Interview with Congress President Prof. Pieter ter Wee

The Lancet-Symposium and the plenary lectures are only a few of the highlights that Prof. Pieter ter Wee, President of the 51st ERA-EDTA congress entrusts to all the nephrologists that are coming to Amsterdam for the Congress. In this interview he takes a glance at the programme.

Prof. ter Wee, what will be the main highlights of the scientific programme?

Prof. ter Wee: The agreed mission of the ERA-EDTA is to promote nephrological science – clinical science as well as basic research – in order to benefit patients with kidney disease. To this end, the programme committee chaired by David Wheeler from London has compiled an attractive programme for this Congress, reflecting all the key areas of nephrology (e.g. transplantation, dialysis, prevention of CKD, hypertension, diabetes, vascular disease, glomerular diseases, acute kidney injury, hereditary disorders). Some of these are of particular topical relevance.

Cardiovascular complications, for example, are still a major problem – and secondary prevention strategies have therefore acquired special importance. Polycystic kidney diseases are another hot topic because many promising research results have been published in recent years – and the topic is enjoying a renaissance. The CME programme on intensified dialysis strategies is also striking a chord, and of course there are the plenary lectures.

I am especially looking forward to the talk Hans Clever will deliver on the talk Hans Clever will deliver on course there are the plenary lectures. 

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ving translational projects.

What, in your opinion, makes this Congress attractive for young nephrologists?

Prof. ter Wee: First of all, the poster presentations and abstracts – more than 2,000 abstracts have been submitted. So the Congress gives a full picture of the state of the art in nephrology. Latest developments and research projects are presented, and young colleagues especially should not miss the chance to become part of this community.

In addition to that, we also have a special symposium of the Young Nephrologists’ Platform. Its aim is to involve young nephrologists in all the activities of the ERA-EDTA – so I want to recommend young nephrologists to join this platform. So for everyone who is interested in nephrology.

Continued on page 2
Water in the future: a scarce resource

ESA-scientist Bernard Foing and groundwater expert Arjen de Vries will speak at the Welcome Ceremony

Nephrologists by the nature of their profession appreciate the value of clean water. Water is necessary for life on earth, it is of utmost importance for dialysis. Lack of clean water especially in the developing world increases the risk of diseases that may lead to acute kidney injury. The choice of the Congress theme ‘water in the future’ therefore comes quite natural - so much the more in Amsterdam, where the Python bridge looks like a path into the future.

The Congress theme “Water in the future” suits an event in Amsterdam, where the Python bridge looks like a path into the future.

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The Congress theme "Water in the future" suits an event in Amsterdam, where the Python bridge looks like a path into the future.

...Continued from page 1

young and ambitious and planning a career in nephrology, Amsterdam is definitely the place to be right now! The Congress also hosts the national societies – why is that? What other networking activities have been planned?

Prof. ter Wee: The interchange and collaboration among the different national societies has become vital, because the funding of research projects is becoming more and more difficult. Nowadays, investigators often have to approach the EU for project funding, but an important condition is that the project involves the collaboration of at least two different EU countries. Therefore, it is always good to know some potential project partners.

But I am also very pleased about another partnership that is having its premiere at our Congress, namely the collaboration between the ERA-EDTA and “The Lancet”. This renowned journal will publish several nephrology papers the day they are presented in two joint symposia at our Congress. The papers have passed the tough review process of “The Lancet” and are high-quality contributions. This partnership will sharpen ERA-EDTA’s profile as one of the leading scientific societies worldwide.

What makes this Congress “your” Congress? Are there any Dutch topics, aspects or studies reflected in the Congress programme?

Prof. ter Wee: Well, as I discovered, even the Congress President has only a limited influence on the Congress programme – but joking aside, of course, the programme does highlight some Dutch initiatives and scientists. We have a symposium in which CKD-MBD is topicalised and in which the NIGRAM Consortium will be presented. The consortium, located in the Netherlands, consists of three collaborating university medical centres and its particular focus is on the axis of fibroblast growth-factor-23, klotho and vitamin D.

There is also a EuroPD symposium, during which data of an important European initiative, of which the principal investigator is located in the Netherlands, EUTRIPD will be presented. Apart from that, I made sure that all of the eight Dutch universities are represented in our lectures and scientific sessions. A special session will also be devoted to epidemiology and registries, with specific emphasis on the ERA-EDTA Registry, whose head office is located in Amsterdam. So there seems to be quite a bit of Dutch influence – although to be honest, the Netherlands have always been well-represented in the Congress programme because there is a lot of research going on in this rather small country!

And lastly, of course, the local committee chose the Congress logo, which I really like. The picture of a watermill in the sunlight is an early painting of the famous Dutch painter Piet Mondrian and the vibrant joyful colors are an appealing invitation to come to Amsterdam!

Speaking of Amsterdam – what should participants from abroad who are in Amsterdam for the first time make sure they see or do?

Prof. ter Wee: Apart from the Congress and its interesting programme, one has to experience a boat tour through the canals. This is the best way to appreciate the flair of Amsterdam. Of course, we also have many cultural places, such as the recently renovated ‘Rijksmuseum’, ‘the Van Gogh’ museum, or the ‘Concertgebouw’, which is home to one of the world’s top orchestras, the ‘Royal Concertgebouw Orchestra’. For the evening, there are many nice restaurants and pubs inviting you in to discuss the latest scientific findings with colleagues over a glass of wine or beer.

Enjoy your stay in the Netherlands, and I bid you all a warm welcome to Amsterdam!
The Immunonephrology Working Group (IWG) published data from the VALIGA study in Kidney International

**Growing interest**

*Working Group on Inherited Kidney Disorders*

Education is a major priority for the Working Group on Inherited Kidney Disorders (WGfKD). More than 300 participants joined the CME symposium organised during the 50th ERA-EDTA Congress in Istanbul last year. The symposium covered a wide range of topics that are important for inherited kidney disorders, which initiated stimulating discussions during the day. In September 2013, the WGfKD organized a symposium in collaboration with the University of Oxford and the Tranchey network, to give an update on clinical and scientific advances in the management of patients with ADPKD. These two successful courses will be followed by a new CME course in Amsterdam: This year the symposium will focus on new developments and genetic testing in Europe.

Another priority, mentioned by Olivier Devuyst, President of the WGfKD, is to encourage research on inherited kidney disorders. Since 2012, the working group provides Impulsion Grants (funded each with 20,000 - 30,000 euros) to young investigators having a clear focus on such disorders. Six projects have been funded thus far, covering a wide range of diseases and expertise. The WGfKD is also supporting EU-wide initiatives and networks such as TranCyST, EURenOmics, and EuroCyST, the European cohort of patients with ADPKD. In collaboration with European Renal Best Practice, the official guideline body of ERA-EDTA, the WGfKD is working to develop specific recommendations for rare disorders such as Gitelman syndrome and cystinosis. The challenges, opportunities and perspectives in the field of inherited kidney disorders have been detailed in a review article that will be published in the May issue of the Lancet.

**CME 8: Inherited Kidney Disorders: new developments and genetic testing in Europe**

*Room: G102-G103*
*Date: 31-05-2014*
*From 11:00 to 13:00*

**Bridging gaps**

*Working Group on CKD-MBD*

The ERA-EDTA Working Group on Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD) is one of the younger Working Groups of the Society, yet the members around Chairman Mario Cozzolino and co-Chairman Marc Vervloet look back on a successful year and forward to new projects and meetings in 2014. The group was founded “because of the potential beneficial impact of increased awareness of mineral bone disorders in CKD, but also because ERA-EDTA recognises the huge scientific efforts that are required to bridge enormous gaps in knowledge and bring this to the bedside of patients with CKD”, explains Mario Cozzolino. A first workshop of the Working Group was held in Milano, Italy in December 2013. A second opportunity for discussion and updates will be the next workshop in December 2014, again in Milano.

Different publications have been initiated, among them contributions to an edition of Current Vascular Pharmacology about Vitamin D therapy. Only recently NDT published an article of Mario Cozzolino and CKD-MBD Advisors on the question “Is chronic kidney disease - mineral bone disorder really a syndrome?” The issue will also be discussed during a symposium on Monday.

The CKD-MBD Working Group supports the pan-European calciphylaxis registry which was presented by Vincent Brandenburg at the 50th ERA-EDTA Congress in Istanbul.

**CKD-MBD CME 17: Update 2014**

*Room: E 104 - E 107*
*Date: 31-05-2014*
*From 15:30 to 17:30*

**S23: Bone and mineral disorders in ESKD**

*Room: Hall 2*
*Date: 02-06-2014*
*From 11:45 to 13:15*
Dedicated to innovative therapies

Recent activities of the EuDial Working Group

EuDial is an official Working Group of the ERA-EDTA. EuDial is dedicated to the development and evaluation of innovative renal replacement therapies for chronic kidney disease patients, with particular emphasis on convective therapies. Over the past 12 months, EuDial has organized CME courses and endorsed several other scientific and educational meetings on dialysis therapies in general and on hemodiafiltration in particular.

In 2013 EuDial published a comprehensive review on the definition, dose quantification and safety revisited of online hemodiafiltration (Nephrol Dial Transplant 2013; 28: 542-50). In a second paper, published early 2014, a meta-analysis was done of the presently available data on the effects of hemodiafiltration on clinical outcome (Sem Dial 2014 27(2):119-27). EuDial has initiated a platform to combine all individual data of some recent major trials on the effects of hemodiafiltration. Aim is to perform more detailed analysis on this combined dataset on various questions which could not be addressed in the individual trials. Data sets have recently been combined. First results are to be expected in the coming months. Also in 2014, EuDial will organize and endorse several scientific and educational meetings.

Combined strength for renal transplantation

The DESCARTES Working Group attracts a growing number of specialists

Developing Education, Science and Care for Renal Transplantation in European States: The name DESCARTES is a program in itself, full of ambition. The growing number of therapists - 406 had joined the ERA-EDTA working group until January 2014 - is a proof of its success. And the activities speak for themselves: 89 participants attended the 10th Transplant Academy in November 2013 in Amsterdam. Its success motivated DESCARTES to organise an 11th Academy together with the Organ Expert Section of ESRF on kidney transplantation in Europe (EKITA) on October 31st 2014 in Prague. Another CME event will take place on November 28th in Parma on “renal transplantation in the elderly”. The joint DESCARTES/Nantes investigation on operational tolerance has had a very successful start. As of today, more than 120000 renal transplant patients have been surveyed for tolerance, and more than 20 new tolerant patients have been identified throughout Europe. Towards the end of 2014 a think-tank will be set up to address such issues as tolerant patients sampling and biological investigations. DESCARTES, under the heading of Klemens Budde, is also launching the largest randomized controlled trial aiming at finding safe ways to reduce immunosuppression in elderly transplant recipient. The combined project of the Senior Registry and the Reduce study is planned to include 1000 patients in the registry of whom 400 are to be included in the study. It is expected that the study starts recruiting patients in early 2015. Daniel Abramowicz, Chairman of DESCARTES is happy to announce a publication of Working Group members: NDT will soon publish an article of Umberto Maggiore et al. about “strategies to increase the donor pool and access to kidney transplantation: an international perspective”. A review on immunosuppression in the elderly, conducted by Julio Pascual, will follow.

CME 2: “Back to the basics of renal transplantation”
Room: E 104 - E 107
Date: 31-05-2014
From 9:00 to 12:00

LUST study is on its way

EURECA-m Working Group promotes research and education in cardiovascular and renal disease

The overlapping area of cardiovascular and renal disease urgently needs cooperation of different specialities and specialists throughout in Europe. In this field the European RENal and Cardiovascular Medicine Working Group (EURECA-m) has been most successful in the past years and the fruitful work continues. Gérard Michel London, the chairman of the EURECA-m board, can look back on diverse activities in the past months.

The LUST study, a trial endorsed by the EURECA-m ERA-EDTA Working Group and funded by the ERA-EDTA has started in March 2013. 22 renal units cooperate in this study. “The goal of the trial is to test whether a treatment policy guided by US-B lines may prevent death, decompensated heart failure and myocardial infarction as well as progression of LVH and LV dysfunction and hospitalization in high risk dialysis patients with myocardial ischemia or overt heart failure”, Carmine Zoccali informed in a recent newsletter. The high-grade CME meetings in 2013 - a CME course at the Istanbul Congress of ERA-EDTA and another CME course in Lyon – will be followed by three events in 2014, starting with today’s CME programme on therapeutic strategies to address the high cardiovascular mortality of CKD patients. Another course will follow in July in Warsaw, Poland. It will be organised by Andrzej Wieczek. A third event will take place in September in Iasi, Romania, hosted by Adrian Covic.

EURECA-m CME 1: Therapeutic strategies to address the high cardiovascular mortality of CKD patients
Room: FORUM
Date: 31-05-2014
From 9:00 to 13:00
New Artis Physio™ system
Because every patient is different

If every patient is different is there a simple way to treat them all?

The Artis Physio system provides a complete range of HD modalities giving you the freedom to effectively individualize treatment according to the needs of your patient.

Visit us at booth E4
From bench to bedside

Tomorrow Bruce A. Molitoris, Past President of the American Society of Nephrology, will hold a plenary lecture about the “pathophysiology of acute kidney injury: from bench to bedside”.

Past President of the American Society of Nephrology

Molitoris is Professor of Medicine, Director of Nephrology and Director of the Indiana Center for Biological Microscopy at Indiana University. He graduated from the Washington University School of Medicine in St. Louis, Missouri and completed his residency and fellowship training at the University of Colorado School of Medicine in Denver, Colorado. He was faculty at the University of Colorado from 1983 until 1993 when he moved to Indiana University to become Director of Nephrology there.

Main focus on cell biology of AKI

The major area of his research studies over the last 20 years has centered around the cell biology of acute kidney injury with an emphasis on proximal tubule cell injury secondary to ischemia and/or nephrotoxins. He also focuses on the use of 2-photon microscopy in live animals to understand the normal physiology, disease pathophysiology and therapeutic responses. He has been continuously funded by both the NIH and the VA for over 20 years.

Plenary Lecture 1: Pathophysiology of Acute Kidney Injury: from bench to bedside

Bruce A. Molitoris
Room: Hall 2
Date: 01-06-2014
From 10:45 to 11:30

More fairly or more effectively?

How to select patients for treatment

When I was 10, along with the whole world I was pleased with each of the 18 days lived by Louis Washkansky who received a heart transplant by Professor Barnard in December 1967. Naturally I am not wondering why this particular patient was chosen, nor how was the brain death in the donor diagnosed. The Harvard Criteria for Brain Death appeared first in the next year, and the world bioethics three years later.

Since that time transplantation has developed as a serious medical discipline, and overgrown with numerous ethical and legal regulations. The public’s expectations have also risen significantly. The life with a transplanted organ has ceased to surprise anyone, but the number of needy is still significantly higher than the possibility of achieving organs.

Transplantation has become a “scarce resource”, but the society rejected in almost all countries, typical for such situations the way for regulation by free market. This happened not only in relation to the acquired organ, in more healthy) and significantly shorten the waiting list (unfortunately also at the cost of the most seriously ill). Using only the criterion of justice (a derivative of the waiting time and the risk of death) is likely to reduce efficiency and increase costs (more complications in more ill).

Equal sharing of misery

The pursuit of justice at the expense of efficiency is somewhat like the choice of equal sharing of misery instead of the unequal distribution of wealth. On the other hand a sense of justice is very strong and fulfills an important social function. The high costs of administration of justice, including the earnings of lawyers, are the indirect evidence. The simplest imagination of justice is equality: who comes first will be first accepted.

Unfortunately, the reality of medicine often does not allow us to realise this principle. We need to treat those first, who most urgently need our help, who would else die, or by waiting suffer irreparable harm.

In reality, treatment is much more complicated: besides the medical care there is the problem of its effectiveness and many non-medical factors arising that influence our selection with the economic issue on top. There are many opponents of such thinking, but I think that even the biggest supporter of equal treatment of all patients will agree, that among the many sick on board of the aircraft, the pilot in charge of the plane needs to be treated before others, because its efficiency is a prerequisite for the survival of all other sick and healthy.

Unfortunately the rules are not perfect

Therefore, we resorted frequently to develop rules, which doctors have to respect in such situations, being aware of their imperfections. In this way, a very complex system for the control turns into a simple ‘zero-one system’. The rules have been followed, or have been broken. Unfortunately, the rules are not perfect, and their absolute following in the name of justice sometimes leads to a significant increase in costs and / or a reduction of the effectiveness measured by the number of cured or covered by an effective aid. Selection of patients for treatment from persons in need of such treatment for a doctor is something terrible.

Naturally it is much more scary for a man who has not been selected, and suddenly found out not only that he is sick, but even, as a result of just one (!) choice he is attended to die without treatment which is for the other “justly chosen” (!) available. And if he or she is rich should we guilt him, that he tried to “buy life” for himself or a loved one. Our contemporary regulations leave him a choice, between “black market” and “black despair”. Maybe it is time to talk about this seriously?
Learning and progressing in a young network

Young Nephrologists’ Platform (YNP) activities and future plans

The Young Nephrologists’ Platform (YNP) was funded by ERA-EDTA in late 2012. Our aim is to represent young nephrologists and their interests within the Society. Every ERA-EDTA member under the age of 40 with at least one congress presentation is eligible for membership in the YNP.

Since the foundation of the YNP, the number of members increased significantly up to 136 members from 39 different countries at the end of March 2014. Italy has the most members, but a significant number of members come from Poland, Turkey, Germany, UK, Hungary and India as well.

The members of the Platform are starting to enjoy the benefits of their membership since the Platform has launched several different programmes in the last 1.5 years.

Free membership program

To encourage young nephrologists to submit abstracts to the ERA-EDTA congresses and to publish in ERA-EDTA affiliated journals (NDT, CKJ), a merit–based free-membership programme was accepted by the ERA-EDTA Council in 2013 and will be applied this year for the first time. There are two tracks: the first is based on abstracts accepted at an ERA-EDTA congress; the second requires an original or review publication accepted in NDT or CKJ in the current or past year. In the paper–based track, no more than 20 free memberships will be offered annually to first or last ERA-EDTA members who are no YNP members; for ERA-EDTA members the registration fee is only 50 Euro. The next course to be held in 2015 will focus on glomerulonephritis and will include pathophysiology, clinical aspects and novel treatment modalities of glomerulonephritis in the light of current guidelines.

YNP funded Advisory Programme

The ERA-EDTA YNP Advisory Programme is a strategic effort to support personal and professional growth of young nephrologists. The programme is based on a personal relationship between an advisee and an advisor. The advisee is a developing junior professional or trainee, who is paired up with an advisor from whom to learn and receive guidance and perspectives.

Annual teaching courses

The board of YNP has decided to organise a teaching course every year focusing on different topics in the field of nephrology. These courses will be 1–2 days long and always organised around a bigger ERA-EDTA organized/supported meeting. The first course will take place in Budapest, Hungary (August 24–25, 2014) as a joint meeting to the Budapest Nephrology School. This course is focusing on landmarks, on clinically relevant studies, which help the young nephrologist to provide the best clinical care in the everyday practice. Problem/case-based lectures will be presented. ERA-EDTA supports young nephrologists in participating in this course by providing travel grants and special very low registration fees. There is no registration fee for YNP members; for ERA-EDTA members who are no YNP members the registration fee is only 25 Euro. All other non-members are welcome too; their registration fee is 200 Euro.

Program structure of the YNP

Figure 1: Program structure of the YNP

The Board of YNP will review the results of these programmes and will launch future projects according to the results and future expectations. All present and future members are asked to send their ideas and requests directly to me (ypn@era-edta.org) to improve the success of our Platform.

From 17:00 to 18:30
Room: ELICIUM 1
Date: 02-06-2014
A unique example of international collaboration

The 50th anniversary of the ERA-EDTA Registry

In 1964, just one year after the birth of ERA-EDTA during its first Congress in Amsterdam it was decided to start a renal registry that was to include all European patients on renal replacement therapy (RRT) for end-stage renal disease. The first registry Chairman was the famous Dutch nephrologist Willem Drukker and already one year later, during the second EDTA congress in Newcastle, the first Registry Report was presented. In those early days dialysis and transplantation were innovative medical treatments and the numbers of patients and renal centres were relatively small. This report therefore included data on only 187 transplanted patients and 271 patients treated with haemodialysis in whom mortality after one year was as high as 44%.

All was voluntary work

The European ERA-EDTA Registry on RRT was a “unique example of international cooperation”. Collaborating nephrologists invested substantial time in data collection on paper to send them to the Registry headquarters and all was voluntary work. Soon thereafter, similar registries were started in Canada, the United States, and Australia-New Zealand. Nowadays renal registries exist in virtually all developed and also in many developing countries.

In the meantime the Registry had moved to Germany and in 1976 it moved to St. Thomas’s Hospital in London. At that time the Registry archive contained only 1.5 meters of files that were transferred to London by the new Chairman Tony Wing in his Volkswagen. Since 1971 a paediatric RRT registry had been added to the ERA-EDTA Registry and many papers both on adult and paediatric nephrology were published in this highly successful period. However, at the beginning of the 1990s the Registry began to experience difficulties. There were problems with the computerisation of the database, with newly introduced computer systems and with the fact that the number of renal centres across Europe had grown to almost 4000. Therefore the ERA-EDTA Council decided to move it to the Academic Medical Center (AMC) in Amsterdam where, under the chairmanship of Douglas Briggs and the managing director Kitty Jager, the Registry made a new start in the year 2000.

As of today the ERA-EDTA Registry is still based in the AMC. It is a collaborative effort by the Registry office and the national and regional renal registries from 30 countries. The database includes core data on demography, renal disease, treatment and outcomes of half a million RRT patients. Additional data for specific studies are collected on a regular basis and for a number of registries further clinical data have been added to the dataset. A collaborative international research network of registry representatives and other interested researchers has been set up to work on the different data sets. There is also a close collaboration with the ESPN/ERA-EDTA Registry; the new paediatric registry which started in 2007 and has a separate collection of extensive clinical data.

Spirit of the early years

In the spirit of the early years where progress was only possible by international cooperation, the ERA-EDTA Registry has extended its activities to education. Last March it organised the 25th Introductory Course on Epidemiology for nephrologists and nephrology researchers and has now educated more than 750 nephrologists from all over Europe on the principles of clinical epidemiology and clinical research. In addition, visiting researchers can conduct specific research projects under the guidance of registry staff under the umbrella of the ERA-EDTA Registry Clinical Epidemiology Learning and Research Centre at the AMC.

A major challenge in nephrology: diabesity

During the 50th annual Congress, ERA-EDTA decided to create a new Working Group: DIABESITY. The word is a combination of Diabetes and Obesity – a major challenge for nephrologists because people who suffer from these conditions may develop complications such as albuminuria, overt proteinuria and decreasing renal function which untreated may lead to end-stage renal disease. The new Working Group aims to gain and disseminate knowledge on the nephrological impact of diabetes and obesity. Renowned European investigators joined the group, chaired by Carl-Erik Mogensen, Arhus, Denmark, who is supported by Secretary Esteban Porrini, Tenerife, Spain. Facing the pandemic proportions of obesity and type 2 diabetes worldwide, the group has set up a list of themes that will be developed in the future. It is published on www.era-edta.org/diabesity/diabesity.htm.

Education and training for both the medical community and patients will be encouraged. A CME course on ‘DIABESITY: Diabetes and Obesity in Renal Disease’ will take place on Tenerife on November 1st and 2nd, 2014 (diabesity.eichucan.es/tenerife2014/)


ISSUE 1 / May 31, 2014
Diagnostic challenges in thrombotic microangiopathies

Sunday 1 June 2014, 18:45–19:45

Chair: Professor Dirk Kuypers, Department of Nephrology and Renal Transplantation, University of Leuven, Belgium

Venue: Room G102-103, first floor

Programme

18:45–18:55 Welcome and introduction to TMA
Dirk Kuypers

Josep M Campistol

19:20–19:40 Management of aHUS in 2014
Christophe Legendre

19:40–19:45 Conclusion and Q&A
Dirk Kuypers

A buffet dinner will be served after the symposium.

Register for the symposium

Go to www.alexionsymposium-era-edta.com, or scan the QR code below, and complete the quick registration form.

Visit the Alexion booth for more information about aHUS and TMA: Stand B2, Hall 1
Dialysis patients have a high mortality and morbidity and their expected remaining lifetime is lower than that of the general population. Mortality in patients undergoing a conventional dialysis regimen of three 4h sessions per week is quadruple that in the general population over 65 years old and new therapeutic regimens are required to improve patient survival, increase dialysis time and frequency, and develop techniques with a higher depurative capacity.

**Daily on-line hemodiafiltration**

The frequency of hemodialysis was established as thrice weekly in the 1960s and it has been mainly accepted and maintained for logistic, pragmatic and economic reasons. However, there is a growing interest in the use of more frequent dialysis schedules since long-term experiences using higher frequencies have shown good results. Daily dialysis experiences have shown excellent clinical results because a higher frequency of dialysis is more physiological and it decreases the fluctuation of liquid, solutes and electrolytes. Improvement in comfort during and between dialysis, clinical and biochemical parameters, anemia correction, hypertension control, nutrition status and quality of life have been reported.

In our first experience (1), we combined the more physiological and effective dialysis schedule (daily dialysis) with the dialysis modality which offers higher solute and uremic toxin removal, the on-line hemodiafiltration (OL-HDF). Patients on standard 4 to 5 hours thrice weekly OL-HDF were changed to 2 to 2.5 hours six times weekly on-line hemodiafiltration. Although dialysis time was similar during both treatment schedules, an increase in the dialysis dose was obtained with the daily scheme which confirms the beneficial effect of higher frequency. The principal advantages observed in this work were: the excellent patient clinical tolerance and acceptance, disappearance of postdialysis fatigue, improvement of sleep disorders, a higher removal of middle and large molecules with a 21% reduction in predialysis plasma β2-microglobulin levels, a reduction of phosphate binders, an improvement of nutritional status (body weight increased more than 3 kg after one year), a better control of blood pressure without antihypertensive medications and a regression of left ventricular hypertrophy.

**Conventional HD**

3-4 hours/session  
3 sessions/week  
Low-flux diffusion

**Figure 1: How to improve the results in long term hemodialysis?**

**Nocturnal hemodiafiltration**

The results of the Tassin experience of long, slow-flow hemodiafiltration sessions were first reported 25 years ago and showed excellent fluid and blood pressure control with the highest survival rates achieved at that time. Since then, multiple publications have evaluated the superiority of long-duration hemodialysis over conventional therapy in blood pressure control, reduction of left ventricular hypertrophy (LVH) and reduced serum phosphate levels, often allowing phosphate binders to be discontinued. In 1972, the Lecco center started a scheme of every-other-day dialysis to avoid long weekend periods and reported a 60% survival at 10 years with a lower incidence of ischemic heart disease, stable high depurative efficiency and improvements in anemia, acid-base and nutritional status.

In this second experience (2), we sought to combine a more physiological and effective dialysis schedule – long (nocturnal) and more frequent (every-other-day) dialysis – with the dialysis modality offering the highest solute and uremic toxin removal.

**OL-HDF**

Figure 2: Short daily on-line HDF

**Dry body weight**

**Figure 2: Short daily on-line HDF**

**LV mass (g)**

**Conventional HD**

Higher Duration

**OL-HDF**

Higher Frequency

**New Strategies**

**References:**


**Francisco Maduell, Barcelona, Spain**

**S2: Haemodialysis versus haemodiafiltration**

**Room:** AUDITORIUM  
**Date:** 01-06-2014  
**From 8:00 to 9:30**
Sunday 1 June 2014, 13.30–14.30
Forum, RAI Congress Centre

Current and future management strategies in a changing ADPKD landscape

Professor Albert Ong
Symposium Chair

Topics

Introduction – Evolution and new insights into the management of ADPKD
Prof Albert Ong (UK)

Clinical perspectives on assessing the natural progression of the disease
Prof Bertrand Knebelmann (France)

Current clinical management and new and emerging treatment options
Dr Andreas Serra (Switzerland)

Summary – A changing paradigm – what can we hope to achieve?
Prof Albert Ong (UK)

Lunch bags will be available at the start of the symposium.
Sponsored by Otsuka Pharmaceutical Europe Ltd.
Lessons learned from CONTRAST

Pooling project on individual patient data has been started

In patients with end-stage kidney disease, both morbidity and mortality are unacceptably high. As retention of middle molecular weight (MMW) substances (0.5–40 kD) has been implicated in the pathogenesis of the uremic syndrome, removal may improve prognosis. MMW substances are not cleared by diffusion, which is the main elimination mechanism in hemodialysis (HD), but by convection, as occurs in hemofiltration. In hemodiafiltration (HDF) diffusion is combined with convection. In modern HDF, fluid balance is maintained by administration of online prepared substitution fluid which can be infused before (pre-dilution) or after (post-dilution) the dialyzer. Currently, controversy exists as to whether the positive effect of HDF on MMW solutes translates into a superior clinical outcome. In addition, the minimal amount of convection volume required to obtain a clinical benefit is unknown.

Convective TRANsport Study (CONTRAST)

CONTRAST was designed to investigate whether treatment with online post-dilution HDF is superior to low-flux HD in terms of morbidity and mortality. 714 patients were included to detect a difference (type two error). Third, the dose of HDF was too low.

Table 1: Convective volume and survival in three recent large RCTs comparing HDF with HD (ref 3)

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<thead>
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<th>Reference</th>
<th>CV (L/treatment)</th>
<th>SV (L/treatment)</th>
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<td>&gt;25.4</td>
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<td>-</td>
<td>0.55</td>
<td>0.34 to 0.84</td>
</tr>
<tr>
<td>Turkish HDF study</td>
<td>18.8</td>
<td>16.2</td>
<td>2.6</td>
<td>1.10</td>
<td>0.68 – 1.76</td>
</tr>
<tr>
<td>CONTRAST</td>
<td>&lt;18.18</td>
<td>-</td>
<td>-</td>
<td>0.80</td>
<td>0.52 – 1.24</td>
</tr>
<tr>
<td></td>
<td>18.18 - 21.95</td>
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<td>0.84</td>
<td>0.54 – 1.29</td>
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<td></td>
<td>&gt;21.95</td>
<td>-</td>
<td>-</td>
<td>0.61</td>
<td>0.38 – 0.98</td>
</tr>
</tbody>
</table>

Figure 1: Pooled results of overall mortality HDF versus HD (ref 3)

Dose-response effect

When CONTRAST was designed the optimal convection volume (CV = ultrafiltration [UF] + weight loss) was unknown. According to manufacturer’s instructions the UF rate was arbitrarily set at 4–6L/hour. Recently, the magnitude of the CV was considered the best quantification of the ‘dose’ in HDF (2), more or less comparable to the amount of active ingredients of a medication. Therefore, in a patient factors (e.g. age and comorbidity) are most decisive in this respect. As these data were obtained retrospectively, lately the Feasibility Study (FEAST) was started in selected CONTRAST facilities. In FEAST, the CV is stepwise increased by optimising treatment fraction, blood flow rate and filtration fraction in consecutive order. Preliminary data in 40 patients indicate that a CV >22L/session is feasible in nearly all patients.

Determinants of the convection volume

Next the question arose which factors determine the magnitude of the CV. Recently we showed that centre policy rather than individual patient factors (e.g. age and comorbidity) are most decisive in this respect. As these data were obtained retrospectively, lately the Feasibility Study (FEAST) was started in selected CONTRAST facilities. In FEAST, the CV is stepwise increased by optimising treatment fraction, blood flow rate and filtration fraction in consecutive order. Preliminary data in 40 patients indicate that a CV >22L/session is feasible in nearly all patients.

Systematic review and meta-analysis

To further explore the existence of a type two error as aforementioned, a systematic review and a meta-analysis was performed by CONTRAST investigators on behalf of the EuDial group. From this study, it appeared that HDF offers beneficial effects on both overall and cardiovascular survival (RR 0.83, 95CI 0.71-0.98 and RR 0.73, 95%CI 0.58-0.92 resp. figure 1)(3).

As of January 2014 a pooling project on individual patient data (IPD) has been started, also under the auspices of EuDial. In this project, IPD are collected and combined to create a new database encompassing > 2400 participants. The first aim is to confirm (or reject) a survival advantage in HDF patients, if compared to HD. Other aims include the confirmation of the aforementioned dose-response effect, a survey on potential mechanisms behind the beneficial effect of high volume HDF and the analysis of HDF in selected subgroups, such as patients with diabetes or known cardio-vascular disease.

Conclusion

Although multiple lessons are learned from CONTRAST, more lessons can be learned by combining individual datasets of separate RCTs. We are grateful to the EuDial working group for their indispensable support in this respect.

References:
Cardiac failure and the kidneys

A significant proportion of patients treated for acute decompensated heart failure (ADHF) suffer from worsening renal function, which is often associated with medical therapy resistance and poor clinical outcome. In this setting, haemofiltration has been used for more than 30 years, despite inconclusive evidence for its advantages. In the last decade, major technological advances have made a new technique available, ultrafiltration, which works at lower blood flow rates and requires only a venous access. As in a first proof-of-concept study (EUPHORIA), ultrafiltration proved to be efficacious in fluid removal in ADHF patients; this treatment was further investigated in randomized controlled trials. The RAPID-CHF trial demonstrated that ultrafiltration was more effective than medical therapy in fluid removal, even though it did not provide a greater weight loss. The UNLOAD trial thereafter showed a greater weight loss with ultrafiltration compared with diuretic therapy at 48 h after admission and a lower readmission rate at 90 days. Based on these results, the American Heart Association/American College of Cardiology and the European Society of Cardiology guidelines consider ultrafiltration as a reasonable approach in ADHF patients with unresolved congestion notwithstanding optimal medical therapy and/or hyponatraemia. The CARRESS-HF trial would appear to challenge these recommendations as it failed to demonstrate an advantage of ultrafiltration compared with medical therapy, based on the finding of subtle clinically irrelevant changes in renal function between treatments. Various observations point to fluid redistribution in the form of pulmonary congestion rather than to the net fluid gain as the critical event precipitating symptoms in ADHF, a phenomenon depending on arterial and venous constriction induced by neural and endocrine mechanisms, inflammation and kidney dysfunction.

The degree of lung congestion may be now reliably measured by an ultrasound (US) based, simple, easy to learn, reproducible technique. Lung US has recently been applied in studies in patients with end-stage kidney disease, and these studies have clearly documented that this technique not only serves to refine prognosis in this high-risk population, but also reliably detects changes in lung water by dialysis. Lung US allows detection of water accumulation even at a preclinical stage and appears therefore well suited to be applied in ADHF trials to tailor UF and diuretic treatment, and its potential for a new breed of clinical trials in heart failure is well recognized. Thus, estimates of lung water by US may represent the biomarker that we need to tailor treatments in these trials. A trial comparing fluid subtraction guided by systematic monitoring of lung water in ADHF via lung US and/or bioimpedance may indeed provide a unique opportunity for establishing whether and when UF may be advantageous when compared with diuretic treatment.

Carmine Zoccali, Reggio Calabria, Italy

Carmine Zoccali, Reggio Calabria, Italy
Looking for the cause of renal hypoxia

Direct measurement of intrarenal oxygen in vivo

Chronic kidney disease (CKD) is a global public health problem. It has been postulated that progression of CKD is partly due to disturbed kidney oxygenation, i.e. renal hypoxia (Figure 1). Yet we know little about causes of renal hypoxia or how to treat it. The critical barrier to investigate this is lack of methods to chronically measure kidney tissue oxygen. To be able to directly link hypoxia to impaired renal health, we have developed a telemetry-based solution to measure partial pressure of oxygen in the kidney (pO2) of chronically instrumented, conscious, freely moving rats (Figure 2, Koeners ea. Am J Physiol Renal Physiol 2013).

With this family of new telemetry-based electrochemical sensors we were able to track changes in both renal medulla and cortical pO2 and measure tissue pO2 over time. Renal cortical pO2 was more sensitive to angiotensin-II than to phenylephrine, at equi-pressor doses. This observation may reflect sensitivity of the renal vasculature to AngII. In addition, we recorded cortical pO2 in conscious rats either during early stages of CKD after 5/6 subtotal nephrectomy or after sham surgery. CKD induced decreased renal cortical pO2 progressively in the two weeks after ablation. Thereafter hypoxia was stable for at least 5 subsequent weeks. The decrease in tissue pO2 in the remnant kidney coincided with uremia, but preceded the development of hypertension and proteinuria suggesting that hypoxia precedes symptoms of CKD and therefore could be a major driver of renal fibrosis. This supports the hypothesis that kidney hypoxia is central in the progressive pathogenesis of CKD.

Cardiovascular diseases are increasing in epidemic proportions globally. Hence there is an essential need for novel insights, ultimately leading to new treatments. The connection between kidneys, heart and brain in cardiovascular pathology offers exciting new research perspectives that are waiting to be explored. We propose that hypoxia (often but not always secondary to ischaemia or hypoperfusion) in heart, brain and kidneys and the overactivity of sympathetic nervous system is not simply a consequence of cardiovascular disease but rather is intimately involved in driving the progression of disease and loss of tissue function even before any histological damage is apparent (Figure 3).

Sophisticated technologies

Cardio Renal Paradigms Elucidated through an International Exchange Scheme (CARPEDIEM), an EU FP7 consortium, combines a unique approach and common interest to employ novel sophisticated technologies to understand the relationship between oxygen deprived tissues (hypoxia) and sympathetic hyperactivity in cardiorenal pathology. By sharing knowledge and expertise between leading researchers at 6 recognised centres of excellence; 3 in Europe: Bristol (UK), Uppsala (SE) and Utrecht (NL), and 3 outside Europe: Tokyo (JP), Melbourne (AUS) and Auckland (NZ), we are convinced that significant progress can be achieved in answering important research questions that one institution could never do on its own. Combining our strengths we can now address in a systematic, collaborative and multidisciplinary way the association, induction and reversibility of hypoxia, identify and relate gene expressions and molecular mechanisms in pathological signalling, and, by using large animal models, computational modelling and imaging in humans, collectively allowing translation towards the clinic.

Maarten Koeners, University Medical Centre Utrecht, NL, University of Auckland, NZ, University of Bristol, UK

S 3: Renal Hypoxia in Renal Disease: cause or consequence?

Room: ELICIUM 2
Date: 01-06-2014
From 8:00 to 9:30
Common fight against renal disease
Cooperation of ERA-EDTA and the European Society of Pediatric Nephrology established in January

The collaboration established in January 2014 between the two societies taking care of children (ESPN) and adults (ERA-EDTA) with renal diseases is aimed at strengthening the scientific synergies to promote a ‘global care’ of patients with disease potentially progressive to CKD and need of renal replacement therapy. The proposal is to empower early diagnosis, starting form the early ages of life in order to improve the outcome. Rosanna Coppo, ESPN Secretary General: “We are happy to report the start-up of this collaboration presenting the most relevant ongoing projects and achievements. The liaison between the Working Groups of the ERA-EDTA and the ESPN has been launched and focused on a series of relevant projects.”

Among the most interesting are the preparation of the European Renal Best Practice on ‘Pre-emptive renal transplantation in children and in adults: comparison of living versus cadaveric donation’, an area of advanced work of a committee with members of both societies (ESPN representatives: Licia Peruzzi, Pierre Cochat). Another project is the study of hemodiafiltration expanded from adults to children (ESPN representative Ruskana Shroff). A substudy is ongoing which involves congenital renal diseases, called CAKUT: Progression of Renal Insufficiency in Patients with Congenital Malformations oft he Kidney and Urinary Tract. Here the ESPN representative Stephanie Weber and the coordinator of the Registry for renal replacement therapy in children, Karlijn van Stralen work together.

ERA-EDTA and ESPN representatives Alessandro Amore and Loreto Gesualdo launched a survey on renal biopsy which is expected to report data on indication to perform kidney biopsy in children and in adults. One of the major sources of important publications and an increase in both scientific knowledge and clinical care improvement is the ESPN/ERA-EDTA registry, developed to increase the amount and the quality of information on paediatric renal replacement therapy (RRT).

In the past months many papers have been accepted for publication. NDT published a paper on underweight and overweight for a special issue on obesity and another on graft loss in recurrent diseases. A paper on transplantation policies in Europe, was published on AJT. CJASN published a paper on Congenital Anomalies of the Kidney and Urinary Tract, showing that this is not only a pediatric problem, and one on final height of children in RRT. Finally, NDT accepted a paper on the lipid profile.

In recent years the ESPN-ERA-EDTA Registry group has published more than 15 papers and one of the most appreciated was ‘Demographics of blood pressure and hypertension in children on renal replacement therapy in Europe’.

The relevance of the new activities originated from the collaboration between ERA-EDTA and ESPN and the ESPN/ERA-EDTA Registry publications testifies how important can be the outcome from a common fighting activity against renal disease both from childhood and adult age aspects.

Rosanna Coppo, Torino, Italy
How uremic toxins harm the kidney
Dysregulated oxygen metabolism: Hypoxia can induce epigenetic changes

Oxygen is essential for living, whose energy production depends on aerobic metabolism. The deficiency of oxygen plays a major role in the pathogenesis of a number of diseases, and chronic hypoxia in the tubulointerstitium serves as the final common pathway to end stage renal disease (ESRD) in chronic kidney disease (CKD) patients. The causes of chronic hypoxia in the tubulointerstitium of CKD patients are multifactorial and include mechanisms such as hemodynamic changes, disturbed oxygen metabolism of resident kidney cells, and renal anemia.

Patients with advanced CKD are exposed to uremic toxins. In addition to causing uremic symptoms, uremic toxins accelerate the progression of renal failure. Indoxyl sulfate (IS), a representative uremic toxin, increases oxygen consumption in freshly isolated rat and human proximal tubules, which is dependent on aerobic metabolism. The enhanced oxygen consumption aggravates hypoxia of the kidney and progression of the kidney disease. In addition, IS induces endoplasm reticulum (ER) stress and thereby contributes to the progression of cellular damages in tubular epithelial cells.

Cells are endowed with a powerful defensive mechanism against hypoxia. Hypoxia inducible factor (HIF) is a master transcriptional regulator of adaptive responses against hypoxia and regulates expression of erythropoietin, angiogenic factors, glycolytic enzymes, glucose transporters, anti-oxidative enzymes and other protective mechanisms. IS causes suppression of the HIF system in addition to aggravating hypoxia of the kidney.

IS caused functional impairment of the HIF-1α C-terminal transactivation domain (CTAD). Among factors that impeded the recruitment of transcriptional coactivators to the HIF-1α CTAD, IS markedly up-regulated Cbp/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 2 (CITED2) through a mechanism of post-transcriptional mRNA stabilization.

While IS suppresses HIF activation, IS also suppresses gene expression in a HIF-independent manner. As described above, IS induces ER stress, and pharmacological induction of ER stress suppressed transcription of erythropoietin in an activating transcription factor (ATF) 4-dependent manner. Furthermore, uremia is associated with increased formation of advanced glycation end-products (AGE). AGE are formed under non-enzymatic glycate stress conditions. Glycate stress suppresses HIF activation by impaired binding of the HIF α subunit to the coactivator p300. Covalent modification of p300 by the dicarboxylic metabolite methylglyoxal, a local mediator of glycate stress, is responsible for this decreased association. Suppression of HIF activation by glycate stress-induced modification of p300 under uremic conditions can lead to a decrease in target gene expression and increase susceptibility to hypoxia.

As observed in covalent modification of p300 by glycate stress under uremic conditions, epigenetic regulation of gene expression is a focus of intensive researches in CKD patients. The recent and rapid advent of next-generation sequencing has made this technology broadly available. Utilizing next-generation sequencing, we can perform ChIP-seq (chromatin immunoprecipitation with sequencing) and RNA-seq for sample preparation and interpretation of raw data in the investigation of biological phenomenon in renal diseases. ChIP-seq identifies genome-wide transcriptional DNA-binding sites as well as histone modifications. Utilizing this technique, we identified novel HIF-1 target genes. We also found that HIF1 functioned as an enhancer of glucose transporter 3 (GLUT3, SL2A3) by interaction with lysine (K)-specific demethylase 3A (KDM3A). Glycolytic genes are regulated by both HIF1 and KDM3A and respond to hypoxia in a manner independent of cell type specificity. We elucidated that both the chromatin conformational structure and histone modification change under hypoxic conditions and enhance the expression of GLUT3 based on the combined results of chromatin conformation capture (3C) and ChIP assays. KDM3A is recruited to the SL2A3 locus in an HIF1-dependent manner and demethylates H3K9me2, a suppressive histone mark, so as to up-regulate its expression. These findings emphasize the interaction between HIF and histone modifying genes and also the epigenetic regulation of HIF.

In conclusion, uremia suppresses the expression of adaptive genes against hypoxia, rendering the kidney susceptible to a decrease in oxygen tensions. Hypoxia can also induce epigenetic changes, and a long-term effect of gene regulation by hypoxia remains an important subject to be investigated.

Pathbreaking clinical data
Investigators present their recent findings

A wide range of clinical data is presented at the ERA-EDTA Congress and will be published in the abstract book. As in previous years the most interesting and promising of the latest data will be presented in the always highly anticipated session “Late breaking clinical trials”.

CCL2 inhibition with Emapticap pegol

In the first session on Sunday morning Dirk Eulberg will present the finding of his group from Hannover and Berlin in Germany about “CCL2 inhibition with Empaticap pegol (NOX-E36) in type 2 diabetic patients with albuminuria.”

Brian Bradbury, Thousand Oaks, California, USA, will discuss the subject of “red blood cell (RBC) transfusion and heart failure (HF) in advanced chronic kidney disease (CKD).”

“The efficacy and safety of canagliflozin (CANA) in patients with type 2 diabetes mellitus who had estimated glomerular filtration rate reduction during treatment” is the title of a talk presented by Ronan Roussel. He represents a multinational group with partners in Paris, France, and Groningen, The Netherlands.

Assessing the risk of all-cause mortality in the REGARDS Study

David Warnock, Birmingham, Alabama, USA, will explain that “C-reactive protein out-performs Cystatin C for assessing risk of all-cause mortality among participants in the REGARDS study.” A multinational cohort study about “dental health and risk of all-cause and cardiovascular mortality in adults with end-stage kidney disease” will be presented by Giovanni Strippoli, Bari, Italy.

The second session will follow on Monday morning with more news and more data from scientific teams in the US, in Spain, France and the Netherlands.

Emapticap pegol

CCL2 inhibition with Emapticap pegol (NOX-E36) in type 2 diabetic patients with albuminuria.

E36) in type 2 diabetic patients with albuminuria.
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Designed for Patient as the Operator • Advanced Patient Safety Features
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The ISN ‘0 by 25’ project

Acute renal failure: an unacceptable death sentence globally

Acute kidney failure (AKF) is an important cause of morbidity and mortality worldwide. The AKF global burden is calculated to be 13.3 million cases per year, 11.3 of which are in low-income countries. In industrialised nations, AKF is seldom a community-acquired disease; the condition develops primarily in hospitalised patients. In these regions the incidence of hospital-acquired AKF exceeds that of community-acquired AKF by five to ten-folds, having an estimated yearly incidence of 0.15-7.2%. On the other hand, AKF commonly occurs in the community in less developed nations. However, it is difficult to define the incidence of AKF, since no nationwide disease registries are available, and data are usually derived from single-center experience.

In the developing world, AKF is generally a disease of the young; 46% of patients were less than 40 years of age in one Nigerian series, and the average age was 34 years in a study from India. Children are often affected in developing nations, in some series constituting more than 15% of patients. The impact of AKF in the young has important socio-economic implications. What is particularly tragic is that children and young adults continue to die in large numbers in low-resource regions as a consequence of this disorder, which in many cases is preventable and treatable with simple measures with few long-term health consequences.

Those patients with AKF who progress to the stage at which renal replacement therapy would be indicated die because dialysis is simply not available. This is unacceptable because there is an excellent chance of survival with full recovery when the kidney is given enough time to recover and life is sustained by dialysis. Dialysis may lower the mortality from AKF in resource-limited settings. In particular, gravity-driven peritoneal dialysis (PD) can be chosen because of the ability to deliver renal replacement therapy without the need for additional equipment beyond consumable supplies, thus reducing cost and complexity when used in an acute low-resource setting as compared to automated PD or hemodialysis.

Treatment of AKF has to become as much a part of human rights as it is to give antiretroviral drugs to treat people living with AIDS in low- and middle-income countries received antiretroviral treatment. Thus ISN has created the human right case statement ‘0 by 25’, which advocates that zero people should die of untreated AKF in the poorest part of Africa, Asia and Latin America by 2025 (Figure 1).

There is much goodwill in the international nephrology community to assist in the development of AKF programmes in low-income countries. This project has created the human right case statement ‘0 by 25’, which advocates that zero people should die of untreated AKF in the poorest part of Africa, Asia and Latin America by 2025 (Figure 1).

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The project is overseen by an Executive committee and managed by a project leader (Ravindra Mehta) with project teams assigned for various components of the 0 by 25 initiative (Figure 2).

The project is overseen by an Executive committee and managed by a project leader (Ravindra Mehta) with project teams assigned for various components of the 0 by 25 initiative (Figure 2).
Ready to Grow Your Nephrology Career?

JOIN DAVITA IN SAUDI ARABIA

DaVita, a leading provider of kidney care with over 2,000 centers globally, recently signed a tender from the Kingdom of Saudi Arabia’s Ministry of Health to treat half of the nearly 10,000 patients currently under the Ministry’s care. It’s an important job; the prevalence of chronic kidney disease has accelerated faster in Saudi Arabia over the past three decades than in many parts of the world, and the need for nephrologists committed to high-quality patient care has never been greater.

DaVita is looking for nephrologists to help us meet this challenge. These nephrologists will oversee outcomes, patient care, quality, safety, training and policies and procedures to pioneer a new age of kidney care in Saudi Arabia. Joining DaVita in Saudi Arabia could also include training as an interventionist in DaVita’s vascular access centers and the opportunity to build relationships with other world-class physicians while setting a new standard for clinical care and patient outcomes.

If you are looking to improve patient care and quality of life on a larger scale, DaVita would like to hear from you.

Grow your career with DaVita in Saudi Arabia.
Stop by the DaVita booth at ERA-EDTA or visit DaVita.com/SA.
Saving young lives in Africa and Asia

A key part of ISN’s ambitious ‘0 by 25’ project

Children and young adults continue to die in large numbers in the developing world as a direct result of treatable acute kidney injury (AKI). Common causes in these populations include volume depletion (e.g. diarrhoea) or blood loss (e.g. post-partum haemorrhage), or acute severe infections (e.g. malaria, pneumonia).

Almost every aspect of the care pathway which is taken for granted in the developed world may be insecure or indeed unavailable in many low-resource settings: this includes awareness of the importance of AKI; early detection; early intervention to avoid progression to uraemia; near-patient testing to help assess AKI severity; triage and transport of appropriate cases to a hospital; availability of dialysis therapy; appropriate follow up after recovery of renal function.

Saving Young Lives is a unique collaborative project started in 2012 that is addressing these challenges by supporting the development of sustainable programmes for treating AKI in Sub-Saharan Africa and South East Asia. PD is the chosen dialysis therapy because of its simplicity and lack of dependence on infrastructure including electricity and pure water.

Saving Young Lives has four equal partners: ISN (International Society of Nephrology), IPNA (International Pediatric Nephrology Association), ISPD (International Society for Peritoneal Dialysis), and SKCF (Sustainable Kidney Care Foundation).

IPNA, ISN, and ISPD lead the education and training of physicians, nurses, and other healthcare professionals needed to support the programmes. These three professional societies have no role in meeting the direct costs of patients care. SKCF on the other hand uses its resources and expertise to enable PD programmes to start by making available PD catheters, PD fluid and other necessary consumables, but only in the context of a contractual agreement that the host hospital will in due course take on the long term costs of the programme.

Training and education in the community

This project requires the coordinated planning and delivery of several elements: initial site selection; the identification, education and training of medical and nursing staff; ongoing support for those staff including the rapid availability of expert case discussion; the provision of the necessary consumables. And then once an acute PD programme is established, the Saving Young Lives project goes on to focus in the catchment area of the hospital on training and education in the community to improve awareness and equip local health practitioners for prevention, as well as identification of cases needing hospital care.

The support given by Saving Young Lives is customised for each selected centre, based on a careful assessment of the specific needs. There are many and varied challenges. For SKCF there is the groundwork necessary to ensure registration of products in each country, to secure the delivery of products often by land across multiple borders, as well as negotiating the contractual arrangements with the institution. For ISN, ISPD, IPNA working together there are the challenges of identifying local clinical leaders who will champion the programme on a long term basis in settings where the clinical work force may not be stable, and of providing ongoing education and training that are both relevant and practical. For two years Saving Young Lives has supported carefully selected doctors and nurses to attend a one week practical training programme in dialysis and acute care held at Red Cross Children’s Hospital in Cape Town, South Africa – the only course of its kind in Africa.

The Saving Young Lives project builds on success at a pilot site – Kilimanjaro Christian Medical Center in Moshi, Tanzania – which was established through the efforts of SKCF with the support of ISN. Programmes delivering acute PD have now been established in Ghana, Benin, and Cambodia, and other centres will soon be treating patients in Ethiopia and Nigeria. People are being treated, and lives are being saved. The establishment of an acute PD programme is only the beginning.

Saving Young Lives will go on to work with the local team supporting the development of locally relevant awareness campaigns, leading on to training for health workers in the catchment of the specialist unit in early detection and intervention. Telemedicine will also be explored for its potential role in all aspects of these patients.

Five years of funding for the initial period

Five years of funding has been given by a charitable foundation to enable the Saving Young Lives project to be tested in action. During this initial period we are confident that we will demonstrate ‘proof of principle’ that sustainable low cost programmes for AKI care, including acute PD, and be established in low-resource settings, and that this model can then be spread to other countries in Africa, South East Asia and beyond.

Saving Young Lives is a key part of ISN’s ambitious ‘0 by 25’ project launched in 2013 with the goal of eliminating preventable deaths from AKI worldwide by 2025. Saving Young Lives is proving that implementation of management programmes for AKI is possible in low resource settings.

John Feehally, Leicester, UK

Published: May 31, 2014
Preventing AKI-related death in poor settings

Clean Water, Sanitation facilities, and Hygiene education (WASH)

It is estimated that more than 750 million people do not have access to safe, clean water, and that more than 2.5 billion people are without proper sanitation of human waste, according to the WHO/UNICEF Joint Monitoring Programme for water supply and sanitation. Most of these individuals reside in Africa or Asia, although individuals lacking these resources may also be found in South America, Central America and Eastern Europe.

Lack of clean water, sanitation facilities and hygiene education is a significant contributor to childhood deaths, chronic malnutrition and ongoing poverty. Poverty is exacerbated by the loss of income and treatment expenses from water related diseases and parasites and also from time needed to carry water, sometimes from long distances, back to the household.

Causes of acute kidney injury in low income countries usually differ from those in high income countries and can vary by region and also by season. In these settings, acute kidney injury usually occurs in young, previously healthy individuals or in the context of predisposing disease, often diarrheal or tropical infectious diseases. Diarrhea resulting in volume depletion contributes substantially to acute kidney injury in children in low income countries. Other causes of acute kidney injury can include nephrotoxins, surgical or obstetrical complications. In addition, epidemics of acute kidney disease can develop due to volume depletion after severe outbreaks of gastroenteritis (typhus or cholera). The estimated WASH related mortality rate in the developing world is about 0.4 deaths per thousand per year, with rates as high as 1.3 deaths per thousand per year in Sub-Saharan Africa (figure 1). This translates into 2 million WASH related deaths per year in the developing world, including more than 1 million deaths per year in Sub-Saharan Africa.

Long-term, it is estimated that from 2012 to 2050, there will be an additional 29 to 104 million WASH related deaths in the developing world, with more than half of these deaths occurring in Sub-Saharan Africa. The economic impact of eliminating WASH related mortality in the developing world for the period from 2012 to 2050 is estimated to be between 283 and 1036 billion US dollars, with a median estimate of 698 billion dollars.

More than 50% of all WASH related deaths are due to diarrhea and nearly 90% of these deaths occur in children less than 5 years of age. Thus, of the 2 million WASH related deaths per year, almost one million are attributed to diarrhea that occurs in children less than 5 years of age. These diarrhea related deaths account for more than 10% of all childhood deaths.

Note that acute renal failure is not listed in the Liu study (reference 2) as a leading cause of childhood death. One may surmise, however, that this gap in our knowledge about acute kidney injury in the developing world.

The integrated provision of clean water, sanitation infrastructure and hygiene education has been designated in the global aid community as WASH programmes. A number of non-governmental organizations (NGOs) have implemented WASH programs in Central and South America, Europe, Africa and Asia.

It is estimated that one person needs at least 20 liters of clean water per day. There are many methods by which clean water can be provided to those in need. Sometimes a broken water system needs to be repaired. In other instances, water may need to be supplied by drilling deep or shallow borehole wells, hand-digging wells (using augers), with additional groundwater harvesting systems or capping natural spring systems. Community volunteers take responsibility for maintaining the water system and for collecting fees for any repairs needed to these systems. They also educate households on the safe handling and storage of water.

Equally important are sanitation and hygiene interventions. Community volunteers work with households to motivate families to build, maintain and regularly use their own latrines. Latrines are also built and maintained in schools, clinics and churches. In addition, hygiene education is provided so that family members wash their hands and household dishes with either soap or ash.

A key component of successful long-term WASH programs is the active involvement of community members along with repetitive educational programmes and long term monitoring of all aspects of the WASH intervention, including maintenance of clean water supplies, continued use of latrines and consistent use of hand and household dish washing using soap or ash.

Successful implementation of WASH programmes has resulted in a 50% decrease in the incidence of both diarrhea and pneumonia. It is not known, however, how WASH programmes may reduce the incidence of acute kidney injury. A growing number of non-governmental organizations (NGOs) have implemented WASH programmes. The ISN hopes to partner with one or more of these NGOs as part of a comprehensive strategy to decrease the incidence of acute kidney injury in the developing world.

Figure 1: WASH related disease burden in terms of estimated number of deaths, by region. The regions are denoted as: EAP (East Asia and Pacific), EURCA (eastern Europe and former Soviet Union), LAC (Latin America and Caribbean), MIDEAST (Middle East), SA (South Asia), SSA (Sub-Saharan Africa). Jeuland MA et al. PLoS One 8(10) e74804, 2013

Selected references:

Michael V. Rocco, Winston-Salem, North Carolina, USA

S 15: The International Society of Nephrology (ISN) for treatable acute renal failure in poor countries
Age is no longer a contraindication

How to select elderly transplantation candidates?

For many years advanced age has been considered as a barrier to renal transplantation. Most old patients were not admitted to the waiting list because of their limited reserve and complications following transplantation could result in loss of mobility, cognitive decline, loss of independence and early death. Even those patients selected as suitable candidates for transplantation were often penalised in favor of younger adults. However, as kidney transplantation kept becoming more and more successful, the indications have been widening and most barriers related to old age have been abated. Today elderly age does not represent a contraindication to transplant any more.

In fact, a number of studies showed that transplantation extends the life expectancy in comparison with old patients who remain on the waiting list. This has been demonstrated not only for patients in the ‘early elderly’ (65 to 74 years) but also for those in the ‘late elderly’ (older than 75 years). The same studies also reported that frailty, comorbidity and/or poor adherence to pre-requisites, and cost are being used only for few centers. In clinical practice, decisions on the suitability of an elderly candidate to kidney transplantation is important to evaluate not only the presence but also the severity of comorbidities. A number of scales have been proposed to assess a score of comorbidity and/or poor adherence to pre-requisites.

Frailty

Accordingly, the first step to assess whether an old patient is a suitable candidate to transplant is to evaluate the presence and the severity of frailty. There is agreement among gerontologists that frailty increases an individual’s vulnerability for developing increased dependency and/or death. However, the method to establish the presence and the severity of frailty is more discussed. Several scales have been proposed to test frailty in the general old population. Two of them have been more frequently adopted. Fried et al. assessed the presence of FRAILTY by asking five simple questions to the patient that allow to evaluate the fatigue, resistance, ambulation, illnesses, and loss of weight. A positive answer to three questions can define the patient as a ‘frail’ subject. Nevertheless, only two small studies from the same team used an adjusted Fried scale in transplant recipients. In these studies the mean age of participants was for 53 years and they were followed for only few weeks. Rockwood et al. proposed another simple frailty scale composed of 7 different degrees of frailty ranging from very fit (1) to completely dependent on others (7). At any time point considered, the risk of death progresses progressively increased from degree 4 to 7. No report on the use of this scale in transplant recipients has been reported. Thus, we do not have any relevant information about the impact of the presence and the degree of frailty on old patient survival after transplantation.

Comorbidity

More attention has been paid to comorbidity conditions. It has been reported by regional, national and multinational surveys that most patients older than 65 years have comorbidity at the start of renal replacement treatment. Therefore, in testing the suitability of an elderly candidate to kidney transplantation it is important to evaluate not only the presence but also the severity of comorbidities. A number of scales have been proposed to assess a score of comorbidity and the relative risk of death in the elderly. Some scales are based on complicated mathematical models that are difficult to adopt for routine clinical activity. Other scales take into account only few comorbidities. The scale more used by gerontologists is the Charlson comorbidity index (CCI). This index takes into account a score of possible comorbidities, by assigning 1 to 6 points to each comorbidity according to its potential impact on survival: the score is then corrected by adding a further point for every decade of age over 40 years (Figure 1). This scale has been validated in many different diseases and is considered by some authorities the best parameter for evaluating the prognostic significance of comorbidity conditions in renal transplant and for selecting candidates to transplant. Yet, these conclusions have been partially challenged by some investigators who found that for patients aged >70 years CCI loses importance. This partial discrepancy may be explained by the fact that neither frailty nor poor adherence to prescription were taken into account. In fact, independently of the degree of comorbidity a frail patient is more susceptible to life-threatening complications. On the other hand, patients with treatable comorbidities are at high risk of death if they are poorly compliant to prescribed therapy. Concerning this, one should keep in mind that adherence to treatment is frequent in renal transplant recipients, particularly in aged patients. Screenings in older persons reported that many patients either do not remember to refill prescriptions or get confused whenever changes to prescriptions or dosages are made.

In summary, age does not represent a contraindication to transplant any more. Yet, older patients are more frequently affected by frailty, comorbidity and/or poor adherence to pre-requisites. Each of these factors can put transplant patients at risk of death or graft failure. At present, no clear guidelines on the criteria to use for selecting elderly candidates to transplant are available and the scores indicating the degree of frailty and comorbidity are being used only by few centers. In clinical practice, decisions on the suitability of a transplant candidate are often based on the opinion of a team of experts or by a single transplant doctor. Such an approach can be biased by subjectivity and can raise conflicts between patients and caretakers or among doctors themselves. The transplant community urgently needs clear recommendations coming from panels of transplant experts, ethicists, and renal patients in order to know which criteria to use for admitting elderly patients to a programme of kidney transplantation.

Claudio Ponticelli, Milano, Italy

S7: Pro-con debate: should we transplant everybody?

Room: AUDITORIUM
Date: 01-06-2014
From 11:45 to 13:15

SCORE 1 (apply 1 point each)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
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<tbody>
<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>1</td>
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<tr>
<td>Ulcer</td>
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<tr>
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<td>Diabetes with end-stage organ damage</td>
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<tr>
<td>Tumor</td>
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SCORE 3 (apply 3 points)

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<tbody>
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<td>Age &gt; 70</td>
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SCORE 4 (apply 4-6 points)

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<td>4-6</td>
</tr>
<tr>
<td>AIDS</td>
<td>4-6</td>
</tr>
<tr>
<td>Age : 1 point each decade over 40 yrs</td>
<td>4-6</td>
</tr>
</tbody>
</table>

Figure 1: The Charlson comorbidity index adjusted for age.

Figure 2: Clear recommendations are needed.
**Magnesium in transplantation: new challenges**

*Should hypomagnesemia be corrected?*

Hypomagnesemia often predicts inferior outcome in the general population or in subpopulations such as patients with CKD or diabetes. Transplant recipients still have a higher cardiovascular burden than the general population. They remain exposed to a multitude of cardiovascular risk factors, potentially amplified by immunosuppressive drugs such as corticosteroids and calcineurin inhibitors (CNI). It is a little striking that hypomagnesemia after transplantation is not considered a patient relevant outcome by most transplant physicians and accordingly is not assessed as a potential risk factor for whatever endpoint. Therefore it remains unclear whether this electrolyte disturbance should be corrected and if so, how this should be pursued. Reminiscent of this continuous disregard is its absent reporting in the majority of all groundbreaking RCTs in transplant recipients over the last decades. We can speculate on a few explanations for this finding:

1) **Hypomagnesemia in the tacrolimus era occurs in the majority of all transplant recipients** (Figure 1). The more common things are, the less they seem to bother us.

2) **We lack methodological data on whether hypomagnesemia in transplant recipients is truly a good surrogate for magnesium deficiency.** As magnesium in the human body is mostly located in the cellular compartment, we seem to be short of a sensitive diagnostic and therapeutic guiding instrument.

3) **Magnesium supplements are freely accessible and not overly expensive.** This precludes many efforts by pharmaceutical companies.

Where are we now?

Some excellent research in the field of renal physiology led to the discovery of the mechanism whereby CNI and especially tacrolimus drive the development of hypomagnesemia, which already develops in the first two weeks post-transplantation and in the majority of all patients (Figure 1). These drugs dose-dependently decrease the expression of the magnesium absorber TRPM6 at the luminal side of the distal convoluted tubule (DCT), leading to excessive renal magnesium wasting. As hypomagnesemia was already observed in the pre-CNI era, additional contributory factors seem conceivable, such as insulin resistance, hyperalbuminemia and post-transplantation polyuria. As serum magnesium concentrations dose-dependently decrease with increasing CNI exposure, we should refrain from falsely interpreting signals of CNI toxicity as being caused or potentiated by hypomagnesemia. But possibly magnesium acts as a modifier in a few conditions.

Hypomagnesemia in patients with biopsy-proven cyclosporine nephrotoxicity predicts a faster decline of kidney function in renal transplant recipients, in line with recent findings in CKD patients. Importantly, this association was independent of drug concentrations but as it was not further explored in larger populations with more refined statistical techniques, we are uncertain whether this finding is unflawed.

In the general population, both serum magnesium and magnesium intake predict the development of type 2 diabetes in large population cohorts. In transplant recipients, some research groups including ours, have observed an association between early post-transplantation hypomagnesemia and the development of new-onset diabetes after transplantation (NODAT) in both renal and liver transplant recipients. Recent observations also confirmed a role of pre-transplantation serum magnesium as a predictor of NODAT which virtually excludes that hypomagnesemia merely reflects CNI-toxicity with simultaneous depression of beta-cell function. To address the ongoing question of reverse causality, interventional trials should refute or encourage potential use of magnesium supplementation in patients at risk. In this regard, we designed an open label randomized pilot trial to assess potential effects on correcting incidental hypomagnesemia after transplantation on fasting glycerinaemia, assessed at month three post-transplantation. We observed a significantly lower fasting glycerinaemia in the treatment group versus the control group, which was deprived from magnesium supplementation. However, the study was inadequately powered to detect differences in fasting glycerinaemia among both groups between baseline and the assessment at month three, nor on insulin resistance.

Definitely, a mean rise of serum magnesium by just 0.13 mg/dL by a mean of 1145 mg of magnesium already develops, is too small and too low to affect glycemia among both groups between baseline and the assessment at month three, nor on insulin resistance. This study emphasizes a common difficulty in daily transplant outpatient clinics: refractoriness to supplementation is the rule rather than the exception. We observed that those patients whose serum magnesium failed to increase despite supplementation (with persisting hypomagnesemia) were more glucose intolerant than those with a rise in serum magnesium (Figure 2).

In another prospective study, we demonstrated that renal transplant recipients, and especially those older than 55 years, had a higher degree of vascular stiffness independent of classical risk factors. This surrogate measure, which was assessed by pulse wave velocity, elegantly predicts cardiovascular outcome and mortality in renal transplant recipients. We can consider that a beneficial role of magnesium on endothelial function, which was proven in RCT in the elderly and in patients with coronary artery disease, partially explains these findings. These observations can alter our interpretation of clinical trials, whereby conversion of CNI to mTOR inhibitors improved vascular stiffness independent of effects on blood pressure or kidney function, in analogy with lowering of endothelin-1 (ET-1) concentrations.

Finally, magnesium is a second messenger in intralymphocytic physiology and plays a role in T cell and NK cell cytotoxicity. Magnesium deficiency activates macrophages and increases cytokine production, while magnesium supplementation attenuates these processes. Magnesium is a cofactor for the synthesis of immunoglobulins and hypomagnesemia predicts a higher infection-related mortality in hemodialysis patients. Thus its role in post-transplantation infection susceptibility or – not automatically beneficial – even key transplantation outcomes such as tolerance and both cellular or humoral rejection, is elusive but definitely deserves further exploration.

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**Figure 1:** Pretransplantation serum magnesium concentrations of patients receiving a kidney transplantation between 2003 and 2014 (n=867) are depicted in blue and their corresponding serum magnesium at week 2 or at dismissal from the hospital in red. The dashed lines represent the normal reference interval for serum magnesium.

**Figure 2:** An oral glucose tolerance test was performed in renal transplant recipients treated with magnesium supplements. Glycemia at 60 and 120 min was higher in those with versus without persisting hypomagnesemia (both with a p-value of <0.01). Error bars: ± 1 SEM.
Magnesium is essential for a number of metabolic activities since it is associated with a variety of enzymes which control carbohydrate, fat, protein end electrolyte metabolism. Several hundreds of enzymes, directly or indirectly are dependent on magnesium. Most important among these enzymes are those which hydrolyse and transfer phosphate groups, including enzymes that are concerned with reactions involving energy production and ATP.

Magnesium deficiency or reduction in dietary intake of magnesium plays an important role in the etiology of diabetes and numerous cardiovascular diseases including thrombosis, atherosclerosis, ischaemic heart disease, myocardial infarction, hypertension, cardiac arrhythmias and chronic heart failure (CHF) in humans. Magnesium deficiency may lead to reduced energetic metabolite production and the sense of fatigue and/or 'chronic fatigue syndrome'. The modern life and Western industrial diet enhanced the reduction of magnesium in our food which contributes to the marginal or absolute magnesium deficiency. It is mostly evidenced in the elderly population, those with myocardial infarction and/or CHF, diabetics, patients with chronic airway obstruction, pre- or toxemia of pregnancy, in post transplantation patients (especially in heart transplantation), patients with malignancies who receive cytotoxic chemotherapy, in competitive athletes and in metabolic syndrome patients.

It should be noted that magnesium deficiency can be easily treated by supplementation if we are aware of the situation. Since magnesium deficiency is hard to treat only by increasing the consume of high magnesium food products, it is recommended to take magnesium supplements which officially and safely correct the deficit.

Magnesium supplementation improves myocardial metabolism, inhibits calcium accumulation and myocardial cell death; improves vascular tone; peripheral vascular resistance; afterload and cardiac output; reduces cardiac arrhythmias and improves lipid metabolism. Magnesium also reduces vulnerability to oxygen-derived free radicals, improves human endothelial function and inhibits platelet function, including platelet aggregation and adhesion.

The data regarding its use in patients with acute myocardial infarction (AMI) is conflicting. Although some previous, relatively small randomised clinical trials demonstrated a remarkable reduction in mortality when administered to relatively high risk AMI patients, two recently published large-scale randomised clinical trials (the Fourth International Study of Infarct Survival and Magnesium in Coronaries) failed to show any advantage of intravenous magnesium over placebo.

Nevertheless, there are theoretical potential benefits of magnesium supplementation as a cardioprotective agent in CAD patients, as well as promising results from previous work in animal and humans. These studies are cost effective, easy to handle and are relatively free of adverse effects that gives magnesium a place in treating CAD patients, especially high-risk groups such as CAD patients with heart failure, the elderly and hospitalized patients with hypomagnesemia. Furthermore, magnesium therapy is indicated in life-threatening ventricular arrhythmias such as Torsades de Pointes and intractable ventricular tachycardia.

It should be remembered that magnesium is neither 'panacea' nor a 'wonder drug' which is aggressively pushed by the pharmaceutical industry. After all it is a relatively simple nutrient, relatively non-expensive and easy to administer with relatively few adverse events but a ‘nutrient which is the sparkle of life’ and an important life gatekeeper.

Disturbances are frequent

Mineral metabolism in paediatric transplant recipients

As paediatric end-stage renal disease (ESRD) is such a rare condition, international collaboration is needed to perform epidemiological studies. Therefore, in 2007, the European Society of Paediatric Nephrology (ESPN) together with the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) established a pan-European registry collecting data on European children on RRT. Currently, 36 countries provide information of over 10,000 patients. Such a large registry provides the unique opportunity to study potential risk factors in relation to patient outcomes. Today, several interesting research projects on a variety of topics have resulted from these data. An ongoing project within the framework of the ESPN/RPDWG target levels stratified by age.

* The number of subjects was too small.

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A major step forward

Biomarkers in the diagnosis of AKI

A cute kidney injury (AKI) occurs in a substantial proportion of hospitalised patients. Similar to myocardial infarct and stroke, AKI needs proper diagnosis, risk assessment and urgent treatment. Acute tubular damage is a key pathomechanism of AKI often occurring before filtration function decline develops.

The Kidney Diseases Improving Global Outcomes Initiative suggested that delay in the diagnosis of AKI, at least in part, results from currently used diagnosis parameters basing on renal function such as serum creatinine and urine output (1). Such delay contributes to aggravation of AKI and complications such as hypervolemia and metabolic disorders.

At the time of diagnosis of established AKI, irreversible organ damage may already have occurred. To protect as much salvageable kidney tissue as possible, in their recently published clinical practice guideline (1), the KDIGO recommends clinicians to carry out risk assessment for a given patient whether AKI may develop de novo - or progress if already present - and highlights the importance of risk assessment for individual patient management. The KDIGO concludes that acute tubular damage markers may feature AKI diagnosis once proving better diagnostic performance than the classical clinical and routine biological parameters.

Currently, several acute tubular damage markers have been introduced, including neutrophil gelatinase-associated lipocalin (NGAL), TIMP-2/IGFBP7, interleukin-18, liver-type fatty acid-binding protein and kidney injury molecule 1 and many others. Exemplary for other acute tubular damage markers, the following presentation will focus on NGAL and TIMP-2/IGFBP7.

NGAL fulfils many of the characteristics important for a useful AKI biomarker. The marker may represent a significant component in the pathophysiology of the disease. The concentration of NGAL in urine or plasma rises rapidly in a dose-dependent manner that is proportional to the degree of damage. NGAL is expressed early after kidney damage, when such injury is still potentially limitable or reversible. NGAL may further allow differentiation between the causes of AKI (intrinsic versus transient ‘pre-renal’ AKI), risk stratification, therapy monitoring and prognostication with respect to the need for acute dialysis, duration of hospital stay and mortality (2). In >4.000 patients admitted to an Emergency Room or an Intensive Care Unit, NGAL- (or KIM)-positivity indicated worse renal and overall outcomes even in the absence of classical AKI (creatinine increase or urine output decline) (3,4). The marker is non-invasive, clinically actionable and reliably measureable on available standardized clinical platforms. Furthermore, NGAL incrementally adds value to the baseline clinical risk assessment, potentially enabling physicians to intervene early to limit the extent of renal injury (4). Clinical studies that substantiate these statements but also limitations of these biomarkers are to be discussed.

In a discovery cohort of 522 critically ill patients using mass spectrometry analysis, out of over 300 markers TIMP-2 and IGFBP7 have been identified to predict moderate to severe AKI (KDIGO stage 2 to 3) within 12 hours of sample collection (5). Such findings have been confirmed in a validation study including 728 critically ill patients (5) and by other work groups also including critically ill patients (6).

Despite some limitations, acute tubular damage biomarkers may guide earlier initiation of nephroprotection, improved fluid management or withdrawal of nephrotoxins directed at improvement of outcomes in patients developing AKI. Since, the recent ‘Acute Dialysis Quality Initiative’ Consensus Conference has now suggested the use of tubular damage markers for AKI diagnosis complementary to renal function markers (Figure 1).

Michael Haase, Magdeburg, Germany

S13: Novel diagnostics and treatments in AKI

Room: ECLICUM 1
Date: 01-06-2014
From 15:15 to 16:45

References

Marjolein Bonthuis, Amsterdam, The Netherlands

S9: The ERA-EDTA Registry
Room: ECLICUM 1
Date: 01-06-2014
From 11:45 to 13:15
The dose makes the poison

Which dialysate sodium concentration in 2014?

Paracelsus, German-Swiss Renaissance physician wrote: “All things are poison and nothing (is) without poison; only the dose makes the poison, not the thing”. This sentence seems to apply perfectly to sodium chloride. Why bother with sodium? Sodium is the main extracellular ion and defines osmolality and size of the extracellular volume; increased plasma sodium concentration results in a rise of osmolality, thirst and extracellular volume expansion. The latter results in cardiovascular diseases, such as arterial hypertension and left ventricular hypertrophy.

Sodium mass balance in hemodialysis patients is primarily dependent on two factors: dietary salt intake and sodium removal during dialysis. Salt intake during the inter-dialysis period is dependent on the patient’s behaviour. Most Western societies consume between 150 and 250 mmol/day. There is evidence that hemodialysis patients ingest similar amounts of sodium. A small series of Spanish dialysis patients showed baseline sodium intake of ~173 mmol/day. Likewise, a study of 28 English hemodialysis patients showed an average estimated sodium intake of 251 mmol/day. NKF-K/DOQI guidelines recommend an upper limit of daily salt intake of 6 grams (~100 mmol of sodium).

Therefore, one of the most important goals of the dialysis therapy is to remove exactly the mass of sodium that has been accumulated in the interdialysis period in order to reach a zero sodium mass balance. The latter can be achieved through convection and diffusion. Current prescribing practices for maintenance hemodialysis rely primarily on convective and less on diffusive losses. This relative distribution, however, is dependent on the amount of ultrafiltration occurring during any given dialysis session (i.e. convective losses), and the prescribed dialysate sodium concentration and its relationship with the patient’s own plasma sodium (the so called inlet dialyzer diffusion concentration gradient between dialysate and plasma).

When comparing dialysate sodium and plasma sodium concentration, the issue of sodium measured in water (for the dialysate sodium) versus sodium measured in plasma, where the electrolyte concentrations are roughly 6% higher because of the latter’s nonaqueous components, must be taken into account. Negatively charged proteins moreover trap positively charged ions, like sodium, which reduces the effective sodium concentration (Gibbs-Donnan effect). Both effects, namely the Gibb’s-Donnan effect and the ‘dilution’ effect of the nonaqueous components in the plasma, essentially cancel each other out so that the simple difference between dialysate sodium and plasma sodium concentration can be assumed clinically to be the actual effective gradient (Figure). The diffusive loss (or gain) depends on the inlet dialysate diffusion concentration gradient between dialysate and plasma. Actually, Basile et al. showed in a very recent study that convection was the main determinant of the sodium mass balance, with diffusion counterbalancing convection-driven mass balance by about 17% (the mean dialysate sodium concentration was 138.7 mmol/L). Oduolu et al. reported that the diffusive component of ionic mass balance was 29% of total sodium removal, when dialyzing with a fixed dialysate sodium concentration of 140 mmol/L. Thus, it can be concluded that the diffusive gradient between plasma and the inlet dialysate sodium concentration is an important factor in the ‘fine tuning’ of sodium mass balance in hemodialysis.

In the early years of dialysis (1960s), there was no hydrostatic ultrafiltration (osmotic ultrafiltration was accomplished using large amounts of glucose in the dialysate), dialysis time was 6–12 hours; dialysate sodium concentration was kept low, in the order of 126 to 130 mmol/L. In the eighties, hydrostatic ultrafiltration was applied, dialysate sodium concentration was ~136 mmol/L; dialysis time 4–5 hours. In the last years a higher dialysate sodium concentration (> 140 mmol/L) is widely accepted promulgated by continued trends toward shorter dialysis time that result in the use of hypertonic saline, high dialysate sodium concentration and sodium modeling as a pervasive and system-wide practice to avoid hemodynamic collapse during the shortened dialysis treatment.

The evidence is compelling that reduction of the dialysate sodium concentration to 134–138 mmol/L in both standard and nocturnal in-center dialysis decreases inter-dialytic weight gain and decreases pre-dialysis systolic blood pressure, without increasing the frequency of adverse events during dialysis. On the other hand, the conclusions of three large observational studies, taken together, are:

1. low pre-dialysis serum sodium concentration is associated with higher mortality;
2. low pre-dialysis serum sodium concentration is associated with high inter-dialytic weight gain;
3. low dialysate sodium concentration slightly decreases inter-dialytic weight gain;

The next question is: should we move to a lower dialysate sodium prescription in the order of 134–138 mmol/L, as strongly advocated by chief medical officers of 14 mayor dialysis providers? We believe it is premature to make such substantial changes in the dialysis prescription without convincing evidence and balance of the advantages and disadvantages of such a change.

Then, what is the answer to the main question: Which dialysate sodium concentration in 2014? Until there is new evidence from randomised controlled trials, we believe that the dialysate sodium concentration should not be lowered. The current range of 138–140 mmol/L should be maintained until well-designed trials will offer new insights (Table).
Towards a patient-tailored strategy

Since chronic metabolic acidosis in ESRD haemodialysis patients represents a potential hazard from the prognostic viewpoint (i.e. morbidity and mortality), the need for buffered bicarbonate-based replacement therapy (peroral citrate is to be avoided because it fosters aluminium absorption) is unquestioned and substantiated by guidelines (e.g. mid-week venous bicarbonate target levels should be maintained at ≥ 22 mmol/L as per KDOQI guideline 14 [evidence] and between 20 and 22 mmol/L as per EBPG no. 6 [evidence level III; based on observational and case-control studies]).

The dialysis session is a valuable opportunity to compensate for metabolic acidosis and both the KDOQI and EBPG guidelines recommend the use of dialysate to correct acidosis as a support or alternative strategy to peroral replacement therapy. Therefore, dialysis machines make it possible for clinicians to deploy broad-spectrum adjustments to dialysate bicarbonate concentrations (e.g. up to 40 mmol/L from baseline in patients with resistant metabolic acidosis and venous pre-dialysis bicarbonate persistently < 20 mmol/L; EBPG no. 6 [Evidence Level III]).

In the absence of tolerability and physiological limitations to the viability of intra-dialytic correction of metabolic acidosis, the issue could be easily solved by up-regulating dialysate bicarbonate concentrations in order to achieve a pre-dialysis bicarbonate concentration above the minimum target recommended by guidelines at monthly follow-ups (KDOQI 16 [Opinion]).

Unfortunately, the correction of metabolic acidosis during the dialysis run temporally exposes the patient to hemodynamic instability [1] and, especially at the end of the session, to the risks and to the potential symptoms induced by metabolic alkalosis such as cramps, reduced cerebral perfusion as well as electrolytic imbalance-related symptoms, such as hemodynamic instability, during and immediately after dialysis.

The limitations posed by intra-dialytic replacement therapy raise the question concerning the best strategy to pursue: should we limit intra-dialytic bicarbonate substitution and prescribe peroral replacement therapy during interdialytic intervals? Should we deploy parallel strategies in an attempt to reduce the risk of hemodynamic instability during dialysis and curb the potential negative impact induced by metabolic alkalosis and bicarbonate administration? Should we use other buffer substances in the dialysate, such as citrate, in addition to bicarbonate in order to change the kinetics of acidosis correction?

The first strategy is unquestionably viable, but it will automatically result in increased interdialytic sodium intake, which may pose some restrictions for some patients. Moreover, if, on the one hand, increased internal-dialytic bicarbonate intake may prevent hypotension due to less intradialytic bicarbonate intake may prevent hypotension due to less intradialytic bicarbonate administration, the induction of intradialytic hypotension was demonstrated (Figure 1) [1]. The pathophysiology mechanism explaining the observed reduction of blood pressure related to the use of supra-physiological dialysate bicarbonate concentrations has not been elucidated, although the consequences of pH changes on potassium and calcium concentrations (Figure 2) could play a role. Significant hemodynamic fluctuations leading to pressure changes (esp. systolic) have in fact been experimentally induced by modifying the dialysate concentrations of the two above-mentioned electrolytes [2,3].

Therefore, haemodialysis patients are exposed to the two extremes of the acid-base imbalance. On the one hand to a chronic tendency towards metabolic acidosis and, consequently, to bone density loss, catabolism, hyperphosphatemia, worsened hyperparathyroidism and increased mortality; and on the other to acute metabolic alkalosis and to an array of potential imbalance-related symptoms, such as hemodynamic instability, during and immediately after dialysis.

The second question points to the multitude of measures that can be implemented to control intradialytic hypotension and to the fact that the potential hypotensive properties of high-dose bicarbonate could be controlled applying the usual recommended strategies (e.g. dialysate temperature modelling; ultrafiltration modelling; sodium and calcium concentration modulation; adjustment of dry weight; individualized dialysis protocol paying special attention to duration and type; customized anaemia therapy; use of supportive medications such as midodrine, carnitine and sertraline; reducing interdialytic salt intake, etc.).

The third question stems from the experience of using citric acid instead of acetic acid in the dialysate, which led surprisingly to an increase in predialytic bicarbonatemia [4]. This finding could be experimentally further investigated by adding citrate to bicarbonate in the dialysate thus hoping for a more favourable kinetics of bicarbonate correction due to potential latency in the conversion of citrate into bicarbonate.

To sum up, the correction of metabolic acidosis as well as the modulation of dialysate bicarbonate concentration are extremely sensitive and crucial steps. The complexity of the topic, together with patient specificities and the variety of potential viable options, mandate the adoption of a patient-tailored strategy in order, on the one hand, to control acidosis and on the other, to preserve the hemodynamic profile, avoiding both symptoms of transient secondary metabolic alkalosis and potential harm.

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Figure 1: Incidence of intradialytic hypotensions and of the need of saline infusion, comparing a physiologic to a supraphysiologic dialysate bicarbonate concentration (P<0.05 for both comparisons) [1].

Figure 2: Ionized calcium concentration and potassium (mmol/L) at the end of dialysis comparing a physiologic to a supraphysiologic dialysate bicarbonate concentration [1].
Combined effort for better survival rates

Membrane permeability, dialysate purity and clinical outcomes

Cardiovascular mortality is substantially higher in patients undergoing maintenance hemodialysis (HD) as compared to the non-uremic population. Several risk factors unique to uremia are implicated in the high rates of cardiovascular disease and mortality in these patients, for example accumulation of medium-sized or large molecules and predominance of a chronic inflammatory state. Consequently, use of high-flux synthetic membranes, providing enhanced removal of higher molecular weight uremic toxins coupled with better biocompatibility, together with ultrapure dialysis fluid, might be expected to improve patient outcomes.

High-flux dialysis

Many observational studies have suggested that the use of high-flux dialyzers improves survival [1]. However, primary analyses of the two randomised clinical trials (RCT) failed to demonstrate improvement in overall survival with the use of high-flux dialyzers [2,3]. A non-statistically significant 8% mortality risk reduction with high-flux membrane was reported in the HEMO study; subgroup analyses revealed that high-flux dialysis is associated with better overall survival in patients with HD duration longer than 3.7 years [2]. High-flux use was associated with decreased cardiac mortality and the composite outcome of first cardiac hospitalization or death from cardiac causes in secondary analyses [4]. The European Membrane Permeability Outcome (MPO) study was started in incident patients with albumin levels below 4 g/dl but later expanded to include patients with albumin levels over 4 g/dl [3]. The survival advantage with high-flux dialyzers (24%) was resulting in clinically relevant improvements including amelioration of erythropoietin response in anemia, better nutritional status and reduction in the incidence of β2-microglobulin amyloidosis. Although preliminary reports suggested lower cardiovascular morbidity with the use of ultrapure dialysis fluid, no randomised and controlled trial has been performed addressing hard clinical outcomes.

Effect of high-flux dialyser and ultrapure dialysate combination

We recently conducted a RCT to determine whether membrane permeability and dialysate purity affects the incidence of fatal and non-fatal cardiovascular events and overall survival in prevalent maintenance HD patients [EGE Study] [5]. EGE Study is the third RCT addressing the topic of membrane flux, and the first RCT investigating the impact of dialysate microbial purity. 704 maintenance dialysis patients were randomised to high-flux/low-flux dialyzer and to ultrapure/standard quality dialysate arms in a two-by-two factorial design. Primary outcome was the composite of fatal and non-fatal cardiovascular events. The main secondary outcome was overall mortality. Primary and secondary outcomes were evaluated during a minimum three years of follow-up period.

At the baseline, mean age was 58.6±4.2 years, prevalence of diabetes 22.7%, Blood pressure was adequately controlled in 79.9% of the subjects. Fatal and nonfatal cardiovascular event rate was 5.03 per 100-patient year [n=104] in the entire study population.

In patients with AV fistula (81.8% of the overall population), the risk for fatal and non-fatal cardiovascular event was 39% lower in the high-flux compared to the low-flux group (HR=0.61, 95% CI 0.38-0.97, p=0.03). Overall survival was also better in the high-flux group (p=0.04).

In this subgroup, cardiovascular event-free and overall survivals were not different between dialysate arms. However, subjects treated with a combination of high-flux and ultrapure dialysate had the highest overall survival rate compared to other combination groups (p=0.03).

In diabetic subjects [n=160], high-flux dialysis was associated with lower risk for primary outcome compared to low-flux (HR=0.49, 95% CI 0.25-0.94, p=0.03). Also, overall survival was better in the high-flux group compared to the low-flux group [60.5% versus 41.6%, p=0.02].

In patients with dialysis duration longer than 3 years [n=399], the risk for primary outcome was significantly lower in the ultrapure dialysate arm compared to the standard dialysate group (HR=0.55, 95% CI 0.31-0.97, p=0.04). EGE study demonstrated for the first time better outcomes with high-flux membranes in the subgroup of patients dialyzed with AV fistula. Although it was not a pre-specified subgroup analysis, patients with AV fistula constitute the majority of the population (81.8%). Prevalence of patients with AV fistula was 33.2% in the HEMO and 80.1% in the MPO. Neither the HEMO nor the MPO study reported the impact of high-flux membrane on survival in patients with AV fistula. It can be speculated that higher blood flow rate observed in patients with AV fistula compared to those with catheter is a prerequisite to improve outcomes with use of high-flux dialyzer. Alternatively, catheter-related complications or patient factors associated with having a catheter could negatively influence patient outcome, as also shown in this study.

Beneficial effects of high-flux dialysis in diabetics are in line with the 38% risk reduction with high-flux reported in the MPO study [3]. Clearance of circulating advanced glycosylated end products and oxidised low-density lipoproteins with high-

![Image](https://via.placeholder.com/150)

**Membrane Permeability Outcome (MPO) study**

- **Objective:** To compare the effect of high-flux and low-flux dialysis on cardiovascular mortality and morbidity in patients with HD.
- **Design:** Randomised clinical trial.
- **Participants:** 704 prevalent maintenance HD patients.
- **Main outcomes:** Cardiovascular mortality and morbidity.
- **Results:** Lower risk for primary outcome (HR=0.55, 95% CI 0.31-0.97, p=0.04) and overall survival was better in the high-flux group compared to the low-flux group [60.5% versus 41.6%, p=0.02].

**Figure:** Cumulative Survival Rates

- **Graph:** Shows the cumulative survival rates for patients with AV fistula.
- **Key findings:** The combination of HF and UD is associated with the best overall survival rate in patients with AV fistula.

**Table:**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>High-flux vs. Low-flux</td>
<td>0.77</td>
<td>0.57-1.04</td>
<td>0.09</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>High-flux vs. Low-flux</td>
<td>0.61</td>
<td>0.38-0.97</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiac event-free survival</td>
<td>High-flux vs. Low-flux</td>
<td>0.49</td>
<td>0.25-0.94</td>
<td>0.03</td>
</tr>
<tr>
<td>Overall survival</td>
<td>High-flux vs. Low-flux</td>
<td>0.55</td>
<td>0.31-0.97</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Key points:**
- High-flux dialysis is associated with reduced cardiovascular mortality and morbidity.
- The use of ultrapure dialysate improves overall survival.
- In diabetic subjects, high-flux dialysis offers significant survival benefits.
- Further research is needed to elucidate the mechanisms underlying these benefits.
How to measure volume expansion

Lung congestion in dialysis patients: detection, risk factors and interventions

Carmine Zoccali, Reggio Calabria, Italy

Chronic expansion of the extracellular volume is one of the most common and time-honored dangers which compose the syndromic set of end-stage renal disease (ESRD). Mild-to-moderate degrees of volume expansion may go undetected or are overlooked in ESRD, but marked fluid overload in these patients is eventually a medical emergency demanding hospitalisation and extra dialyses. Even though interdialysis weight gain is not necessarily tantamount to volume expansion, this simple parameter has been associated with an excessive death risk. Improving volume control in the dialysis population is perceived as an urgent public research issue. Noninvasive methods for estimating body fluid volume and tailoring excess volume removal in ESRD have been developed over the last 20 years, including total body water, continuous hematocrit monitoring, vena cava diameter and left atrial volume measurements. Measurement of volume expansion by diffrerent parameters predicts mortality, but the usefulness of fluid volume measurements in clinical practice still remains to be proven.

The issue is of major relevance because in a randomised clinical trial that tested the effect of probing dry weight by blood volume monitoring a higher mortality and hospitalisation rate was registered in the group randomised to the active arm of the trial. Correction of volume expansion in the dialysis patients is difficult to achieve. Due to underlying cardiomyopathy encompassing left ventricular (LV) systolic and diastolic function, the majority of these patients is hemodynamically fragile and may often not tolerate the standard ultrafiltration rate imposed by current dialysis schedules. However accurate and precise, estimates of fluid volume per se are not sufficient information for prescribing excess volume removal in most patients.

Extravascular lung water is a relatively small but fundamental component of body fluid volume. This component, water content in the lung interstitium, is associated with LV filling pressure estimated by pulmonary capillary wedge pressure (PCWP), i.e. the gold standard parameter for guiding fluid therapy in patients with severe heart disease. Evidence that lung permeability is altered in ESRD patients was produced 50 years ago implying that alterations intrinsic to the lung may contribute to the high risk of cardiopulmonary complications in this population.

Recent experimental studies show that bilateral nephrectomy per se triggers lung injury via inflammatory mechanisms, supporting the view that lung alterations may amplify the risk of pulmonary edema in ESRD patients with volume overload and LV disorders. I will review the basic concepts of hemodynamic and pulmonary congestion and the relevance of these concepts for patients in clinical practice, and we then move to describe asymptomatic and symptomatic lung congestion in ESRD and the prognostic relevance of this disorder in the same population. Even though studies performed so far are quite consistent and methodologically valid, some limitations should be clearly acknowledged. A large, multicenter study in Italy and a cohort study in Romania, showed that lung US may be precise for the prognostic stratification of the dialysis population, these studies included Caucasian patients only. Therefore, the prognostic ability of chest US should be confirmed in other dialysis populations including other ethnicities. Finally, the usefulness of chest US remains to be tested in a formal clinical trial. A clinical trial funded by the European Renal Association/European Dialysis and Transplant Association is underway to test the hypothesis that a lung comet-guided clinical policy may improve clinical outcome in high-risk HD patients with cardiac disease.

References


Entwined with water

Explore Amsterdam by boat

The image of Amsterdam is one of a city entwined with water. Amsterdam’s Canal Ring is one of the world’s most unique urban landscapes. Four centuries ago people in Amsterdam began constructing the nowadays world-famous Canal Ring which

A boat cruise is an excellent way to explore Amsterdam ©Amsterdam Marketing

Since 2010 is part of the UNESCO World Heritage list. It was built during Amsterdam’s “golden age” in the 17th century. The “Grachtengordel” as it is called locally, is comprised of a network of intersecting waterways.

Today it is one of the city’s most popular attractions. A boat cruise is an excellent way to explore the city (www.amsterdamcanalcruises.nl).
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