completely unraveled, but clinical trials show an initial acute dip in GFR and its subsequent stabilization compared to the placebo groups. Upon cessation of treatment, the GFR values quickly return to the baseline, proving the kidney hemodynamic effect of SGLT2 inhibitors.

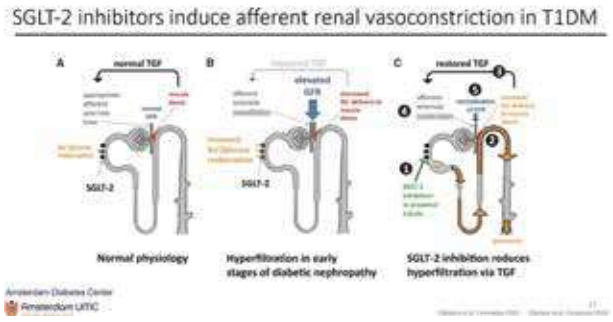


Figure 1.
Postulated tubuloglomerular feedback mechanisms in the normal nephron, early stages of diabetic nephropathy, and after SGLT2 inhibition (from ref. 1)

The study by Cherney et al. on type 1 diabetes (T1D) patients with hyperfiltration proved that SGLT2 inhibitors induced an immense efferent arterial constrictive response, which was suggested to be their renoprotective mechanism. The Amsterdam trial, led by Van Bomel, concluded that similarly to renin-angiotensin-system (RAS) blockers, the SGLT2 inhibitors in people with type 2 diabetes (T2D) provide post-glomerular vasodilation that induces the drop in GFR. A similar trial was

conducted by the German group, led by Ott and Schmieder. It observed a reduction in vascular resistance and concluded that post-glomerular vasodilation is the underlying mechanism of hemodynamic function change in T2D patients.

Another two potentially protective mechanisms are currently being explored, both of which are linked to kidney energy metabolism and oxygen availability. Since the SGLT2 inhibitors shift the metabolism toward the usage of ketones from fatty acids rather than glucose, the research is based on the hypothesis that SGLT2 inhibitors make the kidney more energy efficient by altering the energy metabolism. The central hypothesis of SGLT2 inhibitors' cardiovascular benefits, on the other hand, focuses on hematocrit. SGLT2 inhibitors induce natriuresis and osmotic diuresis, which in turn reduce plasma volume and consequently increase hematocrit. Nevertheless, numerous facts call this hypothesis into question. The DAPASALT trial recently evaluated the effects of dapagliflozin on sodium excretion, 24-h blood pressure, and extracellular, intracellular, and plasma volumes in patients with type 2 diabetes and preserved kidney function. It showed that dapagliflozin reduced blood pressure unrelated to urine sodium excretion during standard sodium intake, suggesting that factors other than natriuresis and volume changes may contribute to the blood-pressure-lowering effects.

Future research into the effects of SGLT2 inhibitors on cardiorenal illness is anticipated to focus on combination therapy involving finerenone, GLP-1 receptor agonists, and endothelin receptor antagonists, with the issue of putting together combined medication guidelines waiting ahead. Another unmet need is the use of SGLT2 inhibitors to protect the kidneys of patients with T1D, with an emphasis on euglycemic diabetic ketoacidosis mitigation strategies.

Novel mineralocorticoid receptors antagonists: an update of mechanisms and recent trials

Frederik Persson, Sweden

The mineralocorticoid receptors (MR) are present in many different tissues, including the kidney. They play a key role in blood pressure regulation and electrolyte homeostasis. By binding either aldosterone or cortisol, and together with a range of different cofactors, MR affect different processes. They are essential for maintaining electrolyte homeostasis, but their overactivation contributes to inflammation and fibrosis that are associated with long-term chronic conditions, such as diabetes or hypertension. Furthermore, the high salt load of the western diet increases the renal MR expression, eventually leading to heart and kidney damage.

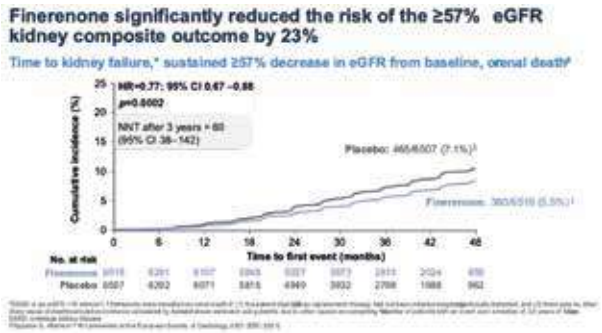


Figure 2.
The impact of finerenone on kidney function

Developing a selective mineralocorticoid antagonist to prevent these effects has been a long-term endeavor. The two already established mineralocorticoid antagonists, spironolactone and eplerenone, still have not shown any hard outcomes for CKD. Some smaller studies analyzing the effect of spironolactone in diabetic nephropathy exhibited positive effects, but they were never included in CKD guidelines. Eplerenone/enalapril in diabetic hypertensive patients with proteinuria showed a significant reduction of albuminuria but was often discontinued due to hyperkalemia, a known side effect of mineralocorticoid antagonists.

Finerenone, the new selective nonsteroidal mineralocorticoid antagonist, selectively blocks MR overactivation which contributes to inflammation and fibrosis, leading to kidney and cardiovascular (CV) damage. In the FIDELIO-DKD trial finerenone slowed CKD progression and improved cardiovascular outcomes in patients with CKD and type 2 diabetes. The FIDELITY analysis pooled the data from the FIDELIO-DKD and FIGARO-DKD trials and measured the CV (time to CV death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization due to heart failure) and the renal outcomes (time to kidney failure, sustained ≥57% decrease of eGFR from baseline or renal death). Finerenone significantly reduced the risk of the composite CV outcome by 14%, and the risk of the kidney composite outcome by 23%.

Finerenone showed no effect on HbA1c, no sexual side effects, a modest impact on blood pressure, and increased hyperkalemia but with minimal clinical repercussion. The 438 subjects in the FIDELITY analysis who were on combined therapy with SGLT2 inhibitor and finerenone showed no difference in the renal outcome and no increase in potassium. The combination is approved by the FDA and EMA and has recently been included in the guidelines of the American Diabetes Association (ADA).

The future of exploring finerenone effects lies in two new trials: the CONFIDENCE trial, which studies the combination of finerenone and an

SGLT2 inhibitor – Empagliflozin, and the FIND-CKD trial, looking at the slope of eGFR as the primary outcome in non-diabetic CKD patients. Also, two large outcome trials using the spironolactone in hemodialysis patients, the ALCHEMIST, and the ACHIEVE studies, are currently in the pipeline.

New kidney protective drugs: how do they impact the guidelines

Paola Fioretto, Italy

In the last years, two classes of glucose-lowering agents, the SGLT2 inhibitors and the glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been demonstrated to exhibit cardio and nephroprotective effects. This led to the inclusion of SGLT2i and GLP-1RA in the guidelines of diabetes, nephrology, and cardiology societies.

Since the publication of guidelines from the ADA and the European Association for the Study of Diabetes (ESC/EASD), along with the cardiology and the 2020 KDIGO guidelines for diabetes management in CKD, several very important clinical trials with SGLT2i and finerenone have been published. There are no new completed trials with GLP-1RA but several are expected in the coming years.

The results of the latest studies have been taken into consideration in ADA 2022 Standards of Medical Care, which include several treatment options for patients with T2D and CKD. The KDIGO guidelines underwent a major revision of the clinical data and a draft of the new 2022 version is already prepared and released for public review.

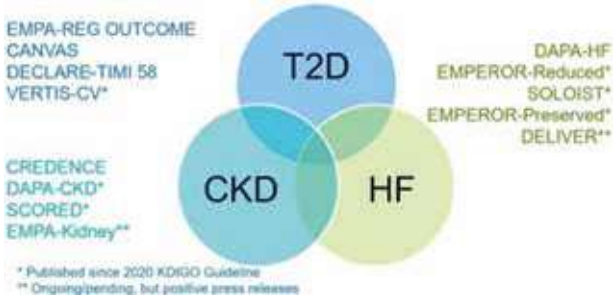


Figure 3.
Major clinical trials of SGLT2 inhibitors

The new KDIGO guidelines suggest that diabetic patients, in general, are to receive RAS blockade and statins, and patients with T2D should be treated with SGLT2 inhibitors and metformin. The major difference from the 2020 KDIGO guidelines is that the eGFR threshold at which SGLT2 inhibitors can be used is lowered to 20mL/min. Patients with T2D who have not achieved individualized glycemic targets or are unable to use metformin and/or SGLT2 inhibitors may receive GLP-1RA, especially if they are also overweight. A non-steroidal MRA with proven kidney or CV benefit is also recommended in T2D patients with an eGFR ≥25mL/min, normal serum potassium, and albumin to creatinine ratio >30mg/g on the maximum tolerated dose of RAS inhibition. If blood pressure is not well controlled, both type 1 and type 2 diabetes patients should be treated with dihydropyridine calcium channel blocker and/or diuretic, and in case of resistant hypertension, steroidal MRA is introduced if eGFR ≥45mL/min.

Nevertheless, there are still some open questions, requiring more data and more studies to be resolved. The first one is how to manage patients with diabetic kidney disease, low eGFR, and normoalbuminuria. The other question is the efficacy and safety of SGLT2i in kidney transplant recipients, and finally the management of T1D patients with diabetic kidney disease. In the last years, clinical trials with SGLT2 inhibitors, and now also with finerenone, have demonstrated that the progression towards end-stage renal disease in patients with T2D can be delayed even further from results achieved with RAS blockade. Thus, if this treatment is applied to patients with T2D and CKD, the trajectory of GFR loss may be changed, to approach what is considered the physiologic loss of GFR associated with aging.

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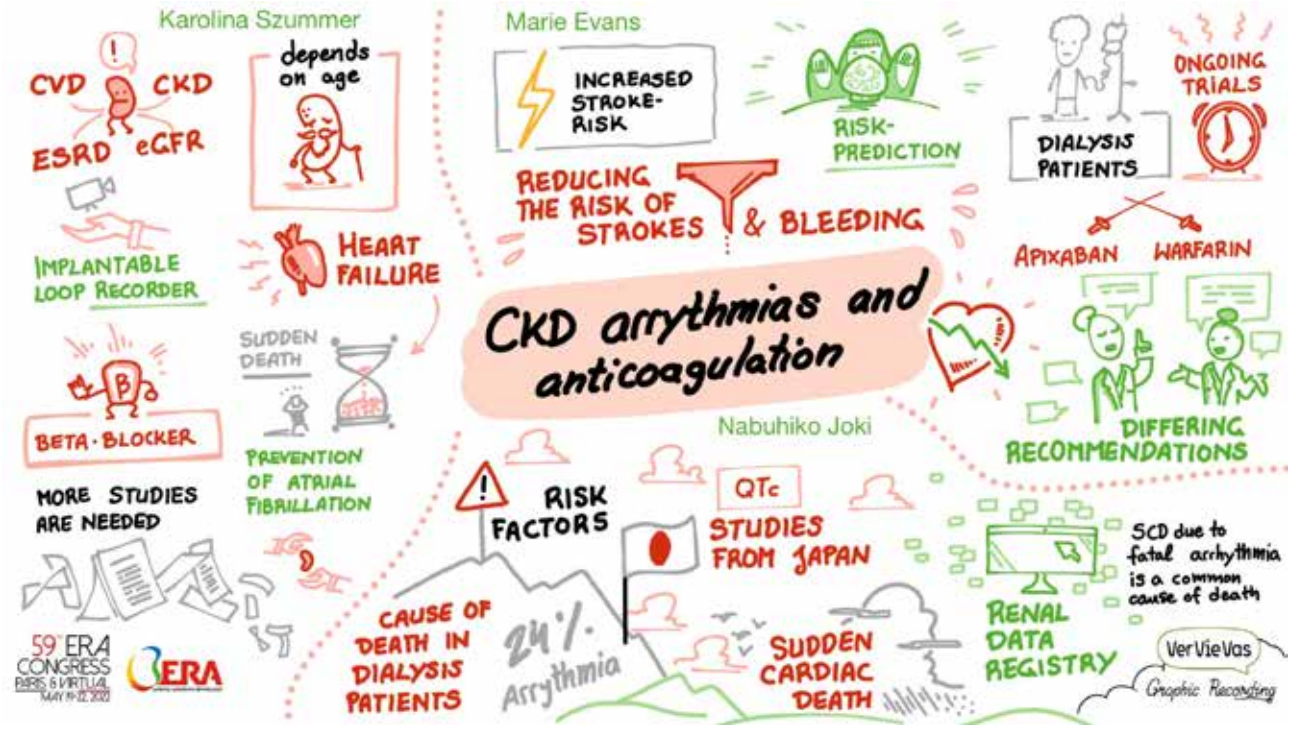
Written by Jasna Trbojevic-Stankovic.
All the speakers reviewed and approved the content.

Symposium 5.1
CKD Arrhytmias and Anticoagulation



Arrhythmias and heart failure in CKD and ESKD

Karolina Szummer, Sweden

Chronic kidney disease (CKD) progression is often associated with structural and functional alterations of the heart. Renal patients commonly exhibit an elevated cardiovascular risk manifesting as ischemic heart disease, heart failure, arrhythmias, and sudden cardiac death. Arrhythmias are notably more common in CKD patients compared to the general population, even the elderly. Numerous mechanisms are involved in the occurrence of CKD-associated arrhythmias, including uremia, electrolyte imbalance, diabetes, inflammation, myocardial structural alterations, coronary artery disease, disturbed left ventricular function, left ventricular hypertrophy, and repolarization.

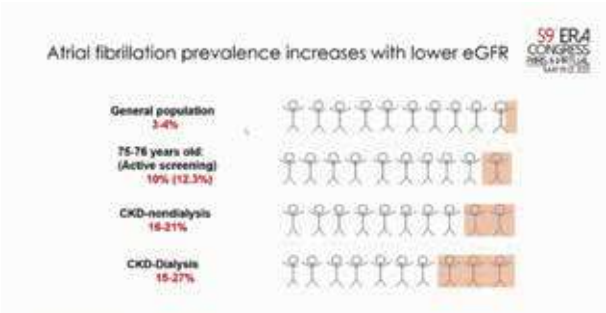


Figure 1.
The prevalence of atrial fibrillation in the general and the CKD population

Atrial fibrillation (AF) is generally considered the most common type of arrhythmia in this population, but ventricular tachycardia, bradyarrhythmias, and AV blocks can also be present. A recent study by Kim et al. showed that lower eGFR, and particularly albuminuria, were consistently associated with a higher prevalence of AF and nonsustained ventricular tachycardia. Another study by Sacher et al. identified potassium >5.0 mmol/l to be associated with a higher risk for conduction disorder, and potassium <4.0 mmol/l with a higher risk for ventricular arrhythmias in hemodialyzed patients.

CKD patients also exhibit structural and functional left- and right ventricular abnormalities, with or without changes in left ventricular (LV) ejection

fraction. eGFR is directly associated with LV ejection fraction, right ventricular systolic function, and death due to heart failure in this population. The beta-blockers reduce mortality from sudden cardiac death in both predialysis and dialysis CKD patients with reduced LV ejection fraction and dilated cardiomyopathy. The recently introduced SGLT2-inhibitors also showed very promising results in reducing the risk of cardiovascular death or hospitalization for heart failure with or without preserved ejection fraction regardless of the presence of diabetes. Furthermore, it appears that treatment with SGLT2-inhibitors is also associated with a significantly lower risk of incident AF compared to placebo, but more research is needed to evaluate the clinical significance of this effect. The novel mineralocorticoid receptor antagonist, finerenone, also reduces the risk of new-onset AF and flutter and cardiovascular events with a favorable safety profile. Thus, heart failure treatment has an important role in preventing and reducing the frequency of arrhythmias in CKD and end-stage kidney disease (ESKD) patients, but more studies are needed to further explore clinical outcomes in these cohorts.

Anticoagulation in patients with CKD and ESKD

Marie Evans, Sweden

Atrial fibrillation (AF) is the most common arrhythmia worldwide. The risk of developing it is higher in males and increases with age. As many as one-third of dialyzed patients may develop AF and the condition is associated with a three-fold higher risk of cerebrovascular events, predominantly ischemic stroke. A similar risk level for cerebrovascular events is observed in CKD patients with AF. Therefore, the European Society of Cardiology (ESC) 2020 Guidelines strongly recommend introducing oral anticoagulant therapy (OAC) for stroke prevention in AF patients with CHA2-DS2-VAS scores ≥2 in men and ≥3 in women. This guidance is supported by the results of several randomized controlled trials which showed a consistent and significant stroke risk reduction with OAC. Nevertheless, the decision to introduce OAC should be evaluated cautiously and include several risk assessments, especially in the populations with a known high risk for bleeding. The risks for the thromboembolic event and bleeding should be assessed simultaneously with CHA2-DS2-VASc and rHAS-BLED scores before introducing OAC. The latest ESC guidelines also strongly favor the use of the novel direct OACs (DOACs) for stroke prevention in AF instead of the traditional vitamin K antagonists (VKA), except for patients with mechanical heart valves or moderate-to-severe mitral stenosis. This recommendation is based on the DOACs' higher efficacy and superior safety profile compared to VKA.

Still, the CKD population is highly specific and requires distinct evaluation. Firstly, in the most clinically relevant stages of CKD, the predictive performance of the majority of risk scores is poor. Therefore, the Modified CHADS2 score should be preferred for risk estimation in this population. Secondly, more than half of patients with CKD stages 4 to 5 exhibit an INR result within the therapeutic range <75% of the time, which is potentially associated with a higher risk of adverse events, including bleeding. Finally, warfarin treatment is associated with a higher risk of developing calciphylaxis, while its efficacy in CKD patients is ambiguous.

Among the currently available DOACs, dabigatran has the highest, and apixaban exhibits the lowest renal elimination. Their dependence on renal clearance and several troubling safety signals still impedes DOACs' use in Europe, while the FDA has allowed the use of apixaban in CKD, ESKD, and even dialyzed patients in the USA.

In the currently available studies, certain DOACs appear to be associated with a higher incidence of fatal or intracranial bleeding while exhibiting no substantial benefit in lowering the incidence of a new stroke, transient ischemic attack, or systemic thromboembolism compared to no anticoagulation. On the other hand, meta-analyses show that the DOACs exhibit similar benefits as warfarin in preventing all strokes and systemic embolic events without increasing the risk of major bleeding events among patients with CKD and AF. The several compelling ongoing trials (AXADIA, SAFE-D, DANWARD, ApiDP, AVKDIAL, SACK) are expected to provide a more specific answer to the remaining question of whether DOACs are efficient and safe in CKD patients.

Figure 2.
Regional differences in recommendations for DOAC use in patients with CKD (from ref. 9)

Sudden death in patients with ESKD

Nabuhiko Joki, Japan

Sudden cardiac death (SCD) is the leading cause of cardiovascular mortality among ESKD patients in most parts of the world. It is attributed to sudden fatal arrhythmias, such as ventricular tachycardia or fibrillation. Nevertheless, in Japan, the major cause of cardiac death is heart failure. One possible reason for this discrepancy might be the lack of a universally established and accepted definition of SCD in the clinical setting. However, recent lines of evidence suggest that similar to other countries, SCD might be more common in the Japanese dialysis clinical setting than previously thought.

Prolongation of the QT interval has been directly associated with ventricular arrhythmias and SCD. The risk factors for QT prolongation include age, female gender, existing cardiac condition or electrolyte disturbances, and certain medications. Among dialyzed patients, additional risk factors also involve hypokalemia, hypocalcemia, and cardiovascular disease, rendering this population especially vulnerable and disposed to SCD associated with QT prolongation. These patients already have a longer median corrected QT (estimated at a standard heart rate of 60 bpm) at the initiation of dialysis and it continues to prolong further during the time on dialysis.

The prolonged corrected QT (QTc) has been linked with incident cardiovascular events in middle-aged and older adults without prior cardiovascular disease. Each 10 ms increase in the QTc baseline is associated with growing incident cardiovascular events. Similar findings have been reported for hemodialyzed patients inspiring a national cross-sectional study among Japanese dialysis patients based on the Renal Data Registry from the Japanese Society for Dialysis Therapy. The authors tried to identify the factors associated with QT and its relationship with SCD in this population.

Nearly 230,000 hemodialyzed patients were enrolled. The selection included only patients with ECG data and no AF. All automatically measured QT intervals and heart rates were analyzed and QTcs were calculated with the Bazzet correction formula (Qtc = QT / RR). QTc>500ms was considered prolonged. The results showed a nearly normal distribution of Qtc and virtually no difference in mean Qtc between males and females. Patients with prolonged Qtc more often had diabetes, cardiovascular and/or cerebrovascular disease, lower serum albumin, calcium, transferrin saturation, and higher CRP.

The odds for prolonged Qtc increased linearly at predialysis serum calcium levels below 2.25mmol/L. A U-shaped association was observed between serum phosphorus and prolonged QTc, with the lowest odds at a serum phosphorus level of 1.45mmol/L. At serum phosphorus of 0.65mmol/L and 2.4mmol/L, the odds ratio was 1.5. Transferrin saturation (TSAT) was strongly and almost linearly associated with odds for QTc prolongation, whereas serum magnesium, PTH, and ferritin levels were only weakly associated with prolonged QTc.

The cross-sectional design of this study precludes the decision on the causal effects of investigated variables on prolonged QTc. However, further investigation is on the way to examine the association between QTc prolongation and cardiovascular disease in hemodialyzed Japanese patients.

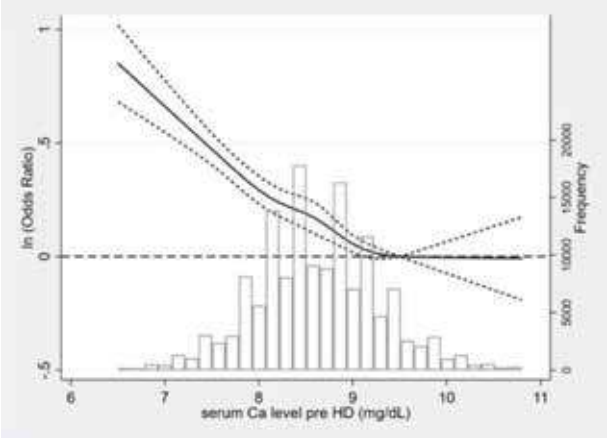


Figure 3.
Association between QTc>500ms and predialysis serum calcium levels

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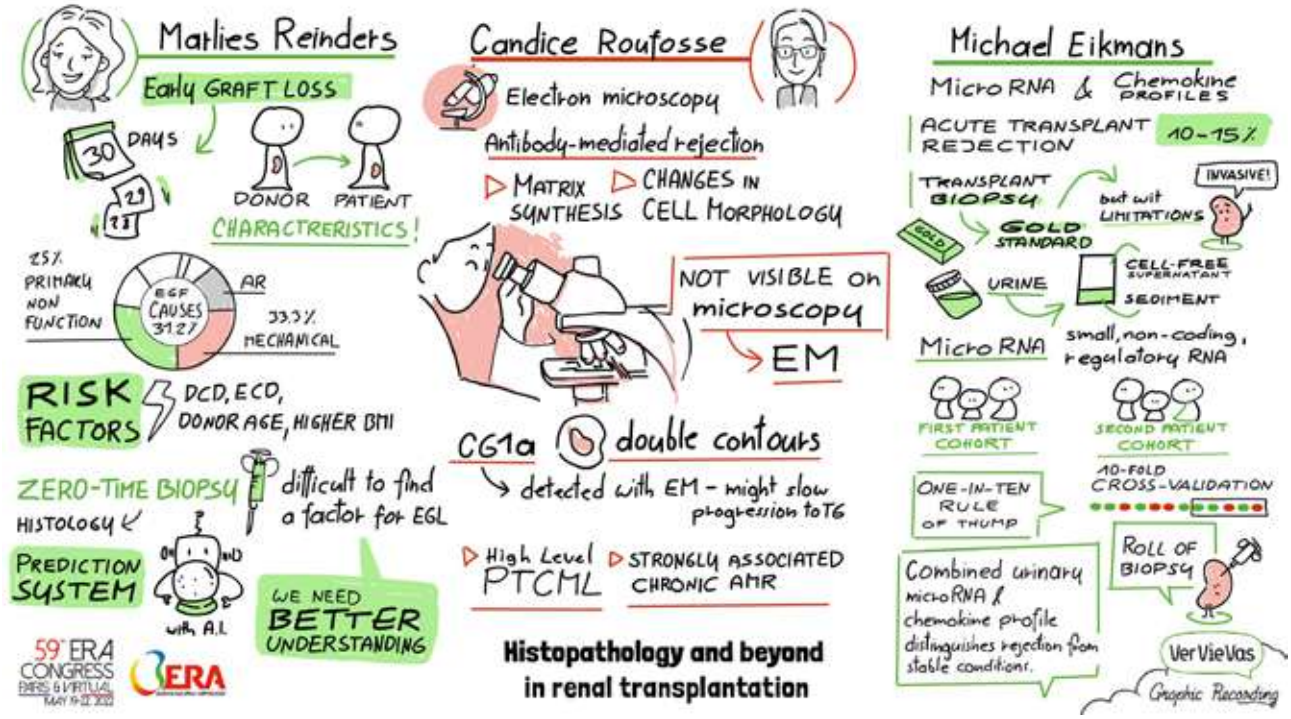
Written by Jasna Trbojevic-Stankovic.
All the speakers reviewed and approved the content.

Symposium 6.4
Histopathology and beyond in Renal Transplantation



Determination of early graft loss: what we learn from histopathological findings?

Marlies Reinders, Netherlands

Early graft loss (EGL) is defined as graft nephrectomy or permanent loss of kidney transplant function resulting in dialysis dependence or death up to one year after transplantation. A notable inconsistency in the definition of the period for EGL, ranging from 30 days to 1 year following transplantation hinders interstudy reproducibility.

The factors associated with EGL include organ quality, surgical factors, delayed graft function (DGF), and acute rejection, while late outcomes encompass graft and recipient factors, chronic rejection, diabetes, cardiovascular disease, recurrence of primary kidney disease, and adherence to immunosuppressive therapy. Recipients with EGL have 12 times increased risk of death within the first year. Current trends in the renal transplant population show a rising incidence of a transplant from deceased donors with circulatory death, higher body mass index and prevalence of diabetes among recipients, prolonged cold ischemia time, higher rate of panel reactive

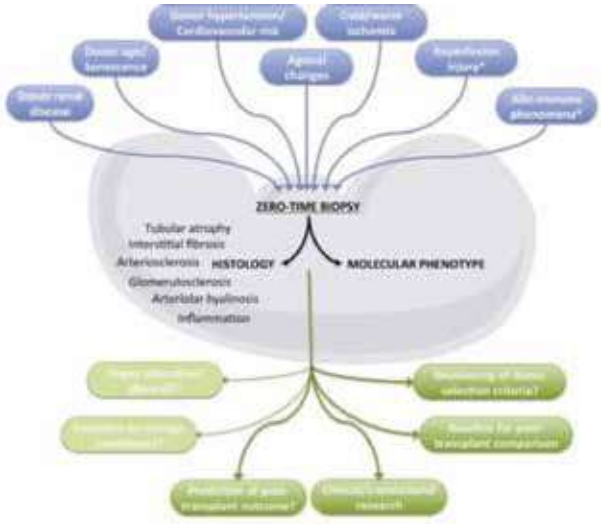


Figure 1.
Applications of performing zero-time biopsies and factors affecting histology and molecular phenotype (from ref. 6)

antibody, HLA mismatch, and DGF.

European data show a considerable improvement in terms of EGL from 1986 till 2000, but we witness a stagnation in the last decades thus calling for innovation in this field. Over half of the graft loss cases are due to recipient death, mainly caused by malignancy, infections, and cardiovascular disease. The major causes of graft failure include non-specific chronic injury, acute and chronic rejection, and mechanical injury. Graft loss within the first year of transplantation is mainly caused by mechanical injury, primary non-function, and acute rejection, while later failures are mostly related to non-specific chronic injury. A compelling number of lost transplants show overlapping histopathological features of multiple active and chronic lesions and their prevalence increases over time. Late loss is characterized by a high prevalence of arteriolar hyalinosis, interstitial fibrosis, and tubular damage.

The elderly recipients exhibit a 90% one-year survival, with infections and cardiovascular events being the major causes of death. The independent risk factors for death or graft failure in this population are arrhythmia, left-ventricular ejection fraction under 56%, HLA antibodies, a deceased donor from cardiovascular cause, and acute rejection. These results underline the importance of cardiac evaluation and immunosuppression optimization in this population.

Graft biopsies performed at the time of transplantation ("zero biopsies") provide valuable insight into risk factors for posttransplant events and serve as a baseline for comparison with posttransplant histology. However, the predictive performance of individual histological lesions and composite scores for the posttransplant outcome is at best moderate and no single histological lesion or composite score is sufficiently robust to be included in algorithms for kidney discard. Novel techniques, including single-cell genomics, should also be considered as a tool to detect potential therapeutic targets to prevent rejections in the future.

The importance of electron microscopy in diagnosing renal transplant rejection

Candice Roufosse, United Kingdom

Electron microscopy (EM) is extensively used in native kidney histopathological analysis which significantly contributes to correct diagnosis. On the other hand, it is only rarely applied in transplant kidney pathology unless recurrence of the native kidney disease is suspected.

The primary cause of kidney allograft loss is still chronic rejection, followed by death with a functioning allograft and primary kidney disease recurrence. Kidney allograft rejection can be classified into two types - T cell- and antibody-mediated rejection (AMR) representing two out of six categories from the Banff 2013 classification of allograft pathology. EM can provide useful information for AMR diagnosis, but also in BK-virus nephropathy, recurrent disease, and de novo glomerulopathy.

The characteristic light microscopy histopathological features of AMR include microvascular inflammation, presenting as glomerulitis and peritubulitis with or without positive staining for the C4d component of the complement. However, alterations at the cellular level, such as changes in cytoskeleton and cell morphology, as well as matrix synthesis can only be detected with EM. The distinctive AMR features seen with EM in the glomeruli include double contours of capillary walls associated with

endothelial widening (cg1a) and in tubulointerstitium, peritubular capillary basement membrane multilayering (PTCML). The combination of EM glomerular endothelial cell swelling, subendothelial electron-lucent widening, and early glomerular basement duplication, with or without C4d positivity, is strongly associated with AMR. These EM-only features precede double contours visible by light microscopy and their timely treatment might attenuate the progression of transplant glomerulopathy (TG) associated with AMR. Progression from EM-only cg1a to more severe cg may be a useful surrogate endpoint when developing novel treatments for AMR.

The EM presentation of PTCML is characterized by a growing number of peritubular capillaries basement membrane layers. Studies have confirmed a strong association between the presence of high-level PTCML and AMR, but low-level PTCML should not be overlooked as it precedes chronic AMR. The current threshold for establishing

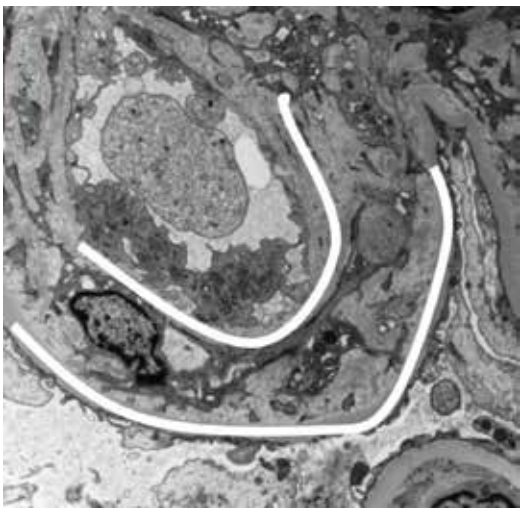


Figure 2.
Ultrastructural changes in a glomerular endothelial cell in AMR (multiplication of basement membrane marked with white lines)

The EM presentation of PTCML is characterized by a growing number of peritubular capillaries basement membrane layers. Studies have confirmed a strong association between the presence of high-level PTCML and AMR, but low-level PTCML should not be overlooked as it precedes chronic AMR. The current threshold for establishing chronic active AMR is at least one peritubular capillary with ≥7 basement membrane layers or at least two with ≥5 layers. However, in transplanted patients with donor-specific HLA antibodies, the presence of higher levels of PTCML (>2.5 layers) in a biopsy specimen around one-year post-transplantation is predictive of future TG.

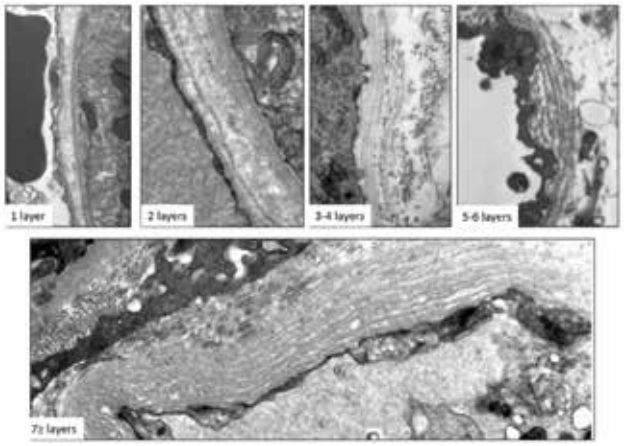


Figure 3.
Peritubular capillary membrane multi lamination in AMR

MicroRNA and chemokine profiles in urine to identify renal transplant rejection

Michael Eikmans, Netherlands

Around 10-15% of kidney transplant patients develop acute rejection (AR). The main histopathological patterns of AR include mononuclear cell infiltrate, tubulitis, and sometimes even vasculitis. AR is commonly diagnosed based on the sudden decline in estimated glomerular filtration rate, and graft biopsy is the gold standard for the diagnosis. However, the major limitations of this procedure are invasiveness, sampling errors, and inter-individual variations. Thus, there is an unmet need for noninvasive tools for the timely diagnosis of AR.

A recent study explored an integrated approach to diagnosing AR consisting of a combination of serum creatinine, graft biopsy, and urine biomarkers. Urine samples were taken at transplantation and centrifuged to determine the levels of CXCL-9 and CXCL-10. Both CXCL-9 and CXCL-10 are inflammatory chemokines, previously shown to be actively involved in AR. Urine sediment was also analyzed for microRNAs (miRNA). MiRNAs are small, highly conserved non-coding RNA molecules involved in the regulation of gene expression. Due to their prolonged stability compared to standard RNA, miRNAs represent a compelling target for biomarker research. The pilot study for miRNA screening included 31 patients transplanted between 2007 and 2015, of whom 15 had AR. This was followed by a validation study on another 140 patients transplanted in the same period, of whom 90 had AR. In the pilot study, several miRNAs exhibited higher or lower levels in patients with AMR compared to the other group. In the validation study, a total of 15 miRNAs were tested in urine and some of them showed different expression between the AR and non-AR groups. Specifically, miRNA-155-5p exhibited significantly higher, while miRNA-615-3p exhibited significantly lower levels in patients with AR. Both CXCL-9 and CXCL-10 levels were significantly higher in the AR cohort. Further multivariate analysis identified a combination of two miRNAs and CXCL-9, with or without recipient age to have the highest sensitivity and specificity in predicting AR. Further cross-validation tested the model's ability to predict new data that was not used in the initial estimation. The stratified 10-fold cross-validation showed similar results as the initial model, thus confirming its reliability.

The study concluded that the combination of urinary miRNA- and chemokine profiles successfully distinguishes kidney transplant rejection from stable transplant conditions. Further investigation should address the adequate frequency of transplant biopsies to timely detect rejection episode and define how much in advance a particular analyte predict the first signs of rejection. The specificity of biomarkers in distinguishing rejection from infection should also be evaluated.

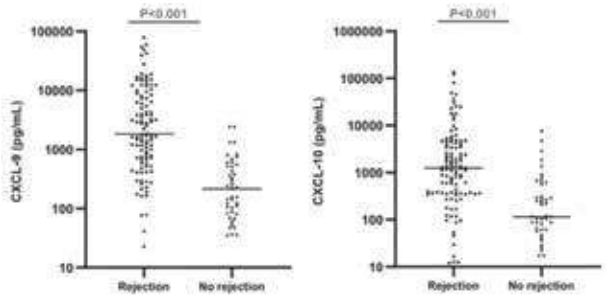


Figure 4.
Urine levels of CXCL-9 and CXCL-10 in transplanted patients with and without AR (from ref. 15)

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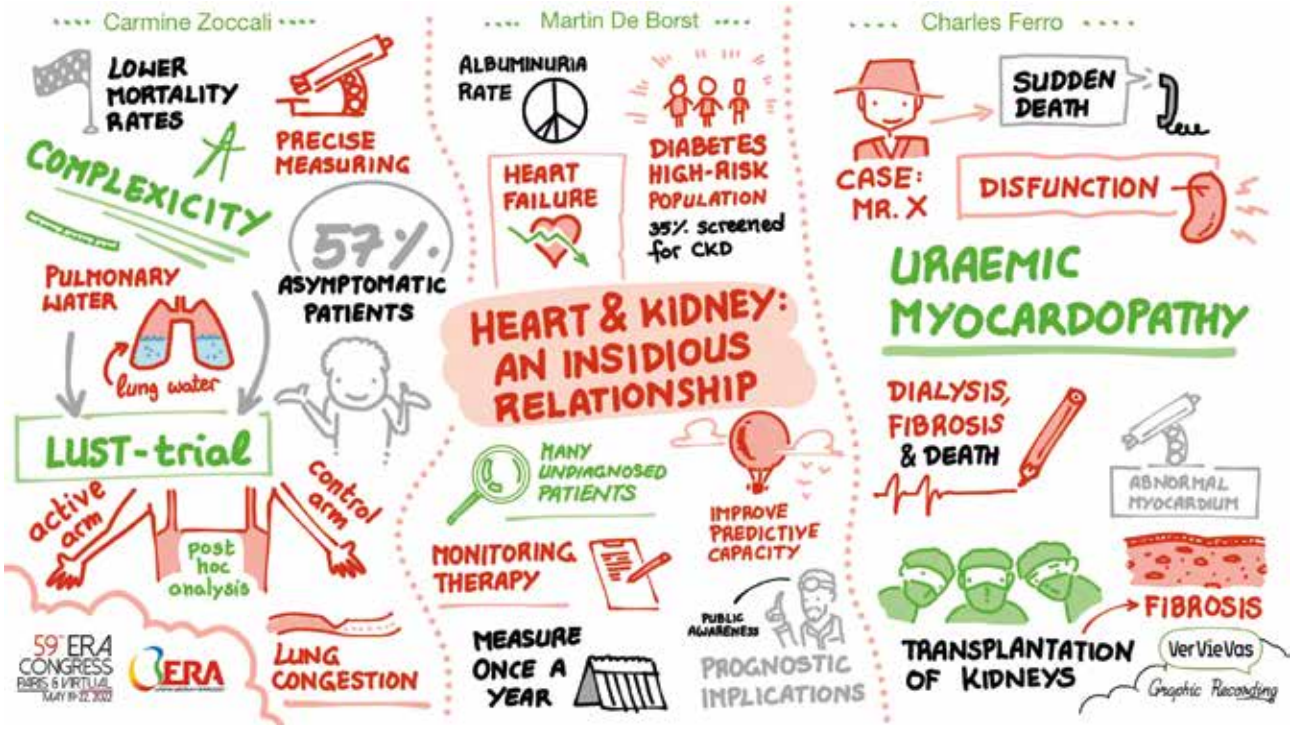
Symposium 7.1
Heart and Kidney: an insidious relationship



Lung congestion in chronic kidney failure

Carmine Zoccali, Italy

Despite many available dialysis-related performance measures, there is still none addressing fluid volume and cardiac status. The available fluid volume indicators, such as symptoms, vena cava diameter, and radio-isotopic methods, are either unreliable or impractical. The body impedance assessment (BIA) is the most commonly used measure of whole-body fluid, but it does not provide insight into a fluid burden in the lungs. Lung ultrasound (LUS) has recently emerged as a possible objective measure of fluid overload in dialysis patients.

The optimal fluid volume depends on extracellular fluid volume and cardiac function, which is represented by left ventricular (LV) filling pressure. LV filling pressure is a surrogate measure of LV preload and operating compliance and corresponds to the alveolar capillary pressure. High pulmonary capillary pressure increases extravascular lung water, which can be detected by the presence of comet-tail artifacts (the so-called B-lines) on the LUS image. The number of B-lines is proportional to alveolar capillary pressure and the degree of lung congestion.

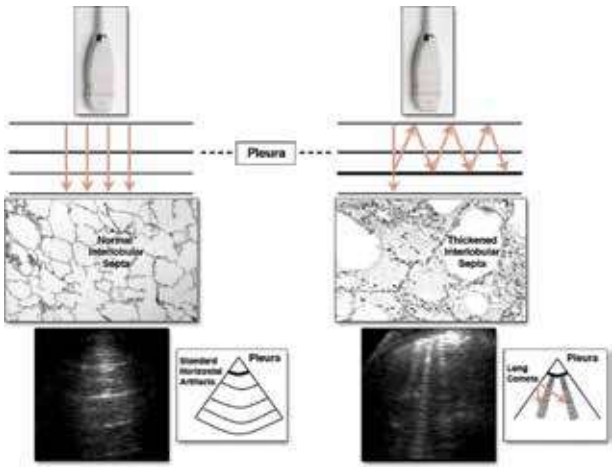


Figure 1.
Ultrasound in normal lung and pulmonary congestion: the image from the normal lung surface contains horizontal A-line artifacts, while the so-called B-lines indicate the presence of interstitial edema (from ref. 1)

Early detection of pulmonary congestion is of fundamental importance in dialysis patients. One of the first studies evaluating LUS as a tool for early diagnosis of fluid overload in the dialysis population found that the vast majority of hyperhydrated dialysis patients were completely

asymptomatic. The number of B-lines poorly correlated with hydration status measured by BIA, suggesting that the crucial factor underlying lung congestion was LV dysfunction and LUS was able to capture this congestion at a pre-clinical stage. Furthermore, pulmonary congestion in hemodialysis patients was strongly and independently associated with cardiac events and mortality.

A recent international, multi-center randomized controlled trial investigated whether an LUS-guided treatment strategy improved a composite endpoint (all-cause death, non-fatal myocardial infarction, decompensated heart failure) vs usual care in patients receiving chronic hemodialysis with high cardiovascular risk. Three hundred and seven patients completed the study, 152 in the active and 155 in the control arm. During a mean follow-up of 1.5 years, lung congestion was significantly more frequently relieved in the active than in the control arm and the intervention was safe. The primary composite endpoint, the risk for all-cause and cardiovascular hospitalization, and the changes in LV mass and function did not significantly differ between the groups. Thus, in patients on chronic hemodialysis with high cardiovascular risk, a treatment strategy guided by LUS effectively relieved lung congestion but was not more efficient than usual care in improving the overall outcomes. A larger trial focusing on decompensated heart failure in hemodialysed patients is still needed to validate the value of LUS in this population.

The importance of screening and assessment of kidney function in patients with heart failure and DM2

Martin de Borst, Netherlands

Effective screening strategies contribute to earlier disease detection ensuring timely treatment initiation, better disease control, and fewer or delayed complications. Unlike certain other diseases with established screening programs, there is still no consensus on whether health systems should prioritize early identification and intervention for chronic kidney disease (CKD), even though this condition does meet the World Health Organization principles for screening.

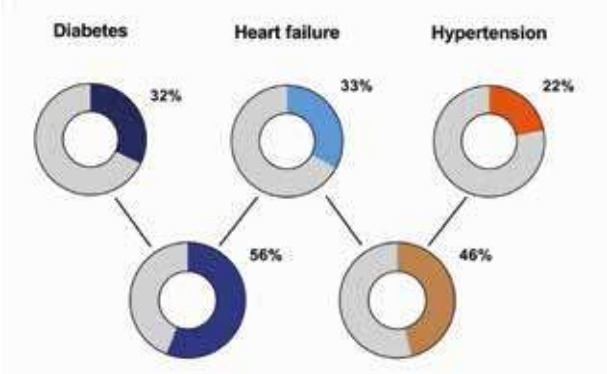


Figure 2.
Prevalence of increased albuminuria in high-risk populations (based on ref. 6)

Type 2 diabetes (T2D) and heart failure patients are at high risk for developing CKD. The prevalence of proteinuria in these populations is 32% and 33% respectively and reaches 56% in individuals with combined conditions. Nevertheless, according to the latest reports relying on data from very large international cohorts, only 35% of T2D patients and merely 4.1% of hypertensive patients are screened for albuminuria, and there is no data whatsoever for individuals with heart failure. Furthermore, screening was largely unrelated to the predicted risk of prevalent albuminuria. Nevertheless, there is strong evidence that the addition of creatinine-based eGFR and albumin-to-creatinine ratio significantly improves the discrimination of cardiovascular outcomes beyond traditional risk factors in the general population, especially in individuals with T2D or hypertension.

There are currently several lines of therapy available for patients with diabetic CKD. The choice is guided by the level of eGFR and the presence of albuminuria, thus presenting yet another argument for albuminuria screening in this population. Nevertheless, the cost-effectiveness of such a measure is still open to debate, even though large systematic reviews report results in favor of screening. The latest guidelines support this strategy and suggest at least annual eGFR and albuminuria assessment in T2D patients.

As for the patients with heart failure, the added benefit of albuminuria measurement might be less compelling since the treatment for the underlying disease is in line with measures directed at albuminuria. Nevertheless, this population could still benefit from the periodic assessment of kidney function.

Uremic cardiomyopathy – is it truly reversible by transplantation?

Charles Ferro, United Kingdom

Uremic cardiomyopathy represents cardiac remodeling that occurs in CKD patients and is associated with high morbidity and mortality rates in this population. Even though the links between kidney disease, left ventricular hypertrophy and heart failure were recognized as early as the

19th century by Richard Bright, this particular finding was described 50 years ago. The current understanding of uremic cardiomyopathy describes the condition as a unique cardiovascular phenotype characterized by progressive heart muscle disease, increased arterial stiffness, atherosclerosis, and hypertension appearing early in CKD and progressing to diastolic and systolic dysfunction and myocardial fibrosis in end-stage kidney disease. Endomyocardial biopsies in hemodialysis patients with dilated cardiomyopathy without coronary artery disease revealed severe myocyte hypertrophy and interstitial fibrosis which was strongly associated with cardiac mortality. Non-invasive cardiac assessment with magnetic resonance (CMR) imaging using gadolinium to identify the presence of myocardial fibrosis identified two main myocardial pathologies in this population. Left ventricular hypertrophy was the predominant cardiomyopathy specific to uremia, while left ventricular dilation and systolic dysfunction were related to underlying ischemic heart disease. More recent studies used measurement of native T1 through CMR to avoid concerns related to gadolinium and nephrogenic systemic fibrosis in dialysis patients.

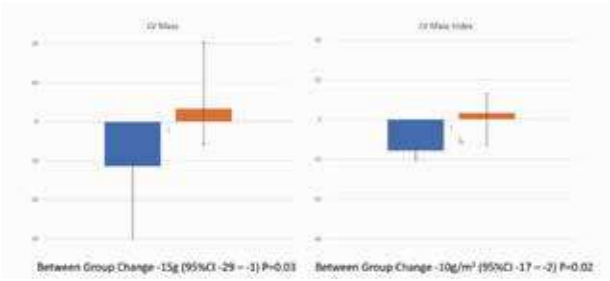


Figure 3.
Changes in left ventricular mass 12 months after transplantation (blue boxes) and in controls (orange boxes)

It was common grounds that these severe functional abnormalities of the heart could be reversed following transplantation. However, this idea relied on the results from small, opportunistic, and uncontrolled echocardiographic studies that were perpetuated in later review articles. A recent systematic review and meta-analysis challenged these assumptions by revising all studies published from 1950 to 2020 that evaluated left ventricular systolic and diastolic function with imaging modalities before and after renal transplantation. The review found poor methodological quality of evidence and no support for the belief that uremic cardiomyopathy is reversible by renal transplantation. These conflicting results urged the initiation of a prospective study of the effects of transplantation on CKD-associated cardiomyopathy using magnetic resonance imaging which started in 2018. It aimed to recruit 55 transplanted patients and 30 controls to detect a change in left ventricular fibrosis following kidney transplantation using T1 mapping CMR. The study was heavily impeded by the outbreak of COVID19, but the preliminary results show a significant decline in left ventricular mass one year after transplantation. Further research is expected to provide more evidence on this issue.

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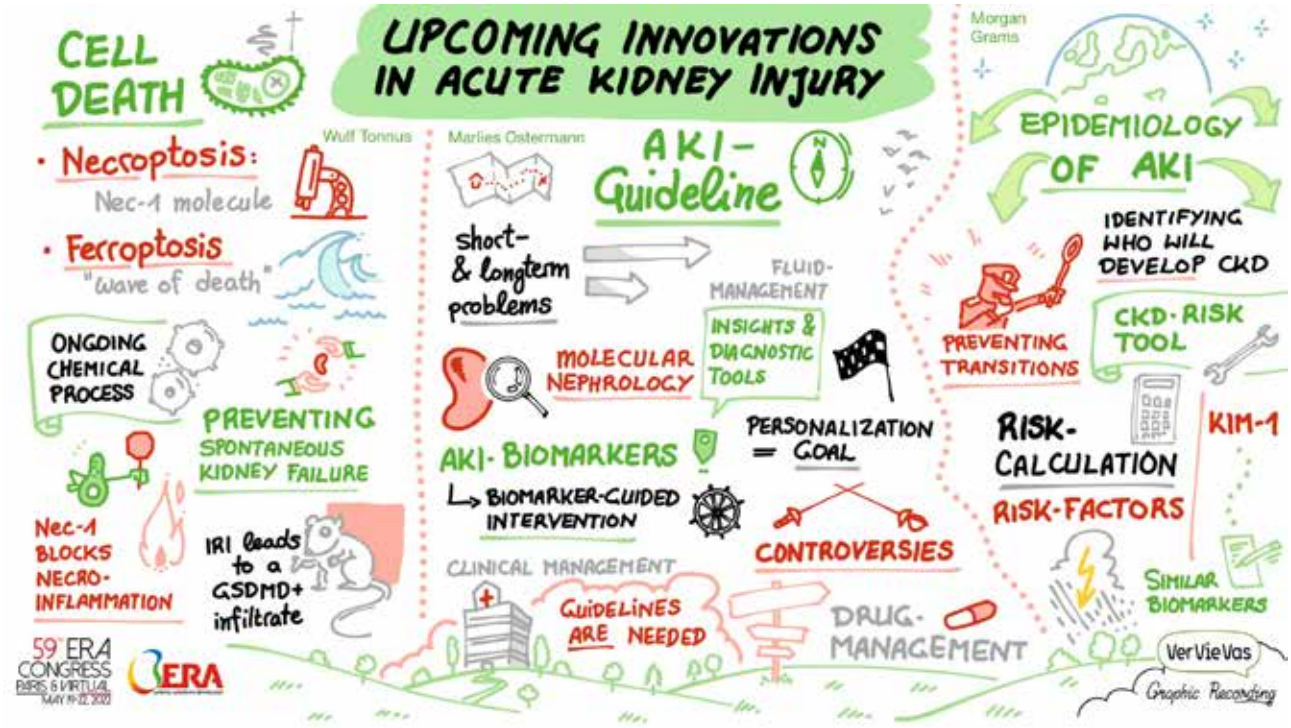
Symposium 8.1
Upcoming innovations in acute kidney injury



Deciphering the molecular mechanisms of necroinflammation in acute tubular necrosis

Wulf Tonnus, Germany

Cell death can occur in both physiological and nonphysiological conditions. Homeostasis is maintained by apoptosis, whereas most pathophysiologically important cell death is necrotic. Necrosis is defined as cell death by plasma membrane rupture, followed by a release of damage-associated molecular patterns (DAMPs) that trigger an immune response, referred to as necroinflammation. Regulated necrosis may come in the different forms including necroptosis, ferroptosis, and pyroptosis. These processes trigger a necro-inflammatory environment which may cause organ failure. Recent studies highlight these pathways as potential, but still neglected, therapeutic targets for the prevention of necrosis, inflammation, and organ failure.

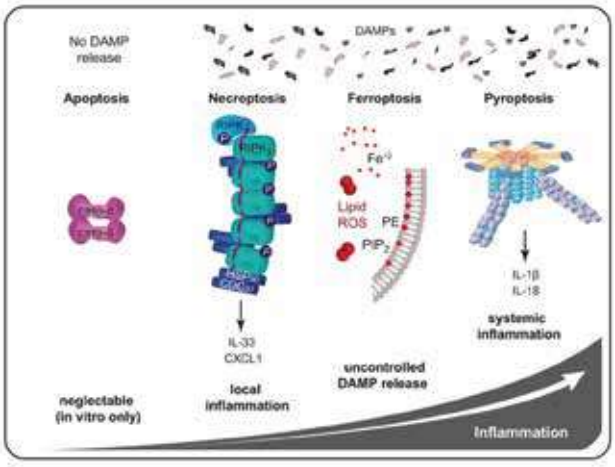


Figure 1.
Types of cell death and their pathways (adopted from: Sarhan M. et al., Physiological Reviews 2018)

The kinase RIPK3 and its substrate MLKL are crucial players in the necroptosis pathway. The phosphorylated MLKL translocates to the plasma membrane and mediates its rupture. Necroptosis was first linked with acute kidney injury (AKI) a decade ago through an observation that treatment with a highly specific receptor-interacting protein kinase 1 inhibitor, necrostatin-1, reduced organ damage and renal failure, even when administered after ischemia-reperfusion injury (IRI). Later studies

corroborated these findings in renal tissue samples from humans with AKI.

Ferroptosis is dependent on iron-mediated lipid peroxidation. The typical feature of a ferroptotic cell is a "wave of death", characterized by a progressive synchronized tubular necrosis, eventually resulting in the formation of granular casts. A lipophilic radical scavenger, ferrostatin-1 (Fer-1), was identified as an effective inhibitor of ferroptosis, blocking the "wave of death", thus attenuating tubular damage and decreasing serum urea and creatinine levels in renal IRI. Genetic evidence for ferroptosis in renal ischemic-reperfusion injury has been substantiated in both glutathione peroxidase 4 (GPX4)-deficient and ferroptosis-suppressor protein 1 (FSP1) knock-out mice. A significant breakthrough was achieved when a combined small molecule inhibitor (Nec-1f), which simultaneously targets necroptosis and ferroptosis and improves survival in mouse models of ischemia-reperfusion injury in AKI, was generated. Nec-1f also reduces the influx of F4/80+ macrophages; thus, ameliorating inflammatory responses related to the IRI.

Pyroptosis is a highly inflammatory form of regulated necrosis and the most potent known trigger of the immune system. Its execution requires caspase activation for cleavage of proinflammatory cytokines IL-1B and IL-18, and gasdermin D (GSDMD). GSDMD is an effector for pyroptosis downstream of the inflammasome signaling pathways and its cleavage leads to the destruction of the cell membrane and lytic cell death. While healthy tubular cells do not express GSDMD, tubular necrosis following IRI leads to a GSDMD-positive infiltrate which is associated with higher tubular damage scores, and increased serum urea and creatinine levels.

These novel pieces of information shall be helpful for clinicians as new inhibitors of necroptosis (necrostatins), ferroptosis (ferrostatins), and inflammasomes are expected to emerge in future clinical trials.

What is to come in the next KDIGO AKI guideline?

Marlies Ostermann, United Kingdom

The previous KDIGO AKI guideline, issued a decade ago, relied on evidence from over 18,000 studies and represented a landmark that steered both clinical practice and research. These guidelines covered four major areas: diagnosis, staging, and risk assessment; prevention and treatment of AKI; drugs and contrast-induced AKI; and dialysis interventions for AKI treatment. The insight into AKI mechanisms, and long- and short-term consequences, have since evolved, thus necessitating an update to inform clinical practice and guide the allocation of health resources.

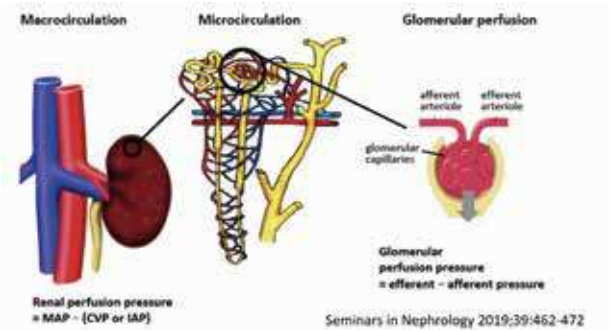


Figure 2.
Relationship between mean arterial pressure (MAP) and renal perfusion pressure

AKI is considered a multifactorial condition with variable presentation and outcomes. The underlying pathophysiology may differ even in patients with similar manifestations of the disease. The knowledge of fundamental molecular mechanisms has also expanded recognizing many separate AKI subtypes with distinct patterns of molecular markers of tubular injury, functional dysfunction and trajectories. Many new biomarkers of AKI stemming from different parts of the nephron have been discovered and assessed. Some of them may even predict the development and outcomes of AKI, thus supporting the reassessment of the concept and incorporation of biomarkers in the definition of AKI. It has also been observed that patients with similar serum creatinine levels may have substantially different underlying renal function and hence the risk of developing AKI under certain circumstances. This finding warrants introducing renal function reserve as a novel risk factor for AKI. Measuring patients' renal functional reserve preoperatively offers opportunities to identify those who may benefit from specific preventive measures.

The new AKI guidelines are expected to address the many previously not covered AKI-related issues, such as the newly developed terminologies and defining criteria for recovery from AKI. They are also expected to incorporate new diagnostic and monitoring tools, including potentially e-alerts and digital health. Therapeutic interventions should also be addressed and more precisely described. Several fluid studies have been conducted in the last 10 years with conflicting results on the optimal timing, amount, and fluid type to prevent and treat AKI, as well as on the type and timing of vasopressors to maintain the mean arterial pressure (MAP). Furthermore, the target MAP to support adequate renal function is also elusive, especially since the relationship between the MAP and renal hemodynamics is complex. Very likely, there can be no universal

answer to these questions. It is possible that individually tailored therapies targeted at preserving renal perfusion pressure, which is easily calculated from MAP and central venous pressure, might be the favored approach.

Contrast-induced AKI is another important issue where new evidence has evolved since the publication of the KDIGO guideline in 2012. It appears that the level of risk for developing this condition is decreasing with the growing use of modern contrast agents. Furthermore, recent studies have challenged the renoprotective effect of the commonly used saline, sodium bicarbonate, and/or N-acetylcysteine in the prevention of contrast-induced AKI. The future KDIGO guidelines should also examine the current concept of nephrotoxicity and address the fact that not all drugs that lead to a creatinine rise are indeed nephrotoxic. The timing, prescription, and duration of renal replacement therapy to treat AKI should also be elaborated on relevant to the abundance of recently published data on these points. Finally, the optimal principles of post-AKI follow-up are also expected to be specified in the anticipated new guidelines.

Identifying patients at risk of the AKI-to-CKD transition

Morgan Grams, USA

AKI is a common condition with higher incidence at older age. Outcomes after AKI hospitalization are poor, especially if patients required acute dialysis. In one study of older patients who survived AKI, as many as 70% progressed to chronic kidney disease (CKD). Moreover, approximately one-third of patients discharged after an AKI hospitalization are readmitted for AKI hospitalization in the next 24 months, presenting yet another risk for worsening kidney function.

The transition from AKI to CKD remains incompletely understood but involves numerous complex mechanisms. Animal models have implicated maladaptive repair as a major underlying factor, with cell death, endothelial dysfunction, tubular epithelial cell senescence, and inflammatory processes driving the transition. These alterations eventually may progress to scarring, with the secretion of profibrotic factors, collagen deposition, accelerated aging, and CKD.

Preventive therapy of the AKI-to-CKD transition may be most easily deployed during or after the AKI episode. Many suggest that renin-angiotensin-aldosterone system blockade could be helpful. Research on animal models showed that pre-AKI treatment with losartan prevented the development of proteinuria and creatinine clearance decline, while post-treatment with spironolactone prevented tubulointerstitial fibrosis, glomerulosclerosis, proteinuria, and decrease in renal blood flow.

Efficient targeting of AKI-to-CKD transition further requires timely identification of patients at risk of developing CKD. Several models that have been developed to predict risk for CKD occurrence in the general population may be helpful in the AKI setting as well. The Incident CKD Risk Tool predicts the risk of eGFR decline below 60 mL/min at 5 years based on demographics, comorbidities, body mass index, smoking history, current eGFR, and albumin to creatinine ratio. For patients with diabetes, the model also includes diabetes medications and HbA1c. The Risk of Decline in eGFR by 40% Tool uses similar, readily available patient characteristics to estimate the probability of eGFR decline within the next 3 years. Finally, the Kidney Failure Risk Equation estimates the risk of progression to end-stage kidney disease in 2 and 5 years based on age, sex, eGFR, albuminuria in people with eGFR below 60 mL/min/1.73 m2.. All these tools are user-friendly and publicly available online for everyday practice. Similar risk factors are relevant when assessing AKI-to-CKD transition. As seen in the recent ASSESS-AKI study, the strongest predictor of a 50% decline in eGFR in the post-AKI period was albuminuria and lower eGFR.

Biomarkers may add to risk prediction tools. Certain urine biomarkers correspond to specific kidney compartments, which may help distinguish the type of injury, and both blood and urine biomarkers have been investigated with respect to disease outcomes. For example, basic fibroblast grown factor (bFGF), N-terminal pro-B-type natriuretic peptide (NT-proBNP), kidney injury molecule-1 (KIM-1), and tumor necrosis factor receptor 1 (TNFR1)) biomarkers were predictive of the AKI to CKD transition following cardiac surgery. TNFR 1 and 2 as well as KIM-1 have also been tested in the general population, with evidence that they may add information to the current models for predicting CKD progression based on clinical variables

Figure 3.
The Incident CKD Risk Tool and the Decline in eGFR by 40% Risk Tool (available at ckdpcrisk.org)

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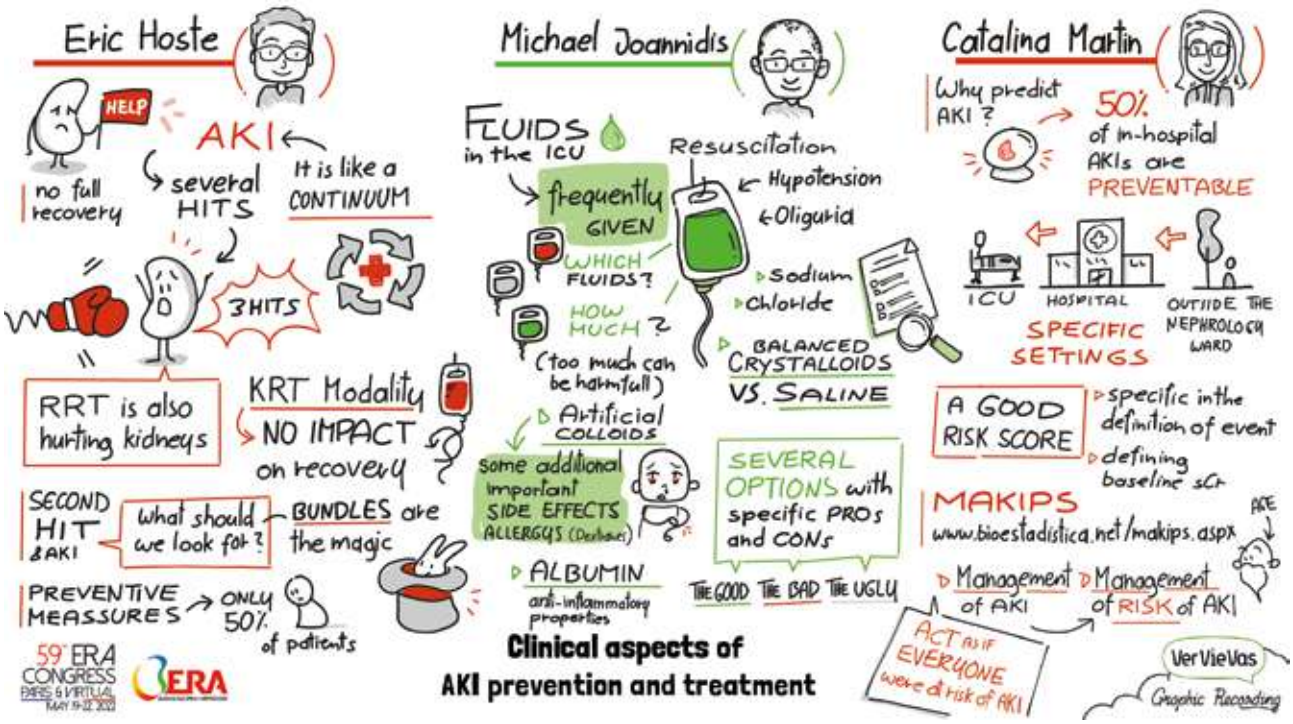
All the speakers reviewed and approved the content.

Symposium 8.3
Clinical aspects of AKI prevention and treatment



The second hit hypothesis – What should we look for?

Eric Hoste, Belgium

The KDIGO guidelines define acute kidney injury (AKI) based on the RIFLE criteria as an abrupt decrease in kidney function occurring over seven days or less and manifesting with an increase in serum creatinine accompanied by a decrease in urine output. The presence of AKI stage 1 or greater ≥7 days after the initiating event indicates a condition named acute kidney disease (AKD). The trajectory of AKD can take many forms depending on the severity of the initial AKI episode. One of the possibilities is the so-called "second hit" episode of AKI, when the initial deterioration lasting for at least 48 hours is followed by a period of sustained reversal, before the second episode of AKI ensues, leading to AKD. In some circumstances, as in COVID-19, in patients with acute myocardial infarction and cardiogenic shock, or those with multiple infectious complications, the primary injury can even be followed by more than one exacerbation. The common issue in all these cases is that a higher degree of kidney injury in single hits is associated with worse overall outcomes. Furthermore, renal replacement therapy (RRT), even adds to the risk of developing a decline in urine output, especially when more intensive protocols and

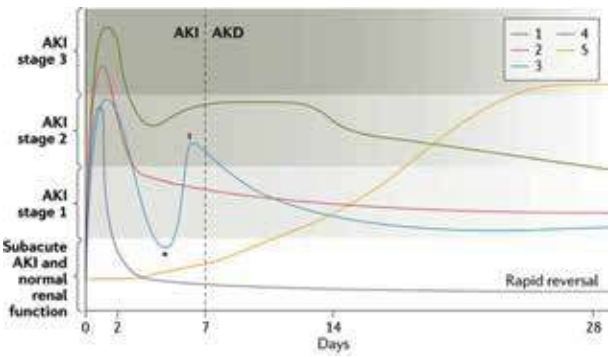


Figure 1.
Evolution of AKI into AKD – represented with a blue line is an episode of persistent AKI followed by a period of sustained reversal and then a second AKI episode (from ref. 1)

early initiation are implemented. A recently published analysis of randomized clinical trials involving critically ill patients with AKI treated with continuous, intermittent, or hybrid RRT hypothesized that RRT-related hypotensive episodes might also affect renal outcomes. However, the studies included presented such high heterogeneity in terms of outcome definitions and measurement that the conduction of the projected meta-analysis ended up being impossible. Nevertheless, a very interesting observation was made that there was no significant difference in the achieved hemodynamic stability and kidney survival related to different RRT modalities.

There are several possible approaches to preventing the second-hit AKI. The post-surgery "care bundles" recommended by the KDIGO include avoidance of nephrotoxic and radiocontrast agents, discontinuation of ACE inhibitors and ARBs for the first 48h after surgery, close hemodynamic monitoring, and optimization of volume status. These measures proved efficient in reducing AKI frequency and severity in high-risk patients after cardiac surgery. Further analysis of the treatment effects of individual bundle components identified hemodynamic optimization as the most powerful preventive measure. Regrettably, despite their simplicity, it appears that in clinical practice these preventive measures are seldom thoroughly followed. It is therefore essential to actively institute measures to hamper the second-hit AKI episodes, specifically focusing on the modifiable factors such as hemodynamic status, increased intra-abdominal pressure, and RRT.

Fluids in ICU – Which is the right one?

Michael Joannidis, Austria

Intravenous fluid therapy is among the most common interventions in critically ill patients. Fluids are administered for resuscitation, replacement, maintenance, and/or organ protection. The most frequent indications for resuscitation are hypotension and oliguria. The main considerations when planning intravenous fluid therapy should be the type and amount of solutions.

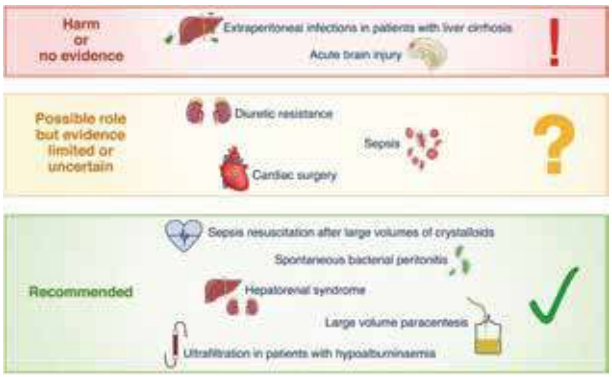


Figure 2.
Albumin therapy in critical care (from ref. 15)

Normal saline is the most often used crystalloid solution. Even though it is commonly called a „physiological solution", NaCl 0.9% has higher sodium and chloride levels than plasma, contains neither bicarbonates nor lactates, and can even induce metabolic acidosis and renal hypoperfusion. Nevertheless, in clinical practice, there has been no report of any marked long-term harm in critically ill patients receiving normal saline. Various balanced crystalloid solutions have been developed to overcome the disadvantages of normal saline, such as Ringer's lactate, Plasma-Lyte, and ELO-MEL Isoton. Nevertheless, even though they all have sodium and chloride levels closer to those of the plasma, the results of their application are conflicting. Some studies report only a moderate advantage of balanced solutions compared to normal saline in restoring hydration status and electrolyte balance. The Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) study concluded that the amount of fluid, rather than composition, was associated with favorable outcomes. Another study, however, stated a lower rate of the composite outcome of death from any cause, new RRT, or persistent renal dysfunction with the use of balanced solutions compared to normal saline. One of the largest trials comparing the effects of a balanced multielectrolyte solution and saline, which included over five thousand ICU patients, found no evidence that the risk of death or AKI was lower with the balanced solution, and serum creatinine levels over time exhibited a virtually identical pattern in both groups. Also, in this cohort, the rate of fluid administration seemingly made no difference.

Colloid solutions are another therapeutic option in critically ill patients. It is commonly believed that their administration would reduce the overall need for fluid as compared with the administration of crystalloids. In fact, this impact is only moderate, whereas their use is associated with potential adverse effects. Nevertheless, albumin administration in patients with cirrhosis and ascites may help prevent AKI and it does improve fluid removal by preventing intradialytic hypotension during RRT.

Identifying patients at high risk of in-hospital AKI

Catalina Martin, Spain

AKI is an important risk factor for new-onset CKD and is strongly associated with an increased risk of death in hospitalized patients. Therefore, early recognition of this common, but highly preventable condition, is of fundamental importance to improve the outcomes.

A good risk score should be simple, accurate, easily interpreted, and inexpensive. A good AKI risk score should be highly specific, externally validated, well-calibrated, digitizable, and able to discriminate between community- and hospital-acquired AKI, and between CKD and AKI. Despite a myriad of available risk scores for AKI associated with conditions requiring intensive care, there are very few such scores for non-critical patients and only one for community-acquired AKI.

Currently, there are four available models to predict hospital-acquired AKI in non-critically ill patients: by Bedford et al, by Martin-Cleary et al, by Segarra et al., and the Acute Kidney Injury Prediction Score (APS). All are based on historical serum creatinine, but they also incorporate 7 to 22 other variables to predict the development of AKI. For example, the Madrid Acute Kidney Injury Prediction Score (MAKPIS) by Martin-Cleary et al. contains 23 variables, obtainable automatically from electronic clinical records at admission, such as age, comorbidities, surgical interventions, and laboratory parameters (white blood cells, serum sodium, potassium, calcium, glucose, urea, and uric acid). The tool is freely available at http://www.bioestadistica.net/MAKIPS.aspx.

Until now there is no data on the impact of clinical implementation of the available AKI prediction scores. AKI management still relies on supportive therapy to optimize renal perfusion, preventive measures to minimize nephrotoxicity, and causal treatment when applicable. In the majority of cases, appropriate follow-up is still lacking. Therefore, future work should focus on timely AKI prediction based on baseline serum creatinine and age as the crucial parameters, as well as on the evaluation of AKI risk scores' significance in clinical practice.

Figure 3.
The MAKIPS acute kidney injury risk calculator

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Mini Lectures

Zebrafish larvae to study and treat glomerular diseases

Anna Iervolino, Italy

The zebrafish pronephros is a well-established model to study glomerular development, structure, and function since it contains the same cell types as humans and mice. Furthermore, the zebrafish larvae are optically transparent, allowing researchers to observe the processes in real-time. The filtration in the glomerulus begins two days post-fertilization, making this model highly relevant for the investigation of human glomerular kidney diseases. Several transgenic zebrafish models have been developed in the recent decade to examine glomerular disease by visualizing the podocyte body, monitoring the primary foot processes, and investigating renal progenitor cells. By using the Morpholino system to knock down specific podocyte markers, researchers discovered ultrastructural glomerular damage, proteinuria, edema, increased embryonic mortality, and deformities.

Focal segmental glomerulosclerosis (FSGS) was the focus of the research of the group from the University of Medicine in Greifswald. Although causative factors, such as mutations in key podocyte genes have already been identified, the pathogenic cause of the majority of FSGS cases is unknown. The group used a nitroreductase/metronidazole (NTR/MTZ) transgenic zebrafish model to achieve podocyte ablation and mimic FSGS. MTZ-treated larvae developed edema as a hallmark of the glomerular filtration barrier damage and severe proteinuria occurred due to podocyte apoptosis and progressive effacement of the foot process. Additionally, activation of proximal tubule-like parietal epithelial cells identified by ultrastructural cytomorphology, and expression of proximal tubule markers were observed. The glomeruli were then isolated from MTZ-treated zebrafish larvae using the fluorescence microscope to perform mRNA and miRNA sequencing. Gene ontology enrichment analysis revealed an up-regulation of metabolic processes, immune response, and ion transport and down-regulation of nephron development and slit membrane-associated proteins.

In many important aspects, the glomerular response to podocyte reduction in larval zebrafish is comparable to that of human FSGS. A thorough understanding of these mRNA and miRNA-based gene regulatory mechanisms will aid in the discovery of the pathomechanism and the development of therapeutics for the treatment of FSGS.

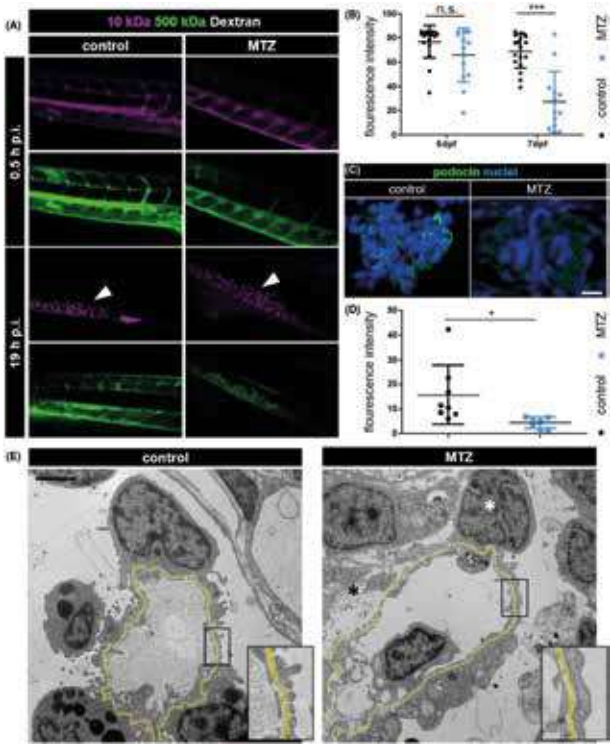

Figure 1.
Metronidazole induces podocyte injury and progressive effacement of foot processes (from ref. 3)

The role of SGLT2 inhibition in heart failure: What can nephrologists learn from cardiologists?

Nikolaus Marx, Germany

Current guidelines by the European Society of Cardiology recognize three types of heart failure: heart failure with preserved ejection fraction (HFpEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with reduced ejection fraction (HFrEF). All types exhibit high morbidity and mortality and there is a clear need for upgrading current treatment strategies. The prognosis is even worse in patients with HFrEF and CKD.

The DAPA-HF trial was the first to assess the effect of the sodium-glucose cotransporter-2 (SGLT2) inhibitor dapagliflozin in patients with HFrEF. It concluded that SGLT2 inhibition significantly reduces cardiovascular death or worsening of heart failure in this population irrespective of diabetes. The EMPEROR-reduced trial showed similar results for empagliflozin. Meta-analysis of these trials showed a very robust and significant reduction of the combined risk of cardiovascular death or hospitalization for heart failure. The results were consistent in patients with and without chronic kidney disease (CKD) and even suggested that these agents also improve renal outcomes. HFpEF and HFmrEF patients were the focus of the EMPEROR-preserved trial which investigated the safety and efficacy of empagliflozin. It showed a highly significant and robust risk reduction of cardiovascular death or hospitalization for heart failure in these patient cohorts, regardless of the presence or absence of diabetes. Looking at kidney function, the results were consistent both in patients with preserved kidney function as well as in those with eGFR ≤60mL/min. Finally, the DAPA-CKD trial found that dapagliflozin reduced the risk of kidney failure, cardiovascular death or hospitalization for heart failure, and overall mortality in patients with CKD, with and without type 2 diabetes. Therefore, SGLT2 inhibitors are associated with a convincing reduction of heart failure-related events in patients with CKD, patients with HFrEF, and patients with HFpEF.

Various mechanisms seem to contribute to the beneficial effects of SGLT2 inhibitors. EMPA Hemodynamics study in patients with type 2 diabetes and high cardiovascular risk looked at echocardiographic parameters of cardiac function as a secondary endpoint and showed that empagliflozin significantly improved diastolic function. Research suggests that, in comparison to loop diuretics, SGLT2 inhibitors may selectively inter-reduce interstitial fluid, which may limit the reflex neurohumoral stimulation that usually occurs in response to intravascular volume contraction with traditional diuretics. Mediation analysis from the EMPA-REG outcome trial suggested that the increase in hematocrit and hemoglobin may contribute to the overall result, and the EMPA Hemodynamics showed that empagliflozin leads to an increase in hemoglobin and hematocrit. Finally, it has been suggested that metabolic effects may play a role in this context: if an SGLT2 inhibitor is introduced, glucose levels decrease and other energy sources, such as ketones and branched-chain amino acids, may come into metabolic play again.

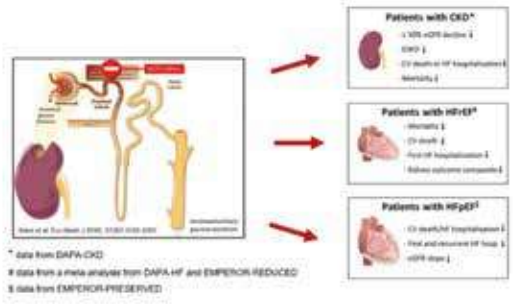

Figure 2.
The mechanism of action of SGLT2 inhibitors

Food as medicine – can it link the gut microbiota to an improved renal phenotype?

Peter Stenvinkel, Sweden

Foodome is a new discipline that studies the food and nutrition domains through the application and integration of advanced omics technologies to improve well-being, health, and knowledge, and it includes a pool of all the compounds that make up the human diet. Current research in this domain focuses on linking individual eating patterns to the individual genome and the individual diseases and providing a tailor-made composition of nutrients that would have a favorable impact on health. A landmark study published in 2019 showed that a suboptimal diet is responsible for more deaths than any other traditional risk factor, including tobacco smoking, and fueled interest in the potential of the concept of food as medicine. Further works suggested that food could be used as a novel strategy to target the uraemic phenotype, characterized by epigenetic alterations, gut dysbiosis, mitochondrial dysfunction, inflammation, oxidative stress, and premature aging. One of the approaches would be targeting transcription factors involved in inflammation and oxidative stress, such as sulforaphane in broccoli, curcumin in turmeric,

anthocyanins in berries, etc. Another opportunity is to target senescent cells which have a pro-inflammatory effect by using nutrients that act as as senolytics and lead to apoptosis. Using the quercetin from apples, curcumin from turmeric, fisetin from strawberries, and epigallocatechin from green tea, it may be possible to down-regulate the senescence-associated secretory phenotype (SASP) response.

The major opportunity of using food as medicine is to target gut dysbiosis, which is promoted by the metabolic alterations of uremia and associated with inflammation and increased cardiovascular risk. Nutrients like fibers, prebiotics found in soybeans and wheat, polyphenols in grapes, coffee, and berries, as well as urolithin from berries and pomegranate, could alter the diversity of the gut microbiota. Research into the footprint of the systemic microbial biodiversity in advanced CKD shows that the decline of renal function is accompanied by altered microbial biodiversity. Gut dysbiosis predict increased mortality in dialysis patients. The links between gut microbiota and CKD are multifold, and research shows that one of the most important links is Trimethylamine N-oxide (TMAO). TMAO promotes pro-thrombotic effects and is associated with all-cause mortality. Preliminary data indicate that a diet rich in red meat and low in fish may increase the risk of death and shorten the time to initiation of renal replacement therapy. The generalized application of food as medicine should be based on solid scientific support. Thus, more studies are needed to prove the exact links, in order to utilize bioactive nutrients that benefit health and/or counteract the negative effects of drug treatment on the gut microbiota.

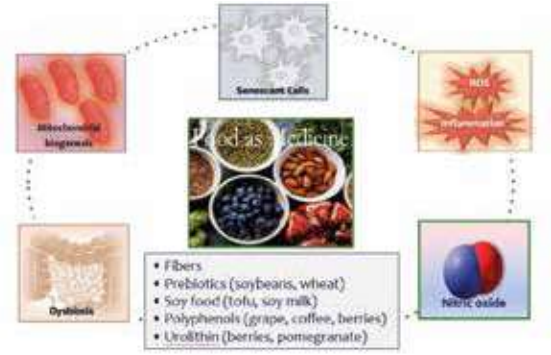

Figure 3.
Foods to target gut dysbiosis

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) & Acute Kidney Injury (AKI)

Mehmet Kanbay, Turkey

SGLT2 inhibitors showed compelling improvement in the outcome of patients with diabetic kidney disease by hindering the progression of albuminuria and eGFR decline, in addition to blood glucose regulation, blood pressure control, and body weight management. In the light of the strong evidence presented in the CREDENCE and DAPA-CKD trials, KDIGO 2020 Clinical Practice Guidelines for Diabetes Management in CKD recommend the use of SGLT2i as part of first-line therapy for patients with eGFR ≥30mL/min. Nevertheless, renin-angiotensin system inhibitors or angiotensin receptor blockers (ARBs) should remain the first-line therapy for diabetic patients as they reduce albuminuria, the decline in filtration rate, fibrosis, inflammation and regulate hypertension.

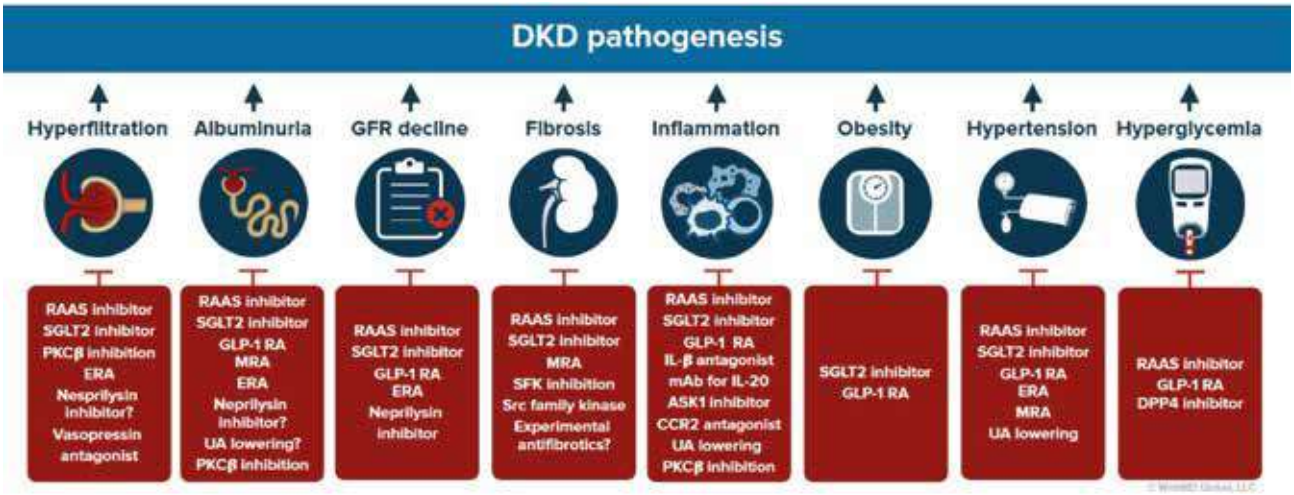

Figure 4.
Mechanisms of renoprotection with glucose-lowering therapies (from ref. 12)

However, despite the well-documented long-term renoprotective effects of SGLT2 inhibitors, postmarketing reports suggested an early onset of acute kidney injury (AKI) events, particularly with canagliflozin and dapagliflozin. These data have recently been questioned, since the research did not include a specified control group, and a propensity analysis suggested that SGLT2i carry an overall reduced AKI risk, compared to patients with type 2 diabetes with similar clinical characteristics. Some cases of AKI might relate to the acute reduction in eGFR that occurs with the initiation of SGLT2i therapy, likely due to the hemodynamic effect of the drugs to reduce glomerular pressure, and others may be caused by volume depletion triggered by the use of diuretics and angiotensin-converting enzyme (ACE) inhibitors or ARBs that augment the salt and water loss associated with SGLT2-dependent osmotic diuresis.

Many studies were initiated to explore whether SGLT2 inhibitors were related to the development of AKI. Dekkers et al. study looked at the effects of dapagliflozin on glomerular and tubular injury markers and showed that dapagliflozin significantly decreased kidney injury molecule 1 (KIM1) and interleukin 6 levels, pointing at beneficial effects on renal inflammation and reduction in proximal tubular cell injury. No change in global damage markers was observed. Katsuhara et al. studied the correlation between SGLT2i and acute renal failure in patient groups from Japan and outside of Japan. In non-Japanese patients with diabetes, there was a correlation between SGLT2 inhibitors use and the onset of acute renal failure that was not seen in cases reported in Japan. Furthermore, this study indicated that the signal of acute renal failure tended to be reduced in cases with the concomitant use of either an ACEi or ARB. Real World Data retrospective propensity match study from Canada compared SGLT2i and other glucose-lowering drugs concluding that SGLT2i use was not significantly associated with a higher risk of AKI compared to other drugs.

The mechanisms of reducing the AKI incidence with SGLT2 inhibitor use in type 2 diabetes are unclear. Some potential factors contributing to SGLT2 inhibitors-associated renoprotection may include decreasing oxygen and energy requirements of the tissue, diminished signals promoting tubular growth, reduced ischemia-reperfusion injury, and AKI, cardiorenal protection due to immunomodulatory effects, reduced inflammation and preservation of tubular integrity.

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