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

Issue #3 June 15th

Clinical Trials

The prospective, randomized, open-label UBI trial provides strong evidence that treating metabolic acidosis with sodium bicarbonate is safe and improves kidney and patient survival in chronic kidney disease (CKD). The trial randomized 740 patients with CKD stages 3b and 4 to sodium bicarbonate (n = 376) or standard care without sodium bicarbonate (n = 364). Mean (SD) daily dose of sodium bicarbonate was 1.13 (0.10), 1.12 (0.11), and 1.09 (0.12) mmol/kg-bw/day in the first, second, and third years of follow-up, respectively. After mean (SD) follow-up of 29.6 (9.8) months for standard care and 30.3 (10.7) months for bicarbonate, serum creatinine doubling occurred in significantly fewer patients randomized to bicarbonate: 6.6 % vs 17.0 % for standard care (HR 0.36; 95 % CI 0.22–0.58; p < 0.001). By the end of the study, 6.9 % receiving sodium bicarbonate had start-

s in Hyperkalaemia

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Leader, AstraZeneca
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Issue #3 June 15th

Late Breaking Clinical Trials

The DPP-4 inhibitor linagliptin improved albuminuria, but had no effect on eGFR and cardiovascular risk in type-2 diabetes and nephrotic-range proteinuria (NRP) in the CARMELINA trial. These results come weeks after publication of the positive CREDENCE trial with the SGLT2 inhibitor canagliflozin. CARMELINA lead investigator Christoph Wanner said: "The study clearly showed that there is a group of patients with diabetes who clearly are in need of outcome-enhancing therapies, because their prognosis is rather poor. NRP might be a good marker to stratify these patients. I would advise to treat these patients with SGLT2 inhibitors instead, or a combination of SGLT2 inhibitor and DPP-4 inhibitor. Apart from diabetes control, SGLT2 inhibitors have been shown to be effective in renal and cardiovascular risk reduction." CARMELINA was a multicenter, randomized, double-blind trial comparing linagliptin 5 mg with placebo, added to standard care, in people with type-2 diabetes and cardiovascular disease and/or kidney disease. Of 6,979 randomized participants, 646 had NRP (UACR ≥ 2200 mg/g at baseline). During the study, regression to normoalbuminuria or UACR reduction ≥ 50 % from baseline was more likely with linagliptin than in the placebo group. There was no between-group difference in loss of kidney function: NRP eGFR-slopes: linagliptin –6.51 ml/mm/year vs placebo –7.07 ml/mm/year. Linagliptin did not reduce risks for major adverse cardiovascular events (HR1.02 [95 % CI; 0.89–1.17]), cardiovascular mortality (0.96 [0.81–1.14]), or all-cause hospitalization (0.93 [0.85–1.00]) in people with or without NRP (all interaction p-values > 0.05). ◘

CHRISTOPH WANNER

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The prospective, randomized, open-label UBI trial provides strong evidence that treating metabolic acidosis with sodium bicarbonate is safe and improves kidney and patient survival in chronic kidney disease (CKD). The trial randomized 740 patients with CKD stages 3b and 4 to sodium bicarbonate (n = 376) or standard care without sodium bicarbonate (n = 364). Mean (SD) daily dose of sodium bicarbonate was 1.13 (0.10), 1.12 (0.11), and 1.09 (0.12) mmol/kg-bw/day in the first, second, and third years of follow-up, respectively. After mean (SD) follow-up of 29.6 (9.8) months for standard care and 30.3 (10.7) months for bicarbonate, serum creatinine doubling occurred in significantly fewer patients randomized to bicarbonate: 6.6 % vs 17.0 % for standard care (HR 0.36; 95 % CI 0.22–0.58; p < 0.001). By the end of the study, 6.9 % receiving sodium bicarbonate had start-

Consequences and Challenges in Hyperkalaemia in Chronic Kidney Disease

Worldwide, an estimated 200 million people have chronic kidney disease (CKD), placing them at risk for hyperkalaemia. [1] As their kidney disease progresses and renal function declines, their ability to maintain potassium homeostasis is increasingly impaired, leading to hyperkalaemia. [2]

Moreover, patients with end-stage renal disease (ESRD) suffer from recurrent hyperkalaemia despite being on adequate dialysis. [3] Dialysis therapies are meant to restore the balance of potassium, but due to the intermittent treatments, typically delivered three times a week, patients on haemodialysis experience high levels in serum potassium concentration. [3] Potassium concentrations increase between dialysis sessions, and prevalence and severity of hyperkalaemia is highest after the long interdialytic interval (LIDI). [3,4,5]

The potential impacts of hyperkalaemia are many, putting ESRD patients at high risk of serious consequences if left untreated. Hyperkalaemia is associated with increased all-cause mortality and cardiovascular (CV) mortality. [5] Higher mortality rates are observed after the LIDI. [6–8] In patients on haemodialysis, arrhythmias and cardiac arrests caused by hyperkalaemia account for 40 percent of deaths. [9] *(continued on page 3)*

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ed renal replacement therapy vs 12.3 % of the standard care group (p = 0.004; HR 0.5; 95 % CI: 0.31–0.81; p = 0.005). Overall mortality was significantly lower in sodium bicarbonate-treated patients: 3.1 % vs 6.8 % for standard care (p = 0.004; HR 0.43; 95 % CI 0.22-0.87; p = 0.01). Sodium bicarbonate was well tolerated, with no significant effects on blood pressure, total body weight or hospitalizations. "There are relatively few treatments that have been shown to slow progression of CKD. As nephrologists, we have used sodium bicarbonate to correct metabolic acidosis in people with CKD for some time, but definite evidence of benefit has been lacking. Our study shows that this very cost-effective treatment is safe and improves kidney and patient survival," concluded lead investigator Antonio Bellasi.

In the VITALE study, compared with recommended doses, high doses of oral vitamin D_3 (cholecalciferol) were safe and lowered the risk of fractures in kidney transplant recipients, but had no effect on non-skeletal outcomes. Lead VITALE investigator Marie Courbebaisse commented: "Our study shows that currently recommended doses of vitamin D are not sufficient to protect patients from the risk of fracture after kidney transplantation. This challenges advice in the current international KDIGO guidelines, which recommend using low doses of cholecalciferol similar to those recommended for the general population." The VITALE study was a prospective,

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multicenter, double-blind, controlled trial including 536 adult renal transplant recipients with serum 25(OH)-vitamin D levels < 30 ng/mL. Patients were randomized 12–24 months after kidney transplant to high doses (100,000 IU) or low doses (12,000 IU corresponding to minimum recommended intake of 400 UI/day) of cholecalciferol every two weeks for two months, then monthly for 22 months. At the end of the study, the incidence of fractures was significantly lower in the high-dose group (1 % vs 4 % for low dose, p = 0.02). There was no difference between the groups on the composite primary endpoint of diabetes, major adverse cardiovascular events, de novo cancer and patient death (15 % for high dose vs 16 % for low dose). There were no differences in infections (51 % vs 47 %), acute rejection episodes (3 % vs 2 %) and graft loss (0.37 % in both groups). There were also no significant differences in risks of hypercalcemia, hyperphosphatemia, urinary calcium:creatinine ratio or vascular calcification.

In a phase 3 study, daprodustat was non-inferior to epoetin beta pegol (continuous erythropoietin receptor activator; CERA) in maintaining hemoglobin (Hb) levels within target range in Japanese non-dialysis patients with anemia of chronic kidney disease (CKD). According to the investigators, these results suggest that daprodustat could offer a new treatment option for anemia in this group of patients. Daprodustat is an oral hypoxia-induc-

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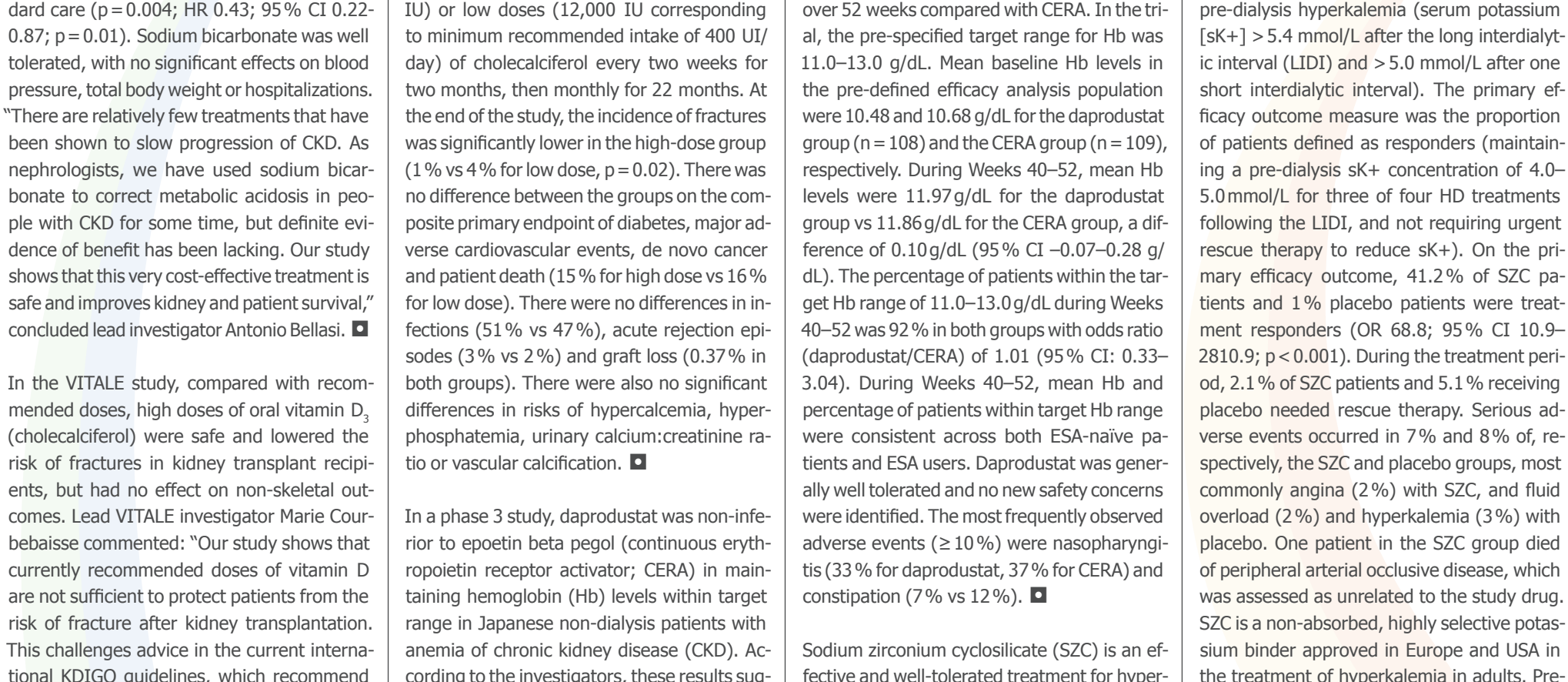
ible factor-prolyl hydroxylase inhibitor that is currently under investigation for the management of anemia of CKD. The multicenter, open-label, randomized controlled trial evaluated the efficacy and safety of daprodustat over 52 weeks compared with CERA. In the trial, the pre-specified target range for Hb was 11.0–13.0 g/dL. Mean baseline Hb levels in the pre-defined efficacy analysis population were 10.48 and 10.68 g/dL for the daprodustat group (n = 108) and the CERA group (n = 109), respectively. During Weeks 40–52, mean Hb levels were 11.97 g/dL for the daprodustat group vs 11.86 g/dL for the CERA group, a difference of 0.10 g/dL (95 % CI –0.07–0.28 g/dL). The percentage of patients within the target Hb range of 11.0–13.0 g/dL during Weeks 40–52 was 92 % in both groups with odds ratio (daprodustat/CERA) of 1.01 (95 % CI: 0.33–3.04). During Weeks 40–52, mean Hb and percentage of patients within target Hb range were consistent across both ESA-naïve patients and ESA users. Daprodustat was generally well tolerated and no new safety concerns were identified. The most frequently observed adverse events (≥ 10 %) were nasopharyngitis (33 % for daprodustat, 37 % for CERA) and constipation (7 % vs 12 %).

Sodium zirconium cyclosilicate (SZC) is an effective and well-tolerated treatment for hyperkalemia in patients with end-stage renal disease (ESRD) managed by hemodialysis. This is the conclusion of the randomized, dou-

STEVEN FISHBANE

Great Neck, USA

ble-blind, placebo-controlled, international phase 3b DIALIZE study. Investigators assigned 196 patients managed ≥ 3 months with three-times-weekly HD to SZC (n = 97) or placebo (n = 99) for four weeks. All patients had pre-dialysis hyperkalemia (serum potassium [sK+] > 5.4 mmol/L after the long interdialytic interval (LIDI) and > 5.0 mmol/L after one short interdialytic interval). The primary efficacy outcome measure was the proportion of patients defined as responders (maintaining a pre-dialysis sK+ concentration of 4.0–5.0 mmol/L for three of four HD treatments following the LIDI, and not requiring urgent rescue therapy to reduce sK+). On the primary efficacy outcome, 41.2 % of SZC patients and 1 % placebo patients were treatment responders (OR 68.8; 95 % CI 10.9–2810.9; p < 0.001). During the treatment period, 2.1 % of SZC patients and 5.1 % receiving placebo needed rescue therapy. Serious adverse events occurred in 7 % and 8 % of, respectively, the SZC and placebo groups, most commonly angina (2 %) with SZC, and fluid overload (2 %) and hyperkalemia (3 %) with placebo. One patient in the SZC group died of peripheral arterial occlusive disease, which was assessed as unrelated to the study drug. SZC is a non-absorbed, highly selective potassium binder approved in Europe and USA in the treatment of hyperkalemia in adults. Previous clinical studies demonstrated the efficacy and safety of SZC, but these studies excluded patients with ESRD.



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(continued from page 1) Hyperkalaemia is independently associated with greater short-term risk of hospitalisations and emergency room visits. [10]

For many patients with CKD, well-tolerated and effective therapies to manage hyperkalaemia and to control potassium levels are urgently needed.

As a company, we continue to explore medicines that could potentially address multiple points of the disease journey – from modifying the progression of the disease itself to managing potentially life-threatening complications that may arise in later stages of CKD. We are determined to make a difference for patients with CKD.

I'm grateful for the opportunity to be at ERA-EDTA to connect with leading experts in nephrology to discuss the greatest clinical challenges today, including hyperkalaemia, and how together, we can solve them.

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ASSOCIATION

ERA-EDTA leads the way to 'greener' healthcare

An interview with Peter J Blankestijn, Utrecht, The Netherlands

PETER J BLANKESTIJN

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Environmental safety is fundamental for human health and wellbeing, and it is increasingly recognized that environmental factors contribute to the risk of kidney and other serious non-communicable disorders. To date, healthcare has been seen as part of the solution, but how is it contributing to the problem?

We must recognize that there is a bi-directional relationship between health/disease and the environment/climate change. Not only does a polluted environment cause disease, but at the global level the healthcare sector also has a clear negative impact on the environment, with an estimated 5–10 % of the global greenhouse gas emissions coming from healthcare-related activities. Although awareness of climate change and environmental problems is certainly rising – one recent example is the publicity surrounding the effects of plastic waste on the life of the oceans – the fact that the healthcare sector itself is a contributor to greenhouse gas emissions is still, with a few exceptions, largely ignored by most health professionals and by the community at large.

As the leading society in Europe for physicians working in the field of the care of patients with kidney disease, the ERA-EDTA has traditionally focused its activities on improving the quality of healthcare. How are ecological issues being added to the association's agenda?

The negative contribution of healthcare to the environment is in clear conflict with the guiding principle followed by all physicians of primum non nocere or 'first, do no harm'. As health professionals we have both the ability and the responsibility to act as public health advocates by communicating the threats and opportunities to the public and policy makers, and ensuring climate change is understood as being central in human wellbeing. In my view, every health professional needs to be aware of, and contribute to, the development and implementation of greener health care.

The ERA-EDTA is the first medical association to try to contribute to the implementation of greener healthcare as suggested by the Lancet Countdown Group [1]. This collaboration among 24 academic institutions and intergovernmental organizations brings together climate scientists and geographers, mathematicians and physicists, transport and energy experts, development experts, engineers, economists, social and political scientists, and health professionals, and has called for a global transformation for public health. The Group aims to track progress on health and climate change, and provides an independent assessment of the health effects of climate change and actions that are developed to prevent it.

The key message of the Lancet Countdown is the definition of 40 indicators. While Indicator 3.9 identifies the healthcare sector as an important contributor to greenhouse house emissions, Indicator 5.2 identifies science as pivotal in increasing our understanding of the links between climate change and health. The ERA-EDTA recognized sustainability as a domain of quality in healthcare, and will therefore start to define actions to undertake to support the creation of carbon-smart health care. This means that the general goals defined by the global institutions should be translated into concrete actions, and that these two indicators should be adopted as main focus areas for the ERA-EDTA with the objective of providing a positive contribution to this emerging problem.

How does the ERA-EDTA aim to contribute to the development of a more environmentally friendly healthcare sector?

We first need to create awareness among ERA-EDTA members of this bi-directional relationship. Many of our members are active in patient care, research and education. In all these three areas, we face challenges.

The main contributors to the carbon footprint of a hospital generally include: (i) the buildings themselves through temperature regulation (heating and cooling); (ii) electricity for lighting and medical equipment; (iii) transport to and from the hospital by patients, visitors, employees and others; (iv) waste handling; and (v) cleaning of textiles and other surfaces. Actions aimed at to reducing the resulting carbon footprint will include both general interventions that affect multiple departments of the whole institution, and more specific interventions for specific specialties. In field of nephrology, hemodialysis (HD) is an obvious example. It is very energy consuming, uses large quantities of water (usually at least 120 liters per patient per session heated up to 37 °C and then discarded, not taking into account that the central water plant uses an additional considerable amout of water for preparation, cleaning and desinfection purposes, which is not used for the dialysis procedure itself), and creates substantial waste. For the treatment of the 329,000 patients receiving HD three times weekly in the European Union, this usage amounts to more 6000 billion liters of water at 37 °C, 92 billion kg waste, and 500 billion kWh electricity. Multiply these numbers by the global HD population of 2.65 million and the magnitude of the impact on the environment is clear. An important first step to more sustainability would be to create awareness within dialysis centers of the importance of reducing water use by smarter technology and avoiding waste. Similarly, a number of initiatives have already been launched by industry, and the ERA-EDTA is open to collaboration by providing a platform to support these and other activities through discussion about priorities, defining research questions, creating tools and programs, and promoting period-

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Green Nephrology Committee

ic reporting to members, the public and other stakeholders.

We also need to design new educational tools and programs using modern technologies to prepare our students and doctors for the healthcare of the future. This way, we hope to reduce nephrology's carbon footprint. At the same time, we need to translate general goals of sustainable healthcare into concrete actions.

Do you envisage any opportunities from the transition to sustainable healthcare?

In the short term, greener nephrology will involve some financial investment. However, it is likely that in the long-term, more sustainable healthcare will eventually reduce costs. Indeed, this has already been the experience of large dialysis providers running multiple centers. At the same time, we need to be very clear to governments, healthcare providers and other stakeholders that savings in water and energy use must not made at the expense of our patients' outcomes, and that any changes necessary to move to sustainable dialysis must maintain the highest possible medical standards. However, in my view, greener nephrology has the potential to offer real benefits to our patients.

Obviously, preventing or delaying progression kidney disease is clearly advantageous for the health and wellbeing of individuals and their families, as well for healthcare systems in terms of less use of resources for dialysis. So, investing in prevention is for multiple reasons very important. More access to e-health and greater use of self- and homecare could be very helpful.

The effect of the environment on health and disease is a largely unexplored field, so there will be many new opportunities for young researchers. They will, for example, be able to use modern data handling and management technologies to explore the exposome (the totality of external influences that humans experience everyday). I am sure that public and private funding organizations, both nationally and across Europe, will respond in the near future to the need for more research into sustainable healthcare. Finally, there will be the opportunity to play a role in designing new educational tools and programs that make use of modern technologies to prepare healthcare workers for the future.

In summary, as an organization the ERA-EDTA, and also its members, should recognize and accept the responsibility, task and opportunity to translate the general aims formulated by global institutions into concrete actions within the field of nephrology. Together, we must become active contributors to the global task to lead by example in the transformation to a more climate-smart healthcare sector. ◘

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New Guideline on Vascular Access in Haemodialysis

The new ERBP 'Clinical practice guideline on vascular access for haemodialysis in adults' has just been published in 'NDT – Nephrology Dialysis Transplantation'. It replaces the 2007 European Best Practice Guidelines on vascular access and focuses on peri- and postoperative care of arteriovenous fistulas and grafts. A second part, under development when this guideline went to press, will cover aspects related to access choice, preoperative vessel assessment and central venous catheters.

The guideline was developed by European Renal Best Practice (ERBP), the guidance body of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), in collaboration with the Vascular Access Society, a multidisciplinary association of nephrologists, surgeons, interventional radiologists, dialysis nurses and technicians. As with previous ERBP guidelines, it was felt such a collaboration would increase relevance, avoid duplication, and hopefully boost implementation.

A functioning vascular access is imperative for successful haemodialysis. Vascular access dysfunction is not only stressful for the patient and the team, but also means that treatment is not efficient enough. As patients become increasingly old on average, arteriovenous conditions are rarely optimal, so creating and maintaining well-functioning access for dialysis is one of the greatest challenges for nephrological therapy. For those patients, in particular, for those whom peritoneal dialysis or transplantation are not options, life itself is entirely dependent on this 'umbilical cord'. The new Guideline is aimed at helping nephrologists and all others involved to make the right decisions, to facilitate management and to maintain a functioning vascular access.

At the outset, a decision was made to cover the highest priority questions for both healthcare providers and patients, as opposed to directly updating the previous work. An extensive scoping procedure took place, and input from > 1,000 patients and health care workers was processed to create a topic list to choose from [1]. Also, the system of guideline development has changed since ERBP's predecessor published its first guideline. The need for explicit definition of research questions, systematic search procedures, and formal critical appraisal of the evidence base, have made it resource-intensive and time-consuming. As a result, certain sacrifices were required in terms of scope. The current guideline does not cover the same topics as the previous version. Some are shared, but some were archived in favour of new questions prioritised by both healthcare providers and the people they care for.

The most important new recommendations

The authors spotlight the most important changes in an editorial also published in NDT. The guideline makes a basic distinction between arteriovenous fistulas and grafts as two different types of vascular access that differ with regard to available data and evidence.

Another distinction is made between fistula maturation and maintaining openness and function over the long term (patency). These concepts are sometimes not separated from each other strictly enough in everyday practice, even though the pathophysiological mechanisms of maturation and patency, and thus the potential problems and their remedies, are quite different in nature. Two separate chapters are therefore dedicated to these issues.

Some good evidence is now available regarding the timing of first cannulation of an arteriovenous shunt. This should be done at the earliest two weeks after their operative creation, because puncture of an arteriovenous fistula within the first two weeks is associated with twice the risk of subsequent fistula failure [2]. Waiting for more than 28 days does not show any consistent additional benefit.

In the case of patients with grafts, however, it is recommended that early graft puncture be given preference over catheter placement – if commencement of dialysis is necessary within the first two weeks after the operation [3]. Peri-operative antibiotic prophylaxis is also recommended for graft placement. The guideline advises against combining high dose acetylsalicylic acid and clopidogrel or other antiplatelet agents with warfarin in patients with grafts, because such combinations do not improve graft outcomes, but increase bleeding risk significantly [4].

Access the "Clinical practice guideline on peri- and postoperative care of arteriovenous fistulas and grafts for haemodialysis in adults" from NDT or the ERBP website: http://www.european-renal-best-practice.org ◘

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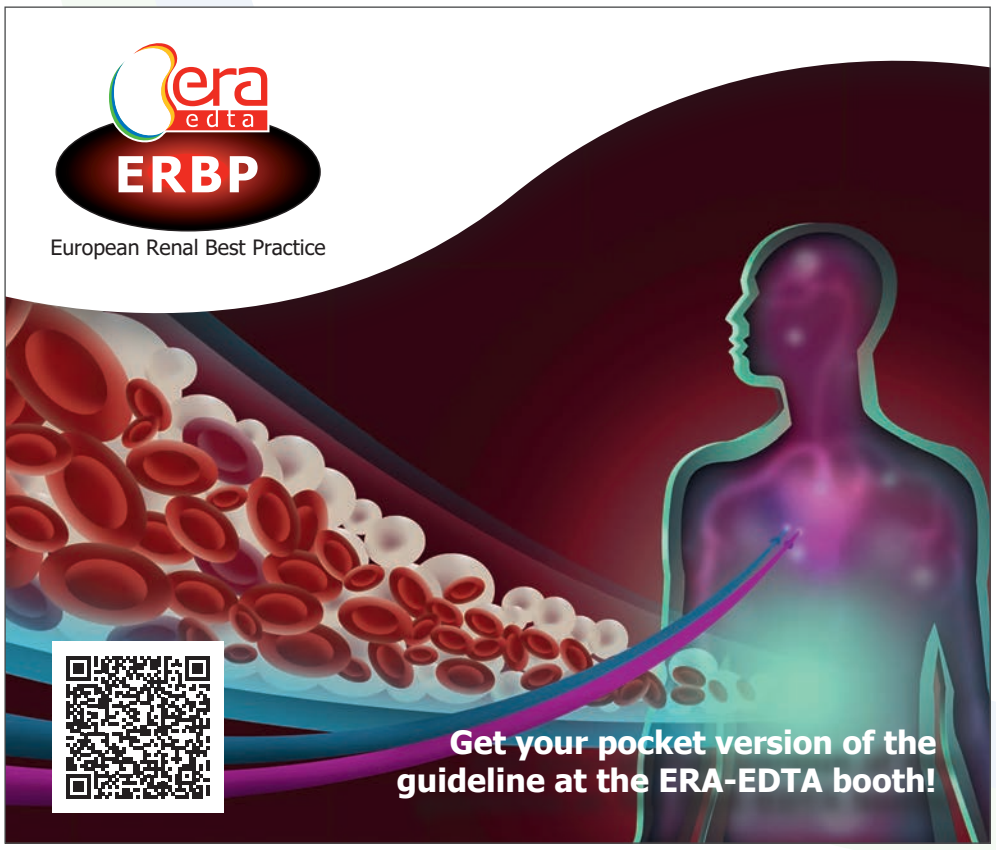

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ZIAD A. MASSY

Paris, France
Chair of the ERA-EDTA Clinical Governance branch (NPPC) and Registry, Div of Nephrology, Ambroise Paré Hospital, Paris, France

Epidemiological and clinical research and public policy in Europe are generally considered to be comprehensive and successful, but there is potential for improvement and scope for new opportunities. A review published by Ziad Massy and colleagues in NDT on 14 June 2019 [1] describes the considerations that form the basis for the Nephrology and Public Policy Committee's (NPPC) research plan to be supported by the ERA-EDTA over the next five years (Table 1). This article is a shortened version of the review.

Kidney disease cohorts in Europe

Standalone national cohort studies are a valuable resource, but their scientific quality and impact may be further increased by European collaboration. This may be especially valuable when studying rare kidney diseases and special patient subgroups, the occurrence and external validation of novel biomarkers based on large scale omics data, or prediction models, and comparison of preventive strategies, clinical practices, services and costs. Since the NPPC believes that AKI should be part of ERA-EDTA's missions and objectives, the creation of a dedicated European nephrology network is also recommended to organize, coordinate and improve practices, research and education in this important field.

National kidney registries and the ERA-EDTA Registry

Most European countries have national renal registries. If more countries were able to supply the ERA-EDTA Registry with an extended dataset on clinical performance indicators, it would be possible to compare countries' achievement of treatment targets. Registry data should continue to be used to study international differences and secular trends, with the potential for registry-based randomized controlled trials in Europe. Finally, the ERA-EDTA could facilitate valid comparisons of data resulting from the inclusion of CKD Stages 4–5 patients in national and regional registries.

European pediatric nephrology

Clinical research in pediatric nephrology has a 30-year history, and the ESPN/ERA-EDTA Registry was launched in 2007. Patient-centered outcome research is less well studied, and evaluation of the social determinants of kidney health and integration of social aspects would help optimize care and long-term outcomes for children and their families. There is an unmet need for new drug development and high-quality clinical research, and studies are needed to improve outcomes during and after the transition from pediatric to adult nephrology care. The latter requires active collaboration between pediatric and adult nephrology services, and registries for lifelong follow-up of patients' psychological and medical outcomes.

European Renal Best Practice (ERBP)

Dissemination of ERBP evidence-based guidelines does not ensure their use in daily clinical practice. International and European cohorts and registries with center-level data could help to monitor downstream effects of guideline development. Such initiatives need agreed quality indicators, covering structure, process and outcome. The inclusion of such indicators in prospectively collected cohorts, especially the ERA-EDTA Registry, may require revitalization of the QUality European STudies (QUEST) initiative, as well as the development of further and closer collaboration between ERBP and ERA-EDTA Registry.

European Union priorities

The European Kidney Health Alliance (EKHA) includes all stakeholders in kidney care, including patients, and works with EU policy makers to promote sustainable kidney care, prevention of CKD, and greater patient choice of RRT. More action is needed to reduce variation in living- and deceased-donor transplantation in Europe through the 'Gift of Life' campaign and the EC Thematic Network on Transplantation. There is also scope to support further research to guide policy to promote home therapies and transplantation, personalized medicine, regenerative medicine, and better quality of life for RRT patients.

Clinical research topics

Western European researchers have led several major, practice-changing, investigator-initiated trials, but there are concerns about the region's ability to recruit to trials. The ERA-EDTA has an important role in bringing together academics and other partners to define research questions and methodology, and clinical trial processes. Similarly, the ERA-EDTA could support development of Big Data research through networks of researchers, education programs and workshops, by encouraging adoption of information standards to improve data quality, and through recommendations on essential database parameters.

Eastern Europe faces its own challenges in the form of limited funding for kidney care, lack of awareness, and higher rates of problems such as obesity and diabetes and air pollution, and lower transplantation rates. ERA-EDTA could help support action to address these issues by increasing knowledge of CKD among the public, healthcare authorities, and other primary and secondary healthcare professionals. Research is also needed into the epidemiology and economic burden of CKD, to provide national authorities with evidence for greater healthcare funding and support for prevention.

Conclusions

The discussion above demonstrates why additional efforts are needed to improve nephrology research in Europe. The NPCC has concluded that such improvements depend on a research plan with restricted key topics that will stimulate collaboration, and the grant applications needed to translate research findings into public policy. In this way, the ERA-EDTA's focused support for research projects may contribute to improving the scientific quality of clinical research and evidence-based nephrology in Europe and worldwide. ◘

1. To conduct collaborative research designed to uncover non-invasive diagnostic tests or new predictive markers for kidney disease complications, aimed to further improve the classification and prognosis of kidney diseases based on large-scale omics data using available European patient cohorts.
2. To review the feasibility and relevance of the development of CKD stage 4–5 registries based on ongoing experiences at national level, and explore if and how these can be brought together for quality assurance and research at the European level.
3. To plan a successful transition process from pediatric to adult care of CKD by active collaboration between pediatric and adult nephrologists and cohorts/registries.
4. To reinforce the collaboration between ERBP experts and ERA-EDTA Registry staff in order to extend the number of indicators to include the thresholds of the ERBP recommendations as part of prospectively collected datasets stemming from different national or regional cohorts and from the ERA-EDTA Registry, and to adapt those as new recommendations are published.
5. To continue supporting EKHA with its established links with the European Union, allowing it to target key nephrology topics prioritized by patients and professionals, such as better quality of life in RRT patients and improving kidney transplantation and home treatment modalities, which also include regenerative and personalized medicine.
6. To support the development of world-leading Big Data research in a number of ways including the creation of data networks and the development of educational programs.
7. To help the Eastern European nephrology community to optimize patient care and patient-oriented research in their countries by increasing public awareness, encouraging/supporting clinical nephrology and epidemiology studies and improving training in nephrology.
8. To create a European network of kidney units in order to extend our understanding of AKI progression and complications, including transition of AKI to CKD.

Table 1: Research plan with eight hot topics to stimulate research collaboration and grant applications in Europe AKI = acute kidney injury; CKD = chronic kidney disease; EKHA = European Kidney Health Alliance; ERBP = European Renal Best Practice; RRT = renal replacement therapy

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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

PACE-CME

Supported by an unrestricted educational grant from Novo Nordisk.

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EDUCATION

The 'fetal organ niche system'

Kidney regeneration using induced pluripotent stem cells

TAKASHI YOKOO
Tokyo, Japan

In recent times, there has been a significant increase in the total number of dialysis patients owing to aging and the spread of diabetes; approximately 2.6 million people are currently undergoing dialysis worldwide. This is proving to be a heavy burden on national finances, as the annual medical expenses related to dialysis are more than $ 88,000 per person, amounting to a total cost of over $ 34 billion for patients in the US.

These circumstances suggest the need for an alternative therapy that may substitute dialysis. Organ regeneration shows promise for this purpose, however, owing to the complex 3D structure of the kidney, its regeneration is critically perceived by researchers. Against this background, we have been working on this for over 20 years. Our concept is quite unique. Because human kidneys are formed by differentiation of one fertilized ovum, the kidneys are made from this single cell. At this stage of development, it is not only differentiating into nephron progenitor cells (NPCs) but also creating a environment (niche), where the programs to build kidney run.

Many researchers have tried to elucidate these programs in the niche stepwise, but our concept is different: we tried to borrow this program from xeno embryo by applying the stem cells at the niche of organogenesis. Using this method (termed the 'fetal organ niche system'), we recently succeeded in regenerating tissue that can produce urine from induced pluripotent stem (iPS) cells. We examined whether the tissue can differentiate into the kidney by injecting foreign NPCs into the niche. As a result, it was confirmed that kidney differentiation is possible. However, since native NPCs exist in the niche, a chimeric kidney consisting of two lines of NPCs was formed. Therefore, we developed and added another system in which only exogenous NPCs mature in the niche, by removing existing NPCs under the presence of an agent by gene manipulation. Then, we succeeded in establishing nephrons derived from 100 % exogenous NPCs. Furthermore, by transplanting them into the living body, it became possible to attract blood vessels, and urine production was confirmed.

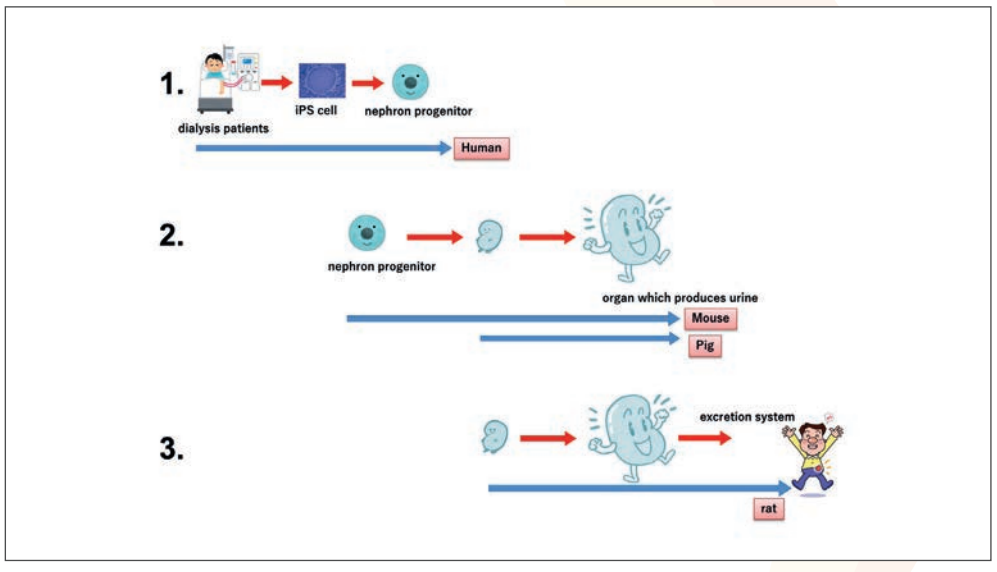
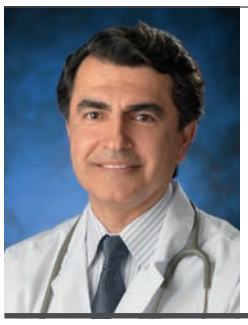


Figure: The three steps to kidney regeneration in humans © Takashi Yokoo

Our whole system consists of three steps: Step 1 is the establishment of NPCs from iPS cells Step 2 is the establishment of the regenerating functional kidney from NPCs by the 'fetal organ niche system', and Step 3 is the construction of the urinary excretion pathway to release urine into the bladder. All three steps were essentially proved using different animal models, and the final stage is to reproduce these in the human environment. In other words, this success is based on experiments conducted in rats and mice, and hence we need to verify these results with NPCs derived from human iPS cells. Thereafter, we will proceed to clinical trials involving human subjects. ◘

S 21
Regenerative medicine
Saturday, 08.00–09.30, Hall A1

Clinical experiences with incremental hemodialysis schedules Starting twice weekly may help to optimize early patient survival



KAMYAR KALANTAR-ZADEH

Orange, CA, USA

Mortality is highest in the first months of maintenance hemodialysis (HD) therapy. In many Western and affluent nations, patients who transition to kidney replacement therapy usually begin thrice-weekly HD regardless of their level of residual kidney function (RKF). RKF is a major predictor of survival. RKF may decline more rapidly with thrice-weekly HD treatments, is associated with a reduced need for dialytic solute clearance, and is an important factor in the prescription of peritoneal dialysis.

Nearly a half-century ago, the thrice-weekly HD schedule was empirically established as a means of providing an adequate dialysis dose while also treating the greatest number of end-stage renal disease (ESRD) patients using limited resources. Landmark trials of HD adequacy have historically been anchored to thrice-weekly regimens, but a recent randomized controlled trial demonstrated that frequent HD (six times per week) confers cardiovascular and survival benefits, while such frequent HD regimens may lead to faster loss of RKF. Based on these collective data and experience, clinical practice guidelines advise against a less than thrice-weekly treatment schedule in patients without residual renal function, yet provide limited guidance on the optimal treatment frequency when substantial native kidney function is present. Thus, during the transition from Stage 5 CKD to ESRD, the current paradigm is to initiate HD on a 'full-dose' thrice-weekly regimen even among patients with substantial RKF. However, emerging data suggest that frequent HD accelerates RKF decline, and infrequent regimens may provide better preservation of native kidney function.

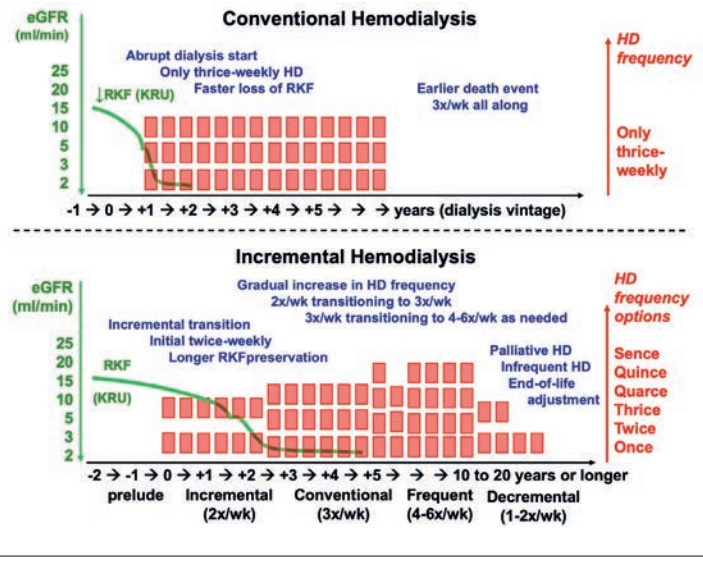


Figure: Juxtaposition of conventional (only thrice-weekly) and incremental (with initial twice-weekly) hemodialysis regimens. From: Kalantar-Zadeh K et al. Semin Dial 2017 May;30(3):251-261. doi: 10.1111/sdi.12601. Epub 2017 Apr 18; permission conveyed through Copyright Clearance Center, Inc.

In this presentation we review the concept of incremental HD, in which weekly dialysis dose, in particular HD treatment frequency, is based on a variety of clinical factors, such as RKF (including urine output > 0.5 L/d), volume status, cardiovascular symptoms, body size, potassium and phosphorus levels, nutritional status, hemoglobin level, comorbid conditions, hospitalizations, and health-related quality of life. These 10 clinical criteria will determine the timing for increasing dialysis dose and frequency.

We recognize that twice-weekly HD represents a major paradigm shift for many clinicians and jurisdictions. Therefore, we propose conducting randomized controlled trials of twice-weekly versus thrice-weekly HD to assess the potential of twice-weekly HD to improve survival and health-related quality of life while simultaneously reducing costs, protecting fragile vascular accesses, and optimizing resource use during the first year of hemodialysis therapy. Such incremental and individualized HD therapy may prove to be the most appropriate approach for transitioning to dialytic therapy. Given the high mortality rates during the first six months of hemodialysis and the survival benefits of preserved native kidney function, initiation with twice-weekly treatment schedules ('infrequent hemodialysis') with an incremental increase in frequency over time may provide an opportunity to optimize patient survival. ◘

References

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02. Ghahremani-Ghajar M et al. Semin Dial. 2017;30(3):262–269.
03. Kalantar-Zadeh K et al. Am J Kidney Dis. 2014;64(2):181–6.

S 20
Haemodialysis. From incremental approaches to frequent treatments
Saturday, 08.00–09.30, Hall F1

EDUCATION

Diabesity-induced CKD and the role of the CB1 receptor

JOSEPH TAM

Jerusalem, Israel

Diabetes and obesity (diabesity), chronic diseases that are now reaching epidemic proportions, have been described as catalysts for many conditions, most notably, cardiovascular disease, liver disease, and chronic kidney disease (CKD). The latter is manifested by hemodynamic and morphological changes in the kidney, which together with renal inflammation and oxidative stress, may lead to reduced renal function and ultimately, to glomerulosclerosis and tubulointerstitial fibrosis. Although multiple metabolic factors have been proposed to contribute to diabesity-induced CKD, the underlying signaling mechanisms are not completely understood.

The recreational, psychoactive, and medicinal effects of marijuana, many of which have important therapeutic potential, have been recognized for thousands of years. Yet, it is only in the last several decades that our understanding of these effects has grown, following some landmark discoveries in the field of cannabinoid research. Endocannabinoids (eCBs) are endogenous lipid ligands that bind to cannabinoid receptors (CB1 and CB2) that also mediate the effects of marijuana. The eCB system is present in both the central nervous system and peripheral organs including the kidney. Accumulating evidence has described the role of the eCB system in various renal pathologies. CB1 receptors are expressed in podocytes, mesangial cells, and particularly in renal proximal tubular cells (RPTCs). Their blockade with CB1 receptor antagonists improves renal function and reduces albuminuria and glomerular lesions in obese and diabetic mouse models. However, most of these studies failed to determine whether the eCB system plays a role in diabesity-associated renal pathologies. And if it does, is it mediated centrally, peripherally, or via a specific cell type within the kidney?

Our results, which will be presented during this conference, will describe novel cellular mechanisms by which the CB1 receptor regulates glucose and fat utilization as well as mitochondrial shape and function in RPTCs. Our findings indicate that diabetes-induced upregulation in renal glucose absorption via the facilitative glucose transporter 2 (GLUT2) is mitigated by pharmacological blockade or genetic ablation of the CB1 receptor in RPTCs, by inducing changes in Ca2+ influx and PKC-β1 expression to reduce glucose reabsorption and prevent the development of CKD [1]. In parallel, lipid accumulation and reduced fatty acid β-oxidation in RPTCs, associated with obesity-induced renal abnormalities, are governed by a CB1 receptor-coupled Gαi/o-PKA axis, which mediates the downstream activation of the LKB1/AMPK/ACC signaling pathway [2]. The direct role of the CB1 receptor in renal lipotoxicity and kidney damage is also mediated, in part, by inducing mitochondrial fragmentation via changing the phosphorylation levels of the canonical fission protein dynamin-related protein 1. This, in turn, is associated with mitochondrial dysfunction in RPTCs [3].

Since the therapeutic potential of globally acting CB1 receptor antagonists in diabesity is limited due to their neuropsychiatric adverse effects, our recent findings support the pre-clinical development and clinical testing of peripherally restricted CB1 receptor antagonists in treating renal diseases. ◘

References

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S 19
Molecular mechanisms of kidney atrophy and fibrosis
Saturday, 08.00–09.30, Hall G2B

RAASi and hyperkalaemia in cardiorenal disease: Opportunities for optimizing outcomes

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

CHAIRMEN

John Cunningham, MD – *London, United Kingdom*

Matthew Weir, MD – *Baltimore, MD, USA*

AGENDA

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

09:50 – 10:05 **RAAS inhibition in patients with kidney disease: Balancing the benefits and risks**
Patrick Rossignol, MD – *Nancy, France*

10:05 – 10:20 **Addressing the risk of hyperkalaemia: Is there a sweet spot for potassium binding?**
Peter van der Meer, MD – *Groningen, the Netherlands*

10:20– 10:35 **Managing hyperkalaemia in cardiorenal patients: Novel therapeutic insights to optimize outcomes**
Matthew Weir, MD – *Baltimore, MD, USA*

10:35 – 10:45 **Panel discussion & summary**
John Cunningham, MD

SATURDAY, JUNE 15, 2019 | 09:30 – 10:45 HRS | HALL G2B

Supported by an unrestricted educational grant from Vifor Fresenius Medical Care Renal Pharma.

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Looking for the evidence in CKD-MBD
Should we treat or should we wait?

JORDI BOVER
Barcelona, Catalonia, Spain

The systemic nature of chronic kidney disease-mineral and bone disorder (CKD-MBD) may explain, at least partially, the extremely high mortality of CKD patients. KDIGO guidelines were created as a global initiative designed, not only to provide information, but also to assist in decision-making. Independent evidence review teams ensure a rigorous appraisal of the existing evidence, and the use of the GRADE system (adopted by over 100 organizations) provides a much more sophisticated hierarchy of evidence (grading the quality and strength of recommendations).

As stated by Djulbegovic & Guyatt [1], medicine has struggled to balance the uncontrolled experience of 'healers' with observations obtained by rigorous investigation of claims about the effects of health interventions. The term *eVidence*-based medicine (EBM) was first coined by G. Guyatt in 1991, who contended that although there is a role for all empirical observations, randomized controlled trials (RCTs) and systematic reviews provide the most trustworthy evidence (versus *eMinence*-based medicine). EBM and evidence-based clinical practice integrate the 'best available evidence' with clinical expertise and patient values and expectations, also taking into account the healthcare setting and circumstances in which we practice.

After the initial publication of the CKD-MBD KDIGO Clinical Practice Guidelines in 2009, several national societies and/or organizations followed up with commentaries, interpretations, updates and local adaptations. Based on new evidence, an update of the guidelines was published in 2017. Given that both guidelines represent the most important academic work on the subject to date, it was rather disappointing to see a lack of strong clinical evidence in almost all areas. In an era in which we have moved from ignorance to infoxication, this highlights the need for rigorous RCTs in this field, and for most of us offers a lesson in the need for humility.

As a matter of fact, not many things really changed in 2017. The new guidelines are mostly graded as suggestions (level 2) or are 'not graded' (not based on systematic review) at all. Moreover, the quality of supporting evidence is mainly low (grade C). The evolution of these guidelines will be reviewed at the symposium, underlining important new diagnostic and therapeutic challenges such as bone mineral density evaluation (treatment?), restriction on calcium-based phosphate binders in adults, and the 'not graded' statement about the indication for calcitriol and vitamin D analogs only for SEVERE hyperparathyroidism in CKD 4–5. Although there is a rationale behind these changes, absence of evidence is not evidence of absence (argumentum ad ignorantiam), and there is a danger that the consequences of a 'misunderstood' EBM may be therapeutic nihilism, especially under financial pressures.

All these ethical/practical dilemmas actually extend to most areas within Nephrology, leading nephrologists to struggle to choose between passivity (adopting a 'wait and see' approach, knowing that RCTs in Nephrology are and probably will remain scarce) and an exceedingly proactive attitude based on long-lasting 'beliefs'.

While clinical experience can, of course, be criticized and must be analyzed, its significance cannot be completely disregarded. We shall go to the balcony and, from that wider perspective, guidelines assist us in the provision of recommendations that we might adapt at the individual personalized patient-level. ◘

References

01. Djulbegovic B, Guyatt GH. Progress in evidence-based medicine: a quarter of a century on. Lancet 2017;390: 415–423

S 26
CKD-MBD patterns and therapeutic approaches: update 2019
Saturday, 11.45–13.15, Hall F1

EDUCATION

PCSK9 inhibitors in kidney disease

Specific studies are mandatory to prove efficacy and safety in CKD

THIMOTEUS SPEER

Homburg/Saar, Germany

Chronic kidney disease (CKD) is associated with a substantially increased risk for the development of atherosclerotic cardiovascular disease (CVD). Accordingly, cardiovascular mortality is increased even in the earliest stages of CKD. In the general population and in CKD patients, high plasma levels of low-density lipoprotein cholesterol (LDL-C) are crucially involved in the initiation and progression of atherosclerotic vascular lesions. In addition, it has been documented that LDL accumulating in the vascular wall is prone to be posttranslationally modified; e.g. by oxidation or carbamylation, which is particularly relevant to patients with CKD.

Lowering LDL-C by use of statins and/or ezetimibe represents the gold standard of lipid-lowering therapy with a great body of evidence from several large clinical trials. Statin therapy reduces cardiovascular events in patients with normal and impaired kidney function alike, while the evidence for patients on maintenance hemodialysis is weaker. Moreover, reduced kidney function may represent a risk factor for statin-related adverse outcomes such as myopathy.

The inhibition of proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) represents a novel lipid-lowering tool directly modulating hepatic LDL metabolism. PCSK9 protein reduces the expression of LDL-receptor (LDLR) on the surface of liver cells and, thereby, decreases cellular uptake of LDL and thus its clearance from the circulation. Currently, the monoclonal antibodies evolocumab and alirocumab are approved PCSK9 inhibitors. Despite maximum-tolerated statin therapy, they efficiently further reduce LDL-C plasma levels without any major adverse effects.

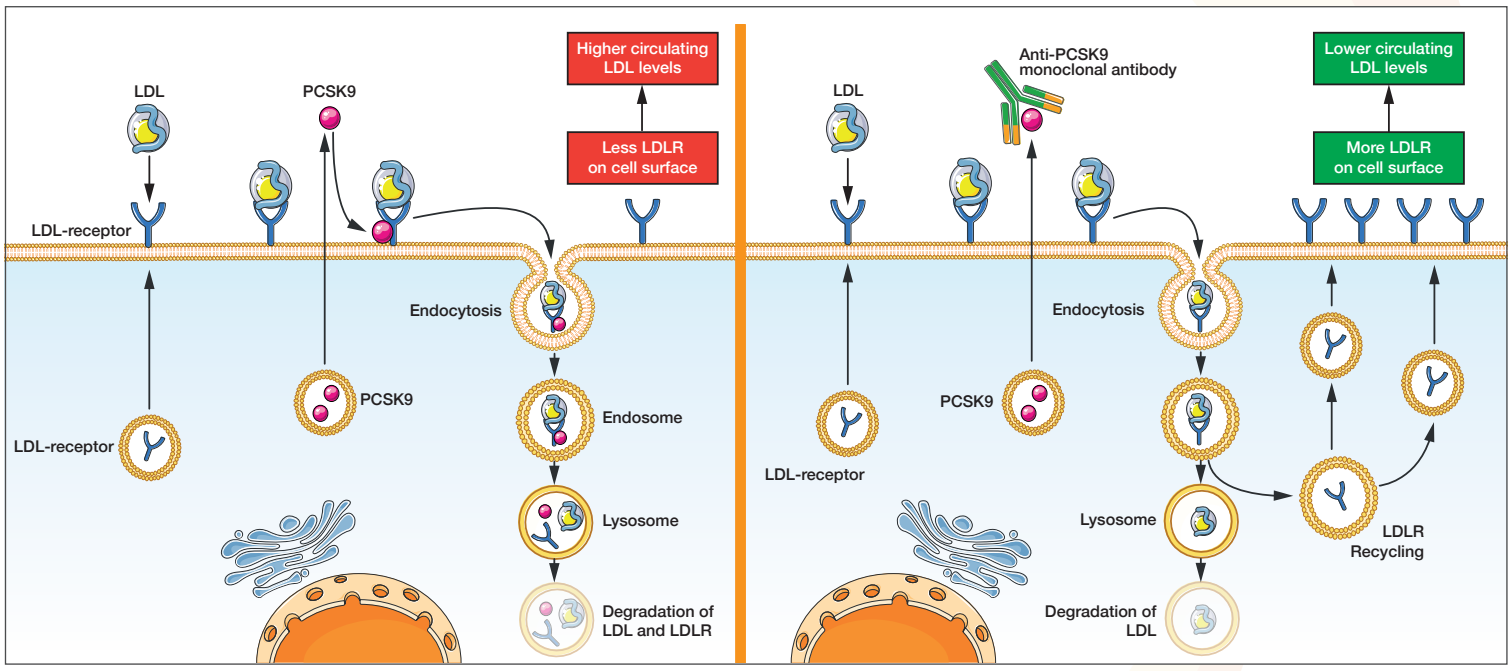


Figure: Hepatic LDL metabolism in the absence (left) and presence (right) of PCSK9 inhibiting antibodies © Thimoteus Speer

Moreover, in large clinical outcome trials, both antibodies have been proven to lower cardiovascular events. Notably, the LDL-lowering capacity was independent of baseline kidney function and also efficient in patients with moderate CKD. However, patients with severely impaired kidney function – i.e. the population at the highest cardiovascular risk – have been excluded from those trials. The relevance of the LDL-independent effects of PCSK9 inhibitors such as lowering lipoprotein(a) or ameliorating dyslipidemia in patients with nephrotic syndrome has to be determined. In particular in patients with advanced CKD, the high annual costs of therapy with PCSK9 inhibitors have to be balanced against weak evidence for a benefit.

High cardiovascular morbidity and mortality remains a persisting problem in patients with CKD. Many efforts have been made in subjects with normal kidney function to prevent and to reduce progression of cardiovascular diseases. However, in most of these studies, patients with advanced CKD have been excluded. Moreover, results from the general population can be only partially transferred to patients with CKD. PCSK9 inhibition represents a novel and successful treatment approach to reduce LDL-C in patients with normal to moderately impaired kidney function. Specific studies in CKD patients are mandatory to prove the efficacy and safety of PCSK9 inhibitors and to determine their ability to improve outcomes in these patients. ◘

Read the full review "PCSK9 in kidney disease" by Timo Speer and Danilo Fliser in NDT!

FC 20
Improving cardiovascular complications in CKD
Saturday, 11.45–13.15, Hall A4

EDUCATION

Insights from PDOPPS

Optimizing PD initiation and reducing early switches to HD

SIMON DAVIES

Stoke-on-Trent, United Kingdom

On behalf of the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS)

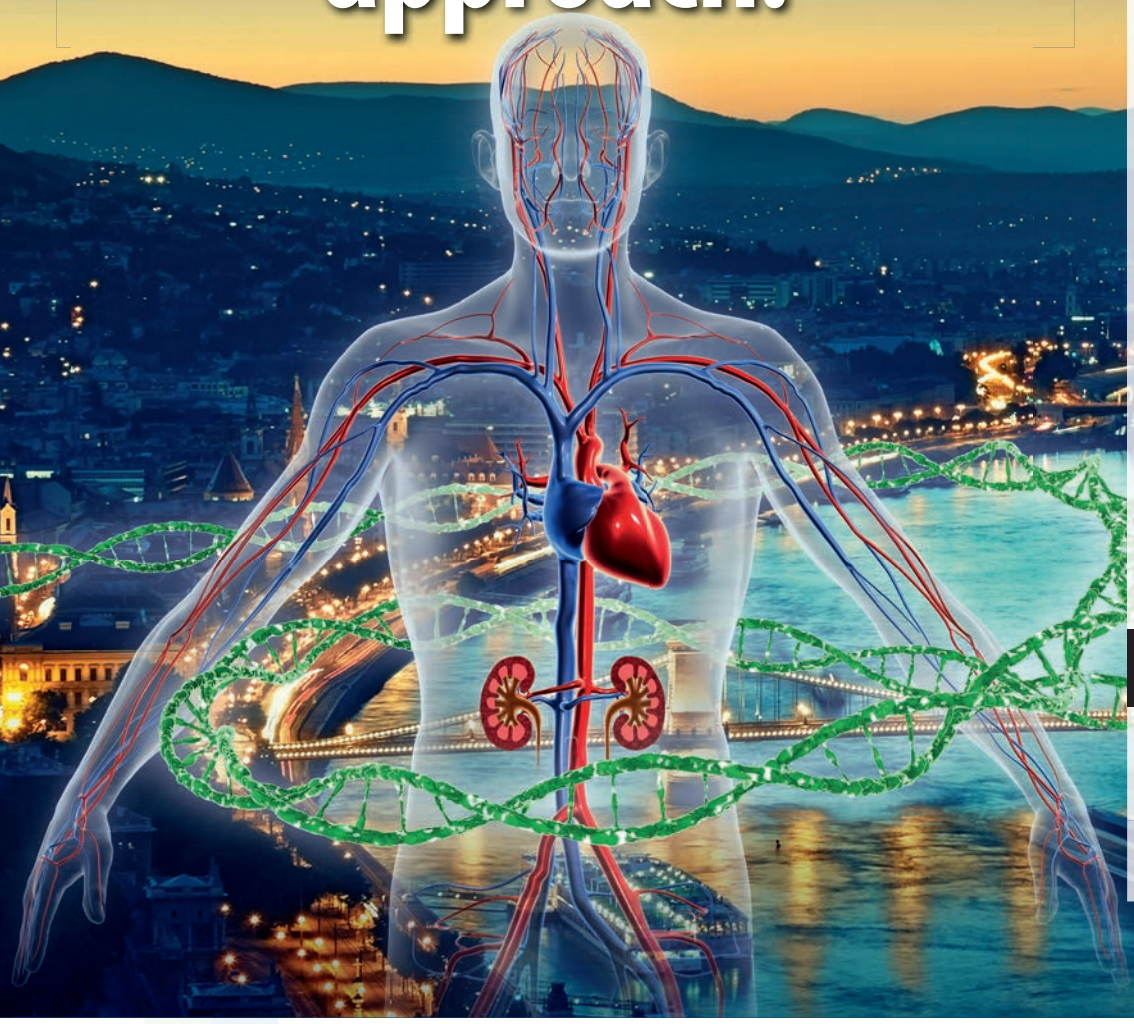
The survival of patients commencing their journey of kidney replacement treatment with peritoneal dialysis (PD) has continued to improve over the last 20 years. This improvement means that PD is truly competitive with hemodialysis for patient survival. However, the same cannot be said for technique survival, and PD is still associated with an unacceptable risk of either temporary or permanent switch to HD. This robs patients of their modality of choice, causes significant morbidity in some cases and is not a cost-effective use of expensive resources.

Increasingly, the evidence shows that, whereas patient survival on PD is primarily a function of patient-related factors such as age and co-morbidities, death-censored technique failure, which varies considerably between dialysis units, is more strongly predicted by characteristics of the dialysis unit. In particular, smaller dialysis units, or those that use PD in a lower proportion of their patients appear to have higher technique failure rates. This all points to variation in dialysis-unit practices, or how well they are adhered to, as being the most likely cause of this unacceptable variation in technique failure – and thus the most fruitful target for improving outcomes for PD patients. This was why the PDOPPS study was set up, and why death-censored technique failure was chosen as the study's primary endpoint.

PDOPPS, a collaboration between the International Society for Peritoneal Dialysis and the Arbor Research Collaborative, is already running in seven countries: US, UK, Canada, Australia, New Zealand, Japan, Thailand – and this is now extending to include Korea. It is already the largest study ever of PD patients (more that 7,500 patients consented), capturing unit-level practices, patient-level characteristics, their treatment and subsequent outcomes. Its study design and analysis plan are informed by several internationally representative work-groups, each with a focus in a particular aspect of PD that is related to a cause-specific reason for technique failure, e.g. infection, catheter function.

Early technique failure has been a recent focus of the study. It is already known, especially from the ANZDATA registry, that early technique failure is dominated by catheter dysfunction and infections. PDOPPS has extended these observations, allowing both international comparisons, as well as comparing patterns of technique failure early in the course of treatment with those occurring later. Overall, the incidence of patients stopping PD early on (first 180 days) is approx-

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

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RESVERLOGIX

imately linear, happening in just over 10 % of patients, and in two thirds of these it was because of permanent transfer to HD, one third due to mortality. This translates into an early annualized death-censored technique failure rate of just under 20 %, whereas later on treatment this rate falls to about 12 %. However these average figures disguise significant differences between countries.

Death-associated and death censored technique failure is lower in Japan, both being less than 50 % of the US reference rates. When deaths and permanent transfers are combined, the differences between other countries are less obvious, as in general a higher death rate is mirrored by a lower technique failure and vice versa. Even greater variation is seen when comparing dialysis centers within all countries, with annualized permanent transfer rates varying between 3 % and 45 %! As would be expected, the causes of the relatively high technique failure rate seen during the first 180 days of PD are different to those observed later. In particular, various catheter-related problems, leaks and hernias predominate, whereas infections are less common, although still the largest single cause. Later on, catheter-related problems fall to about 15 %, whereas almost half of technique failures are due to infection.

Given the relatively high technique-failure rate early on in PD and the preponderance of catheter-related problems, PDOPPS has focused on the different practice patterns related to PD catheter insertion and catheter care. Who puts the catheter in and by what technique varies considerably by country, ranging from predominantly nephrologists using a percutaneous technique to variously trained surgical specialists using open surgical or laparoscopic methods. There are also important differences in approach to patient selection according to which methods of catheter insertion are available. UK-Cath, which is an ancillary PDOPPS study related to PD catheter insertion pathways, strongly suggests that availability of percutaneous catheter insertion methods means that more comorbid patients can be started on PD. Understanding how these different practices relate to early catheter function has the real potential to improve early technique failure, reduce unacceptable variation in practice and improve the experience and choices for people with kidney failure. ◘

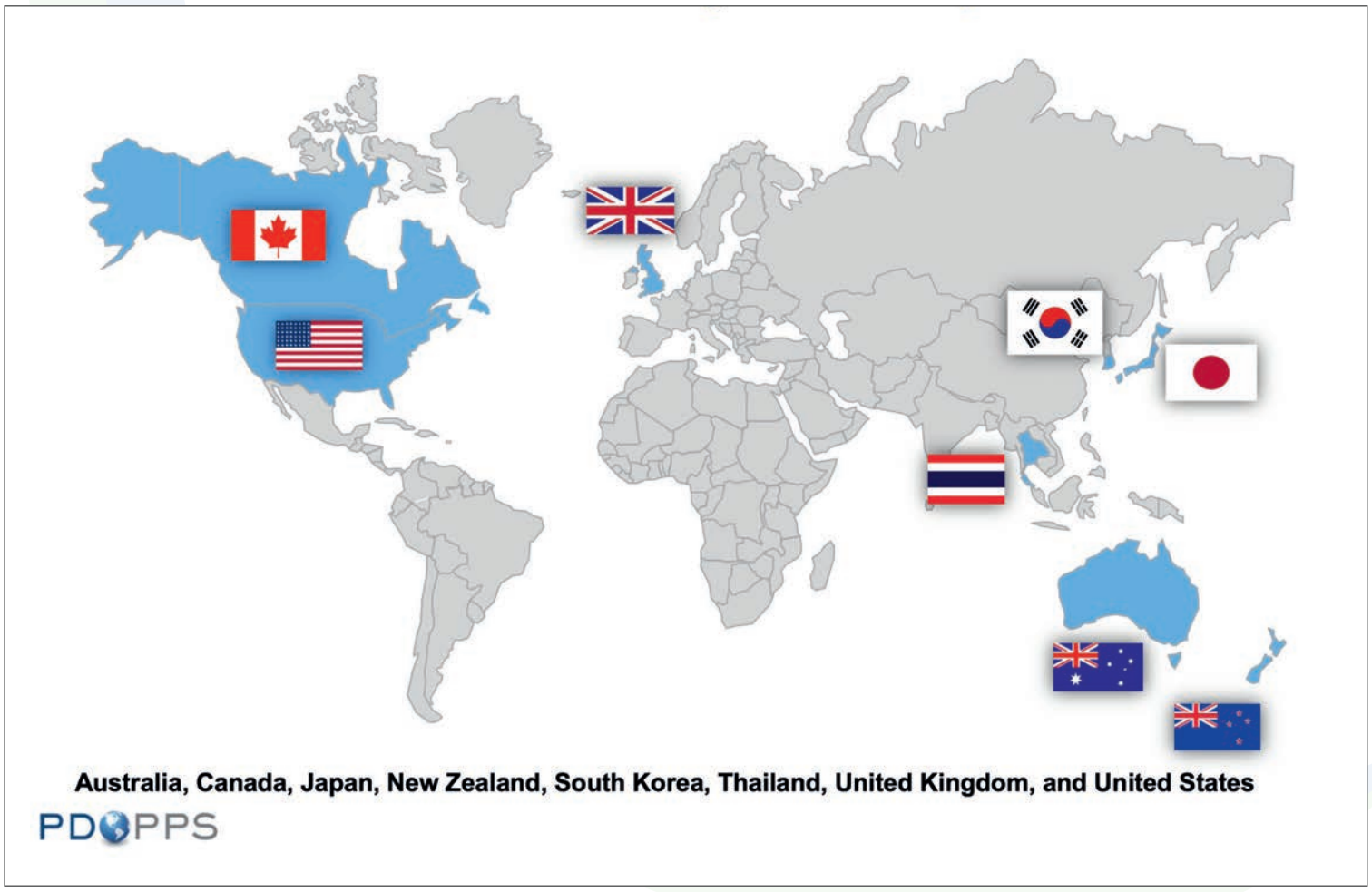

Figure: PDOPPS Country Participation © Arbor Research Collaborative. Courtesy of Arbor Research Collaborative

S 23
Optimizing peritoneal dialysis prescription
Saturday, 11.45–13.15, Hall G1

Controversy: Does haemodiafiltration improve patient outcomes and survival?

PETER J BLANKESTIJN

Utrecht, The Netherlands

– YES

Despite progress in the quality of treatment, the risk of mortality for patients with end-stage kidney disease (ESKD) is still substantial. So, there is an urgent need to improve the quality of treatment. Hemodiafiltration (HDF), which offers better clearance of larger middle molecules than hemodialysis (HD) was introduced decades ago. Over the past decade, four European randomized controlled clinical trials have been performed to find out whether HDF offers any clinical benefit above standard HD.

Taken individually, none of the trials delivered an undisputable answer. However, an individual patient-level data meta-analysis of these trials, which comprised 2,753 patients with a median follow-up of 2.5 years, indicates an approximate 22 % reduction in mortality risk when convection volume dosages of > 23 L/session were used [1]. The main beneficial effect was demonstrated by an observed 30 % reduction in cardiovascular mortality and specifically cardiac mortality [2]. Importantly, the pooled analysis also suggested a 31 % reduction in the rate of sudden death of borderline significance. Observational studies support the notion that increased clinical benefit is related to higher dosages. Despite these clear suggestions of a beneficial effect, the scientific community remains critical, largely due to the fact that the beneficial effects might be explained by patient selection (i. e. a healthier patient receives more convection volume). Furthermore, the mechanism(s) of a possible beneficial effect is/are unproven. This also reduces the acceptance of the idea of superiority of HDF.

CONVINCE is an international, multicenter, prospective, randomized, controlled study comparing high-dose HDF versus conventional high-flux HD, which aims to address the remaining uncertainties. The study is funded by the European Commission Research & Innovation Horizon 2020 program under grant agreement No. 754803, and is addressing clinical endpoints. Patient experiences are the most important secondary endpoint. The study will be performed in multiple European countries in approximately 70 centers, including university and non-university based centers and centers of three large dialysis providers. The CONVINCE study will deliver an answer on the question which intervention gives the best value for money, not only on clinical endpoints, but hopefully also with respect to patient' experiences. ◘

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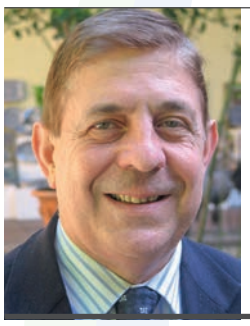


FRANCESCO LOCATELLI

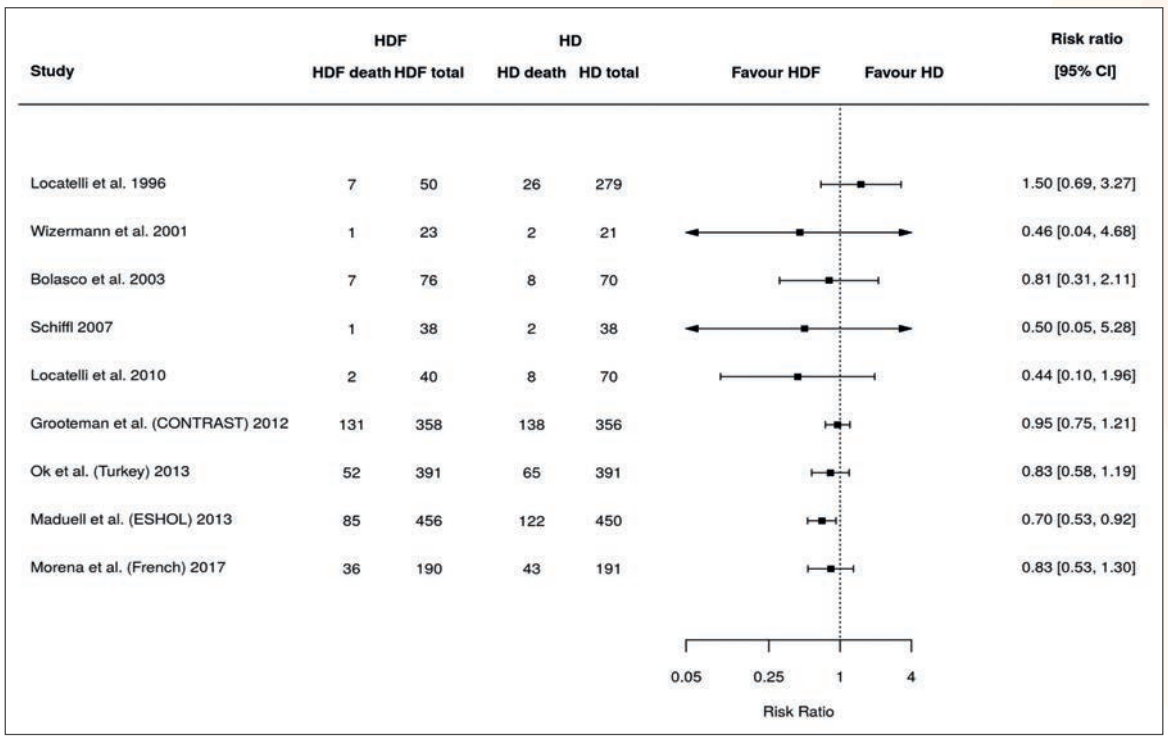
Lecco, Italy

– NO

First of all I should declare my major conflict of interest on the topic: "I have been a believer in on-line haemodiafiltration (HDF) for 30 years". Although, according to evidence-based medicine, the clinical superiority of HDF versus hemodialysis (HD) still needs confirmation.

HDF enhances clearances of middle solutes, like β2-microglobulin, while maintaining comparable or slightly higher clearances of small solutes like urea and may plausibly improve clinical outcomes. However only one [1] out of five large randomized controlled trials (RCT) [2–5)] showed a better survival in patients treated with HDF compared to HD; thus they are inconclusive in clarifying the impact of HDF on patient outcomes.

In fact, the solidity of the data depends on the quality of randomization; unfortunately the patients randomized to HDF in the ESHOL trial [1] were younger, more likely to be male, with less diabetes, more likely to use a fistula and less likely to use a catheter, and had a lower comorbidity index. Moreover, a post-randomization exclusion of the patients randomized to HDF unable to reach a reinfusion volume > 18 liters was foreseen by the protocol, thus creating an important bias. Patients with better vascular access flow tend to be generally healthier and would be more likely to achieve larger replacement fluid volumes, resulting in a potential selection bias [6].



Randomized Studies on HDF

From Locatelli F, Carfagna F, Del Vecchio L, La Milia V. Haemodialysis or haemodiafiltration: that is the question. Nephrol Dial Transplant. 2018 Nov 1;33 (11): 1896-1904. doi: 10.1093/ndt/gfy035 © NDT. Courtesy of NDT

A pooled individual patient analysis of four of these five trials [7] suggested a substantial survival benefit, especially when a convection volume of at least 23 liters/session was delivered. However, achieved convection volumes were a secondary analysis and thus no longer followed the randomization protocol. As RCT data outside the context of randomization are considered to reach only observational evidence levels with insufficient data on potential confounders, their conclusions should be interpreted with caution. This meta-analysis has also underlined the methodological limitations of the included trials.

In conclusion, although there are some suggestions about a favorable effect of HDF on mortality, according to evidence-based medicine, we need a well-designed randomized clinical trial comparing HDF to HD to clearly prove a clinical superiority of HDF. In this respect, I should thank Professor Peter Blankestijn for his strong support of my point of view by leading a new randomized control trial (CONVINCE Study) on the effect of high-volume HDF versus HD on patient survival, quality of life and costs. This clearly acknowledges that, at present, according to evidence-based medicine, there are no clear data supporting the superiority of HDF versus HD; otherwise the clinical implementation of this trial should have been unethical. ◘

S 25
Controversy: Does haemodiafiltration improve patient outcomes and survival?
Saturday, 11.45–13.15, Hall G2B

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EDUCATION

A fundamental part of good end-of-life care

Identifying organizational barriers to organ donation in hospitals

AXEL RAHMEL

Frankfurt, Germany

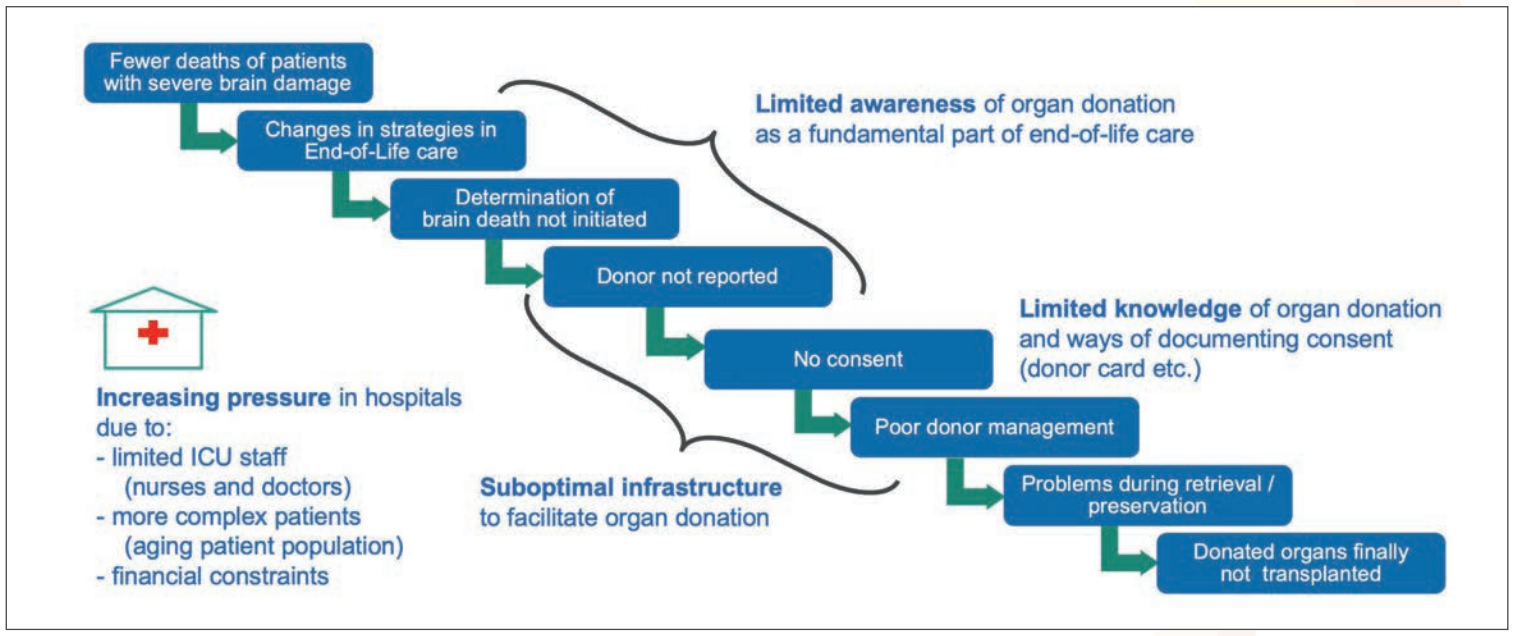

Figure © DSO (Deutsche Stiftung Organtransplantation)

Organ donation rates have traditionally been relatively low in Germany compared with other European countries. In recent years, the number of donors per million population (pmp) dropped further from 15 donors pmp in 2010 to less than 10 pmp in 2017. Lack of public trust into organ donation and transplantation is often named as the main reason for these dismal figures. In contrast to this assumption, repeated surveys showed that more than 80 % of the German population support organ donation and transplantation.

To get a better view on the reasons for the low donation figures in Germany, different scientific groups involving intensivists, neurologists and epidemiologists started systematic analysis of the donation potential and processes, together with the German organ procurement organization *Deutsche Stiftung Organtransplantation* (DSO). The following possible factors have been investigated:

- Decrease in the number of deaths with primary and secondary brain damage
- Change in end-of-life care of patients with severe brain damage
- Omission of brain death diagnosis when indicated
- Not reporting potential donors to the organ procurement organization
- Lack of consent to organ donation
- Increase in the number of potential donors with medical contraindications to organ donation
- Inadequate donor management
- Problems with organ procurement, preservation or transport
- Decrease in organ acceptance after procurement by the transplant centers.

In a first study, most of the above factors could be excluded as the main reason for the low donation figures: over recent years, the number of potential donors actually increased by 15 % and, although the number of extended-criteria donors increased, the acceptance rate did not drop. Modern organ preservation technology, and strict quality management of the procurement, preservation and transport process reduced organ losses to a minimum. However, the number of potential donors reported by the hospitals to the DSO went down by 30 %.

In a second study the reasons for this drop in donor reporting were analyzed in depth. In a substantial number of patients, brain death had probably already occurred but brain death diagnosis was not initiated. Often doctors stopped therapy when prognosis was considered futile without evaluating the option of organ donation and approaching the family. In a third group of patients advanced directives presumably prohibited organ donation. It turned out that often the advanced directives were sometimes inconsistent or not studied thoroughly, so that organ donation might in fact have been possible. If all potential donors were reported to the DSO, the number of transplants would probably increase by more than 50 %.

These missed opportunities for donation are not the result of an active decision against organ donation in the hospitals. With the increasing workload in intensive care units (ICU), and at the same time a lack of intensivists and specialized ICU nurses, organ donation is repeatedly not considered in daily practice. Establishing a culture of organ donation is essential, in which organ donation is not perceived as something inflicted upon the family after the death of a patient. Thinking of organ donation has to be established as a fundamental part of good end-of-life care. To achieve this goal, adequate continuous training of hospital staff, selection of highly committed in-house transplant coordinators, together with a supportive organizational framework and adequate financing, are essential. ◘

S 28
Improving the organ donor pool
Saturday, 15.00–16.30, Hall G1

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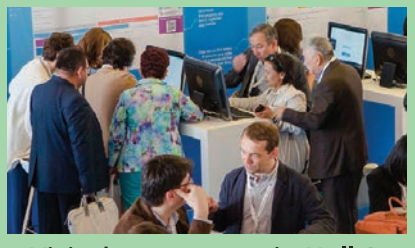

Visit the e-campus in Hall A

Estimated GFR in 2019 A paradox in the era of precision medicine

ESTEBAN PORRINI

La Laguna, Spain

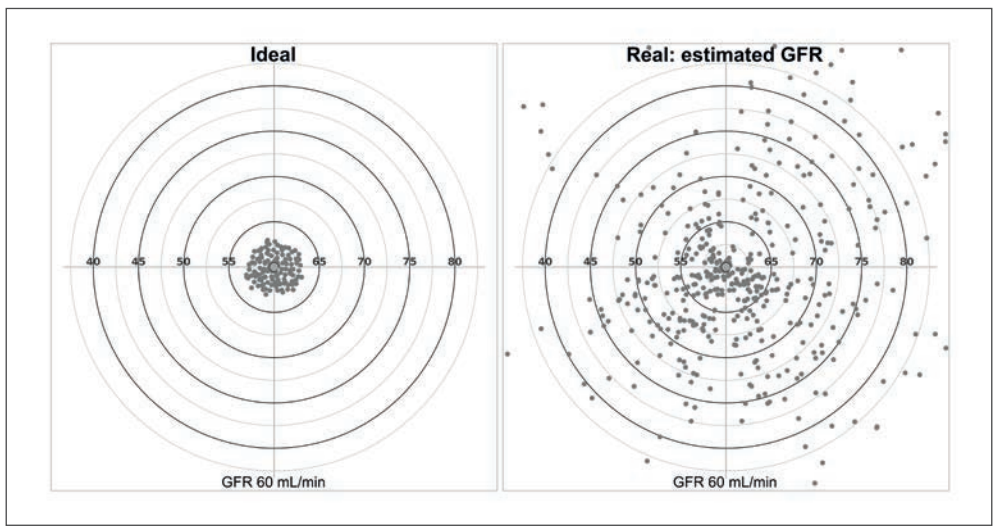

Figure 1: Ideal (left) and estimated (right) GFR vs measured GFR © Esteban Porrini

Renal function is an important parameter in nephrology and clinical medicine. The conditions that particularly need an accurate determination of renal function include (a) evaluation of patients with established renal disease; (b) classification in chronic kidney disease stages; (c) risk prediction for disease progression; (d) assessment of renal function changes over time; (e) guidance of therapeutic indications like the starting of dialysis therapy; (f) screening living donors; and (g) dose adjustment of toxic drugs in patients with renal impairment, among others. Thus, a method that properly reflects renal function is crucial in day-to-day clinical practice.

Today, renal function is frequently estimated by serum creatinine, 24-hour creatinine excretion or estimation formulas that use creatinine and or cystatin-C as the main marker of glomerular filtration rate. However, formulas are far from being a reliable tool. In fact, several publications showed that the average error of formulas averages ±30 % of real renal function. This means that in patients with a value of measured GFR of 60 ml/min, estimated GFR may range from 42 to 78 ml/min. Moreover, this error is wider in 10 to 20 % of the cases. This error happens at random and the same formula can over- or underestimate a similar value of GFR in two different patients. This error can induce relevant over- or underestimation of real GFR, misclassification into higher or lower CKD stages, undetected renal function loss, over- or under dosing of toxic medications (chemotherapy), rejection of living donors with acceptable renal function or, on the other hand, acceptance of a donor with low GFR.

All these aspects have been evaluated and discussed in several publications and reviews in the field. Of note, these limitations pertain to old and new formulas, reflecting almost no advance in accuracy and precision in the field of estimated GFR in the last 50 years. In the era of precision medicine, several areas of clinical medicine use sophisticated devices and techniques to help patients; e. g. tomography, magnetic resonance, PET scans, endoscopic procedures, etc. A 30 % error would have never been accepted for these methods or even for those tools considered more straightforward, like a sphygmomanometer or a weighing scale.

So, why are we accepting a procedure with such a wide error as eGFR? Perhaps it is time to consider that in some specific conditions a more accurate evaluation of GFR is needed. Given the unreliability of eGFR, the use of measured GFR in these conditions is an alternative. Although measured GFR by gold-standard methods has been always considered as burdensome and time consuming, it actually requires the same amount of time as other methods (i. e. renal biopsy, colonoscopy) whose 'burden' is not criticized. Moreover, efforts have been made to simplify the procedure by the reduction in time and the use of the dried blood spot (DBS) technique in the case of the iohexol clearance. So, precision medicine, and of course precision nephrology, cannot be achieved with eGFR. ◘

S 35
The paradox of estimated GFR in the era of precision medicine
Saturday, 17.00–18.30, Hall F1

Debate: We should recommend a low protein diet for patients with CKD stages 3–5 before dialysis

CKD-MBD working group
Chronic Kidney Disease Mineral and Bone Disease

ERN working group
European Renal Nutrition

DENIS FOUQUE

Lyon, France

– PRO

There has been a great deal of experimental and clinical research on food intake in patients with chronic kidney disease (CKD). In the 1930s, doctors were aware that meat intake replacement by a diet composed of egg and potatoes would improve uremic symptoms. Since then, more experiments have been published, peaking in the 1980s in the findings of Dr Brenner's team. Where do we stand now at the start of the third millennium?

Clearly, toxin accumulation that occurs when CKD progresses is the major pathogenic phenotype of CKD [1]. This is highlighted by the lower patient survival for higher quartiles of serum P-cresylsulphate, indoxylsulfate, TMAO and others. These toxic compounds result from the catabolism of food proteins in the colic lumen, facilitated by an impaired microbiome. Because these toxins are not adequately cleared by the failing kidneys, they will induce insulin resistance and further impair organ cross-talk (liver, muscle, adipocyte, bone and heart will be affected).

Each reduction in protein intake immediately reduces toxin production, which can be easily monitored by following urea generation (which drops both in blood and urine). There are also important indirect metabolic changes paralleled by a lower protein intake: reduction in phosphate intake, which improves serum PTH, improves anemia and reduces serum FGF23; and reduction in sodium chloride intake, which helps to better control blood pressure (BP) and reduces BP pills.

What is the optimal diet in CKD? Most probably moving progressively to a vegetarian diet is the best option. Patient education is mandatory, as it is difficult to know a patient's preference at the start of dietary therapy. About 30 % of patients will not accept and will never follow any diet. The remaining patients may progressively reduce protein; some will be fine with 0.6 g/kg/day and others (possibly 20–30 %) will go further down to 0.3–0.4 g/kg/day (see Reference 2). The biological quality of vegetal protein is sufficient in most situations, and supplements with aminoacids or ketoanalogs will only be required for protein intakes below 0.5 g/kg/day.

Following optimization of diet in late CKD, patients will present with less metabolic complications, better appetite, maintenance of body composition, and will avoid the risk of renal cachexia. This will defer the start of maintenance dialysis for many months – a reasonable alternative when waiting for a transplant or choosing conservative treatment in elderly patients.

In conclusion, nutritional counseling is an important step of care in CKD patients. It is not an easy task, and needs patient education, training and participation. When successful, it will improve quality of life, uremic symptoms, maintain body composition and defer the start of maintenance dialysis. Worth trying! ◘

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MARC VERVLOET

Amsterdam, The Netherlands

– CONTRA

In clinical practice, protein restriction as either a low-protein diet (LPD) or very low protein diet with supplements (SVLPD) is advised to many patients with advanced CKD. However, the evidence base to do so is thin, the effect size small, and the burden for patients of this component of their complex treatment particularly high.

Although the landmark Modification of Diet in Renal Disease (MDRD) trial, which addressed the potential benefit on CKD progression of LPD or SVLPD and was performed over 25 years ago, was negative in its primary endpoint, additional studies and meta-analysis confirmed that these diets may delay CKD progression. However, the effect size in patients that managed to adhere to this dietary intervention is in the range of 0.5–1.0 ml/min/year [1]. This small, albeit statistically significant, effect is of limited clinical significance. Importantly, many patients consider this dietary intervention is not acceptable. In a recent trial comparing a vegetarian SVLPD with LPD in patients with advanced CKD, only 17 % of eligible patients were randomized, because 42 % refused participation after obtaining study information, and an additional 44 % dropped out during the run-in phase before randomization in which participants were exposed to the milder diet (Figure 1) [2]. There is no reason to assume that in real life clinical practice tolerance and adherence are better.

Dietary protein can be the source of specific uremic toxins that especially in advanced CKD may contribute to symptoms referred to as the uremic syndrome. Indeed, observations showed that dialysis initiation, a clinically relevant endpoint, can be postponed for several months by LPD, presumably because of a reduction in uremic symptoms. However, nowadays the goal for many patients in CKD stage 5 should be pre-emptive kidney transplantation instead of postponement of dialysis, except for those not suitable for transplantation. In turn, patients not qualifying for transplantation, many of whom may be the elderly, are at risk for malnutrition, which must be weighed against the possible postponement of dialysis.

Instead of devoting lots of effort and time, both on the side of the treatment team and the patients, to educate, motivate and maintain this cumbersome dietary intervention with very limited effect, the focus should be directed to improved implementation of well-established interventions. Optimizing blood pressure control, preferential use of ACE inhibitors or ARBs, prescribing statin therapy based on cardiovascular risk, sodium restriction, cessation of smoking, and optimizing treatment (including use of SGLT2 inhibitors) for those with type 2 diabetes, will most likely have much more impact on overall primary or secondary prevention of comorbidity and mortality.

The question arises if there is any position left for dietary intervention in CKD. Obviously, the answer is yes, but the way forward is not likely to be protein restriction but promoting an overall healthy diet, which takes into account fiber intake, source of protein (such as a vegetarian instead of animal and dairy), restriction of phosphate-containing additives, and optimized constellation of macronutrients and energy intake. ◘

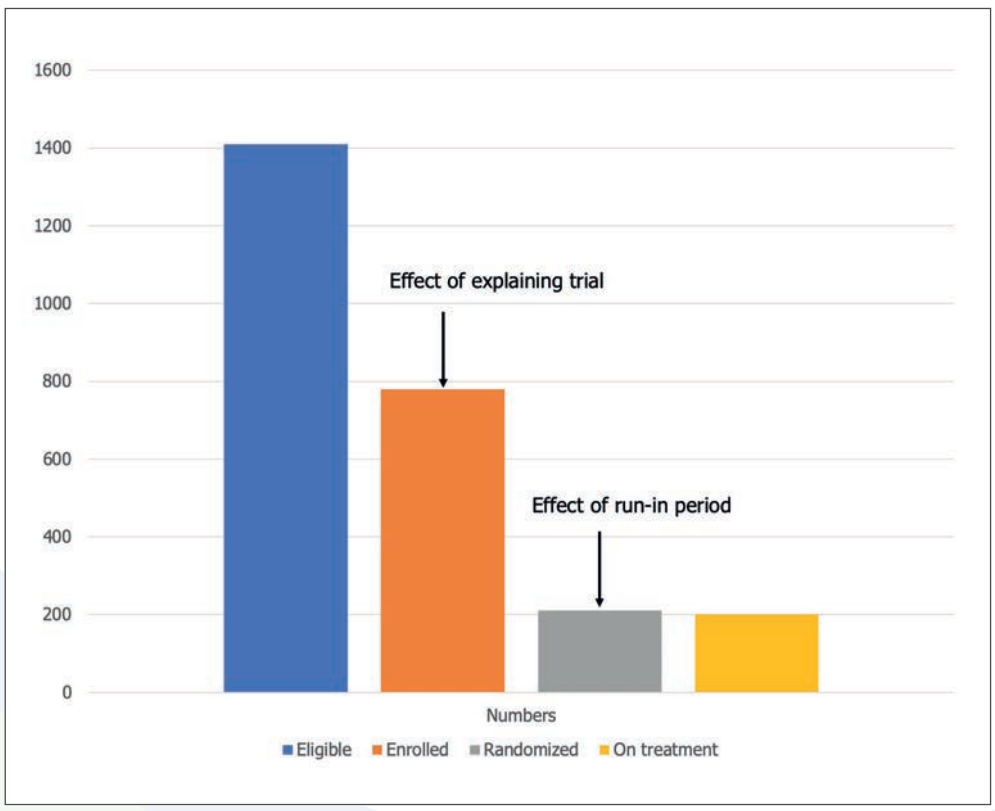

Figure 1: Example of acceptance by patients to adhere to low protein diet. The blue bar indicates the numbers of eligible patients. After explaining the study and diets to adhere to, many refused participation (orange bar). Those that consented started on low-protein diet (LPD) before randomization. Many dropped out during that period (grey bar). Most that were randomized adhered to the diets (yellow bar) Data from Ref [2]: Garneata et al. © Marc Vervloet

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S 31
The role of diet in the prevention of CKD progression: food for thought
Saturday, 15.00–16.30, Hall F1

Time for a new approach Clinical trials and research priorities in dialysis patients

CSABA P. KOVESDY

Memphis, TN, USA

Patients with end-stage renal disease (ESRD) experience extremely high morbidity and mortality, and there are virtually no therapeutic interventions besides the dialysis treatment that are proven in properly designed randomized controlled trials (RCTs) to improve their outcomes. Historically, the number of RCTs performed in the ESRD population has been very low compared to other medical subspecialties. Furthermore, several of the few large RCTs conducted in patients with ESRD have yielded inconclusive or negative results, dampening enthusiasm for future investment in similar trials. It is therefore important for the Nephrology community to examine its research priorities and to adopt novel approaches to scientific inquiry. More patient participation in determining research priorities and the prioritization of patient-centered outcomes could result in improved recruitment and retention in clinical trials of ESRD patients, and the implementation of novel design strategies could potentially lead to more affordable RCTs with improved internal and external validity.

A recent systematic review of hemodialysis RCTs found that, among 10,713 outcome measures, the most common were surrogates such as phosphate, dialysis adequacy, anemia, inflammatory markers, and calcium. Patient-centered outcomes such as mortality, cardiovascular disease, and quality of life were reported very infrequently. Recent initiatives promoting a focus on patient-centered outcomes and more active patient and caregiver involvement in the planning and conduct of clinical trials may result in more clinically relevant RCTs and broader participation from patients representing the diversity of the ESRD population. For example, the Standardized Outcomes in Nephrology (SONG) initiative established fatigue, cardiovascular disease, vascular access and mortality as the core outcomes that are critically important to all stakeholders. Other initiatives by national organizations in the US, Canada and Australia have also emphasized the importance of patient-centered outcomes such as enhanced quality of life.

The ESRD population is diverse and complex, making it difficult to test interventions within the framework of a traditional RCT design that has resulted in unexpectedly low event rates and high drop-out and cross-over rates, rendering results internally invalid and yielding inconclusive results. The recent emergence of various RCT designs could aid in making ESRD clinical trials more successful. Pragmatic clinical trials (PCTs) have been introduced as a means of enhancing the external validity of clinical trials, by implementing broad enrollment criteria, clinically relevant comparators, evaluation of interventions within clinical practice, and the testing of practically meaningful outcomes. The broad utilization of electronic health records (EHRs), the standardized application of multiple medical and technical interventions within the framework of routine clinical practice, and the clustering of patients within dialysis units using uniform clinical practices make PCTs particularly feasible in the hemodialysis population. In addition to PCTs, there are other emerging RCT designs that could result in more successful testing of interventions in ESRD, such as adaptive platform designs. The application of such novel RCT designs could result in benefits such as reduced trial cost, the examination of a broader, more representative population, and the testing of a higher number and more clinically relevant interventions. ◘

Read the full review "Clinical trials in end-stage renal disease – priorities and challenges" by Csaba P. Kovesdy in NDT.

S 29
Cardiovascular disease in CKD: Risk factors and remedies
Saturday, 15.00–16.30, Hall G2A

INSTITUTIONAL

A new opportunity for you from the ERA-EDTA
Find out about the Scientific and Educational Interaction Day

Are you interested in education that you can put into practice in your next renal clinic? Then the Scientific and Education Interaction Day (Vienna, October 26) is for you.

Professor Danilo Fliser, ERA-EDTA Renal Science Chair, comments: "We hope that, by offering multiple educational opportunities, this practical two-day meeting will appeal particularly to young nephrologists. There are updates on current approaches to diagnosis and treatment, and data on ongoing studies and emerging treatment options. You will also hear from experts on hot topics like how to use new investigations responsibly and how to predict patient survival. All of this in one single event!"

During the SEID, there is the chance to learn more about systemic diseases that affect the kidney like ANCA-associated vasculitis, lupus nephritis, and anti-GBM disease. There will also be stimulating discussions on the ethical aspects and implications of using results of genetic testing in daily clinical practice, as well as the many factors influencing the choice between hemodialysis, peritoneal dialysis and transplantation.

Vascular access is a particular concern for both nephrologists and patients. During the SEID, the session on this essential topic includes demonstrations of ultrasound scanning and fistula imaging on real patients, and also offers delegates the chance to practice imaging under expert supervision and guidance.

And do not miss the Satellite 'New Drugs in Kidney Disease' Symposium, which precedes the SEID on October 25. This half-day symposium is industry-independent and designed as a fully educational experience with a therapeutic focus. Key European speakers will provide updates on recent studies related to the treatment of anemia, hyperkalemia and diabetes in chronic kidney disease. "When planning the SEID, we asked all the Working Groups to suggest topics and chose the best four proposals. So the event reflects not only the continuing educational mission of the ERA-EDTA, but also the innovative character of our discipline," concludes Professor Fliser.

Sessions will be available after the event as e-materials. The ERA-EDTA offers up to a maximum amount of EUR 30,000.00 in travel grants to ERA-EDTA members (categories A and B), who are no older than 40 in 2019. For information and applications, please contact seid@era-edta.org

Contact ERA-EDTA Group for more information about SEID at organisation@era-edta.org (telephone: +39 0521 989078). ◘

EDUCATION

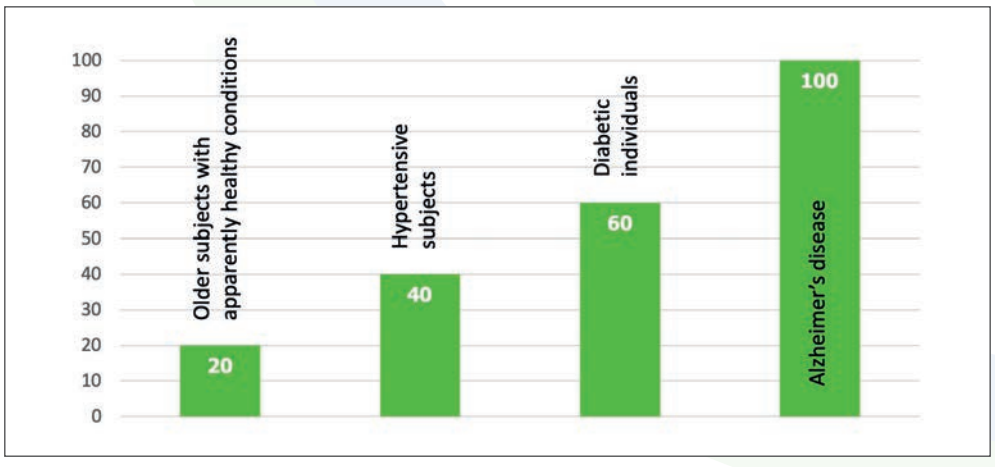
Equality, autonomy and informed consent
Ethical aspects in frail recipients and the organ pool

FRANCESCO P. SCHENA

Bari, Italy

There are numerous definitions of 'frailty', but in practice it is the expression of an increased vulnerability to adverse outcomes among individuals of the same chronological age. Frailty is the union of aging and accumulation of such deficits as decreased muscle strength, fatigue, mood disturbance and high susceptibility to diseases. Frailty must be firstly screened and diagnosed for clinical-decision making and healthcare planning. For these approaches it is necessary to have an interdisciplinary team that enables the adoption of an individualized approach for every patient and caregiver. The number of older patients on the waiting list for kidney transplantation increases yearly and the prevalence of frailty continues to rise. Therefore, relevant ethical aspects must be taken into consideration. Frailty occurs in 20 % of older, apparently healthy subjects, but the percentage increases with the presence of one or more pathological conditions (see Figure) that are frequently present in patients undergoing periodic hemodialysis who are on waiting list for kidney transplantation. In fact, more than 20 % of kidney transplant recipients are frail. Therefore, frailty must be periodically scored in these individuals.

Today, frailty is scored using the Edmonton Frail Scale, but it interacts frequently with altered cognition that is the expression of mental decline associated with aging. Thus, cognition must also be scored using the Montreal Cognitive Assessment. Recently, Haugen et al [1] have demonstrated that frailty is associated with a lower chance of listing, higher cumulative incidence of waitlist mortality and a lower rate of kidney transplant. Therefore, ethical considerations are necessary before deciding to include frail patients who need accurate surveillance in waiting list. The ethics of frailty is based on two fundamental norms: equality and autonomy. Equality protects against discrimination and ensures fair and equitable treatment, and is related to individual needs, circumstances and capacity to benefit. It can mitigate age-based discrimination and other personal characteristics. Autonomy is based on informed choice; thus, the patient must be able to choose without coercion. In the presence of autonomy the patient is able to act in his or her best interests. Respect for autonomy is predominantly operationalized through care providers' obligation to enable others to act on their own understanding of their own best interest when making healthcare decisions.



Frailty percentage in older people (>60 years) © Francesco P. Schena

As reported by McNally et al [2], five elements of informed choice or informed consent must be respected: (i) patient voluntariness in absence of coercion; (ii) capacity to understand information relevant to a decision; (iii) comprehension of all pertinent information; (iv) provision of all pertinent information; and (v) authorization of a choice by the patient. Treatment without valid informed consent is a criminal act. Informed consent implies that the choice is authorized by someone who has the capacity to make decisions based on his or her ability to understand information, as well as the foreseeable consequences of a decision. When a patient lacks capacity, the law requires that the informed consent should be signed by a capable person who has legal authority (e. g. kidney transplantation in children). Informed consent must be voluntary; duress or coercion is not a genuine choice.

Disclosure must address all information on the likelihood of the predicted clinical outcomes and the gravity of associated risks that a patient should know. Of course, it is important to recognize that the individual has the capacity to understand information about informed consent. Technical or unfamiliar language may impede the patient from understanding and taking a decision. Therefore, information must be disclosed in a clear manner to enable a patient to make a decision or to choose the type of treatment. An adequate disclosure should indicate different choices of treatment.

Finally, the high demand and poor supply of kidneys suggest an accurate screening of frailty, mainly in older patients, according to the ethical principles of organ donation. Methods for resolving ethical dilemmas may assist decision-making in difficult situations. ◘

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S 33
Overcoming age with frailty evaluation in the kidney transplant recipient
Saturday, 17.00–18.30, Hall G2A

EDUCATION

Transition is not a failure

Striving to achieve an integrated home dialysis system

MARÍA FERNANDA SLON ROBLERO

Pamplona, Spain

Each year, over 83,300 Europeans transition from nondialysis-dependent chronic kidney disease to renal replacement therapies. [1] A single therapy option might not be adequate over an entire lifespan, and many patients, especially young patients, will require a switch in treatment modality to adapt their treatment to their clinical and psychosocial needs.

In recent years there has been an increasing interest in home dialysis therapies, probably because there is more and more evidence that home dialysis, including peritoneal dialysis (PD) and home hemodialysis (HD), represents an important alternative to in-center hemodialysis. It is cost effective and patient-centered, with many benefits related to patient outcomes, including not only improved quality of life but also patient survival. [2] However, despite these benefits, both home therapies continue to have a low prevalence within worldwide dialysis populations. [1]

It is true that the majority of home dialysis patients start with PD, because it is a simple technique with lower cost, and is associated not only with better preservation of residual kidney function, but also with protection of potential vascular access. But sometimes, PD is not possible because of medical contraindications, or continuation of PD beyond the first few years is frequently limited by technique failure. So in all these situations home HD plays a fundamental role as an alternative that we can offer to our patients to enable them to stay at home. Home HD is a unique modality, insofar as it offers the opportunity to individualize treatment and, specifically, to increase treatment intensity beyond what is typically feasible in the center setting. It has multiple benefits, especially when prescribing more intensive regimens, but above all with benefits directly related to patient survival. [3]

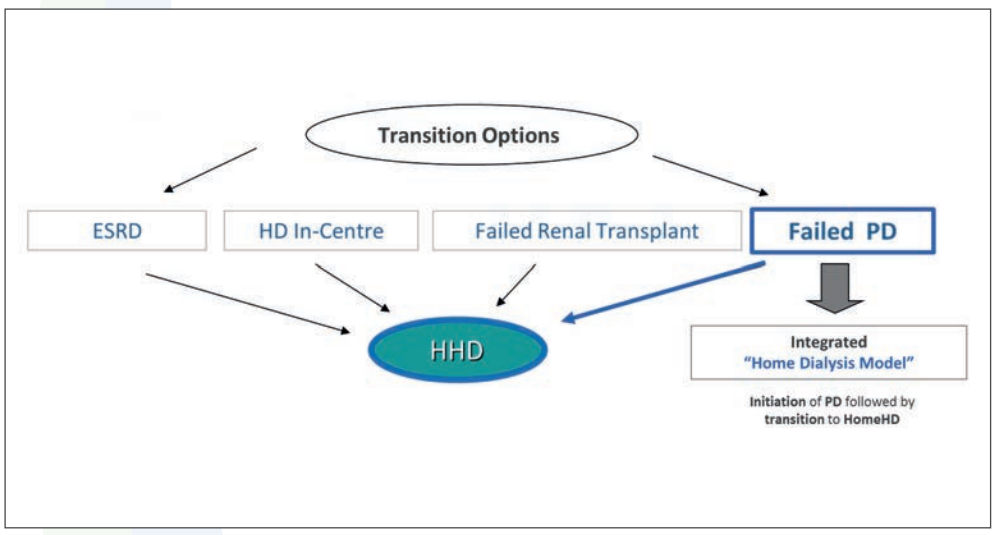

Figure © María Fernanda Slon Roblero

The 'integrated home dialysis model' (Figure) involves the initiation of PD followed by a timely transition to home HD, at the time of PD completion. There is little data about dialysis transition in home-based therapies. However the evidence has shown that patients who start on PD and transition to home HD have some of the best outcomes among patients undergoing renal replacement therapy. These are achieved by maximizing home-based dialysis therapy benefits, while still capitalizing on the putative early advantages of PD and the potential survival advantages afforded by home HD. [4–6] This model could be considered as an ideal dialysis strategy especially if a kidney transplant is unavailable. In spite of all this evidence, the majority of patients who present with PD failure are transferred to facility HD, and only a few patients transition to home HD. This demonstrates that we are still missing opportunities to facilitate continuation at home, and that there are still a lot of barriers that we need to break down to facilitate this transition [4, 7].

As we all know, there are many barriers that prevent the growth of home treatments, but there is one that is fundamental. It represents a barrier that depends on us, the nephrologists, and is a barrier that is easy to break down: we must believe in home dialysis and we must offer more of these treatment options. And when one of these modalities fails (usually PD) we should try to keep 'home dialysis patients at home', regarding this transition not as a 'failure,' but rather an expected progression of the patient's treatment options. It should be considered as a gradual move from one therapy to another. This way of thinking represents one of the fundamental ways to break down barriers if we want to help the 'home dialysis patient' maintain their quality of life and autonomy, plus many other benefits, without losing them because of the need for a change of modality. ◘

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S 32
Home haemodialysis: on the move
Saturday, 17.00–18.30, Hall G1

EDUCATION

New therapeutic targets in Alport syndrome

A specific disease-modifying therapy remains an unmet need

ROSER TORRA

Barcelona, Spain

Alport syndrome (AS) is a hereditary type IV collagen disease that leads to progressive proteinuria, renal fibrosis, and kidney failure. Depending on the mutated gene and the pattern of inheritance, there are three types of AS. Mutations in *COL4A5* cause severe disease in males and a disease of variable severity (but usually much less severe) in females. Mutations in *COL4A3* and *COL4A4* are the cause of the autosomal forms of AS. Homozygous or compound heterozygous mutations in *COL4A3* or *COL4A4* are the cause of autosomal recessive AS (ARAS), while a single mutation in either of these genes causes autosomal dominant AS (ADAS) (Figure 1).

Having only one mutation in *COL4A3* or *COL4A4* can cause a phenotype that ranges from nothing (i.e. some parents of children with ARAS) to hematuria alone or to proteinuria and subsequent renal failure on top of hematuria. Over the past several years it has become increasingly apparent that more patients reach end-stage kidney disease (ESKD) due to ADAS than due to classical X-linked AS or ARAS, even though this progression occurs at a much older age. The seminal determinant of disease progression in AS logically seems to be the amount of damage in the glomerular basement membrane (GBM).

A surrogate pathological marker may be tubulointerstitial fibrosis, which has been recognized as the key feature in progressive renal damage leading to ESKD. The glomerular disease and the podocyte stress response lead to the secretion and distribution of profibrotic chemokines and cytokines, which are the main causes of interstitial fibrosis and tubular atrophy. Progression from hematuria to microalbuminuria and progression from microalbuminuria to overt proteinuria represent very important steps in the course of AS. As for many renal diseases, the primary endpoint for AS clinical trials is or will be the decline in GFR. But again, similarly to other renal diseases, this is probably too late an endpoint to make a significant impact on the course of the disease. Theoretically, treatment prior to the appearance of renal fibrosis offers more

promising long-term renal outcomes. GBM aspect and degree of fibrosis on renal biopsy and proteinuria could be excellent endpoints for clinical trials.

At present, there is no curative treatment for AS, so all males with X-linked disease and all males and females with ARAS, as well as a certain percentage of patients with ADAS, will ultimately show progression to ESKD. The only recommended treatment nowadays for this disease is RAAS (renin-angiotensin-aldosterone system) blockade. Currently RAAS is being tested in children even before the onset of proteinuria.

AS has become a very attractive disease for pharmaceutical companies to target. There are several reasons for this interest: (1) it is an excellent model of chronic kidney disease (CKD) with proteinuria and fibrosis that may be extrapolated to other more common causes of CKD; (2) any drug approved for this disease will have an orphan drug designation with its consequent benefits, such as shortened approval timeline, financial incentives, and a period of market exclusivity; (3) the number of patients to be treated will be substantial, AS being the second more frequent inherited kidney disease after ADPKD; (4) patients are young and have very few comorbidities, which facilitates clinical trials; and (5) there is no approved treatment for AS. Currently there is an ongoing trial using bardoxolone and another using anti miRNA21 is expected to start soon. Other drugs under study for AS are paricalcitol, lipid-lowering agents, epidermal growth factor receptor inhibitors, chaperones, stem-cell based therapies, inhibitors of STAT3, etc.

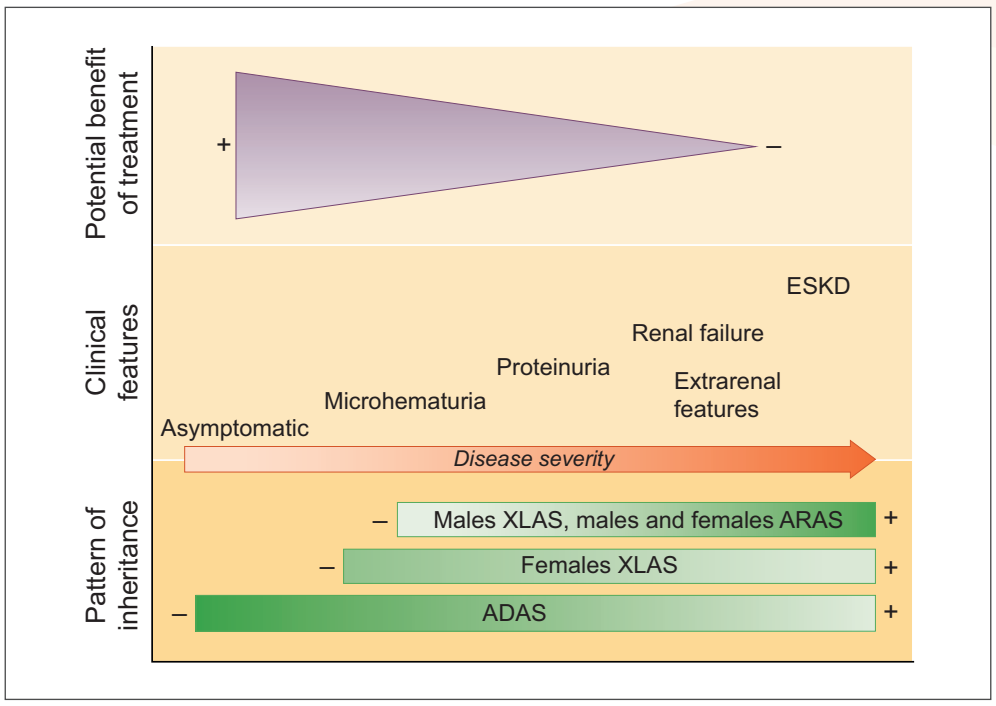

Figure From Torra et al. New therapeutic option for Alport syndrome. NDT 2019. © NDT. Courtesy of NDT

A specific disease-modifying therapy for AS remains an unmet need. In view of its proteinuric and fibrotic nature, AS represents an excellent disease from which to extrapolate results to many other diseases that cause CKD. ◘

Read the full review "New therapeutic option for Alport syndrome" by Roser Torra in NDT!

S 38
Novel therapies in hereditary kidney diseases
Sunday, 08.30–10.00, Hall G2B

EDUCATION

Addressing potentially inappropriate medications in older adults with kidney disease

RASHEEDA HALL
Durham, NC, USA

Compared to older adults without kidney disease, older adults receiving dialysis are twice as likely to fall, develop severe cognitive impairment, and become hospitalized. Each of these adverse outcomes is associated with potentially inappropriate medications (PIMs). PIMs are medications that should be avoided in older adults because their risks usually outweigh their benefits. Established lists of PIMs to guide clinician decision-making include the American Geriatrics Society Beers Criteria and the Screening tool of older people's prescriptions and screening tool to alert to right treatment (STOPP/START) criteria.

In addition to age-related changes in pharmacokinetics and pharmacodynamics, older adults receiving dialysis also have uremic toxins that can alter hepatic drug metabolism of PIMs (i. e. cytochrome p450 inhibition). Older dialysis patients commonly take PIMs to treat symptoms associated with end-stage renal disease (ESRD), such as anxiety, muscle cramps, or pain (e. g. benzodiazepines, muscle relaxants, opioids), or to lower blood pressure (e. g. α-blockers and central α agonists). Because older dialysis patients have increased vulnerability to PIMs, reducing PIM use may prevent geriatric problems and related hospitalizations.

Current evidence highlights prevalence and potential risk of PIMs in older adults across the continuum of kidney disease severity, which gives hints to PIMs to deprescribe. Using the Beers Criteria, ~13–60 % of older adults with CKD are taking one or more PIM. The United States Renal Data System shows that opioids are one of the most commonly prescribed medications for dialysis patients, while data from Japan and Norway shows that benzodiazepines, first-generation antihistamines, and α blockers were each prescribed in 12 % of older dialysis patients. Anticholinergic antidepressants have been associated with falls, fractures, and altered mental status in older adults receiving dialysis. Studies not limited to older adults demonstrate CNS-active medications, including opioids, muscle relaxants, and gabapentin, may increase risk of falls, altered mental status (or cognitive impairment), and related hospitalizations.

Existing deprescribing interventions have only targeted older adults without kidney disease, showing that deprescribing facilitates prescriber decision-making and reduces PIM use and hospitalizations. Deprescribing refers to a patient-centered, systematic approach to stopping or reducing a PIM. For example, engaging a patient to discuss deprescribing a medication that is known to contribute to falls. As shown in the Figure, this cyclical process involves 5 steps: (1) medication reconciliation, (2) medication review, (3) deprescribing decision-making, (4) implementation of deprescribing, and (5) monitoring for withdrawal or intolerance. Such interventions frequently involve electronic consults, pharmacist engagement, multidisciplinary care teams and/or patient education tools. The deprescribing decision-making step should ideally take a shared decision-making approach that may need to involve the patient's caregiver.

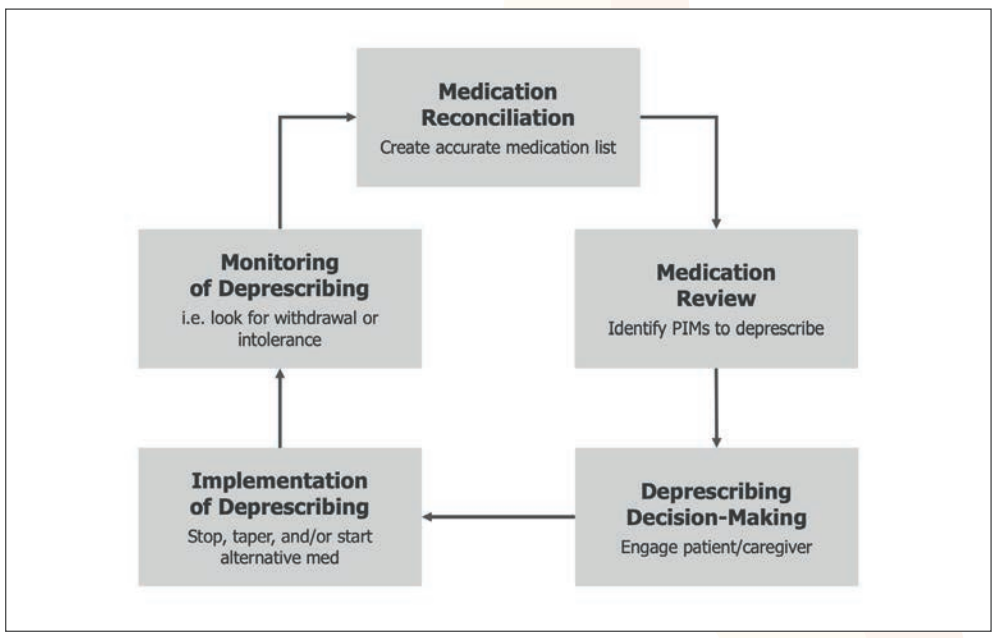

Figure: Five steps to deprescribing © Rasheeda Hall. Modified from: Reeve E, Shakib S, Hendrix I et al. Br J Clin Pharmacol. 2014 Oct;78 (4):738-47

This process may also involve other clinicians and/or multiple patient discussions over time.

In dialysis units, there is an urgent need to establish an approach for deprescribing PIMs to reduce PIM adverse effects, including geriatric syndromes and hospitalizations. Our research team is conducting numerous studies to build and test a model of care for deprescribing in dialysis units. ◘

S 37
Frail elderly: management best at home
Sunday, 08.30–10.00, Hall G2A

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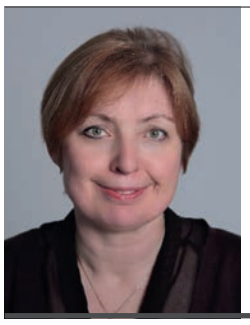
Insights from adverse effects of anti-cancer drugs

Managing hypertension in patients with cancer and kidney impairment



PETRA TESAROVA

Prague, Czech Republic

Oncology has dramatically changed during the last 20 years as the therapeutic armamentarium has steadily expanded. New treatment confers benefit on not only patients with curable, earlier stages of cancer, but also patients with advanced and/or metastatic cancer, significantly prolonging their life with a good quality. Generalized cancer has become a chronic disease.

Acute kidney injury (AKI) and chronic kidney disease (CKD) are not infrequent among patients with cancer. The combination of cancer with impaired renal function worsens the outcome and complicates the treatment. The association between cancer and hypertension is also a growing problem considering the high prevalence of both conditions. Anti-VEGF treatment is most frequently associated with high blood pressure, mainly because of the decrease in NO synthesis with subsequent defective vasodilation. VEGF inhibition also induces endothelial cell death and rarefaction of resistance vessels. Angiogenesis inhibitors are divided into two main groups: monoclonal antibodies against VEGF (e.g. bevacizumab) and small-molecule inhibitors of VEGF-dependent tyrosine kinase (e.g. sunitinib, sorafenib). First-line agents to be used in the treatment of anti-VEGF treatment-associated hypertension are angiotensin-converting enzyme inhibitors (ACEI) and/or calcium channel blockers (CCB – most often amlodipine or felodipine). Choice is based on the mechanism of hypertension induced by VEGF inhibition nitrates, or phosphodiesterase inhibitors could be also considered. Non-dihydropyridine CCB (verapamil and diltiazem) should be avoided in patients treated with sorafenib or sunitinib due to the relevant pharmacokinetic interactions (both inhibit CYP3A4).

Erythropoietin (EPO) is a glycoprotein hormone that controls bone marrow erythropoiesis. It is produced by predominantly by renal interstitial cells. In about 33 % to 35 % of patients treatment with recombinant human EPO (rhuEPO) and other erythropoiesis stimulating agents (ESA) is associated with increased peripheral vascular resistance and mild decrease in cardiac output with subsequent elevation of blood pressure levels. Hypertension usually occurs two to 16 weeks after the start of rhuEPO administration. Several pathophysiological mechanisms have been proposed to explain the development of ESA-related hypertension. The following should be highlighted: (1) increase in erythrocyte mass with increase in blood viscosity; (2) change in production and sensitivity of endogenous vasopressor agents; (3) change in the vascular smooth-muscle ionic milieu hindering response to vasodilating factors; (4) direct vasopressor effect of rhuEPO; and (5) remodeling through stimulation of vascular cell growth. CCB and alpha-adrenergic blockers were shown to be effective in ESA-related hypertension in patients with CKD. On the other hand, ACEI and angiotensin II receptor blockers (ARB) are less effective because of suppressed production of angiotensin II. The effect of diuretics in patients with advanced CKD is also limited.

Among other drugs used in patients with CKD, corticosteroids and NSAID may also increase blood pressure.

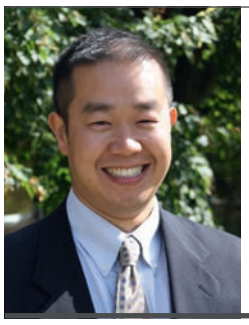
Treatment goals for hypertensive patients with cancer do not differ from those in other hypertensive patients, although we must always take into consideration limited survival of patients with metastatic cancer competing with cardiovascular risk. ◘

S 39
Digging the aetiology of hypertension
Sunday, 08.30–10.00, Hall F1

EDUCATION

Genetic susceptibility and acute kidney injury

Identification of susceptibility genes could help guide development of future therapies



MICHAEL HEUNG

Ann Arbor, MI, USA

Acute kidney injury (AKI) is one of the most common complications among hospitalized patients, affecting more than one in 5 adults admitted to the hospital setting. The development of AKI is associated with greater healthcare resource utilization, high patient morbidity and increased mortality. At present, there remain no proven therapies to attenuate or reverse established AKI, beyond supportive care. As such, an important focus for clinicians is the prevention of AKI.

Prevention of AKI requires appropriate risk stratification. Many predisposing risk factors have been identified, including pre-existing chronic kidney disease (CKD), diabetes mellitus, proteinuria, etc. Yet one area that has received relatively little attention is genetic susceptibility to AKI. In recent years, pathophysiologic pathways to kidney injury have been further elucidated, particularly with the role of inflammation. It is biologically plausible that genetic variants in components of these pathways could predispose to injury, and indeed animal models of AKI susceptibility have been developed [1]. However, human genetic studies have so far been limited and disappointing.

Larach and colleagues recently conducted a literature review of studies examining AKI genetics [2]. There was significant heterogeneity in the published literature, in part because most studies were hypothesis-driven and targeted specific candidate polymorphisms. There was also heterogeneity even in how AKI was defined between studies. Perhaps not surprisingly then, there were conflicting results between studies and no clear consensus regarding any particular genetic variants. The overall heterogeneity among studies also precluded formal meta-analysis, and the authors concluded that large, unbiased studies are necessary to identify candidate genes in AKI. The largest AKI-related genome-wide association study to date examining AKI did identify two genetic loci of interest, but these findings require further confirmation [3].

Moving forward, what is needed to further elucidate genetic variants that may play a role in AKI susceptibility? First, it will be important to define specific AKI syndromes that ideally share a similar pathophysiology. For example, AKI occurring in the setting of sepsis may not have the same predisposing genetic factors as AKI developing post-cardiac surgery; and these may both differ from toxin-mediated AKI syndromes. Second, adequately powered, large, unbiased examinations are needed to identify potential novel genetic variants predisposing to AKI. Third, beyond predisposition to AKI, future studies should explore genetic variants that may be protective for AKI and/or mediate post-AKI outcomes such as kidney function recovery versus progressive kidney disease. Ultimately, the identification of AKI susceptibility genes could provide further insight into mechanisms of AKI, and thereby guide development of future therapies. ◘

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S 36
AKI: current problems in clinical practice
Sunday, 08.30–10.00, Hall G1

EDUCATION

Geriatric assessment and routine dialysis care

EDWINA BROWN

London, United Kingdom

Ignoring the healthcare and social challenges of the aging dialysis population leads to poor patient experience and outcomes, and inappropriate use of expensive healthcare resources. The gold-standard Comprehensive Geriatric Assessment is a multidimensional, interdisciplinary diagnostic process; it is time consuming and labor intensive. This is a deterrent to both the dialysis provider and to patients, who already have a high healthcare burden.

We have carried out a feasibility project to determine whether a renal nurse could deliver a modified geriatric assessment (MGA) followed by referral to the appropriate support service(s). The MGA included an assessment of dependence on mobility aids, falls, presence of vision or hearing problems, and social support provided by family or other caregivers, as well as assessment of frailty and cognitive dysfunction (Figure). The assessment takes up to an hour, so could be completed while waiting for hemodialysis (HD) or in a peritoneal dialysis (PD) clinic, either as a whole or in smaller components on separate occasions.

All patients > 70 years old or considered as frail on PD or on HD in one of our satellite centers were assessed (50 PD; 68 HD). Thirty five percent of patients scored 5 (mild frailty) and 35 % scored 6 (moderate frailty) on the Canadian Frailty Scale. Services to which patients were referred following assessment included dietician (42 %), social services (30 %), renal counselor (18 %), palliative care (9 %), memory clinic (12 %) or falls clinic (8 %). All patients completed a distress thermometer score and the renal treatment satisfaction score. These showed improvement in patient experience over a 12-month period. At initial assessment, 32 % HD (n = 40) and 31 % PD (n = 31) patients had a distress thermometer score > 4; at 12 months this had fallen to 12 % for HD and 16 % for PD patients. The Renal Treatment Satisfaction score was analyzed with an optimal cut-off score of 80 %; 46 % HD and 16 % PD patients scored < 80 % at initial assessment compared to 20 % HD and 0 PD patients at 12 months.

These initial results are encouraging and show that geriatric assessment can be integrated into routine dialysis care using the existing renal multidisciplinary team. The next phase of the project is to develop an education program for kidney nurses so that the MGA can be incorporated into routine care across the whole department to include all dialysis areas as well as predialysis assessment, transplantation, etc. At the same time we shall be developing literature for patients informing them about their diagnosis of frailty, what this means and what support and activities could help improve things. Guidance will also be given about the types of decision they should consider regarding their healthcare. This literature will be co-written with a patient and caregiver group.

There is now considerable data about the burden of geriatric syndromes for older people with advanced kidney disease. Nephrology teams will have to develop ways of incorporating geriatric assessment and care into routine management. How they do this will depend on local healthcare systems, expertise and resources. ◘

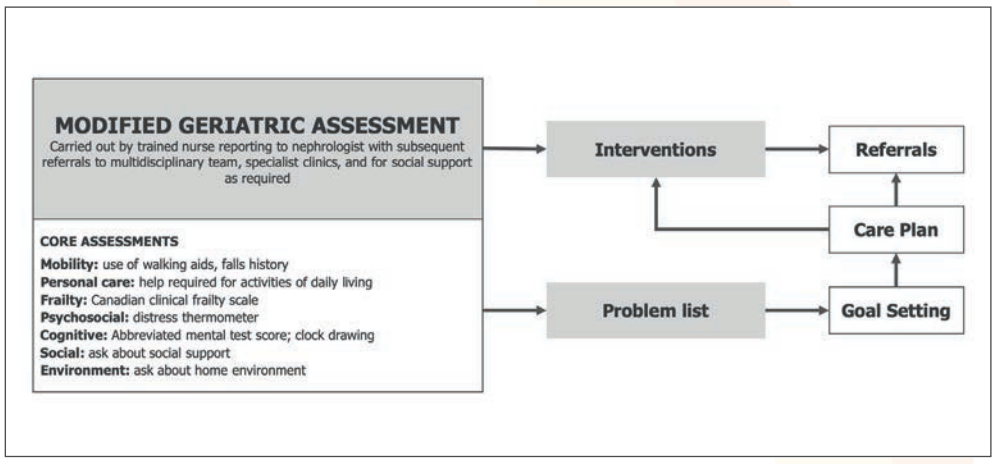

Figure: Modified Geriatric Assessment © Edwina A. Brown. Modified from: Brown EA, Farrington K. CJASN May 2019, CJN.14771218; DOI: https://doi.org/10.2215/CJN.14771218

S 37
Frail elderly: management best at home
Sunday, 08.30–10.00, Hall G2A

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