ST HUNGARY – JUNE 13th – 16th 2019

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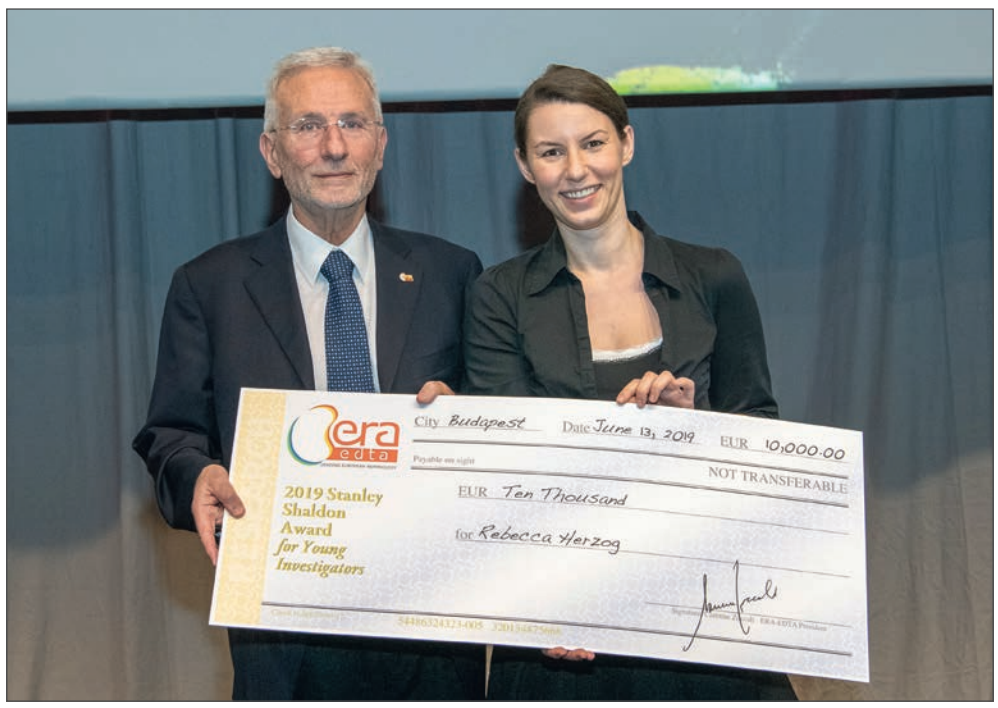
ERA-EDTA Operative Headquaters
Via XXIV Maggio, 38 – 43123 Parma, Italy

Issue #2 June 14th



ERA-EDTA President Professor Carmine Zoccali gives Dr Rebecca Herzog the ERA-EDTA Stanley Shaldon Award, which is accompanied by a cheque for € 10,000

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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 (WGIKD) of the ERA-EDTA in 2011. He was recognised as a Distinguished Fellow of the ERA-EDTA in 2013.

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

CLAUDIO RONCO

Vicenza, Italy

Claudio Ronco is Full Professor of Nephrology at the University of Padova and Director of the International Renal Research Institute

56th ERA-EDTA CONGRESS BUDAPEST HUNGARY – JUNE 13th – 16th 2019

Daily Congress Newspaper

Imprint: Editor in chief Dr. Bettina Albers – ERA-EDTA Press Office

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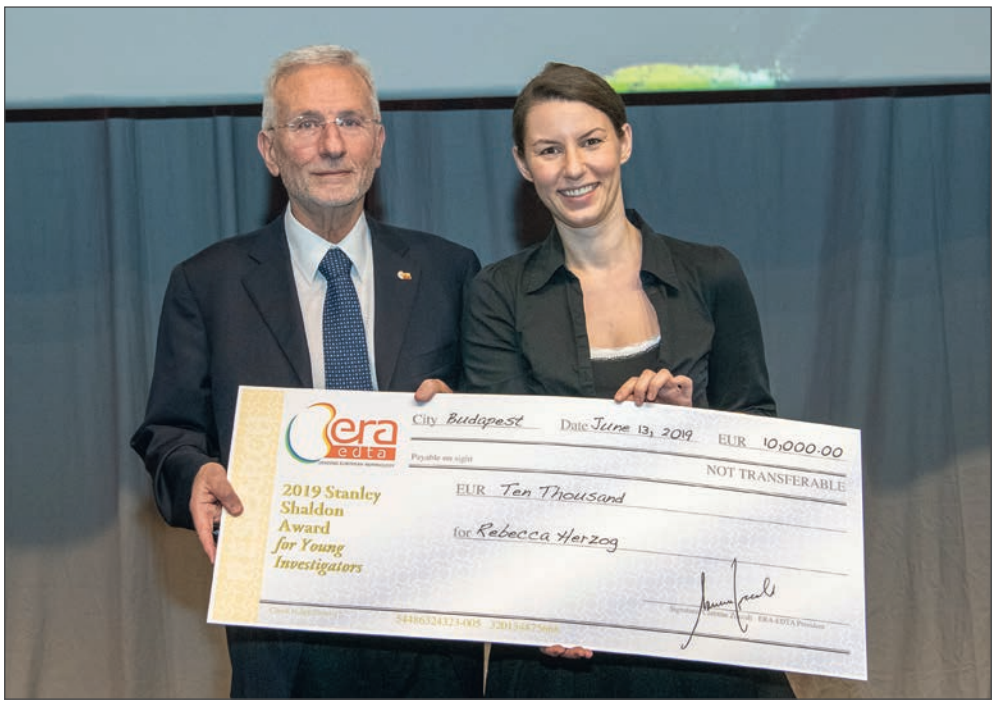
Via XXIV Maggio, 38 – 43123 Parma, Italy

Issue #2 June 14th

Grand welcome ceremony

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). ◘



ERA-EDTA President Professor Carmine Zoccali gives Dr Rebecca Herzog the ERA-EDTA Stanley Shaldon Award, which is accompanied by a cheque for € 10,000

ERA-EDTA Awards 2019

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

OLIVIER DEVUYST

Zurich, Switzerland

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 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.

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Vicenza, Italy

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 organises renown international courses in Vicenza attended by an international audience.

He authored 1,530 papers, 1,200 of them listed in Pub-Med, 82 books and 215 book chapters. He is honorary professor at the University of Virginia and Fudan & JaoTong Universities in Shanghai. He received an honorary degree in Medicine and Human Sciences at the University of Patras.

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

He is editor in Chief of 3 indexed journals: Cardiorenal 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.

Doctor Rebecca Herzog is the recipient of the 2019 ERA-EDTA Stanley Shaldon Award for Young Investigators

REBECCA HERZOG

Vienna, Austria

Rebecca Herzog is a translational researcher aiming to link omics-driven basic science and patient centred-clinical research in peritoneal dialysis. She received her PhD at the Medical University of Vienna in 2017. As research fellow of the Paediatric Nephrology Laboratory, in collaboration with Zytoprotec, a start-up spin-off company, she and her colleagues successfully developed a novel PD-fluid from experimental discovery to clinical application. As PostDoc at the "Christian Doppler Laboratory for Molecular Stress Research in PD" she now investigates molecular interventions to modulate cytoprotective mechanism in the dialysed peritoneal cavity. In her recent career Dr. Herzog discovered the role of a specific post-translational protein modification in PD, developed an immune-competence assay to clinical application and revealed the PD effluent proteome. She received 15 national and international awards and an ERA-EDTA short-term research fellowship. In 2019, Dr. Herzog has become a principal investigator in "IMPROVE-PD", a new EU-Horizon2020 MSCA-ITN project. ◘

INSTITUTIONAL

The hidden epidemic: Worldwide, over 850 million people suffer from kidney diseases

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 (422 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 there are 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

EBAC ACCREDITED SYMPOSIUM TO BE HELD DURING ERA EDTA 2019, BUDAPEST, HUNGARY

CHAIRMAN

John Deanfield, MD
London, United Kingdom

AGENDA

09:45 – 09:50 **Introduction**
John Deanfield, MD – *London, United Kingdom*

09:50 – 10:05 **Outcomes of SGLT2i in Diabetic Kidney Disease: Is it all diabetes?**
Rajiv Agarwal, MD – *Indianapolis, IN, USA*

10:05 – 10:20 **The knowns and unknowns of SGLT2 inhibition in CKD**
Paola Fioretto, MD – *Padua, Italy*

10:20 – 10:35 **The clinical landscape of managing patients with CKD: Where are we now and what can we expect?**
Will Herrington, MD – *Oxford, United Kingdom*

10:35 – 10:45 **Discussion**
All faculty

FRIDAY, JUNE 14, 2019 | 09:30 – 10:45 HRS | HALL F1

Supported by an unrestricted educational grant from Boehringer Ingelheim / Lilly.

"In compliance with EBAC guidelines, all speakers/chairpersons participating in this programme have disclosed or indicated potential conflicts of interest which might cause a bias in the presentations. The Organising Committee/Course Director is responsible for ensuring that all potential conflicts of interest relevant to the event are declared to the audience prior to the CME activities."

EDUCATION

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

NICHOLAS CHESNAYE
Amsterdam, The Netherlands

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, uremic 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, uremic 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. ◘

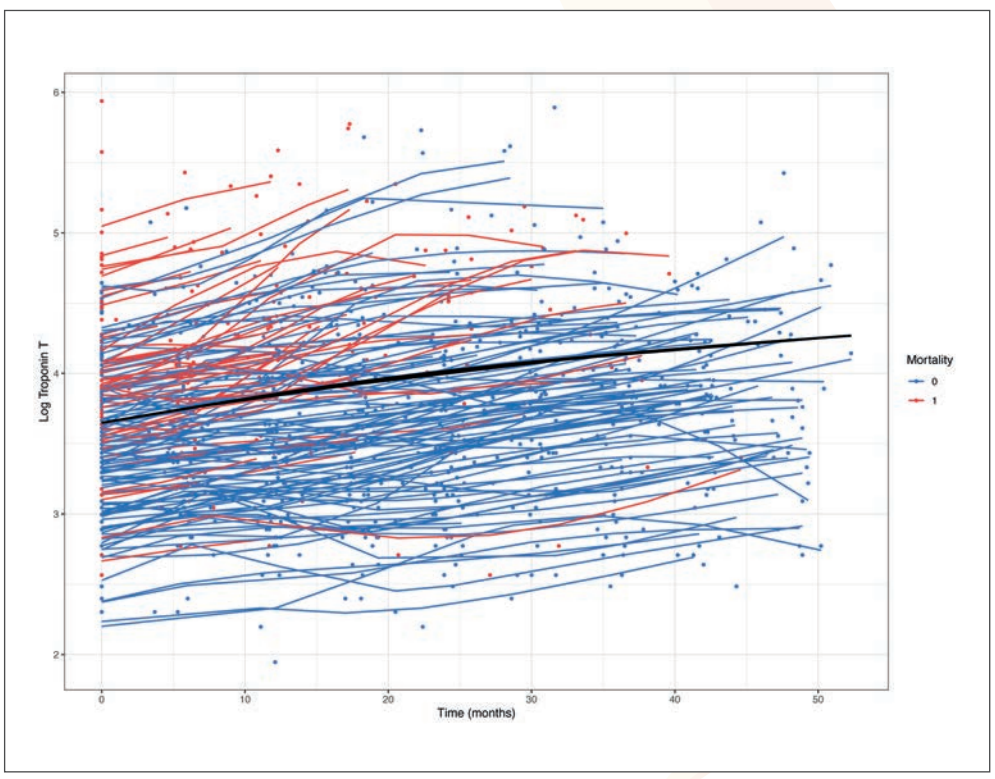


Figure: Individual TnT measurements (dots), individual predicted TnT trajectories (lines), and the population average predicted TnT trajectory. Individuals TnT trajectories are color coded by vital status. © Nicholas Chesnaye

S 01
ERA-EDTA Registry
Friday, 08.00 – 09.30, Hall G1

INSTITUTIONAL

"Looking forward to a positive future"
Interview with Carmine Zoccali, President of the ERA-EDTA

CARMINE ZOCCALI
Reggio Calabria, Italy
President of the ERA-EDTA

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 Massy 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-DOPPS) 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 research at a European level. This document will be soon 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 Fliser, 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 CME 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 Epidemiology, 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. It seems that the number of congress participants in Budapest will be higher than the number we had last year in Copenhagen – and this was already really high. 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 the special ERA-EDTA initiatives fit into the new structure?

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 forces to optimize 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, Andrzej Wiecek, 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.

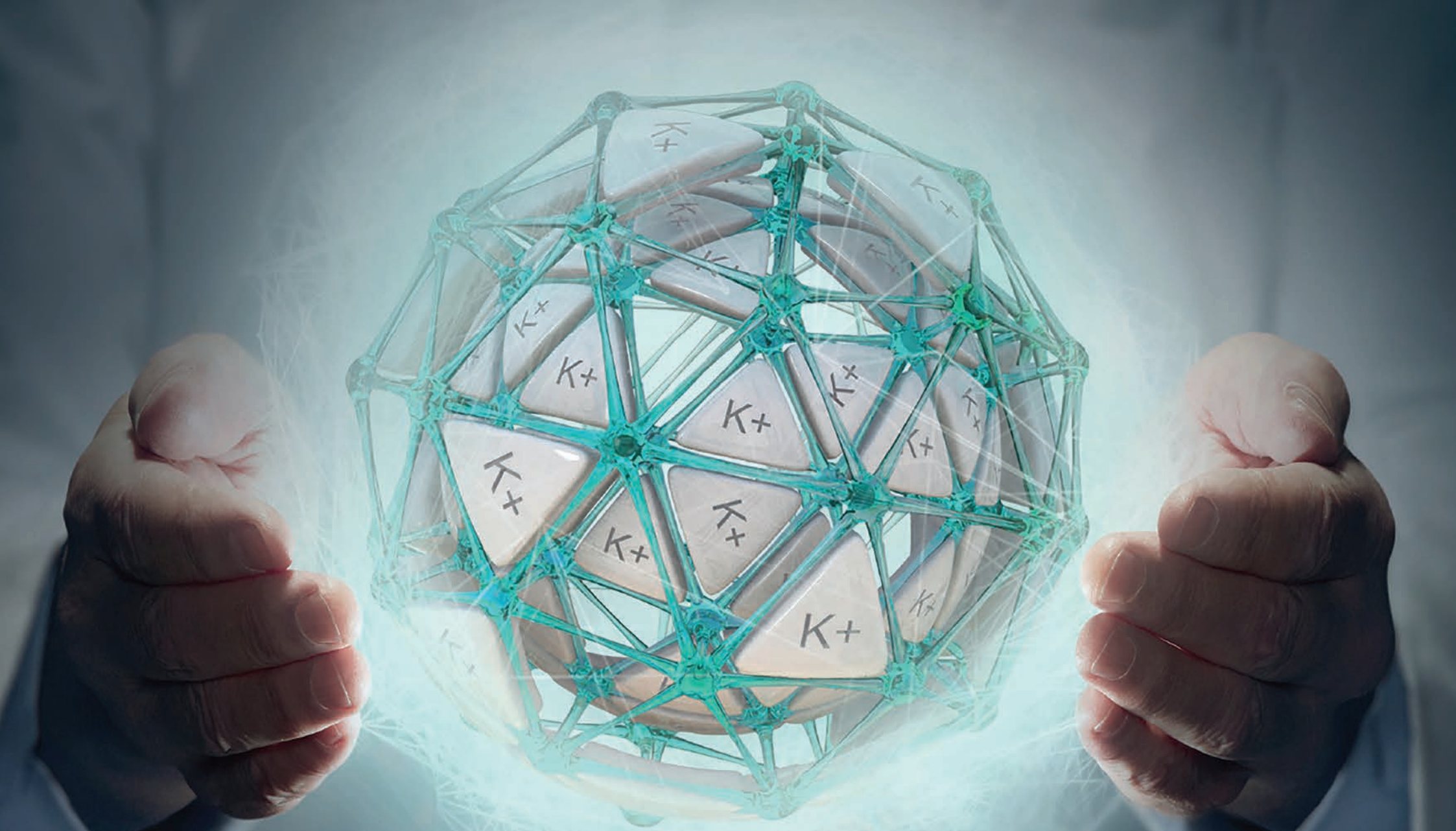
Over one third of ERA-EDTA members are women. Could you describe initiatives to support the representation and involvement of female nephrologists at all levels of the Society?

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 focus on ensuring 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. Hemodialysis, 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. I believe that by consolidating 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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Adverse events should be reported. Reporting forms and information can be found at https://aereporting.astrazeneca.com.

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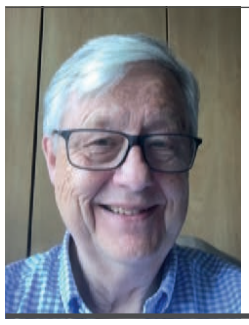
EDUCATION

Blood pressure in children

Important differences from hypertension in adults



KJELL TULLUS

London, United Kingdom

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. ◘

S 03
Paediatric Nephrology
Friday, 08.00–09.30, Hall G2B

EDUCATION

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

REINHOLD G. ERBEN

Vienna, Austria

Fibroblast growth factor-23 (FGF23) belongs to the group of endocrine fibroblast growth factors (FGFs), together with FGF19 and FGF21. FGF23 is a 32 kDa glycoprotein circulating in the blood stream. Only intact FGF23 is biologically active. Under physiological circumstances, the main site of FGF23 production is bone. Osteocytes and osteoblasts are the main FGF23-secreting cells in bone.

All FGFs signal through four tyrosine kinase receptors, FGF receptor (FGFR) 1, 2, 3, and 4. For high-affinity binding to FGFRs, endocrine FGFs require the presence of a co-receptor in the cell membrane, α- or β-Klotho. In the case of FGF23, the co-receptor is α-Klotho, and the most important FGFR in the kidney is FGFR1. The 3D atomic structure of the FGFR1/Klotho/FGF23 complex has recently been elucidated [1].

The kidney is one of the organs with the highest expression of αKlotho, and the main target organ of FGF23 signaling under normal conditions. It was previously believed that αKlotho is mainly expressed in distal renal tubules. However, several independent lines of evidence have shown that αKlotho 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 hyperphosphatemia 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.

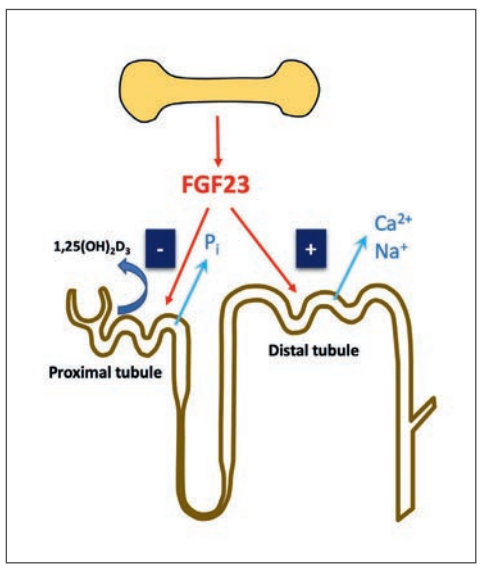


Figure © Reinhold Erben. Modified from: Erben, R. G. Nephrologe (2019). https://doi.org/10.1007/s11560-019-0344-9

In distal renal tubules, FGF23 enhances calcium and sodium reabsorption by increasing the abundance of the epithelial calcium 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]. Although solid experimental evidence so far is lacking, the sodium- and calcium-conserving functions of FGF23 in the distal nephron may have important implications for the pathophysiology of chronic kidney disease (CKD), because elevated circulating intact FGF23 may drive volume overload and vascular calcification in CKD patients. ◘

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S 02
Phosphate and FGF23
Friday, 08.00–09.30, Hall G2A

EDUCATION

Trends in excess mortality in European adults on RRT Excess mortality has fallen over time in all age groups

RIANNE BOENINK

Amsterdam, The Netherlands

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. ◘

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S 01
ERA-EDTA Registry
Friday, 08.00–09.30, Hall G1

EDUCATION

Monoclonal gammopathy of undetermined significance Establishing the causality is the hardest job

JOLANTA MALYSZKO

Warsaw, Poland

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 MGRS (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.

MGRS 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.

MGRS 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 (RI) and MGRS relates largely to the degree of underlying plasma malignancy, which clinically translates into varying treatment approaches.

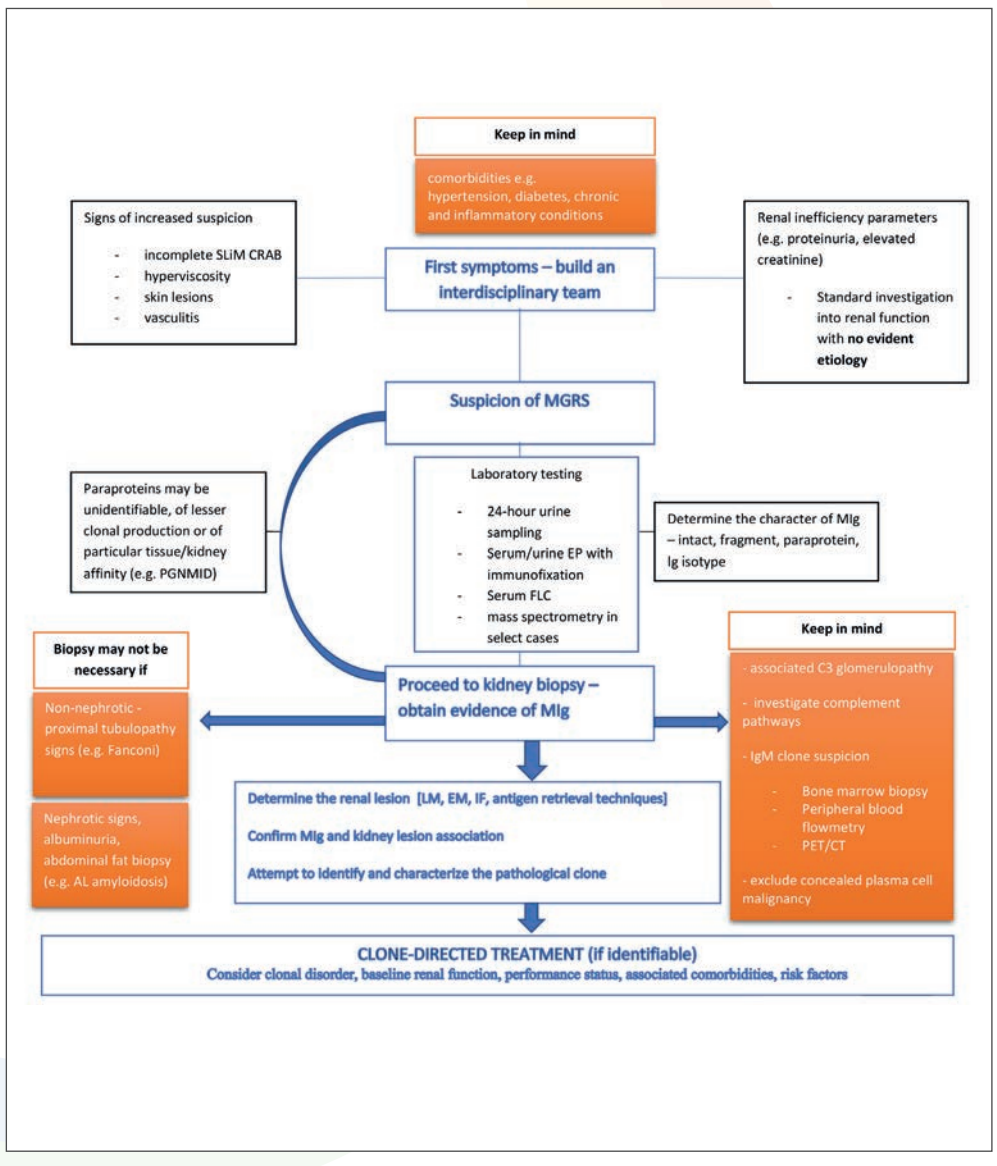

Figure From [1]. © NDT. Courtesy of NDT

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Kidney biopsy should be a binding feature of current diagnostic strategy, with immunofluorescence (IFE) and electron microscopy (EM) to evaluate the findings. There are certain pitfalls that support this approach, such as nodular sclerosis absent in many cases of MIDD (monoclonal immunoglobulin deposition disease). Amyloid deposits can be limited to the vasculature, also marking a different clinical profile, therefore biopsy remains necessary. It should be noted that the spectrum of pathology in MGRS is still being discovered.

Presenting symptoms should firstly be assessed. AL is likely suspected with > 50 % albuminuria, nephrotic syndrome and relatively retained kidney function as opposed to MIDD. Serum free light chain assay (sFLC) should be a first-line tool for screening in MGRS with light chain dyscrasia. On the other hand, an abnormal sFLC ratio should not be immediately attributed to monoclonal gammopathy. MIg detection can be achieved by serum and 24-hour urine collection electrophoresis. However, sensitivity is insufficient for the broad spectrum of MGRS. It can be improved by immunoelectrofluorescence-IFE, performed to discover MIg isotype. It is most sensitive for small B-cell masses producing intact immunoglobulins, but negative IFE does not rule out a clonal pathology.

There is a problem with test standardization for MGRS due to different disease subtypes. sFLC are not universal and have to be used in combination with urine and serum studies due to the vast heterogeneity of MGRS, with disease character dictating the findings. Noninvasive screening tools for plasma dyscrasia, especially with unexposed origin in MGRS are of interest. With the heterogeneity of MGRS, aside from determining conclusive histopathology character, exclusion of concealed plasma cell malignancy is necessary. In MGRS the most important issue is to find the responsible clone for timely introduction of the appropriate therapy. ◘

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S 06
The many faces of monoclonal gammopathy of undetermined significance
Friday, 11.45–13.15, Hall G2A

EDUCATION

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

GIOVAMBATTISTA CAPASSO

Naples, Italy

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 [1]. Is this a coincidence or actually evidence of a link between kidney disease and brain dysfunction? This 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 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 problem 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. ◘

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S 09
Brain and nervous system in CKD
Friday, 11.45–13.15, Hall A1

Impacting progression and outcomes of DKD:

Translating novel insights with GLP-1 RA to practice

EBAC ACCREDITED SYMPOSIUM TO BE HELD DURING ERA EDTA 2019, BUDAPEST, HUNGARY

CHAIR

Melanie Davies, MD
Leicester, United Kingdom

AGENDA

09:45 – 09:50 **Introduction**
Melanie Davies, MD – *Leicester, United Kingdom*

09:50 – 10:05 **Importance of protection and prevention in cardiorenal disease**
John Deanfield, MD – *London, United Kingdom*

10:05 – 10:20 **The science behind vascular and renal benefits of GLP-1 receptor agonists**
Filip Krag Knop, MD – *Copenhagen, Denmark*

10:20– 10:35 **Clinical outcomes of GLP-1 RA in kidney disease: Current evidence and ongoing trials**
Frederik Persson, MD – *Copenhagen, Denmark*

10:35 – 10:45 **Discussion**
All faculty

SATURDAY, JUNE 15, 2019 | 09:30 – 10:45 HRS | HALL F1

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EDUCATION

The genetic landscape of hereditary amyloidosis

Research is showing the way forward to treatment

LUÍSA LOBATO
Porto, Portugal

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 to expect more pathogenic proteins in the future years [1].

The most common renal amyloidoses are acquired and related to immunoglobulin light chain, AA amyloidosis and, at least in US, leukocyte chemotactic factor 2 amyloidosis. Initially regarded as contingent to particular regions, the hereditary forms are open to a large landscape of variants proteins, most of them with kidney involvement.

Renal amyloidosis is associated with altered proteins encoded by eight genes: transthyretin (*TTR*), fibrinogen A alpha chain (*FGA*), apolipoprotein AI (*APOA1*), apolipoprotein AII (*APOA2*), lysozyme (*LYZ*), gelsolin (*GSN*), apolipoprotein CII (*APOC2*) and apolipoprotein CIII (*APOC3*). Mutations in the *FGA* gene represented the most common cause of hereditary renal amyloidosis in the UK and the second in Portugal.

The diagnostic approach involves pathologic evidence, reliable precursor identification, genetic assessment and estimation of amyloid burden. Recent studies also associated hereditary amyloidosis with a mutation in the immunoglobulin k-light chain constant region, avoiding inappropriate chemotherapy in those patients.

Across all the nephropathic autosomal dominant forms, the mechanisms that lead to imbalance of multisystem involvement, variability of age of onset and lack of penetrance across generations do not help to proceed to a timely and correct classification of the diseases.

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 epidemiological 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] ◘

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S 08
Redefining the ontology of kidney diseases using genomic analysis
Friday, 11.45–13.15, Hall A1

EDUCATION

GLP-1-RA in the treatment of diabetic kidney disease

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

JOHANNES F. E. MANN

Munich, Germany

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 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 hypoglycemias. One GLP-1-RA, liraglutide, 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 or only collected as safety signals. This article summarizes kidney outcomes with GLP-1-RA based on large outcome trials. DPP-4 inhibitors that inhibit GLP-1 breakdown and increase endogenous GLP-1 will not be reviewed here. DPP-4 inhibitors did not in fact result in major CV or kidney benefits, including in those with diabetic kidney disease.

To date, four large CV outcome trials, each including 4,000 to 15,000 patients and a two to four year mean follow-up, have been reported, together with one smaller mechanistic study over one year with some 500 patients. Those trials examined lixisenatide (ELIXA), liraglutide (LEADER), semaglutide (SUSTAIN-6), exenatide (EXSCEL) and dulaglutide (AWARD-7). A further large trial (REWIND) with dulaglutide had a press release reporting CV benefits, but results will only be published in mid-June 2019. The above GLP-1-RA trials did show quite divergent results.

ELIXA tested lixisenatide, a relatively short-acting GLP-1-RA in very high CV risk patients and showed safety, but no CV or mortality benefits. As for the kidney, urine albumin creatinine ratio (UACR) increased less with lixisenatide than with placebo, but changes in GFR were no different between groups.

LEADER examined liraglutide, a long-acting, once-daily GLP-1-RA in high CV risk patients with a minimum follow-up of 3.5 years, and demonstrated significant reduction in both CV events and in mortality compared to placebo. Those benefits appeared to be greater in patients with eGFR < 60 ml/min. In addition, a composite kidney outcome was defined as a key secondary outcome: new macroalbuminuria, doubling of serum creatinine, end-stage renal disease (ESRD) or renal death. That kidney outcome was also reduced by this GLP-1-RA, mainly driven by the macroalbuminuria outcome. Also, the decrease in eGFR in those with CKD stage 3–4 was substantially lower with liraglutide.

SUSTAIN-6 tested semaglutide, a once-weekly GLP-1-RA in a study designed for safety analysis over two years with somewhat less than 4,000 participants. Surprisingly, that trial exhibited substantial and significant reductions in CV events and in the main composite kidney outcome (same outcome as in LEADER). Also, the decline in eGFR was substantially slower with this GLP-1-RA than with placebo.

EXSCEL examined exenatide in a huge trial with almost 15,000 participants and resulted in a small, though not significant, benefit for CV outcomes, but mortality was significantly less than with placebo. There were quite modest though significant benefits on UACR. Even ESRD was numerically less frequent with exenatide, but total numbers were low. AWARD-7 was a small (only 500 participants, one year) but very intriguing study because the control group was injected with insulin glargine, not with placebo as in the other four trials discussed above. In addition, all participants had CKD stage 3–4, with mean eGFR at baseline approximately 35 ml/min. The investigators were able to reduce HbA1c by > 1 % similarly with insulin and with dulaglutide (two doses). Despite identical metabolic control, the decline in eGFR was much faster with insulin than with the GLP-1-RA, supporting other analyses that changes in HbA1c over two to four years are unlikely explanations for the kidney benefits observed in LEADER and SUSTAIN-6.

There is convincing evidence that the woeful CV fate of people with diabetic kidney disease is improved by some, but not all, available GLP-1-RA. Additional evidence suggests, again for some GLP-1-RA, that survival is prolonged and progression of kidney disease can be alleviated. Those surprising and impressive findings will lead to focused kidney outcome trials. ◘

S 07
Improving outcomes in DKD
Friday, 11.45–13.15, Hall G2B

EDUCATION

MGRS treatment and the nephrologist

Should we follow the haematologist or take the lead?

BEN SPRANGERS

Leuven, Belgium

Monoclonal gammopathy of renal significance (MGRS) is a clonal proliferative disorder that produces a nephrotoxic monoclonal gammopathy that by itself does not meet hematologic criteria for treatment. The number of renal diseases possibly being MGRS-associated has grown substantially since its first description in 2012.

From the definition of MGRS it should already be clear that the management of patients with MGRS requires a close collaboration between nephrologists, hematologists/oncologists, and renal pathologists. Nephrologists are needed at several stages of the disease. At the time of diagnosis, nephrologists and renal pathologists are central in making the correct diagnosis of an MGRS-associated renal disease. Furthermore, in collaboration with the clinical biologist, a causal link should be established between the renal manifestations and the underlying B cell disease. This can often be challenging, especially in the context of MGRS-associated C3 glomerulopathy, aHUS and TMA, as there is no renal deposition of the monoclonal protein in these MGRS-associated renal diseases.

Nephrologists should also be actively involved in deciding whether a patient with an MGRS-associated renal disease should receive treatment and which treatment is optimal. Whereas in overt hematologic diseases the decision to treat is determined by hematologic criteria, this decision is much more complex in MGRS-associated renal diseases, and critically depends on input from the nephrologist regarding severity of renal involvement, speed of renal progression and functional status of the patient. Especially when no monoclonal protein can be identified in the serum (as often is the case in proliferative glomerulonephritis with monoclonal immunoglobulin deposition), the nephrologist sometimes has to persuade the hematologist to consider treatment. In the follow-up of MGRS-associated renal diseases, in addition to classic hematologic response criteria, nephrologic parameters should be included in determining treatment response in MGRS-associated renal diseases. The goal of the therapy should be a hematologic response of very good partial response (VGPR) or better and, in addition, improvement in proteinuria and/or GFR should accompany the VGPR.

In order to be a valid partner in decision making regarding MGRS treatment, nephrologists should develop and maintain expertise in different areas. First and foremost, to make a correct diagnosis of MGRS-associated renal diseases, up-to-date knowledge regarding the different renal manifestations of MGRS is essential. MGRS-associated renal diseases are rare and the spectrum has expanded substantially in the last years. Second, treatment decisions in the context of MGRS-associated renal diseases imply knowledge concerning the natural course of the different MGRS-associated renal diseases. At this moment, this information is lacking regarding several MGRS renal disease entities and research efforts should focus on this. Finally, the treatment of MGRS is clone directed, and nephrologists should have profound knowledge regarding available chemotherapies, side effects and dose adjustment in patients with decreased kidney function.

In conclusion, nephrologists should be actively involved in all stages of management of patients with MGRS-associated renal diseases. In order to be a valid partner, onco-nephrology should be further developed as a subdiscipline of nephrology. ◘

S 06
The many faces of monoclonal gammopathy of undetermined significance
Friday, 11.45–13.15, Hall G2A

EDUCATION

A good day for patients with diabetic kidney disease Update on SGLT2 inhibition in CKD

CHRISTOPH WANNER

Würzburg, Germany

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 RENAAL and IDNT trials.

Patients in CREDENCE had a median baseline eGFR of 56 ml/min/1.73 m^2 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 m^2. 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 m^2. 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 m^2.

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 the session. ◘

S 07
Improving outcomes in DKD
Friday, 11.45–13.15, Hall G2B

EDUCATION

Understanding the role of rituximab in AAV
Do we still need to shed lights on it?

FEDERICO ALBERICI

Milan, Italy

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-inferior to cyclophosphamide (CYC) in different clinical scenarios as induction regimen, RTX use in AAV is going to expand further thanks to the availability of biosimilars.

The identification of a role for this drug in maintenance of remission has been also game changing . The MAINRITSAN trial showed RTX superiority compared to azathioprine (AZA) in a cohort of patients mainly at the first flare of the disease and with remission induced with CYC. Retrospective studies also support its role in refractory-relapsing cohorts with remission induced with RTX; the on-going trial RITAZAREM will provide more information on this population.

It is now debated whether a RTX-based maintenance treatment (RMT) should rely on a fixed-interval schedule of administration or if a biomarker-guided approach might be considered. Simultaneous ANCA positivity and detectable circulating B-cells six months after induction with RTX is associated with negative response and there is therefore a rational for considering ANCA and B-cells as biomarkers for retreatment. This has been investigated in the MAINRITSAN2 trial, which explored a fixed-interval RTX-based maintenance regimen ('fixed-schedule' group) compared to a retreatment scheme guided by an increase of ANCA or B-cells repopulation ('individually tailored' group); of note, the latter allowed a median cumulative saving of 1 g of RTX. This study, powered to detect a 20 % between-arm difference in relapse rate, did not identify a statistically significant difference between the two groups, although flares were more frequent in the 'individually tailored' cohort (overall relapse rate 17.3 % versus 9.9 %, major relapse rate 7.4 % versus 3.7 %). Importantly, relapses without detectable B-cells or increase of ANCA were recorded, suggesting that more data are still needed in order to identify the ideal RMT strategy.

Several other aspects need to be clarified regarding RMTs. The majority of the schemes employed so far lasted 18–24 months; however, data on longer cycles are available, and for difficult-to-treat patients a prolonged RMT might be considered. Other unclear aspects are the ideal interval between administrations as well as the dose of each infusion and how these two variables may impact on long-term outcomes. Circulating B-cells may not in fact reflect what happens in other compartments, and relapses in B-cell-depleted patients, but with B-cells detectable in tissues, have been described. Of note, time to B-cell repopulation after an RMT is associated with the relapse-free survival and it may be hypothesized that more intensive RMT regimens might improve B-cell depletion, impacting on post-RMT relapse profile.

Although on average well tolerated, there are still concerns regarding RTX-related side effects. The infective risk in this population is increased, especially in patients with lung involvement and bronchiectasis, and of interest the prophylactic use of trimethoprim–sulfamethoxazole may be protective. Hypogammaglobulinemia may be recorded especially 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. ◘

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

EDUCATION

To transplant or not to transplant
A 'Hamletic' dilemma in obese candidates

ERBP European Renal Best Practice

DESCARTES working group Developing Education Science and Care for Renal Transplantation in European States

DAVIDE BOLIGNANO

Reggio Calabria, Italy

The clinical approach to obesity in patients with end-stage kidney disease (ESKD) being considered for transplantation, on the transplant waiting list, and in those who have received a kidney transplant poses striking challenges. In fact, conflicting evidence exists in this particular population setting for several key issues, including access to transplantation, transplant outcome and the role of interventions to address obesity.

Of note, despite its relevance, this issue has been only marginally addressed by previous international guidelines. To overcome this gap in clinical guidance, the DESCARTES working group and the European Renal Best Practice (ERBP) team of ERA-EDTA have recently finalized a compact clinical practice guideline on the management of obesity in renal transplant candidates and in renal transplant recipients. The guideline addresses the main challenges in defining obesity, the interventions to address obesity in waitlisted patients and in kidney transplant recipients, the impact of obesity on the likelihood of being waitlisted and on the transplant outcomes, and the management options and timing for interventions 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 transplantation 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.

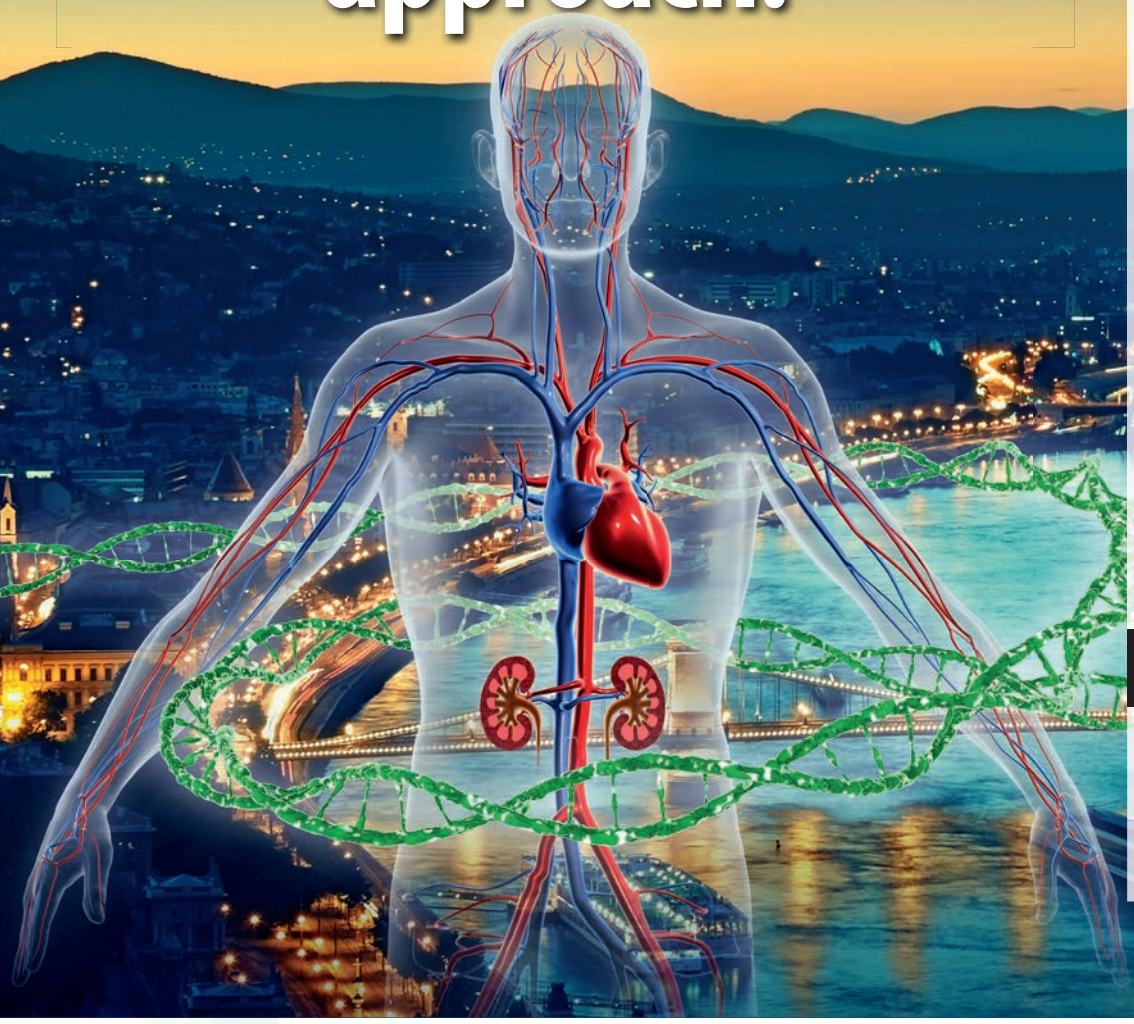
In obese patients evaluated for transplantation, waist circumference (WC) and/or waist-hip ratio (WHR) should be measured in addition to the BMI when looking at the impact on post-transplant outcomes. Although a high BMI (≥ 30) does not appear to be an independent predictor of mortality, obese ESKD candidates 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 supervised by a multidisciplinary dietary team. In transplant candidates, as well as in transplant recipients, bariatric surgery should be strongly advised for morbidly obese patients (BMI > 40) or in those with BMI > 35 and at least one major comorbid condition. Laparoscopic sleeve gastrectomy should be preferred over other surgical approaches, because it appears to have the lowest morbidity and because it allows the vast majority of patients to reach the required BMI with minimal surgical complications. Conversely, in transplant recipients, roux-en-Y gastric bypass should be avoided, as it may be associated with an increased risk of under-immunosuppression and hyperoxaluria.

The full DESCARTES-ERBP mini-guideline on the clinical management of obesity in renal transplant candidates and in renal transplant recipients will be soon made available to the nephrology audience. Hopefully, it will help to inform clinicians' management decisions and provide additional information to steer discussions with the patient. ◘

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

Vascular calcification in kidney disease: Epigenetics as a novel approach?



EBAC ACCREDITED SYMPOSIUM TO BE HELD DURING ERA EDTA 2019, BUDAPEST, HUNGARY

CHAIRMEN

Peter Stenvinkel, MD – *Stockholm, Sweden*
Jürgen Floege, MD – *Aachen, Germany*

Lunch will be provided

AGENDA

13:30 – 13:40 **Introduction**
Peter Stenvinkel, MD – *Stockholm, Sweden*

13:40 – 13:55 **Epigenetic mechanisms targeting ALP: A pathway for prevention?**
Marta Ruiz-Ortega, PhD – *Madrid, Spain*

13:55 – 14:10 **The role of ALP as predictor of cardiovascular events and vascular calcification in CKD**
Mathias Haarhaus, MD – *Stockholm, Sweden*

14:10 – 14:25 **Targeting residual cardiovascular risk & vascular calcification: The clinical perspective for BET inhibition**
Vincent M Brandenburg, MD – *Aachen, Germany*

14:25 – 14:30 **Discussion & summary**
Jürgen Floege, MD – *Aachen, Germany*

SATURDAY, JUNE 15, 2019 | 13:15 – 14:30 HRS | HALL A1

PACE-CME

Supported by an unrestricted educational grant from Resverlogix.

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RESVERLOGIX

New BP goals and updates from SPRINT

More intensive BP reduction and falling GFR: hemodynamiceffects or intrinsic tubular damage?

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

DEBBIE COHEN
Philadelphia, PA, USA

Hypertension is a major public heath 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 that 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 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 decreased, 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 investigators 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. ◘

S 10
ASN Highlights
Friday, 15.00–16.30, Hall G1

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EDUCATION

Tailoring a transplant route for the sensitized patient on dialysis

DESCARTES working group
Developing Education Science and Care for Renal Transplantation in European States

MARTA CRESPO BARRIO

Barcelona, Spain

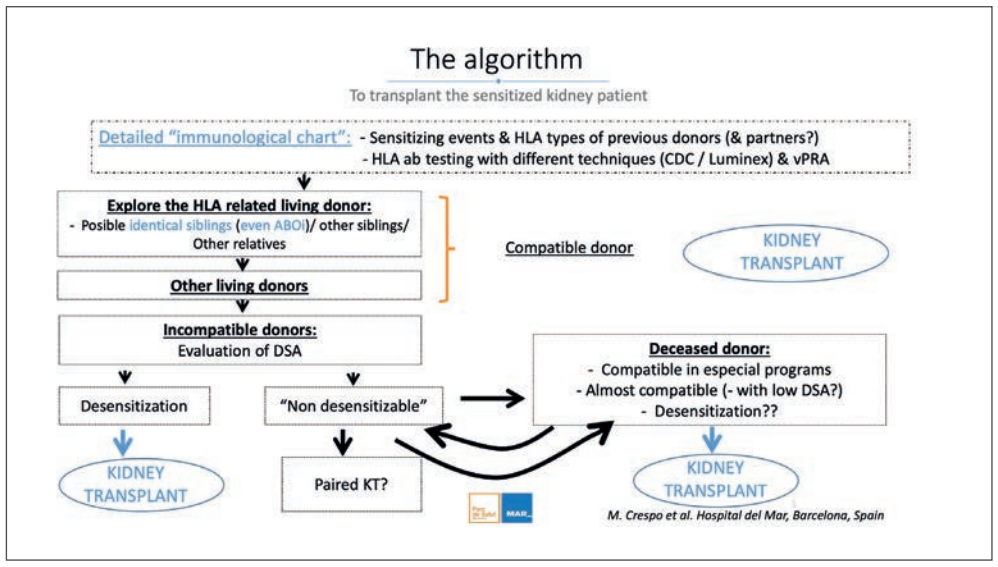

Figure © Marta Crespo Barrio

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 solid-phase assays with much higher sensitivity to detect antibodies against a wide panel of HLA antigens – not always specific, as some of the 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 lists 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 enter the plan. 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. ◘

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

EDUCATION

Extrarenal involvement in AAV

VLADIMIR TESAR

Prague, Czech Republic

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 retroorbital 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 ANCA, but also putative extrarenal 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, ophthalmologists and ENT and/or lung specialists, must be warranted. ◘

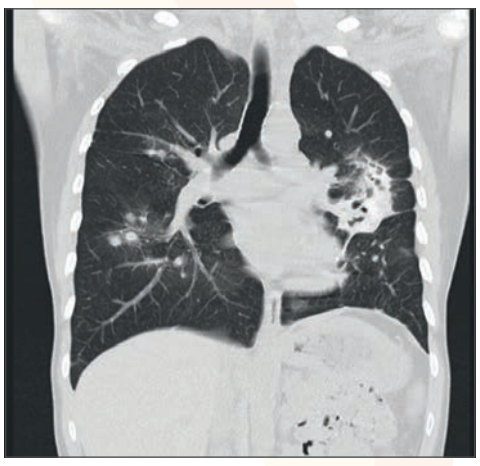

Figure © Vladimir Tesar

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

Managing resistant hypertension
What do the latest guidelines recommend?

ANDRZEJ WIĘCEK

Katowice, Poland

According to the recent 2018 ESC/ESH guidelines (Table 1), hypertension is defined as resistant to treatment when the recommended treatment strategy fails to lower office systolic blood pressure (SBP) and diastolic blood pressure (DBP) values to < 140 mmHg and/or < 90 mmHg respectively. The inadequate control of blood pressure (BP) is confirmed by ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM) in patients whose adherence to therapy has been confirmed [1].

Additionally, according the ESC/ESH guidelines, the recommended treatment strategy should include appropriate lifestyle measures and treatment with optimal or best-tolerated doses of three or more drugs. These should include a diuretic, typically an ACE inhibitor or sartan (ARB) and a calcium channel blocker (CCB). Pseudo-resistant hypertension and secondary causes of hypertension should also have been excluded [1].

Patients with resistant hypertension are at higher risk of hypertension-mediated organ damage, chronic kidney disease (CKD) and premature cardiovascular events [1, 2]. Recommended treatment of resistant hypertension according to the ESC/ESH guidelines [1] is to reinforce lifestyle measures, especially sodium restriction (particularly in patients with CKD) (3), the addition of low-dose spironolactone to the existing treatment (up to 50 mg/day) [3] or the addition of further diuretic therapy if intolerant to spironolactone (due to anti-androgenic side effects) with either eplerenone (50–100 mg/day) [4], amiloride (10–20 mg/d), a higher dose thiazide/thiazide-like diuretic (chlorthalidone or indapamide) or a loop diuretic (when the GFR is < 30 ml/min) [1]. Finally, addition of bisoprolol (5–10 mg/d) or doxazosin modified release (4–8 mg/d) is recommended [5]. It is emphasized that the use of mineralocorticoid receptor antagonists should be restricted to patients with eGFR ≥ 45 ml/min and a plasma potassium concentration ≤ 4.5 mmol/l, because of the risk of hyperkalemia [1].

New BP-lowering drugs (nitric oxide donors, vasopressin antagonists, aldosterone synthase inhibitors, neutral endopeptidase inhibitors and endothelin antagonists) are all under investigation [1, 6].

Novel treatment options of resistant hypertension include renal denervation, baroreceptor stimulation, central arteriovenous anastomosis and unilateral carotid body resection. However we need longer, sham-controlled studies before device-based therapy can be recommended for the routine treatment of resistant hypertension [1]. ◘

Recommendation (IC)	Recommendation (IB)
It is recommended that hypertension be defined as resistant to treatment (i.e. resistant hypertension) when:	Recommended treatment of resistant hypertension is:
• Optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy, which should include a diuretic (typically an ACE inhibitor or an ARB with a CCB and a thiazide/thiazide-type diuretic), fails to lower clinic SBP and DBP values to < 140 mmHg and/or < 90 mmHg, respectively; and • The inadequate control of BP has been confirmed by ABPM or HBPM; and • After exclusion of various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension.	• Reinforcement of lifestyle measures, especially sodium restriction. • Addition of low-dose spironolactone to existing treatment; • Or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone, amiloride, a higherdose thiazide/thiazide-like diuretic, or a loop diuretic; • Or the addition of bisoprolol or doxazosin.

Table 1: Definition and treatment of resistant hypertension according to the 2018 ESC/ESH Guidelines adapted from: Williams B, Mancia G, Spiering W et al 2018 ESC/ESH Guidelines for the management of arterial hypertension, European Heart Journal, Volume 39, Issue 33, 01 September 2018, Pages 3021–3104, https://doi.org/10.1093/eurheartj/ehy339

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S 12
Blood pressure targets
Friday, 15.00–16.30, Hall G2B

EDUCATION

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

ROLF A. K. STAHL

Hamburg, Germany

Thrombospondin type 1 domain-containing 7A (THSD7A) is a highly glycosylated 250-kD transmembrane protein. It has a large extracellular 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 pathogenetic 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. Consecutively, 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 PLA2R1 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 autoimmune disease compared to patients having 'secondary' MN, which is related to other diseases and has a different pathogenesis. Consecutively, 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)*

PLENARY LECTURES

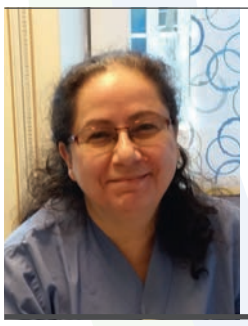
Interface of molecular mechanisms, pathology and genetics of developmental kidney diseases
Sanjay Jain - St. Louis, MO, USA
Today, 10.45-11.30 - Hall G1

Single-cell transcriptomics in kidney disease
Katalin Susztak - Philadelphia, PA, USA
Saturday, June 15, 10.45-11,30 - Hall G1

The pre-dialysis to renal replacement therapy transition
Csaba P. Kovesdy - Memphis, TN, USA
Sunday, June 16, 10.15-11.00 - Hall G1

EDUCATION

Targeting cytokine release The anti-inflammatory role of the parasympathetic system in CKD



ANNETTE BRUCHFELD
Stockholm, Sweden

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 disease severity in clinical studies of rheumatoid arthritis, which have also shown that inflammation correlates with autonomic dysfunction, and in particular reduced vagus nerve tone [2]. Neuroimmune interaction is also gaining attention as a novel therapeutic target in acute kidney injury (AKI) [3].

Increased morbidity and mortality in CKD remains a major challenge. Approximately one third of deaths among dialysis patients may be attributable to autonomic nervous system dysfunction. Increased sympathetic activity is also common in patients with chronic renal failure prior to end-stage kidney disease and has been shown to contribute to the increased risk of cardiovascular disease (CVD), and also to CKD progression. Although identified as a possible modifiable target, most of the focus in this research field has until recently focused on increased sympathetic activity and less on parasympathetic or vagus activity.

We investigated whether immune cells from chronically inflamed dialysis patients with autonomic dysfunction were able to react in a functional way after endotoxin exposure with lipopolysaccharide (LPS) and cholinergic suppression. 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 hemo- 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. ◘

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S 09
Brain and nervous system in CKD
Friday, 11.45–13.15, Hall A1

(continued from page 18) 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 pathogenetic 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 in 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. ◘

S 15
Primary glomeruloephritides
Friday, 17.00–18.30, Hall G2A

EDUCATION

Treatment of IgA nephropathy
What is the optimal approach in 2019?

JÜRGEN FLOEGE
Aachen, Germany

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'. 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 nobody 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 life-style (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 all 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, cyclosphosphamide, 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 therapy using enteric-coated budesonide, based on evidence of an altered intestinal mucosal barrier in IgAN. There are also several ongoing trials focusing on complement inhibition, including MASP, C3, C5, and components of the alternative pathway, and hopefully these will yield new approaches beyond systemic high dose corticosteroid therapy.

Our current stratified approach to the therapy of IgAN is shown in Figure 1. We are currently updating the 2012 KDIGO guidelines on the treatment of glomerular disease and publication can be expected in early 2020. ◘

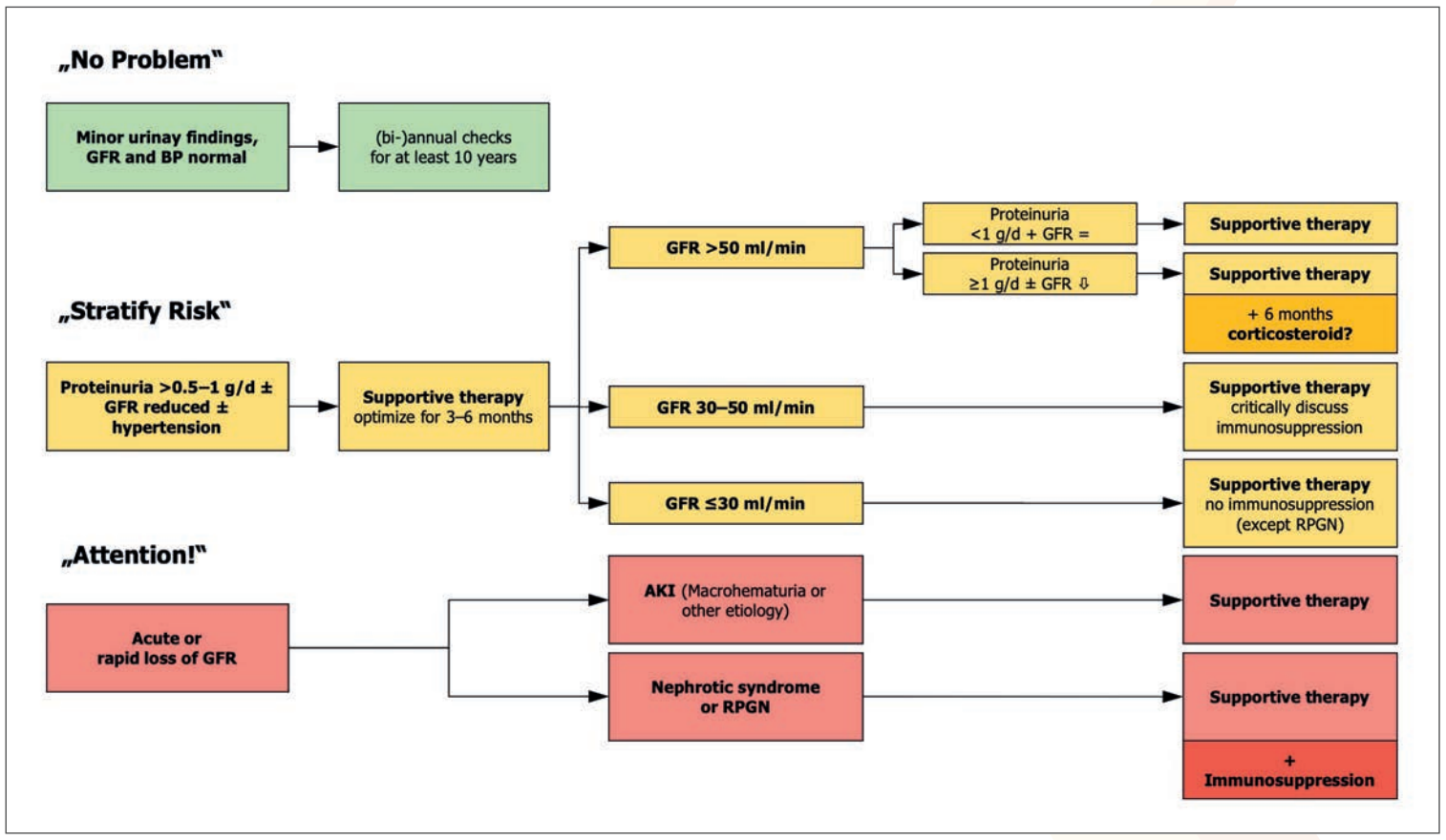

Figure: Synopsis of suggested therapeutic approaches to patients with IgAN depending on the clinical setting © Jürgen Floege

References

01. Rauen T, Investigators ST-I: Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. N Engl J Med 2015; 373:2225–36.
02. Lv J, et al: Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: The TESTING randomized clinical trial. JAMA 2017; 318:432–42.

S 15
Primary glomeruloephritides
Friday, 17.00–18.30, Hall G2A

RUN FOR KIDNEYS

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LEADING EUROPEAN NEPHROLOGY

Held jointly with
HUNGARIAN SOCIETY OF NEPHROLOGY

BUDAPEST JUNE 14 2019

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.

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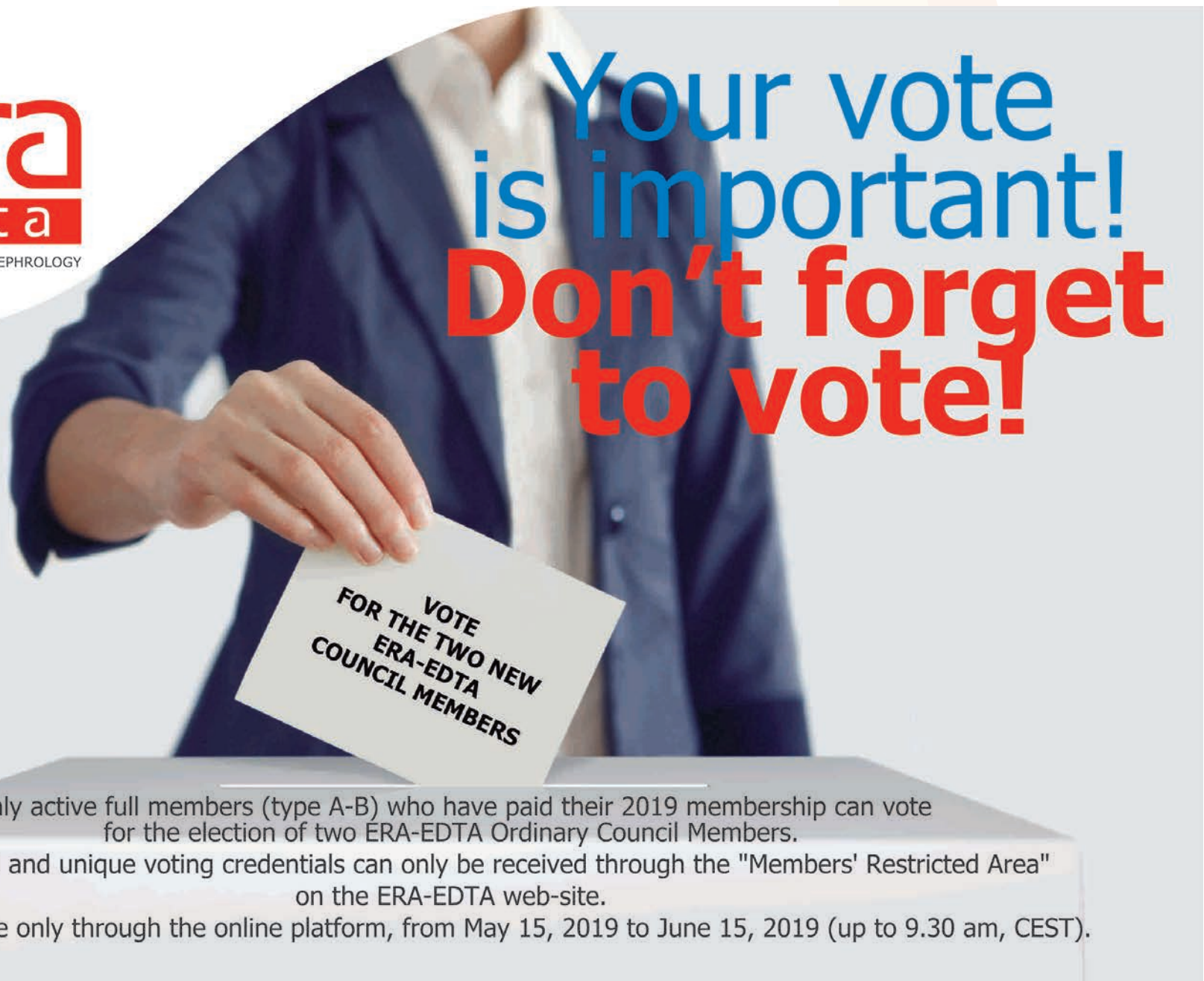

Only active full members (type A-B) who have paid their 2019 membership can vote for the election of two ERA-EDTA Ordinary Council Members.
The personal and unique voting credentials can only be received through the "Members' Restricted Area" on the ERA-EDTA web-site.
Voting is possible only through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

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LEADING EUROPEAN NEPHROLOGY

ERA-EDTA announce the first Scientific and Educational Interaction Day

SEID

to be held on October 26, 2019

A day of succinct sessions focussing 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"

EDUCATIONAL

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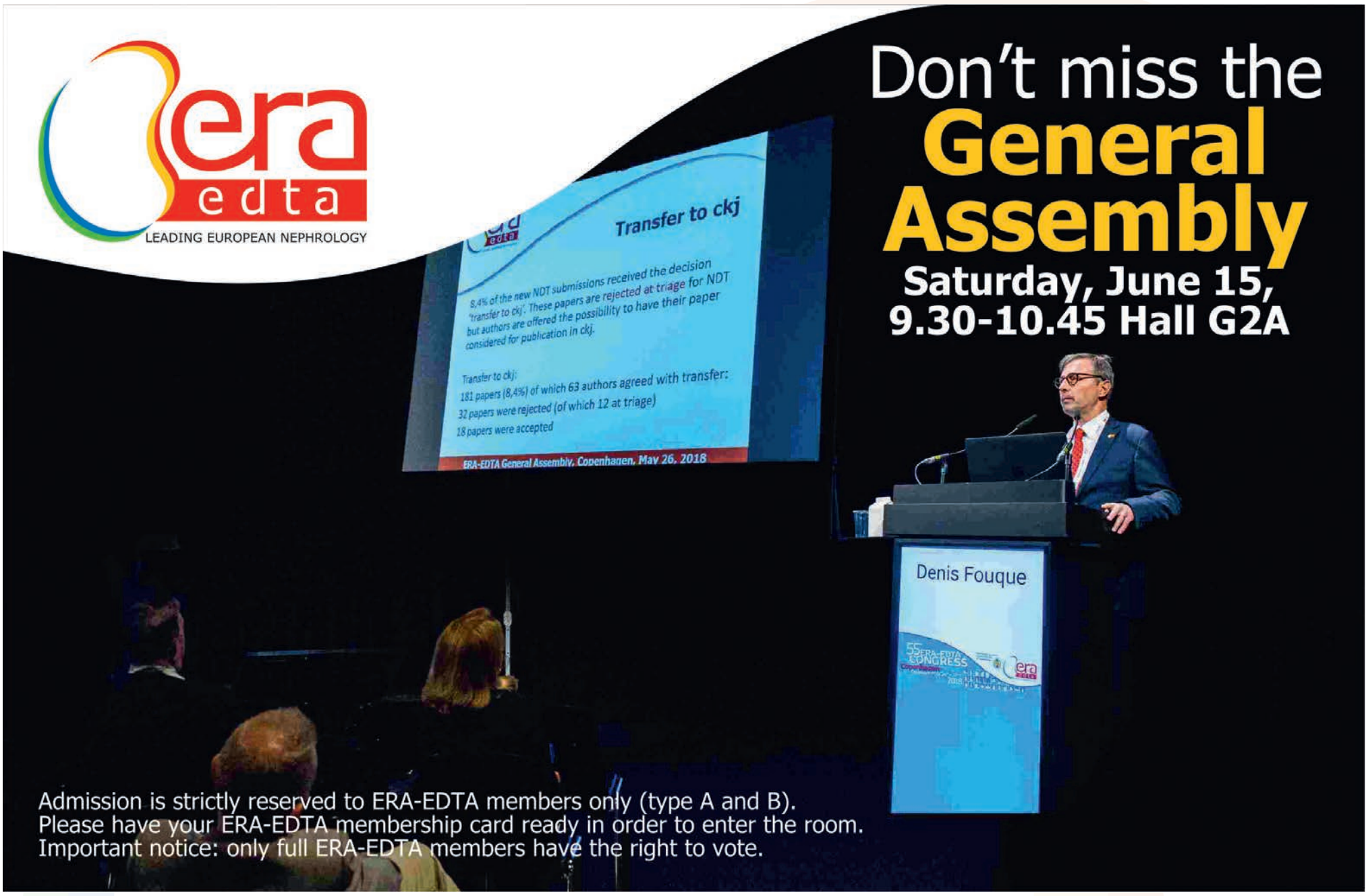
LEADING EUROPEAN NEPHROLOGY

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



Impressions of Day 1

Visit the new website!

Simple, clear, intuitive and easily navigable from every device

Lots of advantages for our members!

- Very easy access to exclusive content in the restricted area
- Stay updated with ERA-EDTA's new initiatives
- Find out about the latest novelties of the Committees and Working Groups
- Actively participate in the growth of the Association

Impressions of Day 1