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the crucial role of water channels (aquaporins) in peritoneal dialysis and he developed preclinical strategies to improve the efficiency of dialysis and to reduce structural damage in the peritoneal membrane.

O. Devuyst has authored more than 350 articles that are cited > 16,000 times. He is funded by national and international agencies including the EU and the NIH. Dr. Devuyst has been the laureate of several international prizes and is a Fellow of the Royal Academy of Medicine of Belgium. He is Associate Editor of Kidney International, Nephrology Dialysis Transplantation, and Orphanet Journal of Rare Diseases; and he serves in the Editorial Board of Clin J Am Soc Nephrol, Peritoneal Dialysis International, Frontiers in Physiology and Pflügers Archiv.

O. Devuyst coordinated several EU-funded research networks and has founded the Working Group on Inherited Kidney Disorders (WGKID) of the ERA-EDTA in 2011. He was recognised as a Distinguished Fellow of the ERA-EDTA in 2013.

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A very warm welcome to beautiful Budapest and the 56th ERA-EDTA Congress! This was the message to delegates to the congress from George Reusz, Congress President, Béla Merkely, Rector of Semmelweis University of Budapest, and Carmine Zoccali, ERA-EDTA President. In their welcome addresses, speakers noted the dramatic changes that have taken place in Hungary since 1986, when the ERA-EDTA Congress was last held in Budapest. This transformation has been especially notable for the Hungarian nephrology community. In 1986, there was an “economy of scarcity”, in which access to dialysis was limited by age and comorbidities – a situation that is almost impossible to imagine for today’s young nephrologists. Societies throughout Europe are facing many new challenges, but there also continue to be opportunities for scientific innovation. This environment is reflected in the congress’s exciting scientific program, as well as in the keyword for this year, ‘Precision Nephrology’, which summarizes what we know, what we think we know and what we need to know to achieve our goal – to provide the best care for kidney patients. The Welcome Ceremony ended with a wide-ranging and exciting plenary lecture on ‘Diseases of emergence’ by Professor Rafael Yuste (New York, USA).

Doctor Olivier Devuyst is the recipient of the 2019 ERA-EDTA Award for Outstanding Basic Science Contributions to Nephrology

Olivier Devuyst, M.D., Ph.D., graduated from UCLouvain in Brussels (Belgium), trained in Brussels and at the Technion Institute (Haifa, Israel) and at the Johns Hopkins Medical School (Baltimore, USA). He is Full Professor of Medicine at the University of Zurich (Switzerland) and has a joint appointment in nephrology at Saint-Luc Academic Hospital in Brussels. Dr. Devuyst and his group use a multi-level approach combining innovative disease models, deep phenotyping, and molecular and population genetics to investigate the mechanisms of solute and water transport in different cell types, and the pathophysiology of inherited kidney diseases. This joint work identified new mechanisms involved in rare genetic disorders affecting tubular cells and their relevance for kidney physiology. These findings substantiate the genetic architecture of kidney diseases and offer novel targets to treat common disorders including hypertension, kidney stones and urinary tract infections. In parallel, O. Devuyst demonstrated the crucial role of water channels (aquaporins) in peritoneal dialysis and he developed predilutional strategies to improve the efficiency of dialysis and to reduce structural damage in the peritoneal membrane.

O. Devuyst has authored more than 350 articles that are cited > 16,000 times. He is funded by national and international agencies including the EU and the NIH. Dr. Devuyst has been the laureate of several international prizes and is a Fellow of the Royal Academy of Medicine of Belgium. He is Associate Editor of Kidney International, Nephrology Dialysis Transplantation, and Orphanet Journal of Rare Diseases; and he serves in the Editorial Board of Clin J Am Soc Nephrol, Peritoneal Dialysis International, Frontiers in Physiology and Pflügers Archiv.

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Professor Claudio Ronco is the recipient of the 2019 ERA-EDTA Award for Outstanding Clinical Contributions to Nephrology

Claudio Ronco is Full Professor of Nephrology at the University of Padova and Director of the International Renal Research Institute.
of Vicenza and the Department of Nephrology, Dialysis and Transplantation of San Bortolo Hospital in Vicenza Italy.

Born in 1951, he graduated in Padova in 1976 and became a specialist in nephrology (Padova 1979) and pediatric nephrology (Naples 1986). In 1999 and 2000 he acted as Director of the Renal Research Institute and Professor of Medicine at Albert Einstein College of Medicine in New York.

He is considered the father of Critical Care Nephrology and a pioneer in the field of Extracorporeal Therapies and Peritoneal Dialysis as well as the inventor of new devices such as CARPEDIEM (the miniaturized dialysis machine for neonates). He is a recognised mentor for many physicians, engineers and scientists, given his capacity to bridge several disciplines such as medicine, physics, chemistry, engineering and design. Since 1982 he organizes renowned international courses in Vicenza attended by an international audience.

He authored 1,530 papers, 1,200 of them listed in Pub-Med, 80 books and 215 book chapters. He is honorary professor at the University of Virginia and Fudan & Jiao Tong Universities in Shanghai. He received an honorary degree in Medicine and Human Sciences at the University of Potras.

He has received numerous awards including the Belding Scribner Award for hemodialysis, the Bywaters Award for AKI and the ESDA award for innovation. His H-index censored by Google Scholar is 106.

He is editor in Chief of 3 indexed journals: Cardiological Medicine, Blood Purification and Contributions to Nephrology. He is Editor Emeritus of the International Journal of Artificial Organs. He is Associate editor and editorial board member in several international journals including Nephrology Dialysis and Transplantation and Critical Care. He is considered to be a polymath for his extensive knowledge and excellent capabilities.

Kidney diseases have so far been underestimated in many respects: most people are not aware of their impaired kidney function. In general, kidney diseases are “silent diseases”, most often there are no apparent early symptoms. Many people with kidney diseases are not aware that they have been living with higher risks of cardiovascular diseases, infections, hospitalizations, and of course kidney failure which requires dialysis or transplantation.

Kidney diseases to date have not had a major role in most health promotion and public awareness campaigns. This, however, is completely unjustified. We estimate that over 850 million people worldwide have some form of kidney disease, which is roughly double the number of people who live with diabetes (30 million, [1]) and 20 times more than the prevalence of cancer worldwide (42 million [2]) or people living with AIDS/HIV (36.7 million [3]). Thus, kidney diseases are one of the most common diseases worldwide, but the public is unaware of the extent of this health issue. "It is high time to put the global spread of kidney diseases into focus," explained Professor David Harris and Professor Adeera Levin, Past-Presidents of the ISN.

Chronic kidney diseases (defined as abnormalities of kidney structure or function that are persistent for greater than 3 months) make up the majority of current estimates of kidney diseases; the prevalence of chronic kidney diseases worldwide is 10.4% among men and 11.8% among women [4]. Those requiring dialysis or transplantation are between 5.3 and 10.5 million people, although many who do not receive these treatments due to lack of resources or financial barriers. Acute kidney injury (AKI), experienced by 13.3 million patients each year, may resolve or lead to chronic kidney diseases or kidney failure in the future. "Using all these sources of data, and existing estimates of acute and chronic kidney diseases, we estimate approximately 850 million kidney patients...a number which surely signifies an ‘epidemic’ worldwide", says Levin.

However, it is not only the number, which is dramatic, but also the outcome: "Even, if many patients with impaired kidney function do not feel ill over a long period of time, they are at a particularly high risk of many other health outcomes due to this condition", explained Professor Carmine Zoccali, president of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA). As he points out, the average age standardized mortality rate due to low kidney function (GFR) is 21 deaths per 100,000 [4]. In particular, the cardiovascular death toll from chronic kidney diseases is huge: In 2013, there were 1.2 million cardiovascular deaths attributed to kidney diseases [5]. "The death rate among people with kidney diseases is incredibly high! AIDS, for example, accounts for "only" 1.9 deaths per 100,000 [6] – but think about all the campaigning with celebrities and the resulting recognition of HIV as a priority health issue. There is only little active campaigning on behalf of people with kidney diseases, even though the number of people who die from kidney deterioration is 11 times higher." "It is time for constructive change in kidney care policy", confirms Professor Mark D. Okusa, president of the American Society of Nephrology (ASN). "The number of people with kidney diseases is alarmingly high, but the public is not aware of this reality. These patients have outcomes and kidney diseases impose a heavy financial burden on healthcare budgets, as the annual cost per patient for hemodialysis (HD) are, for example, US$ 88,195 in the USA [8], up to US$ 58,812 in Germany, US$ 83,616 in Belgium or US$ 70,928 in France [9].

ASN, ERA-EDTA and ISN collaboratively aim to raise worldwide awareness of kidney diseases and to improve prevention efforts. The joint aim of all three associations is to reduce the burden of kidney disease globally and improve awareness. Communicating openly about the current burden of the kidney diseases worldwide is the first step.

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SGLT2 inhibition in CKD: Discussing the key questions and evidence

The European QUALity (EQUAL) study on when to start dialysis is an ongoing, prospective, observational cohort study in chronic kidney disease (CKD) stage 4 and 5 patients aged over 65 in six European countries. EQUAL focuses on a combination of patient quality of life, survival, uraemic signs and symptoms, nutritional status, and treatment preferences, to provide insight in the benefits and burden of dialysis initiation. The ultimate goal is to determine whether and, if so, when, to initiate dialysis in this population. Since EQUAL’s inception in 2012, around 1,700 patients have been included, and data on numerous clinical parameters have been collected over the span of 9,000 study visits. Presently, an EQUAL biobank containing patient serum and urine samples is under way, and will open up interesting future possibilities for studies in various ‘omics’ fields.

To date, EQUAL has enabled numerous studies in the advanced CKD population, with subjects varying from sex disparities, polypharmacy, quality of life, uraemic signs and symptoms, and the prediction of mortality. The latter study, which will be presented during the ERA-EDTA Registry symposium on Friday (8 am, Hall G1), aims to determine whether we can dynamically and accurately predict individual survival probabilities using high-sensitive Troponin T (hs-TnT) measurements over time. To achieve this, we applied joint models in the Swedish cohort where hs-TnT was collected over time. Joint models are capable of updating individual survival probabilities as additional measurements become available, thus allowing for dynamic and individualized predictions of survival during follow-up.

Preliminary results show an overall three-year survival of 70% (95% CI 63%–77%), which was inversely correlated with baseline hs-TnT tertile (p < 0.0001). Longitudinal hs-TnT exhibited a strong and independent prognostic effect on mortality (Figure), and addition of hs-TnT to a model including established baseline risk factors (AUC = 0.77) improved model discrimination (AUC = 0.83). We conclude therefore that longitudinally measured hs-TnT may contain valuable predictive information on the mortality risk in older CKD stage 4 and 5 patients, supporting the use of repeated TnT measurement for the identification and surveillance of patients with a high mortality risk.

Figure: Individual TnT measurements (dots), individual predicted TnT trajectories (lines), and the population average predicted TnT trajectory. Individuals TnT trajectories are color coded by vital status. © Nicholas Chesnaye

Results from the EQUAL study
Dynamic prediction of mortality in advanced CKD using high-sensitive Troponin T

EDUCATION
This is your second year as President of the ERA-EDTA, and you have previously served as Chair of the Registry and Editor in Chief of Nephrology, Dialysis and Transplantation. From the vantage point of your great experience, how do you view the evolution of the ERA-EDTA?

The ERA-EDTA has gradually and successfully grown to respond to the challenges posed by scientific research on renal diseases, to the need to provide high-quality education on these diseases, and the importance of effective relationships with the institutions that fund scientific research in Europe. Consequently, the Society has evolved incrementally as new initiatives have been added to existing activities. While this demonstrates the continuing vitality of nephrology as a medical specialty, it does raise concerns about complexity and duplication. These latter considerations prompted the Council’s decision to redesign the ERA-EDTA’s organization into two main branches: Clinical Nephrology Governance and Renal Science Coordination and Administration.

Led by Professor Ziad Massry as Chair, the Clinical Nephrology Governance branch is now responsible for coordinating the ERA-EDTA Registry and the European Renal Best Practice (ERBP). The Registry has long been a primary focus in the Society and continues to be the major promoter of epidemiology research and education in nephrology both in Europe and globally. It is therefore a natural partner for the ERBP, another successful initiative by the ERA-EDTA, which is internationally recognized for its evidence-based clinical guidelines and educational activities. The activities of this branch will also encompass the newly created Nephrology and Public Policy Committee (NPPC), the European chronic kidney disease (CKD) cohorts initiative, a collaboration with various CKD cohorts established by the ERA-EDTA Registry, and existing European Dialysis Outcomes and Practice Patterns study cohort (EURO-QOPS) data. The Nephrology and Public Policy Committee (NPPC) has already completed a comprehensive document providing detailed information about the plans aimed at sustaining efforts to advance the fight against renal diseases and to promote renal care at a European level. This document will soon be published in the official journals of the society.

The Renal Science and Co-ordination Administration branch includes the Scientific Advisory Board (SAB), which is now responsible for coordinating the important activities of the ERA-EDTA Working Groups, and for the conception and coordination of projects in translational nephrology to be submitted to the European Commission and other funding bodies. From this year, the Scientific Advisory Board (SAB) is also advising the Council about all the ERA-EDTA Awards, ranging from the annual Senior Awards to the Stanley Shaldon award for young investigators. The Renal Science branch is led by Professor Danilo Flisci, who is taking the lead in developing the ERA-EDTA Scientific and Educational Interaction Day (SEID). This new event (see below) aims to create an opportunity for face-to-face meetings to promote collaboration among Working Group investigators and to enlarge the educational portfolio of the ERA-EDTA.

Which are the educational initiatives planned by the Council that will have an immediate impact on the life of the ERA EDTA this year?

This year in Budapest we will restructure the CHE Courses that are now the Continuous Education and Professional Development (CEPD) Courses. We have replaced the Working Group-led courses with a series of 13 brief educational courses covering the whole spectrum of nephrology, from Acute Kidney Injury and Chronic Kidney Disease to Clinical Epilepsy, Immunopathology, and Dialysis and Transplantation. These brief courses adopt a standard format, and each presentation will succinctly recapitulate established knowledge to form the basis for a review of new evidence accrued during the last two years. Participants in the CEPD need to pre-register themselves and all pre-registered participants will receive the articles on which the presentations for each particular course are based. The aim of these courses is to create a clear, well-organized way for nephrologists to keep themselves updated on the main advances in the various areas of nephrology. Furthermore, in October we will inaugurate in Vienna an entirely new event, the ERA-EDTA Scientific and Educational Interaction Day (SEID), where the ERA-EDTA Working Groups will have the opportunity to interact with the aim of conceiving shared research projects. During the same event, brief education courses (proposed by the same Working Groups) will also be held. Overall, this event will serve to integrate scientific knowledge and to facilitate the conception of articulated research projects to be submitted to funding institutions in Europe and result from the joint efforts of investigators from diverse areas of knowledge.

Can you already tell, if these new educational formats, the CEPD as well as the SEID, will be successful?

Yes, I am very optimistic about this. The concepts of both formats have been elaborately worked out and continuously improved and we have already received a very positive echo. The format of the CEPD course: In the past, participants in Budapest will be higher than the number we had last year in Copenhagen—and this was really already great. We observe a rising interest and a continuously growing number of people who attend the ERA-EDTA congress. This is a definite proof that the ERA-EDTA congress meets the high expectations of its members as well as of all European and non-European nephrologists in general. Especially the interest of nephrologists from the USA and from Asian countries has risen immensely—a clear sign of the international reach of our society, well beyond Europe.

How will the new organizational structure ensure co-ordination between the two branches of the ERA-EDTA and how do you view the evolution of the ERA-EDTA?

As part of this new organizational model, the Clinical Governance and Renal Science Chairs are now ex officio members of the Scientific Advisory Board (SAB). The Chairs will be joining the Council to organize integration and collaboration within and between clinical- and basic-sciences-oriented Working Groups and will produce a joint document describing their annual action plan. The Chairs will in addition jointly organize an annual webinar covering themes that bridge basic and renal science designed to facilitate cross-fertilization between these two strands of research.

Important ERA-EDTA initiatives such as the Young Nephrology Platform and the Green Nephrology Initiative are now under the direct control and supervision of the Council. This also applies to the Ethics Committee, our relationships with international societies, such as the American Society of Nephrology (ASN) and International Society of Nephrology (ISN), national societies within the geographical area of the ERA-EDTA, and the European Kidney Health Alliance (EKHA). The Society was the driving force for the formation of the EKHA, which plays a key role in advancing the increasingly essential public health agenda in CKD.

The Young Nephrology Platform is a comparatively recent ERA-EDTA initiative. How has it progressed since it was established?

This platform was founded in 2014 by my predecessor as President, Andrey Wiesock, and I believe that few other international scientific societies have been so proactive in reaching out to young doctors in the early stages of their careers. Feedback from young nephrologists themselves has been very positive, and the Council has decided to expand the initiative to promote the involvement of young investigators in scientific activities and in the Annual Congress program. Young nephrologists with relevant research interests will join the boards of each Working Group, and we hope that their presence and their effective participation will encourage other young colleagues to support Working Group projects.

Each Working Group Chair will also encourage and support feasible scientific projects suggested by young nephrologists. To optimize involvement in the Annual Congress, the Young Nephrology Platform (YNP) Board will propose the names of young nephrologists to be included into the symposia and mini-lectures.

Over one third of ERA-EDTA members are women. Could you describe initiatives to support the representation and involvement of female nephrologists at all levels of the Society?

Women do indeed represent a substantial part of the nephrology workforce and over half of the Young Nephrologists Platform are now women. Although young male nephrologists with families also face pressures relating to their family/work life balance, it is undoubtedly the case that the issue of balancing career and family continues to be of paramount importance among women in nephrology and other medical disciplines. One result is that, while women are increasingly visible on the ERA-EDTA Council and Committees, they remain insufficiently involved in the activities of our Society. So the Society aims to increase the contribution of women and their involvement and visibility at all levels of the ERA-EDTA. By establishing an inclusive policy for the Council and other bodies of our society, national societies will be specifically invited to promote women as candidates to the Council and other organs of the ERA-EDTA. The Council will also ensure an adequate representation of women as speakers at the Annual Congress and at other scientific and educational activities of the ERA-EDTA.

Continuing the theme of youth, it is clear that young people in many countries are increasingly aware of and vocal about the threats to the environment and their future. How is the ERA-EDTA investing in the transformation to greener healthcare?

There is a complex and two-way relationship between the environment and healthcare. Climate change will have adverse effects on human health, while an estimated 5–10% of global greenhouse gas emissions come from healthcare-related activities. The ERA-EDTA Council has recognized the importance of sustainability as a domain of quality in healthcare and has created a new committee to create awareness among members of the environmental challenges we face. Healdolation, for example, uses a great deal of energy and large quantities of water, and creates substantial waste. The ERA-EDTA is open to collaboration with industry to strengthen initiatives to promote more sustainable dialysis that maintains high standards of patient care—which may have the added benefit of expanding access to treatment in low- and middle-income countries.

As an organization, the ERA-EDTA has had a proud record of responding positively to many challenges over the years, and climate change is no exception. It is our belief that by coordinating and integrating its activities, the ERA-EDTA will continue to grow and serve its membership, and promote high standards of kidney care for our patients. 
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References


Adverse events should be reported. Reporting forms and information can be found at https://aereporting.astrazeneca.com.
There are similarities in the treatment of high blood pressure between children and adult patients, but there are also some major differences. I will here describe some of them in this article.

It is more difficult to measure blood pressure in children compared to adult patients. The oscillometric devices that are commonly used in adult practice tend to overestimate blood pressure in children, and high readings should be validated by manual recordings. The definition of high blood pressure in children is different from that in adult patients. There are no longitudinal studies that can help to define the level of blood pressure that is required in each child. To date, hypertension in children is unfortunately purely a statistical definition, where children with consistent blood pressure above the 95th percentile will be defined as having hypertension.

A further major difference between children and adults is that at least 50% of hypertension in children has a secondary cause. This varies at different ages of the child. Typically, a large group of different kidney disease are the main reason for the hypertension. Essential (primary) hypertension is, however, increasing in children, in particular due to the obesity epidemic. Children with hypertension do therefore need much more investigation than is generally used in adults.

Treatment of hypertension is in most ways quite similar. We start with an effort to improve lifestyle and salt intake. Calcium channel blockers and ACE inhibitors are the two most commonly used classes of drug. It is important to remember that small children in particular are more susceptible to the use of ACE inhibitors and angiotensin 2 receptor blockers, and during dehydration in particular the risks for acute kidney injury and even death exist with these drugs.

It is very important to treat hypertensive emergencies carefully in children. These children can present with severe cerebral or cardiovascular symptoms, but a proportion are asymptomatic. In those with no symptoms, the treatment can start slowly by introducing oral drugs. In those with severe life- or organ-threatening symptoms there is a need for intravenous treatment. For this to be done safely there is a need for high-dependency care with close monitoring of the child.

In summary, as always the treatment of hypertension in children needs experience in treating children, as they are in many ways different from adult patients.
FGF23 signaling in the kidney

Elevated circulating intact FGF23 may drive volume overload and vascular calcification in CKD

The kidney is one of the organs with the highest expression of α-Klotho, and the main target organ of FGF23 signaling under normal conditions. It was previously believed that α-Klotho is mainly expressed in distal renal tubules. However, several independent lines of evidence have shown that α-Klotho is expressed in both proximal and distal renal tubules, albeit at higher levels in distal tubules. In proximal renal tubules, blood-borne FGF23 directly suppresses phosphate reabsorption by a signaling cascade leading to phosphorylation of the scaffolding protein Na+/H+ exchange regulatory cofactor (NHERF)-1 and subsequent internalization and degradation of sodium-phosphate cotransporters [2].

In addition, FGF23 suppresses the production of the biologically active vitamin D hormone, 1α,25-dihydroxyvitamin D3, by down-regulating 1α-hydroxylase expression in proximal renal tubules. Renal 1α-hydroxylation of the precursor 25-hydroxyvitamin D3 is the rate-limiting step in the production of the vitamin D hormone. Hence, FGF23 is an important hormone protecting against hyperparathyroidism by directly increasing renal phosphate excretion, and by indirectly downregulating intestinal phosphate absorption through suppression of vitamin D hormone production. Interestingly, the other major phosphaturic hormone, parathyroid hormone, also targets NHERF1, and both hormones interact in proximal renal epithelium.

In distal renal tubules, FGF23 enhances calcium and sodium reabsorption by increasing the abundance of the epithelial sodium channel TRPV5 and of the sodium-chloride cotransporter NCC at the apical cell membrane through a Klotho-dependent activation of with-no-lysine kinase-4 (WNK4). Thus, FGF23 is not only a phosphaturic, but also a calcium- and sodium-conserving hormone [3].

Interestingly, the other major phosphaturic hormone, vitamin D, secures calcium, sodium handling and blood pressure. EMBO J 2012; 31:621–628.

References


S 02
Phosphate and FGF23
Friday, 08.00—09.30, Hall G2A
In the last decades, survival of patients on renal replacement therapy (RRT) has increased [1]. Part of this increase may reflect the overall increase in the survival of the general population. An additional increase in survival in RRT patients relative to the general population may likely be due to an improved effect of interventions in RRT patients over time.

One way of comparing survival in the RRT population with that in the general population is by looking at the excess mortality. Excess mortality is defined as the mortality in the RRT population minus the expected mortality in the matched general population. Recently, Foster et al [2] published a paper on the excess mortality in patients on RRT in the United States. They showed that between 1995 and 2013 the all-cause excess mortality risk in patients on RRT decreased for all age categories.

The results of this study may, however, not be generalizable to Europe, due to important differences in the RRT population, including differences in case-mix (e.g. comorbidities, primary kidney disease distribution, and ethnicity) and a better patient survival in Europe.

During our presentation at the ERA-EDTA Registry symposium, we will present the results on time trends from 2002 to 2015 in excess mortality in a large cohort of 280,081 patients on RRT living in Europe.

For this study we used the data from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry database and general population data from the World Health Organization. We will show that the absolute excess mortality rate in patients on RRT was higher in the United States than in Europe. Regardless of this difference, both in the United States and in Europe the all-cause absolute excess mortality rate decreased over time in all age categories, showing that the better survival observed in patients on RRT is not only due to the better survival in the general population, but also due to an additional improved survival in the RRT population.

Of note, we show that the decrease of the absolute excess mortality rate in patients on RRT was mainly the result of a decrease in the excess mortality among dialysis patients. In transplanted patients the excess mortality rate was low throughout the study period.

Although not presented in the study by Foster, we also examined the cause-specific excess mortality. Interestingly, our results showed that RRT patients had a decrease in excess mortality for all specific causes of death, in particular for atheromatous CVD.

Monoclonal gammopathy of undetermined significance (MGUS), first described by Kyle in 1978 in an asymptomatic patient, is associated with increased risk for plasma cell malignancy. The current diagnostic approach defines MGUS vaguely, as a plasma cell dyscrasia under a threshold criterion of protein M levels in serum <3 g/L and bone marrow infiltration state <10%, with no disease related end-organ damage.

Patients are screened for clinical manifestations of multiple myeloma (MM) under the acronym CRAB, namely hypercalcemia, Renal dysfunction, Anemia and Bone lesions, which is usually seen with an exacerbation of a benign primary condition. However, the concept of MGDS (renal significance) was introduced in 2012 and opens a new perspective to several well-known disease entities on the borders of nephrology, hematology and pathology. The academic discussion of the disease spectrum is constantly changing, warranting the need to establish a protocol of action, based not only on expert advice but also supported by currently ongoing, as well as previous, research and discussion.

MGDS is a disease of the kidney, secondary to a clonal or immune dysfunction; hence both must be treated accordingly. To fully understand the disease’s character, a full scope of why unspecified significance can, in fact, be significant must be acknowledged. The diagnostic procedure should be extensive due to the wide heterogeneity, always beginning with symptoms through to the decisive kidney biopsy.

MGDS encompasses an array of diseases linked to relatively benign proliferation of plasma/B cells, with subsequent overload of monoclonal immunoglobulin (Mig), fragment of, or paraprotein aggregating in kidney tissues. This may lead to loss of function, inefficiency and ultimately failure. It is usually secondary to sub-MM clonal expansion, or complement dysregulation. Mortality is associated with elevated risk of developing chronic kidney disease (CKD), and also malignancy, infection and other organ dysfunction. Neuropathy and autoimmune disease association is suspected but unclear. The impediment in the classification of MM with renal involvement (R1) and MGDS relates largely to the degree of underlying plasma malignancy, which clinically translates into varying treatment approaches.
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Please join us on June 14 from 1:15 to 2:00 p.m. in the Presentation Theater in Exhibition Hall A to hear Eric Dube (Retrophin), Jon Barratt (Leicester) and Josh Tarnoff (NephCure) discuss “Glomerular Disease: Patient-Centric Collaborations in Drug Development.”

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The list of well-known persons affected by chronic kidney disease (CKD) who also suffered from mental illness is quite long. Just to quote few, Stephen Bathory, King of Poland, and Wolfgang Amadeus Mozart were both affected by depression and CKD [2]. This is a coincidence or actually evidence of a link between kidney disease and brain dysfunction? is a question. Studies showed that CKD patients have a higher risk of cognitive decline, including dementia, than the general population. The reasons for this effect are still unclear. An attractive hypothesis is that the kidney produces neurotrophic factors that are necessary for normal cognition in the long term. However, several other hypotheses are equally possible at this stage.

Although the first description of uremic encephalopathy was published some 80 years ago, our understanding of brain dysfunction in CKD, prevention and treatment, is still in its infancy. Why should we be more optimistic today about an advance in this field? There are several reasons including a technological one. Indeed new high-throughput tools have become available that may provide new information on the early identification and pathogenesis of MCI-CKD. These techniques promise to unravel novel (neuro)toxins and to systematically verify their neurotoxic potential. In particular, fMRI and brain tractography, with their ability to combine morphological and functional imaging of the human brain in vivo with neuro-psychological testing are a unique opportunity. Furthermore, new transgenic animal models are now available that allow study of brain activity at the single neuron level in vivo that can be selectively activated using laser pulses (optogenetics). New technologies such as 2-photon microscopy and super-resolution microscopy should allow us to overcome some of the major limitations of previous imaging techniques. The ‘Clarity’ method can facilitate an unprecedented ability to investigate the 3D location of neurons in great detail. The possibility of deriving stem cells from patients and brain organoids could represent a new in vitro model for studying the pathogenesis and reversibility of MCI.

Finally, to shed light on MCI-CKD it is essential that we liaise closely with our clinical colleagues in neurology, neuro-psychology, and radiology, as well as basic scientists in neuroscience to address this anticipated major personal health and socioeconomic burden.

References

Cognitive impairment and kidney disease A major personal health and socioeconomic burden

The list of well-known persons affected by chronic kidney disease (CKD) who also suffered from mental illness is quite long. Just to quote a few, Stephen Bathory, King of Poland, and Wolfgang Amadeus Mozart were both affected by depression and CKD [1]. Is this a coincidence or actually evidence of a link between kidney disease and brain dysfunction? It is not a merely an academic question, because all forms of mental illness can seriously impair an individual’s quality of life, and are frequently associated with progression of disease and premature mortality. So it is worth the effort of trying to answer it.

Most industrial countries are experiencing growing numbers of patients with CKD within their aging populations [2]. Although the prognosis of patients with CKD remains poor, their increasing life expectancy has shifted the medical attention from life-threatening emergencies to long-term complications and sequelae, and how to improve quality of life. In this respect one of the major problems is the cognitive decline that is one of the behavioral manifestations of brain damage in CKD.

Cognitive decline can manifest with a continuum from mild cognitive impairment (MCI), up to clinically relevant dementia. What is new, however, is the finding that MCI may already be present in earlier stages of CKD, affecting approximately one in two CKD patients (prevalence varies in studies between 30% and 60%). In contrast to ‘normal’ dementia, CKD-related MCI is not age-dependent, meaning the cognitive impairment exceeds that expected from the normal aging process. It usually worsens with declining glomerular filtration rate (GFR) – the lower the GFR, the higher the risk of being affected by cognitive impairments. The pathogenesis appears complex, involving a variety of factors besides vascular disease – the most frequent trigger for ‘standard’ dementia in elderly people [3].

Dialysis does not help or stop the process of cognitive decline, thus it is high likely that factors that are not corrected completely by dialysis (for example the clearance of middle molecules, uncontrolled secondary hyperparathyroidism and anemia) may further the process of cognitive impairment.

On the other hand, kidney transplantation appears to reduce MCI and this change is likely to be stable a few years after transplantation, suggesting the potential for some reversibility. The reasons for this effect are still unclear. An attractive hypothesis is that the kidney produces neurotrophic factors that are necessary for normal cognition in the long term. However, several other hypotheses are equally possible at this stage.

Although the first description of uremic encephalopathy was published some 80 years ago, our understanding of brain dysfunction in CKD, prevention and treatment, is still in its infancy. Why should we be more optimistic today about an advance in this field? There are several reasons including a technological one. Indeed new high-throughput tools have become available that may provide new information on the early identification and pathogenesis of MCI-CKD. These techniques promise to unravel novel (neuro)toxins and to systematically verify their neurotoxic potential. In particular, fMRI and brain tractography, with their ability to combine morphological and functional imaging of the human brain in vivo with neuro-psychological testing are a unique opportunity. Furthermore, new transgenic animal models are now available that allow study of brain activity at the single neuron level in vivo that can be selectively activated using laser pulses (optogenetics). New technologies such as 2-photon microscopy and super-resolution microscopy should allow us to overcome some of the major limitations of previous imaging techniques. The ‘Clarity’ method can facilitate an unprecedented ability to investigate the 3D location of neurons in great detail. The possibility of deriving stem cells from patients and brain organoids could represent a new in vitro model for studying the pathogenesis and reversibility of MCI.

Finally, to shed light on MCI-CKD it is essential that we liaise closely with our clinical colleagues in neurology, neuro-psychology, and radiology, as well as basic scientists in neuroscience to address this anticipated major personal health and socioeconomic burden.

References

S 09 Brain and nervous system in CKD Friday, 11.45–13.15, Hall A1
The genetic landscape of hereditary amyloidosis

Research is showing the way forward to treatment

Amyloidoses are diseases associated with deposits of amyloid fibrils, usually in a systemic manner. The fibrils are aggregated proteins that self-agglomerate under a variety of circumstances, both physiologically and in vitro. The model of formation is of central interest because the treatment of each disease associated with human amyloidogenic proteins depends on its physical and chemical properties. In humans, the International Society of Amyloidosis Nomenclature Committee recognized 36 proteins that received the name amyloid, but naturally gave notice of the balance of multisystem involvement, variations and the kidney. The diagnostic approach involves pathologic evidence, reliable precursor identification, genetic assessment and estimation of amyloid burden. Recent studies also associated hereditary renal amyloidosis with a mutation in the FGA gene that represented the most common cause of hereditary renal amyloidosis in the UK and the second in Portugal.

The hereditary transthyretin amyloidosis (ATTRv), worldwide the most common form, was the first well-characterized route of knowledge concerning the protein and gene structure (now more than 130 mutations). Its research has enabled comprehensive epidemiologic and genetics studies related to a wide range of disease phenotypes.

The same amyloidogenic variants may have different presentations, in which manifestations of one organ, like the kidney, dominate at the beginning of the disease. However, progression of the disease may lead to a more monomorphic and standardized picture typically related to some mutations. Hereditary ATTR amyloidosis is an excellent example of this kind of course, including its renal profile. [2]

Advances in understanding the crucial steps in the amyloidogenic force can be effectively converted into therapeutic goals. These comprise amyloid fibril disruptors, inhibitors of fibrillogenesis, stabilizers of the amyloid precursor protein, and promoters of amyloid clearance. Pioneering drugs, aiming at gene knockdown and immunotherapy are in development, with the hope of specific targets and advantageous long-term achievements. [3]
#### GLP-1-RA in the treatment of diabetic kidney disease

Some, but not all, improve cardiovascular and clinical outcomes in RCTs

Glucagon-like-peptide-1 receptor agonists (GLP-1-RA) stimulate insulin secretion in a glucose-dependent manner using cyclic AMP (cAMP) for signal transduction via protein kinase A (PKA) and cAMP-regulated guanine nucleotide exchange factor 2 (Epac2). GLP-1-RA also inhibit gastric and small bowel motility and reduce appetite. The first GLP-1-RA was approved for clinical use in 2005 based on studies showing improved glucose control and less hypoglycemia. One GLP-1-RA, lixisenatide, is also approved for the treatment of obesity.

As stipulated by the Food and Drug Administration in 2008, cardiovascular (CV) safety of new antidiabetic drugs has been investigated in large outcome trials. In the end, those trials reported safety for most, if not all, new drugs. However, not only CV but also mortality benefit was demonstrated for a few new drugs, including some GLP-1-RA. In some of those CV outcome trials, kidney outcomes were also examined as secondary outcomes.

In order to be a valid partner, onco-nephrology should be further developed as a subdiscipline of nephrology.
RAASi and hyperkalaemia in cardiorenal disease: Opportunities for optimizing outcomes

April 15, 2019 was a good day for patients with diabetic kidney disease. The results of the CREDENCE study were published in the New England Journal of Medicine, demonstrating a significant 34% relative risk reduction in the progression of diabetic kidney disease in individuals with type 2 diabetes mellitus using canagliflozin 100 mg/d versus matching placebo.

Why was it such a good day? First of all, the results of the CREDENCE study clearly demonstrated a huge success in slowing the rate of progressive kidney function decline (composite primary endpoint consisting of a doubling of serum creatinine, initiation of renal replacement therapy, renal and cardiovascular death). This type of signal was seen first in the EMPA-REG OUTCOME trial with empagliflozin in 2016 (also published in the New England Journal of Medicine) and subsequently confirmed in the CANVAS program and in the DECLARE TIMI 58 study. Therefore in more than 30,000 trial participants, although studied for cardiovascular outcome reductions, SGLT2 inhibitors have shown the potential not only to reduce cardiovascular outcomes, but also to protect kidney function.

However, the big difference of the CREDENCE trial was that kidney outcomes, for the first time, constituted the primary endpoint. The other three earlier studies had the kidney outcomes as secondary endpoints and thus were considered exploratory. Most important, the relative risk reduction in CREDENCE had the same magnitude as in EMPA-REG OUTCOME, CANVAS and DECLARE TIMI 58, and this robust signal even appears to be greater than that seen with an angiotensin 2 receptor blocker in the RENAL and IDNT trials.

Patients in CREDENCE had a median baseline eGFR of 56 ml/min/1.73 m² and high albuminuria with a median daily urinary albumin excretion of close to 1 gram, and they were on stable ACE and ARB medication. Inclusion criteria even encompassed patients with a minimum eGFR of 30 ml/min/1.73 m². Therefore, the indication for treatment initiation may be expected to include lower ranges of kidney function, at least for canagliflozin in the near future.

In most parts of the world SGLT-2 inhibitors currently do not have an indication to start treatment in patients with an eGFR below 60 ml/min/1.73 m². This initial treatment indication was based on the rationale that a lower number of nephrons do not spill out glucose at a sufficient rate in order to provide adequate glycemic control. However, the field has moved forward beyond glycemic control, and CREDENCE has demonstrated a significant reduction in cardiovascular and renal outcomes even in patients with an eGFR of 30 ml/min/1.73 m².

Ongoing trials (EMPA KIDNEY, DAPA-CKD) are including non-diabetic kidney disease patients with even lower ranges of kidney function and no albuminuria. The supporting hypothesis is based on the assumption that tubulo-glomerular feedback is activated with subsequent reduction in intraglomerular pressure and single nephron hyperfiltration. All outcome data and mechanistic considerations leading to prevention of renal replacement therapy will be discussed in this session.
Since the first report of its effectiveness in ANCA-associated vasculitis (AAV) in 2001, the role of rituximab (RTX) has become increasingly central in AAV management. Non-inferiority of RTX use in patients with low IgG at the moment of RTX infusion, previous exposition to CYC and repeat RTX administrations; importantly hypogammaglobulinemia may be transient, although a minority of patients develop recurrent infections requiring replacement therapy. Of note, new drugs for AAV management are being tested, and future studies will need to provide information on how RTX use will change with the expansion of the therapeutic options.

In conclusion, RTX plays a central role in AAV both for induction and maintenance of remission and its use is going to expand further; however, several aspects still need to be clarified and on-going studies will contribute to further improve patients’ management.

It is now debated whether a RTX-based main- line on the management of obesity in renal transplant candidates, as well as in transplant recipients, bariatric surgery should be considered for transplantation, either from a deceased or living donor, cause it appears to have the lowest morbidity and implications in patients with obesity who have received a kidney transplant. Kidney transplantation, either from a deceased or living donor, remains the optimal treatment for obese patients with ESKD. Hence, wait-listing or transplantion should not be delayed solely on the basis of increased body mass index (BMI), as life expectancy in obese patients is improved by kidney transplantation. In obese patients evaluated for transplantation, wait list circumfer- ence (WC) and/or waist-hip ratio (WHR) should be measured in addi- tion to the BMI when looking at the impact on post-transplant outcomes. Although a high BMI (≥30) does not appear to be an independent predictor of mortality, obese ESKD can- didates for renal transplantation should be informed that it may be associated with an increased risk of graft failure, delayed graft function, wound morbidity, acute rejection and post-transplant diabetes mellitus.

Nevertheless, all obese ESKD waitlisted patients should be encouraged to lose weight and their nutritional status should be super- vised by a multidisciplinary dietary team. In young nephrologists through grants. In 2018 more than €320,000.00 were given in grants.
Vascular calcification in kidney disease: Epigenetics as a novel approach?

New BP goals and updates from SPRINT
More intensive BP reduction and falling GFR: hemodynamic effects or intrinsic tubular damage?

Hypertension is a major public health issue and affects more than 1 billion people worldwide. Hypertension still remains poorly controlled in a large proportion of the population despite effective pharmacotherapy. The new ACC/AHA guidelines now advocate a recommended target BP goal of <130/80 mmHg in most populations, including in the general population, those with chronic kidney disease (CKD) and diabetes mellitus.

These guidelines in the general population and in CKD patients were based primarily on the data from SPRINT (Systolic Blood Pressure Intervention Trial). This study included over 9,000 patients at increased cardiovascular (CV) risk, and approximately one third of patients had CKD and one third were older than 75 years. Subjects were randomized to a systolic blood pressure (SBP) goal of less than 140 mmHg (standard) versus 120 mmHg (intensive). Results showed significant reductions in combined CV outcomes and all-cause mortality in the group randomized to a less intensive SBP goal. A subgroup analysis in the CKD population has been published and showed similar results to those seen in the overall study population. Although CKD patients showed the same reduction in CV and all-cause mortality, there was no effect of the different BP goals on CKD progression.

There are two recent publications focusing on measurement of biomarkers in a subgroup of patients from the SPRINT study; one study focused on subjects with pre-existing CKD and the other on patients without pre-existing CKD who developed incident CKD during the study. Both studies measured a number of biomarkers associated with acute tubular function, injury and repair. Biomarkers were measured at baseline and at one year in both the studies and at four years in the patients with pre-existing CKD. Both studies showed that, in subjects randomized to more intensive BP goals, there was no increase in these biomarkers and surprisingly some of the biomarkers were actually decreasing, indicating that these changes in reduction in GFR were more likely due to hemodynamic changes and were not associated with chronic intrinsic tubular damage.

Another recently published, retrospective study focused on data from the 899 patients from the African American Study of Kidney Disease and Hypertension (AASK) and 761 patients from the Modification of Diet in Renal Disease (MDRD) Trial. The investigations assessed the effects of acute declines in renal function during intensive BP lowering and the effect on future risk of end-stage renal disease (ESRD) and long-term risk of death. The predictor was the percentage decline in estimated GFR (eGFR) (<5%, 5% to <20%, or ≥20%) between randomization and Months 3 and 4 of the trial. The study showed a 5% to <20% eGFR decline in the intensive BP arm was not associated with higher risk of ESRD in the AASK or the MDRD Trial. However, interestingly, eGFR decline of 5% to <20% in the usual BP arm was associated with a higher risk of ESRD in both studies. An eGFR decline of ≥20% was associated with higher risk of ESRD in both strict and usual BP arms. Therefore the study showed that acute eGFR declines of <20% during intensive BP lowering reduced long-term risk for ESRD and death.

In summary, these studies add to the argument that reductions in GFR due to more intensive BP control are most likely hemodynamic and are reversible. As most CKD patients die from CV-related causes, these studies seem to indicate that up to a 20% decline in GFR is acceptable to reduce CV events and death without causing major deleterious effects on kidney function.
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Tailoring a transplant route for the sensitized patient on dialysis

MARTA CRESPO BARRIO
Barcelona, Spain

Events such as transfusions, pregnancies or transplantation may induce antibody responses against foreign HLA antigens in any human being. These HLA antibodies act as a barrier that prevents some people with chronic kidney disease from accessing kidney transplantation. Historically, the approach to transplanting these patients has differed according to the transplant program and has had variable outcomes. In the last 15 years new methods, such as high throughput assays with much higher sensitivity to detect antibodies against a wide panel of HLA antigens – not always specific, as some of the HLA antigens are denatured – have entered the field. In addition, the community has incorporated new ways of expressing the degree of sensitization more accurately against real donors with the calculated panel reactive antibody (PRA). A calculator including the HLA typing of donors in that geographical area transforms the antibodies found in the serum into the possibility for a given donor to match a compatible donor in the deceased donor pool. Therefore, the proportion of sensitized and highly sensitized patients on the waiting list has grown exponentially, posing more challenges to all transplant programs.

It is important to understand these concepts so as to be able to discuss with our patients their best options for kidney transplantation. Highly sensitized patients – those with calculated PRA over a threshold determined by each program, country or organization – merit a special approach, as their rate of transplantation is low and their outcomes worse than in unsensitized patients. Highly sensitized candidates, especially, benefit from living kidney transplantation from potentially HLA-identical siblings. Even non-HLA identical siblings or other genetically related relatives offer a good opportunity for a higher degree of HLA matching and, therefore, less mismatching.

When the living donor is not compatible, paired-exchange donation for compatible or quasi-compatible transplantation, or desensitization, which provides better survival than dialysis, need to be planned. Paired-exchange living donation expands the possibilities of finding a matched compatible donor, with excellent results. Desensitization is nowadays based on plasma exchange and low-dose intravenous immunoglobulin or high-dose immunoglobulin and rituximab. Patient survival after desensitization is comparable to patient survival after HLA-compatible transplantation, but graft outcomes are inferior in the medium- to long-term after transplantation. These results may improve in future as new treatments are tested.

Because deceased donation and transplantation are a professional and efficacious activity in many countries, sensitized wait-listed patients also have good opportunities when specific programs to prioritize them are put in practice. The first and best example is the mature Eurotransplant program for highly sensitized patients. Other sharing programs have modernized their approach to match these recipients with compatible deceased kidneys, based mainly on using the new solid-phase assays to detect HLA antibodies and establishing the infrastructure to transport grafts. Nevertheless, this precious effort of the transplant community may not produce compatible transplantation in up to 35% of highly sensitized cases. These difficult-to-transplant patients need all options to be put in place and combined for the ultimate goal of receiving the best kidney transplant for a better life.

Figure © Marta Crespo Barrio

Extra renal involvement in AAV

ANCA-associated vasculitis (AAV) is a group of systemic diseases associated with antibodies against the cytoplasm of neutrophils (ANCA) targeted either to proteinase-3 (anti-PR3 antibody) or myeloperoxidase (anti-MPO) antibodies. AAV is clinically divided into granulomatosis with polyangiitis (GPA, formerly Wegener’s granulomatosis), microscopic polyangiitis (MPA) and the rarer eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome, with relatively sparse renal involvement). GPA is more frequently associated with anti-PR3 antibodies and MPA is more frequently, but not exclusively, associated with anti-MPO antibodies. Based on recent genetic studies it seems more appropriate to distinguish not between GPA and MPA, but between anti-PR3 and anti-MPO disease.

Kidney involvement (necrotizing crescentic glomerulonephritis) is present in almost all patients with MPA and in about 50–80% of patients with GPA, typically with more activity (necroses, crescents) in GPA and more chronicity (glomerulosclerosis) in MPA.

Extrarenal organ involvement is different in GPA compared to MPA, with ear, nose, throat (ENT) involvement being much more frequent in GPA (80–90%) than in MPA (20–30%) only. Lungs are also affected more frequently in GPA (60–80%) compared to MPA (only 20–30%); moreover the lung involvement is different in both GPA and MPA, respectively, characterized typically by pulmonary granulomas and alveolar hemorrhage in GPA and interstitial lung disease in MPA. Skin, joints and peripheral nerves are affected in both GPA and MPA, involvement of the heart and bowel is infrequent in both GPA and MPA, but may be life threatening. Eye involvement (of which the most serious is retinal infiltrate with proptosis) occurs infrequently almost exclusively in GPA, but may result in permanent loss of sight in the affected eye.

At presentation, compared to anti-MPO disease, anti-PR3 disease has higher clinical activity (in terms of BVAS – Birmingham Vasculitis Activity Score), more affected organs, more frequent ENT and lung involvement, typically granulomas (ENT, lung, eye) and is prone much more frequently to relapses. Anti-PR3 disease (due to its higher activity) may respond better to immunosuppressive treatment, but may require prolonged maintenance treatment and repeated induction treatment because of major (mostly extrarenal, typically pulmonary) relapses that may be life threatening.

Renal involvement significantly impairs the outcome of patients with AAV (4.45 times higher mortality) and mortality rate is even higher in patients with impaired renal function (5.1 times) and with end-stage renal disease (8.2 times). Lung involvement is another independent predictor of mortality (3.74 times higher mortality rate).

Since extrarenal (mostly pulmonary) relapses are more frequent in AAV than renal relapses (although renal relapses may be underdiagnosed), nephrologists must regularly check not only renal function and titers of dose intravenous immunoglobulin or high-dose immunoglobulin and rituximab. Patient survival after desensitization is comparable to patient survival after HLA-compatible transplantation, but graft outcomes are inferior in the medium- to long-term after transplantation. These results may improve in future as new treatments are tested.

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Figure © Vladimir Tesar

S 13
Precision medicine for the sensitized transplant recipient
Friday, 15.00–16.30, Hall F1

S 11
ANCA-associated vasculitis
Friday, 15.00–16.30, Hall G2A

ANCA, but also putative extra renal symptoms and promptly react to severe manifestations (e.g. alveolar hemorrhage) that may require immediate admission to the ICU. Patients with AAV should thus be treated in centers experienced in diagnosis and treatment of all putative extrarenal complications. Cooperation with other specialties, e.g. rheumatologist, ophthalmologist and ENT and/or lung specialists, must be warranted.
Managing resistant hypertension
What do the latest guidelines recommend?

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<tr>
<th>Recommendation (IC)</th>
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<td>It is recommended that hypertension be defined as resistant to treatment (i.e. resistant hypertension) when:</td>
<td>Recommended treatment of resistant hypertension is:</td>
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<td>• Optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy, which should include a diuretic (typically an ACE inhibitor or anARB with a CCB and a thiazide/thiazide-type diuretic), fails to lower clinic SBP and DBP values to &lt;140 mmHg and/or &lt;90 mmHg respectively; and</td>
<td>• Reinforcement of lifestyle measures, especially sodium restriction.</td>
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<td>• The inadequate control of BP has been confirmed by ABPM or HBPM; and</td>
<td>• Addition of low-dose spironolactone to existing treatment;</td>
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<td>• After exclusion of various causes of pseudoresistant hypertension (especially poor medication adherence) and secondary hypertension.</td>
<td>• Or the addition of diacoxin or a loop diuretic.</td>
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References

THSD7A antibody-induced disease
Recent evidence for pathophysiology and clinical patterns

Thrombospondin type 1 domain-containing 7A (THSD7A) is a highly glycosylated 250-kD protein. It has a large extra-cellular region, a transmembrane domain and a short intracellular tail. Following the discovery of THSD7A, its function was studied in zebrafish and it was shown that its soluble extracellular part is involved in angiogenesis. In 2014 anti-THSD7A antibodies were discovered in patients with membranous nephropathy (MN) who were negative for anti-Phospholipase A2 Receptor1 antibodies. Since THSD7A is expressed on human podocytes, it was concluded that THSD7A is an additional endogenous antigen in MN. Autoantibodies against THSD7A are detectable in 2–3% of patients with membranous nephropathy (MN). Its potential pathogenic role in human MN is supported by the finding in a patient, who lost his renal function due to MN and developed recurrent MN while having antibodies against THSD7A in his serum at the time of renal transplantation. Consequently, it was shown that the transfer of human anti-THSD7A antibodies into mice induced a disease similar to MN, which fulfilled Koch’s postulate. THSD7A antibodies can now be measured by a commercially available serum test, which allows, together with a typical increased expression pattern of THSD7A in glomeruli, an exact diagnosis.

Due to the rarity of THSD7A antibody-induced MN, there are no large cohort studies, which would allow sufficient conclusions how the course of the disease relates to antibody levels and how patients respond to therapy. In our cohort of 53 patients, which we observed over time after diagnosis, we found that the response to changes in antibody levels follows the same pattern as for patients with PLA2R antibody levels; i.e. a decrease in THSD7A antibody levels is followed by a reduction of proteinuria.

At the time of the discovery of THSD7A as an additional antigen in MN we assumed that it is a molecule exclusively responsible for the onset of what we still call ‘primary’ MN, considering that those patients have an autonomic disease compared to patients having ‘secondary’ MN, which is related to other diseases and has a different pathogenesis. Consequently, we observed, however, two patients who had malignant tumors in association with THSD7A antibody-positive MN.

When studied in detail, the tumors of those patients did show an increased expression of THSD7A. THSD7A was also found in follicular dendritic cells (FDC) of regional lymph nodes of the tumor, which were infiltrated by metastasis.

Since FDCs are involved in the formation of high-affinity antibodies we concluded that THSD7A, expressed in tumors, might serve as an antigen, induce the formation of antibodies which bind to THSD7A expressed on podocytes and induce MN. These initial findings are now confirmed by other investigators showing that benign (continued on page 20)
The cholinergic anti-inflammatory pathway (CAP) is a regulatory mechanism through which the autonomic nervous system impacts the immune response. Tissue injury, infection or ischemia triggers an immune response that generates signals through the sensory afferent vagus nerve to the central nervous system. An activating response is subsequently returned via the efferent part of the vagus nerve, referred to as the inflammatory reflex. This signal then reaches the celiac ganglion and is propagated in the adrenergic splenic nerve. Located in the proximity of catecholaminergic nerve endings, acetylcholine-synthesizing T-cells, also called ChAT cells, have been identified. These specialized T-cells are required for the attenuation of inflammation by targeting α7-nicotinic acetylcholine receptors (α7nAChR) on immune cells [1].

Vagus nerve stimulation (VNS) has been shown to inhibit cytokine release, attenuate tissue injury, and ameliorate inflammation-mediated injury in models of sepsis, arthritis, colitis and myocardial ischemia-reperfusion. Furthermore, it has recently been demonstrated that VNS implants reduce cytokine production and attenuate inflammation-mediated injury in models of sepsis, arthritis, colitis and myocardial ischemia-reperfusion. We could demonstrate that dialysis patients exposed to an environment of autonomic dysfunction, with decreased vagus nerve activity confirmed by heart rate variability measurements, which is a noninvasive measure of autonomic function, respond to cholinergic agonists ex vivo with reduced inflammation in a similar manner compared to healthy controls, suggesting a functional CAP. There were no differences between hemodialysis and peritoneal dialysis patients [4].

Preliminary results from a short-term VNS study in dialysis patients, using a minimally invasive method, will be presented. Anti-inflammatory effects of renal sympathetic nerve denervation for resistant hypertension in a model of LPS-stimulated cytokine release will also be discussed.
(continued from page 16) Tumors and other diseases that show an increased expression of THSD7A are also associated with THSD7A antibody-positive MN. These recent observations fit very well with what we found in a variety of benign and malignant tumors, which show a great variability in the expression of THSD7A. The tumor-associated THSD7A antibody-induced MN showed all the pathological characteristics as patients with ‘primary’ MN; i.e. autoantibody formation of IgGs predominantly IgG4 and binding of these antibodies to an antigen.

To study this in more detail we evaluated a large cohort of patients who had either ‘primary’ or ‘tumor associated’ MN. These studies demonstrate that there is no difference in the IgG subclass distribution between groups and that all patients had IgG4 subclass antibodies that bound the glomerular antigens. In order to better define the prevalence of tumors and other diseases that show an increased expression of THSD7A antibody-induced MN, we carefully screened our cohort of 53 patients with THSD7A antibody-positive MN and found that 26% of those patients had tumors. Thus, we conclude that each patient with THSD7A antibody-positive MN should be screened for the presence of benign or malignant tumors, which might eventually affect the clinical outcome of these patients.

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IgA nephropathy (IgAN) is a disease with variable clinical courses. At one end of the extremes are patients with microhematuria but no other clinical or laboratory abnormalities, previously referred to as ‘benign IgAN’. The other extreme are the very rare patients of ‘benign IgAN’ setting or in episodes of inflammation-triggered macrohematuria, where no antibody-induced MN showed all the pathological characteristics as patients with ‘primary’ MN; i.e. autoantibody formation of IgGs predominantly IgG4 and binding of these antibodies to an antigen.

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Recent Norwegian data with very long follow-up of 20–25 years show that about 30% of these patients enter spontaneous remission, another 30–50% have persistent urinary abnormalities but no GFR loss, whereas the remaining patients develop chronic kidney disease with 5% progressing to CKD stages 4–5. Unfortunately, these 5% cannot be identified prospectively, and thus only annual or bi-annual follow-up visits over long periods can select out the patients at risk.

The other extreme are the very rare patients with a vasculitic, rapidly progressive course of IgAN. This form of IgAN has a dismal renal prognosis with and without immunosuppression. It is important to interpret glomerular crescents, a central feature of vasculitic IgAN, in the context of the clinical course and to distinguish crescents associated with rapid loss of renal function from rare crescents in the setting of stable GFR and low proteinuria. Although recent large studies associate crescents with an adverse renal outcome, it is essential to realize that single crescents can even occur in the above ‘benign IgAN’ setting or in episodes of infection-triggered macrohematuria, where no body would consider immunosuppression. Thus, crescents need to be interpreted in the clinical context and many crescents will likely resolve with adequate supportive therapy, in particular intraglomerular or systemic blood pressure reduction.

The typical IgAN patient I see is in between the above extremes and exhibits some proteinuria, which is usually below the nephrotic range, has persistent microhematuria, arterial hypertension and frequently already has some degree of GFR loss. These patients benefit significantly from a comprehensive supportive approach, which extends way beyond ‘...I have given an ACE-inhibitor’, and includes advice on optimal blood pressure and, optimizing antiproteinuric measures and lifestyle (including sports activity, body weight, smoking, diet and alcohol). These comprehensive measures can be so effective that corticosteroids no longer add benefit, just adverse events [1]. After instituting these measures, patients with significant persistent proteinuria, defined as proteinuria above 0.75–1 g/day, may benefit from high-dose corticosteroids in terms of slowing down progressive GFR loss, but a recent trial (TESTING) had to be terminated early given an excess of adverse, sometimes lethal, events [2] Following the premature termination of this trial for safety reasons, a follow-up study (TESTING 2) with a lower corticosteroid dose has started.

Other immunosuppressive approaches including azathioprine, cyclophosphamide, rituximab and mycophenolate mofetil are either ineffective or have not yielded consistent therapeutic benefit. Fortunately, industry has ‘discovered’ IgAN and a considerable number of trials are ongoing. These new approaches include intestinal steroid thera-
The Congress Organising Committee is very pleased to announce the Run for Kidneys 2019 event which will take place on June 14, 2019 at 4.30 p.m. during the 56th ERA-EDTA Congress at Hungexpo-Budapest.

The Run for Kidneys 2019 proceeds will be donated directly to the Hungarian Nephrology Foundation.

Schedule:

1 p.m. Opening of the Run Centre
4 p.m. End of on-site registration
4.15 p.m. Opening ceremony & warm up
4.30 p.m. Start of the 5 km run
5.15 p.m. Announcement of results
(On-site registration closes 30 minutes before the start of the given race)

On-site registration:
Entry Hall III - Open on June 13, 2019 from 8 a.m. to 6 p.m. and on June 14, 2019 from 8 a.m. to 1 p.m.

The on-site registration can only be settled by cash payment. The registration fee is 20€. The on-site registration package does not include the unique cotton t-shirt made for the event.

Get fit, challenge yourself and raise awareness for an important issue. For you it’s just a Friday afternoon but for somebody it’s the chance to heal. Stay tuned and support your charity run during the Congress.

Your vote is important! Don’t forget to vote!

Only active full members (type A-B) who have paid their 2019 membership can vote for the election of two ERA-EDTA Ordinary Council Members. The personal and unique voting credentials can only be received through the "Members' Restricted Area" on the ERA-EDTA web-site. Voting is possible only through the online platform, from May 15, 2019 to June 15, 2019 (up to 9.30 am, CEST).
ERA-EDTA announce the first Scientific and Educational Interaction Day (SEID)
to be held on October 26, 2019

A day of succinct sessions focusing on clinical issues related to systemic diseases which affect the kidney; from prevention and diagnosis to therapy. It will also include a vascular access practical session.

On October 25, there will be an exclusive satellite: “New Drugs in Kidney Disease Symposium”

www.era-edta.org
Schedule your scientific and educational updates on your agenda

Save the dates!

SEID: October 26, 2019

57th ERA-EDTA CONGRESS: June 6-9, 2020
58th ERA-EDTA CONGRESS: June 5-8, 2021
59th ERA-EDTA CONGRESS: May 19-22, 2022
Don’t miss the General Assembly
Saturday, June 15, 9.30-10.45 Hall G2A

Admission is strictly reserved to ERA-EDTA members only (type A and B). Please have your ERA-EDTA membership card ready in order to enter the room. Important notice: only full ERA-EDTA members have the right to vote.

Impressions of Day 1
Impressions of Day 1

Visit the new website!

Simple, clear, intuitive and easily navigable from every device

Lots of advantages for our members!

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