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NEPHROLOGY

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INSIDE

Review of

ERA-EDTA 2014

Amsterdam, the Netherlands

CONTENTS

NEPHROLOGY

Editorial Board

Nephrology

Editor-in-Chief: Prof Norbert Lameire

Emeritus Professor of Medicine and Nephrology, Medical Faculty of the Ghent University, Ghent, Belgium; Editor-in-Chief of the Acta Clinica Belgica, Journal of the Belgian Society of Internal Medicine, Clinical Biology and Clinical Chemistry; Chairman of the European Kidney Health Alliance.

Welcome

I would like to welcome you all to this second edition of the *European Medical Journal – Nephrology*. Whatever stage you are at in your career, this journals aims to benefit all healthcare professionals with an interest in nephrology.

Commenting on the subject of nephrology, Prof Raymond Vanholder, President of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), said: "Nephrology is intellectually very demanding and inspiring."

In order for decisions to be made, a wide range of evidence, drawn from clinical studies, is needed. While being an interesting and highly important speciality, evidence from these trials are often lacking. Therefore, guidelines can prove to be useful in these situations. In our 'Congress Review' section, under 'Late Breaking Clinical Trials', we have reported on the new transplant guidelines as set out by the European Renal Best Practice group.

These guidelines hope to improve the outcome of patients with kidney disease. The 112 statements which were drawn-up not only recommend what the treating physician should do in each case, but they have also identified gaps in knowledge where evidence is lacking and clinical trials are needed, and also recommended which evidence-based therapy should be used and when.

With regards to recommendations, '*Autosomic dominant polycystic kidney disease: what do we need to know for counselling*?' is a very enlightening paper written by Dr Giorgina Piccoli, and is helpful for physicians who have to counsel their patients. One of the conclusions suggested in the paper is a diet option, one which consists of low-salt but high-water intake; although the diet may be difficult to follow, there are very few side-effects.

There is a mass shortage of kidneys, one of our most essential organs. A study, reported in our 'Whats New' section, revealed that for those who donate, end-stage renal disease (ESRD) could be a problem. However, it concluded that ESRD was still higher in the general population rather than this group specifically.

Talking at the ERA-EDTA Congress a 75-year-old woman from Amsterdam, the Netherlands, spoke of her experiences donating a kidney. She immediately improved the patient's quality of life, and she was able to carry on with her life as usual. Her hope is that her story will encourage people to be altruistic kidney donors throughout Europe.

In addition to covering the congress we were also privileged to have a stand and showcase the quality of our journals; if you would like more information then please do look at our blog page, http://emjreviews.com/blog/addition-era-edta-2014-emj-cow/, where you can read about our EMJ Cow.

We hope that this second edition of the *European Medical Journal – Nephrology* will provide a great insight into the changing landscape of nephrology and will prove to be an invaluable source of information, as well as a base of continued education and learning.

Spencer Gore

Director, European Medical Journal

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Foreword

Prof Norbert Lameire

Emeritus Professor of Medicine and Nephrology, Medical Faculty of the Ghent University, Belgium.

This second issue of the *European Medical Journal-Nephrology* offers a number of interesting and informative papers on several aspects of acute and chronic kidney diseases. All papers were externally reviewed by an impartial panel, guaranteeing their accurate content.

Dr Schiffl, one of the first to perform a prospective study on dialysis dose in patients with acute kidney injury (AKI), correctly and realistically argues that further improvements and adjustments of renal replacement therapy in AKI patients may have little impact on overall mortality.

Pain is a common complaint in autosomal dominant polycystic kidney disease (ADPKD), occurring in as much as two-thirds of patients. Dr Niemczyk discusses the most common causes of pain, the diagnostic approaches, and their medical and possible surgical management. Dr Piccoli and her colleagues review the most recent changes in diagnosis and management of ADPKD patients as they have evolved from basic and clinical research over the last 5-10 years. Advice on genetic counselling, including prenatal testing and pre-implantation selection, dietary regimens (low salt and high water intake), and therapy with vaptans, is comprehensively provided in this paper.

Pregnancy in patients suffering from lupus kidney disease is certainly associated with increased maternal and foetal/neonatal complications. Drs Pateinakis and Pyrpasopoulou conclude, however, that pregnancy is not contraindicated provided that the disease is stable and inactive for at least 6 months before conception. Thorough preconception counselling and evaluation, close surveillance during gestation, and continued postpartum follow-up by an experienced multidisciplinary team, are the most important measures to take.

Between 31st May and 3rd June, 2014, the 51st Congress of the ERA/EDTA took place in Amsterdam, the Netherlands. A fascinating scientific and highly international programme was presented in the form of invited lectures, symposia, and free communications. For the first time, ERA organised a very successful symposia together with the Chinese Society of Nephrology and the International Society of Nephrology. The whole spectrum of kidney diseases was covered, and the event was a great success.

Join me on this journey as we venture into this latest edition to stay abreast with the latest news in the superb field of nephrology.

Kind regards,

Norbert Lameire

Emeritus Professor of Medicine and Nephrology, Medical Faculty of the Ghent University, Ghent, Belgium; Editor-in-Chief of the Acta Clinica Belgica, Journal of the Belgian Society of Internal Medicine, Clinical Biology and Clinical Chemistry; Chairman of the European Kidney Health Alliance.

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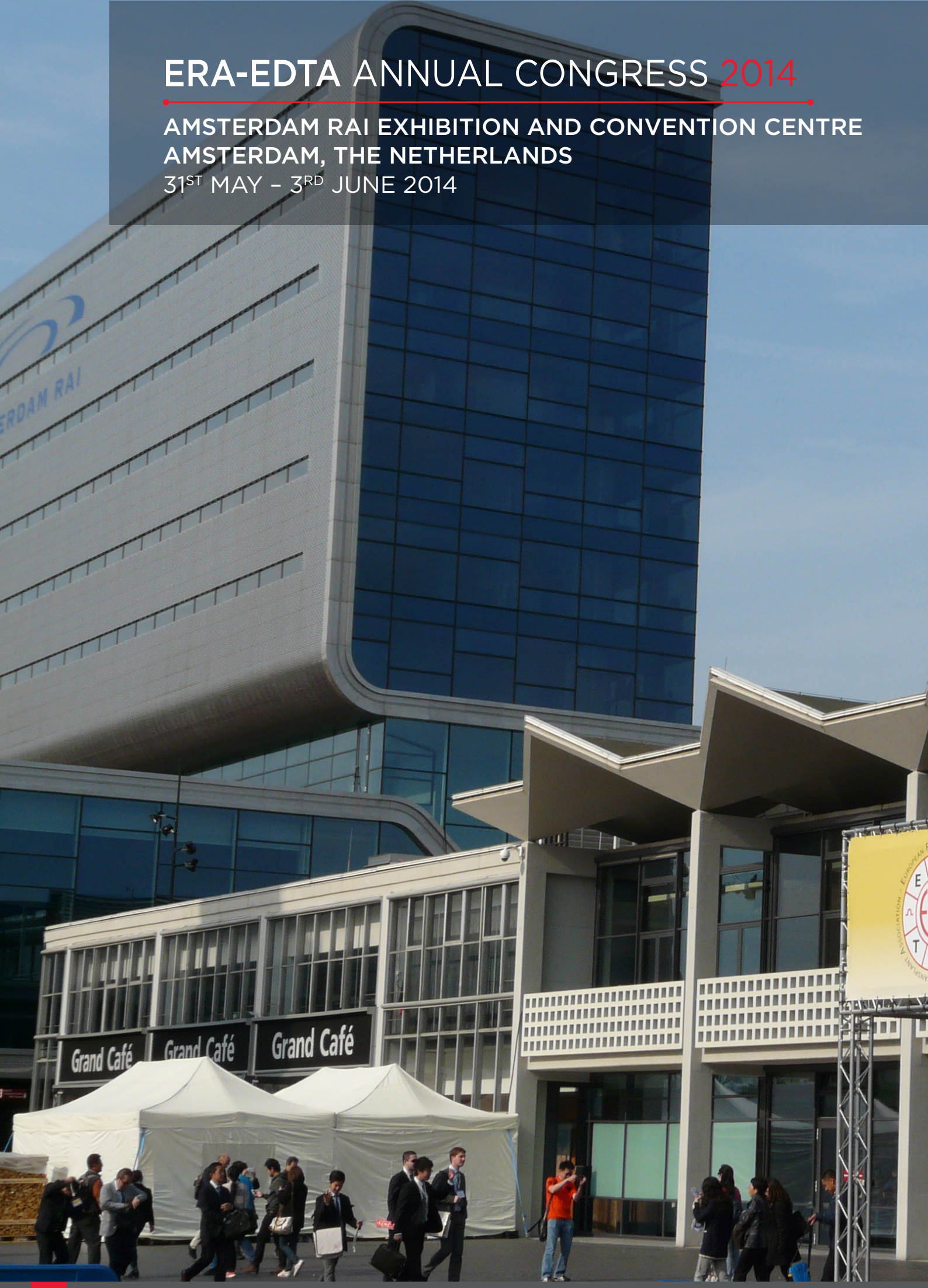

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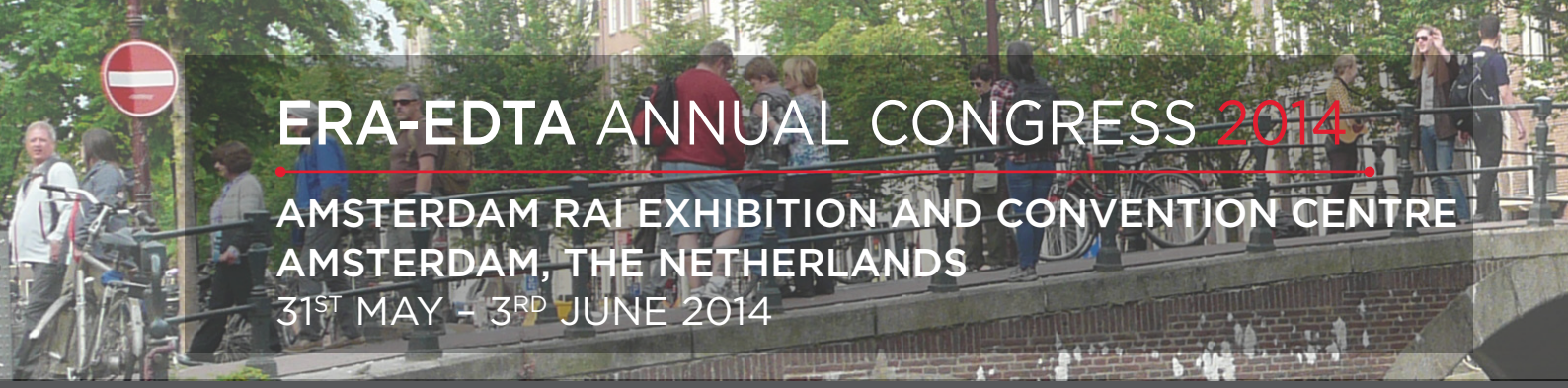


ERA-EDTA ANNUAL CONGRESS 2014

AMSTERDAM RAI EXHIBITION AND CONVENTION CENTRE AMSTERDAM, THE NETHERLANDS

31ST MAY – 3RD JUNE 2014

Welcome to the *European Medical Journal* review of the European Renal Association – European Dialysis and Transplant Association Congress 2014

Known for the enthralling beauty of its cityscape, historical architecture, and immense cultural splendour, Amsterdam, the Netherlands, remains the idyllic location for the 51st Annual European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Congress, which was held this year from 31st May - 3rd June.

Commenting on the Congress location, Prof Pieter ter Wee, Congress President, stated: "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."

Dr Willem Johan Kolff, a Dutch pioneer, set the benchmark for future nephrology discoveries in 1943 with the development of the first practical human haemodialysis machine, with researchers and healthcare professionals today flocking to this city harbouring hopes of accomplishing similar feats.

Memorable Congress highlights included the opening ceremony where the origins of ERA-EDTA were further reminisced, and its growth, from just 82 participants in 1964 to over 8,000 participants in recent years, documented. This fact was particularly emphasised by Prof Raymond Vanholder, President of ERA-EDTA (2011-2014), who is currently completing his last term of presidency. Rapid developments, scientific projects, major collaborations, and a stellar awards ceremony also took place. Additionally, there was a very interesting segment concerning the management of water on Earth and an overview of water sources found on planets in our solar system.

According to Prof Vanholder, the main aim of this society is to disseminate information through

"Networking drives science forward. People meet, discuss ideas, and allow their scientific projects to cross-fertilise."

Prof Raymond Vanholder, President, ERA-EDTA (2011-2014)

clinical, scientific, and political channels. All of this is carried out to increase the awareness of kidney diseases to the medical and general public. To achieve this during his presidency, networking has remained a major factor in this dissemination, about which Prof Vanholder said: "Networking drives science forward. People meet, discuss ideas, and allow their scientific projects to cross-fertilise."

In the eyes of the participants, the Congress was extremely successful. It consisted of 50 symposia and 32 free communication sessions. 150 researchers, whose abstracts received the highest score in their respected areas, presented their data orally, and 31 experts in the field provided state-of-the-art mini-lectures. In the opinion of many, it was an opportunity to discuss ideas and discover new research.

Tasked with building on the tremendous success of Prof Vanholder, Prof Andrzej Wiecek - the new elected president of ERA-EDTA - mentioned: "During my term I would like to continue these activities started during the recent years but I would also like to pay more attention to European matters of ERA-EDTA, with special focus on Central and Eastern European countries. A stricter and more rational system for financial expenditures, and new rules for continuing medical education (CME) courses in European countries and countries surrounding the Mediterranean Sea will be introduced."

In addition to these aforementioned highlights, there were also provisions catering for novices in the nephrology field. There was a special symposium for this target audience that will form the basis on which their future career can be built.

High-dose haemodialysis in the comfort of your own home

THE VIVIA HD system, a home haemodialysis (HD) device, has been unveiled by Baxter International Inc., and is designed to deliver frequent or extended-duration dialysis.

"Many dialysis patients currently do not have access to high-dose HD therapy," said Dr Bruce Culleton, Vice President, Renal Therapeutic Area Lead, Baxter Healthcare Corporation, Deerfield, Illinois, USA. "This research, in combination with the VIVIA HD system's patient-friendly design features, may allow a greater number of dialysis patients suited for home HD to access high-dose HD therapy in the home environment."

In Europe, it is estimated that approximately 40 million people are suffering from chronic kidney disease (CKD), and this number will continue to grow exponentially. On a global scale, roughly 2 million people undergo HD and a large proportion endures conventional HD (CHD) therapy in a centre at a frequency of 3 days per week for 3-5 hours per session.

Fewer than 1% of patients receive high-dose HD therapy, which is associated with more clinical benefits than CHD. This therapy has shorter daily treatments (less than 4 hours) or nocturnal treatments (more than 6 hours).

Understanding this need allows for the development of the VIVIA HD system, which can be used in the convenience of the patient's home. This ergonomic device features an extended use dialyser and blood tubing set, animated user interface, and access disconnect sensor. Additionally there are key patient-friendly features that ensure patient safety and convenience such as: a sensor to detect needle dislodgement and stop the machine pumping, one button fluid infusion to minimise user error and maximise the use of reagents, and automated treatment facilities to tackle device maintenance.

There is also reverse osmosis and electrodeionisation technology ensuring the production of water is of a higher purity. A key feature of the device is the Sharesource web-based connectivity platform which allows the patient's physician to monitor their treatment.

"Bringing the VIVIA HD system with Sharesource to market has been a journey we have taken with great determination because we believe patients deserve access to innovative technologies designed to deliver high-dose HD in their home," said Ms Jill Schaaf, President and Corporate Vice President, Renal Business, Baxter. "We are very excited to have the opportunity to begin to introduce the system to select European dialysis clinics in 2014," she concluded.

"This research, in combination with the VIVIA HD system's patient-friendly design features, may allow a greater number of dialysis patients suited for home HD to access high-dose HD therapy in the home environment."

Dr Bruce Culleton,
Vice President, Renal Therapeutic Area Lead,
Baxter Healthcare Corporation

Diabetes causing trouble in kidney disease

Associated with other risk factors such as hypertension, obesity, and significantly pre-diabetes, insulin resistance could be the engine which powers the incidence of both diabetes and obesity.

TYPE 2 diabetes mellitus (T2DM) and obesity have been found to cause renal dysfunction in patients, which eventually evolves to chronic kidney disease (CKD).

The global increase in CKD has occurred side-by-side with the growing obesity epidemic, with a possible 20-40% of the T2DM/obesity population developing renal dysfunction; this is a very damning statistic.

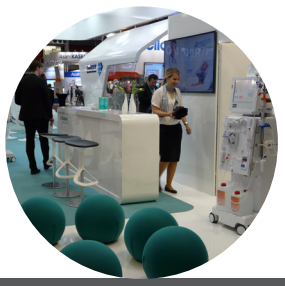
In 2012 it was recorded that 371 million and 200 million people worldwide had T2DM and obesity, respectively. Therefore, a huge amount of the global population is at risk of renal dysfunction, further underscoring diabetes and obesity as massive public health threats.

The likelihood of end-stage renal disease and fatal and non-fatal cardiovascular events is bolstered by this deterioration of renal function; as a result it is clear that early action is needed to prevent renal complication from developing into more severe and often irreversible conditions.

Diabetes and obesity are likely connected, with the two often occurring together in patients. However, the most convincing link of all may be insulin resistance, a condition where normal insulin concentrations provoke a lower than normal biological response; insulin resistance is seen as a major pathogenic factor in T2DM occurrence.

Associated with other risk factors such as hypertension, obesity, and significantly pre-diabetes, insulin resistance could be the engine which powers the incidence of both diabetes and obesity; it represents a potential catalyst for the coexistence of the two diseases, described as the metabolic syndrome.

These metabolic changes and insulin resistance occur in 25% of obese patients, rubber-stamping insulin resistance as a significant pre-cursor to renal disease. Further research is required to determine the potential existence of a similar pattern of renal damage between obesity/insulin resistance and early T2DM.


Chemokine blocked by diabetes drug

DIABETIC nephropathy has been targeted by a cytokine-blocking drug that has boosted the hopes of Type 2 diabetes patients with albuminuria.

A pro-inflammatory cytokine involved in the recruitment of immune cells to inflamed tissues, CCL2/MCP-1, is targeted by a new therapy known as emapticap pegol. The treatment is a Spiegelmer®, a new class of proprietary drugs developed by NOXXON Pharma AG, which consist of chemically synthesised L-stereoisomer oligonucleotide aptamers and act as a non-immunogenic alternative to antibodies.

Emapticap pegol binds and inhibits CCL2/MCP-1. The passage of inflammatory cells into the kidney is halted through neutralisation of this chemokine, allowing existing inflammation to diminish over time; podocyte numbers as well as renal structure and function are preserved as a result.

The renoprotective and antidiabetic potential of emapticap pegol was assessed in NOXXON's randomised, placebo-controlled, Phase IIa clinical trial, which evaluated the effect of the drug in Type 2 diabetic patients with albuminuria. 75 albumineric Type 2 diabetics were put on a stable standard of care regimen with a compulsory renin angiotensin system (RAS) blockade. Emapticap was administered subcutaneously at 0.5 mg/kg twice-weekly over 12 weeks, followed by a 12-week treatment-free observation phase.

The albumin-to-creatinine ratio (ACR), which measures protein in the urine, was -15% at the end of therapy in the full analysis set/intent-to-treat (ITT) group; this was followed by a 24% decrease at the peak effect point for emapticap pegol, recorded after 2 months off therapy. Reductions in glycated haemoglobin (HbA1c) in the blood were also noted for this group.

The novel mechanism of action of emapticap pegol, which distinguishes it from approved drugs, was underlined by the finding that relevant haemodynamic changes did not accompany the effect on ACR.

Prof Hermann Haller, principal investigator and Director, Department of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany, said: "The inhibition of the CCL2:CCR2 axis with emapticap pegol is well tolerated and reduces ACR and HbA1c in Type 2 diabetics with albuminuria. The maintenance of the effects even after cessation of treatment suggests that CCL2 blockade interferes with the underlying pathophysiology. Emapticap pegol may hence be the first disease-modifying drug for this indication."

> "The inhibition of the CCL2:CCR2 axis with emapticap pegol is well tolerated and reduces ACR and HbA1c in Type 2 diabetics with albuminuria."
>
> *Prof Hermann Haller, Hannover Medical School, Hannover, Germany*

The quest to eliminate tuberculosis faces a long road

DEALING with tuberculosis (TB) remains an ominous spectre in the post-transplant era, as a number of unknown variables continue to confound scientists worldwide.

"Collaboration with experts from many other fields is needed to offer the best management to our patients. Even more importantly, well-designed studies in transplant recipients with TB are strictly needed," said Dr Mehmet Şükrü Sever, Department of Nephrology, Istanbul University, Istanbul School of Medicine, Istanbul, Turkey.

Post-transplant TB has been attributed to mortality rates of up to 30%. TB incidence is 27-times higher in transplant patients than in the general population, with fears that it could extend to 10-15% in developing countries.

Current treatments face a number of obstacles; chemical immunosuppression causes a defective immune response, while increasing drug resistance also constitutes as a major obstruction. Treatment is especially problematic in the case of multidrug-resistant TB, in which the microorganism is resistant to both isoniazid and rifampin, the two most powerful anti-TB drugs.

The interaction between the rifamycins and calcineurin inhibitors and/or mammalian target of rapamycin inhibitors, which results in a significant drop in the serum levels of the latter drugs, is seen as the main orchestrator of this complication.

Clinical presentation is different in immunocompetent and immunosuppressive patients. Despite the usefulness of diagnostic methods such as tuberculin skin testing, interferon-gamma release assays, and sputum examination, staining and culture are beneficial in the immunocompetent host, but not so much for immunosuppressive cases.

Combinations of first and second-line drugs can be used over longer periods when treating active TB, although the routine daily treatment of infections constitutes another option.

Due to the controversy surrounding treatment duration, the authors of the study are at odds as to whether the required length of treatment with the rifampicin-containing regimen should be 6 or 9 months. "Of course, local resistance patterns and epidemiologic as well as susceptibility data from the individual patient's isolate should be considered," Dr Sever added.

Isoniazid, supplemented with vitamin B6 for at least 9 months, is currently preferred to prophylaxis for the treatment of latent TB. However, Dr Sever concluded: "The best solution would be individualising the treatment of latent TB."

Therefore TB remains a very difficult disease to predict due to the wealth of unknown variables, but this individualised approach may be the key to illuminating the best path.

Bridging the gap: growing kidneys from cell suspensions

FUNCTIONAL kidney organs grown in the laboratory might be the latest expectation to bridge the gap between organ supply and demand.

This brings hope to the many people suffering from end-stage renal disease who are greatly dependent on dialysis or kidney transplantation.

The cellular complexities of the kidney bring major limitations in the engineering of a complete organ. Past investigations have come close but have resulted in the lack of functional glomeruli, which is essential to kidney function.

"Dealing with this challenge, we attempted to generate functional renal tissue from suspensions of murine E11.5 kidney cells. In the first set of experiments, we employed a new protocol of organoid construction, starting from a large cell aggregate culture that appeared to be of utmost methodological importance to achieve the formation of viable nephrons *in vivo*," explained Dr Christodoulos Xinaris, Mario Negri Institute for Pharmacological Research, Bergamo, Italy.

Despite successful transplantation of the kidney organoid back into the host, which further developed into recognisable kidney structures, there was still no complete glomerulogenesis in this case.

To overcome this issue, Dr Xinaris's team infused vascular endothelial growth factor (VEGF) with the organoids in culture to encourage the development of blood vessels, and it was also injected into the transplanted site. The positive results that were demonstrated by the implanted organoid included: specialised physiologic functions, presence of erythropoietin-producing cells, and manifestation of functional podocytes.

The team further investigated the filtration capabilities of podocytes by injecting fluorescent dextrans of varying sizes into the host's blood stream, which were tracked by fluorescence microscopy. The dextrans were efficiently filtered, proving that they could perform the main function of kidneys.

Future work will continue, especially in the area of creating chimeras from human embryonic-like stem cells based on the mouse self-forming organoids. Fundamentally, this new direction might comprise the future of organ replacements.

> "We employed a new protocol of organoid construction, starting from a large cell aggregate culture that appeared to be of utmost methodological importance to achieve the formation of viable nephrons *in vivo*."
>
> *Dr Christodoulos Xinaris, Mario Negri Institute for Pharmacological Research, Bergamo, Italy*

ERA-EDTA Congress 2014- Europe's premier conference

The 51st Annual Congress of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) was held from 31st May-3rd June 2014 in the alluring city of Amsterdam, the Netherlands. This city with its historical atmosphere combined with a modern metropolis creating a tranquil environment is the perfect backdrop for this prestigious Congress.

The Congress has had over 8,000 delegates registered from different sections of the globe. Its reputation is continuing to grow and is gathering the interest of delegates from Asia (20%), Africa (8%), and North and South America (7%). There is a significant increase in ERA-EDTA members making it nearly 7,000 members, cementing its international status.

"We want to set the highest possible standards," said Prof Raymond Vanholder, President of the ERA-EDTA (2011-2014). "We believe that a successful congress is not only about quantity, but mainly about quality of the presentations. We want to encourage all delegates, especially the young ones, to be ambitious and, thus, to promote nephrology as one of the leading subjects of internal medicine."

The scientific programme covered all fields within nephrology, including renal physiology, hypertension, chronic kidney disease (CKD), dialysis, and transplantation, all of which were presented in stimulating formats of symposia, presentations, and late-breaking clinical trials. There was particular emphasis on CKD where the Congress aims to unite all healthcare professionals and to increase public and medical awareness of this life-changing condition.

There were three pioneering plenary lectures to pique the attention of any individual with an interest in nephrology. Dr Bruce Molitos presented his latest research on '*pathophysiology of ischaemic acute kidney injury*' highlighting the predicament of this condition. Prof Hans Clevers focused mainly on his latest research on '*adult stem cells and regenerative medicine*' which pushes the boundaries in the field of nephrology, and finally the '*mammalian circadian timing system: the daily rhythms of genes, cells, and organs*' which was presented by Prof Ueli Schibler, who dived into the significance of this physiological process.

Another highlight of the Congress was the joint ERA-EDTA Lancet Symposium, which proved to be a successful collaboration, further cementing the Congress's reputation. Prof Vanholder commented: "The fact that The Lancet journals were interested in working with us is a clear indication of the growing importance of the European nephrology within the scientific community. For the ERA-EDTA, this media partnership is a supreme accolade."

"We want to encourage all delegates, especially the young ones, to be ambitious and, thus, to promote nephrology as one of the leading subjects of internal medicine."

Prof Raymond Vanholder, President of ERA-EDTA (2011-2014)

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LATE-BREAKING CLINICAL TRIALS

New transplantation guidelines released

THE INITIATIVE of the European Renal Best Practice (ERBP) group is to improve the outcomes of patients with kidney disease, which is why they have drafted new guidelines to benefit clinicians and healthcare providers alike.

Caring for kidney transplant recipients requires a multi-disciplinary outlook in the areas of nephrology, immunology, pharmacology, endocrinology, infectious disease, and cardiology. As a result, clinical guidelines were drawn up to deliver evidence-based medicine and therapy, improve patient outcomes, and expose gaps in knowledge to illuminate where additional research is needed.

The work group issued a total of 112 statements, 51 (45%) of which were graded as '1' – what the group recommends. 18 (16%) statements were graded as '2' – what is suggested, and 43 (38%) were ungraded.

If evidence is weak or non-existing, guidance still needs to be given to allow clinicians to make informed decisions in their daily practice; in the case of nephrology, evidence is often lacking.

The gap between oral health and CKD patients

PERIODONTITIS and other forms of poor dental indicators can lead to severe consequences in chronic kidney disease (CKD) patients.

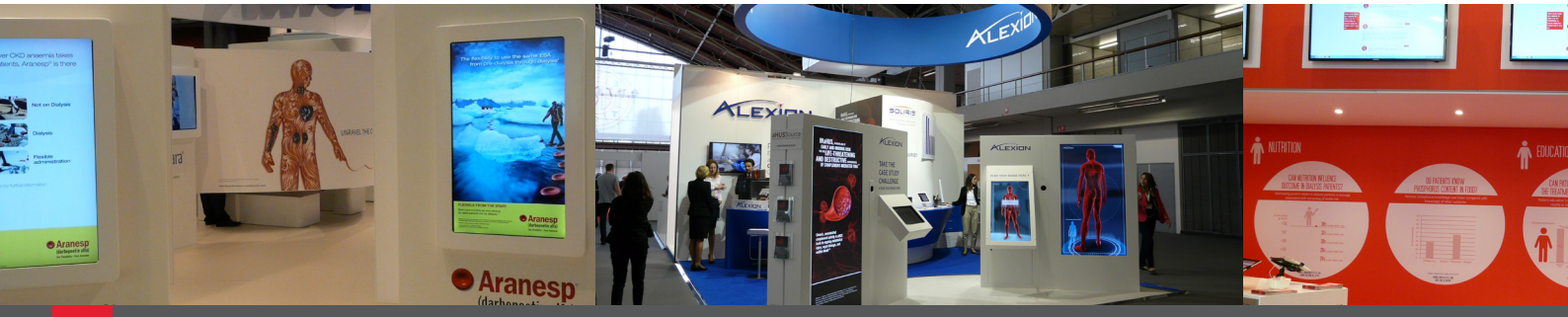
Dental health seems to be an overlooked concern and may even provide a worse overall prognosis; periodontitis is a severe gum infection that can further develop into systemic disease.

This association between dental health and CKD patients was established in past research; it was observed that uraemic patients have more dental issues than their healthy counterparts.

A new study involving more than 4,000 dialysis patients has revealed that poor dental health is an independent risk factor that leads to a detrimental prognosis.

Good dental health such as regular brushing of teeth, flossing, and periodically changing the toothbrush every 3 months was linked to a better outcome, but there was no significant influence based on the starting age of these beneficial dental practices.

This study has the potential to greatly improve dental health among CKD patients.



CCL2 inhibition may hinder CKD progression

INHIBITION of CCL2 may prevent the need for renal replacement therapies in Type 2 diabetic patients with albuminuria, leading to the development of chronic kidney disease (CKD).

In this group, CKD is accompanied by chronic, systemic inflammatory condition, followed by oxidative stress and development of renal failure.

A Phase II study involved the inhibition of the pro-inflammatory chemokine CCL2 (MCP-1) brought about through the specific binding of emapticap pegol (NOX-E36), potentially reducing CKD progression. The drug also has good safety profile and is well tolerated.

"The inhibition of the CCL2:CCR2 axis with emapticap pegol is well tolerated and reduces albumin to creatinine ratio and HbA1c in type 2 diabetics with albuminuria. The maintenance of the effects even after cessation of treatment suggests that CCL2 blockade interferes with the underlying pathophysiology. Emapticap pegol may hence be the first disease-modifying drug for this indication," said Prof Hermann Haller, Director, Department of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany.

Serum calcification fuels death risk

MORTALITY rates in patients with chronic kidney disease (CKD) increase with vascular calcification.

Highly prevalent in renal transplant recipients (RTR), vascular calcification is a strong indicator of all-cause mortality, and is brought about by the kidney's loss of ability to remove excess phosphate in CKD patients. The rising phosphate levels combine with increased serum calcium to form protein-mineral complexes called calciprotein particles (CPPs).

Monitoring the maturation time (T50) of CCPs allowed a recent blood test to provide an overall measure of calcification propensity. The hypothesis that serum T50 is linked to mortality and graft failure in stable RTR was thereby investigated.

Risk of all-cause mortality and graft failure was found to be heavily attributed to a raised serum calcification propensity, i.e. reduced serum T50. Furthermore, T50 boosted mortality prognostication among stable RTR. However, more research is needed to determine whether targeting of serum T50 improves long-term outcomes after kidney transplantation.

ERA-EDTA ANNUAL CONGRESS 2014
AMSTERDAM RAI EXHIBITION AND CONVENTION CENTRE
AMSTERDAM, THE NETHERLANDS
31ST MAY – 3RD JUNE 2014

Comorbidities cancelling out treatments in CKD patients

COMBINATIONS of associated anaemia and heart failure (HF) with chronic kidney disease (CKD) can be a very complicated situation whereby treating one condition can indirectly hinder the effect of another.

Anaemia associated with CKD often occurs when there is lack of production of sufficient erythropoietin from the kidneys. Erythropoiesis-stimulating compounds often take a relatively long time for a pharmacological effect to occur, while the faster route involves the transfusion of red blood cells (RBCs).

'Cardiorenal syndrome' perfectly describes the mutual interaction of impaired renal function and chronic HF. This signifies that when the function of one organ declines/improves, the other is subsequently affected, e.g. severe HF improves after compliance to dialysis therapy while glomerular filtration rate can increase after therapeutic interventions, resulting in cardiac recovery.

The combination of all three heath conditions can result in a complicated situation, e.g. myocardial hypoxia caused by the lack of RBCs which aggravates HF, while correction of the anaemia via a transfusion can put pressure on the heart.

This issue was investigated to clarify if the volume expansion, as a result from the blood transfusion, can cause damage to patients with CKD and HF and if there is any benefit in correcting the anaemia.

The results from this study reveal that transfusions may contribute to the hospitalisation of CKD patients, and medical provision for these high-risk patients should be taken into further consideration.

This retrospective study utilised the OptumInsight medical claims database to analyse 7,829 non-dialysis patients (aged 18-64 years old) with Stage 4 or 5 CKD for a 4-year duration. The outcome of interest is the hospital visitation based on HF diagnosis, enrolment termination, or the occurrence of death.

The findings of the study revealed that a significant number of patients were diagnosed with HF, with mainly older patients and those with comorbidities affected. The results from this study reveal that transfusions may contribute to the hospitalisation of CKD patients, and medical provision for these high-risk patients should be taken into further consideration.

Ray of hope for risky nephropathy therapy

Nephropathy associated with T2DM is almost exclusively linked with the high mortality of Type 2 diabetic patients.

BARDOXOLONE, an oral anti-oxidative inflammatory mediator similar to prostaglandin and a derivative of plant-based oleanolic acid, may have a future in the treatment of nephropathy despite being possibly responsible for the deaths of almost 30 patients in a high-profile study.

An effective nephroprotective agent in patients with Stage 4 chronic kidney disease (CKD) and Type 2 diabetes mellitus (T2DM), bardoxolone methyl reduces pro-inflammatory signalling by activating Nrf2 (nuclear 1 factor related factor 2), a cellular messenger compound that switches on anti-inflammatory signals and cytoprotective genes.

A common cause of kidney failure, nephropathy associated with T2DM is almost exclusively linked with the high mortality of Type 2 diabetic patients. Micro-inflammation and oxidative stress are important factors as interstitial renal fibrosis occurs.

Bardoxolone's inhibitory effect on progression to end-stage renal disease (ESRD) was examined in the 52-week Phase III BEACON trial, which exclusively tested severe kidney disease patients.

1,088 subjects were included in the bardoxolone group; despite a very encouraging effect, 43 subjects developed ESRD and 27 subjects died due to cardiovascular events. In comparison, 51 subjects developed ESRD and 19 cardiovascular fatalities were recorded in the 1,097-subject placebo group. The trial was consequently terminated, although the mechanisms behind the surprising increase in heart failure or mortality, which also led to an improved glomerular filtration rate, remained unexplained. The most common side-effects recorded were muscle spasms and hypomagnesaemia.

However, a platform of knowledge has been established using data from a separate ongoing analysis, which has explained the serious adverse events that caused the termination of the BEACON trial. Through modulation of the endothelin pathway, bardoxolone methyl could pharmacologically promote acute sodium and volume retention in patients with more advanced CKD and other recognised factors associated with heart failure at baseline.

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31ST MAY – 3RD JUNE 2014

Life is the greatest gift

A KIDNEY, donated selflessly, has given an entire family a new lease of life.

Ms Petra Laseur, aged 75, donated a kidney when she was 70-years-old. She experienced no serious side-effects, her wound healed well, and her health was not compromised in any way; any problems which she did experience were temporary and faded after a few days.

This enormous gesture meant that she allowed a young father to lead a 'normal life'. He was able to play with his children and go on holiday, something which he was unable to do for the previous 9 years because he was on dialysis.

Ms Laseur said: "You have two kidneys – one for yourself and one for giving it away as a present." Her hope is that people will feel encouraged to help those in need. In the Netherlands many people are altruistic kidney donors and Ms Laseur hopes this will be repeated throughout Europe.

Accessing all-cause mortality: battle of the serum markers

PREDICTIVE value of cystatin C compared with C-reactive protein (CrP) was investigated in a recent study to investigate all-cause mortality in over 25,000 patients.

A connection between the pathogenesis of a variety of chronic diseases (atherosclerosis, chronic kidney disease (CKD), diabetes, etc.) and chronic micro-inflammatory processes was established in relation to mortality. The serum markers for latent inflammation are CrP and cystatin C.

Cystatin C, an endogenous protein, along with creatinine can be used to determine the glomerular filtration rate (GFR) i.e. the flow rate of filtered fluid through the kidney. Both can produce a better estimation of GFR (GFRCrea and GFRCys, respectively). In the evaluation of all-cause mortality, GFRCys was better than GFRCrea, but in the case of complications associated with CKD, GFRCrea was the better option.

The study revealed that serum CrP exhibits a stronger association with premature deaths and had outperformed cystatin C in predicting all-cause mortality rates.

Iron-clad solution to anaemia control

A TWO-IN-ONE compound, ferric citrate, has been found to both treat iron deficiency anaemia and reduce serum phosphate in patients with non-dialysis-dependent chronic kidney disease (CKD).

Common in CKD patients, anaemia is caused by the inability of the kidneys to continue to synthesise sufficient erythropoietin. Frequently left untreated, anaemia is aggravated by iron deficiency in more than 60% of CKD patients.

Impairment of renal function in CKD patients causes hyperphosphataemia, when progressive serum phosphate levels rise above 4.0 mg/dl. This triggers loss of kidney function, cardiovascular events, and mortality.

Ferric citrate coordination complex was found to safely and effectively treat non-dialysis-dependent CKD in a randomised clinical trial. The compound replenished iron stores, increased haemoglobin without the need for intravenous iron or erythropoiesis stimulating agents (ESAs), and lowered serum phosphate and urinary phosphate excretion.

A drop in costs and pill burden may therefore be just around the corner.

Urinary proteome analysis for use in early CKD detection

TAKING the lead in the diagnosis of chronic kidney disease (CKD) is urinary proteome analysis, competing against the standard analysis of the serum creatinine concentrations.

Statistically, 10% of the general population may suffer from CKD and be unaware of their condition, so early detection is paramount.

The end product of muscle metabolism, creatinine, is easily removed from the blood via the kidneys in healthy individuals. If there is an elevated increase in serum levels, this indicates that there is approximately 50% damage to the renal system, and as such, it is an unacceptable indicator for early detection.

Another indicator of poor kidney function is elevated urinary protein. The urinary proteome test analysed the total number of peptides and identifies specific biomarkers, making it a more sensitive test. In a study involving 1,990 subjects, including 552 participants with follow-up data, a marker - CKD273 - was successfully used in the detection and prediction of CKD.

Protein detection may be the future diagnostic test for early detection of CKD.

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31ST MAY – 3RD JUNE 2014

Is surgery or medicine better for hyperparathyroidism?

MEDICINE has seemingly taken the lead for the treatment of secondary hyperparathyroidism (sHPT) according to a recent study.

Parathyroidectomy - the surgical removal of at least one parathyroid gland - and therapy with active vitamin D (VDRA) have, for many years, been the only treatment options for sHPT. However, Cinacalcet, an allosteric modulator of the calcium-sensing receptor (CaSR), has emerged as a genuinely effective alternative therapy.

sHPT is a common complication of chronic kidney disease leading to increased risk for cardiovascular (CV) and all-cause mortality. It does not incur devastating clinical manifestations, although it can result in severe CV complications.

Over 90% of dialysis patients are believed to develop sHPT over the course of their severe renal insufficiency, although to various extents. A raised serum level of parathyroid hormone (PTH) is typical of the condition, which can result in vascular complications and an increased risk of CV events, thus, creating a higher risk of mortality.

With an inhibitory effect on the production of PTH, VDRA therapy has been the most commonly used method for treating sHPT, while calcitriol or alfacalcidol therapy cause PTH levels to return to normal. However, vascular calcification can be triggered through this kind of therapy, as it causes a notable rise in serum calcium and serum phosphorus levels.

Step forward Cinacalcet: belonging to the group of PTH antagonists, the treatment enhances the sensitivity of the calcium receptors in the parathyroid glands, successfully inhibiting excessive PTH production.

6,251 chronic haemodialysis patients took part in the 3-year COSMOS study, which assessed the effects of parathyroidectomy and Cinacalcet therapy on subject survival. The latter was found to be associated with superior survival, boosted further with additions of VDRAs.

However, randomised controlled trials are still required to answer the burning question; which treatment option has the better outcome: surgical or medical?





Canagliflozin treatment for Type 2 diabetics can lower eGFR

CHRONIC impairment of renal function is significantly reduced in Type 2 diabetics, which is attributed to a novel antidiabetic drug, canagliflozin.

Belonging to the gliflozin family, canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor, and is the first of its kind to be approved in the USA and EU in 2013, and later in Switzerland in 2014.

Gliflozin selectively inhibits the SGLT2 in the proximal renal tubule, which lowers the re-absorption of glucose in the kidney. Blocking this transporter causes blood glucose to be eliminated through the urine. Favourable effects of this drug include the reduction of body weight, glycated haemoglobin (HbA1c), blood pressure, and notably, in estimated glomerular filtration rate (eGFR).

Treatment with this therapy is not recommended for those who do not produce any urine, which includes patients with terminal chronic kidney disease and those undergoing dialysis.

The evaluation of canagliflozin in diabetics was investigated in six randomised, double-blind, placebo-controlled trials, which had included 4,158 Type 2 diabetics for a duration of 18 or 26 weeks. Another analysis (8 randomised, double-blind placebo and active-control trials) evaluating the drug's safety profile involved 9,439 participants and lasted for 26 or 52 weeks.

This subset evaluated the safety profile in patients who experienced baseline eGFR from ≥60 mL/min/1.73 m^2, which fell to <60 but not <45. The subsets had 262 and 664 patients, respectively, in the safety analyses.

The mean eGFR at baseline was ≥60 mL/min/1.73 m^2, and after treatment with canagliflozin at 100 and 300 mg this was reduced to 54.6 and 54.8 mL/min/1.73 m^2, respectively; for placebo it was 55.9 mL/min/1.73 m^2.

Urge to frequently urinate, urinary tract infections, and vaginal mycosis are the potential side-effects of the drug.

"The transient decrease in eGFR that was observed in Phase III studies [of canagliflozin] was further investigated in the current study," said Dr Ronan Roussel, Hôpital Bichat, Paris, France.




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STANLEY SHALDON AWARD FOR YOUNG INVESTIGATORS

Dr Rafael Kramann, Germany

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The pro-PKD score, a new algorithm to predict renal outcome in autosomal dominant polycystic kidney disease (ADPKD).

- **Vincente Torres,** USA

Tolvaptan-treatment of ADPKD confers persistent eGFR improvement: results from the TEMPO 4:4 Extension Trial.

- **Biswanath Basu,** India

Efficacy and safety of mycophenolate-mofetil vs. levamisole in children with idiopathic nephrotic syndrome: results of a randomized chemical trial.

- **Anna Giovanna Sciancalepore,** Italy

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- **Tetsuhiro Tanaka,** Japan

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Survival of calciphylaxis in end-stage renal disease patients from the United States Renal Data System.

- **Shruti Dave,** India

Mesenchymal stem cells induced in vitro generation of regulatory T-cells: a cell-based therapy to promote transplantation tolerance.

- **Josef Coresh,** USA

Decline in estimated glomerular filtration rate and subsequent risk of mortality: a meta-analysis of 35 cohorts in the CKD Prognosis Consortium.

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DIAGNOSTIC CHALLENGES IN THROMBOTIC MICROANGIOPATHIES

Summary of Presentations from the Alexion-Sponsored Symposium, held at the 51st ERA–EDTA Congress, Amsterdam, the Netherlands, on 1st June 2014

Chairperson

Dirk Kuypers[1]

Speakers

Dirk Kuypers,[1] Josep Campistol,[2] Christophe Legendre[3]

1. University of Leuven, Leuven, Belgium
2. University of Barcelona, Barcelona, Spain
3. Necker-Enfants Malades Hospital and Université Paris Descartes, Paris, France

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MEETING SUMMARY

The Alexion Satellite Symposium provided an introduction to thrombotic microangiopathies (TMA) by Prof Dirk Kuypers, who described atypical haemolytic uraemic syndrome (aHUS) as a rare but severe disease that causes TMA and can result in organ failure. Prof Josep Campistol presented two patient cases to illustrate the need to make a differential diagnosis between aHUS, thrombotic thrombocytopaenic purpura (TTP), and Shiga toxin-related-HUS (STEC-HUS). Prof Christophe Legendre then described aHUS clinical management, introduced eculizumab as the only approved treatment for aHUS, and provided an overview of the efficacy and safety data from recent clinical trials.

An Introduction to TMAs

Professor Dirk Kuypers

TMA is mostly caused by three separate conditions, summarised in Figure 1 and described here:

1. The disease can be directly triggered by uncontrolled complement activation[1,2] as with aHUS. There are currently six important CF mutations described that are responsible for dysregulated complement activation in patients with aHUS.[3,4] Although recent reports have identified the genetic underlying condition for aHUS in around 60–68% of patients,[5,6] the remaining patients do not currently have any identifiable genetic mutation and are a target for future research. A low percentage of patients can develop antibodies against factor H, which also results in uncontrolled complement activation.

2. TMA can also be associated with reduced activity of a disintegrin and metalloproteinase with thrombospondin Type 1 motif, 13, (ADAMTS13). ADAMTS13 is a cleavage molecule that acts upon ultra-large von Willebrand factors (vWF) and is related to the development of TTP.

3. The third major cause of TMA is Shiga toxin-related-HUS, which is caused following a Shiga toxin producing *Escherichia coli* infection (STEC-HUS).[7] Of all haemolytic uraemic syndromes, 90% are STEC-HUS and 10% are aHUS.

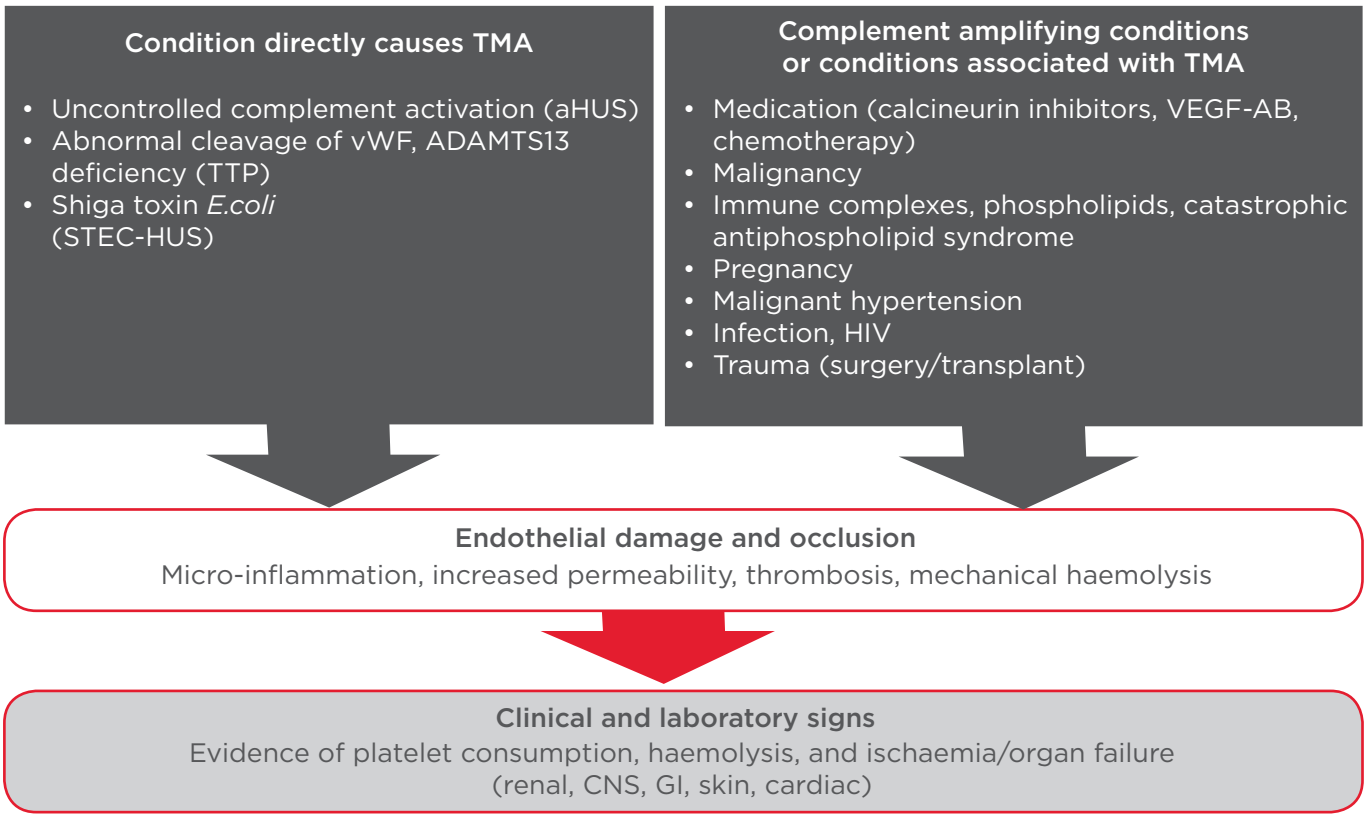

Figure 1: Pathogenesis of TMA.[1–5]

ADAMTS13: a disintegrin and metalloproteinase with thrombospondin Type 1 motif 13; aHUS: atypical haemolytic uraemic syndrome; STEC-HUS: Shiga toxin-producing E. coli haemolytic uraemic syndrome; TMA: thrombotic microangiopathy; TTP: thrombocytopaenic purpura; vWF: von Willebrand factor.

From Dirk Kuypers, presentation at the Alexion Satellite Symposium.

Additional conditions that can be associated with the development of TMA - but where TMA is not an integral part of the disease - are TMA due to calcineurin inhibitors, vascular endothelial growth factor antibodies, and chemotherapy along with malignancies, catastrophic antiphospholipid syndrome, pregnancy, malignant hypertension, infection, HIV, and trauma such as surgery or transplants.[8] As these conditions can amplify complement and endothelial damage; they may in addition precipitate TMA in patients with a predisposition to aHUS.

Although the causes of TMA can differ, there are similarities in regards to clinical symptoms.[9] The Shiga toxins produced by STEC result in damage to the endothelium, thereby activating complement and platelets.[10] Genetic mutations in complement regulatory proteins lead to chronic uncontrolled complement activation, which damages the endothelium and activates platelets,[11] whilst TTP from defective activity of ADAMTS13 allows the formation of ultra-large vWF multimers binding platelets and formation of blood clots. Across all three types of TMA the endothelial damage and occlusion with micro-inflammation and increased permeability cause thrombosis in potentially any organ, which is shown through evidence of platelet consumption, haemolysis, ischaemia, and eventually target organ failure.[12]

Although it is established that aHUS has a significant effect on renal function and development of end-stage renal disease (ESRD), aHUS is a systemic disease that can involve many systems and organs[3,13–16] including the cardiovascular,[11] gastrointestinal,[17] skin,[18] and central nervous system (CNS).[19] The outcome of aHUS is poor: 56% of adult patients either die or have ESRD within the first year after diagnosis, despite plasma exchange (PE) or plasma infusion (PI).[6] Regarding patients with aHUS who have had renal transplants,[20] TMA generally presents again rapidly after transplantation, associated with a mortality rate of 7%, and 50% graft failure within 5 years post transplant.[14]

In summary, TMA is a serious rapidly progressing condition that can lead to severe, irreversible organ damage with considerable morbidity and mortality. TMA can be caused by several conditions that should be managed differently for best patient outcomes. Differential diagnosis of TMA can be very difficult as symptoms are overlapping between conditions, thus it is important to rapidly identify cause of TMA and initiate appropriate treatment.

Clinical Cases: Differential Diagnosis of TMA

Professor Josep Campistol

Prof Josep Campistol presented the differential diagnosis of two clinical cases in order to illustrate the interesting but difficult aspects of identifying the cause of TMA. The first case was a 31-year-old female with no relevant medical background who consulted a community hospital for severe frontal headache that had lasted 1 week. She was admitted to the emergency room and found to be severely hypertensive, approximately 220/120 mmHg. The patient had severe and acute renal failure (ARF), with a serum creatinine of 3.9 mg/dL; severe anaemia, 9.5 g/L haemoglobin; haematocrit around 27%; increased lactate dehydrogenase (LDH: 1200 UI/ml); and also low platelets (~65x10^9/L). The patient was initially diagnosed with probable TMA and then transferred to the university hospital.

At the university hospital the hypertension had raised to 230/120 mmHg, with a Grade 3 hypertensive retinopathy. She was oliguric at that time, with a serum creatinine around 4 mg/dL and proteinuria on the dipstick. The haemoglobin and haematocrit levels were low, along with increased LDH, platelets around 60x10^9/L and importantly, negative Coombs with schistocytes in the peripheral blood. Transaminases were normal at that time, with normal aspartate aminotransferase (AST) test and alanine aminotransferase (ALT) test, so the finding was typical of a Grade 3 hypertensive retinopathy with some small haemorrhages. As the young female had severe ARF, haemolytic anaemia, and thrombocytopaenia, along with severe frontal headache and retinopathy, this presented the typical triad of TMA.

Rapid differential diagnosis of TMA needs to be performed as the therapeutic options differ depending on the cause.[21] For the patient case described, the three important differential diagnoses were TTP, aHUS, and a malignant hypertension-associated TMA. ADAMTS13 would be the initial test advised for the differential diagnosis of the patient, especially to define between TTP and aHUS that can be problematic in adult patients with TMA. As the ADAMTS13 test is sometimes not rapidly available, it has been suggested that a serum creatinine level and platelet count at presentation might help distinguish between aHUS and TTP. In general, TTP patients demonstrate serum creatinine lower than 2.2 mg/dL, a platelet count lower than 30x10^9/L, and antinuclear antibodies <2.26 mg/L.[22,23]

A renal biopsy was performed, and is generally recommended at a later stage in order to confirm the disease and define the prognosis, reversibility, and severity of the disease. However, there is often a high risk of performing the procedure in thrombocytopaenic patients, and the usefulness of the procedure is debatable at the diagnosis stage. The biopsy demonstrated typical TMA with a severe glomerular thrombin, severe endothelial proliferation, and severe kidney involvement with acute tubular necrosis (ATN) and vascular involvement. Inflammation, hypoxia, and ischaemia with the development of ATN were also apparent. Regarding the diagnostic merit of organ involvement, aHUS often affects kidneys (also 10-15% of TTP patients) but can involve other organs. So whilst there is generally an organ privilege, differential diagnosis of various forms of TMA cannot be based solely upon organ involvement.

The patient's ADAMTS13 test showed normal activity of 55%. As an ADAMTS13 activity value of <5% indicates TTP combined with the patient's creatinine value of 3.9 mg/dL and platelets >30x10^9/L, it was determined that the patient was at high risk of having aHUS. Whilst genetic analysis can be useful, treatment has to be initiated before the results are determined due to the time required for the analysis. The C3, C4, and factor H complement levels were shown to be normal, along with the factor H related proteins and the remaining genetic factors. A lower activity of factor I (60%) was identified and a mutation was later identified in factor I.

The patient was initially managed with PE over 6 months and showed a transient recovery of renal function, demonstrated by a serum creatinine concentration of 2.5 mg/dL. 2 months after cessation of dialysis the patient developed another episode

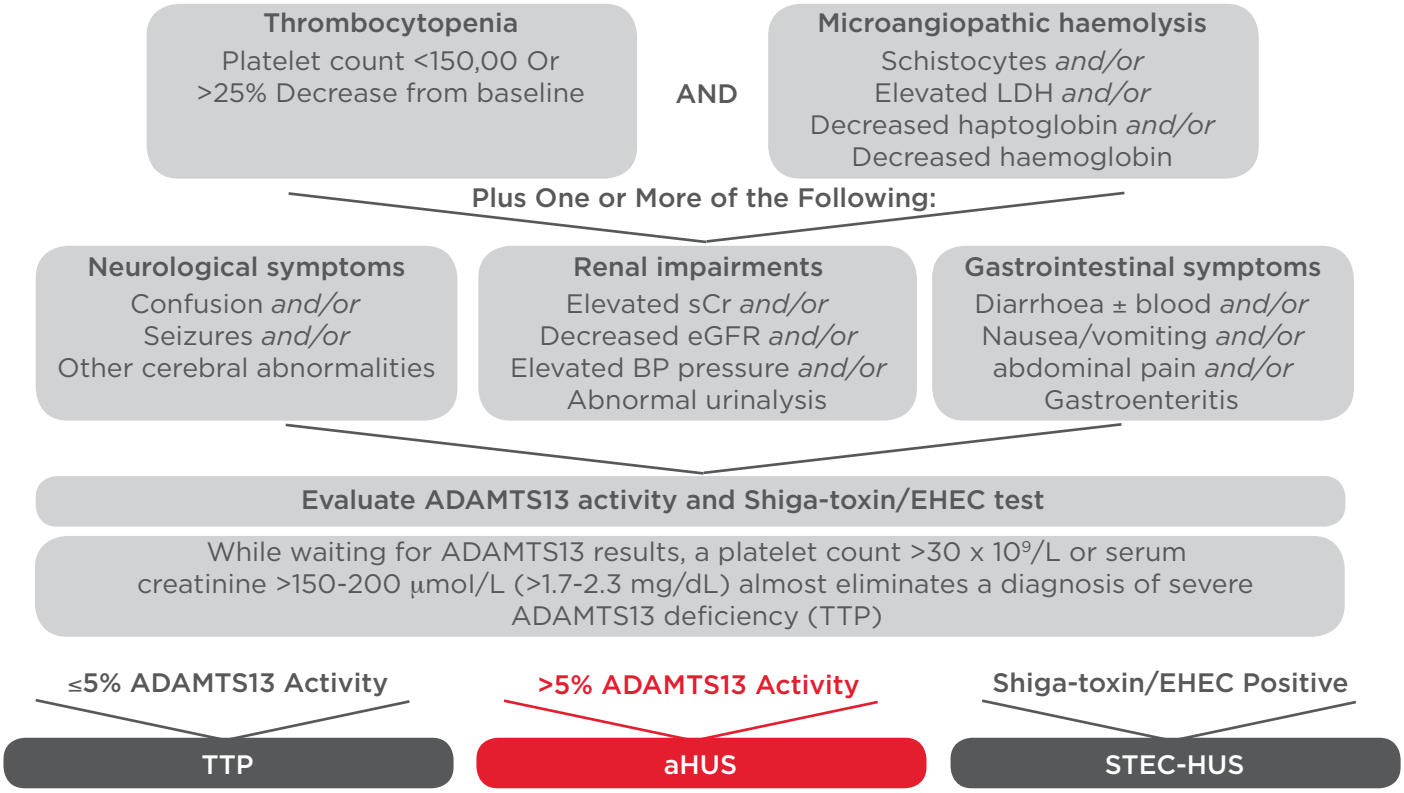

Figure 2: Differential diagnosis for TMAs: aHUS, TTP, and STEC-HUS.[2,17,34]
ADAMTS13: a disintegrin and metalloproteinase with thrombospondin Type 1 motif 13; aHUS: atypical haemolytic uraemic syndrome; BP: blood pressure; LDH: lactate dehydrogenase; sCR: serum creatinine; eGFR: estimated glomerular filtration rate; STEC-HUS: Shiga toxin-producing E. coli haemolytic uraemic syndrome; TTP: thrombocytopaenic purpura; EHEC: enterohaemorrhagic *E. coli*.
From Josep Campistol presentation at the Alexion Satellite Symposium.

of TMA with ARF, with a serum creatinine of 6 mg/dL, haemoglobin of 8 g/L, and platelets at 65x109/L. At that point the patient was started on eculizumab. 1 year after eculizumab initiation the patient was in good condition: renal function and haemoglobin were within normal values of 1.2 and 12.5 g/L, respectively, there was very mild proteinuria of 250 mg/24 hour, and a fairly normal platelet count of 175x10^9/L. Eculizumab was effective in reversing the second TMA with ARF as well as preventing further TMA in a patient with factor I mutation.

The second clinical case was a common but difficult situation; a 41-year-old female with post-partum TMA and no prior familial or personal relevant medical records. 4 days after her first uneventful birth in June 2012, the patient was admitted to the emergency room for asthenia, generalised oedema, and hypertension. ARF was indicated by high serum creatinine of 3.3 mg/dL that had been normal before delivery. Severe anaemia with haemoglobin lower than 5 g/L was also present, along with elevated LDH of around 3,000 UI/mL and severe thrombocytopenia as indicated by a platelet count of 35x10^9/L. The Coombs test was negative. There was presence of schistocytes in the peripheral blood and also normal AST/ALT, so the patient was initially diagnosed with TMA. A recent study has shown that in pregnant women who develop a TMA during pregnancy most will be affected with severe ADAMTS13 deficiency (TTP), whilst aHUS is the most prevalent form of TMA that presents after birth.[24]

After transfer to the university hospital the patient was still hypertensive (175/100 mmHg), with a serum creatinine of 6 mg/dL that indicated quite severe ARF, anaemia, and severe increase of LDH. Platelet count at presentation was >30x10^9/L and serum creatinine was above 2.2 mg/dL thus strongly indicating low risk of TTP. Results were negative for Shiga toxin and demonstrated a normal ADAMTS13 activity of 45%. A diagnosis of postpartum aHUS was given and the patient was started on eculizumab 48 hours after admission.

1 year later the patient was in good condition with a normal health status; normal blood function, haemoglobin, and platelets with negative proteinuria, which demonstrated the effectiveness of early initiation of eculizumab in a female patient affected with aHUS.

In summary, the algorithm of the differential diagnosis of TMAs, as shown in Figure 2, suggest that if there is thrombocytopaenia and microangiopathic anaemia, and evidence of organ damage like renal impairment, neurological symptoms, and/or gastrointestinal symptoms, the Shiga toxin test should be used to exclude the presence of STEC-HUS, whilst the ADAMTS13 test can differentiate between TTP (≤5% activity) and aHUS (>5% activity). If it takes a while for the results of the ADAMTS13 activity, consider that very severe thrombocytopaenia along with moderate renal failure can be indicative of TTP, whilst severe renal failure with platelets above $30x10^9$/L would indicate aHUS.

Management of aHUS in 2014

Professor Christophe Legendre

Previous treatment management guidelines for aHUS published in 2009 recommended PE or PI at presentation and during the first month of aHUS, for both children and adults.[25,26] After 5 days of daily PE, aHUS was considered resistant if the platelet counts were still below $150x10^9$,[3] or if serum creatinine had not decreased by >25% or the haemolysis was persisting. A French cohort study[6] reported a mortality rate of 8% in children (n=89) and 2% in adults (n=125) during the first year after aHUS diagnosis, of whom 39% and 80% received PE or PI at the first episode, respectively. However, incidence of end-stage renal failure or death at 5 years was 36% in children and 64% for adults, clearly indicating that the current treatment options were not very effective.

In 2011 eculizumab was the first approved treatment for aHUS in paediatric and adult patients.[27] Eculizumab is a monoclonal humanised anti-C5 antibody that selectively targets the terminal complement activation, C5, blocking the cleavage to C5a and C5b but leaving the proximal functions of the complement active[27-29] so that there is still weak anaphylatoxin action,[30] immune complex clearance, and microbial opsonisation.[29,31]

The eculizumab clinical development programme is extensive for an orphan disease, with 100 patients enrolled in prospective clinical trials.[32-39] Two prospective 26-week clinical trials enrolled adult and adolescent patients ≥12 years of age (study C08-003 enrolled 20 patients, study C08-002 enrolled 17 patients[32]).[36,37] Two additional prospective trials were in children (study C10-003, 22 patients)[33] and adults (study C10-004, 41 patients),[34] whilst study C09-001 generated retrospective data from 15 paediatric patients <12 years of age.[35] Patients from all the trials described could enlist on to the long-term follow-up study C11-003 for at least 5 years,[38] or will be monitored through the aHUS registry that is running at least until 2023.[36]

According to the inclusion criteria for the two pivotal prospective studies (C08-003 and C08-002) patients needed to receive prior PE/PI. Patients had either a long duration of aHUS and chronic kidney disease (CKD) as in study C08-003, or aHUS with progressing TMA as in study C08-002.[32,34] The third adult (≥18 years) prospective trial (C10-004) enrolled patients with a broad disease presentation, severe renal failure with no specification for PE/PI prior to enrolment. None of the three adult prospective trials required genetic mutations, polymorphism or presence of autoantibodies for inclusion, but the tests were performed during the trial by one central laboratory.

Eculizumab dosage regimen were 900 mg per week during the first month and then 1,200 mg fortnightly, whereas eculizumab dosages for patients <18 years of age are based upon body weight.[35] Administration is through an intravenous (IV) infusion over 35 minutes, with prophylaxis against meningococcal infection through prior vaccination and antibiotic treatment for 2 weeks after the vaccination if given alongside eculizumab. Dose adjustment every 12 days is permitted, with TMA complications seen in five patients (n=18) following a missed dose (four of whom were reinitiated with eculizumab).[35]

After 26 weeks of eculizumab treatment across the prospective C08 trials in adult and adolescent patients, there was overall normalisation of platelets, no need for new PE in any patient, and haematological normalisation in ≥88% of the population. Additionally, patients within the C08-003 trial who had a longer duration of aHUS along with CKD and had previously been managed with PE/PI still demonstrated improved estimated

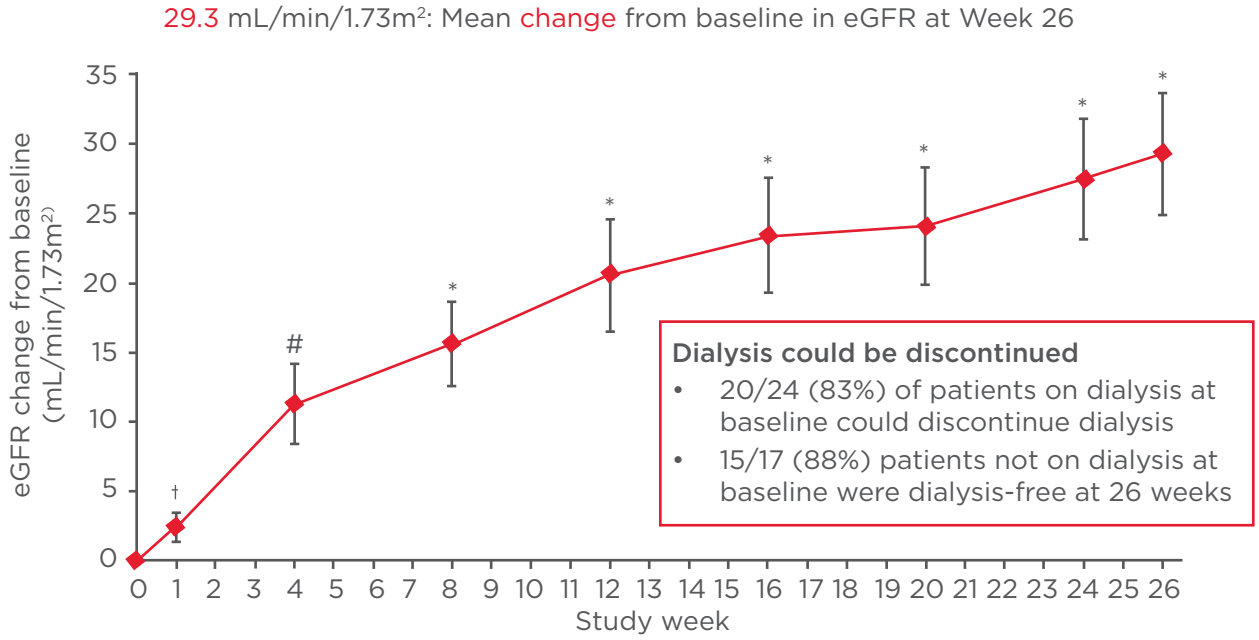

Figure 3: eGFR change from baseline (mL/min/1.73 m²) in patients on sustained eculizumab treatment.[36]
†p<0.05, #p<0.001, *p<0.0001.
eGFR: estimated glomerular filtration rate.
From Christophe Legendre, presentation at the Alexion Satellite Symposium.

glomerular filtration rate (eGFR), increasing by 6.1 and 7.2 mL/min/1.73 m² from baseline after 26 weeks and 2 years (median treatment duration 114 weeks), respectively.[32] Patients who had progressive TMA in the C08-002 trial also demonstrated improvements over 2 years, with an increased eGFR from baseline of 35.2 mL/min/1.73 m² after 2 years.[32] Patients treated within 1 month of clinical manifestation of TMA with eculizumab saw greater improvement in renal function compared with those treated between 1–4 months after TMA manifestation, whilst safety data demonstrated that the number of adverse events remained steady or declined with longer duration of eculizumab, along with no infection-related serious AEs. There was one death at 1.9 years of treatment, which was considered to be unrelated to eculizumab treatment.[32]

The most recent prospective study of a broad adult aHUS population (C10-004) also led to improvements in eGFR, including 83% (20/24) of patients on dialysis at baseline who discontinued dialysis during the 26 week period of eculizumab treatment (Figure 3).[34] Eculizumab was again well tolerated with mostly mild-to-moderate AEs, apart from two patients who had meningococcal infections, both of whom recovered (one patient continued in the trial without interrupting eculizumab). The primary and secondary endpoints were met by most patients, including 73% (30/41) of patients who had a complete TMA response (platelet count >150x10⁹/L and LDH within the upper limit of normal, together with preserved renal function demonstrated by <25% increase from baseline in serum creatinine) after a median of 56 days, whilst 88% (36/41) of patients demonstrated haematological normalisation (platelet count and LDH normalisation) after a median of 55 days and 98% (40/41) of patients showed platelet count normalisation after 8 days (median).[34] As well as the proven efficacy of eculizumab for restoring renal function and preventing further TMA,[32-40] numerous case reports have shown that eculizumab also seems to play a role in the rescue of CNS involvement (Table 1), as patients who reported seizures among other symptoms were reported to show full recovery after 1–56 days.[41-47]

Recommended management for the first episode of aHUS in paediatric patients is to use eculizumab as a first-line treatment in order to avoid PE and central catheterisation and maximise outcomes.[35] As differential diagnosis of aHUS may be more complex in adults presenting for the first time PE is recommended whilst TTP is ruled out. It is recommended to switch to eculizumab if there is plasma resistance (either no constant trend

Table 1: Results of eculizumab use in patients with aHUS and central nervous system involvement.[43-49]

Author	Age (years)	Neurological manifestations	MRI	Time to eculizumab initiation (days)	Outcome
Pu 2013	85	Seizures, mental disturbances	ND	18	Improvement over 2 weeks Full recovery
Salem 2012	66	Seizures, mental disturbances, coma	Focal Lesions	3	Awoke and verbal after 8 weeks Nearly complete recovery
Beye 2013	64	Status epilepticus, focal defects, nystagmus, confusion	Normal CTS	9	Improvement within 24 hours Full recovery
Ohanian 2011	50	Seizures, unresponsiveness	Right parietal infarction	3	Improvement after 1 week Full recovery
Chaudhary 2014	20	Seizures, lethargy	ND	42	Slow initial improvement (sub-therapeutic doses) Full recovery after increase of dose
Gulleroglu 2013	11	Seizures, visual loss, confusion	Bilateral occipital and posterior parietal hyperdensities/ oedema	<1	Improvement after 4 days Full recovery after 1 month
Gulleroglu 2013	6	Seizures, visual loss	Bilateral occipital and posterior parietal hyperdensities	<1	Normal vision within 24 hours Full recovery after 5 weeks
Hu 2013	1.7	Seizures, haemiparesis, lethargy, unresponsiveness	Subtle bilateral anomalies	<1	Improvement over 3 weeks Full recovery with residual weakness of right thumb/index

ND: no data; CTS: computerised tomography scan.
From Christophe Legendre, presentation at the Alexion Satellite Symposium.

upwards of platelet count, no constant trend downwards of LDH, or no decrease of serum creatinine by ≥25% after five daily PE) or if there is TMA during tapering of treatment. When the diagnosis of aHUS is unequivocal, such as in patients with familial history, TMA in a previously diagnosed patient, eculizumab can be used as first-line within 24 hours or as soon as possible after diagnosis. It is not necessary to confirm and define a complement anomaly before starting eculizumab as it can be administered for any type of complement mutation including those without any yet identified mutations. However, it is still advised to obtain the anti-factor H antibody results rapidly and use genetic screening to inform further decisions.[35]

In conclusion, eculizumab is licensed as first-line therapy for aHUS and allows normalisation of haematological outcomes, renal function recovery, and improvement of extra-renal TMA such as that described in Table 1.[18,32,34,35,42,44,46-49] Earlier treatment has also been shown to improve renal

outcomes.[32,50,51] Eculizumab is well tolerated, but prevention of meningococcal infection is mandatory and long-term follow up of eculizumab treatment has yet to be reported.[48] Withdrawal could be considered on a case by case basis, however currently we do not have data to inform our decision, thus treatment duration is still a matter of discussion.

REFERENCES

1. Schmidtko J et al. Treatment of atypical hemolytic uremic syndrome and thrombotic microangiopathies: a focus on eculizumab. Am J Kidney Dis. 2013;61:289–99.

2. Campistol JM et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. Nefrologia. 2013;33:27–45.

3. Noris M et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol. 2010;5(10):1844–59.

4. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med. 2009;361:1676–87.

5. Maga TK et al. Mutations in alternative pathway complement proteins in American patients with atypical hemolytic uremic syndrome. Hum Mutat. 2010;31:E1445–60.

6. Frémeaux-Bacchi V et al. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. Clin J Am Soc Nephrol. 2013;8:554–62.

7. Laurence J. Atypical hemolytic uremic syndrome (aHUS): making the diagnosis. Clin Adv Hematol Oncol. 2012;10(Suppl 17):1–12.

8. Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011;6:60.

9. Karpman D. [Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. Current perspectives on EHEC, complement mutations and ADAMTS13]. Läkartidningen. 2008;105:1096–101.

10. Desch K, Motto D. Is there a shared pathophysiology for thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome? J Am Soc Nephrol. 2007;18:2457–60.

11. Noris M et al. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. Nat Rev Nephrol. 2012;8: 622–33.

12. Scully M et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012;158:323–35.

13. Sellier-Leclerc AL et al. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol. 2007;18:2392–400.

14. Caprioli J et al. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. Blood. 2006;108:1267–79.

15. Sallée M et al. Myocardial infarction is a complication of factor H-associated atypical HUS. Nephrol Dial Transplant. 2010;25:2028–32.

16. Larakeb A et al. Ocular involvement in hemolytic uremic syndrome due to factor H deficiency --are there therapeutic consequences? Pediatr Nephrol. 2007;22:1967–70.

17. Zuber J et al. New insights into postrenal transplant hemolytic uremic syndrome. Nat Rev Nephrol. 2011;7:23–35.

18. Ardissino G et al. Skin involvement in atypical hemolytic uremic syndrome. Am J Kidney Dis. 2014;63:652–5.

19. Neuhaus TJ et al. Heterogeneity of atypical haemolytic uraemic syndromes. Arch Dis Child. 1997;76:518-21.

20. Le Quintrec M et al. Complement genes strongly predict recurrence and graft outcome in adult renal transplant recipients with atypical hemolytic and uremic syndrome. Am J Transpl. 2013;13:663–75.

21. Keir L, Coward RJ. Advances in our understanding of the pathogenesis of glomerular thrombotic microangiopathy. Pediatr Nephrol. 2011;26:523–33.

22. Coppo P et al. Severe ADAMTS13 deficiency in adult idiopathic thrombotic microangiopathies defines a subset of patients characterized by various autoimmune manifestations, lower platelet count, and mild renal involvement. Medicine (Baltimore). 2004;83:233–44.

23. Coppo P et al. Predictive features of severe acquired ADAMTS13 deficiency in idiopathic thrombotic microangiopathies: the French TMA reference center experience. PLoS One. 2010;5:e10208.

24. Fakhouri F et al. Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. J Am Soc Nephrol. 2010;21:859–67.

25. Ariceta G et al. Guideline for the investigation and initial therapy of diarrhea-negative hemolytic uremic syndrome. Pediatr Nephrol. 2009;24: 687–96.

26. Taylor CM et al. Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. Br J Haematol. 2010;148:37–47.

27. Alexion Pharmaceuticals, Inc. Soliris® (eculizumab): Prescribing information. 2011. Available: http://soliris.net/sites/default/files/assets/soliris_pi.pdf.

28. Alexion Pharmaceuticals, Inc. Soliris® (eculizumab): Summary of product characteristics. 2011. Available: https://www.medicines.org.uk/emc/history/19966/SPC/Soliris#08/09/2011. Accessed: June 2014.

29. Rother RP et al. Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. Nature Biotechnol. 2007;25:1256–64.

30. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. Clin Microbiol Rev. 1991;4:359–95.

31. Walport MJ. Complement. First of two parts. N Engl J Med. 2001;344:1058–66.

32. Legendre CM et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med. 2013;368:2169–81.

33. Greenbaum L et al. 2013; Abstract 5579. Presented at: ASN, 5–10 November 2013, Atlanta, USA.

34. Fakhouri F et al. 2013; Abstract 5593. Presented at: ASN, 5–10 November 2013, Atlanta, USA.

35. Alexion Europe SAS. Soliris® (eculizumab): Summary of product characteristics. 2014.

36. Licht C et al. Eculizumab (ECU) safety and efficacy in atypical hemolytic uremic syndrome (aHUS) patients with long disease duration and chronic kidney disease (CKD): 2-year results. ASH 8–11 December 2012, Atlanta, USA. Poster Presentation 985.

37. Greenbaum L et al. Eculizumab (ECU) in atypical hemolytic uremic syndrome (aHUS) patients with progressing thrombotic microangiopathy (TMA): 2-year data. ASH, 8–11 December 2012, Atlanta, USA. Poster Presentation 2084.

38. Alexion Pharmaceuticals. aHUS observational long-term follow-up (LTFU). NCT01522170. Available: clinicaltrials.gov/show/NCT01522170. Accessed: June 2014.

39. Licht C et al. 2013; Abstract Presentation 5184. ASN, 5-10 November 2013, Atlanta, USA.

40. Fakhouri F et al. Insights from the use in clinical practice of eculizumab in adult patients with atypical hemolytic uremic syndrome affecting the native kidneys: an analysis of 19 cases. Am J Kidney Dis. 2014;63:40–8.

41. Pu JJ, Sido A. Successful discontinuation of eculizumab therapy in a patient with aHUS. Ann Hematol. 2013. [Epub ahead of print].

42. Salem G et al. Profound neurological injury in a patient with atypical hemolytic uremic syndrome. Ann Hematol. 2013;92:557–8.

43. Beye F et al. [Eculizumab: effectiveness of a shortened dosing schedule in the treatment of atypical haemolytic uremic syndrome of unknown origin]. Therapie. 2013;68:119–22.

44. Ohanian M et al. Eculizumab safely reverses neurologic impairment and eliminates need for dialysis in severe atypical hemolytic uremic syndrome. Clin Pharmacol. 2011;3:5–12.

45. Chaudhary P et al. Atypical haemolytic-uraemic syndrome due to heterozygous mutations of CFH/CFHR1-3 and complement factor H 479. Blood Transfus. 2014;12:111–3.

46. Gulleroglu K et al. Neurologic involvement in atypical hemolytic uremic syndrome and successful treatment with eculizumab. Pediatr Nephrol. 2013;28:827–30.

47. Hu H et al. Eculizumab in atypical haemolytic uraemic syndrome with severe cardiac and neurological involvement. Pediatr Nephrol. 2014;29:1103–6.

48. Wong EK et al. Complement therapy in atypical haemolytic uraemic syndrome (aHUS). Mol Immunol. 2013;56:199–212.

49. Noris M, Remuzzi G. Cardiovascular complications in atypical haemolytic uraemic syndrome. Nat Rev Nephrol. 2014;10:174–80.

50. Zuber J et al. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. Nat Rev Nephrol. 2012;8:643–57.

51. Cataland SR, Wu HM. How I treat: the clinical differentiation and initial treatment of adult patients with atypical hemolytic uremic syndrome. Blood. 2014;123:2478–84.

BRINGING THE BENEFITS OF HIGH-DOSE HAEMODIALYSIS TO THE HOME WITH A NOVEL HAEMODIALYSIS SYSTEM

Summary of Presentations from the Baxter-Sponsored Symposium, held at the 51st ERA-EDTA Congress Amsterdam, the Netherlands, on 2nd June 2014

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Dialysis Inadequacy: Understanding the Limitations of Conventional Haemodialysis

Professor Chris McIntyre

Haemodialysis (HD) is a haemodynamically traumatic practice that is known to cause ischaemic insult to a variety of organs. Reductions in perfusion pressure as well as the stress of ultrafiltration are thought to give rise to these ischaemic insults. In turn, these stresses are associated with an increased risk of mortality.[1]

Investigations have been assessing the haemodynamic stress of dialysis and its effects on a number of organs, specifically the heart, gut, and brain. As HD patients exhibit a high incidence of heart failure and cardiovascular death, two studies were conducted to determine whether HD was capable of driving recurrent myocardial ischaemia.[2,3] Four patients had measurements of myocardial perfusion using a positron emission tomography (PET) scanner during dialysis.

Myocardial blood flow (MBF) was acutely reduced during dialysis and became progressively worse over time.[2] Two-dimensional (2D) echocardiography was performed to evaluate regional wall motion abnormalities (myocardial stunning) before, during, and after dialysis.[2] In a second study, approximately two-thirds of the 70 patients analysed had significant regional wall motion abnormalities during and after dialysis.[3]

Factors associated with the development of myocardial stunning were ultrafiltration volume and blood pressure (BP) levels during dialysis.[3] At 12-month follow-up there was a marked reduction in contractile function in the regions of the heart that stunned upon dialysis with almost half the contractile function lost.[3,4] In contrast, heart regions that did not stun showed no reduction in contractile function. Patients with myocardial stunning also displayed significantly lower left ventricular ejection fraction at rest and on HD (Figure 1). Myocardial stunning also has an impact on survival, with decreased survival in the patient group that exhibited stunning. Other studies have

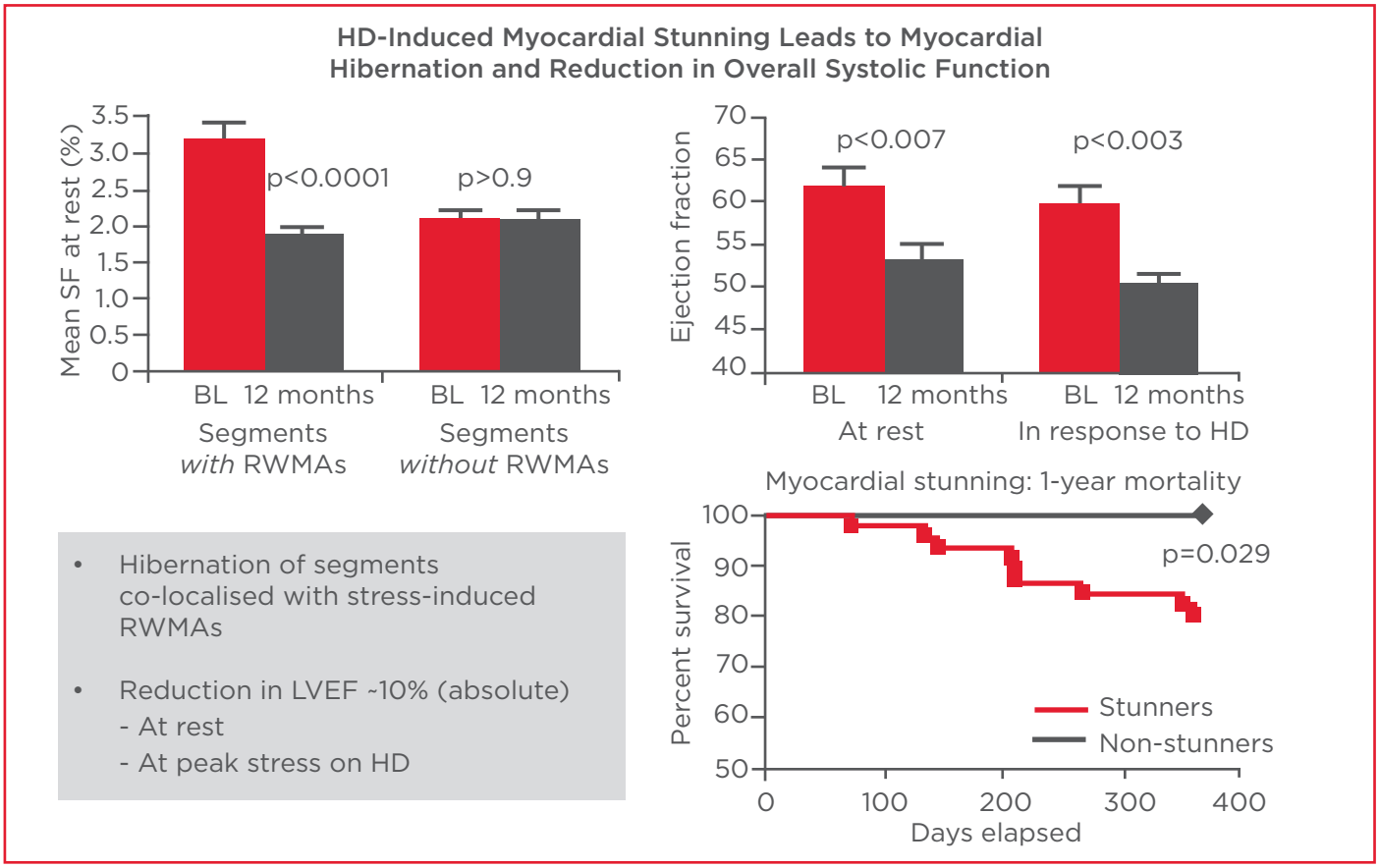

Figure 1: The consequences of haemodialysis (HD)-induced myocardial stunning.
BL: baseline; LVEF: left ventricular ejection fraction; SF: systolic function; RWMA: regional wall motion abnormality.
Modified from Burton et al.[3] and Burton et al.[4]

shown a gradation between myocardial stunning and death; a greater number of stunned segments being associated with higher mortality.[5]

To assess uraemia and dialysis in a patient population where diabetes, smoking, and epicardial large vessel disease are not factors, a paediatric sample was used. Using the same echo-based methods, all 12 children tested exhibited significant myocardial stunning.[6] A link between stunning and post-dialysis fatigue has also been shown where patients who experience increased myocardial stunning are more likely to feel exhausted in between treatments.[7] Serum endotoxin levels were assessed in 250 patients including those with chronic kidney disease (CKD) Stage 3, Stage 4, Stage 5, those receiving peritoneal dialysis (PD), HD, and a comparison group of non-CKD patients. Significantly high endotoxin levels were observed in the HD and PD groups ($p<0.001$), in comparison to CKD patients not receiving dialysis. These effects were also associated with mortality.[8] Dialysis has also been shown to have effects on the brain. Specifically, HD patients exhibit an increase in generalised cerebral atrophy, silent cerebral infarcts, effects on cerebral blood flow, and leukoaraiosis.

To measure white matter ultra-structural injury, a cohort of 55 HD-naïve patients underwent diffusion tensor imaging, matched with 25 normal volunteers for age, BP, and arterial stiffness (McIntyre personal comm.). The scans of all patients were merged to generate a 3D organisational map of the brains and similarly for the volunteers, and both data sets were analysed for areas that were significantly more disrupted. The patients' cohort displayed widespread white matter ultrastructural injury (Figure 2). Functional significance was tested by subjecting patients to cognitive function testing, specifically the Montreal Cognitive Assessment Test and trail-making tests. Dialysis patients were markedly worse, with the biggest difference seen in the subcortical white matter tests, showing that it was functionally significant and correlated to the level of brain injury (McIntyre personal comm.).

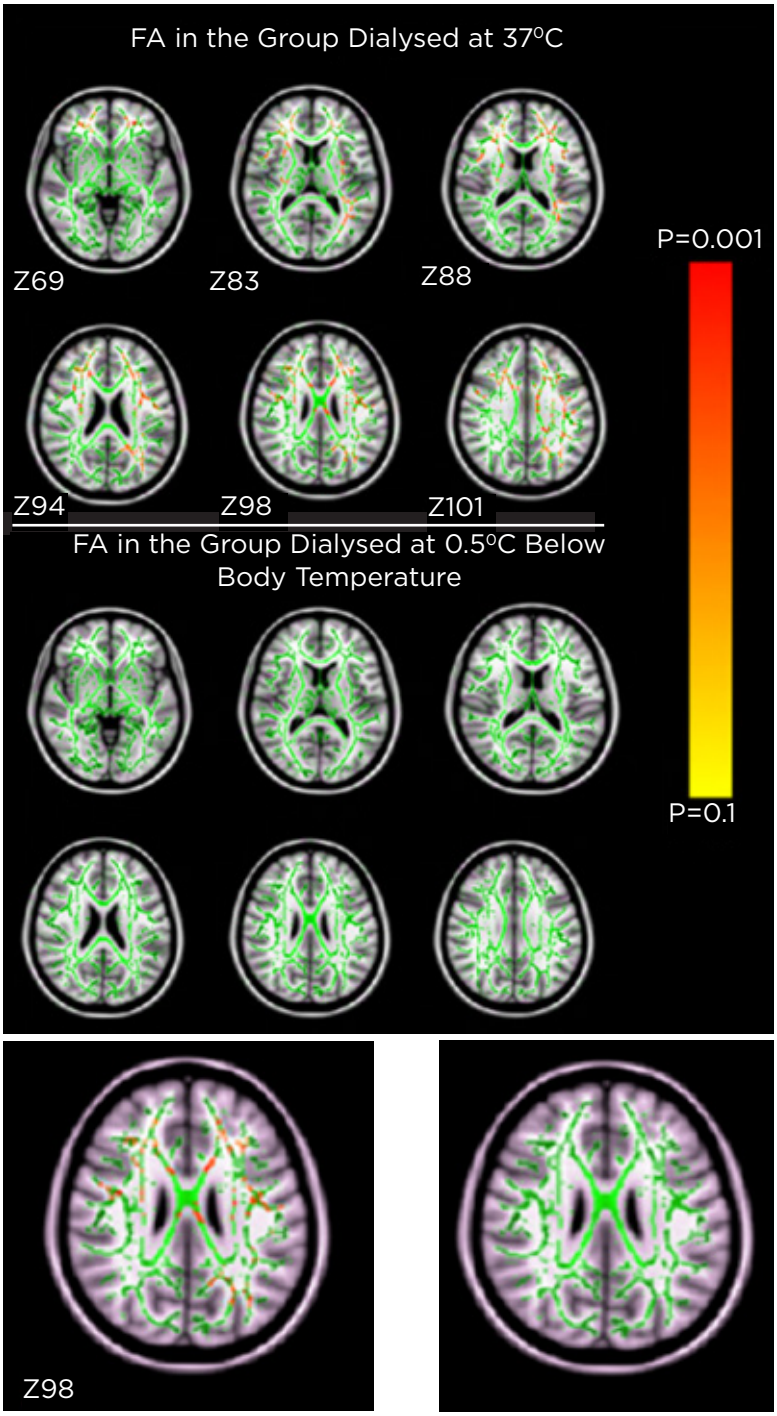

Figure 2: Brain - protection against progressive white matter ultrastructural injury.
McIntyre, personal communication.

A systematic analysis revealed that cooling the dialysate may be an effective and safe way to resolve ischaemic insults to the heart, gut, and brain. In initial studies, individuals were cooled to 35 ºC; however, it is difficult for patients to experience this temperature in the long term,[9] and in further studies patients were cooled sequentially. The tympanic temperature appears to be the ideal temperature. A randomised controlled trial was then conducted in 72 HD-naïve patients randomised to conventional temperature or individualised cooling. At 12-month follow-up, brains of patients who were not cooled had evidence of progressive brain injury, whereas patients who were cooled had no evidence of brain injury (McIntyre personal comm.). Cardio-protection was evidenced by ventricular size, preservation of systolic function, and protection of diastolic dysfunction.[9]

The effect of dialysis on weight gain was assessed in patients receiving treatment in-centre three times a week (CHD3), in-centre five times a week (CSD), short daily (SDHD), and nocturnal (NHD) at home.[10] The SDHD and NHD groups showed a much lower weight gain and less change in BP during dialysis. Echocardiography revealed that all the patients in the CHD3 group displayed myocardial stunning. In addition, intensive dialysis resulted in normalised serum endotoxin levels (as shown by the endotoxin levels in the short daily and nocturnal groups). Dialysis results in recurrent ischaemic injury with the heart and brain being particularly vulnerable. It is possible to protect against this stress and thus increase survival.

Improving Clinical Endpoints and Health-Related Quality of Life with High-Dose HD

Doctor Tom Cornelis

Studies have shown that high-dose HD has several clinical benefits such as optimised anaemia control, left ventricular systolic function, arterial compliance, sleep apnoea, autonomic nervous system functioning, and improvements in phosphate control.[11]

Using conventional dialysis modalities such as HD and PD, patients at CKD Stage 5 remain at this stage with clearances of 15 mL/minute, which results in suboptimal volume and phosphate control. Upon kidney transplantation, CKD Stage 3 or even 2 can be achieved, resulting in optimised phosphate and volume control. In between conventional HD and transplantation, high-dose HD modalities such as SDHD, NHD can result in a decrease of CKD Stage from 5 to 3. Observational studies conducted in the USA, Australia, and New Zealand comparing intensive HD to conventional HD show significantly reduced mortality ratios in intensive cohorts.[12-16]

It is assumed that patients on high-dose HD have an improved quality of life (QoL) as they are not dependent on HD schedules within a dialysis unit, enabling them to have increased autonomy/independence.[17] Furthermore, such patients also experience the clinical benefits of high-dose HD, have a reduced pill burden as they require fewer hypertensive pills and phosphate binders,[18,19] and have a more liberal diet and fluid intake.[20] Travel to and from the hospital is eliminated; instead they experience the convenience of dialysing at home, allowing them to alter the treatment schedule as they wish. When dialysis is conducted in a nocturnal fashion it enables them to continue with employment.[21] High-dose HD also decreases the incidence of sleep apnoea, resulting in improved sleep quality and consequently reduced daytime sleepiness.[22] Furthermore, there is evidence to support that high-dose HD produces a reduction in uraemic symptoms and inflammation.[23,24] All of these factors contribute to an improvement in QoL in high-dose HD.

Multiple studies have shown that high-dose HD has resulted in improvements in kidney-specific QoL and burden of kidney disease.[25-28] Moreover, the FREEDOM study showed a reduction in depression score (Beck Depression Inventory [BDI]) after 12 months of SDHD.[29] The Daily FHN trial showed no significant change in BDI but an improvement in mental health composite ($p=0.007$) and emotional subscale ($p=0.01$) scores.[30]

A meta-analysis conducted by Susantitaphong et al.[31] included studies on frequent HD and extended HD on left ventricular hypertrophy, and showed a significant reduction in left ventricular mass index to -31 g/m^2 and an improvement in left ventricular ejection fraction with high-dose HD.

Gene expression in rat cardiomyocytes showed a significant downregulation of genes involved in cardiac apoptosis and fibrosis and a significant upregulation of *S100a*, a gene involved in cardiac contractility when exposed to plasma from patients converted from conventional to nocturnal HD.[32] Another study showed a significant improvement in endothelial function;[33] microvascular perfusion of ischaemic rat hindlimb tissue was improved after injection of endothelial progenitor-like cells from nocturnal HD patients and healthy controls compared with saline (negative control), whereas cells derived from conventional HD patients had no beneficial effect when compared with saline.

A randomised cross-over trial was conducted in HD patients who underwent a single session of 4-hourly HD, 4-hourly haemodiafiltration, 8-hourly HD, and 8-hourly haemodiafiltration with a 2-week interval when they underwent conventional HD.[34] The results showed a reduction in the change of peripheral and central systolic BP, also a decrease in the change of cardiac output and relative blood volume. These results provide further evidence of the cardioprotective effects of high-dose HD (Table 1). Uraemic toxin studies showed that

Table 1: Acute haemodynamic (HD) effects in extended dialysis.

Parameter	4h HD	4h HDF	8h HD	8h HDF
Peripheral SBP, mmHg	-21.7	-23.3	-6.7*	-0.5*†
Peripheral DBP, mmHg	-5.0	-11.5	-1.1†	-1.2†
Central SBP, mmHg	-19.2	-24.2	-7.1	-3.8
Central DBP, mmHg	-5.0	-12.1*	-2.6	+3.5†
CO, L/minute	-1.4	-1.6	-0.4†	-0.5†
RBV, %	-1.8	-9.1	-4.4†	-3.3*†
ET rate, W	-13.1	-16.2	-14.2	-14.5

*p<0.05 vs 4h HD; †p<0.05 vs 4h HDF
CO: cardiac output; DBP: diastolic blood pressure; ET: energy transfer; RBV: relative blood volume; SBP: systolic blood pressure; HDF: haemodiafiltration.
Cornelis et al.[34]

extending dialysis optimised the reduction in β2 microglobulin and fibroblast growth factor (FGF)-23,[34] providing further evidence of the improved cardiovascular outcomes in extended dialysis. However, longer-term studies are required to confirm this.

The benefits of high-dose HD, such as reduction of uraemic toxin levels, peripheral vascular resistance, hypervolaemia, BP, and endothelial dysfunction, were thought to result in improved pregnancy outcomes such as optimisation of placental development, reduction of pre-eclampsia, prevention of polyhydramnios, and better fetomaternal outcomes. A recent study investigated pregnancy outcomes in a nocturnal home HD cohort in Toronto and compared these with conventional HD pregnancy outcomes in the American Registry of Pregnancy in Dialysis.[35] A significant dose-response relationship was established between hours of HD and live birth rate. This was further confirmed in a time-to-event analysis where the higher dose showed a greater cumulative survival compared to the lower-dose HD group. There is also evidence from a single study that sex hormones may be better regulated in high-dose HD.[36]

Despite the many beneficial effects of high-dose HD, there are some adverse events. The Frequent Haemodialysis Network (FHN) trial showed an increased loss of residual renal function after 12 months in nocturnal patients in comparison to conventional patients,[37] and not in the short daily trial. Furthermore, an in-depth review showed that patients in the high-dose or intensive group exhibited an increase in vascular access events in comparison to the conventional group, which may be related to cannulation.[38]

A Canadian study, investigating adverse events in the home setting, found that although adverse events are minimal, human errors do occur such as lapses in protocol adherence.[39] This points to the need for a quality assurance framework where programmes and cases are discussed as well as techniques of patients, among other issues.

In conclusion, there appears to be much evidence to support high-dose HD as an option for patients with end-stage renal disease; however, this method is still underutilised. Potential adverse events of high-dose HD still require further study. However, randomised controlled trials are difficult to perform and this raises the question of whether we should be relying on observational studies and day-to-day clinical experience. The option of incremental home HD should also be considered, where patients are started conventionally and up-titrated in the intensity of the dose while monitoring residual kidney function as well as other clinical parameters.

Overcoming Barriers to the Growth of Home HD through Device Innovation

Doctor Bruce Culleton

High-dose HD is associated with numerous clinical benefits, and a better QoL.[13,18,27] However, it has

also been established that high-dose and home HD have associated risks to the patient.[40] It is important to remember that some of these risks are inherent to the HD procedure itself. Similarly, there are inherent risks to the user-device interaction, which could be reduced or prevented with improved innovation in HD devices.

A survey conducted by Dr Sandip Mitra along with the European Renal Association found that 70% of nephrologists believed that there was sufficient evidence in the literature in favour of longer, more frequent HD schedules. Of the respondents, 75% believed that the HD modality that offers the best patient outcome in any setting was either frequent nocturnal, alternate nightly, or short daily HD.[41] Only 6% opted for three times per week haemodiafiltration. Using data published in registries and internal data, a wide variance in the prevalence of home HD was observed, with 10% use in Australia, 3% in the Netherlands, and <1% in France and Germany.

There are several reasons why home HD is not more widespread, including lack of education of the patient and carer to be able to make an informed choice of the different types of treatment modality, and patients may not feel motivated or confident enough to perform the therapy in the home/themselves.[42-44] There is also a general fear surrounding cannulation, and 'learned helplessness', where patients feel helpless as they are well looked after within the dialysis unit. Increased comorbidity plays a role as patients get older and sicker. On the organisational side, healthcare practitioners are in need of more education on the different dialysis modalities and also how to perform these procedures.[44] Misaligned economic incentives is another contributing factor as is operation and infrastructure demands, and uncertainties such as questions around how to actually initiate/grow a programme determine how many nurses/technicians are needed, etc.[44] These factors make it difficult to send patients to the home environment for HD.

When Baxter Healthcare came to designing an HD device for the home, three main goals were set: 1) deliver superior clinical and health-related QoL outcomes through device design and services; 2) deliver best-in-class safety, simplicity, and support services; and 3) deliver favourable economics for all stakeholders.

Baxter, in partnership with other key companies, developed a HD device named Vivia™. One of the key features of the device is a tablet/screen that plays animated clips to help guide the patient through set-up and resolving alarms. In an effort to limit the fear associated with venous access disconnection, the device includes a built-in access-disconnect sensor. Wires are embedded within the arterial and venous tubing, meaning that if a needle should fall from the venous or arterial access then the blood pump will stop automatically, resulting in minimal blood loss in the patient. The device also includes an extended-use dialyser, allowing short daily treatments at least 5 days per week for sessions that typically run for fewer than 4 hours, or as nocturnal treatments where sessions are conducted for >6 hours while the patient sleeps, thereby reducing the burden of home treatment. Multiple uses of the blood treatment-set combined with hot water disinfection mean the device is environmentally friendly. Furthermore, Vivia comes with a web-based connectivity platform called Sharesource™ which allows communication to and from the clinic, enabling healthcare professionals to monitor their patient's treatment data and remotely edit device settings as required. As well as keeping the clinic informed, the aim is also to give the patient confidence in performing dialysis in the home. It is hoped that these features will tackle some of the barriers for patients to conduct HD in the home.

A first-in-human clinical study using the Vivia system was conducted in the USA with 22 subjects who were dialysed four times per week for 10 weeks. The standard weekly Kt/V urea was above the values stated by the guidelines, blood flow on average was 316 mL/minute, and the dialysate flow was 395 mL/minute.[45,46] The feasibility of extending use of the dialyser and blood set was also studied. Approximately 40% of the treatments (269) were delivered on dialysers that were used ten or more times, and about 25% of the treatments with dialysers were used five-to-nine times (Figure 3).

Over the course of extending the use of the dialyser, there was only a minimal change in small molecule clearance as assessed using urea clearance, even after more than ten uses. Middle molecule clearance declined after several uses of the dialyser; however, the baseline mean β2 clearance was 77 mL/minute, which is considered very good, meaning that a 10% reduction in this value over time is not a significant decline, especially if patients receive longer treatments. None of the

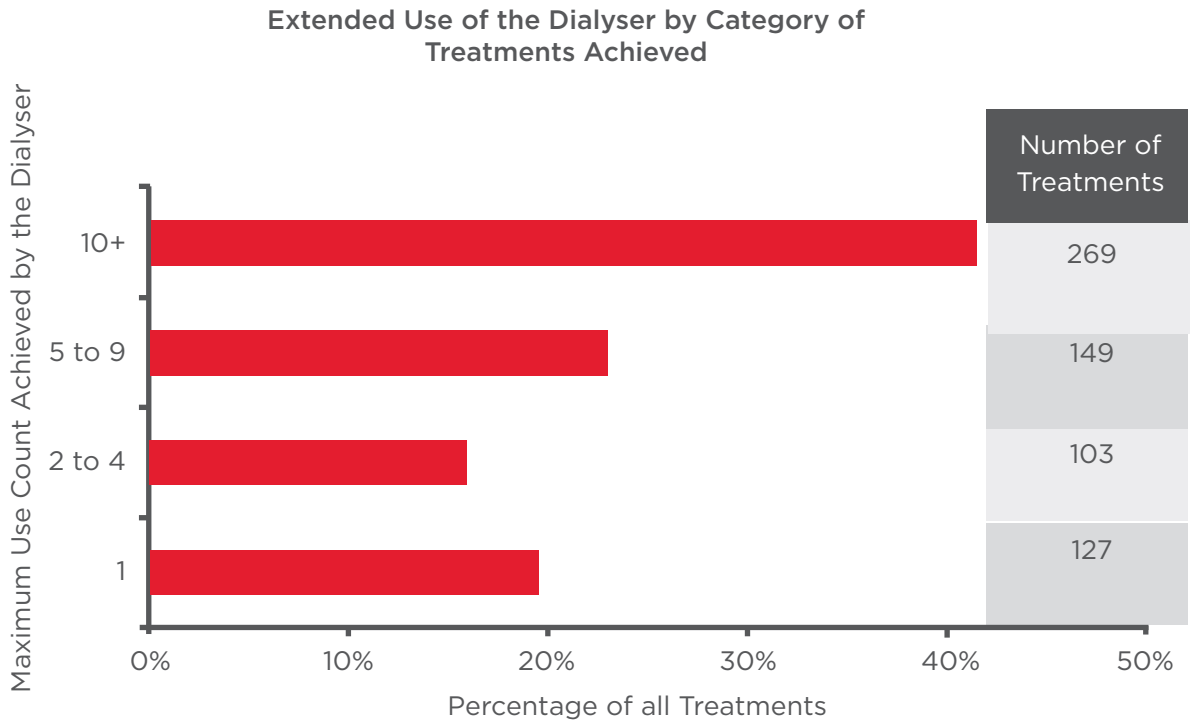

Figure 3: Safety and efficacy of the Vivia™ HD system; results from the first-in-human clinical study. *2014 ERA-EDTA Annual Meeting; SP415.*

271 dialysate samples taken at different counts of dialysis use (ranging from first use to more than ten times) revealed any bacteria, and all samples met the international standards for bacteria as well as endotoxin.

A nocturnal clinical study assessed the feasibility of extending dialyser use under longer treatments.[46] All subjects underwent three treatments per week for 6 weeks. Results revealed that a large between-patient and within-patient variability exists for dialyser use, with some patients using only 3 dialysers during treatment and others using up to 17. This variability points to the importance of establishing an optimal anticoagulation blood circuit in order to extend the use of the dialyser and blood set.

In conclusion, high-dose HD has numerous clinical and QoL benefits, yet relatively few patients are provided this therapy due to a number of factors. Some of these issues could be addressed with improved HD device innovation and design as well as improvement in the services and support patients receive.

REFERENCES

1. McIntyre CW. Effects of hemodialysis on cardiac function. Kidney Int. 2009;76: 371-5.

2. McIntyre CW et al. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. Clin J Am Soc Nephrol. 2008;3:19-26.

3. Burton JO et al. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clin J Am Soc Nephrol. 2009;4:914-20.

4. Burton JO et al. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. Clin J Am Soc Nephrol. 2009;4:1925-31.

5. Assa S et al. Hemodialysis-induced regional left ventricular systolic dysfunction: prevalence, patient and dialysis treatment-related factors, and prognostic significance. Clin J Am Soc Nephrol. 2012;7:1615-23.

6. Hothi DK et al. Hemodialysis-induced acute myocardial dyssynchronous impairment in children. Nephron Clin Pract. 2013;123:83-92.

7. Dubin RF et al. Association of segmental wall motion abnormalities occurring during hemodialysis with post-dialysis fatigue. Nephrol Dial Transplant. 2013;28:2580-5.

8. McIntyre CW et al. Circulating endotoxemia: a novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:133-41.

9. Odudu A et al. Rationale and design of a multi-centre randomised controlled trial of individualised cooled dialysate to prevent left ventricular systolic dysfunction in haemodialysis patients.

BMC Nephrol. 2012;13:45.

10. Jefferies HJ et al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). Clin J Am Soc Nephrol. 2011;6:1326-32.

11. Perl J et al. Home hemodialysis, daily hemodialysis, and nocturnal hemodialysis: Core Curriculum 2009. Am J Kidney Dis. 2009;54:1171-84.

12. Johansen KL et al. Survival and hospitalization among patients using nocturnal and short daily compared to conventional hemodialysis: a USRDS study. Kidney Int. 2009;76:984-90.

13. Marshall MR et al. Home hemodialysis and mortality risk in Australian and New Zealand populations. Am J Kidney Dis. 2011;58:782-93.

14. Lockridge RS et al. Nightly home hemodialysis: outcome and factors associated with survival. Hemodial Int. 2011;15:211-8.

15. Nesrallah GE et al. Intensive hemodialysis associates with improved survival compared with conventional hemodialysis. J Am Soc Nephrol. 2012;23:696-705.

16. Weinhandl ED et al. Survival in daily home hemodialysis and matched thrice-weekly in-center hemodialysis patients. J Am Soc Nephrol. 2012;23:895-904.

17. Hall YN et al. Effects of six versus three times per week hemodialysis on physical performance, health, and functioning: Frequent Hemodialysis Network (FHN) randomized trials. Clin J Am Soc Nephrol. 2012;7:782-94.

18. Chertow GM et al. In-center hemodialysis six times per week versus three times per week. N Engl J Med. 2010;363:2287-300.

19. Daugirdas JT et al. Effects of frequent hemodialysis on measures of CKD mineral and bone disorder. J Am Soc Nephrol. 2012;23:727-38.

20. Sikkes ME et al. Improved nutrition after conversion to nocturnal home hemodialysis. J Ren Nutr. 2009;19:494-9.

21. Pierratos A. Nocturnal home haemodialysis: an update on a 5-year experience. Nephrol Dial Transplant. 1999;14:2835-40.

22. Pierratos A et al. Nocturnal hemodialysis improves sleep quality in patients with chronic renal failure. J Am Soc Nephrol. 1997;8:169A.

23. Manohar NL et al. Success of frequent short hemodialysis. Trans Am Soc Artif Intern Organs. 1981;27:604-9.

24. Ayus JC et al. Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. J Am Soc Nephrol. 2005;16:2778-88.

25. Manns BJ et al. Nocturnal hemodialysis does not improve overall measures of quality of life compared to conventional hemodialysis. Kidney Int. 2009;75:542-9.

26. Finkelstein FO et al. At-home short daily hemodialysis improves the long-term health-related quality of life. Kidney Int. 2012;82:561-9.

27. Culleton BF et al. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. JAMA. 2007;298:1291-9.

28. Heidenheim AP et al. Patient quality of life on quotidian hemodialysis. Am J Kidney Dis. 2003;42:36-41.

29. Jaber BL et al. Effect of daily hemodialysis on depressive symptoms and postdialysis recovery time: interim report from the FREEDOM (Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements) Study. Am J Kidney Dis. 2010;56:531-9.

30. Rocco MV et al. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. Kidney Int. 2011;80:1080-91.

31. Susantitaphong P et al. Effect of frequent or extended hemodialysis on cardiovascular parameters: a meta-analysis. Am J Kidney Dis. 2012;59:689-99.

32. Chan CT et al. Impact of frequent nocturnal hemodialysis on myocardial mechanics and cardiomyocyte gene expression. Circ Cardiovasc Imaging. 2012;5:474-80.

33. Yuen DA et al. Nocturnal hemodialysis is associated with restoration of early-outgrowth endothelial progenitor-like cell function. Clin J Am Soc Nephrol. 2011;6:1345-53.

34. Cornelis T et al. Acute hemodynamic response and uremic toxin removal in conventional and extended hemodialysis and hemodiafiltration: a randomized crossover study. Am J Kidney Dis. 2014.

35. Hladunewich MA et al. Intensive hemodialysis associates with improved pregnancy outcomes: a Canadian and United States cohort comparison. J Am Soc Nephrol. 2014;25:1103-9.

36. van EC et al. Changes in serum prolactin, sex hormones and thyroid function with alternate nightly nocturnal home haemodialysis. Nephrology (Carlton). 2012;17:42-7.

37. Daugirdas JT et al. Effect of frequent hemodialysis on residual kidney function. Kidney Int. 2013;83:949-58.

38. Cornelis T et al. Vascular access vulnerability in intensive hemodialysis: a Significant Achilles' Heel? Blood Purif. 2014;37:222-8.

39. Wong B et al. Procedure-related serious adverse events among home hemodialysis patients: a quality assurance perspective. Am J Kidney Dis. 2014;63:251-8.

40. Pauly RP et al. Patient and technique survival among a Canadian multicenter nocturnal home hemodialysis cohort. Clin J Am Soc Nephrol. 2010;5:1815-20.

41. Jayanti A MS. Home Hemodialysis: Survey Results. http://ndt-educational.org/hhd.htm. Accessed: 2014.

42. Cafazzo JA et al. Patient-perceived barriers to the adoption of nocturnal home hemodialysis. Clin J Am Soc Nephrol. 2009;4:784-9.

43. Young BA et al. How to overcome barriers and establish a successful home HD program. Clin J Am Soc Nephrol. 2012;7:2023-32.

44. Golper TA et al. Systematic barriers to the effective delivery of home dialysis in the United States: a report from the Public Policy/Advocacy Committee of the North American Chapter of the International Society for Peritoneal Dialysis. Am J Kidney Dis. 2011;58:879-85.

45. Bernardo A et al. Safety and performance of a home haemodialysis device: results from the first in-human study with a novel home HD system. 2014; Abstract SP415. Presented at: the 51st ERA-EDTA Congress, 31 May-3 June 2014, Amsterdam, the Netherlands.

46. McFarlane P et al. Nocturnal haemodialysis with the vivia haemodialysis system. 2014; Abstract SP431. Presented at: the 51st ERA-EDTA Congress, 31 May-3 June 2014, Amsterdam, the Netherlands.

PAIN IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder affecting 1 in 1,000 people and is responsible for 10% of cases of end-stage renal disease. Apart from renal manifestations, changes in other organs may be present, including arterial hypertension, intracranial aneurysms, liver cysts, and others. Pain is a common complaint in ADPKD, afflicting as many as two-thirds of patients. It begins relatively early in the course of the disease, and may be associated with polycystic kidneys, extrarenal manifestations of the disease, or may be of the origin which is unspecific for ADPKD. The aim of the paper is to review the subject of pain in ADPKD patients, with its possible sources, diagnostics, and management.

Keywords: Autosomal dominant polycystic kidney disease, complications, pain, polycystic liver disease.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder affecting 1 in 1,000 people and responsible for 10% of cases of the end-stage renal disease (ESRD). Apart from renal manifestations, changes in other organs may be present, including arterial hypertension (AH), intracranial aneurysms (ICANs), liver cysts, and others. In 85% of cases, ADPKD is caused by a mutation in the PKD1 gene, encoding polycystin 1 (Type 1 ADPKD), and the remaining 15% are connected to the mutated PKD2 gene, encoding polycystin 2 (Type 2 ADPKD). The type of the mutation has a prognostic significance, as the average age of ESRD amounts to 53 years in Type 1, and 69 years in Type 2.[1]

Pain is commonly observed in ADPKD, afflicting as many as two-thirds of patients.[2] It begins relatively early in the course of the disease,[3,4] and may be associated with polycystic kidneys, extrarenal manifestations of the disease, and, of course, may be of the origin which is unspecific for ADPKD. The aim of the paper is to review the subject of pain in ADPKD patients, with its possible sources, diagnostics, and management.

LUMBALGIA AND ABDOMINAL PAIN

Lower back pain is observed in 71-77%, and abdominal pain in 61-66% of ADPKD cases.[2,3] The pain related to the polycystic kidney may be both acute or chronic. The most common reasons of acute pain include cyst infection, cyst rupture, and nephrolithiasis.

The cyst infection may lead to acute pain with accompanying elevated body temperature. The pain may be unilateral or bilateral. If there is no communication between the lumen of the infected cyst and the urinary tract, the result of urinalysis is normal and the urine culture is negative. Thus, the diagnosis may be difficult.[5] In 2012, Suwabe et al.[6] proposed the diagnostic criteria for kidney or liver cyst infection. According to them, for the diagnosis of infection, the patient must have: A) no other source of fever detectable and no evidence for acute cyst haemorrhage; B) at least 2 items from: maximum body temperature >38°C, maximum

white blood cell (WBC) count >10,000/μl, or maximum serum C-reactive protein (CRP) >15 mg/dl; C) at least 1 item from: gas inside the cyst, high density of the cyst on magnetic resonance imaging (MRI) (diffusion-weighted imaging [DWI]), fluid-fluid level in the cyst on MRI, or cyst wall thickening on MRI or computed tomography (CT); and D): at least 1 item from: abdominal pain or tenderness, or sequential changes of the cyst on imaging. In diagnostic difficulties, ^{18}fluorodeoxyglucose (^{18}FDG) positron-emission computed tomography (PET/CT) may help to confirm and locate the infection of the cyst.[7,8] *Escherichia coli* accounts for almost three-quarters of cases.[8] In the therapy of cyst infection, the antibiotics of good penetration to the cyst lumen are recommended, including fluoroquinolones, co-trimoxazole, clindamycin, metronidazole, vancomycin, and chloramphenicol.[5,8] Combination of antibiotics seems superior compared to monotherapy.[8] A 6-week course of antibiotics is recommended.[9] However, invasive approach with drainage of the infected cysts may be required, especially when their diameter exceeds 5 cm.[5,8,10]

The cyst rupture accompanied by haemorrhage causes acute pain, with gross haematuria (when there is a communication between the involved cyst and the urinary tract) or without haematuria (when there is no such communication).[5] Except for intracystic bleeding, retroperitoneal haematoma, or, in extremely rare cases, haemoperitoneum, may complicate the cyst rupture in the latter case.[11] If haematuria is present, it is usually self-limited after a few days. In more serious cases, the bleeding may be complicated with formation of clots that may cause the obstruction of the urinary tract.[5] In patients with persistent or recurrent symptoms, imaging with CT or MRI is indicated.[12] According to the criteria of Suwabe et al.,[6] acute cystic haemorrhage may be diagnosed when: A) there is abdominal pain and/or gross haematuria; B) the maximum body temperature does not exceed 38°C, the maximum WBC count does not exceed 10,000/μl, and the maximum serum CRP is <15 mg/dl; and C) CT reveals irregular high-density mass inside the cyst, or the cyst density on CT exceeds 25 Hounsfield units (HU). In most cases, conservative management with bedrest, hydration, and analgesics, is sufficient. In severe haematuria, transfusion may be required, and, in the most severe cases, nephrectomy or embolisation of the renal artery should be considered.[5]

It is also possible that the ADPKD patient suffers from combined cyst haemorrhage and infection. It may be diagnosed when the patient: A) is pyrexial, and complains of abdominal pain and/or gross haematuria; B) the patient has at least two items from: maximum body temperature >38°C, maximum WBC count >10,000/μl, or maximum serum CRP >15 mg/dl; and C) the CT scans correspond to cyst haemorrhage.[6]

The incidence of nephrolithiasis is higher in ADPKD compared to the general population. It is complicated with renal colic in 20% of ADPKD patients. In such cases, the use of non-steroidal anti-inflammatory drugs (NSAIDs) for up to 3 days seems reasonable. Opioids may be also required. The impaired anatomy in ADPKD may cause difficulties in diagnostics and treatment of renal stones.[5] CT, preferably with contrast administration, seems to be the most informative.[12] The invasive procedures including ureteroscopy, extracorporeal shock wave lithotripsy (ESWL), and nephrolithotomy are challenging.[5] However, the safety and efficacy of flexible ureteroscopy with holmium laser lithotripsy,[13] and percutaneous nephrolithotomy,[14] were proven.

Rarely, the enlarged kidney may cause the occlusion of the mesenteric vein leading to strangulation necrosis of the intestine.[15] A very rare case of sudden-onset pain localised in hypogastrium was also reported, in which the compression of enlarged kidneys and liver on the bony pelvis led to the insufficiency-type fracture of the pelvis.[16]

Compression of cysts on the surrounding tissues, traction on the pedicle of the kidney, and distention of the renal capsule may cause chronic pain,[5] defined as daily pain lasting more than 4 weeks.[12] The cyst-related pain is described as a steady discomfort, exacerbated in vertical position and during walking.[5] In general, pain correlates with the kidney size;[4,5,17] however, there are numerous exceptions from this rule. In effect, patients with mild or moderate cystic changes may complain of severe pain.[5,12,17] Additionally, the pain is unrelated with renal function. Early satiety may be the additional complaint.[5] A rare case of intestinal obstruction caused by compression of cystic kidney, successfully treated with percutaneous aspiration of the largest cysts, was also reported.[18] In general, in patients with chronic kidney pain, the goal of treatment is adaptation of the patient to the pain, because curing the pain is not always achievable.[5] Bajwa et al.[5] proposed a sequential approach

to the pain management in ADPKD, in which, at the beginning, non-invasive methods are used, with slow progress towards more complex and invasive measures.

Non-pharmacologic therapy with physical measures should be sequentially followed by acetaminophen, NSAIDs, tramadol, adjuvant analgesics (clonidine, gabapentin, or pregabalin), and opioids. Transcutaneous electrical nerve stimulation (TENS), acupuncture, and autonomic plexus blockade may be used. Invasive procedures include spinal cord stimulation, neuraxial opioids, and local anaesthetics. A case was reported[19] in which satisfactory analgaesia was achieved with sequential celiac plexus blockade, and intercostal nerve radiofrequency ablations, followed by dorsal column neurostimulation. Surgical approaches include cyst aspiration in cases of only one or a few large cysts, and surgical cyst decompression. While cyst aspiration relieves pain only temporarily,[5] cyst ablation may be used for long-lasting effect using absolute ethanol[20] or a mixture of N-butyl cyanoacrylate (NBCA) and iodised oil.[21] Surgical cyst decortication, including laparoscopic cyst decortication, is effective in the management of chronic pain associated with ADPKD.[22-25] Also, renal denervation, both via a laparoscopic[26] or thoracoscopic[27] approach, may be considered. A new method is the catheter-based renal denervation; successful treatment with this method in an ADPKD patient was recently reported.[28] Ultimately, nephrectomy may be the last option. In patients with chronic pain, ESRD, and contraindications for nephrectomy, transcathether arterial embolisation (TAE) may be considered.[5,12] TAE may be performed using either intravascular coils or ethanol.[29,30]

The common extrarenal manifestation of ADPKD is polycystic liver disease (PLD), which affects up to 94% of ADPKD subjects.[12] PLD is more common in females,[5] due to the fact that oestrogen stimulates the growth of liver cysts.[31] PLD is usually of low clinical significance; however, in some cases it may manifest with a pain which is often more severe than the pain caused by renal cysts. The pain connected to PLD is exacerbated by the standing position, and is accompanied by early satiety.[5] In patients with pain associated with PLD, invasive procedures may be considered when medical therapy is ineffective, including cyst drainage or fenestration, liver resection with fenestration, or TAE.[5,12,32-34]

The rupture of a hepatic cyst may present as an acute abdomen.[35-37] Additionally, acute episodes of pain may be caused by cyst haemorrhage, torsion, or infection.[12] In the analysis of Suwabe et al.,[6] liver cyst infections were more common compared to renal cyst infections; however, in another report[8] the prevalence of renal cyst infections was higher. In case of abdominal pain combined with a fever in an ADPKD patient, liver cyst infection should be included into the differential diagnosis. It is a potentially lethal condition in which antibiotics may be ineffective.[38] In such infections, antibiotics combined with drainage are superior to antibiotics alone. Additionally, when the diameter of the infected cyst is >5 cm, drainage is mandatory.[8,12]

Pancreatic cysts are observed in almost 20% of ADPKD patients. In very rare cases, they cause pancreatitis due to obstruction of the pancreatic duct.[12] An anatomical defect may lead to the recurrence of pancreatitis.[39] Additionally, Naitoh et al.[40] reported a case of adenocarcinoma of the pancreas leading to acute pancreatitis, and suggested a possible association between ADPKD and pancreatic carcinogenesis.

Colonic diverticula were thought to be associated with ADPKD, especially in the fifth stage of the chronic kidney disease. However, data on the frequency of diverticular disease and diverticulitis in ADPKD remain conflicting. An additional problem connected to ADPKD is increased frequency of hernias. Therefore, complications of abdominal hernias should be considered in patients with ADPKD and acute abdomen.[41]

As described below, vascular manifestations belong to the clinical picture of ADPKD. A rare case of acute abdominal pain with concomitant haemorrhagic shock, due to the rupture of a gastroepiploic artery aneurysm, was reported.[42] It should not be forgotten that there are also other possible sources of lower back pain in ADPKD. The most severe cases of chronic lumbalgia in my practice were due to the spine disease. The disorders of the spine in ADPKD are presented below.

CHEST PAIN

The prevalence of chest pain in ADPKD is estimated at 4-30%.[2,3] Vascular manifestations of the disease are due to the fact that both polycystins are expressed within arterial smooth muscle cells.[43-45] A systemic vascular defect was observed already at the oligosymptomatic stage of the disease.[46-47]

As a consequence, the most common extrarenal manifestation of the disease is AH, which often precedes impairment of kidney function,[48,49] and is complicated with left ventricular hypertrophy (LVH).[50] Both AH and LVH are well-known risk factors for ischaemic heart disease (IHD).[51] Therefore, patients with ADPKD and chest pain should be diagnosed for IHD.

Additionally, there are some disease-specific sources of chest pain in ADPKD, which should be included into the differential diagnosis. A rare cause of myocardial ischaemia and infarction may be spontaneous coronary artery dissection.[52,53] Furthermore, an association between ADPKD and non-atherosclerotic coronary aneurysm was suggested, and the latter may be - in very rare cases - connected to myocardial infarction.[54] Also, several case reports on the coexistence of ADPKD with aortic dissection, both acute[55-58] and chronic,[59] were published. They may manifest with pain localised either in the front of the chest, or in the interscapular region.[55,56]

Another disease-specific source of chest pain may be the polycystic liver. A case of ADPKD patient with chest pain caused by infected liver cyst with compression of the right atrium was reported.[60] Then, accurate imaging of the thorax is of a great value in ADPKD patients suffering from the chest pain.

HEADACHE

Headache is observed in 15-49% of ADPKD patients.[2,3] The two most common ADPKD-specific reasons of it are AH and ICAN. It is believed that up to 60% of young ADPKD patients with normal renal function have AH,[48] and its overall prevalence may exceed 80%.[49] Therefore, at the beginning, patients with headache should be examined for elevated blood pressure and treated when it is observed. Due to the fact that the non-dipping pattern is associated with ADPKD,[48,61] the special role of ambulatory blood pressure monitoring (ABPM) in the diagnosis of AH in ADPKD needs to be underlined.

ADPKD is connected to increased frequency of ICANs compared to the general population.[62] According to the literature data, the overall prevalence of ICANs in the ADPKD population ranges from 4%[63] to 22.5%.[64] In our recent study,[65] the prevalence of ICANs in ADPKD patients was 16.9%, and the only risk factor for ICANs was age; after 45 years-of-age the frequency of ICANs reached 22.4%. However, the subarachnoid haemorrhage (SAH) due to a rupture of an ICAN in ADPKD patients often occurs in relatively young subjects, with mean age below 40 years. Additionally, SAH is often observed in normotensive patients with preserved renal function.[66] Despite these facts, the universal screening for ICANs remains controversial, and only selected indications for screening are widely accepted in the clinical practice.[67] According to my unpublished, retrospective analysis of a series of ADPKD patients with nonfatal rupture of an ICAN in their medical history, more than half of them had neurological symptoms for at least a few months preceding SAH, with headache as the most common one. Therefore, in my opinion, each normotensive ADPKD patient with a new onset or chronic headache should be examined for an ICAN. Some other authors share my point of view.[41] On the other hand, according to Bajwa et al.,[3] the only indication for screening for ICANs in ADPKD is a family history of aneurysm formation, and patients with a negative family history for an ICAN should not be screened, even in case of chronic headache.[3] Due to safety reasons, MR-angiography is a method of choice in detecting ICANs in ADPKD patients, as there is no X-ray exposure or need for contrast media administration. The positive result of MR-angiography should be verified with CT-angiography, and when confirmed, the patient should be referred to the specialist in neurosurgery.[65]

Additionally to arachnoid haemorrhage, carotid artery dissection may occur in an ADPKD subject.[68] In very rare cases, headache may be a manifestation of an arachnoid cyst. Arachnoid cysts are found in fewer than 10% of ADPKD patients, compared to fewer than 1% in the general population, and are usually asymptomatic. They may be found on MRI scans performed as a screening for ICANs.[69]

OTHER LOCALISATIONS OF PAIN

Radicular pain, defined as a back pain radiating to the hips or lower extremities, is observed in 27% of patients with ADPKD.[3] Enlargement of cysts causes increased abdominal girth and leads to increased lumbar lordosis. In effect, degenerative changes of the spine appear, which manifest with pain. Bajwa et al.[5] suggested hypertrophy of the lumbodorsal muscle group in ADPKD patients as a basis of the spine 'imbalance'.

Additionally, asymmetry in renal cyst enlargement leads to chronic postural alteration, and results in the disc disease in the lumbosacral region. The diagnostic method of choice is MRI of the spine and postural muscles. Additionally, the sacroiliac joint is thought to be a common source of pain in ADPKD. Physical therapy techniques, together with local anaesthesia, can be used in such situations.[5]

CONCLUSIONS

In summary, ADPKD is a common and multi-organ disease. Therefore, the awareness of its manifestations, and possible sources of pain in ADPKD, is important not only for nephrologists but also for general practitioners and specialists in other areas of medicine. The proper and quick diagnosis may improve not only the patients' health and quality of life, but, in some cases, may save their life. Additionally, current treatment modalities enable the provision of optimal therapy for a substantial group of patients.

REFERENCES

1. Chang MY, Ong ACM. Autosomal dominant polycystic kidney disease: recent advances in pathogenesis and treatment. Nephron Physiol. 2008;108(1): 1-7.

2. Eloi SR et al. Translation, cultural adaptation and aplication of a pain questionnaire for patients with polycystic kidney disease. J Bras Nefrol. 2010;32(4):386-99.

3. Bajwa ZH et al. Pain patterns in patients with polycystic kidney disease. Kidney International. 2004;66(4):1561-9.

4. Nishiura JL et al. Pain determinants of pain in autosomal dominant polycystic kidney disease. J Bras Nefrol. 2013;35(3):242-3.

5. Bajwa ZH et al. Pain management in polycystic kidney disease. Kidney Int. 2001;60(5):1631-44.

6. Suwabe T et al. Clinical features of cyst infection and hemorrhage in ADPKD: new diagnostic criteria. Clin Exp Nephrol. 2012;16(6):892-902.

7. Jouret F et al. Positron-emission computed tomography in cyst infection diagnosis in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2011;6(7):1644-50.

8. Sallee M et al. Cyst infections in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2009;4(7):1183-9.

9. Pirson Y. Extrarenal manifestations of autosomal dominant polycystic kidney disease. Adv Chronic Kidney Dis. 2010;17(2):173-80.

10. Tsuchiya Y et al. The renal cyst infection caused by Salmonella enteritidis in a patient with autosomal dominant polycystic kidney disease: how did this pathogen come into the renal cysts? Clin Exp Neprol. 2011;15(1):151-3.

11. Tarrass F, Benjelloun M. Acute abdomen caused by spontaneous renal cyst rupture in an ADPKD haemodialysed patient. Nephrology (Carlton). 2008;13(2):177-8.

12. Hogan MC, Norby SM. Evaluation and management of pain in autosomal dominant polycystic kidney disease. Adv Chronic Kidney Dis. 2010;17(3):e1-16.

13. Yili L et al. Flexible ureteroscopy and holmium laser lithotripsy for treatment of upper urinary tract calculi in patients with autosomal dominant polycystic kidney disease. Urol Res. 2012;40(1):87-91.

14. Umbreit EC et al. Percutaneous nephrolithotomy for large or multiple upper tract calculi and autosomal dominant polycystic kidney disease. J Urol. 2010;183(1):183-7.

15. Yoshikawa T et al. Strangulation necrosis of the intestine in a patient with giant polycystic kidney disease: a rare cause of acute abdomen. Int Surg. 2008;93(1):15-8.

16. Ubara Y et al. Pelvic insufficiency fracture related to autosomal dominant polycystic kidney disease. Am J Kidney Dis. 2005;46(6):e103-11.

17. Miskulin DC et al. Health-related quality of life in patients with autosomal dominant polycystic kidney disease and CKD stages 1-4: a cross-sectional study. Am J Kidney Dis. 2014;63(2):214-26.

18. Kakinoki K et al. Intestinal obstruction in autosomal dominant polycystic kidney disease. Intern Med. 2002;41(6):441-4.

19. Walsh N, Sarria JE. Management of chronic pain in a patient with autosomal dominant polycystic kidney disease by sequential celiac plexus blockade, radiofrequency ablation, and spinal cord stimulation. Am J Kidney Dis. 2012;59(6):858-61.

20. Lee YR, Lee KB. Ablation of symptomatic cysts using absolute ethanol in 11 patients with autosomal-dominant polycystic kidney disease. Korean J Radiol. 2003;4(4):239-42.

21. Kim SH et al. Cyst ablation using a mixture of N-butyl cyanoacrylate and iodized oil in patients with autosomal dominant polycystic kidney disease: the long-term results. Korean J Radiol. 2009;10(4):377-83.

22. McNally ML et al. Laparoscopic cyst decortication using the harmonic scalpel for symptomatic autosomal dominant polycystic kidney disease. J Endourol. 2001;15(6):597-9.

23. Lee DI et al. Laparoscopic cyst decortication in autosomal dominant polycystic kidney disease: impact on pain, hypertension, and renal function. J Endourol. 2003;17(6):345-54.

24. Haseebuddin M et al. Long-term impact of laparoscopic cyst decortication on renal function, hypertension and pain control in patients with autosomal dominant polycystic kidney disease. J Urol. 2012;188(4):1239-44.

25. Millar M et al. Surgical cyst decortication in autosomal dominant polycystic kidney disease. J Endourol. 2013;27(5):528-34.

26. Casale P et al. Follow-up for laparoscopic renal denervation and nephropexy for autosomal dominant polycystic kidney disease-related pain in pediatrics. J Endourol. 2008;22(5):991-3.

27. Chapuis O et al. Thoracoscopic renal denervation for intractable autosomal dominant polycystic kidney disease-related pain. Am J Kidney Dis. 2004;43(1):161-3.

28. Casteleijn NF et al. Chronic kidney pain in autosomal dominant polycystic kidney disease: a case report of successful treatment by catheter-based renal denervation. Am J Kidney Dis. 2014;63(6):1019-21.

29. Ubara Y et al. Renal contraction therapy for enlarged polycystic kidneys by transcatheter arterial embolization in hemodialysis patients. Am j Kidney Dis. 2002;39(3):571-9.

30. Rim H et al. Transcatheter arterial embolization using ethanol in a dialysis patients for contracting enlarged polycystic kidneys. Korean J Radiol. 2010;11(5):574-8.

31. Sherstha R et al. Postmenopausal estrogen therapy selectively stimulates hepatic enlargement in women with autosomal dominant polycystic kidney disease. Hepatology. 1997;26(5):1282-6.

32. Park HC et al. Transcatheter arterial embolization therapy for a massoive polycystic liver in autosomal dominant polycystic kidney disease patients. J Korean Med Sci. 2009;24(1):57-61.

33. Patel A, Shah R. Polycystic liver disease presenting as acute abdomen. QJM. 2014; doi:10.1093/qjmed/hcu014. [Epub ahead of print].

34. Montgomery TA, Yeo FE. Recalcitrant pain in a patient with ADPKD. Kidney Int. 2009;76(5):581.

35. Chung TK et al. Acute abdoment in a haemodialysed patient with polycystic kidney disease – rupture of a massive liver cyst. Nephrol Dial Transplant. 1998;13(7):1840-2.

36. Carels RA, van Bommel EF. Ruptured giant liver cyst: a rare cause of acute abdomen in a haemodialysis patient with autosomal dominant polycystic kidney disease. Neth J Med. 2002;60(9):363-5.

37. Chaudhary S, Qian Q. Acute abdomen and ascites as presenting features of autosomal dominant polycystic kidney disease. World J Hepatol. 2012;4(12): 394-8.

38. Himeno A et al. Multiple liver cyst infection caused by Salmonella ajiobo in autosomal dominant polycystic kidney disease. J Infect Chemother. 2013;19(3):530-3.

39. Basar O et al. Recurrent pancreatitis in a patient with autosomal-dominant polycystic kidney disease. Pancreatology. 2006;6(1-2):160-2.

40. Naitoh H et al. Intraductal papillary mucinous tumor of the pancreas associated with autosomal dominant polycystic kidney disease. J Gastrointest Surg. 2005;9(6):843-5.

41. Luciano RL, Dahl NK. Extra-renal manifestations of autosomal dominant polycystic kidney disease (ADPKD): considerations for routine screening and management. Nephrol Dial Transplant. 2014;29(2):247-54.

42. Nagaba Y et al. Spontaneous rupture of a left gastroepiploic artery aneurysm in a patient with autosomal-dominant polycystic kidney disease. Clin Nephrol. 2005;63(2):163-6.

43. Griffin MD et al. Vascular expression of polycystin. J Am Soc Nephrol. 1997;8(4):616-24.

44. Kim K et al. Polycystin 1 is required for the structural integrity of blood vessels. Proc Natl Acad Sci USA. 2000;97(4): 1731-6.

45. Torres VE et al. Vascular expression of polycystin-2. J Am Soc Nephrol. 2001;12(1):1-9.

46. Ramunni A et al. Cutaneous microcirculation is impaired in early autosomal dominant polycystic kidney disease. Nephron Clin Pract. 2009;113(2):c71-5.

47. Heffernan KS et al. Peripheral augmentation index and vascular inflammation in autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 2011;26(8):2515-21.

48. Li Kam Wa TC et al. Ambulatory blood pressure in hypertensive patients with autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 1997;12(10):2075-80.

49. Ecder T, Schrier RW. Hypertension in autosomal-dominant polycystic kidney disease: early occurence and unique aspects. J Am Soc Nephrol. 2001;12(1): 194-200.

50. Pietrzak-Nowacka M et al. Autosomal dominant polycystic kidney disease and hypertension are associated with left ventricular mass in a gender-dependent manner. Kidney Blood Press Res. 2012;36(1):301-9.

51. Taddei S et al. Hypertension, left ventricular hypertrophy and chronic kidney disease. Heart Fail Rev. 2011;16(6):615-20.

52. Basile C et al. Spontaneous coronary artery dissection: one more extrarenal manifestation of autosomal dominant polycystic kidney disease? J Nephrol. 2009;22(3):414-6.

53. Afari ME et al. Spontaneous coronary dissection in polycystic kidney disease. R I Med J (2013). 2013;96(12):44-5.

54. Kucukdurmaz Z et al. Polycystic kidney disease with coronary aneurysm and acute coronary syndrome. Intern Med. 2009;48(22):1989-91.

55. Gignon M et al. Sudden death caused by aortic dissection in a patient with polycystic kidney disease. Genet Couns. 2011;22(4):333-9.

56. Ramineni R, Daniek GK. Use of endovascular stent-graft repair for type B aortic dissection in polycystic kidney disease. J Invasive Cardiol. 2010;22(9):E171-4.

57. Peczkowska M et al. The coexistence of acute aortic dissection with autosomal dominant polycystic kidney disease – description of two hypertensive patients. Blood Press. 2004;13(5):283-6.

58. Osawa Y et al. Thoracic aortic dissection in a patient with autosomal dominant polycystic kidney disease treated with maintenance hemodialysis. J Nephrol. 2000;13(3):193-5.

59. Minami T et al. Thoracic aortic dissection complicating autosomal dominant polycystic kidney disease; report of a case. Kyobu Geka. 2009;62(10):924-7.

60. Rodrigues L et al. Uncommon cause of chest pain in a renal transplantation patient with autosomal dominant polycystic kidney disease: a case report. Transplant Proc. 2012;44(8):2507-9.

61. Chapman AB et al. Hypertension in autosomal dominant polycystic kidney disease. Adv Chronic Kidney Dis. 2010;17(2):153-3.

62. Vlak MHM et al. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and the time period: a systematic review and mets-analysis. Lancet Neurol. 2011;10(7):626-36.

63. Chapman AB et al. Intracranial aneurysms in autosomal dominant polycystic kidney disease. N Engl J Med. 1992;327(13):916-20.

64. Belz MM et al. Recurrence of intracranial aneurysms in autosomal-dominant polycystic kidney disease. Kidney Int. 2003;63(5):1824-30.

65. Niemczyk M et al. Intracranial aneurysms in autosomal dominant polycystic kidney disease. AJNR Am J Neuroradiol. 2013;34(8):1556-9.

66. Chauveau D et al. Intracranial aneurysms in autosomal dominant polycystic kidney disease. Kidney Int. 1994;45(4):1140-6.

67. Torres VE et al. Cerebral aneurysms. N Engl J Med. 2006;355(25):2703-4.

68. Roth C et al. Ruptured cerebral aneurysm and acute bilateral carotid artery dissection in a patient with polycystic kidney disease and polycystic liver disease. Cerebrovasc Dis. 2013;35(6):590-1.

69. Niemczyk M et al. Arachnoid cyst in autosomal dominant polycystic kidney disease patient. Nephrology (Carlton). 2013;18(11):745.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE: WHAT DO WE NEED TO KNOW FOR COUNSELLING?

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ABSTRACT

In the new millennium, few kidney diseases changed their perspectives as much as autosomal dominant polycystic kidney disease (ADPKD). New diagnostic approaches, including the evaluation of renal or liver volume by computerised tomography (CT) scan, the detection of cyst infections by positron emission tomography (PET) scan, and new therapeutic approaches (including vaptans, mTOR inhibitors, and somatostatin analogues) pose new clinical and ethical dilemmas. Therefore, the analysis of the recent advances offers an occasion for reviewing our counselling policy. The aim of this narrative review is to discuss a few crucial points concerning counselling in ADPKD: should all ADPKD patients undergo genetic testing for characterisation of the involved gene? What is the role of prenatal counselling and preimplantation selection? Should all ADPKD patients be followed in a nephrology clinic? Which imaging to use in which patients? Whom should we treat, when, and by which drugs, and how to communicate the treatment options? The working conclusions highlight the trends towards earlier referral of ADPKD patients, the importance of offering the diet options, including low-salt, high-water intake, difficult to follow, but devoid of side-effects, and the expectancy for the new therapeutic options, alone or in combination, aimed at reduction of cyst volume and/or control of cyst growth.

Keywords: Polycystic kidney disease, genetic and prenatal diagnosis, complications, infection, dialysis, vaptans, mTOR inhibitors, liver cysts, somatostatin analogues, imaging.

INTRODUCTION

In the last few years the panorama faced by patients affected by autosomal dominant polycystic kidney disease (ADPKD), and by their treating physicians, has remarkably changed.[1,2] As usual, the progress brings more than new diagnostic techniques or therapeutic tools; it poses also new clinical and ethical problems and, in the era of patient empowerment, the analysis of the recent advances offers an occasion for reviewing our counselling policy.[3-5]

In this context, the present narrative, non-systematic review, has been focused on some 'hot' points in ADPKD, which the authors considered as fundamental for the clinicians. In keeping with the complexity of the disease, we have tried to highlight different opinions and uncertainties.[6]

Hence, we addressed our discussion at the following questions: should all ADPKD patients undergo genetic testing for characterisation of the involved gene? What is the role of prenatal counselling and preimplantation selection? Should all ADPKD patients be followed in a nephrology

clinic? Which imaging in which patients? Whom should we treat, when, and by which drugs, and how to communicate the treatment options?

SHOULD ALL ADPKD PATIENTS UNDERGO GENETIC TESTING?

ADPKD is the most common monogenic severe kidney disease, with an average incidence of 1 in 500-1,000 live births.[1,2,7,8] Mutations in the two major genes (polycystic kidney disease 1 [PKD1] on chromosome 16 and polycystic kidney disease 2 [PKD2] on chromosome 4) account for about 90% of cases, while, thus far, in the remaining approximately 10%, the genetic diagnosis is elusive and no mutation has been identified.[8-11]

While penetrance is complete, and virtually all patients with PKD1 or PKD2 mutations develop kidney cysts, the expressivity is highly variable, and the reasons for this wide variability are only partially understood.[12,13]

On average, PKD1 mutations correlate with a poorer renal prognosis and a younger age at start of renal replacement therapy (RRT); the peak of RRT start is presently in the late fifties in PKD1, and in the late seventies in PKD2 patients.[8-10] The difference is strong enough to suggest that the family history may predict the gene involved.[12] However, within-family variability is well documented, suggesting the presence of modifier effects of other genes, or from not yet defined environmental factors. In this regard, the clinical evolution of ADPKD may represent a challenging field for epigenetic analysis.[13]

Hence, the question on the clinical relevance for genetic testing is not easily answered. Indeed, several authors hold that the genetic tests are of use only in selected situations, such as non-typical ADPKD, absence of family history, or in view of a living kidney donation.[14,15] Other authors, however, consider that the genetic analysis will influence, if not now then in the near future, the therapeutic choices.[16]

There are pragmatic limits to a universal extension of the genetic tests: the first one is obviously economical, the second one is linked to the tests used. While the new generation of genetic tests allow a specific definition of the involved mutation, the older tests, based upon a linkage analysis, are not able to provide such information and should probably be considered obsolete.[17]

The opinion of our group is that genetic analysis will be needed in all patients in the near future. As the genetic tests are undergoing profound changes, leading to simplification (and lower costs), our present attitude is to perform genetic testing in cases with treatment indications, severe disease, or unclear family history, and in patients who wish to have a child. We usually test one individual per family, being ready to extend genetic analysis as soon as the availability of the tests will increase and their cost will decrease.

WHAT IS THE ROLE FOR PRENATAL COUNSELLING AND PREIMPLANTATION SELECTION?

The prenatal counselling of ADPKD may be seen as very easy or exceedingly difficult. It is easy since ADPKD is an autosomal dominant disease with complete penetration.[1-3] It is difficult since ADPKD has different expressivity and the clinical manifestation may occur as late as the sixth-to-seventh decade of life.[7-11] If we consider that the history of RRT is only in its fifth decade of life, we appreciate that forecasting life with end-stage kidney disease in the next 50 years is almost impossible.[18-20]

Hence, in the face of the clinical uncertainty, several approaches are possible: a negative one underlines that 50% of the children inherit the gene, counselling the patients not to have children, also taking into account the possibility of pregnancy-related complications in the mother, or supporting pregnancy interruption in the presence of the affected gene in the foetus.[21-24]

Preimplantation selection is considered by some authors an alternative, because it avoids the physical and emotional trauma of a pregnancy termination in the case of an affected foetus.[25] The value of such a statement is different in the case of recessive polycystic disease, with its grim prognosis, and of ADPKD. Preimplantation diagnosis is synonymous with *in vitro* fertilisation; hence the clinical and ethical problems of *in vitro* fertilisation - including also a higher rate of malformation and prematurity - cannot be avoided, as well as the physical and emotional stress of the assisted fertilisation procedure.[26-31]

On the other hand, the continuous therapeutic advances may lead to a more optimistic view, underlying also that early (*in utero*) diagnosis may be of help in planning preventive interventions

(such as control of urinary tract infections [UTIs], dietary habits, and prompt treatment of hypertension) and is potentially effective in postponing overt kidney disease.[1-3]

In a setting where the uncertainties largely overcome the certitudes, the policy adopted in our outpatient clinic dedicated to pregnancy in chronic kidney disease (CKD), is to underline that we are not able to forecast the future of an affected baby. If a woman over 35 years and/or with impaired kidney function considers pregnancy termination in the case of an affected foetus, we remind that the chances of a further pregnancy are not 100% and that increasing maternal age is associated with a steep rise in chromosome derangements, leading to diseases whose severity is way above that of ADPKD.[32]

A detailed discussion on pregnancy in ADPKD is beyond the scope of this review; however, two open problems may be cited: the need for strict blood pressure (BP) control as, for unknown reasons, pre-eclampsia has been reported as more frequent in ADPKD, also with normal BP and kidney function at the start of pregnancy.[23,33,34] The second one is the risk of intracystic bleeding at delivery, linked to the increase in intra-abdominal pressure during parturition.[33-35] The old tenet that women with ADPKD should deliver with Caesarean section is no longer shared, as the risks of a surgical intervention and of catheter-associated UTI may exceed those of intracystic bleeding. However, the risk of intracystic bleeding has to be borne in mind and, at least in our centre, we suggest close ultrasound (US) monitoring of the largest cysts, also in non-symptomatic patients, at least in the proximity of delivery and immediately after.[36,37]

SHOULD ALL ADPKD PATIENTS BE FOLLOWED IN A NEPHROLOGY CLINIC?

The pattern of the ADPKD patients referred to outpatient nephrology units has been changing over time, with an overall earlier referral of the patients.[38] There are at least three reasons for this: the wider availability of US leading to preclinical diagnosis, the higher awareness, and the increasing therapeutic options.[1-3,7] Once more, the indications are not uniform and reflect both the sanitary system and the opinions of the physicians. As pointed out by a brilliant recent editorial in the *New England Journal of Medicine*, entitled: '*From sick care to health care — reengineering prevention into the U.S. system*',[39] disease prevention encompasses all efforts to anticipate the genesis of disease and forestall its progression to clinical manifestations. Hence, focus on prevention is not synonymous of elimination of the disease, but of 'morbidity compression,' extending the symptom-free lifespan.[39]

The chronic lack of resources of the healthcare systems often leads to a minimalist attitude, limiting the care to the patients with overt disease, with the idea that the present therapeutic tools contrast only the macro-effects of the disease, such as hypertension, and the metabolic cascade of maladaptive changes characteristic of advanced CKD.[40,41]

There is a wide agreement on the importance of timely treatment of the UTIs and on the full normalisation of hypertension, although opinions on the diet are mixed.[40-43] Some authors maintain that low protein diets are of minor efficacy in ADPKD patients, while on the contrary, animal studies suggest that an early start of moderate protein restriction may slow the progression of the disease.[44] Furthermore, the dietary approaches include also a very high water intake, and a drastic reduction of salt intake.[45-48] The potentials of this 'difficult' diet are underlined also by the promising and likewise 'difficult' results obtained with Tolvaptan, through the pharmacologic inhibition of the action of vasopressin on its receptors.[45,46] Promising results have occasionally been reported with the use of statins at the highest tolerated doses, and the recent studies on glucose metabolism may suggest an early approach to glycaemic intolerance.[49-52] Consequently, the start of follow-up is directly related to the therapeutic options (the more, the earlier) and to the indications for the new therapies.[53,54]

In our unit, ADPKD patients represent about 10% of cases who performed at least one nephrology consultation. In 2012, we started a baseline nuclear magnetic resonance assessment in all the patients with large kidney, symptomatic disease, or advanced CKD, leading to the selection for octreotide therapy, of a first group of cases with relevant symptoms and liver involvement. The availability of this option had a strong effect in recruiting more family members, often at earlier stages of the disease.

Our unit follows a policy of the wide use of low protein diets.[55,56] So far, ten ADPKD patients have been enrolled in a moderate protein restriction (0.6 g/kg/day) with a vegan schema, with the

addition of alpha keto-analogues.[55,56] Within the limitations of small numbers, and of the nonlinear glomerular filtration rate decrease, long-term stabilisation and prolongation of dialysis-free interval were attained at least in a few cases (Figure 1). The indications for a high-water, low-sodium diet are contextually given to all patients. We suggest following all ADPKD patents in pregnancy, considering them 'at risk pregnancies', paying particular attention to infectious complications and to the development of pregnancy-induced hypertension and pre-eclampsia.[36,37]

WHICH IMAGING IN WHICH PATIENTS?

Imaging is the basis not only of diagnosis, but also of the assessment of prognosis, since cyst growth correlates with the progression of renal function impairment.[57,58] However, the best way to assess progression is not yet established, and the same holds true for the detection of the complications. Each imaging method has advantages and drawbacks. US are the mainstay for family screening, and are the basis for diagnosis and follow-up in children and in pregnancy.[59] Their role is limited mainly by the operator dependence.[59]

Hence, CT and magnetic resonance imaging (MRI) scans, each with advantages and drawbacks, are now becoming the gold standard for the three-dimensional analysis of the involved kidneys or liver, allowing comparison over time.[59] Some problems remain open; for instance, it is not clear if the evolution of a few large cysts is superimposable to the effect of numerous small cysts (Figure 2).

In this regard, more sophisticated approaches, aimed at assessing the fibrous kidney tissue, have been attempted.[60] The limits of this clever strategy, showing a strong correlation with renal functional impairment and the need for computerised tomography (CT) scan with contrast media, raise obvious issues of radioprotection and nephrotoxicity.[60]

Further problems arise in the presence of complications. CT scan is the gold standard for stone disease, of particular importance in these cases in which the altered kidney structure impairs the detection of stones.[61,62] CT angiography scan is the technique of choice for massive bleeding (Figure 3). The detection of infected cysts is more challenging because of the various, often non-specific, clinical manifestations ranging from mild abdominal discomfort to a severe life-threatening disease.[63-65] MRI and CT are both valuable in discriminating between non-complicated and complicated cysts, but are usually unable to discriminate between bleeding, infection, or neoplasia.[65,66] Furthermore, the presence of several 'complicated' cysts is common in severely enlarged liver or kidneys, further impairing the localisation of the infectious process.[63-66] Hence, scintigraphy with leukocytes labelled with indium or gallium was employed, with the limits being the lack of prompt availability, the high costs, and the relatively poor spatial discrimination.[67,68]

Consequently, fludeoxyglucose-PET (FDG-PET), able to identify metabolically active tissues, is becoming the gold diagnostic standard in this setting.[65,66,69] Among the advantages of this sophisticated technique is also that the tracer, a glucose analogue, is non-nephrotoxic also in advanced CKD stages (Figure 4).

WHOM SHOULD WE TREAT, WHEN, AND BY WHICH DRUGS, AND WHAT SHOULD WE ADVISE?

Finally, the great open question for the clinical nephrologist: is it already time for treating our patients with any, or a combination of new drugs? Indeed, in the new millennium, almost suddenly a rapidly growing number of drugs potentially slowing the progression of renal cysts has been tested in animals and in humans.[1-3,7,21,41-54] A detailed insight into the basic mechanisms and into the results is not in the scope of this clinical review. However, in a rapidly evolving world and in the presence of an increased involvement of the patients in their medical choices, often through long and perilous sailing on the vast seas of the Internet, every clinical nephrologist is increasingly questioned on the 'new therapies'. When we typed 'ADPKD therapy' into Google we found minimalist opinions such as: 'The only available treatment for kidney failure from ADPKD is dialysis. The only available cure is kidney transplantation.' Together with the crosslink to the paper: '*Therapy for polycystic kidney disease? It's water, stupid!*'[45] Wikipedia extensively cites Tolvaptan, the PKD foundation offers a detailed list of the on-going trials, while the PKD Charity UK dedicates a webpage to complementary therapies and includes data on diet, Tolvaptan, everolimus, somatostatin, and lanreotide. The latter represents the three major therapeutic approaches aimed at interfering at different levels with cyst formation and growth.

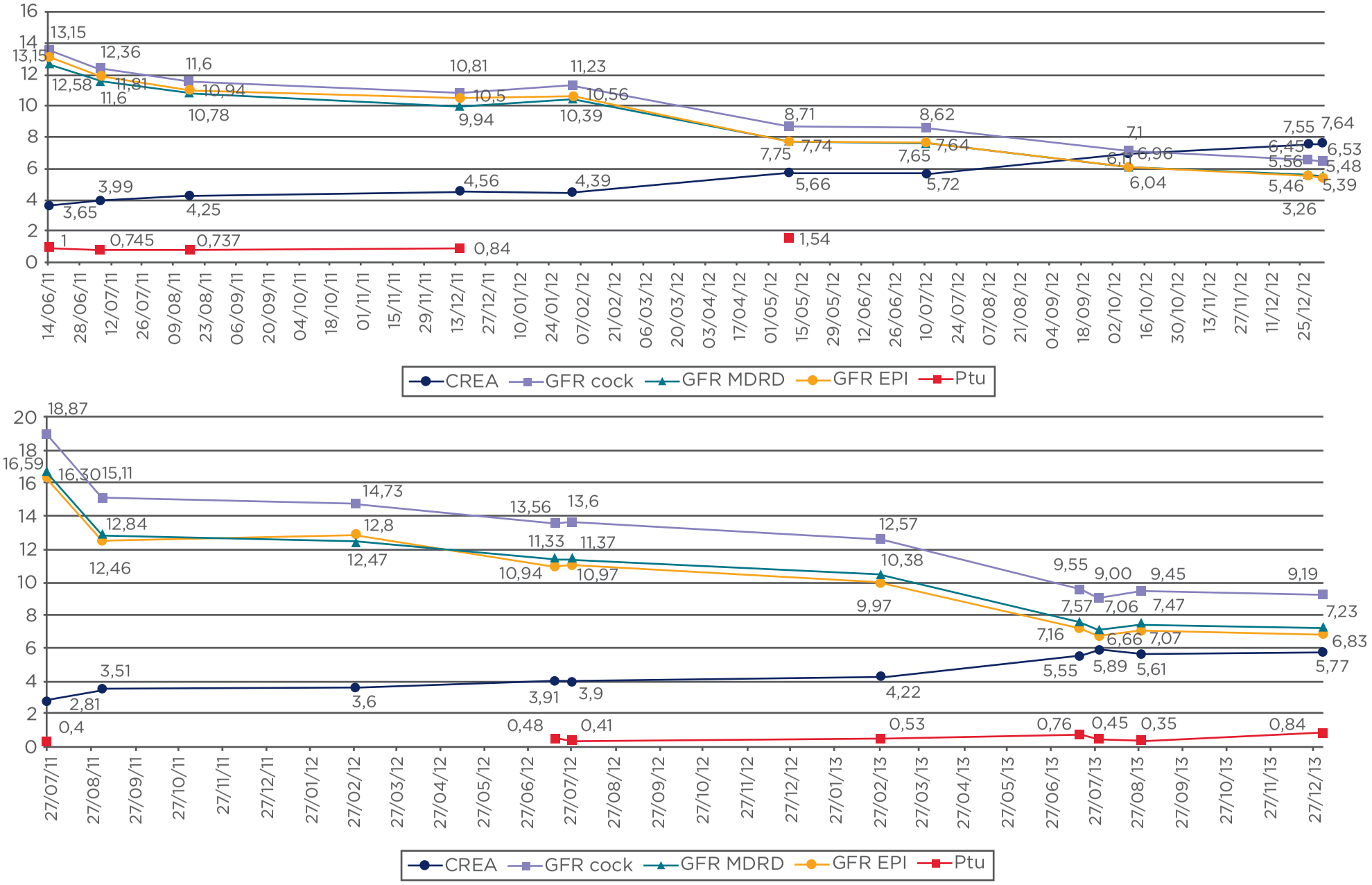

Figure 1: Long-term follow-up of ADPKD patients on a vegan supplemented (0.6 g/day) LPD.

ADPKD: autosomal dominant polycystic kidney disease; LPD: low protein diet; CREA: creatinine; GFR: glomerular filtration rate; cock: Cockcroft-Gault; MDRD: modification of diet in renal disease; EPI: epidemiology collaboration; Ptu: propylthiouracil.

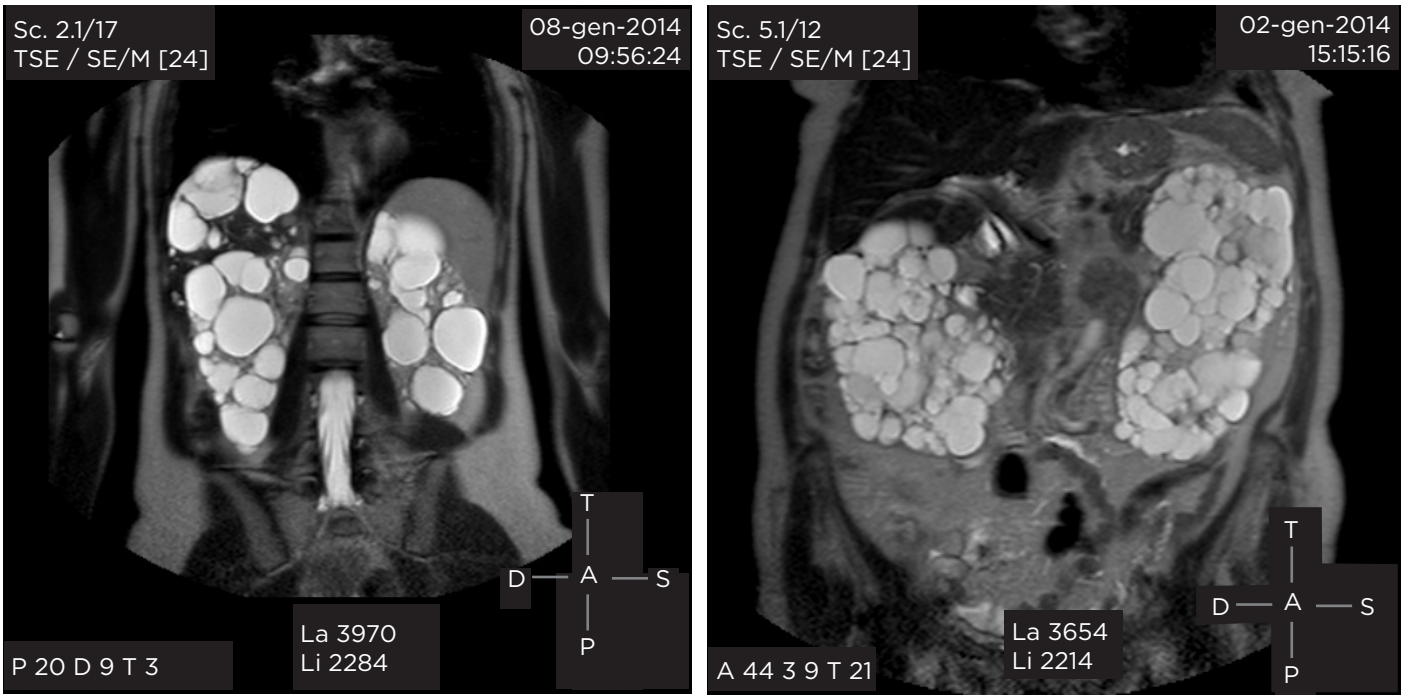

Figure 2: NMR in two cases, exemplificative of the spectrum of ADPKD: a few large renal cysts versus complete structural derangement, mainly linked to a myriad of small cysts.
NMR: nuclear magnetic resonance; ADPKD: autosomal dominant polycystic kidney disease.

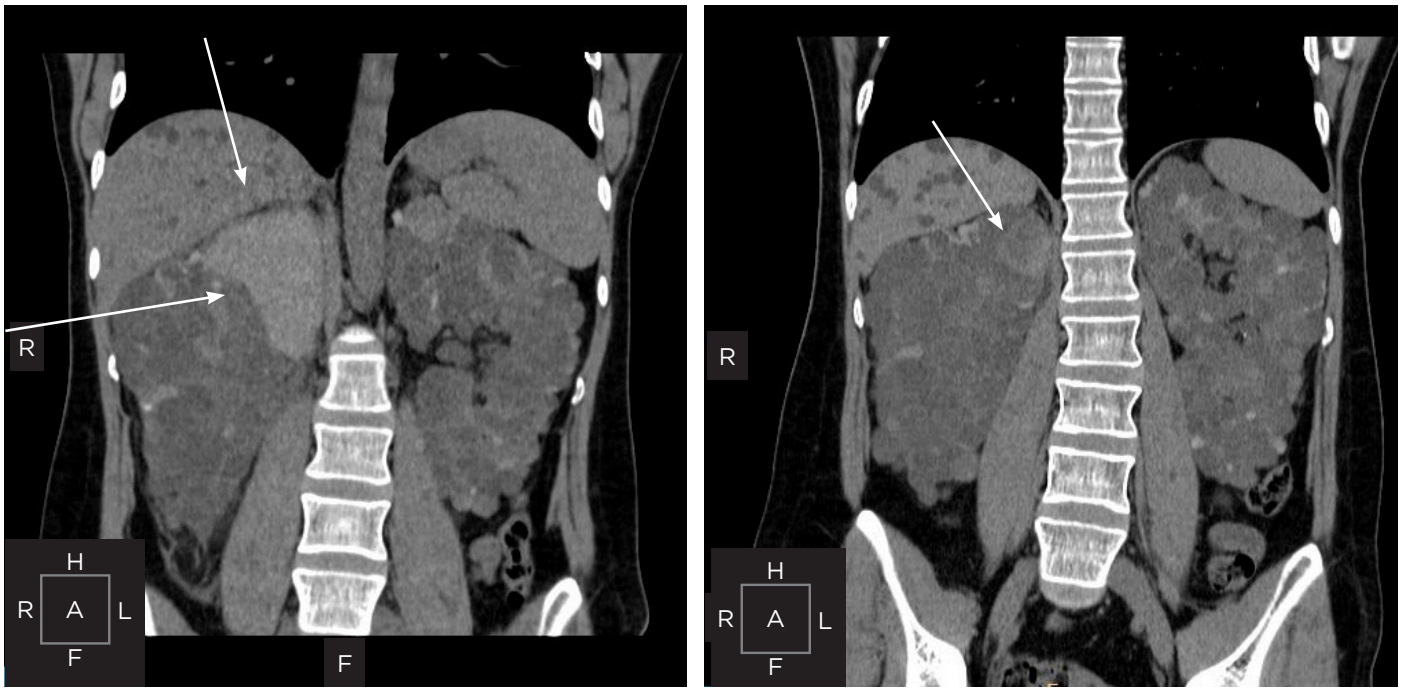

Figure 3: Massive intracystic bleeding, mimicking kidney rupture in the first computerised tomography scan, and evolution of the lesion over time. On the account of the residual chronic pain, and of the large polycystic kidneys and liver, the patient was started on once-monthly therapy with octreotide LAR.

All trials opened new questions and provoked further issues, such as the best compromise between toxicity, long-term risk and advantages - in particular in the case of rapamycin and the other mTOR inhibitors - and of the effect on quality of life in the case of Tolvaptan and other vaptans. The high costs of therapies, and of vaptans in particular, adds to the difficulty in widening the experience out of the research setting.[70-75]

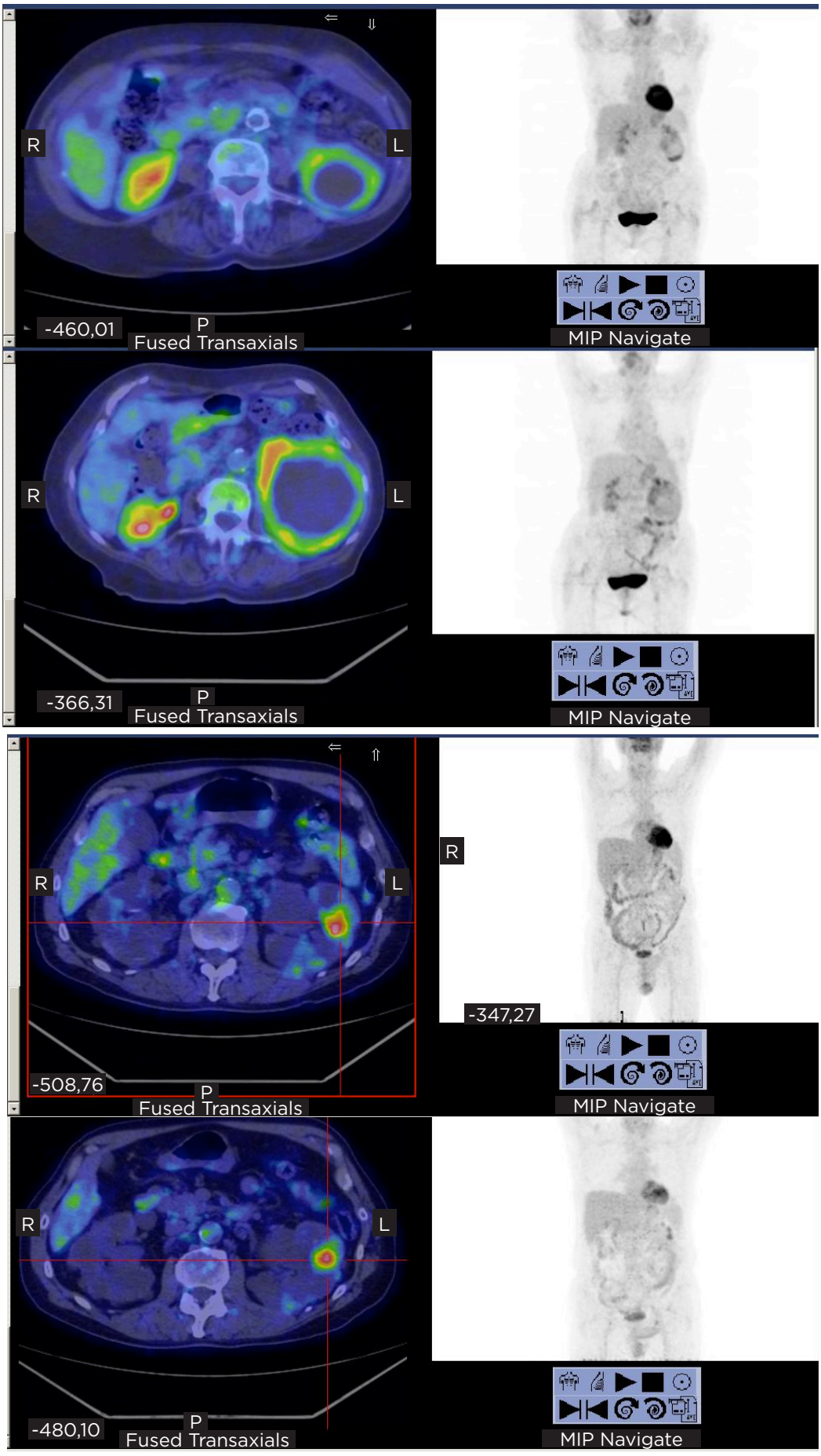

Figure 4: Fludeoxyglucose-positron emission tomography scan of infected liver and kidney cysts, and evolution after long-term antibiotic therapy.

A partial exception to the inconsistency of the trial results regards somatostatin, or its analogues in the hepatorenal variant of ADPKD, as well as in the isolated polycystic liver, genetically different but phenotypically similar. The reduction of the cysts, overall significant in the large polycystic livers, is also recorded in the kidneys, albeit at a lower degree. However, as highlighted by the ALADIN study, the lack of significant side-effects and the absence of a 'rebound effect' after discontinuation may alter the cost-benefit balance in favour of therapy, whose effects appear to be more consistent in women of childbearing age.[74-76]

Hence, the discussion on the indications is ongoing, at least in the countries where ADPKD with liver involvement is considered as a rare disease, easing the prescription process. Consequently, octreotide and analogues are slowly entering into clinical practice, while the other options are still limited to the research setting. Regarding patients with isolated kidney involvement, mainly because of prescription constraints, the 'new' therapeutic options are presently limited to the research setting.

Three main indications are presently followed for octeotide therapy: the presence of large and rapidly growing cysts, chronic pain, and abdominal distension.[54] However, the suggestion that the best results are recorded in relatively young patients, and the focus shift from reduction of the volume to stabilisation of the lesions, may lead to an anticipation of this therapy whose costs are, however, a relevant drawback in this era of healthcare cost constraints.[76]

In this interlocutory phase, our choice has been to start treatment for ADPKD patients with liver involvement and symptomatic disease. The discussion on the rapid progress of knowledge should, in our opinion, be a part of the counselling to patients and should be the basis for planning a regular follow-up also in presymptomatic cases.

CONCLUSIONS

The working conclusions of this clinical non-systematic review may be summarised in four major points. The first is the increasing knowledge in the face of therapeutic uncertainties. The balance between rapidly growing knowledge and a long list of unanswered questions poses a challenge for counselling, but may also set the basis for a constructive patient-physician relationship. The second is the suggestion to start follow-up early and to characterise the preclinical cases since the indications to 'new' treatments are changing and the timing for intervention is switching to earlier phases. Furthermore, an earlier follow-up may allow easier timely interventions on BP and on UTIs. The third is to consider that dietary interventions are not expensive and may be effective. Following a diet may be difficult and is probably not 'fitting' for all patients but, considering the high costs and the low availability of other 'specific' treatments, a diet trial may be worth offering to all cases, at least for selecting those in which a better balance compliance-diet may be attained. Lastly, we would like to call for attention on some specific situations: pregnancy that should be followed as a high-risk condition, also in the presence of normal renal function and BP; intracystic infections, whose diagnostic gold standard is the PET scan; the association with polycystic liver; and the presently better defined 'niche' for 'new' treatments. All of these are but working conclusions and the authors are aware that all of them may be shortly out-dated by the rapid improvement in diagnosis and therapy that render this disease a fascinating field not only for the researcher, but also for the clinical nephrologist.

REFERENCES

1. Wilson PD. Polycystic kidney disease. New Engl J Med. 2004;350(2):151-64.

2. Torres VE et al. Autosomal dominant polycystic kidney disease. Lancet. 2007;369(9569):1287-301.

3. Anonymous. Who owns medical technology? Lancet. 1995;345(8958): 1125-6.

4. Pilnick A, Dingwall R. Research directions in genetic counselling: a review of the literature. Patient Educ Couns. 2001;44(2):95-105.

5. Smets E et al. Comparing genetic counseling with non-genetic health care interactions: two of a kind? Patient Educ Couns. 2007;68(3):225-34.

6. Krzywinski M, Altman N. Points of significance: importance of being uncertain. Nat Methods. 2013;10(9): 809-10.

7. Torres VE, Harris PC. Autosomal dominant polycystic kidney disease: the last 3 years. Kidney Int. 2009;76(2): 149-68.

8. Harris PC, Hopp K. The mutation, a key determinant of phenotype in ADPKD. J Am Soc Nephrol. 2013;24(6):868-70.

9. Cornec-Le Gall E et al. Type of PKD1 mutation influences renal outcome in ADPKD. J Am Soc Nephrol. 2013;24(6):1006-13.

10. Harris PC, Rossetti S. Determinants of renal disease variability in ADPKD. Adv

Chronic Kidney Dis. 2010;17(2):131-9.

11. Watnick TJ, Germino GG. Polycystic kidney disease: polycystin-1 and polycystin-2-it's complicated. Nat Rev Nephrol. 2013;9(5):249-50.

12. Barua M et al. Family history of renal disease severity predicts the mutated gene in ADPKD. J Am Soc Nephrol. 2009;20(8):1833-8.

13. Li X. Epigenetics and autosomal dominant polycystic kidney disease. Biochim Biophys Acta. 2011;1812(10): 1213-8.

14. Pei Y. Diagnostic approach in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2006;1(5):1108-14.

15. Barua M, Pei Y. Diagnosis of autosomal-dominant polycystic kidney disease: an integrated approach. Semin Nephrol. 2010;30(4):356-65.

16. Harris PC, Rossetti S. Molecular diagnostics for autosomal dominant polycystic kidney disease. Nat Rev Nephrol. 2010;6(4):197-206.

17. Turco A et al. Linkage analysis for the diagnosis of autosomal dominant polycystic kidney disease, and for the determination of genetic heterogeneity in Italian families. Clin Genet. 1991;40(4): 287-97.

18. Scribner BH. A personalized history of chronic hemodialysis. Am J Kidney Dis. 1990;16(6):511-9.

19. Blagg CR. A brief history of home hemodialysis. Adv Ren Replace Ther. 1996;3(2):99-105.

20. Ross W. God panels and the history of hemodialysis in America: a cautionary tale. Virtual Mentor. 2012;14(11):890-6.

21. Harris PC, Torres VE, Polycystic Kidney Disease, Autosomal Dominant, Pagon RA et al. (eds), SourceGeneReviews™ [Internet] (1993-2013), Seattle: University of Washington.

22. Torra Balcells R, Ars Criach E. Molecular diagnosis of autosomal dominant polycystic kidney disease. Nefrologia. 2011;31(1):35-43.

23. Vora N et al. Reproductive issues for adults with autosomal dominant polycystic kidney disease. Am J Kidney Dis. 2008;51(2):307-18.

24. Macnicol AM et al. Education and attitudes in families with adult polycystic kidney disease. Nephrol Dial Transplant. 1991;6(1):27-30.

25. Gigarel N et al. Preimplantation genetic diagnosis for autosomal recessive polycystic kidney disease. Reprod Biomed Online. 2008;16(1):152-8.

26. Flicker LS. Acting in the best interest of a child does not mean choosing the "best" child. Am J Bioeth. 2012;12(4): 29-31.

27. Savulescu J. Procreative beneficence: why we should select the best children. Bioethics. 2001;15(5-6):413-26.

28. de Melo-Martin I. On our obligation to select the best children: a reply to Savulescu. Bioethics. 2004;18(1):72-83.

29. Gutarra-Vilchez R et al. Birth defects in medically assisted reproduction pregnancies in the city of Barcelona. Prenat Diagn. 2013;doi:10.1002/pd.4286. [Epub ahead of print].

30. Pinborg A et al. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. Hum Reprod Update. 2013;19(2):87-104.

31. McDonald SD et al. Preterm birth and low birth weight among in vitro fertilization singletons: a systematic review and meta-analyses. Eur J Obstet Gynecol Reprod Biol. 2009;146(2):138-48.

32. Kenny LC et al. Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. PLoS One. 2013;8(2):e56583.

33. Chapman AB et al. Pregnancy outcome and its relationship to progression of renal failure in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1994;5(5):1178-85.

34. Fernandes SD, Suvarna D. Anesthetic considerations in a patient of autosomal dominant polycystic kidney disease on hemodialysis for emergency cesarean section. J Anaesthesiol Clin Pharmacol. 2011;27(3):400-2.

35. Rajanna DK et al. Autosomal recessive polycystic kidney disease: antenatal diagnosis and histopathological correlation. J Clin Imaging Sci. 2013;3:13.

36. Piccoli GB et al. Pregnancy in CKD: whom should we follow and why? Nephrol Dial Transplant. 2012;27(Suppl 3):iii111-8.

37. Piccoli GB et al. Pregnancy and chronic kidney disease: a challenge in all CKD stages. Clin J Am Soc Nephrol. 2010;5(5):844-55.

38. Helal I et al. Changing referral characteristics of patients with autosomal dominant polycystic kidney disease. Am J Med. 2013;126(9):832.e7-832.e11.

39. Fani Marvasti F, Stafford RS. From sick care to health care--reengineering prevention into the U.S. system. N Engl J Med. 2012;367(10):889-91.

40. Luciano RL, Dahl NK. Extra-renal manifestations of ADPKD: considerations for routine screening and management. Nephrol Dial Transplant. 2013. [Epub ahead of print].

41. Masoumi A et al. Developments in the management of autosomal dominant polycystic kidney disease. Ther Clin Risk Manag. 2008;4(2):393-407.

42. Davis ID et al. Can progression of autosomal dominant or autosomal recessive polycystic kidney disease be prevented? Semin Nephrol. 2001;21(5):430-40.

43. Cowley BD Jr et al. Modification of disease progression in rats with inherited polycystic kidney disease. Am J Kidney Dis. 1996;27(6):865-79.

44. Klahr S et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol. 1995;5(12):2037-47.

45. Grantham JJ. Therapy for polycystic kidney disease? It's water, stupid! J Am Soc Nephrol. 2008;19(1):1-7.

46. Wang X et al. Vasopressin directly regulates cyst growth in polycystic kidney disease. J Am Soc Nephrol. 2008;19(1):102-8.

47. Nagao S et al. Increased water intake decreases progression of polycystic kidney disease in the PCK rat. J Am Soc Nephrol. 2006;17(8):2220-7.

48. Wang CJ et al. Water prescription in autosomal dominant polycystic kidney disease: a pilot study. Clin J Am Soc Nephrol. 2011;6(1):192-7.

49. Cadnapaphornchai MA et al. Effect of statin therapy on disease progression in pediatric ADPKD: design and baseline characteristics of participants. Contemp Clin Trials. 2011;32(3):437-45.

50. van Dijk MA et al. Effect of simvastatin on renal function in autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 2001;16(11):2152-7.

51. Takiar V et al. Activating AMP-activated protein kinase (AMPK) slows renal cystogenesis. Proc Natl Acad Sci U S A. 2011;108(6):2462-7.

52. McCarty MF et al. Activation of AMP-activated kinase as a strategy for managing autosomal dominant polycystic kidney disease. Med Hypotheses. 2009;73(6):1008-10.

53. Torres VE et al. Rationale and design of the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) 3-4 Study. Am J Kidney Dis. 2011;57(5):692-9.

54. Hogan MC et al. Somatostatin analog therapy for severe polycystic liver disease: results after 2 years. Nephrol Dial Transplant. 2012;27(9):3532-9.

55. Piccoli GB et al. Vegetarian low-protein diets supplemented with keto analogues: a niche for the few or an option for many? Nephrol Dial Transplant. 2013;28(9): 2295-305.

56. Piccoli GB et al. Which low protein diet for which chronic kidney disease patient? An observation personalized approach. Nutrition. In press.

57. Chapman AB. Approaches to testing

new treatments in autosomal dominant polycystic kidney disease: insights from the CRISP and HALT-PKD studies. Clin J Am Soc Nephrol. 2008;3(4):1197-204.

58. Hadjidemetriou S et al. Volumetric analysis of MRI data monitoring the treatment of polycystic kidney disease in a mouse model. MAGMA. 2011;24(2): 109-19.

59. Rahbari-Oskoui F et al. Renal relevant radiology: radiologic imaging in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2013. [Epub ahead of print].

60. Caroli A et al. Intermediate volume on computed tomography imaging defines a fibrotic compartment that predicts glomerular filtration rate decline in autosomal dominant polycystic kidney disease patients. Am J Pathol. 2011;179(2):619-27.

61. Tisdale BE et al. Correlation of CT scan versus plain radiography for measuring urinary stone dimensions. Can J Urol. 2007;14(2):3489-92.

62. Parsons JK et al. Urinary stone size: comparison of abdominal plain radiography and noncontrast CT measurements. J Endourol. 2003;17(9):725-8.

63. Gibson P, Watson M. Cyst infection in polycystic kidney disease: a clinical challenge. Nephrol Dial Transplant. 1998;13(10):2455-7.

64. Chaveau D et al. Liver involvement in autosomal dominant polycystic kidney disease: therapeutic dilemma. J Am Soc Nephrol. 2000;11(9):1767-75.

65. Jouret F et al. Positron-emission computed tomography in cyst infection diagnosis in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2011;6(7):1644-50.

66. Sallée M et al. Cyst infections in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2009;4(7):1183-9.

67. Amesur P et al. Infected cyst localization with gallium SPECT imaging in polycystic kidney disease. Clin Nucl Med. 1988;13(1):35-7.

68. Lahiri SA et al. In-111 WBC scan localizes infected hepatic cysts and confirms their complete resection in adult polycystic kidney disease. Clin Nucl Med. 1998;23(1):33-4.

69. Piccoli GB et al. Positron emission tomography in the diagnostic pathway for intracystic infection in adpkd and "cystic" kidneys. a case series. BMC Nephrol. 2011;12:48.

70. Erickson KF et al. Cost-effectiveness of tolvaptan in autosomal dominant polycystic kidney disease. Ann Intern Med. 2013;159(6):382-9.

71. Tuot DS, Powe NR. Translating science to improve health: hope for patients with kidney disease at what cost? Ann Intern Med. 2013;159(6):430-1.

72. Caroli A et al. Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. Lancet. 2013;382(9903):1485-95.

73. Qian Q, Wang HY. ALADIN: wish granted in inherited polycystic kidney disease? Lancet. 2013;382(9903):1469-71.

74. Walz G et al. Everolimus in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2010;363(9): 830-40.

75. Serra AL et al. Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. N Engl J Med. 2010;363(9):820-9.

76. Gevers TJ et al. Young women with polycystic liver disease respond best to somatostatin analogues: a pooled analysis of individual patient data. Gastroenterology. 2013;145(2):357-65. e1-2.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE: REVIEW AND MANAGEMENT UPDATE

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited nephropathy. Initially, it is characterised by the growth of renal cysts. Later, progressive deterioration of renal function determines the prognosis of ADPKD, depending on the main factors of progression (genetic, renal volume, and hypertension). Ultrasonography is the diagnostic technique of choice in the screening for relatives of ADPKD patients. Due to the absence of specific treatment it is necessary, in many cases, to start with renal replacement therapy. ADPKD can also be associated with extrarenal manifestations, mainly polycystic liver disease and cerebral aneurysms, which contribute to increased morbidity and mortality of these patients.

Keywords: Autosomal dominant polycystic kidney disease (ADPKD), diagnosis, cysts complications, renal disease progression, extrarenal manifestations.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent inherited renal disease with an estimated prevalence of approximately 1 in 800 live births. It is caused by mutations in two genes: *PKD1* in 85% and *PKD2* in 15% of cases.[1] Offspring have a 50% risk of inheriting the mutated gene; however, there are sporadic mutations in 10-15% of patients. ADPKD is the cause of 6-10% of patients undergoing renal replacement therapy (RRT).[2]

The *PKD1* and *PKD2* genes encode for proteins polycystin 1 and polycystin 2, respectively, which are an associated complex in the cell membrane, acting as a receptor and non-selective cation channel.[3] The polycystin complex is localised mainly in the primary cilium of the tubular epithelium, but also in focal adhesions between cells and cell-matrix. Its functions are receptor-sensor of the urinary flow, orientation of the cell, and regulation of the cell cycle.

In ADPKD, these alterations in cilia function cause a cascade of biochemical signals with the increase of intracellular cyclic adenosine monophosphate (cAMP)[4] that stimulate cell proliferation and transverse growth instead of longitudinal tubule. The cell loses its orientation,[5] initiating the formation of renal cysts. The Na-K-ATPase pumps translocate from the basolateral membrane to the luminal membrane, whereby promoting sodium and water secretion into the cyst, stimulating its growth.[6]

With reference to the *two-hit* hypothesis, the second hit could explain the variable phenotypic expression of the disease in families with the same mutation and all renal cysts are forming only from 1% of tubular cells. Although a mutated allele is inherited, cyst genesis begins when a somatic mutation in the normal allele (*second hit*) appears.[7] The severity of ADPKD in the individual depends on the precocity of this mutation occurring, as has been observed in experiments with mice.[8] Environmental factors (chronic inflammation, cytokines, renal ischaemia) may accelerate this process.[9]

The progressive growth of renal cysts can cause tubular obstruction and renal ischaemia, which increase activity of the renin-angiotensin system (RAS) with arterial hypertension.[10] Deterioration of renal function is not observed until the destruction of at least 50% of the parenchyma. Histological lesions are hyperplasia of the cystic epithelium,

vascular sclerosis, and interstitial fibrosis. The kidneys increase their volume greatly.

DIAGNOSIS

Screening diagnosis should be performed in all first-degree adult relatives (>18 years) of patients with ADPKD.[11] Ultrasonography is the technique of choice to diagnose and follow-up ADPKD patients, detecting cysts >1 cm and abdominal extrarenal features such as hepatic cysts. Ultrasonography is cheap and safe, and its sensitivity for *PKD1* is significantly higher than for *PKD2*.[12] Computed tomography (CT) and magnetic resonance imaging (MRI) can detect cysts as small as 0.5 cm but are reserved for limited cases (suspicion of kidney stones or renal tumours) as they are more expensive and expose patients to radiation. MRI is the best imaging modality to monitor renal volume as used in research studies but not in clinical practice.[13]

Ultrasonographic diagnostic criteria[14] are applied to patients with unknown genotype and a family history of ADPKD (Table 1). In the case of a negative family history, the presence of renal cysts with increased kidney size, deterioration of renal function, and liver cysts may suggest the diagnosis of ADPKD;[15] however, it must be differentiated from other cystic acquired disorders (multiple simple cysts, acquired renal cystic disease, medullary sponge kidney) or genetic disorders (autosomal recessive PKD, tuberous sclerosis, orofaciodigital syndrome Type 1, medullary cystic disease).[16]

Genetic testing should not be used as a screening tool when imaging diagnosis is clear. It is only indicated in specific situations: diagnosis of exclusion in younger at-risk individuals with a family history of ADPKD (such as a potential living-related kidney donor), patients with cystic disease but without affected relatives, individuals with early onset of PKD in families with ADPKD, and couples who wish a prenatal or preimplantation genetic diagnosis.[17] There are two methods to perform genetic testing: genetic linkage analysis (indirect study that requires several affected family members) or mutation analysis by Sanger sequencing (direct study, useful in sporadic mutations).[18]

Urinary Findings

The urinary concentration defect is one of the earliest findings and may be associated with symptoms of thirst and polyuria.[19] It has been demonstrated that urinary osmolality is less in

Table 1: Ultrasonographic criteria diagnosis for patients with a positive family history of autosomal dominant polycystic kidney disease.

Years	Number Of Cysts
15-39	≥3 cysts (unilateral or bilateral)
40-59	≥2 cysts in each kidney
>60	≥4 cysts in each kidney
>40	<2 cysts for diagnosis of exclusion

ADPKD after water restriction test.[20] Proteinuria is usually minimal and is associated with more advanced renal dysfunciton.[21] Urolithiasis occurs in 20-36% of cases, mainly because of the cystic collector compression system.[22] In addition, the stones are favoured by other alterations in the urine which may be present: low urine pH, hypocitraturia, hyperoxaluria, or hypercalciuria.

Cyst Compilations

Cystic infection causes sudden acute pain, localised in the flank, and fever with elevated markers of inflammation. Imaging tests should be performed for diagnosis since blood or urine cultures are often negative.[23] The treatment of choice is soluble antibiotics (quinolones) that penetrate the walls of the cyst for several weeks. Depending on the severity of infection, other treatment options to consider are percutaneous or surgical drainage, or even nephrectomy in recurrent infections.

In symptomatic cystic bleeding, the management is typically conservative with rest, hydration, and analgesia. In persistent bleeding, the following may be necessary: transfusion, desmopressin, percutaneous embolisation, or nephrectomy.[24] When haematuria persists for more than 1 week or when the first episode occurs in over 50 years, screening for kidney cancer with MRI or CT with contrast is recommended. The prevalence of kidney cancer is not increased in patients with ADPKD.[25]

RENAL DISEASE PROGRESSION

Although during the first decades of life the renal function remains normal, the growth and development of renal cysts continues. After starting the deterioration, the annual reduction of glomerular filtration rate (GFR) is 4.4-5.9 ml/minute.[26] Depending on the GFR, the patients

should be regularly monitored by the nephrologist, although there are no established protocols. ADPKD is considered by some authors the prototype of cardiorenal syndrome Type 4,[27] associated with lower prevalence of cardiovascular disease. The main factors that determine progression of chronic kidney disease (CKD) are: genetic, renal volume, and hypertension (Table 2).

The mutation in *PKD1* has a worse prognosis, beginning the RRT several years before *PKD2* (53 years versus 69 years). A recent study in patients with *PKD1* observed that individuals with *truncating mutations* progress faster to RRT than patients without this mutation (55 years versus 67 years).[28]

Total renal volume is the best predictor of progression of CKD.[29] The increase of renal volume rate is 1-10% per year. Data from CRISP (Consortium for Radiologic Imaging Studies of polycystic kidney disease) of kidney volume, measured by MRI, demonstrated that the growth in renal volume is associated with deterioration of renal function,[30] reduction of blood flow renal,[31] and hypertension.[32]

The control of blood pressure slows the progression of CKD and usually precedes the decline of GFR.[33] Initial treatment option is the use of RAS inhibitors to achieve blood pressure of <130/80 mmHg;[34] however, these have not demonstrated superiority in the progression of CKD versus beta-blockers[35] or calcium channel blockers,[36] only with diuretics.[37] 45% of ADPKD patients have a non-dipping circadian rhythm on ambulatory blood pressure monitoring.[38]

Table 2: Factors that determine progression of CKD in ADPKD patients.

Major	Minor
Genotype PKD1 > PKD2	Early onset of symptoms
	Proteinuria
TRV	HDL cholesterol
TRC	Defect in urinary concentration
Hypertension	LVH

CKD: chronic kidney disease; ADPKD: autosomal dominant polycystic kidney disease; TRV: total renal volume; TRC: total renal cyst; HDL: high-density lipoprotein; LVH: left ventricular hypertrophy.

Others relevant factors include: early age of onset of symptoms,[39] low high-density lipoprotein cholesterol levels, proteinuria, haematuria, left ventricular hypertrophy, and defect in urinary concentration (Table 2).[40] Although traditionally the male sex has been considered a risk factor for progression, in many articles there are no differences.[41] Normotensive pregnant women with normal renal function usually have uncomplicated pregnancies without reduction of GFR; however, several pregnancies may accelerate progression to CKD.[42]

TREATMENT

Experimental studies with vasopressin V2 receptor antagonist (tolvaptan) in mice with PKD found lower renal cAMP levels and inhibition of cystogenesis.[43] The TEMPO study included 1,445 ADPKD patients with GFR >60 ml/minute and renal volume >750 ml, who received treatment with tolvaptan or placebo (double-blind) for 3 years. In the results of the tolvaptan group, a slowing of the deterioration in renal function was observed and there was a smaller increase in renal volume, although adverse effects were higher (hypernatraemia, polyuria, or hyperuricaemia).[44] Other treatments, such as somatostatin analogues[45] and the mammalian target of rapamycin (mTOR) inhibitor[46] have shown no beneficial effect in these patients.

RRT is required in 50% of patients older than 60 years. In recent years, it has been observed that the age at initiation of RRT has increased, attributable to therapeutic advances. However, one study found no difference in the last 25 years in ADPKD patients who started RRT, despite a delay of 9 years in the age of onset of RRT in patients without ADPKD.[47]

Kidney transplantation is the best therapeutic choice for ADPKD patients in RRT.[48] Nephrectomy is indicated previously in presence of repeated cystic infections or bleeding and when an enormous renal size may complicate a correct placement of the graft. Peritoneal dialysis is a technique of first choice[49] which gives a better prognosis than haemodialysis for some authors;[50] however, in patients with massive polycystic liver disease, very large kidneys, abdominal hernias, or recurrent diverticulitis it is not recommended.

In most articles, the survival of the ADPKD patients in RRT was higher than non-ADPKD patients, may be in relation to: starting RRT at younger age, lower prevalence of cardiovascular risk factors,

and higher haemoglobin levels.[51] In another study, ADPKD patients showed a higher survival rate than diabetes-free non-ADPKD patiens.[52] The primary cause of death in these patients was cardiovascular disease, followed by infections.[53,54]

EXTRARENAL MANIFESTATIONS

Polycystic liver disease is the most common extrarenal manifestation and is associated with increased renal volume, older age, and female sex[55] (several pregnancies or oestrogen intake),[56] as oestrogen can stimulate cyst hepatic growth. Liver cysts are usually asymptomatic and the liver function is normal, so follow-up of these patients is not necessary. The diagnosis is performed by ultrasonography; however, MRI is more sensitive for the detection of small cysts.[57]

The increased liver volume may cause symptoms of extrinsic compression: abdominal pain, early satiety, and obstruction of the hepatic veins or biliar duct.[57] Partial hepatic resection or even liver transplantation may be necessary in the case of massive polycystic liver.[58] Treatment with somatostatin analogues for 2 years has shown decreased liver volume but more studies are needed. The mTOR inhibitors have not obtained any results.[59] Liver cyst infection causes fever, right upper abdominal pain, and possible elevated CA19.9 and alkaline phosphatase levels. Treatment consists of antibiotics that penetrate the cyst wall, and the response to percutaneous drainage is better than in cysts kidney.[60]

The prevalence of cerebral aneurysms (CA) is 5-times higher in the general population and is increased with a positive family history of CA.[61] A rupture of a CA, resulting in an intracerebral or subarachnoid haemorrhage, is the most severe complication of ADPKD,[62] and depends on size of the CA and other factors such as age, uncontrolled hypertension, tobacco, cocaine, or anticoagulants.[63] Patients with CA are usually asymptomatic.

Magnetic resonance angiography (MRA) or CT angiography are the procedures of choice for diagnosis of CA.[64] Screening is indicated in ADPKD patients with previous family history of aneurysm or cerebral bleeding, previous rupture, or neurological symptoms.[65] In high-risk patients, when the diagnostic test detects no aneurysms, it should be repeated every 5 years. When an aneurysm is diagnosed, the therapeutic options are:[66] conservative management with radiological monitoring in CA <7 mm, and surgical intervention or endovascular repair[67] in AC >7-11 mm or rapidly growing.

With regards to cysts in other organs, heart or abdominal manifestations are less common and usually asymptomatic so screening is not recommended. The cysts in the epididymis and seminal vesicles are a rare cause of infertility,[68] arachnoid cysts are usually asymptomatic, although they may increase the risk of subdural haematoma, and there does not appear to be an increased risk of ovarian cysts.[69]

Left ventricular hypertrophy is the most frequent cardiac manifestation, usually associated with hypertension, but it has also been observed in normotensive patients.[70] The mitral valve prolapse is the most common valve disease;[71] others that are less common are tricuspid valve prolapse and aortic regurgitation due to aortic root dilatation, which increases the risk of aortic dissection. Studies suggest an increased incidence of coronary and aortic abdominal aneurysms.[72] The increased risk of colonic diverticula and abdominal hernias in ADPKD patients may contraindicate the peritoneal dialysis.[73]

CONCLUSIONS AND RECOMMENDATIONS

ADPKD is a hereditary systemic disorder characterised by the growth of renal cysts. The first symptoms appear from adulthood, such as hypertension, haematuria, nephrolithiasis, or cyst complications (infection and bleeding) that usually are due to the number and size of renal cysts. Total renal volume is the best predictor of prognostics for ADPKD, and factors of progression of CKD should be controlled.

ADPKD patients should be regularly followed-up by the nephrologist with renal function and ultrasonograhy, and screening diagnosis should be performed in all first-degree adult relatives with ultrasonograhy. A diet low in salt (<6 g/day) and protein (<1 g/day) is recommended. Blood pressure should be maintained at <130/80 mmHg since the treatment of choice is RAS inhibitors. In addition, ADPKD patients should drink 2-3 litres of water per day and avoiding caffeine, which may stimulate cAMP levels and cystogenesis. It is recommended to normalise cholesterol levels with diet or treatment. A ruptured cerebral aneurysm is the most severe complication, so screening

with MRA should be performed in high-risk ADPKD patients.

Despite the absence of a specific treatment for ADPKD as yet, the initial results of treatment with tolvaptan showed a slowing reduction in deterioration of renal function and a smaller increase in renal volume; however, comparisons with more long-term studies are necessary in the search for a definitive treatment. Therefore, we should follow the recommendations in this review to slow the progression of CKD in ADPKD patients.

REFERENCES

1. Hateboer N et al. Comparison of phenotypes of polycystic kidney disease types 1 and 2. Lancet. 1999;353(9147):103-7.

2. Bleyer AJ, Hart TC. Polycystic kidney disease. N Engl J Med. 2004;350(25):2622.

3. Sharif-Naeini R et al. Polycystin-1 and -2 dosage regulates pressure sensing. Cell. 2009;139(3):587-96.

4. Ortiz A. [Cilia and cystogenesis]. Nefrología. 2004;24(4):307-11.

5. Chapin HC, Caplan MJ. The cell biology of polycystic kidney disease. J Cell Biol. 2010;191(4):701-10.

6. Davidow CJ et al. The cystic fibrosis transmembrane conductance regulator mediates transepithelial fluid secretion by human autosomal dominant polycystic kidney disease epithelium in vitro. Kidney Int. 1996;50(1):208-18.

7. Pei Y et al. Somatic PKD2 mutations in individual kidney and liver cysts support a "two-hit" model of cystogenesis in type 2 autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1999;10(7):1524-9.

8. Joly D et al. Ciliary function of polycystins: a new model for cystogenesis. Nephrol Dial Transplant. 2003;18(9):1689-92.

9. Karihaloo A et al. Macrophages promote cyst growth in polycystic kidney disease. J Am Soc Nephrol. 2011;22(10):1809-14.

10. Jafar TH et al. The effect of angiotensin-converting-enzyme inhibitors on progression of advanced polycystic kidney disease. Kidney Int. 2005;67(1):265-71.

11. O'Neill WC et al. Sonographic assessment of the severity and progression of autosomal dominant polycystic kidney disease: the Consortium of Renal Imaging Studies in Polycystic Kidney Disease (CRISP). Am J Kidney Dis. 2005;46(6):1058-64.

12. Nicolau C et al. Autosomal dominant polycystic kidney disease types 1 and 2: assessment of US sensitivity for diagnosis. Radiology. 1999;213(1):273-6.

13. Kistler AD et al. Increases in kidney volume in autosomal dominant polycystic kidney disease can be detected within 6 months. Kidney Int. 2009;75(2):235-41.

14. Pei Y et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol. 2009;20(1):205-12.

15. Gabow PA. Autosomal dominant polycystic kidney disease. N Engl J Med. 1993;329(5):332-42.

16. Thauvin-Robinet C et al. Clinical, molecular, and genotype–phenotype correlation studies from 25 cases of oral-facial-digital syndrome type 1: a French and Belgian collaborative study. J Med Genet. 2006;43(1):54-61.

17. Pei Y. Diagnostic approach in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2006;1(5):1108-14.

18. Rossetti S et al. Identification of gene mutations in autosomal dominant polycystic kidney disease through targeted resequencing. J Am Soc Nephrol. 2012;23(5):915-33.

19. Seeman T et al. Renal concentrating capacity is linked to blood pressure in children with autosomal dominant polycystic kidney disease. Physiol Res. 2004;53(6):629-34.

20. Zittema D et al. Vasopressin, copeptin, and renal concentrating capacity in patients with autosomal dominant polycystic kidney disease without renal impairment. Clin J Am Soc Nephrol. 2012;7(6):906-13.

21. Chapman AB et al. Overt proteinuria and microalbuminuria in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1994;5(6):1349-54.

22. Torres VE, et al. Renal stone disease in autosomal dominant polycystic kidney disease: contribution of extrarenal complications to mortality. Am J Kidney Dis. 1993;22(4):513–9.

23. Jouret F et al. Diagnosis of cyst infection in patients with autosomal dominant polycystic kidney disease: attributes and limitations of the current modalities. Nephrol Dial Transplant. 2012;27(10):3746-51.

24. Gabow PA et al. Clinical profiles of gross hematuria in autosomal dominant polycystic kidney disease. Am J Kidney Dis. 1992;20(2):140-3.

25. Keith DS et al. Renal cell carcinoma in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1994;4(9):1661-9.

26. Klahr S et al. Dietary protein restriction, blood pressure control and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol. 1995;5(12):2037-47.

27. Virzi GM et al. ADPKD: prototype of cardiorenal syndrome type 4. Int J Nephrol. 2010;2011:490795

28. Cornec-Le E et al. Type of PKD1 mutation influences renal outcome in ADPKD. J Am Soc Nephrol. 2013;24(6):1006-13.

29. King BF et al. Magnetic resonance measurements of renal blood flow as a marker of disease severity in autosomal-dominant polycystic kidney disease. Kidney Int. 2003;64(6):2214-21.

30. Fick-Brosnahan GM et al. Relationship between renal volume growth and renal function in autosomal dominant polycystic kidney disease: a longitudinal study. Am J Kidney Dis. 2002;39(6):1127-34.

31. Torres VE et al. Magnetic resonance measurements of renal blood flow and disease progression in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2007;2(1):112-20.

32. Chapman AB et al. Renal structure in early autosomal-dominant polycystic kidney disease (ADPKD): the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort. Kidney International. 2003;64(3):1035-45.

33. Ecder T, Schrier RW. Hypertension in autosomal-dominant polycystic kidney disease: early occurrence and unique aspects. J Am Soc Nephrol. 2001;12(1):194-200.

34. Grantham JJ. Clinical practice. Autosomal dominant polycystic kidney disease. N Engl J Med. 2008;359(14):1477-85.

35. Zeltner R et al. Renal and cardiac effects of antihypertensive treatment with ramipril vs metoprolol in autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 2008;23(2):573-9.

36. Ecder T et al. Effect of antihypertensive therapy on renal function and urinary albumin excretion in hypertensive patients with autosomal dominant

polycystic kidney disease. Am J Kidney Dis. 2000;35(3):427-32.

37. Ecder T et al. Diuretics versus angiotensin-converting enzyme inhibitors in autosomal dominant plycystic kidney disease. Am J Nephrol. 2001;21(2):98-103.

38. Handa SP. Cardiovascular manifestations of autosomal dominant polycystic kidney disease in young adults. Clin Invest Med. 2006;29(6):339-46.

39. Johnson AM, Gabow PA. Identification of patients with autosomal dominant polycystic kidney disease at highest risk for end-stage renal disease. J Am Soc Nephrol. 1997;8(10):1560-7.

40. Torres VE et al. Potentially modifiable factors affecting the progression of autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2011;6(3):640-7.

41. Dicks E et al. Incident renal events and risk factors in autosomal dominant polycystic kidney disease: a population and family-based cohort followed for 22 years. 2006;1(4):710-7.

42. Chapman AB et al. Pregnancy outcome and its relationship to progression of renal failure in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1994;5(5):1178-85.

43. Devuyst O, Torres VE. Osmoregulation, vasopressin, and cAMP signaling in autosomal dominant polycystic kidney disease. Curr Opin Nephrol Hypertens. 2013;22(4):459-70.

44. Torres VE et al. TEMPO 3:4 trial investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012; 367(25): 2407-18.

45. Caroli A et al. Effect of long acting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicenter trial. Lancet. 2013;382(9903):1485-95.

46. Serra AL et al. Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. N Engl J Med. 2010;363(9):820-9.

47. Martinez V et al. Renal replacement therapy in ADPKD patients: a 25-year survey based on the Catalan registry. BMC Nephrol. 2013;14:186.

48. Alam A, Perrone RD. Management of ESRD in patients with autosomal dominant polycystic kidney disease. Adv Chronic Kidney Dis. 2010;17(2):164-72.

49. Li L et al. Peritoneal dialysis as the first-line renal replacement therapy in patients with autosomal dominant polycystic kidney disease. Am J Kidney Dis. 2011;57(6):903-7.

50. Abbott KC, Agodoa LY. Polycystic kidney disease at end-stage renal disease in the United States: patient characteristics and survival. Clin Nephrol. 2002;57(3):208-14.

51. Abbott KC, Agodoa LY. Polycystic kidney disease in patients on the renal transplant waiting list: trends in hematocrit and survival. BMC Nephrol. 2002;3:7.

52. Perrone RD et al. Survival after end-stage renal disease in autosomal dominant polycystic kidney disease: contribution of extrarenal complications to mortality. Am J Kidney Dis. 2001;38(4):777-84.

53. Orskov B et al. Changes in causes of death and risk of cancer in Danish patients with autosomal dominant polycystic kidney disease and end-stage renal disease. Nephrol Dial Transplant. 2012;27(4):1607-13.

54. Rahman E et al. Analysis of causes of mortality in patients with autosomal dominant polycystic kidney disease: a single center study. Saudi J Kidney Dis Transpl. 2009;20(5):806-10.

55. Bae KT et al. Magnetic resonance imaging evaluation of hepatic cysts in early autosomal dominant polycystic kidney disease: the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease cohort. Clin J Am Soc Nephrol. 2006;1(1):64-9.

56. Chandok N. Polycystic liver disease: a clinical review. Ann Hepatol. 2012;11(6):819-26.

57. Gevers TJ, Drenth JP. Diagnosis and management of polycystic liver disease. Nat Rev Gastroenterol Hepatol. 2013;10(2):101-8.

58. Chauveau D et al. Liver involvement in autosomal-dominant polycystic kidney disease: therapeutic dilemma. J Am Soc Nephrol. 2000;11(9):1767-75.

59. Page L et al. Somatostatin analog therapy for severe polycystic liver disease: results after 2 years. Nephrol Dial Transplant. 2012;27(9):3532-9.

60. Pirson Y. Extrarenal manifestations of autosomal dominant polycystic kidney disease. Adv Chronic Kidney Dis. 2010;17(2):173-80.

61. Vlak MH et al. Prevalence of unruptured intracraneal aneurysms, with emphasis on sex, age, comorbidity country a time period: a systematic review and meta-analysis. Lancet Neurol. 2011;10(7): 626-36.

62. Rinkel GJ. Natural history, epidemiology and screening of unruptured intracranial aneurysms. J Neuroradiol. 2008;35(2):99–103.

63. Ring T, Spiegelhalter D. Risk of intracranial aneurysm bleeding in autosomal-dominant polycystic kidney disease. Kidney Int. 2007;72(11):1400-2.

64. Irazabal MV et al. Extended follow-up of unruptured intracranial aneurysms detected by presymptomatic screening in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2011;6(6):1274-85.

65. Pirson Y et al. Management of cerebral aneurysms in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2002;13(1):269-76.

66. Williams LN, Brown RD. Management of unruptured intracranial aneurysms. Neurol Clin Pract. 2013;3(2):99-108.

67. Wiebers DO et al. Unruptured intracranial aneurysm: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;62(9378):103-10.

68. Belet U et al. Prevalence of epididymal, seminal vesicle, prostate, and testicular cysts in autosomal dominant polycystic kidney disease. Urology. 2002;60(1): 138-41.

69. Heinonen PK et al. Ovarian manifestations in women with autosomal dominant polycystic kidney disease. Am J Kidney Dis. 2002;40(3):504-7.

70. Perrone RD et al. Cardiac magnetic resonance assessment of left ventricular mass in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2011;6(10):2508-15.

71. Lumiaho A et al. Mitral valve prolapse and mitral regurgitation are common in patients with polycystic kidney disease type 1. Am J Kidney Dis. 2001;38(6): 1208-16.

72. Torra R et al. Abdominal aortic aneurysms in autosomal dominant polycystic kidney disease. J Am Soc Neph.1996;7(11):2483-6.

73. Kumar S et al. Duodenal diverticulosis in autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 2006;21(12):3576-8.

CHRONIC KIDNEY DISEASE – WHERE NEXT? PREDICTING OUTCOMES AND PLANNING CARE PATHWAYS

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ABSTRACT

With the introduction of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative chronic kidney disease (CKD) guidelines, CKD has been identified as common, particularly in the elderly. The outcomes for those with CKD can be poor: mortality, initiation of renal replacement therapy, and progressive deterioration in kidney function, with its associated complications. In young people with CKD, the risk of poor outcome is high and the social cost substantial, but the actual number of patients affected is relatively small. In the elderly, the risk of poor outcome is substantially lower, but due to the high prevalence of CKD the actual number of poor outcomes attributable to CKD is higher. Predicting which patients are at greatest risk, and being able to tailor care appropriately, has significant potential benefits. Risk prediction models in CKD are being developed and show promise but thus far have limitations. In this review we describe the pathway for developing and evaluating risk prediction tools, and consider what models we have for CKD prediction and where next.

Keywords: Chronic kidney disease, outcome, risk prediction.

CHRONIC KIDNEY DISEASE: THE BURDEN OF CARE

The recognition of chronic kidney disease (CKD) prior to 2002 was inconsistent, with no standard definition and, in some cases, led to late referral of patients to specialised renal services.[1,2] This was associated with poor outcomes on renal replacement therapy (RRT)[1-3] and missed clinical opportunity to improve disease course.[1] The introduction of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) CKD definitions,[4] international acceptance of these definitions, and instigation of CKD guidelines[5-9] has led to a recognition that the prevalence and incidence of CKD is far in excess of earlier estimates.[10-12] Reports based on data from the National Health and Nutrition Examination Survey (NHANES) suggested 13.1% (26 million) of the US adult population in 2000 had CKD.[13] The prevalence of CKD increases with age; in NHANES approximately 50% of those aged 70 years and older were reported to have CKD.[13] This is set to grow as the global population ages.[14] A recent study estimated that the lifetime risk of developing CKD Stage 3-5 was approximately 60%; three out of five babies born today are destined to develop CKD in their lifetime.[15]

The natural history of CKD is perceived to be one of loss of renal function over time with associated complications, leading ultimately to the need for RRT and finally death. With declining estimated

glomerular filtration rate (eGFR) the risk of reaching end-stage renal disease (ESRD) increases, estimates vary. A Chronic Kidney Disease Prognosis Consortium (CKD-PC) patient-level meta-analysis reported increasing hazard ratios (HRs) with declining eGFR up to an adjusted ESRD HR of 51 (32-83) 95% confidence interval (CI) for eGFR<15 (versus 45-74 ml/min/1.73 m^2).[16] Worsening proteinuria is also associated with increasing risk of ESRD; CKD-PC report a HR of 9 (2-50) for ACR ≥1000 (versus <30) mg/g.[16] All-cause mortality also increased with worsening eGFR and worsening proteinuria.[17] Other outcomes for those with CKD include a high cardiovascular morbidity and mortality.[18] Progressive deterioration in kidney function, short of the requirement for RRT, carries the risk of developing anaemia, acidosis, bone disease, a need to prepare for RRT, or instigation of conservative care. Recent CKD cohort reports confirm that, although many initiate RRT or die, a significant number may still be alive after several years. Our own data on Stage 3b-5 CKD suggest that approximately one-third are still alive and not requiring RRT at 5 years.[19]

CKD and the associated increased use of hospital services[20] come with a significant financial cost – estimated for England's NHS during 2009-10 to be at £1.45 billion (~1.3% of NHS spending), of which just over half was due to RRT costs.[21] Instigation of RRT also involves other costs; these include personal loss of earnings, health, and personal-social costs both for patients and their carers. Thus, in the general population there is a high burden of CKD both in terms of volume of disease and cost of treatment and management.

INDIVIDUAL RISK VERSUS POPULATION BURDEN: AGE MATTERS

The burden from CKD is high, but the risk is not constant for all patients, and age is a major influence on risk and outcome. In the young, the risk of poor outcome is high in those with CKD compared to those of similar age without CKD. The actual numbers of patients affected is, however, relatively small because CKD prevalence is low and the outcomes are uncommon in the 'unexposed' non-CKD population. In the elderly, the relative risk of poor outcome is substantially lower as compared to those of similar age without CKD, but due to the high prevalence of CKD the actual number of poor outcomes attributable to CKD is high.[19]

The effect of this difference in risk is illustrated in Figure 1. Relative risk defines the strength of the association between the outcome and the exposure (in this case CKD and RRT or death). Absolute measures of risk estimate the impact of a disease (here, CKD) on an individual, or indeed population. For an individual this would be the difference in risk of a given outcome depending on whether a person has the disease (CKD) or not – the excess risk associated with having CKD.[22] For populations, the population attributable risk describes how much of an outcome can be accounted for by exposure to a particular disease in the population, and therefore takes into account the disease prevalence.[22]

Figure 1a illustrates the prevalence of CKD for a population. The mortality in those without and with CKD are illustrated in Figure 1b; this uses figures from the CKD-PC meta-analysis reported by Hallan et al.[23] using the mean mortality rates for those with eGFRs of 80 and 45 ml/min/1.73 m^2, respectively to represent an average individual with 'no CKD' and 'CKD', respectively. For those aged 18-54 years the mean mortality rates were 4.0 and 13.0 per 1000 patient-years (py) for 'no CKD' and 'CKD' individuals, respectively, thus, individuals with CKD had an excess mortality risk of 9 per 1000 py, and a mortality HR or relative risk of ~3 as a result of CKD. Given that the prevalence of CKD is low in those aged 18-54, this excess personal risk translates into a relatively small excess number of deaths (the numbers shown in Figure 1d are purely illustrative since they are estimated using outcomes for those with an eGFR of 45 ml/min/1.73 m^2 to represent those with CKD, whereas the majority of those with CKD will have a far better eGFR than this). As shown in Figure 1b, for those aged ≥75 years, mean mortality rates for 'no CKD' and 'CKD' were 57.8 and 85.0 per 1,000 py, an excess individual risk of 27.2 per 1,000 py and a much lower relative risk of ~1.3. However, as illustrated in Figure 1d the far higher prevalence of CKD means that the excess deaths are far higher despite this lower relative risk.

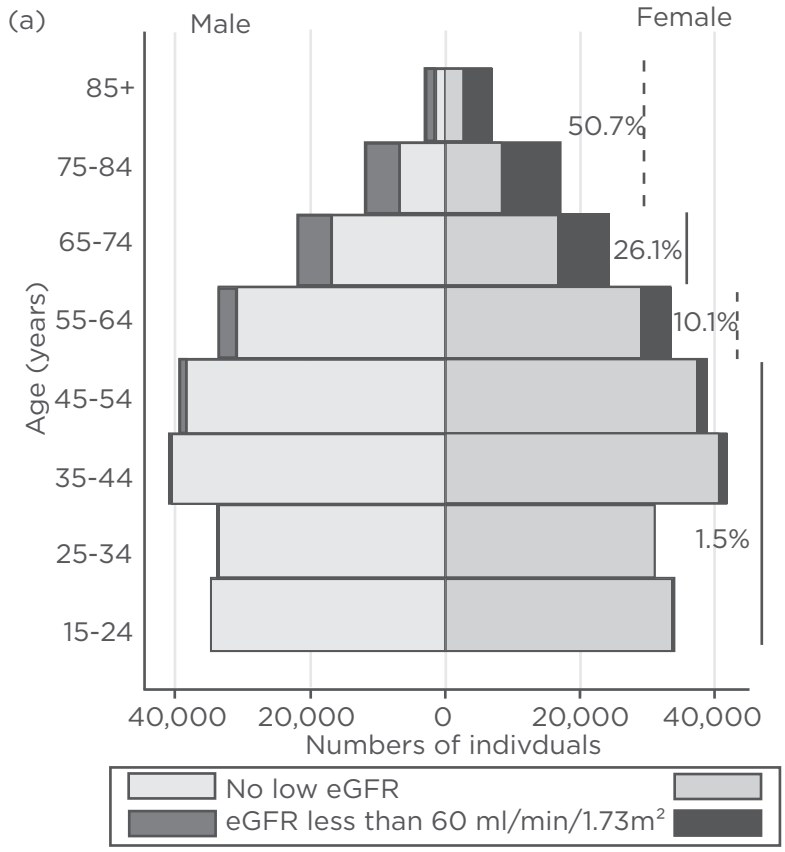
The equivalent mean rates for achieving ESRD reported by Hallan et al.[23] in those with 'no CKD' and 'CKD' (eGFRs of 80 and 45 ml/min/1.73 m^2, respectively) by age are shown in Figure 1c. The rates were higher in the youngest groups, the relative risk was higher in the young also. The excess individual risks were 45.1 and 8.0 per 1,000 py for the youngest and oldest group, respectively.

However, since the numbers at risk are so small in the young, and large in the elderly, the excess cases of ESRD in the illustration are actually a little higher for those over 65 years of age. Thus, amongst the population there are two distinct groups – a group where CKD is uncommon but, for those with CKD the personal risk of poor outcomes are high, and a group where CKD is common but personal risk of poor outcomes is low. However, as a result of the number of individuals in this second group, they contribute a significant number of poor outcomes.

For care planning, although in terms of personal risk there are certain groups at high-risk, the majority of those that actually contribute to the highest volume of care requirements are generally older and have a lower personal risk. Although to have a specialist review of the younger high-risk group is not challenging, identifying those at risk in the low relative-risk elderly group might be, but it is important for care-planning. An ability to accurately determine which of the high volume group with low personal risk are at more risk than their peers would allow directed care for RRT planning, pre-dialysis care, specialist nephrology input, and mortality risk reduction steps. Also, very importantly, it would identify those who will not suffer these poor outcomes, for whom nephrology care is unlikely to be necessary. In other medical fields with high volume disease, such as ischaemic heart disease,[25,26] prediction models for the assessment of risk have been introduced and are commonly used in clinical practice.

CKD OUTCOME PREDICTION AND CARE PATHWAY DEVELOPMENT

Developing safe and effective prediction models takes time and is a complex process.[27-32] Models are developed using previous experience and work of others to inform and check likely prognosis and prognostic variables in a development cohort. Regression models are often then used to relate these variables and the outcome; importantly, indices of model performance are measured to decide on the 'best' model. A description of how well the model performs demonstrates internal validity. To demonstrate that the model performs well in another similar situation, external validation in another population is needed. Once good performance has been demonstrated, ideally a randomised controlled trial (with economic evaluation) would be used to demonstrate the implications of introducing the model into clinical practice. Then finally, if the model improved care or outcomes and had acceptable utility, it would be implemented in clinical practice. However, many of these steps are often not done and many developed models remain untested in clinical practice.



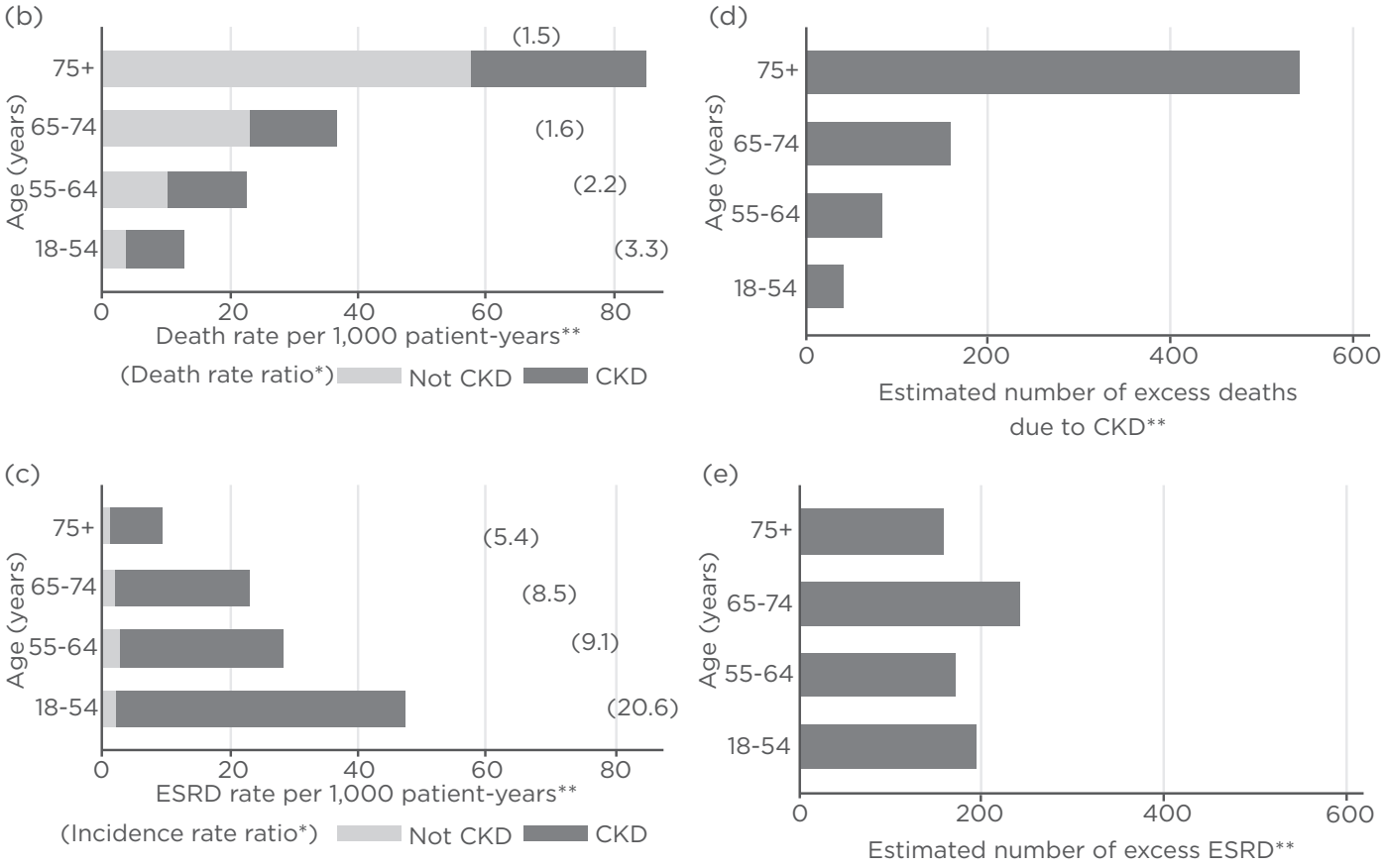


Figure 1: Population chronic kidney disease (CKD) prevalence, personal risk, relative risk, and population attributable risk.

1a shows the prevalence of CKD in an illustrative adult population (*based on unpublished data from Grampian Laboratory Outcomes Morbidity and Mortality 2 Study*[24]); in the darker colour for both males and females are the number with an eGFR of <60 ml/min/1.73 m^2, percentage values shown refer to the age-bands as are demonstrated in b, c, d, and e. ** 1b, 1c, 1d, and 1e are based on rates published in *Hallan et al.*[23] with those with 'not CKD' and 'CKD' are based on figures for those with eGFR 80 and 45 ml/min/1.73 m^2, respectively, although it should be kept in mind that the majority of those with CKD will have an eGFR>45 so this will overestimate CKD excess risk dramatically, but it is used here for illustration purposes only and applied to the population in 1a. 1b shows in light grey the death rates by age for those with an eGFR of 80 ml/min/1.73 m^2 as representative of 'Not CKD', in dark grey is shown the additional risk in those with an eGFR of 45 ml/min/1.73 m^2 as representing 'CKD', the * crude death rate ratio (based on the ratio of these two death rates) is shown in brackets. 1c shows similar for the occurrence of ESRD. 1d shows the excess number of deaths that could be expected in this population based on the difference between the death rates in those with and without CKD and the numbers with 'CKD' in the population. 1e shows the same for ESRD. Both are overestimates as the result of using the rates for 80 and 45 ml/min/1.73 m^2 as estimates for those with 'not CKD' and 'CKD'.

In the field of renal medicine there are no prediction models for CKD outcomes that are in common use in clinical practice. But early work[33] has been done that suggests prediction models could offer ways to plan and tailor care for people with CKD based on their risk of poor outcomes. Potential models have been developed to predict CKD outcome including mortality, cardiovascular disease, and kidney failure; the studies identified in two recent reviews[34,35] are summarised in Table 1.

The identified prediction studies have shown that it is possible to develop models to predict outcome in those with CKD, using a wide range of data sources. The majority of these studies and models sought to predict 'renal failure' (most but not all defined by the initiation of RRT). Five of the identified studies report on models to predict mortality in those with CKD,[34] sometimes as a composite end-point 'death or renal failure'. Just three report cardiovascular event prediction

models, including a comparison with the performance of the Framingham risk equation. These death and cardiovascular models rarely report most performance metrics, except discrimination which were usually reasonable (C-statistics of 0.60 to 0.82).[34]

Of the ten studies developing prediction models for renal failure, two studies were in individuals with IgA nephropathy alone, and two in people with diabetic nephropathy, limiting generalisability for those with CKD of other or unknown cause. Only two studies were in community populations not identified through referral to specialist nephrology care. The variables in the models were important in terms of application to current clinical practice: those that are routinely performed such as creatinine (and eGFR) are easily translated into care; using variables that are only measured if clinically indicated potentially limits utility as does the use of biological measures that are not in common use in routine clinical practice such as cystatin C and NT-pro-BNP. No studies used the pattern or rate of eGFR or creatinine change as a predictor variable.

Table 1: Studies that report CKD outcome prediction models.

Study	Setting, included individuals	Size	Routine plus special measures	Stage in development
Dimitrov[36]	Clinic, RCT, Nondiabetic CKD	344	Routine, calcium phosphate product	P. metrics (D+ C+) Internal validation
Keane[37]	Clinic, RCT, Diabetic nephropathy	1,513	Routine	P. metrics (D- C-) Internal validation
Wakai[38]	Clinic, cohort, IgA nephropathy	2,269	Routine, BP, haematuria Histological grade	P. metrics (D+ C-) Internal validation
Kent[39]	Clinic, RCTs, Nondiabetic CKD	1,860	Routine, BP	P. metrics (D+ C+) Internal validation
Johnson[40]	HMO cohort CKD	9,782	Routine, BP, history of DM	P. metrics (D+ C+) Internal validation
Goto[41]	Clinic, cohort, IgA nephropathy only with eGFR >60 ml/min/1.73m^2	790	Routine, BP, haematuria Histological grade	P. metrics (D+ C+) Internal validation
Hallan[42]	Population, cohort CKD and no CKD	65,589 (not all CKD)	Routine, BP, meds, DM, chol Physical activity	P. metrics (D+ C-) Internal validation Explores potential clinical impact
Landray[43]	Clinic, cohort, CKD	382	Routine, phosphate	P. metrics (D+ C+) Internal validation, External validation (213)
Desai[44]	Clinic, RCT Diabetics with CKD and anaemia	995	Routine, race, BMI, meds, Hx PAD/stroke/ HF/arrhythmia/AKI, ferritin, CRP TnT, NT-pro-BNP	P. metrics (D+ C-) Internal validation
Tangri[33]	Clinic, cohort, CKD	3,449	Routine, (8 variable model) phosphate, bicarbonate, calcium	P. metrics (D+ C+) Internal validation, External validation (4942)
Cardivascular events				
Shlipak[45]	Population, cohort, CKD	1,249	Routine, race, education, meds, Hx of DM/ CVD, education, BP, BMI	P. metrics (D+ C-)
Weiner[46]	Population, cohort, CKD	934	Routine, BP, chol, DM, smoking, race	External validation of *Framingham risk equation* P. metrics (D+ C+) of recalibrated model
McMurray[47]	Clinic, RCT, Diabetics with CKD and anaemia	955	Routine, race, BMI, meds, Hx PAD/stroke/ HF/arrhythmia/ AKI, ferritin, CRP, ECG TnT, NT-pro-BNP	P. metrics (D+ C-)

Table 1 continued.

Study	Setting, included individuals	Size	Routine plus special measures	Stage in development
All-cause mortality				
Keane[37]	Clinic, RCT, Diabetic nephropathy	1,513	Routine, HbA1c *All-cause mortality + ESRD*	P. metrics (D- C-) Internal validation
Johnson[48]	HMO cohort, CKD	6,541	Routine, BP, history of DM	P. metrics (D+ C-)
Landray[43]	Clinic, cohort, CKD	382	Routine, smoking NT-pro-BNP, TnT	P. metrics (D+ C+) Internal validation External validation (213
Berthoux[49]	Clinic, cohort, IgA nephropathy	332	Routine, BP *All-cause mortality + ESRD* Histological grade	P. metrics (D- C+) Internal validation
Desai[44]	Diabetes type 2, CKD and anaemia	995	Routine, race, BMI, meds, Hx PAD/stroke/ HF/arrhythmia/AKI, ferritin, CRP TnT, NT-pro-BNP	P. metrics (D+ C-) Internal validation

Routine might include: age, sex, some creatinine based measure of excretory renal function, some measure of albuminuria, some measure of serum protein, some measure of anaemia; CKD: chronic kidney disease; ESRD: end-stage renal disease; RRT: renal replacement therapy; HMO: health maintenance organisation; RCT: randomised controlled trial; BP: blood pressure or hypertension; DM: diabetes mellitus; CVD: cardiovascular disease; Hx: history of; PAD: peripheral arterial disease; HF: heart failure; BMI: body mass index; AKI: acute kidney injury; CRP: C reactive protein; TnT: troponin T; NT-pro-BNP: N terminal prohormone brain natriuretic peptide. P. metrics: performance metrics; D+/D-: discrimination reported/not reported (usually as ROC or C statistic); C+/C-: calibration reported/not reported (usually as Hosmer-Lemeshow statistic or plot); Chol: cholesterol; ECG; electrocardiogram; BMI: body mass index.

Reporting of the metrics considered of importance in the development of a prediction model (discrimination, calibration, model fit, and reclassification), summarised in Table 2 and previously[34,50] was variable. Discrimination was reported in the majority and was excellent; c-statistics of 0.79-0.94 (compared to the widely accepted Framingham model performance of 0.75-0.81).[25] Calibration was not consistently reported. The clinical implications were explored and reported in only one study,[42] although model application to clinical care was discussed by two authors[33,40] and useable interfaces presented by three.[33,40,43] Only two authors demonstrated external validity.[33,43] Both studies' models were developed and externally validated in individuals referred to renal services and, as such, their performance in individuals from less specialised settings (e.g. community or non-specialist care) have not been demonstrated.[33,43]

The best reported of these models were by Tangri et al.,[33] who recounted model calibration, and for the several models developed report the relative performance of one model over another.[33] The original study included external validation and they have since been externally validated by others.[51] The performance of the Tangri 3 and 4 variable models are illustrated in Figure 2 applying the models to an example CKD population cohort generated from our routine clinical practice in the North East of Scotland.[19] The 3 variable model could be applied to the whole cohort; however, all 1,246 with Stage 4 CKD were labelled as high-risk when in fact only 89 had started RRT by 5 years (very sensitive, very poor specificity). Of the 4,951 with Stage 3b CKD (41 inititating RRT by 5 years) 2,053 were defined as high-risk (sensitivity 0.95, but specificity of only 0.59). The 4 variable model restricted the number for whom there was appropriate data available as part of routine care, so that only 13% of those with Stage 3b CKD could have a risk calculated. However, performance was a little better. Nevertheless, even the best performing of the Tangri models showed better discrimination amongst those with Stage 4 CKD than Stage 3 CKD where the main clinical challenge remains.[52]

Table 2: Common and expected indices for the reporting of prediction model performance.

	Description	How usually measured/reported
Discrimination	Whether the model assigns a higher probability to individuals who have the outcome of interest versus those who do not.	Area under the receiver operating characteristic (ROC) curve, or c-statistic. 0.50 is no better than chance. 0.70-0.80 good. >0.80 excellent.
Calibration	How well the predictions equate to actual outcome.	Calibration plots; variants on the Hosmer-Lemeshow χ^2 statistic, rank into deciles of predicted risk, then compare the expected and observed frequency of the outcome in each decile. If very different then not good calibration.
Goodness of fit	How well the model fits the data concerned.	Akaike or Bayes information criterion, the lower the value the better fit of the model.
Reclassification	How a newer (or more complex) model improves the reclassification of individuals – those with the event to a higher predicted risk and those without the event to a lower predicted risk.	Net reclassification improvement or integrated discrimination improvement. If the direction of the reclassification is correct – those with events to higher risk, those with no events to lower risk, then the newer (or more complex) model is better.

In our local cohort with CKD, using an RRT risk of >5% at 5 years as high-risk, the Tangri 3 and 4 variable models performed as below:

	3 variable model		4 variable model	
CKD stage	3b	4	3b	4
Number of patients with CKD	4,951	1,246	650	153
Number start RRT at 5 years	41	89	14	16
Missed RRT cases	2 (5%)	0 (0%)	2 (15%)	0 (0%)
Number high-risk	2053	1246	15	125
Sensitivity	0.95	1.00	0.86	1.00
Specificity	0.59	0.00	0.83	0.20

Figure 2: Practical example of prediction model performance not illustrated using discrimination, calibration, and model fit indices.
CKD: chronic kidney disease; RRT: renal replacement therapy.

WHERE NEXT?

Thus, the models currently available, although demonstrated to be useable, are limited by a number of issues and flaws and so need further work. Reporting and testing of model performance was inconsistent, and while standard, basic tests of internal validity of the models tended to show promise, more transparent testing on external validation cohorts reporting sensitivity, specificity, false-positives, and false-negatives would be helpful in assessment of clinical utility, particularly using the suggested thresholds for identifying high-risk individuals.

Models that are practical to use in 'real-life' with real-life data such as the Tangri model should be given priority, and model refinement should ensure practical real-life useability. Models need to be judged in terms of the added value for care and service planning over the current use of referral guidelines based on eGFR and proteinuria.[53] The addition of novel biological markers has, thus

far, provided limited improvement in model performace and has restricted immediate clinical implications if testing for such markers is not in widespread clinical use. Greater gains for model refinement might come from taking into account the type of information used in clinical practice to assess long term risks: rate and pattern of kidney function decline, comorbidity, and underlying renal pathology, for example.

Model performance has not been explored in depth in older age populations. Experience from the cardiovascular literature suggests that model performance may not be as good in the elderly.[25,26] In this age group, issues of competing risks from other morbidities and death become increasingly important. Further external validation of refined models in community settings such as primary care is required prior to any use in this context. Once these models have been refined, good quality randomised controlled trials of their introduction should be run to demonstrate any improvement in care and outcome delivery and absence of harm. This would then facilitate the introduction of stratified renal medicine appropriate to the risk profile of individuals concerned. Referral and intensive management with optimal implementation of current treatment guidelines could then be focused to those with the greatest opportunity to benefit. Health economic evaluation of the cost-effectiveness of different models of care delivery, based on stratification using prediction models, will be needed to support service planning, but the opportunity to reduce the need for referral to specialist services and frequency of follow-up has significant potential benefits for patients and health services.[54]

CONCLUSION

With the introduction of the KDOQI CKD guidelines, CKD is being identified more commonly, particularly in the elderly where milder renal impairment is predominant. The outcomes for those with CKD are poor – mortality, initiation of RRT, and progressive deterioration in kidney function, with its associated complications. In young CKD patients, the risk of poor outcome is high and the social cost substantial, but the actual numbers of patients affected is relatively small. In the elderly, the risk of a poor outcome is substantially lower, but due to the high prevalence of CKD the actual number of poor outcomes attributable to CKD is higher. Since >50% of those over the age of 70 years have CKD, prediction models to stratify care by risk group, focusing on intervention, and delivering different models of care based on risk, have great potential particularly at a population level. Risk prediction models in CKD have been developed and show promise but, thus far, have limitations – clinical performance is not fully reported and external validation is rare. The clinical utility of these models lies, for example, in the ability to explore timing of dialysis access placement, but also requires further research. The introduction of such models has great potential to deliver appropriate stratified medical care, but this should be after appropriate randomised controlled trials of effect.

REFERENCES

1. Roderick P et al. Late referral for end-stage renal disease: a region-wide survey in the south west of England. Nephrol Dial Transplant. 2002;17(7):1252-9.

2. Jungers P et al. Longer duration of predialysis nephrological care is associated with improved long-term survival of dialysis patients. Nephrol Dial Transplant. 2001;16(12):2357-64.

3. Kinchen KS et al. The timing of specialist evaluation in chronic kidney disease and mortality. Ann Intern Med. 2002;137(6):479-86.

4. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1-266.

5. Levin A et al. Guidelines for the management of chronic kidney disease. CMAJ. 2008;179(11):1154-62.

6. Renal Diseases Health Network Working Party. Chronic kidney disease model of care. 2008; Available at: http://www.healthnetworks.health.wa.gov.au/modelsofcare/docs/CKD_Model_of_Care.pdf.

7. Japanese Society of Nephrology. Chapter 2: Definition and classification of CKD. Clin Exp Nephrol. 2009;13(3):196.

8. Scottish Intercollegiate Guidelines Network. Diagnosis and management of chronic kidney disease: a national clinical guideline. 2008;103:1-50. Available at: http://www.sign.ac.uk/pdf/sign103.pdf.

9. National Collaborating Centre for Chronic Conditions (UK). Chronic Kidney Disease: National Clinical Guideline for early identification and management in adults in primary and secondary care. (NICE Clinical Guidelines, No. 73.) London: Royal College of Physicians (UK);2008.

10. Khan IH et al. Chronic renal failure: factors influencing nephrology referral. QJM. 1994;87(9):559-64.

11. Magnason RL et al. Prevalence and progression of CRF in Iceland: a population-based study. Am J Kidney Dis. 2002;40(5):955-63.

12. Drey N et al. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. Am J Kidney Dis. 2003;42(4):677-84.

13. Coresh J et al. Prevalence of chronic

kidney disease in the united states. JAMA. 2007;298(17):2038-47.

14. Grams ME et al. Trends in the prevalence of reduced GFR in the United States: a comparison of creatinine- and cystatin C-based estimates. Am J Kidney Dis. 2013;62(2):253-60.

15. Grams ME et al. Lifetime incidence of CKD stages 3-5 in the United States. Am J Kidney Dis. 2013;62(2):245-52.

16. Astor BC et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int. 2011;79(12):1331-40.

17. Chronic Kidney Disease Prognosis Consortium et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073-81.

18. McCullough PA et al. CKD and cardiovascular disease in screened high-risk volunteer and general populations: The Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis. 2008;51(4 Suppl 2):S38-45.

19. Marks A et al. Translating chronic kidney disease epidemiology into patient care--the individual/public health risk paradox. Nephrol Dial Transplant. 2012;27 Suppl 3:iii65-iii72.

20. Nitsch D et al. CKD and hospitalization in the elderly: a community-based cohort study in the United Kingdom. Am J Kidney Dis. 2011;57(5):664-72.

21. Kerr M et al. Estimating the financial cost of chronic kidney disease to the NHS in England. Nephrol Dial Transplant. 2012;27(suppl 3):iii73-iii80.

22. Roderick PJ. Assessing the impact of chronic kidney disease on individuals and populations: use of relative and absolute measures. Nephrol Dial Transplant. 2012;27(suppl 3):iii39-iii42.

23. Hallan SI et al. Age and association of kidney measures with mortality and end-stage renal disease. JAMA. 2012;308(22):2349-60.

24. Marks A et al. Incidence and prevalence of CKD - what is the change over time. Scottish Renal Association Autumn Meeting. Aberdeen, November 2012.

25. Cooney MT et al. Value and limitations of existing scores for the assessment of cardiovascular risk: a review for clinicians. J Am Coll Cardiol. 2009;54(14):1209-27.

26. Hippisley-Cox J et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008;336(7659):1475-82.

27. Hemingway H et al. Prognosis research strategy (PROGRESS) 1: a framework for researching clinical outcomes. BMJ. 2013;346:e5595.

28. Riley RD et al. Prognosis research strategy (PROGRESS) 2: prognostic factor research. PLoS Med. 2013;10(2):e1001380.

29. Steyerberg EW et al. Prognosis research strategy (PROGRESS) 3: prognostic model research. PLoS Med. 2013;10(2):e1001381.

30. Hingorani AD et al. Prognosis research strategy (PROGRESS) 4: stratified medicine research. BMJ. 2013;346:e5793

31. Royston P et al. Prognosis and prognostic research: developing a prognostic model. BMJ. 2009;338:b604.

32. Moons KG et al. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ. 2009;338:b606.

33. Tangri N et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA. 2011;305(15):1553-9.

34. Tangri N et al. Risk prediction models for patients with chronic kidney disease: a systematic review. Ann Intern Med. 2013;158(8):596-603.

35. Echouffo-Tcheugui JB, Kengne AP. Risk models to predict chronic kidney disease and its progression: a systematic review. PLoS Med. 2012;9(11):e1001344.

36. Dimitrov BD et al. Chronic nephropathies: individual risk for progression to end-stage renal failure as predicted by an integrated probabilistic model. Nephron Clin Pract. 2003;95(2):c47-59.

37. Keane WF et al. Risk scores for predicting outcomes in patients with type 2 diabetes and nephropathy: the RENAAL study. Clin J Am Soc Nephrol. 2006;1(4):761-7.

38. Wakai K et al. A scoring system to predict renal outcome in IgA nephropathy: from a nationwide prospective study. Nephrol Dial Transplant. 2006;21(10):2800-08.

39. Kent DM et al. Progression risk, urinary protein excretion, and treatment effects of angiotensin-converting enzyme inhibitors in nondiabetic kidney disease. J Am Soc Nephrol. 2007;18(6):1959-65.

40. Johnson ES et al. Predicting the risk of dialysis and transplant among patients with CKD: a retrospective cohort study. Am J Kidney Dis. 2008;52(4):653-60.

41. Goto M et al. Risk stratification for progression of IgA nephropathy using a decision tree induction algorithm. Nephrol Dial Transplant. 2009;24(4):1242-7.

42. Hallan SI et al. Combining GFR and albuminuria to classify CKD improves prediction of ESRD. Journal of the American Society of Nephrology. 2009;20(5):1069-77.

43. Landray MJ et al. Prediction of ESRD and death among people with CKD: the chronic renal impairment in Birmingham (CRIB) prospective cohort study. Am J Kidney Dis. 2010;56(6):1082-94.

44. Desai AS et al. Association between cardiac biomarkers and the development of ESRD in patients with type 2 diabetes mellitus, anemia, and CKD. Am J Kidney Dis. 2011;58(5):717-28.

45. Shlipak MG et al. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA. 2005;293(14):1737-45.

46. Weiner DE et al. The framingham predictive instrument in chronic kidney disease. J Am Coll Cardiol. 2007;50(3): 217-24.

47. McMurray JJ et al. Predictors of fatal and nonfatal cardiovascular events in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia: an analysis of the trial to reduce cardiovascular events with aranesp (darbepoetin-alfa) therapy (TREAT). Am Heart J. 2011;162(4):748-55.

48. Johnson ES et al. Predicting renal replacement therapy and mortality in CKD. Am J Kidney Dis. 2007;50(4): 559-65.

49. Berthoux F et al. Predicting the risk for dialysis or death in IgA nephropathy. J Am Soc Nephrol. 2011;22(4):752-61.

50. Rigatto C et al. Risk prediction in chronic kidney disease: pitfalls and caveats. Curr Opin Nephrol Hypertens. 2012;21(6):612-8.

51. Peeters MJ et al. Validation of the kidney failure risk equation in european CKD patients. Nephrol Dial Transplant. 2013;28(7):1773-9.

52. Tangri N et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA. 2011;305(15):1553-9

53. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1-150.

54. Black C et al. Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis. Health Technol Assess. 2010;14(21):1-184.

NO ADDED MORTALITY BENEFIT FROM CURRENT APPROACHES TO RENAL REPLACEMENT THERAPY IN ICU PATIENTS

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ABSTRACT

Hospital-acquired acute kidney injury (AKI), a common and harmful renal disorder, is an independent risk factor for short-term and long-term mortality particularly in critically ill patients. The management of this patient subpopulation remains supportive, with renal replacement therapy (RRT) indicated in severe renal failure. RRT prevents immediate death from lethal complications of advanced AKI, and - undoubtedly - reduces the mortality in AKI patients. The field of RRT has undergone remarkable changes to further improve the dismal short-term outcome. However, trials have failed to demonstrate an additional survival benefit of choice of modality or increased dose, or timing of RRT initiation if RRT is adequately performed. Clearly, AKI is not an isolated event but results in multiple negative effects on inflammation or coagulation and in multiple organ dysfunction. The underlying mechanisms are not amenable to current RRT. Thus, we should be realistic in our expectations of what dialysis and haemofiltration could accomplish; they are not renal replacement therapies in the true sense of the word, but only supportive systems. Prevention of AKI by better care, earlier anticipation of AKI by use of novel biomarkers and pharmacologic therapy of emergent AKI, and the introduction of bioreactor systems into clinical treatment of AKI may be future strategies to further improve the poor outcome of these patients.

Keywords: Acute kidney injury, renal replacement therapy, outcome.

INTRODUCTION

Acute kidney injury (AKI) is common in hospitalised patients, in particular in those admitted to the intensive care unit (ICU). AKI complicates the clinical course of approximately 40% of critically ill patients with higher rates in septic ICU patients compared to patients undergoing elective surgery.

Undoubtedly, hospitalised patients affected by AKI have a poor short and long-term prognosis. AKI is associated with significantly increased in-hospital mortality, prolonged length of ICU or hospital stay, longer dependence on mechanical ventilation, or non-recovery of renal function at discharge. Survivors may experience *de novo* development and progression of chronic kidney disease (CKD); they require frequent re-hospitalisations, experience impaired quality of life, need re-institution of dialysis for end-stage renal disease (ESRD), and show dismal long-term survival. Outcomes of hospital-acquired AKI are related directly to the severity of AKI (Risk, Injury, Failure, Loss of function, and End-stage renal disease [RIFLE] staging criteria).

In the absence of causative therapies for established AKI, its management remains supportive. Renal replacement therapy (RRT), using one or more of the modalities of dialysis or haemofiltration, is required in approximately 5% of all patients affected by AKI.[1,2]

MORTALITY OF CRITICALLY ILL PATIENTS WITH SEVERE AKI

The mortality of AKI due to acute tubular necrosis approached 100% during World War II. The introduction of haemodialysis during the Korean War improved mortality from about 90% to 50%. This

remains the best evidence to date that haemodialysis improves short-term outcome of critically ill patients with AKI.[3]

AKI-associated mortality is decreasing[4,5] but the outcome remains poor. In the literature, the mortality rate of patients with AKI plus three failing organs, and a sequential organ failure assessment (SOFA) cardiovascular score of 3 or 4 is 50% at 90 days, whereas 10 years ago it was 65%. Regarding non-septic AKI requiring RRT, the overall mortality can be as low as 40% at 90 days.

Patients die of AKI, not just simply with AKI. Even small changes in serum creatinine concentrations (<0.5 mg/dl) after cardiothoracic surgery are associated with a substantial increase in the risk of death.[6] A prospective multicentre cohort study[7] found that ICU patients with AKI requiring RRT, matched with ICU subjects for age and severity of illness, had a significantly higher hospital mortality. These results provide further evidence that AKI presents a specific and independent risk factor even under conditions of RRT.

Well-known complications of AKI are fluid overload, retention of uraemic toxins, and electrolyte abnormalities which need at least partial correction. New concepts argue that the development of AKI is the consequence of complex interactions between the actual insult and the subsequent activation of inflammation and coagulation cascades. Experimental models of AKI show that AKI instigates and multiplies cardio-pulmonary, hepatic, and neurologic dysfunction. Further studies provide evidence that AKI is associated with higher infection rates.[8-10]

CURRENT APPROACHES TO RRT

The aims of RRT for AKI are to maintain metabolic and volume homeostasis, and to prevent uraemic complications and dysfunction of vital organs during the acute illness until renal function recovers. These benefits must be balanced by potential harms, such as central venous access complications, infection, anticoagulation with heparin and its multiple untoward side-effects, depletion of electrolytes and micronutrients, incorrect dosing of antimicrobial drugs, hypotension, and aggravation of renal and systemic inflammatory effects by the components of the extracorporeal circuit.[11] The introduction of citrate has revolutionised anticoagulation for continuous renal replacement therapy (CRRT). Compared to heparin, citrate anticoagulation reduces the risk of bleeding and requirement for blood products in patients with or without coagulopathy. Regional citrate anticoagulation effectively prevents extracorporeal thrombosis and improves the delivery of RRT. The use of citrate may also be associated with less systemic inflammation.[12] In critically ill patients, different factors modify the elimination of drugs, particularly antibiotics, when CRRT or sustained low-efficiency dialysis (SLED) is performed. Altered pharmacokinetics of many antibiotics must be taken into account, and a modification of dosages is usually necessary to prevent underdosing.[13]

Choice of RRT Modality

RRT is increasingly performed as CRRT, as conventional intermittent haemodialysis (IHD), hybrid techniques (slow extended daily dialysis [SLEDD]), or prolonged intermittent renal replacement therapy (PIRRT), and rarely acute high volume peritoneal dialysis (PD).

CRRT is perceived to offer greater cardiovascular stability. However, IHD interventions, such as daily frequency, augmented duration, volumetric control of ultrafiltration, bicarbonate based dialysate, sodium modelling, ultrafiltration profiles, cooled dialysate, increased dialysate calcium, and biocompatible dialyser membranes, may lead to a reduction in intradialytic hypotensive episodes, and, thus, enable the safe treatment of almost all critically ill patients with AKI.[14]

Based on systematic reviews, there is no convincing evidence that CRRT is superior to IHD in terms of mortality.[15-19] These meta-analyses did not include the recently published monocentric Continuous Versus Intermittent Renal Replacement Therapy on the outcome of critically ill patients with acute renal failure (CONVINT) trial.[20] The authors of these randomised controlled trials (RCTs) observed no significant differences between daily IHD and continuous veno-venous haemofiltration (CVVHF); they concluded that IHD and CRRTs may be considered equivalent. The rate of comparison of CRRT and hybrid techniques (SLED) is low; very few prospective RCTs are done on SLED. In a randomised trial of 60 patients, continuous veno-venous haemodiafiltration (CVVHDF) was compared to 6-8 hours of SLED. There was no difference in ICU or 30-day mortality among treatment arms.[21] The RRT Study in ICU patients (a monocentric RCT) compared SLED with CVVH and observed similar outcome (90-day mortality) between 12-hour SLED

or 24-hour CVVH.[22] However, more data are needed to state that SLED is equivalent to CRRT. Moreover, both published RCTs have significant drawbacks such as a small number of participating patients and an insufficient statistical power to discriminate differences among treatment groups.[21,22]

Data comparing high volume PD to IHD or CRRT are scarce. One RCT compared daily IHD and high volume PD in 120 patients. High-dose continuous PD provided appropriate metabolic control and survival, while recovery of renal function is similar to daily IHD.[23] Another RCT compared high volume PD and extended daily haemodialysis, and found no evidence of a survival benefit.[24]

The recent Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for AKI, recommend that CRRT and IHD are used as complementary therapies, with the suggestion that CRRT be used preferentially for haemodynamically instable patients and exclusively in AKI patients with brain injury or increased intracranial pressure resulting from intracranial haemorrhage or fulminate liver failure. The modality chosen should be guided by the individual patient's clinical status, medical and nursing expertise, and the availability of RRT modes. However, both the frequency and duration of IHD should be adjusted to minimise episodes of intradialytic hypotension by avoiding high ultrafiltration rates.[25]

Choice of RRT Modality and Dialysis Dependence after AKI

Development of *de novo* progressive CKD, acceleration of pre-existing CKD, non-recovery of renal function, or ESRD requiring chronic dialysis are associated with higher long-term mortality. Multiple observational studies, including a recently published retrospective cohort study,[26] but none of several prospective RCTs, indicated that ICU AKI patients initially treated with intermittent rather than continuous RRT are more likely to become dialysis dependent. A retrospective analysis of 145 septic AKI patients who received RRT with CVVHF or extended daily haemofiltration (EDHF) found that patients who underwent CVVHF had significantly improved renal recovery independent of clinically relevant variables, but had similar 60-day all-cause mortality rates.[27] Also, the pooled database and subsequent analysis of the Randomised Evaluation of Normal Versus Augmented Level Replacement Therapy (RENAL) and the Veterans Affairs/National Institutes of Health (VA/NIH) trials showed impressive results regarding renal recovery when CRRT was started first (instead of IHD) in haemodynamically unstable patients.[28]

A Cochrane systematic review comparing IHD with CRRT found similar hospital mortality, ICU mortality, length of hospital stay, and renal recovery in critically ill patients. It is important to keep in mind that only three small RCTs, but none of the observational studies, were included in this part of the analysis.[15] A recently published systematic review and meta-analysis included 23 studies (7 RCTs, 16 observational studies). Pooled analyses of the RCTs demonstrated no significant difference in dialysis dependence rates between the modalities, but pooled analyses of the observational studies showed that patients who initially received IRRT had a 2-fold increased risk of dialysis dependence compared with CRRT. However, the latest meta-analyses have important limitations. The adjusted analyses found a higher rate of dialysis dependence in five observational studies and no difference in two observational studies. There were severe limitations in the observational studies (study design, lack of baseline renal function, cause and severity of AKI, unknown distribution of non-renal comorbid disease and CKD at baseline, days on RRT and prescription of IHD, and number of hypotensive episodes). The investigators acknowledged that their findings rely exclusively on data from observational studies, which might be associated with allocation bias.[29] Given the human and public health implications of better AKI outcomes, large RCTs, focusing on renal recovery after AKI, are needed to fully understand the potential effects of initial modality choice on subsequent dialysis dependence and long-term mortality.

TIMING OF RRT IN CRITICALLY ILL PATIENTS WITH AKI

Classical indications for RRT initiation in ICU patients include uraemic symptoms and signs, hyperkalaemia refractory to medical management, volume overload unresponsive to fluid restriction and diuretics, as well as metabolic acidosis that is severe or accompanied by volume overload, precluding adequate bicarbonate therapy. In this situation, RRT is the rescue therapy of immediately lethal complications of severe AKI. Current practice, however, is to initiate RRT early, although RCTs have not been able to document significant benefits of prophylactic dialysis.[16]

In the absence of robust predictive markers of renal functional recovery, there is no commonly accepted definition for the optimal timing of initiating RRT, and indications remain controversial.

Numerous studies have compared early and late initiation of RRT in critically ill patients with AKI (RIFLE Stage 3 or Acute Kidney Injury Network [AKIN] Stage 3). The majority have been retrospective cohort analyses or prospective observational studies and have used a variety of definitions for 'early' or 'late'. To explore the optimal timing for initiation of RRT different parameters were used, including arbitrary cut-offs for serum creatinine, serum urea, urine output, fluid balance, hyperkalaemia, and time from ICU admission or time after onset of AKI. The data obtained are conflicting. One small RCT indicated that of the 28 CRRT patients treated per protocol, 12 patients in the early group (86%) were alive at 2 weeks compared with only 2 patients (14%) in the late group.[30] The two other RCTs found no significant differences between early or late therapy.[31,32] 208 patients with progressively worsening community-acquired AKI participated in a recently published RCT. Early IHD was initiated when serum urea nitrogen and/or creatinine levels increased to 70 and 7 mg/dl, respectively. Usual start patients received IHD when clinically indicated. 27 (13%) patients recovered kidney function before even receiving RRT. Primary outcome data (in-hospital mortality and dialysis dependence at 3 months) did not support early initiation of IHD in community-acquired AKI.[32]

Three meta-analyses concluded that earlier institution of CRRT or IHD in critically ill patients may be associated with a survival benefit.[33-35] However, the studies were heterogeneous and of variable quality and size with few RCTs. The majority of retrospective analyses used conventional parameters of renal function. However, serum levels of creatinine or urea, as well as urine output, depend on multiple non-renal factors as well. The criterion 'duration of admission to ICU to start of RRT' can only be determined retrospectively; the exact duration of AKI remains often speculative, and the diagnosis of AKI is often delayed or even early AKI is missed when the current gold standard 'serum creatinine' is used. Furthermore, the vast majority of primary studies restricted their analyses to patients who received RRT. However, patients who do not receive early RRT can follow different paths. They may need late initiation of RRT, they may die before initiation of dialysis, or they may recover kidney function. It cannot be excluded that more patients with less severe AKI (less than RIFLE Stage 3) received early RRT and it may be possible that the severity of the underlying illness and patient characteristics were different from those of patients in whom RRT was delayed. Also, earlier initiation of RRT may have been prompted by volume overload or life-threatening electrolyte disturbances, whereas progressive uraemia and distant organ dysfunctions may trigger a late start of RRT.

A recent multicentre retrospective study enrolled 648 ICU patients with post-surgical AKI. The initiation of RRT was categorised according to the time between ICU admission and start of RRT as early (less than 1 day), intermediate (2-3 days), and late (4 or more days). Estimated probability of death and in-hospital mortality rates followed 'U curves', suggesting that very early and late initiation of RRT may equally increase mortality.[36]

Taken together, the additional effect of timing the initiation of RRT on survival of patients with severe AKI is yet to be investigated in large RCTs. There is an urgent need to clarify whether subgroups of critically ill patients with septic AKI or cardiogenic shock benefit from an earlier commencement of RRT. Future trials should use a panel of novel biomarkers to define early and late initiation of RRT.

The KDIGO Clinical Practice Guidelines recommend[25] the decision to initiate RRT should be based on the clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests rather than single blood urea nitrogen or creatinine levels. The initiation of RRT may be deferred if the underlying clinical condition is improving. There may be patients with a futile prognosis in whom RRT would not be appropriate.

INTENSITY OF RRT

Clinical trials of the intensity of RRT for AKI have produced conflicting results. There is no consensus regarding the optimal intensity of RRT to address the high mortality of critically ill patients with AKI requiring RRT. Traditionally, in studies with ICU patients, the dosage of RRT has been assessed by variants of Kt/V urea in dialysis based modalities, all of which have limitations. Due to the difficulty in assessing the volume of distribution of urea, the delivered dosage of IHD can be markedly lower than that prescribed and is not routinely measured in

clinical practice. The weight-adjusted effluent flow rate is used as surrogate for convective therapies. However, any assessment of RRT adequacy based solely on small solute clearance remains incomplete and neglects fluid balance and removal of middle and large-sized molecules.

Although studies assessing the effect of RRT intensity on mortality of AKI patients have been conducted since 1975, there is a paucity of data regarding adequate dosage of RRT to be delivered for AKI, particularly for IHD or SLED. The majority of trials published before 2008 clearly favoured more intensive therapy, whereas trials published after 2008 showed more intensive RRT not to be more effective than less intensive regimens. This difference is probably due to study design (single centre versus multicentre), patient characteristics, and the actual RRT dosages delivered.

Two large-scale multicentre trials of higher versus standard dose RRT in critically ill patients with AKI, the VA/NIH trial,[37] and the RENAL trial,[38] found no improvement in clinical outcomes with the delivery of a higher intensity dose, including endpoints such as survival or renal recovery. Recent meta-analyses are similarly negative, showing no improvement in overall outcome or in patient subsets (septic versus non-septic) with higher doses of RRT.[39,40] A minimum delivered dose of at least 20-25 ml/kg/hour for CRRT and a single pool Kt/V urea of 1.2-1.4 for IHD thrice-weekly appears adequate for many critically ill AKI patients.[25] It is accepted that hypercatabolic or volume overloaded patients may require higher doses or frequencies of RRT. Given the well-known discrepancies between prescribed and delivered doses in RRT in the acute setting, prescribing a modestly higher dose of therapy may be necessary to achieve target doses.

HIGH VOLUME HAEMOFILTRATION FOR SEPTIC AKI

High volume haemofiltration effluent rates >50 ml/kg/hour were believed to improve outcomes in critically ill patients with sepsis or septic shock. However, two recent meta-analyses including three or four RCTs, respectively, did not show any meaningful difference in early mortality between high volume and standard volume haemofiltration. There is insufficient evidence for a therapeutic benefit for the routine use of high volume haemofiltration in septic AKI.[41,42]

Biocompatibility of Haemodialysis Membranes and Outcome of AKI

The effect of bio-incompatibility of haemodialysis membranes on mortality in AKI has been the subject of intense and industry-driven debate, with some - but not all - studies reporting a lower risk of death among patients dialysed with biocompatible membranes compared to bio-incompatible membranes. Two meta-analyses suggested a survival advantage for synthetic membranes over unsubstituted cellulose (cuprophane) membranes.[43,44] As cuprophane membranes have been phased out over time and the price difference between synthetic and modified cellulose membranes is negligible, the impact of membrane choice on patient outcome has become somewhat passé.

CONCLUSIONS

Mortality associated with severe AKI remains unacceptably high, in spite of a number of new advances in RRT technology and approaches to RRT. Although it has been argued that RRT is not yet fully optimised, further adjustments of RRT in ICU AKI may have little impact on overall mortality. In the setting of multi-organ failure, we should be realistic in our expectations of what dialysis and haemofiltration can accomplish. Cell therapy devices are currently developed to replace the filtrative, metabolic, and endocrinologic functions of the human kidneys lost in AKI.[45] The bioartificial kidney, which incorporates a haemofilter with tubular cell lines, may be particularly promising in this regard.

The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) 2009 report on AKI, 'adding insult to injury', identified deficiencies in care in 50% of hospitalised cases, including failures in AKI prevention, recognition, therapy, and timely access to specialised services. 30% of cases of AKI were judged to be preventable.[46] Early identification of AKI with novel candidate biomarkers may be an important step in improving outcome. These biomarkers help not only in the early detection of AKI before the onset of a rise in serum creatinine, but also in the differential diagnosis of the condition.[47]

REFERENCES

1. Bellomo R et al. Acute kidney injury. Lancet. 2012;380(9843):756-66.

2. Cohen SD, Kimmel PL. Long-term sequelae of acute kidney injury in the ICU. Curr Opin Crit Care. 2012;18(6):623-8.

3. Schrier RW et al. Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. J Clin Invest. 2004;114(1):5-14.

4. Bagshaw SM et al. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. Crit Care. 2007;11(3):R68.

5. Waikar SS et al. Declining mortality in patients with acute renal failure, 1988 to 2002. J Am Soc Nephrol. 2006;17(4): 1143-50.

6. Lassnigg A et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol. 2004;15(6):1597-605.

7. Metnitz PG et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med. 2002;30(9): 2051-8.

8. Yap SC, Lee HT. Acute kidney injury and extrarenal organ dysfunction: new concepts and experimental evidence. Anesthesiology. 2012;116(5):1139-48.

9. Lee DW et al. Cytokines in acute kidney injury (AKI). Clin Nephrol. 2011;76(3): 165-73.

10. Singbartl K, Kellum JA. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int. 2012;81(9):819-25.

11. Palevsky PM et al. Renal replacement therapy and the kidney: minimizing the impact of renal replacement therapy on recovery of acute renal failure. Curr Opin Crit Care. 2005;11(6):548-54.

12. Oudemans-van Straaten HM, Ostermann M. Bench-to-bedside review: citrate for continuous renal replacement therapy, from science to practice. Crit Care. 2012;16(6):249.

13. Fissell WH. Antimicrobial dosing in acute renal replacement. Adv Chronic Kidney Dis. 2013;20(1):85-93.

14. Vinsonneau C et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet. 2006;368(9533):379-85.

15. Rabindranath K et al. Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev. 2007;(3):CD003773.

16. Pannu N et al. Renal replacement therapy in patients with acute renal failure: a systematic review. JAMA. 2008;299(7):793-805.

17. Bagshaw SM et al. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Crit Care Med. 2008;36(2):610-7.

18. Friedrich JO et al. Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis. Crit Care. 2012;16(4):R146.

19. Ghahramani N et al. A systematic review of continuous renal replacement therapy and intermittent haemodialysis in management of patients with acute renal failure. Nephrology (Carlton). 2008;13(7):570-8.

20. Schefold JC et al. The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomized controlled trial. Crit Care. 2014;18(1):R11.

21. Abe M et al. Comparison of sustained hemodiafiltration with continuous venovenous hemodiafiltration for the treatment of critically ill patients with acute kidney injury. Artif Organs. 2010;34(4):331-8.

22. Schwenger V et al. Sustained low efficiency dialysis using a single-pass batch system in acute kidney injury - a randomized interventional trial: the REnal Replacement Therapy Study in Intensive Care Unit PatiEnts. Crit Care. 2012;16(4):R140.

23. Gabriel DP et al. Continuous peritoneal dialysis compared with daily hemodialysis in patients with acute kidney injury. Perit Dial Int. 2009;29 Suppl 2:S62-71.

24. Ponce D et al. A randomized clinical trial of high volume peritoneal dialysis versus extended daily hemodialysis for acute kidney injury patients. Int Urol Nephrol. 2013;45(3):869-78.

25. Kidney Disease: Improving Global Outcomes (KDIGO) Acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int. 2012;Suppl.2:1-138.

26. Wald R et al. The association between renal replacement therapy modality and long-term outcomes among critically ill adults with acute kidney injury: a retrospective cohort study. Crit Care Med. 2013.

27. Sun Z et al. Continuous venovenous hemofiltration versus extended daily hemofiltration in patients with septic acute kidney injury: a retrospective cohort study. Crit Care. 2014;18(2):R70.

28. Bellomo R, Schneider AG. The real cost of conventional hemodialysis in critically ill patients. Crit Care Med. 2014;42(4):990-1.

29. Schneider AG et al. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med. 2013;39(6):987-97.

30. Sugahara S, Suzuki H. Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. Hemodial Int. 2004;8(4):320-5.

31. Bouman CS et al. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Crit Care Med. 2002;30(10):2205-11.

32. Jamale TE et al. Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. Am J Kidney Dis. 2013;62(6):1116-21.

33. Seabra VF et al. Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. Am J Kidney Dis. 2008;52(2):272-84.

34. Karvellas CJ et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. Crit Care. 2011;15(1):R72.

35. Wang X, Jie YW. Timing of initiation of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. Ren Fail. 2012;34(3):396-402.

36. Shiao CC et al. U-curve association between timing of renal replacement therapy initiation and in-hospital mortality in postoperative acute kidney injury. PLoS One. 2012;7(8):e42952.

37. Palevsky PM et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359(1): 7-20.

38. Bellomo R et al. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med. 2009;361(17): 1627-38.

39. Van Wert R et al. High-dose renal replacement therapy for acute kidney injury: systematic review and meta-analysis. Crit Care Med. 2010;38(5): 1360-9.

40. Jun M et al. Intensities of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. Clin J Am Soc Nephrol.

2010;5(6):956-63.

41. Lehner G et al. High volume hemofiltration in critically ill patients - a systematic review and meta-analysis. Minerva Anestesiol. 2013.

42. Clark E et al. High-volume hemofiltration for septic acute kidney injury: a systematic review and meta-analysis. Crit Care. 2014;18(1):R7.

43. Subramanian S et al. Influence of dialysis membranes on outcomes in acute renal failure: a meta-analysis. Kidney Int. 2002;62(5):1819-23.

44. Jaber BL et al. Effect of biocompatibility of hemodialysis membranes on mortality in acute renal failure: a meta-analysis. Clin Nephrol. 2002;57(4):274-82.

45. Humes HD et al. The bioartificial kidney: current status and future promise. Pediatr Nephrol. 2014;29(3):343-51.

46. Anathhanam S, Lewington AJ. Acute kidney injury. J R Coll Physicians Edinb. 2013;43:323-9.

47. Schiffl H, Lang SM. Update on biomarkers of acute kidney injury: moving closer to clinical impact? Mol Diagn Ther. 2012;16(4):199-207.

THE MULTIDISCIPLINARY APPROACH TO RENAL DENERVATION: CURRENT EVIDENCES AND OPEN QUESTIONS

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ABSTRACT

Renal denervation (RD) is a new clinical procedure which aims to treat resistant hypertensive patients. As with every new technology introduced into the clinical setting, many aspects were not explored sufficiently in order to be implemented into routine clinical practice. Advances in clinical technology require different steps of development, which start from preliminary *in vitro* experiments and finally arrive in the market, available for physicians when they have been proven to produce benefits for patients. Each stage usually takes many years before acquiring consensus from specialists involved in specific fields. In our opinion, this is a long and blind way and is a disadvantage to patients who need rapid, specific, and effective treatments. Otherwise, a multidisciplinary approach can provide the right evaluation of RD position and its potential for clinical application and research development. Therefore, we decided to draw a well-structured literature review from different specialists' points of view in order to cover the subject in a translational manner. We reported animal models and experimental trials, in chronological order, and their evidences which have created the basis for human research. Technologies and devices were compared to underlined advantages and disadvantages. An update of clinical data was considered to define clinical needs in order to build focused trials. Furthermore, we evaluate the feasibility of routine RD clinical use by means of an economic analysis. Finally, we tried to settle the main unresolved questions and then assessed future RD perspectives, including non-hypertension indications.

Keywords: Resistant hypertension, sympathetic hyperactivity, catheter, radiofrequency, heart failure, incremental cost effectiveness ratio.

INTRODUCTION

Renal denervation (RD) is a newcomer in the field of antihypertensive therapies. Since its arrival a lot of trials and reviews have been published, dividing the scientific community between those for and those against this procedure. In the last few months, several published reviews have focused on epidemiology of resistant hypertension and clinical aspects of RD. Arterial hypertension is a diffuse and complex disease which involves severe complications in different organs and apparatuses, so as a result hypertensive patients are referred to general practitioners as well as to different specialists (cardiologists, nephrologists, internists). In this setting, RD could be defined as a 'translational procedure' which involves different medical specialists but also different professionals, such as engineers and biologists. Nowadays, hypertension treatment has a heavy economic impact on the healthcare system compared to the past, due to technological improvements.

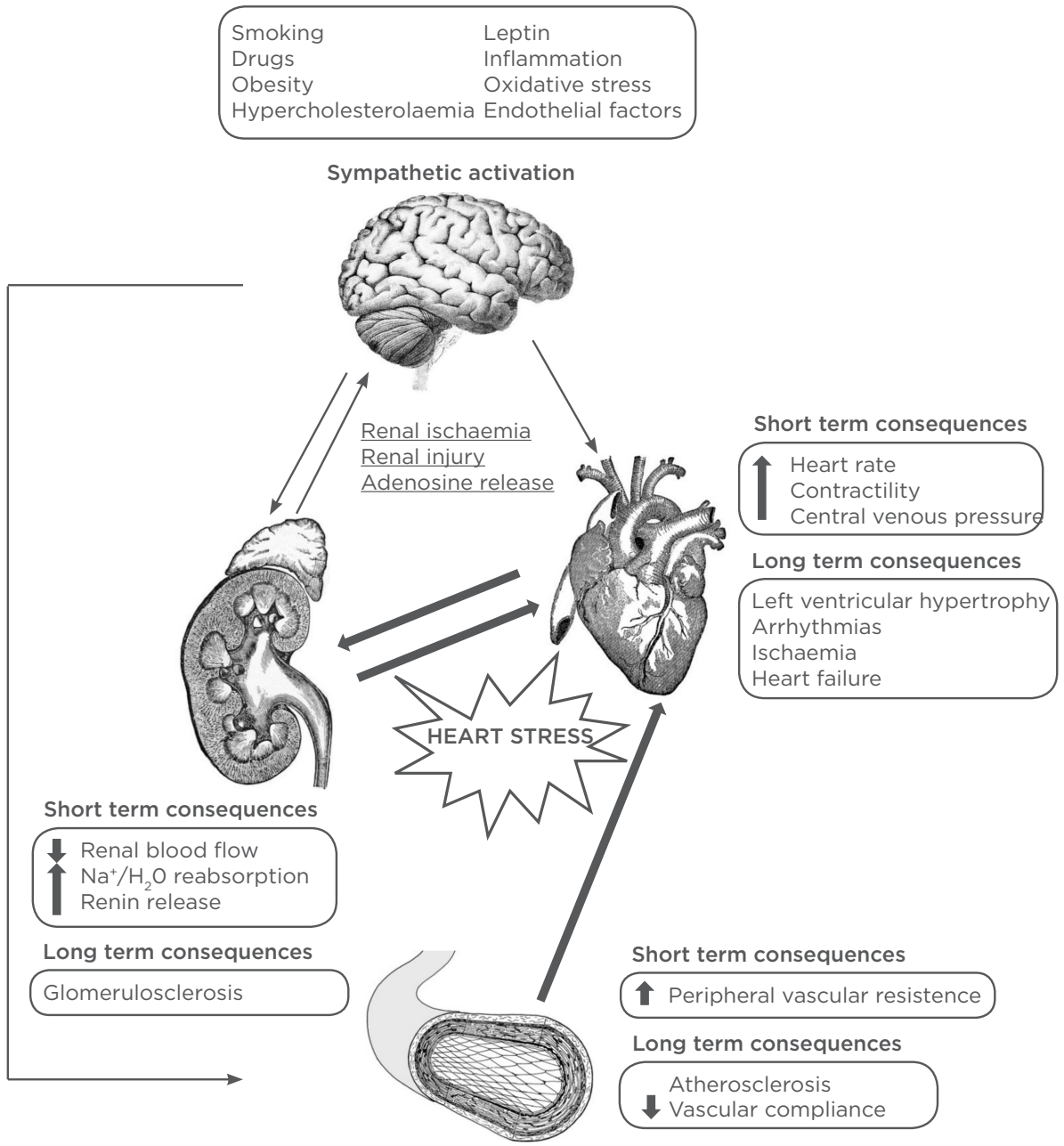

Figure 1: Short and long-term consequences associated with sympathetic activation.

The long-term control of BP has been attributed to the kidney by the mechanisms of pressure natriuresis and diuresis, in which it couples the regulation of blood volume to the maintenance of sodium and water balance. The activation of renal afferent fibres by decreased renal blood flow and by variation of ultrafiltrate composition increases the sympathetic tone. An increased sympathetic tone to the heart increases contractility, heart rate, and central venous pressure; to the peripheral vessels it increases vascular resistance; and to the kidneys it either decreases renal blood flow (effect mediated by α-adrenergic receptors), increases renin release out of the granular cells in the walls of afferent arterioles (effect mediated by β-adrenergic receptors), or increases proximal tubular sodium reabsorption (by means of Na-H antiporters and Na-K pumps). Angiotensin II increases peripheral vascular resistance and, to the kidneys, it increases proximal tubular sodium reabsorption, GFR, prostaglandin, and aldosterone release. Aldosterone increases distal tubular sodium reabsorption (by means of epithelial sodium channel). An increased sympathetic tone is also involved in several pathological conditions such as left ventricular hypertrophy, cardiac arrhythmias, and heart failure, as well as in obstructive sleep apnoea syndrome, hyperinsulinaemia, and chronic kidney disease (thin arrows). In hypertensive patients the increased sympathetic tone, which has been displayed to the kidney and other organs, leads to increased peripheral vascular resistance and hydrosaline retention, which both definitively cause heart stress (thick arrows).

Therefore, it is fundamental to assess the economic sustainability of these new, relatively expensive, procedures through economic analysis. Literature partially covers these issues, so the aim of this paper is to provide a multifaceted review about interdisciplinary techniques for the treatment of a systemic disease.

RD

Kidney and Sympathetic Hyperactivity: the Background for RD

The role of the sympathetic nervous system (SNS) and the involvement of kidneys in the development of sympathetic hyperactivity supporting hypertension has been known since the 1930s, leading to the early practice of surgical sympathectomy.[1,2] Related complications guided the development of a chemical sympathectomy, later displaced by the introduction of new antihypertensive drugs. Progressively, the therapeutic RD has been explored by preclinical experiments that included multiple animal species and different primary diseases.[3] These studies contributed to revealing the role of renal sympathetic efferent and sensory afferent nerves to renal and systemic organ function in normal and pathological conditions (hypertension,[4] heart failure [HF],[5-8] or chronic kidney disease [CKD]),[9] as well as to investigate the potential therapeutic implications of RD.[10] Marked effects of RD on blood pressure (BP) were demonstrated in multiple animal models of hypertension, including salt-sensitive swines[11] and genetically hypertensive rats:[12] two-kidney one-clip Goldblatt hypertension[13] and one-kidney renal hypertension.[14]

In healthy humans, there is a fine physiological balance aimed at maintaining homeostasis between parasympathetic and sympathetic activity.[15] In a pathological condition, the increased sympathetic tone increases sodium reabsorption, acting directly on renal tubules proportionally to the density of the innervation. The association of hydrosaline retention with high peripheral vascular resistance definitively causes hypertension and heart stress (Figure 1). As a proof of this, an increase of renal sympathetic nerve activity (RSNA) is found both in animal models of hypertension and in hypertensive humans.[16] The sympathetic overactivity is the hallmark of CKD and renal failure. Campese[17] found that afferent impulses from the kidney to central integrative structures in the brain are supposed to be responsible for the rise in BP in CKD, in 5/6 nephrectomised rats. This discovery might justify the uncommon practice of bilateral nephrectomy in patients with end-stage renal disease and uncontrollable hypertension. The ligation of renal nerves has been shown to improve the responsiveness to atrial natriuretic peptide in rats with cirrhosis and HF,[5] and to reduce the ventricular filling pressure, improving ventricular function in dogs with high-output HF compared with nondenervated controls.[7]

Resistant Hypertension

The BP reduction through pharmacological intervention is one of the most powerful and successful ways to reduce complications and improve outcomes.[18,19] Although several appropriate and integrated pharmacological strategies are available, BP control still remains largely unsatisfactory;[20] indeed >40% of patients with hypertension are not controlled.[21] In 2007, the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines discriminated among the hypertensive population and those patients with other comorbidities (e.g. diabetes, nephropathies). In December 2013, the ESH/ESC guidelines were revised. Resistant hypertension is now defined as a condition where: "Therapeutic strategy includes appropriate lifestyle measures plus a diuretic, and two other antihypertensive drugs belonging to different classes at adequate doses fail to lower systolic BP and diastolic BP values to <140 and 90 mmHg, respectively."[22] The ESH/ESC guidelines do not discern patients on the basis of BP values: the definition of resistant hypertension includes indistinctly both patients with extreme BP levels and patients with BP levels just above the threshold. For this reason, it is difficult to identify those patients affected by resistant hypertension who may benefit from RD procedure. Furthermore, trials published to date have not adequately divided the hypertensive population into groups defined by BP levels. In the clinical practice, resistant hypertension has to be distinguished from arterial secondary hypertension due to treatable diseases (renal artery stenosis, pheochromocytoma, aldosterone-secreting adrenal adenoma) and pseudo-resistant hypertension caused by inaccurate measurement technique. Furthermore, it is necessary to differentiate between resistant and uncontrolled hypertension related to drug interactions, inadequate therapy,

and/or poor compliance. In this setting the prevalence of resistant hypertension is not well established. However, literature data suggest a widespread value from 5-30% of the overall hypertensive population, indicating that resistant hypertension is relatively common.[23-27]

Technical Aspects of RD

In the case where the patient presents with resistant hypertension, if the anatomy of the renal artery appears suitable for the procedure (artery length >20 mm; artery diameter >4 mm), RD might

Table 1: Specifications for renal denervation on-the-market devices.

	Symplicity™ Renal Denervation System	St. Jude Medical's EnligHTN™ System	Vessix's V2™ Renal Denervation System	Covidien's OneShot™ System	Terumo's Iberis™ System	Recor's Paradise™ System
						
Power source	RF	RF	RF	RF	RF	US
Catheter size	6F	8F	8F	7-8F	4F	6F
Catheter length	90 cm	115 cm	90 cm	74 cm	155 cm	100 cm
Type of power source	Single tip electrode	4 electrodes at a nitinol basket-like	Array of bipolar electrodes	Balloon with continuous spiral electrode	Single tip electrode	One US transducer inside an inflatable low-pressure over-the-wire balloon
Max temperature	75 °C	75 °C	68 °C	60 °C	70 °C	68 °C
Max power	5-8 Watt	6 Watt	1 Watt	25 Watt	8 Watt	12 Watt
Time	2 min/ ablation	90 sec/ ablation	30 sec/ ablation	2 min/ ablation	2 min/ ablation	30 sec/ ablation
Number of recommended ablations	4 APA	8 APA	½ APA	1 APA	4-6 APA	2 APA
Access	Femoral	Femoral	Femoral	Femoral	Radial	Femoral
CE mark	February, 2008	December, 2011	February, 2012	April, 2012	April, 2013	2012
Studies	Symplicity HTN1 Symplicity HTN1 Registry Symplicity HTN2 Symplicity HTN3	EnligHTN I EnligHTN II EnligHTN III EnligHT-Nment	Reduce HTN	RHAS RAPID	IBERIS-HTN	REDUCE REALISE ACHIEVE

RF: radio frequency; APA: ablation(s) per artery; US: ultrasound.

represent a novel solution. Catheter-based RD is a minimally invasive procedure, involving the delivery of radiofrequency (RF) energy along 1-2 cm in the main renal arteries, to ablate the renal nerves located in the adventitia. The procedure is generally performed exploiting a standard femoral vascular access. A contrast angiography can be performed to localise and evaluate the accessibility of the renal arteries. The catheter is advanced near the bifurcation of the renal artery under fluoroscopic guidance, and the electrodes at the distal tip are brought into contact with the endothelium. When the impedance is stable, a RF-wave generator locally provides a signal of controlled energy. The applied frequencies range between 1 MHz and 10 GHz. When the produced current reaches the electrodes, heat is locally generated because biological tissues act like resistors, enhancing the temperature to around 65-70 °C and causing thermal ablation of the renal nerves. Since the relationship between the RF generator output and the tip temperature depends on parameters that widely vary, then impedance, temperature, power, and time intervals are continuously monitored. In the case in which one of these quantities differs from the desired/predicted values, the treatment is automatically stopped by the embedded/control algorithm.

At present, RF ablation is the main technology applied for RD; on the other hand, the first promising results of RD have led to the development of other techniques. Devices exploiting ultrasound (US) waves seem to be a promising alternative; sound waves with a frequency higher than 1 MHz, passing through fluids, generate frictional heating in soft tissues, without direct contact with the intimate endothelium, causing thermal ablation. A very interesting implementation of this technique seems to be the use of externally focused US and low intensity US (frequency=800 kHz and irradiance=2 mW/cm^2),[28] with the potential benefit of a reduced invasive clinical procedure. Moreover, other technologies are under development: cryoablation (at present with reports in animal models only), β-radiations (experimental studies in swine only), and injection of neurotoxins (guanethidine,[29] ethanol,[29] Botox B or vincristine[30]). On-the-market devices and some of their major characteristics are summarised in Table 1.

Current Evidences from Clinical Trials

Since the first proof-to-concept trial performed with the Symplicity RF catheter,[31] several trials performed with different devices have been designed in order to evaluate the efficacy and safety of RD, as summarised in Table 2. Symplicity HTN-1 investigators have recently published the positive results of a 36-month follow-up.[32] While the 6-month follow-up Symplicity HTN-3 data have confirmed a BP reduction from baseline, investigators have found no significant differences between treated and control groups.[33] Symplicity HTN-3 trial remains the only single-blinded randomised controlled trial (RCT), with a sham-control group, designed to evaluate the safety and effectiveness of RD. The study design might explain the different results obtained in the previous clinical trials. Indeed, the presence of a sham procedure can delete the placebo effect, but it does not remove bias due to the Hawthorne effect. Even if Symplicity HTN-3 does not achieve the efficacy primary outcome, it will be followed up for 5 years in order to evaluate potential long-term RD benefits.[33]

At the same time, the perspectives of RD in the treatment of some other diseases associated with sympathetic hyperactivity are still under investigation. The first small clinical trials suggest promising effects of RD in improving glucose metabolism and insulin sensitivity,[34] decreasing sleep apnoea severity,[35] and reducing left ventricular mass,[36] thus, providing protection in patients at high cardiovascular risk. At present, two studies - DIASTOLE[37] and Symplicity HF trial - are ongoing to assess the effectiveness and safety of RD in the treatment of normal and impaired left ventricular ejection fraction HF, respectively. Presently, according to evaluated RCTs, RD does not significantly affect renal functioning as measured by estimated glomerular filtration rate or Cystatin C.[38,39] Moreover, RD needs future RCTs to evaluate renal function for a longer period of follow-up as well as its effectiveness and safety in moderate-to-severe CKD.

Economic Analysis

An economic analysis, through comparisons among technology costs and all relevant long-term benefits, allows us to understand whether RD might replace the current standard of care (SoC).[40] Geisler et al.[41] have made an economic evaluation of RD, which shows that it can be cost-effective when compared to well-accepted medical treatments. Exploiting a Markov state-transition model, they simulated the RD treatment on a cohort of patients to assess its cost-effectiveness and long-term clinical benefits (cardiovascular

Table 2: RD clinical trials in resistant hypertension.

Clinical trial	Trial status	Study design	N° pts	Follow-up	Results
Symplicity HTN1[31]	Concluded	Multicentre proof-on-concept	45	12 months	Office BP reduction (-27/-17 mmHg)* acute procedural and long-term safety (2 adverse events)
Symplicity HTN1 Registry[32]	Active	Multicentre prospective	153		36-month follow-up: office BP reduction (-32/-14 mmHg)**, acute procedural, and long-term safety (8 adverse events)
Symplicity HTN2[46]	Concluded	Multicentre randomised	106	6 months	Office BP reduction in RD group (-32/-12 mmHg, p<0.0001) compared with control group (+7/+1 mmHg)
Symplicity HTN2 with cross-over group[39]	Concluded	Multicentre randomised	106	12 months	Office BP reduction in initial RD group (-28/-10 mmHg, p=0.16) and in cross-over group (-24/-8 mmHg, p<0.001)
Symplicity HTN3[47]	Active, not recruiting	Multicentre single-blinded RCT	535	5 years	6-month follow-up: not significantly office BP reduction, safety through 6 months
EnligHTN I[48]	Active, not recruiting	Multicentre prospective	46	24 months	18-months follow-up: office BP reduction (-24/-10 mmHg, p<0.0001), acute procedural safety, and long-term safety (4 adverse events)
EnligHTN II	Recruiting	Multicentre prospective	500	5 years	N.A.
EnligHTN III	Active, not recruiting	Multicentre prospective	50	24 months	N.A.
EnligHTNment	Recruiting	Multicentre RCT	4,000	5 years	N.A.
Reduce HTN	Active, not recruiting	Multicentre prospective	146	12 months	Office BP reduction (-28/-11 mmHg)*** acute procedural and long-term safety (adverse events in 5.5% of patients)
RHAS[49]	Concluded	First-in-man prospective	8	6 months	Office SBP reduction (30.6±22.0)**** acute procedural and long-term safety (minor adverse events)
RAPID	Recruiting	Multicentre prospective	50	6 months	N.A.
REDUCE	Active, not recruiting	First-in-Man prospective	15	6 months	60-days follow-up: office SBP reduction (31 mmHg)
REALISE	Recruiting	Prospective	20	12 months	N.A.
ACHIEVE	Recruiting	Multicentre prospective	50	24 months	N.A.

RD: renal denervation; BP: blood pressure; SBP: systolic blood pressure.
*At all time points after procedure (1, 3, 6, 9, and 12 months), both systolic and diastolic BP were significantly (p<0.01) lower than baseline BP, with the exception of the 12-month diastolic BP (p=0.02).
**At all time points after procedure (1, 6, 12, 24, and 36 months), both systolic and diastolic BP were significantly (p<0.01) lower than baseline BP. 88 patients had complete data at 36 months.
***At all time points after procedure (1, 3, 6, and 12 months), both systolic and diastolic BP were significantly (p<0.0001) lower than baseline BP. 41 patients had complete data at 12 months.
****At all time points after procedure (1, 3, 6, and 12 months) SBP was significantly lower than baseline.

consequences in hypertension) with respect to SoC. They exploited the systolic blood pressure (SBP) reduction values observed in the Symplicity HTN-2 trial, and estimated the state transition probabilities to the clinical endpoints considered in the model (cardiovascular consequences and mortality) from previous cohort studies.

Assuming a discount rate of 3% per year, they found that the discounted incremental direct medical cost divided by the incremental years of life adjusted for a life quality coefficient (Incremental Cost Effectiveness Ratio [ICER]) is $3,071 per quality-adjusted life-year (QALY). Results are robust even taking into account variations in the model structure; indeed, even in the hypothesis of no persistence of BP reduction, the ICER increases only to $13,300. The 95% ICER confidence interval obtained with a probabilistic analysis ranges from a negative cost (i.e. cost-saving) to $31,460, with a 99.6% probability of being below the commonly accepted threshold of $50,000 per QALY (21% cost-saving).[41] The lack of available data limits the possibility to deepen the analysis. However, even though at the present time there is no conclusive evidence in the scientific literature, further benefits resulting from this therapy could be taken into account in the model, increasing the possibility of offsetting the additional costs borne at the time of treatment.

OPEN QUESTIONS

The results obtained with RD should be balanced against some potentially harmful or still undefined effects of the procedure. A recent study using optical coherence tomography (OCT) analysed 32 renal arteries, before and after RD, using Symplicity or EnligHTN catheters. It showed the occurrence of diffuse renal artery vasospasm and local tissue damage at the ablation site with oedema and thrombus formation, suggesting the beneficial use of dual antiplatelet therapy during RD.[42] These vascular injuries have not been reported after RD using the OneShot system, probably because of the vessel wall's saline irrigation during ablation. Otherwise the possibility of endothelial disruption underlines the importance of catheter measure and operator skills.[43] The development of new devices and technologies might avoid these complications in the future.

Regarding the efficacy of RD, the risk of not reaching the target fibres by RF energy is a technical problem that presently cannot be carried out by non-invasive examinations. Experience in kidney transplantation has shown that sympathetic efferent fibres can regrow after being injured. Nevertheless, it is supposed that clinical consequences of RD are mainly related to afferent fibres' destruction.[44] The possibility of regrowing fibres and the clinical consequences of the damage-repair processes are unknown at present.

Regarding the feasibility of RD, the presence of double and triple or multiple renal arteries, respectively, in 20% and 4% of the population, represents a procedure limit.[45] Finally, the lack of specific inclusion criteria based on BP levels in the prescription of RD, as mentioned above, may represent a gap in clinical practice as well as in the analysis of the results of previous trials. In conclusion, safety and effectiveness combined with long-term effects of RD procedure remain the main objectives on the research agenda. The lack of criteria for RD suggests the need to focus on creating the consensus statement through the translational work-group.

REFERENCES

1. Page IH. The effect on renal efficiency of lowering arterial blood pressure in cases of essential hypertension and nephritis. J Clin Invest. 1934;13(6):909-15.

2. Freyberg RH, Peet MM. The effect on the kidney of bilateral splanchnicectomy in patients with hypertension. J Clin Invest. 1937;16(1):49-65.

3. Kline RL et al. Effect of renal denervation on the development of hypertension in spontaneously hypertensive rats. Can J Physiol Pharmacol. 1978;56(5):818-22.

4. Kline RL et al. Effect of renal denervation on arterial pressure in rats with aortic nerve transection. Hypertension. 1983;5(4):468-75.

5. DiBona GF, Sawin LL. Role of renal nerves in sodium retention of cirrhosis and congestive heart failure. Am J Physiol. 1991;260(2 Pt 2):R298-305.

6. Villarreal D et al. Effects of renal denervation on postprandial sodium excretion in experimental heart failure. Am J Physiol. 1994;266(5 Pt 2): R1599-604.

7. Nozawa T et al. Effects of long-term renal sympathetic denervation on heart failure after myocardial infarction in rats. Heart Vessels. 2002;16(2):51-6.

8. Souza DR et al. Chronic experimental myocardial infarction produces antinatriuresis by a renal nerve-dependent mechanism. Braz J Med Biol Res. 2004;37(2):285-93.

9. Ciccone CD, Zambraski EJ. Effects of acute renal denervation on kidney function in deoxycorticosterone acetate-hypertensive swine. Hypertension. 1986;8(10):925-31.

10. Schlaich MP et al. Renal denervation as a therapeutic approach for hypertension: novel implications for an old concept. Hypertension. 2009;54(6):1195-201.

11. O'Hagan KP et al. Renal denervation decreases blood pressure in DOCA-treated miniature swine with established hypertension. Am J Hypertens. 1990;3(1):62-4.

12. Katholi RE. Renal nerves and hypertension: an update. Fed Proc. 1985;44(13):2846-50.

13. Katholi RE et al. Importance of the renal nerves in established two-kidney, one clip goldblatt hypertension. Hypertension. 1982;4(3 Pt 2):166-74.

14. Katholi RE et al. Role of the renal nerves in the pathogenesis of one-kidney renal hypertension in the rat. Hypertension. 1981;3(4):404-9.

15. D'Elia JA, Weinrauch LA. The autonomic nervous system and renal physiology. Int J Nephrol Renovasc Dis. 2013;6:149-60.

16. DiBona GF. Sympathetic nervous system and the kidney in hypertension. Curr Opin Nephrol Hypertens. 2002;11(2):197-200.

17. Campese VM. Neurogenic factors and hypertension in chronic renal failure. J Nephrol. 1997;10(4):184-7.

18. Turnbull F et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005;165(12):1410-9.

19. Turnbull F et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ. 2008;336 (7653):1121.

20. Krieger EM et al. Resistant hypertension optimal treatment trial: a randomized controlled trial. Clin Cardiol. 2014;37(1):1-6.

21. Bakris G et al. Review of blood pressure control rates and outcomes. J Am Soc Hypertens. 2014;8(2):127-41.

22. Mancia G et al. 2013 practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/EHC task force for the management of arterial hypertension. J Hypertens. 2013;31: 1281-357.

23. Calhoun DA et al. Refractory hypertension: determination of prevalence, risk factors, and comorbidities in a large, population-based cohort. Hypertension. 2014;63(3):451-8.

24. Fagard RH. Resistant hypertension. Heart. 2012;98(3):254-61.

25. De la Sierra A et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. 2011;57(5):898-902.

26. Daugherty SL et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. 2012;125(13):1635-42.

27. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension. 2011;57(6):1076-80.

28. Nonogaki K et al. Low-frequency and very low-intensity ultrasound decreases blood pressure in subjects with hypertension. Int J Cardiol. 2013;168(2):1585-6.

29. Fischell TA et al. Ethanol-mediated perivascular renal sympathetic denervation: preclinical validation of safety and efficacy in a porcine model. EuroIntervention. 2013;9(1):140-7.

30. Stefanadis C et al. Chemical denervation of the renal artery by vincristine in swine. A new catheter based technique. Int J Cardiol. 2013;167(2):421-5.

31. Krum H et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009;373(9671):1275-81.

32. Krum H et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the symplicity HTN-1 study. Lancet. 2014;383(9917):622-9.

33. Bhatt DL et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393-401.

34. Mahfoud F et al. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. Circulation. 2011;123(18):1940-6.

35. Witkowski A et al. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. Hypertension. 2011;58(4):559-65.

36. Brandt MC et al. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. J Am Coll Cardiol. 2012;59(10):901-9.

37. Verloop WL et al. Renal denervation in heart failure with normal left ventricular ejection fraction. Rationale and design of the diastole (denervation of the renal sympathetic nerves in heart failure with normal lv ejection fraction) trial. Eur J Heart Fail. 2013;15:1429-37.

38. Mahfoud F et al. Renal hemodynamics and renal function after catheter-based renal sympathetic denervation in patients with resistant hypertension. Hypertension. 2012;60(2):419-24.

39. Esler MD et al. Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the symplicity htn-2 randomized, controlled trial. Circulation. 2012;126(25):2976-82.

40. Sorenson C et al. Medical technology as a key driver of rising health expenditure: disentangling the relationship. Clinicoecon Outcomes Res. 2013;5:223-34.

41. Geisler BP et al. Cost-effectiveness and clinical effectiveness of catheter-based renal denervation for resistant hypertension. J Am Coll Cardiol. 2012;60(14):1271-7.

42. Templin C et al. Vascular lesions induced by renal nerve ablation as assessed by optical coherence tomography: pre- and post-procedural comparison with the Simplicity catheter system and the EnligHTN multi-electrode renal denervation catheter. Eur Heart J. 2013;34:2141-8.

43. Stabile E et al. Percutaneous sympathectomy of the renal arteries: the OneShot Renal Denervation System is not associated with significant vessel wall injury. EuroIntervention. 2013;9(6):694-9.

44. Hausberg M et al. Sympathetic nerve activity in end-stage renal disease. Circulation. 2002;106(15):1974-9.

45. "Anatomy, Structure and Embryology," Netter FH (eds.), The CIBA collection of medical illustration. Kidneys, ureters and urinary bladder (1987;37), CIBA pharmaceutical.

46. Esler MD et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (the symplicity htn-2 trial): a randomised controlled trial. Lancet. 2010;376(9756):1903-9.

47. Kandzari DE et al. Catheter-based renal denervation for resistant hypertension: rationale and design of the symplicity htn-3 trial. Clin Cardiol. 2012;35(9): 528-35.

48. Worthley SG et al. Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: The EnligHTN I trial. Eur Heart J. 2013;34(28):2132-40.

49. Ormiston JA et al. Renal denervation for resistant hypertension using an irrigated radiofrequency balloon: 12-month results from the Renal Hypertension Ablation System (RHAS) trial. EuroIntervention. 2013;9(1):70-4.

CHRONIC RENAL ALLOGRAFT DYSFUNCTION ANTIBODY-MEDIATED: AN UPDATE

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ABSTRACT

This paper reviews the most important studies on chronic antibody-mediated rejection (cABMR), which is an important cause of late graft dysfunction after renal transplantation. Several antibodies seem to be responsible for chronic rejection; new techniques have allowed us to identify these antibodies in circulation. The pathogenetic role of the antibodies generally includes the complement pathway, but may also be complement-independent. This paper also examines the pathogenesis of chronic endothelial lesions, as well as the histopathological aspects. Antibodies responsible for chronic rejection may preexist before transplantation or may develop after transplantation. The possible therapeutic approaches are poor and principally based on early identification and desensitisation techniques. New B cell targeting drugs are aimed at an improved control of the relevant condition.

Keywords: Chronic rejection, antibodies, complement, donor-specific antibodies, renal transplantation.

INTRODUCTION

Despite improvements in outcomes of renal transplantation, kidney allograft loss remains substantial and is associated with increased morbidity, mortality, and costs.[1,2] Clearly, the identification of critical pathologic pathways responsible for the allograft loss and the development of therapeutic intervention to improve the duration and the quality of allograft function are among the most important targets of transplant medicine. One of the most important advances in the past decade has been the realisation that the insufficient control of the humoral arm of a recipient's immune system by the current immunosuppressive regimens[3] is the factor primarily responsible for allograft dysfunction and loss.[4-6] This notion is now superseding the historical dogma that allograft losses were caused by the calcineurin inhibitors' (CNIs) toxicity and by the chronic allograft nephropathy (CAN). Indeed nephrotoxicity and CAN as causes of late graft failure are being challenged by the findings of the Long-Term Deterioration of Kidney Allograft Function (DeKAF)[6-8] and by other studies.[9,10]

The emergence of sensitive techniques to detect donor-specific anti-human leukocyte antigen antibodies (HLA-DSAs) and other HLA and non-HLA antibodies, together with the advances in assessment of graft pathology, have expanded the spectrum of what constitutes as antibody-mediated rejection (ABMR). The different technologies used by researches and the significance of alloantibody found by such technologies recently led to a consensus conference with the elaboration of consensus guidelines on the testing and clinical management issues associated with HLA and non-HLA antibodies in transplant recipients.[11]

As a consequence of such knowledge increment, since the Banff 2005 meeting report, the term CAN has been deleted,[12] and in Banff 2007 and Banff 2009 Conferences[13,14] the concept of chronic ABMR (cABMR) had been further evaluated and cABMR was definitively included in the Banff classification. The Banff 2011 meeting report[15] and the more recent Banff 2013 Conference[16] further confirmed these data.

Epidemiology

Due to the continuous evolution of techniques, it is difficult to evaluate incidence and prevalence of cABMR as a cause of graft failure. In a prospective study by Einecke,[4] 63% of late kidney failures were attributable to cABMR, whereas glomerulunephritis, T cell rejection, and drug toxicity were uncommon. Similar data reported by Sellares[5] found that in 315 allograft recipients, who underwent indication biopsies, a large prevalence of cABMR was a cause of graft failure.

Histopathology

Transplant glomerulopathy (TG) and peritubular capillary (PTC) basement multilayering represent the histological hallmark of cABMR. TG is a morphological pattern of chronic kidney injury that lacks detectable immune-complex deposits and is associated with poor kidney transplant outcomes. It primarily is an endothelial pathology affecting kidney microcirculation endothelium, which is seen as duplication (double contours) and/or multilamination of capillary basement membranes, along with substantial replacement of endothelial fenestrations with a continuous endothelial lining.[17] The combination of alloantibody, PTC multilamination, C4d, and TG has been called the 'ABCD tetrad' by Halloran and colleagues.[18]

cABMR is characterised by specific and gradually irreversible immune-mediated graft damages that need to be clearly differentiated from isolated interstitial fibrosis/tubular, atrophy, and/or CNI nephrotoxicity, and chronic T cell-mediated rejection (TCMR). To this purpose, a consensus meeting at the National Institutes of Health proposed criteria for cABMR.[19] These elements include:

1) Histological evidence of chronic injury

- Arterial intimal fibrosis without elastosis
- Duplication of glomerular basement membrane
- Multilaminated PTC basement membrane
- Interstitial fibrosis with tubular atrophy

2) Evidence for antibody action/deposition in tissue

3) Serologic evidence of anti-HLA or other anti-donor antibody

If only two of the numbered criteria are present, then the diagnosis is considered 'suspicious' for cABMR.[20]

PATHOPHYSIOLOGY

There is an increased body of evidence suggesting that patients with high quantity anti-HLA antibodies (particularly if they are donor–specific) developed either pre or post-transplant, show a worse outcome. At any given time, approximately 25% of transplant recipients have antibodies against HLA antigens as evaluated with the newest, highly sensitive, and specific techniques for DSA monitoring.[21,22] Moreover, antibodies against non-HLA have also been implicated in ABMR.[23,24] Antibodies can mediate endothelial injury through complement-dependent and independent mechanisms by transducing signals that are pro-inflammatory and proliferative.[20] It is clear that preformed, or *de novo*, HLA-DSAs cause cABMR, but it is less certain what the role and scope of non-HLA antibodies are in mediating graft injury and loss.[25]

One hypothesis is that alloantigen sensitisation occurs from non-HLA polymorphic differences between the donor and recipient (e.g. major histocompatibility complex [MHC] Class I-related chains A and B [MICA, MICB]). Unfortunately the progress in this area has been limited by the lack of validated clinical assays for non-HLA alloantibodies, the confounding presence of HLA-DSAs, and - in the case of MICA antibodies - the lack of proof of specificity.[26] A second hypothesis is that autoantigen sensitisation occurs from the exposure of cryptic epitopes after tissue injury or inflammation (vimentin, K-α I tubulin, collagen V, agrin, etc.).

The pathophysiology of cABMR is still not completely understood. Studies suggest that in renal transplantation *de novo* HLA-DSAs develop post-transplant in up to 25% of non-sensitised patients, often without overt clinical evidence of concurrent rejection. In addition, around 30% of patients on the waiting list have detectable HLA antibodies.[27] In both groups of patients, the presence of these antibodies increases the risk of subsequent cABMR.[9] The development of a histological test to identify antibody-mediated complement activation on transplant biopsies (C4d staining) has provided a way of flagging up potential deleterious interactions between antibody and graft endothelium. In addition, molecular techniques, such as gene expression profiling, have allowed the identification of subclinical endothelial cell damage that can be present even in the absence of complement activation or detectable DSA.[28]

More recently, a study by Lynch and colleagues[29] described a technique that may allow a more global assessment of B cell reactivity to the allograft. Their results suggest that a humoral response to the allograft may be more frequent than previously appreciated. Antibodies reactive to donor HLA molecules, minor histocompatibility antigens, endothelial cells, red blood cells, or autoantigens can trigger or contribute to rejection even late after transplantation.[30] Often the immune system provides an integrated response to achieve allograft rejection with T cell-mediated rejection and ABMR being either linked through time or coexisting.[31] Antibody-mediated injury to allograft is initiated by DSAs binding to HLA antigens or to other targets on the allograft endothelium. If DSAs are complement activating, the classic complement pathway is rapidly activated through IgG binding and activation of C1q.[32] Alternatively, DSAs can bind endothelial cell targets and stimulate cell proliferation or induce antibody-dependent cell-mediated cytotoxicity (ADCC) with interferon γ release.[20] These processes seem to be more important for the development of a type of chronic antibody-mediated injury that is more dependent on natural killer cells than on complement.[33] Antibodies can also bind to HLA and other targets, and incompletely activate the complement system without causing apparent injury. This process is referred to as accommodation.[34]

The clinical significance of cABMR has been increasingly documented in recent years, with some data suggesting that it may represent the leading cause of late allograft loss.[4] cABMR is a long-term process that develops in sequential steps over months to years.[35] cABMR has been proposed to arise through a series of stages or states.[36] The first common event is alloantibody production, followed by antibody interaction with alloantigen resulting in the deposition of C4d in PTC and possibly glomeruli, followed by pathologic changes and graft dysfunction.[37]

DSAs, particularly HLA antigen Class II antibodies, can cause insidious graft injury, and therefore constitute a central causal factor for TG (Figure 1). The pathogenicity of Class II antibodies has been documented in outstanding papers that demonstrated a significant association between Class II antibodies and risk of developing TG.[38,39] The international Banff consensus criteria classify TG as cABMR, if the pattern is accompanied by detectable DSAs and diffuse or focal linear C4d positivity in PTCs; 4-6 Mauiyyedi et al.[40] detected deposition of C4d in PTCs in 61% of chronic

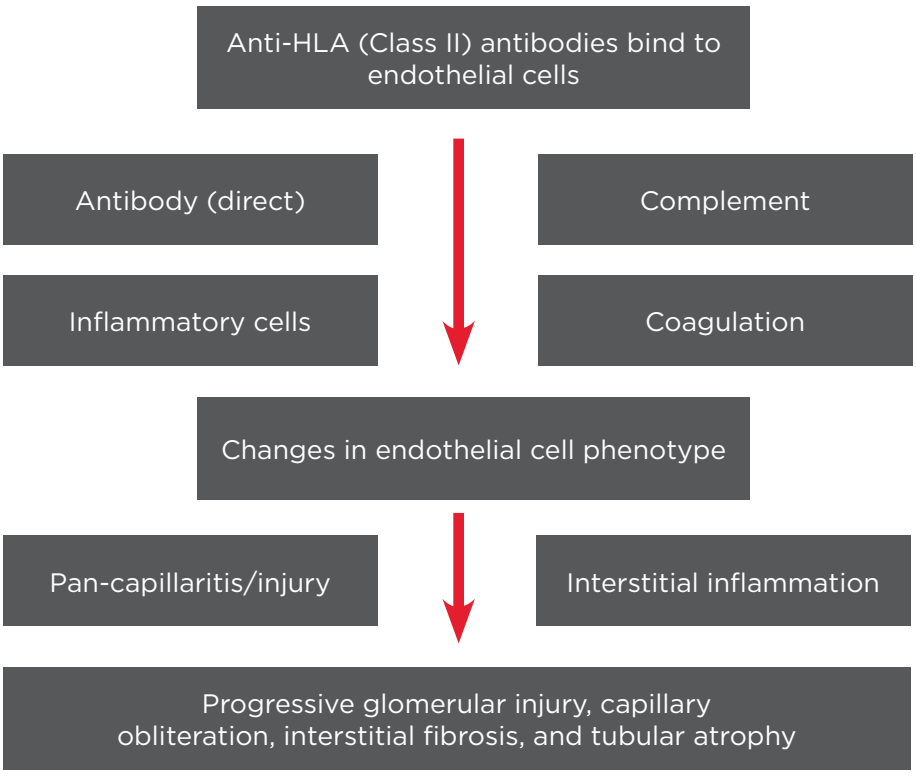

Figure 1: Proposed pathogenetic mechanisms for transplant glomerulopathy.
HLA: human leukocyte antigen.

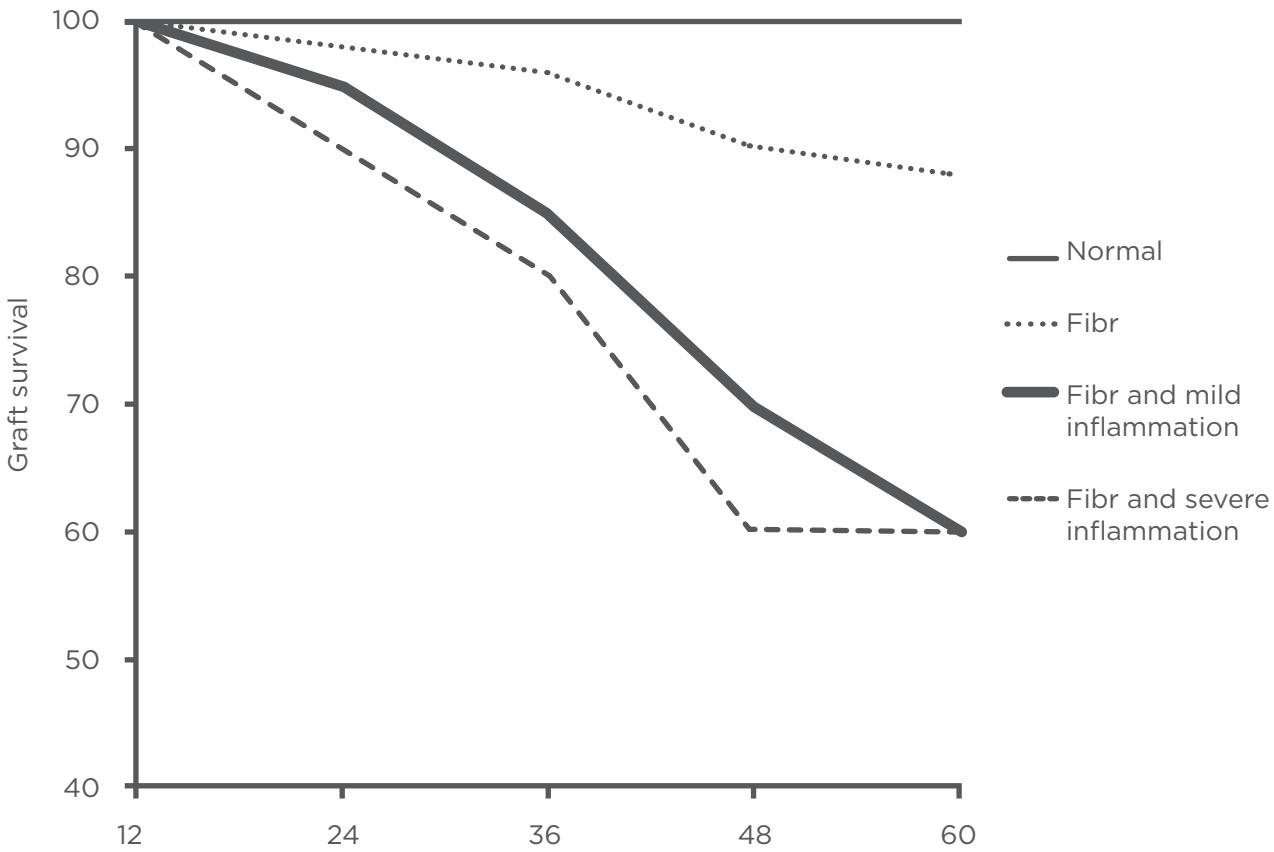

Figure 2: 5-year post-transplant graft survival according to 1-year post-transplant surveillance biopsy. Fibr: fibrosis.

rejection biopsy of patients with TG. In addition, a study by Regele et al.[41] reported the presence of C4d in PTCs in 34% of patients with TG, and this staining presages later TG development.

Pathologic patterns of cABMR are seen in renal biopsies performed either for clinical indications or for protocol, even a long time after kidney transplantation.[5,42] In addition to reduced immunosuppression and non-adherence, early acute rejection seems to have a relevant role on late cABMR. Several years ago Cosio et al.[43] documented that in 1-year surveillance biopsies the degree of inflammation at 1-year post-transplant predicts loss of graft function and graft failure independently of function and other variables (Figure 2).

Recently, El Ters et al.[44] found that early acute rejection, even in the absence of pre-transplant DSAs, increases the risk for alloimmune allograft loss late after transplantation, and the phenotype of this late loss is cABMR. The author hypothesised that the formation of new DSAs, particularly Class II DSAs, can be a consequence of early acute rejection.[45] El Ters et al.[44] also found that cABMR was responsible for 43% of allograft loss. Willicombe et al.,[46] in surveillance biopsies performed at 3 years after transplantation, found that, despite excellent serum creatinine values, only one-third of the biopsies were normal and the lesions seemed to correlate with risks for immunological injury.

As mentioned above, the cause of late graft dysfunction and failure seems increasingly linked to the presence of antibodies or antibody-mediated injury. This has been recently documented by the 5-year follow-up data of the patient cohort from the DeKAF study.[47,48]

Hill et al.[49] described a new insight on the pathogenesis of cABMR. DSA positive patients show a striking acceleration of arteriosclerosis. Pathologic examination reveals that the inner intima is hypercellular, with actively proliferating myofibroblasts laying down collagen, often overlying older, condensed collagen of pre-transplantation donor origin.

DIAGNOSIS

The diagnosis of cABMR is principally based upon the association of deteriorating graft function associated with the pathologic features found

on renal biopsies. Search of circulating DSAs with adequate techniques is also useful. Protocol biopsies may be useful as well-documented by the paper of Wiebe.[42]

Finding of biomarkers associated with cABMR could be extremely useful. Einecke[50] was able to realise a molecular classifier for predicting future graft loss. Sis et al.[28] found that several endothelial transcripts (ENDATs) correlated with histopathological lesions of cABMR. Immunoproteasome beta subunit 10 was found to be increased in the graft and in blood samples during cABMR.[51] Finally, recent studies[52,53] looking at B cell-activating factor (BAFF), a B cell stimulating molecule, showed that the appearance of soluble BAFF levels, early after transplantation, correlates with *de novo* development of DSAs and, ultimately, progression to chronic active ABMR in paediatric and adult first kidney transplant recipients who were highly desensitised before transplantation.

THERAPY

We have clearly documented that cABMR develops in patients with alloantibodies - principally, but not only, DSAs - detectable in the serum. Such antibodies may be present in the recipient before transplantation or may develop after transplantation.

Patients with DSAs Preformed Before Transplantation

Patients waiting for a transplant may be highly immunised and many show detectable DSAs in their serum. Sensitised patients who are DSA-negative with negative complement-dependent cytotoxicity (CDC-XM) may be transplanted safely. They will likely require more immunosuppressive therapy and an induction therapy.[54-56]

Treatment of cABMR may be distinguished in:

a) Prevention of acute ABMR as main cause of cABMR

b) Treatment of established cABMR

Prevention

The different desensitisation protocols apply primarily to DSA-positive patients who are CDC-XM positive. The desensitisation protocols can prevent both acute and cABMR. The majority of the current protocols are modified versions of the high-dose intravenous immunoglobulins (IVIG) initiated at the Cedars-Sinai Medical Center or of the plasmapheresis PP with low dose IVIG initiated at John Hopkins Hospital.[57] Jordan et al.[58] initially provided high-dose IVIGs (2 g/kg) to cross-match positive recipients, and the patients received a kidney transplant when their CDC T cell XM became negative. Subsequently to improve the results, Vo et al.[59,60] decided to use alemtuzumab induction treatment and added rituximab to the protocol.

The other approach to desensitisation comprises the use of PP and low-dose anti-cytomegalovirus IVIG (CMV-IVIG). With such an approach[61] Montgomery et al.[62] successfully desensitised 211 DSA-positive recipients of living donor kidneys with PP and low-dose IVIG.

Stegall et al.[63] added eculizumab during the pre and post-transplant period in DSA positive patients and obtained 7.7% post-transplant acute ABMR, compared with 41.2% in the control group. However, at 2 years after transplantation the incidence of cABMR was similar between the two groups. cABMR remains a major issue when transplanting hyperimmune patients.

In addition to desensitisation, when applicable - in theory - every option available to treat acute ABMR could also be applied to cABMR. However there are no controlled trials for treatment of cABMR reported in literature. The only treatment option with some reported benefit is the combination of rituximab and IVIG.[64] To prevent cABMR, patients with preformed DSAs, when treated immediately post-transplantation with a more intensive prophylactic regimen (PP, IVIGs, and anti-CD20), demonstrated a significant decrease in DSA and a decrease in cABMR rate at 1 year.[65]

For the treatment of established cABMR there are only three case series treated with such combination therapy.[66,67] DSAs went down in only some patients and therapy had limited effects in cases with massive proteinuria, more severe peritubular capillaritis, and previous acute rejection. In a recent paper by Ashimine et al.[68] it was reported that in 320 patients neither pre-transplant splenectomy nor rituximab treatment had an inhibitory effect on *de novo* HLA antibody production after renal transplantation during medium term follow-up.

Smaller studies by Billing et al.[69] and Smith et al.[70] documented a partial response to rituximab

treatment in patients affected by cABMR. Billing et al.[69] documented in 20 paediatric patients that treatment with IVIG and rituximab significantly reduced or stabilised the progressive loss of transplant function with cABMR over an observation period of 2 years, apparently by lowering circulating DSA. Smith et al.,[70] in 31 patients affected by cABMR, reported that rituximab followed by standard maintenance immunosuppression showed a therapeutic effect in the treatment of cABMR, which is confined to a subset of treated subjects that cannot be identified as a priori. Very few patients received bortezomib as a rescue treatment for cABMR and proteinuria with mixed results.[71,72] An interim analysis of a very recent study[73] with eculizumab therapy of cABMR documented an apparent stabilisation of renal function. Taken together these results indicate that any treatment for cABMR using drugs with potential high toxicity should only be performed in the context of a randomised controlled trial.

Patients with *de novo* DSAs after Transplantation

Several authors reviewed the incidence and impact of *de novo* DSAs, both in adult[74] and paediatric recipients.[75] The actual 5-year post-transplantation cumulative incidence of *de novo* DSAs in a low-risk population is 20% (Figure 3). Once DSAs appear, the probability of graft loss within 3 years after DSA appearance is 24% (Figure 4), and respective to patients without DSAs, the relative risk of graft loss is 9-times higher at 1 year after DSA appearance. In a multivariate analysis, the main causes of *de novo* DSAs were deterioration quotient (DQ) locus mismatches, younger age at transplantation, and transplantation from deceased donors.[74] Others claim for prior non-adherence or history of a clinical acute cellular rejection as causes of *de novo* DSAs.[76]

If the appearance of DSAs is associated with clinical signs of acute ABMR, the treatment is that of acute ABMR. The main problem is what to do when the appearance of DSAs is not coupled with acute or chronic rejection. Indeed, detection of *de novo* DSAs in a routine test in patients with stable allograft function represents a step back in the continuum of the natural history of acute and cABMR; it is largely unknown how to treat these patients.[77] To date, prophylactic treatment such as rituximab and splenectomy[68] or eculizumab[63] does not seem to have any effect on DSA appearance.

Monitoring DSAs after transplantation seems to be essential, considering that DSA appearance has a poor prognosis. As procedures including antibody removal by PP, IA, antibody production

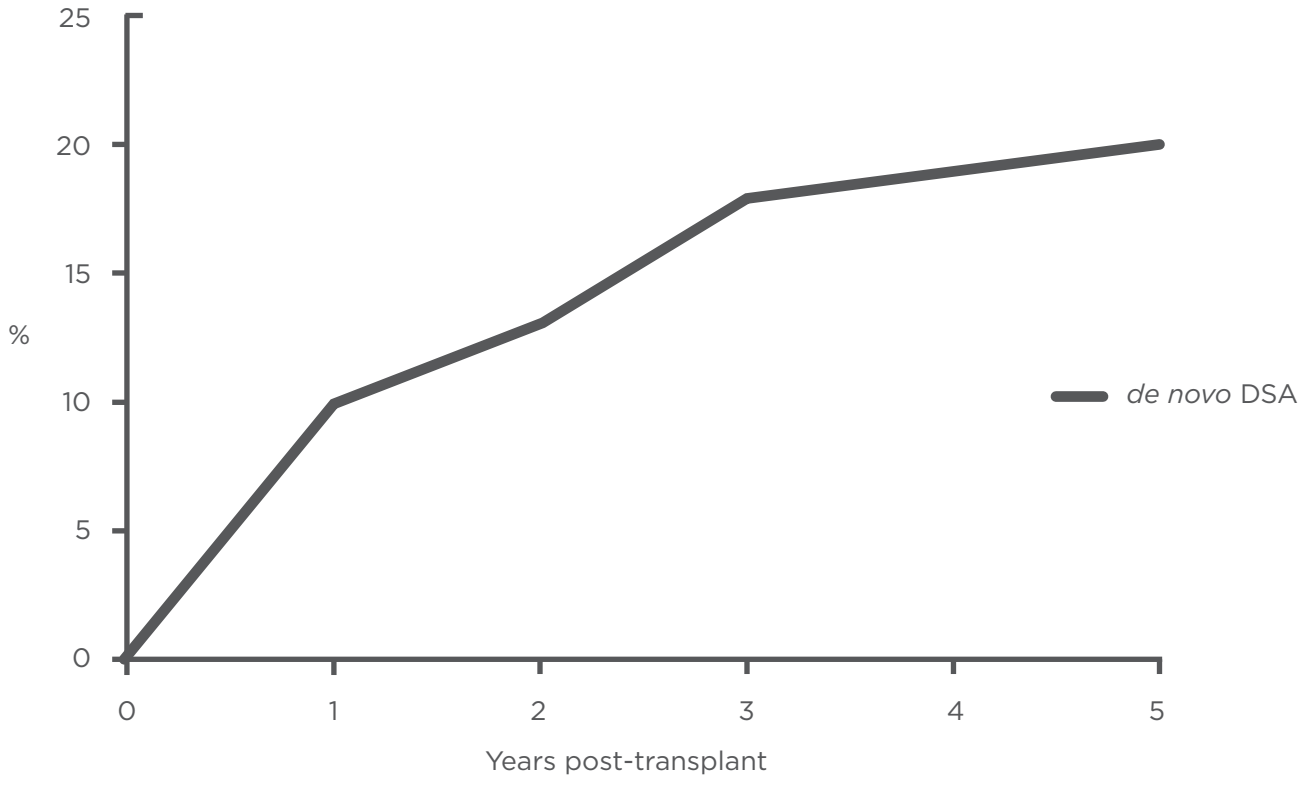

Figure 3: The actual 5-year post-transplantation cumulative incidence of *de novo* DSAs.
DSA: donor specific antibodies.

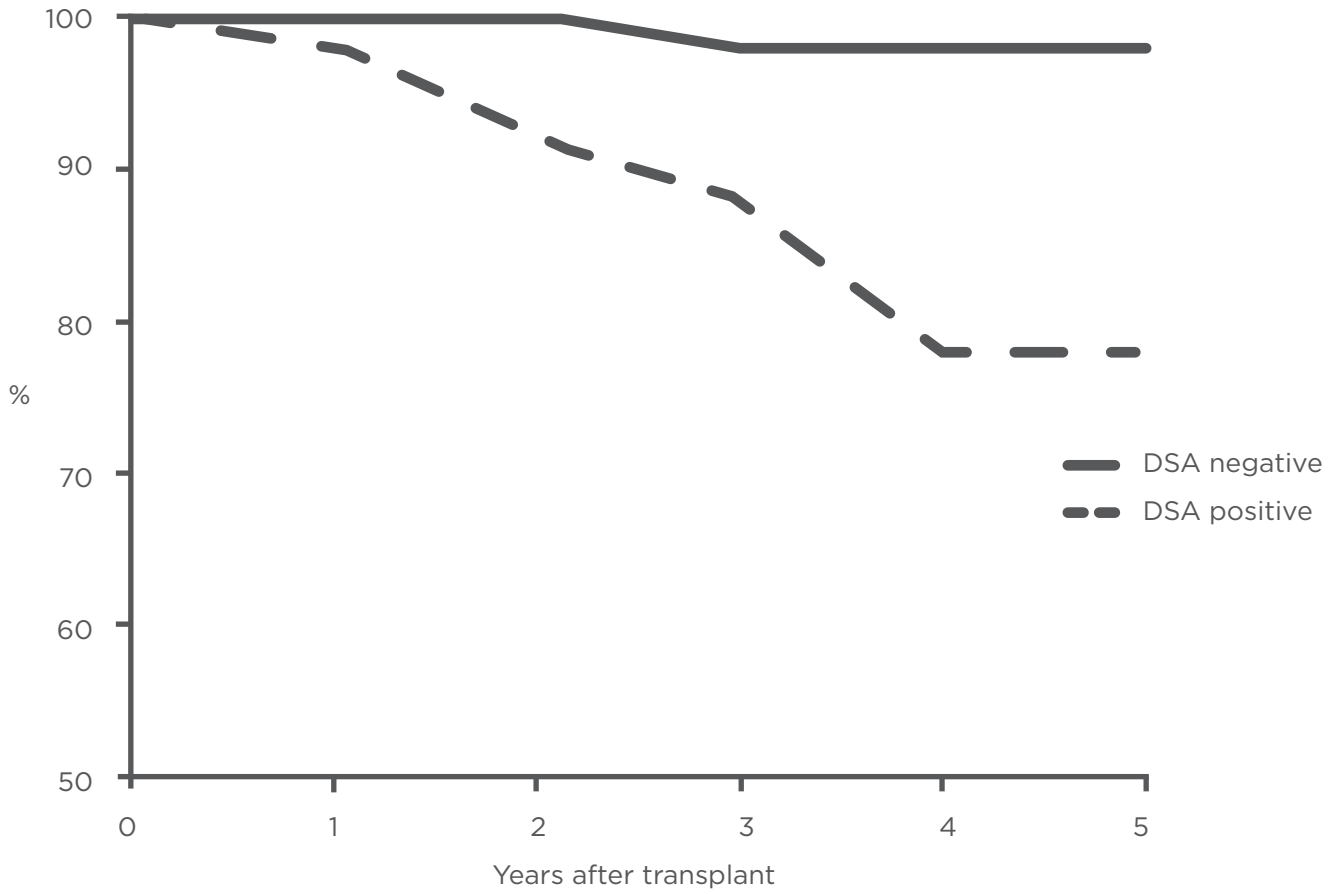

Figure 4: Probability of graft loss within 3 years after *de novo* DSAs appearance.
DSA: donor specific antibodies.

downregulation by B cell, or plasma cell targeting, or complement cascade inhibition have had a very limited success when employed in an advanced phase of cABMR,[56,78,79] the prompt removal of *de novo* DSAs seems to be essential. Notwithstanding, no standard of care on this issue currently exists. To date, only a multicentre antibody removal trial (ART) is ongoing in Italy in a randomised, prospective fashion PP and low-dose CMV-IVIG.[80]

CONCLUSIONS

The lack of improvement in long-term outcomes of kidney transplants has been ascribed to the CNI nephrotoxicity. Indeed, CNIs represent the cornerstone of maintenance immunosuppression in organ transplantation. In the last decade, several studies have challenged this approach; indeed, chronic allograft rejection and death of transplanted patients are now the main causes of long-term graft loss. Chronic rejection has, for a long time, been identified with a lack of adequate T cell control with immunosuppressant. New techniques able to identify circulating antibodies and to reveal their presence and pathogenic role have now allowed us to recognise that in many cases a deficiency in humoral arm control may be the cause of long-term deterioration of graft function. Now both acute and cABMR have been well identified and included in the Banff classification. The early identification and therapeutic approaches to treat cABMR are still limited, and a successful prophylaxis seems the best approach to limit both acute and cABMR. Several studies suggest that monitoring circulating DSAs, protocol, or per cause biopsies and discovering new drugs targeting B cells and complement are the best options for the early identification and control of cABMR.

REFERENCES

1. L'Agence de la biomédecine. Agence de la Biomédecine Annual Report [online], 2011. Available: http://www.agence-biomedecine.fr/IMG/pdf/rapport_reinvdef.pdf. Accessed: 21 February, 2013.

2. Organ Procurement and Transplantation Network [online], 2012. Available: http://optn.transplant.hrsa.gov/. Accessed: 21 February, 2013.

3. Salvadori M, Bertoni E. Is it time to give up with calcineurin inhibitors in kidney transplantation? World J Transplant. 2013;3(2):7-25.

4. Einecke G et al. Antibody–mediated microcirculation injury is the major cause of late kidney transplant failure. Am J Transplant. 2009;9(11):2520–31.

5. Sellares J et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and non adherence. Am J Transplant. 2012;12(2):388–99.

6. Gaston RS et al. Evidence for antibody-mediated injury as a major determinant of late kidney allograft failure. Transplantation. 2010;90(1):68–74.

7. Gourishankar S et al. Pathological and clinical characterization of the 'troubled transplant': data from the DeKAF study. Am J Transplant. 2010;10(2):324-30.

8. Matas AJ et al. Histopathologic clusters differentiate subgroups within the non specific diagnoses of CAN or CR: preliminary data from the DeKAF study. Am J Transplant. 2010;10(2):315-23.

9. Loupy A et al. The impact of donor-specific anti-HLA antibodies on late kidney allograft failure. Nat Rev Nephrol. 2012;8(6):348-57.

10. Hidalgo LG et al. De novo donor-specific antibody at the time of kidney transplant biopsy associates with microvascular pathology and late graft failure. Am J Transplant. 2009;9(11):2532-41.

11. Tait BD et al. Consensus guidelines on the testing and clinical management issues associated with HLA and non-HLA antibodies in transplantation. Transplantation. 2013;95(1):19-47.

12. Solez K et al. Banff'05 meeting report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). Am J Transplant. 2007;7(3):518–26.

13. Solez K et al. Banff'07 classification of renal allograft pathology: updates and future directions. Am J Transplant. 2008;8(4):753-60.

14. Sis B et al. Banff'09 meeting report: antibody mediated graft deterioration and implementation of Banff working groups. Am J Transplant. 2010;10(3): 464-71.

15. Mengel M et al. Banff 2011 meeting report: new concepts in antibody-mediated rejection. Am J Transplant. 2012;12(3):563-70.

16. Haas M et al. Banff 2013 meeting report: inclusion of C4d-negative antibody-mediated rejection and antibody-associated arterial lesions. Am J Transplant. 2014;14(2):272-83.

17. Husain SH, Sis B. Advances in the understanding of transplant glomerulopathy. Am J Kidney Dis. 2013;62(2):352-63.

18. Sis B et al. Transplant glomerulopathy, late antibody-mediated rejection, and the ABCD tetrad. Am J Transplant. 2007;7(7) (S2):1743-52.

19. Takemoto SK et al. National conference to assess antibody-mediated rejection in solid organ transplantation. Am J Transplant. 2004;4(7):1033-41.

20. Colvin RB. Antibody-mediated renal allograft rejection: diagnosis and pathogenesis. J Am Soc Nephrol. 2007;18(4):1046-56.

21. Zito A et al. Increasing relevance of donor-specific antibodies in antibody-mediated rejection. J Nephrol. 2013;26(2):237-42.

22. Terasaki PI et al. Four-year follow-up of a prospective trial of HLA and MICA antibodies on kidney graft survival. Am J Transplant. 2007;7(2):408-15.

23. Rodriguez PC et al. Detection of alloantibodies against non-HLA antigens in kidney transplantation by flow cytometry. Clin Transplant. 2000;14(5):472-8.

24. Sun Q et al. De novo development of circulating anti-endothelial cell antibodies rather than pre-existing antibodies is associated with post-transplant allograft rejection. Kidney Int. 2011;79(6):655-62.

25. Nickerson PW, Rush DN. Antibodies beyond HLA. Am J Transplant. 2013;13(4):831-2.

26. Breimer ME et al. Multicenter evaluation of a novel endothelial cell crossmatch test in kidney transplantation. Transplantation. 2009;87(4):549-56.

27. Clatworthy MR. B cell responses to allograft: more common than we thought? Am J Transplant. 2013;13(7):1629-30.

28. Sis B et al. Endothelial gene expression in kidney transplants with alloantibody indicates antibody-mediated damage despite lack of C4d staining. Am J Transplant. 2009;9(10):2312-23.

29. Lynch RJ et al. Cryptic B cell response to renal transplantation. Am J Transplant. 2013;13 (7):1713-23.

30. Wood KJ, Goto R. Mechanisms of rejection: current perspectives. Transplantation. 2012;93(1):1-10.

31. Nickerson PW, Rush DN. Rejection: an integrated response. Am J Transplant. 2013;13 (9):2239-40.

32. Smith RN, Colvin RB. Chronic alloantibody mediated rejection. Semin Immunol. 2012;24(2):115-21.

33. Hirohashi T et al. A novel pathway of chronic allograft rejection mediated by NK cells and alloantibody. Am J Transplant. 2012;12(2):313–21.

34. Jordan SC et al. Regulation of immunity and inflammation by intravenous immunoglobulin: relevance to solid organ transplantation. Expert Rev. Clin Immunol. 2011;7(3):341–8.

35. Smith RN et al. Four stages and lack of stable accommodation in chronic alloantibody-mediated renal allograft rejection in Cynomolgus monkeys. Am J Transplant. 2008;8(8):1662-72.

36. Colvin RB, Smith RN. Antibody mediated organ-allograft rejection. Nat Rev Immunol. 2005;5(10):807-17.

37. Archdeacon P et al. Summary of FDA antibody-mediated rejection workshop. Am J Transplant. 2011;11(5):896-906.

38. Sis B et al. Transplant glomerulopathy, late antibody-mediated rejection and the ABCD tetrad in kidney allograft biopsies for cause. Am J Transplant. 2007;7(7):1743-52.

39. Gloor JM et al. Transplant glomerulopathy: subclinical incidence and association with alloantibody. Am J Transplant. 2007;7(9):2124-32.

40. Mauiyyedi S et al. Chronic humoral rejection: identification of antibody-mediated chronic renal allograft rejection by C4d deposits in peritubular capillaries. J Am Soc Nephrol. 2001;12(3):574-82.

41. Regele H et al. Capillary deposition of complement split product C4d in renal allografts is associated with basement membrane injury in peritubular and glomerular capillaries: a contribution of humoral immunity to chronic allograft rejection. J Am Soc Nephrol. 2002;13(9):2371-80.

42. Wiebe C et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. Am J Transplant. 2012;12(5):1157-67.

43. Cosio FG et al. Predicting subsequent decline in kidney allograft function from early surveillance biopsies. Am J Transplant. 2005;5(10):2464-72.

44. El Ters M et al. Kidney allograft survival after acute rejection, the value

of follow-up biopsies. Am J Transplant. 2013;13(9):2334-41.

45. Casey E et al. Class I HLA mismatches increase risk of acute rejection, graft loss and formation of de novo class II antibody. Am J Transplant. 2013;13(S5)19:42.

46. Willicombe M et al. Potential importance of 3 year surveillance biopsies in renal transplantation. Am J Transplant. 2013;13(S5)19:41.

47. Gaston RS. Our evolving of late kidney allograft failure. Current Opin Organ Transplant. 2011;16(6):594-9.

48. Rush D et al. DeKAF pathology clusters: follow up at 5 years. Am J Transplant. 2013;13(S5)19:417

49. Hill GS et al. Donor-specific antibodies accelerate arteriosclerosis after kidney transplantation. J Am Soc Nephrol. 2011;22(5):975-83.

50. Einecke G et al. A molecular classifier for predicting future graft loss in late kidney transplant biopsies. J Clin Invest. 2010;120(6):1862-72.

51. Ashton-Chess J et al. Immunoproteasome beta subunit 10 is increased in chronic antibody-mediated rejection. Kidney Int. 2010;77(10):880-90.

52. Comoli P et al. Soluble BAFF levels correlate with de novo DSA development and progression to chronic active antibody-mediated rejection in pediatric recipients of first kidney transplants. Am J Transplant. 2013;13(S5)19:113.

53. Thibault-Espitia A et al. BAFF and BAFF-R levels are associated with risk of long-term kidney graft dysfunction and development of donor-specific antibodies. Am J Transplant. 2012;12(10):2754-62.

54. Noël C et al. Daclizumab versus antithymocyte globulin in high-immunological-risk renal transplant recipients. J Am Soc Nephrol. 2009;20(6):1385-92.

55. Gurk-Turner C et al. Thymoglobulin dose optimization for induction therapy in high risk kidney transplant recipients. Transplantation. 2008;85(10):1425-30.

56. Cai J, Terasaki PI. Current trend of induction and maintenance treatment in positive panel-reactive antibody patients: a report on OPTN/UNOS kidney transplant registry data. Chin Med J (Engl). 2011;124(5):649-54.

57. Montgomery RA et al. Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. Transplantation. 2000;70(6):887-95.

58. Jordan SC et al. Intravenous immune globulin treatment inhibits crossmatch positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients. Transplantation. 2003;76(4):631-6.

59. Vo AA et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med. 2008;359(3):242-51.

60. Vo AA et al. Use of intravenous immune globulin and rituximab for desensitization of highly HLA- sensitized patients awaiting kidney transplantation. Transplantation. 2010;89(9):1095-102.

61. Montgomery RA, Zachary AA. Transplanting patients with a positive donor-specific crossmatch: a single center's perspective. Pediatr Transplant. 2004;8(6):535-42.

62. Montgomery RA et al. Desensitization in HLA-incompatible kidney recipients and survival. N Engl J Med. 2011;365(4):318-26.

63. Stegall MD et al. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. Am J Transplant. 2011;11(11):2405-13.

64. Fehr T, Gaspert A. Antibody-mediated kidney allograft rejection: therapeutic options and their experimental rationale. Transpl Int. 2012;25(6):623-32.

65. Loupy A et al. Combined post-transplant prophylactic IVIg/anti CD 20/plasmapheresis in kidney recipients with preformed donor-specific antibodies: a pilot study. Transplantation. 2010;89(11):1403-10.

66. Ahn G et al. Effectiveness of Rituximab and intravenous immunoglobulin for the treatment of chronic antibody mediated rejection in kidney transplant recipients. Am J Transplant. 2013;13(S5)19:328.

67. Fehr T et al. Rituximab and intravenous immunoglobulin treatment of chronic antibody-mediated kidney allograft rejection. Transplantation. 2009;87(12):1837-41.

68. Ashimine S et al. Neither pre-transplant rituximab nor splenectomy affects de novo HLA antibody production after renal transplantation. Kidney Int. 2014;85(2):425-30.

69. Billing H et al. IVIG and rituximab for treatment of chronic antibody-mediated rejection: a prospective study in paediatric renal transplantation with a 2 year follow-up. Transplant Int. 2012;25(11):1165-73.

70. Smith RN et al. Partial therapeutic response to rituximab for the treatment of chronic alloantibody mediated rejection of kidney allografts. Transplant Immunol. 2012;27(2-3):107-13.

71. Schwaiger E et al. Bortezomib for the treatment of chronic antibody-mediated kidney allograft rejection: a case report. Clin Transpl UCLA Tissue typing laboratory. 2010;391-6.

72. Lonze BE et al. The fate of anti-HLA antibody among renal transplantation recipients treated with bortezomib. Clin Transpl UCLA Tissue typing laboratory. 2009;377-81.

73. Kulkarni S et al. Eculizumab therapy for chronic antibody-mediated injury in kidney transplantation: an interim assessment. Am J Transplant. 2013;13(S5)19:86.

74. Everly MJ et al. Incidence and impact of de novo donor-specific alloantibody in primary renal allografts. Transplantation. 2013;95(3):410-7.

75. Ginevri F et al. Posttransplant de novo donor-specific HLA antibodies identify pediatric kidney recipients at risk for late antibody-mediated rejection. Am J Transplant. 2012;12(12):3355-62.

76. Haririan A et al. The impact of C4d pattern and donor-specific antibody on graft servival in recipients requiring indication renal allograft biopsy. Am J Transplant. 2009;9(12):2758-67.

77. Lionaki S et al. Incidence and clinical significance of de novo donor specific antibodies after kidney transplantation. Clin Dev Immunol. 2013;2013:849835.

78. Vincenti F et al. Novel B cell therapeutic targets in transplantation and immune-mediated glomerular diseases. Clin J Am Soc Nephrol. 2010;5(1):142-51.

79. Jordan SC et al. Advances in diagnosing and managing antibody-mediated rejection. Pediatr Nephrol. 2010;25(10):2035-45.

80. Seveso M et al. Preliminary results from a prospective multi-center study reveal the early appearance of de novo anti-HLA antibodies following renal transplantation. Transpl Int. 2011;24(suppl 2):38.

PREGNANCY IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH NEPHRITIS

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ABSTRACT

Pregnancy in patients with lupus nephritis is a challenging clinical situation. Although not absolutely contraindicated, it is associated with increased risk for foetal and maternal complications, including foetal loss, preterm delivery, intrauterine growth retardation, hypertension, pre-eclampsia, nephritis flare, and, rarely, maternal death. The complication rate is further increased in the presence of antiphospholipid antibodies or the antiphospholipid syndrome. Proliferative classes of nephritis (III and IV) also appear to confer excess risk for complications. Immunosuppressives such as cyclophosphamide and mycophenolate, and antihypertensives such as angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers need to be stopped due to teratogenic effects. Agents like corticosteroids, azathioprine, and probably calcineurin inhibitors are considered compatible with gestation. Lupus activity needs to be assessed and carefully monitored. Thrombotic risk due to antiphospholipid antibodies, thrombotic events, or nephrosis needs to be evaluated and managed accordingly, with the use of aspirin and/or unfractioned or low molecular weight heparin. Differentiating between severe pre-eclampsia and lupus nephritis flare might require a renal biopsy, which might not always be feasible, for example after the 32nd gestational week or in a setting of uncontrolled hypertension or thrombocytopaenia. A 6-month history of quiescent disease on non-teratogenic agents seems to be associated with best chance for favourable outcomes. Pregnancy is optimally managed by a multidisciplinary team of experienced specialists, and close monitoring for disease activity during gestation; additionally, follow-up for maternal flare postpartum is also advised.

Keywords: Nephritis, outcome, pre-eclampsia, pregnancy, systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a potentially fatal, chronic autoimmune disorder with a prevalence that ranges from approximately 20-150 cases per 100,000 population.[1] Its pathogenesis involves aberrant apoptotic mechanisms combined with dysregulated immune responses leading to loss of self-tolerance against nuclear antigens and to autoantibody production. The result is an immune complex disease with inflammation of various organs and tissues.[2] Up to 75% of SLE patients display evidence of renal involvement.[3] Lupus nephritis (LN) manifests clinically with haematuria, proteinuria, and varying degrees of renal impairment, and is associated with increased morbidity and mortality.[4] The histological classification of LN describes the severity of renal lesions.[5] Active, proliferative lesions (Classes 3 and 4) require aggressive immunosuppression to prevent progression to end-stage kidney disease (ESKD),[5] with response rates ranging between 30-80%.[6]

Since 90% of SLE patients are female,[7] and predominantly of childbearing age, pregnancy is not unusual in this clinical setting. Chronic kidney disease (CKD) of all stages has been associated with increased risk of maternal and foetal complications,[8,9] being higher in later stages of

renal insufficiency[10] and with the lowest pregnancy success rates being observed in ESKD.[11] Early studies implied an association between SLE and poor pregnancy outcomes.[12] However, more recent data report live birth rates higher than 85%.[13,14] Besides hypertension and the antiphospholipid syndrome (APS), renal involvement in SLE has been identified as a risk factor for poor pregnancy outcomes[3,15,16] in addition to increasing morbidity and mortality both of the mother and the foetus. This review will discuss current evidence regarding the association of SLE and LN with foetal and maternal complications, as well as recommendations and treatment options for pregnant women with LN.

COMPLICATIONS

Foetal/Neonatal

Although a recent single-centre experience comparing 60 pregnancies in women without LN with 35 pregnancies in patients with previous LN reported similar foetal prognosis,[17] pregnant SLE patients show substantially lower live birth rates than the general population,[18] and active SLE during pregnancy has been associated with poor foetal outcomes.[14,19,20] A recent meta-analysis included 37 studies with 2,751 pregnancies in 1,842 patients with SLE and LN.[15] Excluding induced abortions (5.9%), 23.4% of pregnancies were unsuccessful. Foetal complications included spontaneous abortion (16%), intrauterine growth retardation (12.7%), and stillbirth (3.6%). Among all live births the premature birth rate reached 39.4%. Neonatal deaths were reported at 2.5% (Table 1). In random-effects meta-regression analysis, active LN was significantly associated with premature birth, even after controlling for maternal hypertension.[15] Other studies have also demonstrated that only active LN is associated with poorer pregnancy outcomes, such as preterm delivery and foetal loss, compared to a history of LN or SLE without renal involvement.[16,21] In the aforementioned meta-analysis the cases with biopsy proven LN showed no association between histological classification (proliferative lesions [Classes 3 and 4] versus non-proliferative lesions [Classes 2 and 5]) and unsuccessful pregnancy rates.[15] This may be attributed to scarcity of data, as well as the elapsed time between renal biopsies and relevant pregnancies, limiting the effect of histology on outcome. In these biopsy-proven cases, both active LN and a history of LN approached, but failed to reach, significant association with premature birth rate.[15]

The presence of antiphospholipid antibodies (APAs) has been associated with poor foetal outcomes.[13,22] The aforementioned meta-analysis reported about one-quarter of pregnancies being positive for APAs.[15] Their presence, although not

Table 1: Foetal and maternal complications associated with systemic lupus erythematosus.

Foetal complication	Rate %*
Induced abortion	5.9
Spontaneous abortion	16.0
Stillbirth	3.6
Neonatal death	2.5
Unsuccessful pregnancy	23.4
Intrauterine growth retardation	12.7
Premature birth rate	39.4
Maternal Complication	
Severe (stroke, eclampsia, death)	1.0
Hypertension	16.3
Pre-eclampsia	7.6
Active nephritis	16.1
Flare	25.6

*Estimated event rate from random effect analysis.
Modified from Smyth et al.[11]

associated with the rate of active LN, did correlate significantly with premature birth rate and increased induced abortion rate.[15]

Neonatal SLE may be caused by trans-placental passage of maternal anti-SSA/Ro anti-SSB/La antibodies, causing dermatological, hepatic, haematological, or cardiac manifestations,[23] including potentially fatal congenital heart block.[24]

Maternal

The maternal complications of SLE patients during pregnancy include hypertension, lupus flare, LN, and pre-eclampsia, as well as more severe complications including eclampsia/HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, stroke, and maternal death. The SLE subjects included in the aforementioned meta-analysis[15] experienced lupus flare (25.6%), hypertension (16.3%), LN (16.1%), and pre-eclampsia (7.6%), with severe complications amounting to ~1%.[15] Deaths mainly result from sepsis, opportunistic infections, and pulmonary embolism, in the setting of renal failure, pre-eclampsia/HELLP or aggressive immunosuppression.[12,14-16,20,22,25-27] One case of pregnancy associated cardiomyopathy and one of adrenal failure after abrupt steroid withdrawal, both resulting in maternal death, have also been reported.[28] All three reported fatalities with biopsy proven LN had proliferative lesions.[16,25,27] Single-centre studies have shown an association of active LN, defined by the presence of an active urine sediment and/or proteinuria >0.5 g per 24 hours with or without elevated creatinine, with higher incidence of maternal complications, while renal quiescence at the start of the pregnancy has been associated with favourable maternal outcome.[16,22] However, a recent meta-analysis demonstrated both active LN and a history of LN to be associated with maternal hypertension and pre-eclampsia.[15] The same study reported an association between positive APAs and maternal hypertension, potentially increasing the risk of pre-eclampsia, which is a known complication of the APS.[15]

IMPACT OF PREGNANCY ON LN

During pregnancy there is an increase in the levels of progesterone and estradiol, and although a link between oestrogen and progesterone administration in postmenopausal women and lupus flare has been suggested,[7] the impact of those hormones on aggravating lupus during pregnancy is still unclear.[1] Maternal tolerance to the foetus during normal pregnancy requires immunological alterations, including increased numbers of regulatory T cells (Tregs) and a shift to a Th2 antibody-mediated immune response.[3,21] Since SLE is an antibody mediated disease also characterised by dysregulated Treg responses, pregnancy might theoretically affect disease activity. Lupus flares can occur from any time during pregnancy to several months after delivery.[29] Although the results of studies comparing flare rates between pregnant and non-pregnant SLE patients appear inconclusive, similar studies referring to the patients' own course during and without pregnancy showed an increase of LN flares during pregnancy.[3] In a recent meta-analysis the frequencies of SLE and LN flares were reported at 25.6% and 16.1%, accordingly.[15] Although few women will reach ESKD, about 25% of LN flare cases during pregnancy will prove resistant to treatment, showing progressive renal function decline after delivery.[29] Given the high risk of adverse foetal and maternal adverse events associated with active LN during pregnancy, including maternal death,[28] the importance of close monitoring for disease activity cannot be overemphasised.[3]

Assessing SLE activity during pregnancy is challenging.[29] The utility of complement levels, erythrocyte sedimentation rate, and C-reactive protein for monitoring lupus activity has not been established during pregnancy, and even higher levels of anti-double stranded-DNA (anti-dsDNA) antibodies alone did not predict pregnancy outcomes in SLE patients.[29] On the other hand, a doubling of proteinuria may be indicative of LN flare, while haemolytic anaemia and/or a platelet count of 100,000 may result from both increased SLE activity and severe pre-eclampsia/HELLP syndrome. Apart from possibly occurring simultaneously, both severe pre-eclampsia and LN flare share many clinical and laboratory findings, such as hypertension, proteinuria, oedema, and increasing creatinine.[3] Distinguishing between the pre-eclampsia and LN flare (Table 2), especially after the 20th week of gestation, may prove difficult, if not impossible, without a renal biopsy,[30] which may not be feasible after the 32nd week of gestation.[3,31] A renal biopsy will differentiate a LN flare with the need for immunosuppression from pre-eclampsia requiring delivery,[3] but it may be of extremely high risk in the setting of uncontrolled hypertension, anaemia, and thrombocytopaenia, leaving delivery as the main treatment option.[30]

Table 2: Clinical and laboratory features aiding the discrimination between pre-eclampsia and lupus nephritis flare.

	Pre-eclampsia	Lupus nephritis flare
Gestational age	After week 20	Throughout
Hypertension	Present	May be present
Increased creatinine	Usually absent	May be present
Increased serum uric acid	Increased	Normal (unless CKD)
Anti-dsDNA antibodies	Absent	Present
Low C3, C4	Absent	May be present
Leukopaenia	Absent	Present
Thrombocytopaenia	Absent (unless HELLP)	Present
Active urine sediment	Absent	Present

CKD: chronic kidney disease; HELLP: haemolysis, elevated liver enzymes, low platelets; anti-dsDNA: anti-double stranded DNA; C3: complement 3.

PHARMACOLOGICAL TREATMENT

Cyclophosphamide and mycophenolate mofetil (MMF) are the standard immunosuppressive agents for the treatment of proliferative LN (active Classes 3 and 4). Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, commonly utilised as antiproteinuric agents in LN.[32] All, however, are teratogenic and therefore their use is contraindicated during pregnancy, although cyclophosphamide has been administered as rescue treatment during the third trimester. Azathioprine and corticosteroids may be safely administered, with the caveat that dexamethasone and betamethasone cross the placenta and have been associated with hypertension and cognitive deficits in the offspring, limiting their use for obstetric indications only.[29] Corticosteroids are the only immunosuppressive agents compatible with breastfeeding.[3] Switching from MMF to azathioprine has been reported not to increase risk of renal flares in patients with quiescent LN planning to become pregnant.[33] The administration of cyclosporine and tacrolimus also presents a rather safe alternative for immunosuppression during pregnancy, with safety data being more robust regarding cyclosporine. Dosing should be guided by trough levels and may have to be increased due to the expanded volume of distribution during advanced pregnancy.[3] Hydroxychloroquine should be administered to all patients with LN, according to the latest guidelines, as its use is considered safe during pregnancy.[32] Lymphopaenia has been reported at birth after *in utero* exposure of rituximab,[34] and there are still insufficient data supporting its safe administration during pregnancy.[3]

RECOMMENDATIONS

In order to decrease the risk for foetal and maternal complications, including LN flare, pregnancy should at best be planned in patients with stable inactive lupus for at least 6 months on a treatment regimen that can be safely continued throughout gestation. Baseline testing for proteinuria/urinalysis, serum creatinine, full blood count, APAs and serum levels of anti-ds DNA antibodies, complement (C3 and C4) and liver function tests should be repeated regularly during pregnancy. Presence of anti-SSA/Ro and anti-SSM/La antibodies should prompt frequent evaluations of foetal heart rhythm especially from gestational weeks 16-32. A history of proliferative LN (Class 3 or 4) should receive special attention because of the increased risk for flare and complications. Thromboembolic risk should be assessed and treated accordingly. Postpartum regular follow-up is essential, due to the increased risk for LN flare.[3] Pregnancies are best managed by experienced multidisciplinary teams.[3,29]

SUMMARY

Although at increased risk of complications, pregnancy is not contraindicated in patients with LN. A stable inactive disease with optimal treatment for at least 6 months before conception presents the best clinical setting for a successful pregnancy. Thorough preconception counselling and evaluation, close surveillance during gestation, and continued postpartum follow-up by an experienced multidisciplinary team may be able to favourably manage the risk of foetal/neonatal and maternal complications.

REFERENCES

1. Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365(22):2110-21.

2. Lech M, Anders HJ. The pathogenesis of lupus nephritis. J Am Soc Nephrol. 2013;24(9):1357-66.

3. Stanhope TJ et al. Obstetric nephrology: lupus and lupus nephritis in pregnancy. Clin J Am Soc Nephrol. 2012;7(12): 2089-99.

4. Cameron JS. Lupus nephritis. J Am Soc Nephrol. 1999;10(2):413-24.

5. Seshan SV, Jennette JC. Renal disease in systemic lupus erythematosus with emphasis on classification of lupus glomerulonephritis: advances and implications. Arch Pathol Lab Med. 2009;133(2):233-48.

6. Kalloo S et al. Lupus nephritis: treatment of resistant disease. Clin J Am Soc Nephrol. 2013;8(1):154-61.

7. Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med. 2008;358(9):929-39.

8. Nevis IF et al. Pregnancy outcomes in women with chronic kidney disease: a systematic review. Clin J Am Soc Nephrol. 2011;6(11):2587-98.

9. Piccoli GB et al. Pregnancy and chronic kidney disease: a challenge in all CKD stages. Clin J Am Soc Nephrol. 2010;5(5):844-55.

10. Bili E et al. Pregnancy management and outcome in women with chronic kidney disease. Hippokratia. 2013;17(2):163-8.

11. Hou S. Pregnancy in chronic renal insufficiency and end-stage renal disease. Am J Kidney Dis. 1999;33(2):235-52.

12. Le Thi Huong D et al. Pregnancy and its outcome in systemic lupus erythematosus. Qjm. 1994;87(12):721-9.

13. Wong CH et al. Outcome of pregnancy in patients with systemic lupus erythematosus. Taiwan J Obstet Gynecol. 2006;45(2):120-3.

14. Clowse ME et al. The impact of increased lupus activity on obstetric outcomes. Arthritis Rheum. 2005;52(2):514-21.

15. Smyth A et al. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clin J Am Soc Nephrol. 2010;5(11):2060-8.

16. Wagner SJ et al. Maternal and fetal outcomes in pregnant patients with active lupus nephritis. Lupus. 2009;18(4):342-7.

17. Saavedra MA et al. Impact of previous lupus nephritis on maternal and fetal outcomes during pregnancy. Clin Rheumatol. 2012;31(5):813-9.

18. Vinet E et al. A population-based assessment of live births in women with systemic lupus erythematosus. Ann Rheum Dis. 2012;71(4):557-9.

19. Bramham K et al. Pregnancy outcomes in systemic lupus erythematosus with and without previous nephritis. J Rheumatol. 2011;38(9):1906-13.

20. Chandran V et al. Active disease during pregnancy is associated with poor foetal outcome in Indian patients with systemic lupus erythematosus. Rheumatol Int. 2005;26(2):152-6.

21. Moroni G, Ponticelli C. Pregnancy after lupus nephritis. Lupus. 2005;14(1):89-94.

22. Moroni G et al. Pregnancy in lupus nephritis. Am J Kidney Dis. 2002;40(4):713-20.

23. Boh EE. Neonatal lupus erythematosus. Clin Dermatol. 2004;22(2):125-8.

24. Askanase AD et al. Spectrum and progression of conduction abnormalities in infants born to mothers with anti-SSA/Ro-SSB/La antibodies. Lupus. 2002;11(3):145-51.

25. Huong DL et al. Pregnancy in past or present lupus nephritis: a study of 32 pregnancies from a single centre. Ann Rheum Dis. 2001;60(6):599-604.

26. Imbasciati E et al. Lupus nephropathy and pregnancy. A study of 26 pregnancies in patients with systemic lupus erythematosus and nephritis. Nephron. 1984;36(1):46-51.

27. Georgiou PE et al. Outcome of lupus pregnancy: a controlled study. Rheumatology. 2000;39(9):1014-9.

28. Ritchie J et al. Maternal deaths in women with lupus nephritis: a review of published evidence. Lupus. 2012;21(5):534-41.

29. Clowse ME. Lupus activity in pregnancy. Rheum Dis Clin North Am. 2007;33(2):237-52.

30. Williams WW et al. Case records of the Massachusetts General Hospital. Case 38-2005. A 29-year-old pregnant woman with the nephrotic syndrome and hypertension. N Engl J Med. 2005;353(24):2590-600.

31. Meola M et al. Free-hand ultrasound-guided renal biopsy: report of 650 consecutive cases. Nephron. 1994;67(4):425-30.

32. Bertsias GK et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012;71(11):1771-82.

33. Fischer-Betz R et al. Low risk of renal flares and negative outcomes in women with lupus nephritis conceiving after switching from mycophenolate mofetil to azathioprine. Rheumatology. 2013;52(6):1070-6.

34. Hyrich K, Verstappen S. Biologic therapies and pregnancy: the story so far. Rheumatology. 2013. [Epub ahead of print].

35. Navarra SV et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377(9767):721-31.

THE USE OF VAPTANS IN HYPONATRAEMIA

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ABSTRACT

Hyponatraemia is the most common electrolyte disorder in clinical practice. It is associated with increased morbidity, mortality, and length of hospital stay, and therefore represents a clinical, economic, and social burden for healthcare costs and caregivers. Acute and severe hyponatraemia is associated with severe neurological alterations that may lead to cerebral oedema and death. Even mild chronic hyponatraemia has been associated with neurological and extraneurological disorders, such as gait disturbances, attention deficit, increased risk of bone loss, falls, and fractures. These aspects appear relevant particularly in the elderly. Furthermore, an overly rapid correction of hyponatraemia may cause osmotic demyelination, thus making it necessary to define safe treatment strategies. In the last few years, the availability of new drugs, i.e. the vasopressin receptor antagonists or vaptans, has improved the therapeutic choices for the treatment of hyponatraemia. This review summarises the main aspects regarding the use of these drugs, in particular tolvaptan and conivaptan, which are the only vaptans currently available in clinical practice.

Keywords: Hyponatraemia, vasopressin receptor antagonists, vaptans, tolvaptan, conivaptan.

INTRODUCTION

Hyponatraemia is an electrolyte disorder defined as a serum sodium concentration ([Na+]) <136 mmol/L and represents a very important clinical and economic issue. Firstly because it is a very frequent alteration; in fact, it is the most common electrolyte imbalance in hospitalised patients, with a prevalence of mild forms ([Na+] 130-135 mmol/L) in about 20% of patients, and of moderate-to-severe forms ([Na+] <130 mmol/L) in about 7% of patients.[1,2] It is well known that acute severe hyponatraemia represents a life-threatening condition, causing brain oedema and severe neurological signs and symptoms.[3] However, in the last few years, new evidence has demonstrated that mild and chronic hyponatraemia, traditionally defined as an asymptomatic condition, may also have important clinical consequences such as attention deficits, gait instability, falls, osteoporosis, and increased risk of fractures.[4-8]

The association between hyponatraemia and increased mortality has been demonstrated in numerous conditions, such as myocardial infarction (MI),[9] heart failure (HF),[10] cirrhosis,[11] pulmonary diseases,[12] cancer,[9] in the elderly[13] and in intensive care patients.[14] Recently, in a comprehensive meta-analysis, we confirmed that hyponatraemia is a negative prognostic factor across a large series of hospitalised patients affected by multiple clinical conditions such as MI, HF, cirrhosis, and pulmonary infections.[15] We have also shown, for the first time, that even a moderate serum [Na+] decrease (i.e. 4.8 mmol/L) is associated with an increased risk of mortality.[15] Although these data both confirm and reinforce the strong association between hyponatraemia and poor outcomes such as inpatient mortality, it cannot prove a cause and effect relationship between these variables. Further studies are necessary to establish whether hyponatraemia has a direct effect on adverse outcomes, or is simply a marker for severity of underlying diseases.

Hyponatraemia also represents an economic and social burden. In fact, increased length of hospital stay and also hospital readmission rates have been demonstrated in hyponatraemic patients. Furthermore, economic models have estimated direct costs associated with effective correction of hyponatraemia in hospitalised patients in the US at $1.6-3.6 billion/year.[16] Therefore, hyponatraemia directly causes an increase in total healthcare costs.

Taken together, these data suggest the importance of using the most appropriate therapeutic strategies to correct this electrolyte disorder. The essential requirement to properly manage hyponatraemia is a correct diagnosis because the therapy depends strictly on the subtype and aetiology of hyponatraemia.[17] Hyponatraemia can be classified in hypotonic or non-hypotonic forms, based on plasma osmolality, which can be increased, normal, or reduced. Hypotonic hyponatraemia is the most frequent condition and can be further divided according to the extracellular volume status into hypovolaemic, euvolaemic, and hypervolaemic forms (Table 1). Another important aspect to be considered is the potential of risks associated with inappropriate treatment of hyponatraemia. In particular, an overly rapid correction of hyponatraemia may result in osmotic demyelination syndrome (ODS), a severe and potentially lethal complication.[18] The risk of ODS is particularly high when hyponatraemia is chronic because when the correction rate is too rapid, the cells may not be able to recapture the osmolytes lost through the chronic adaption mechanisms that counteract cellular swelling and brain oedema. The result is an excessive movement of water out of the cells with consequent cellular shrinkage and osmotic demyelination. Several conditions can increase the risk of developing ODS such as hypokalaemia, hypophosphataemia, alcoholism, malnutrition, advanced liver diseases, or a serum level of [Na+] ≤105 mmol/L.[16-18]

CONVENTIONAL TREATMENT OF HYPONATRAEMIA

The treatment of hypotonic hyponatraemia, which is the most common form, depends on the presence of signs and symptoms related to the severity and rapidity of onset of the disorder (i.e. acute versus chronic) as well as on the status of the extracellular volume.[17]

The first-choice treatment of hypovolaemic hyponatraemia is isotonic (0.9% sodium chloride [NaCl]) saline infusion. Symptomatic euvolaemic and hypervolaemic hyponatraemia are effectively treated with hypertonic (3% NaCl) saline infusion and loop diuretics.[19,20] An important point to consider is the correction rate of hyponatraemia, which should not exceed a serum [Na+] correction of 8-12 mmol/L/day or 18-24 mmol/L in the first 48 hours, in order to avoid the occurrence of ODS.[16,18] Recently published expert panel recommendations[16] have suggested that a 6 mmol/L increase in serum [Na+] appears to be sufficient to reverse the most severe signs and symptoms of acute hyponatraemia. This more prudent approach can

Table 1: Classification of hyponatraemia.

Non-Hypotonic Hyponatraemia			
	Hypertonic hyponatraemia	**Isotonic hyponatraemia**	**Pseudohyponatraemia**
Causes	Hyperglycaemia, retention of mannitol, radiographic contrast.	Retention in the extracellular space of osmotically active solutes other than sodium.	Severe hypertriglyceridaemia or hyperparaproteinaemia.
Hypotonic Hyponatraemia			
	Hypervolaemic hyponatraemia	**Euvolaemic hyponatraemia**	**Hypovolaemic hyponatraemia**
Causes	Heart failure, nephrotic syndrome, acute or chronic renal failure, cirrhosis.	SIADH, hypocortisolism, hypothyroidism.	*Renal solute loss*: Diuretic therapy, cerebral salt wasting syndrome, salt wasting nephropathy, Addison's disease. *Extrarenal solute loss*: Vomiting, diarrhoea, pancreatitis.

SIADH: syndrome of inappropriate secretion of antidiuretic hormone.

be considered, especially when risk factors for the development of ODS are present.

The traditional therapeutic approach in asymptomatic euvolaemic or hypervolaemic hyponatraemia is represented by fluid restriction. This treatment has some limits in that it is usually poorly tolerated by patients because of an increased perception of thirst and the improvement of serum [Na+] is often insufficient, especially if the kidneys are not able to excrete free water.[19-21] Other possible options for the treatment of these forms of hyponatraemia include lithium, demeclocycline, and urea. However, these molecules do not have a specific indication for the treatment of hyponatraemia, their efficacy can vary, and there may be potentially severe adverse effects.[16,19] Hence, there is a need to develop new specific drugs to improve the treatment of this electrolyte disorder.

Vasopressin Receptor Antagonists: A New Therapeutic Option

In the early 1990s, the first non-peptide vasopressin receptor antagonists were identified and successfully used for the correction of hyponatraemia.[22,23] The vasopressin receptor antagonists, or vaptans, act by blocking the binding of vasopressin to Type 2 (V2) receptors on the principal cells of the renal-collecting ducts, thus causing the inhibition of the synthesis and transport of aquaporin-2 into the apical membrane, which prevents water reabsorption (Figure 1). The main characteristic of vaptans is that they produce solute-sparing water excretion, as opposed to traditional diuretics that produce simultaneous electrolyte loss.[23] This particular effect of vaptans, known as aquaresis, causes a decrease in urine osmolality and an increase in serum [Na+], thus opening up the potential use of these drugs in hypervolaemic and euvolaemic hyponatraemia. Due to this mechanism of action, it is evident that vaptans are not indicated for the treatment of hypovolaemic hyponatraemia. Four non-peptide vasopressin receptor antagonists have been tested in clinical trials: tolvaptan, conivaptan, lixivaptan, and satavaptan.[16,24] The main properties of these compounds are shown in Table 2. However, only tolvaptan and conivaptan are currently available for clinical use and therefore the remaining part of this review will be focused on these agents.

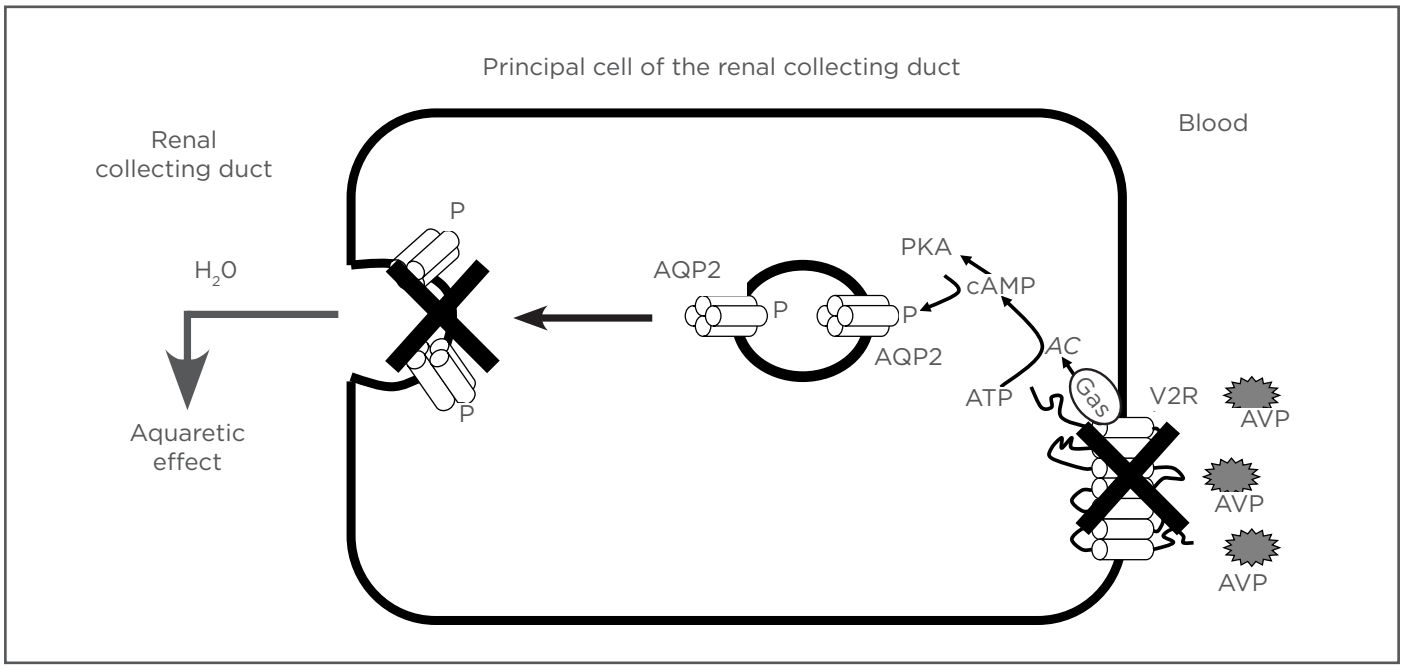

Figure 1: Vaptans mechanism of actions: binding of vaptans to V2R inhibits the activation of the Gs-coupled adenylyl cyclase cascade, thus inhibitng the synthesis, phosphorylation, and insertion of the AQP2 channels into the cell membrane. The final result is a reduction in water permeability of the renal collecting duct.

AVP: arginine vasopressin; V2R: Type 2 vasopressin receptor; AC: adenylate cyclase; ATP: adenosine triphosphate; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; AQP2: aquaporin-2; P: phosphate.

Table 2: Main properties of the vasopressin receptor antagonists evaluated in clinical trials.

	Tolvaptan	Conivaptan	Lixivaptan	Satavaptan
Receptor specificity	V2	V1a /V2	V2	V2
Route of administration	Oral	IV	Oral	Oral
Half-life (hours)	6-8	3-8	7-10	14-17
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic
Dosage (mg/day)	15-60	20-40	10-400	5-50

V1a: vasopressin Type 1a; V2: vasopressin Type 2; IV: intravenous.

CONIVAPTAN AND TOLVAPTAN IN CLINICAL PRACTICE

Indications

Conivaptan, the only combined vasopressin V1a/V2 receptor antagonist available, was approved by the FDA in 2005, and can be used in the US for the treatment of euvolaemic and hypervolaemic hyponatraemia in hospitalised patients. Tolvaptan was approved by the FDA and the European Medicines Agency (EMA) in 2009 and is sold in the US for the treatment of hypervolaemic and euvolaemic hyponatraemia, whereas in Europe, its use is limited to hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). As already highlighted, vaptans are not indicated in hypovolaemic hyponatraemia; therefore, an accurate clinical and biochemical evaluation should always precede the use of these drugs.

Vaptans can be used to correct mildly symptomatic or asymptomatic hyponatraemia as an alternative to fluid restriction (if the latter is not tolerated or does not work effectively), or to treat moderately symptomatic hyponatraemia as an alternative to hypertonic saline solution.[25] The use of vaptans in apparently asymptomatic hyponatraemia appears to be appropriate because of the potential adverse effects on bone, nervous system, and on mortality also observed in this condition.[4-8,15] Severely symptomatic hyponatraemia presenting - for instance - with seizures, respiratory distress, or coma should still be treated with hypertonic saline solution infusion.[16] In some specific clinical settings, the use of vaptans appears particularly useful; i.e. in patients with paraneoplastic SIADH who have to start chemotherapy with drugs that could cause or worsen hyponatraemia,[26] or in patients in surgical or intensive care units, who require a readily effective treatment strategy. In Figure 2 the suggested indications for the use of tolvaptan in Europe are summarised.

It is important to highlight that vaptans should not be used together with or immediately after hypertonic saline because of the risk of overcorrection, and for that same reason, patients should be encouraged to maintain a normal fluid intake and drink in response to thirst.[16]

Pharmacological Properties

Conivaptan is the only vaptan available for intravenous use (an oral formulation has been evaluated in clinical studies but is not available for clinical use) and is restricted to the short-term treatment (of up to 4 days) for hospitalised patients. The loading dose is 20 mg over 30 minutes, followed by a continuous infusion of 20 mg/day. The dosage may be increased to 40 mg/day if the correction of hyponatraemia appears to be inadequate.[27]

Tolvaptan is available in tablet formulation. Although the treatment must be started in the hospital, it can be continued after being discharged once the optimal dose has been established. Tolvaptan use is also indicated for long-term treatment when needed to maintain serum [Na+] within the normal range. The starting dose of tolvaptan is 15 mg once daily; the dosage can be increased to 30-60 mg at intervals ≥24 hours if the correction of the serum [Na+] is insufficient.[28]

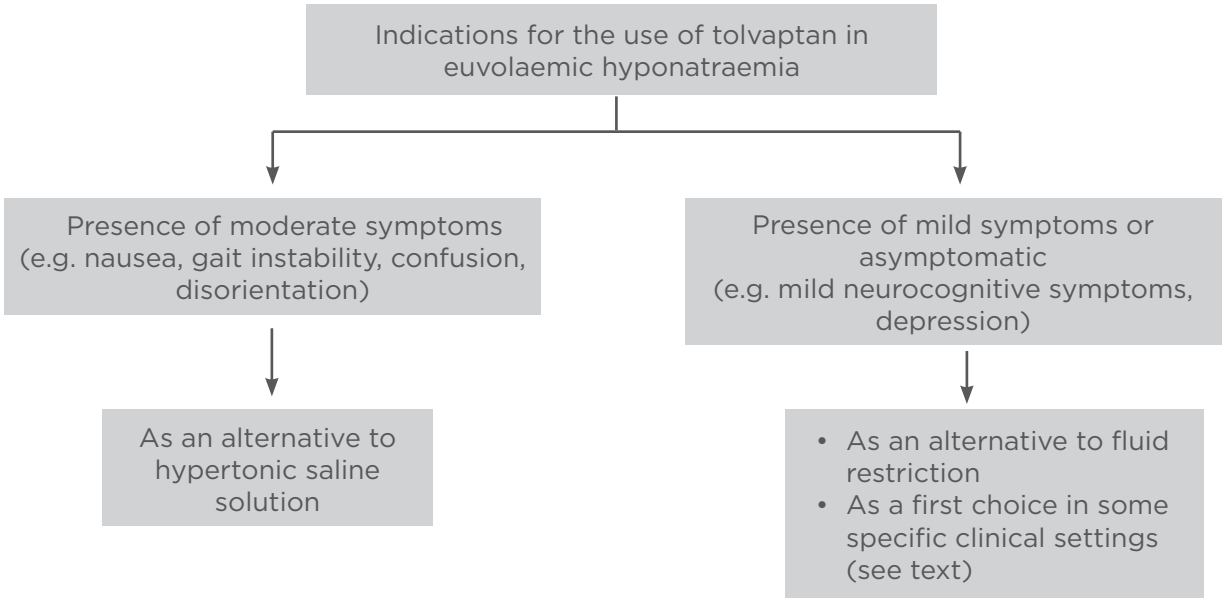

Figure 2: Indications for the use of tolvaptan in the treatment of euvolaemic hyponatraemia, according to the European indication, which restricts its use in patients with hyponatraemia secondary to syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

During the active phase of correction of hyponatraemia with conivaptan or tolvaptan, it is essential to strictly monitor the serum [Na+], which should be measured every 6 hours or more frequently in patients with ODS risk factors.[17,29] In the case of tolvaptan, which can be used for a prolonged time, as already mentioned, a close measurement of the serum [Na+] is no longer necessary once the optimal dosage has been established.

The metabolism of all vaptans is hepatic, through the cytochrome CYP_3A_4 isoenzyme, and therefore, the potential interaction with CYP_3A_4 inhibitors (i.e. macrolide antibiotics, diltiazem, ketoconazole, but also grapefruit) that could increase the effect of vaptans or CYP_3A_4 inducers (i.e. rifampicin, barbiturates), which could reduce their effect, should be considered.[30,31] In contrast, tolvaptan treatment does not interfere with the serum concentrations of other CYP_3A_4 substrates, such as warfarin or amiodarone.[32,33] High and continued doses of tolvaptan (i.e. 60 mg/daily) could increase serum digoxin concentrations (mean maximal concentration: 1.27-fold increase); therefore patients treated with both tolvaptan and digoxin should be monitored for excessive digoxin effects.[33]

Efficacy

The efficacy and safety of conivaptan and tolvaptan have been demonstrated in several clinical trials involving patients affected mostly by hyponatraemia secondary to HF, cirrhosis, and SIADH. In two placebo-controlled, randomised, double-blind studies, oral conivaptan appeared to be safe and effective in increasing and maintaining serum [Na+] in patients with euvolaemic and hypervolaemic hyponatraemia. Similar results were obtained with intravenous use.[27,34] SALT-1 and SALT-2 (Study of Ascending Levels of Tolvaptan in Hyponatraemia 1 and 2) were two multicentre, randomised, double-blind, placebo-controlled trials, which evaluated the efficacy of oral tolvaptan in patients with hyponatraemia secondary to HF, liver failure, and SIADH.[28] These studies showed a higher, progressive increase in serum [Na+] in patients who received tolvaptan versus placebo, without significant side-effects. Similar results were obtained in a subsequent analysis of the SIADH subgroup.[35] Furthermore, a combined analysis of the two trials highlighted a significant improvement in the mean score of the SF-12 Mental Component Summary Scale from the baseline to day 30 in the tolvaptan group, suggesting that the increase in serum [Na+] secondary to tolvaptan therapy was clinically beneficial.

The subsequent extension of the SALT-1 and SALT-2 trials, the Safety and sodium Assessment of Long-term Tolvaptan With hyponatraemia: A year-long, open-label Trial to gain Experience under Real-world conditions (SALTWATER) trial, showed similar

results in terms of efficacy and safety.[36] Another interesting study[37] demonstrated that tolvaptan was better than fluid restriction in improving serum [Na+] (+6 nmol/L versus ≤1 nmol/L in patients treated with fluid restriction) in a cohort of hyponatraemic hospitalised patients.

Two trials conducted specifically on patients affected by HF, the ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin antagonist in Chronic Heart Failure) and the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan), evaluated the impact of tolvaptan on survival as a secondary end-point.[38,39] In a post-hoc analysis of the ACTIV trial, a link between an improvement in hyponatraemia and in survival was observed. In the EVEREST trial, tolvaptan did not show any effects on mortality during the long-term follow-up, but in patients with moderate-to-severe hyponatraemia (<130 mEq/L) tolvaptan was associated with reduced cardiovascular morbidity and mortality after discharge.[40,41] However, it has to be specified that the EVEREST trial was not targeted to study the effects of tolvaptan on hyponatraemia, and it was not specified if the therapy was effectively associated with the normalisation of serum [Na+]. Together with the beneficial effect of not causing electrolyte depletion, these qualities make vaptans particularly useful in the treatment of hyponatraemia secondary to HF, alone or in association with traditional diuretics.[16]

The use of vaptans in patients affected by cirrhosis and renal failure appears more controversial. Furthermore, after a recent alert regarding liver toxicity due to high doses of tolvaptan (see adverse events section), the FDA has contraindicated the use of tolvaptan in patients with underlying liver diseases. In patients with hyponatraemia secondary to nephrotic syndrome and concomitant renal failure, vaptans are not expected to cause a significant aquaretic effect, in particular if the glomerular filtration rate is <50 ml/min or the serum creatinine is >3 mg/dl and its use is not recommended.[16]

Safety and Adverse Events

Conivaptan and tolvaptan are generally well tolerated. The most frequent side-effects are headache, orthostatic hypotension, nausea, increased urinary frequency, and hypokalaemia. Thirst and dry mouth are two common and expected consequences of the aquaretic effect of these drugs.[27,42]

The safety of tolvaptan was confirmed in the SALT-1, SALT-2, and SALTWATER trials, in which an overly rapid correction of serum [Na+] or hypernatraemia were rarely observed (<2% of treated cases).[28,35,36] Nevertheless, both the FDA and EMA have remarked on the necessity of monitoring the fluid and electrolytic balances in patients treated with tolvaptan or conivaptan, following the occurrence of a few ODS cases in patients treated with tolvaptan. However, only one case of ODS occurring after correction of hyponatraemia with tolvaptan alone has been reported very recently.[43] Even though a causal relationship to drug exposure has not been clearly established, a strict monitoring of serum [Na+] in the active phase of correction of hyponatraemia is recommended, especially in patients with serum [Na+] ≤120 mmol/L, in which greater responses have been documented.

Active therapy should be stopped if the rate of correction exceeds 8-12 mmol/L in the first 24 hours (or 18 mmol/L within 48 hours), in agreement with the general recommendations for the correction rate of hyponatraemia. The possible overly rapid increase in serum [Na+] can be limited by stopping the drugs (which both have a half-life <12 hours). Serum [Na+] re-lowering may be optional in patients at low-to-moderate risk of ODS, but is recommended in patients at high risk. This objective can be achieved by infusing or orally administering hypotonic fluids. The use of desmopressin can also be considered to obtain serum [Na+] re-lowering.[16,25]

Recently, the FDA issued an additional warning relating to the potential hepatotoxicity associated with tolvaptan treatment, following the report of a few cases of liver toxicity in patients enrolled in a 3-year trial examining the effects of tolvaptan for a different indication, i.e. for the treatment of autosomal dominant polycystic kidney disease (ADPKD) (TEMPO trial, for Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes).[44] A reversible increase in serum alanine aminotransferase and total bilirubin was observed in three patients treated with tolvaptan, and this effect was related to the administration of this drug. In October 2013 the FDA determined that tolvaptan should not be used for longer than 30 days nor in patients with underlying liver diseases because it can cause an increased risk of liver injury. However, it has to be said that the dosage used in the TEMPO trial was much higher than

the maximum dose approved for hyponatraemia treatment (120 mg versus 60 mg/daily).

Moreover, in clinical trials where the FDA-approved doses of tolvaptan were used (e.g. the SALTWATER and EVEREST trials), hepatic injury was not reported. In agreement with these aspects, the EMA has not limited the long-term use of tolvaptan but suggested to perform liver function tests in patients treated with tolvaptan who have reported symptoms suggesting liver injury (i.e. fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice). Therefore, in patients who could benefit from the long-term use of tolvaptan, the therapy can be confirmed provided that a careful follow-up is maintained. However, the drug must be stopped if liver damage is suspected. Tolvaptan can be re-initiated when it has been clearly established that liver toxicity is not related to treatment with this drug. The use of tolvaptan in patients affected by liver diseases should be evaluated with caution and preferably avoided.[16] In some particular cases - i.e. in the patients already listed for liver transplantation with severe hyponatraemia, which could increase the surgical or anaesthesiological risk - the therapy could be considered because the potential benefit from the correction of hyponatraemia may outweigh the risk.[16]

FINAL CONSIDERATIONS

Vaptans appear to be an effective and substantially safe therapeutic option for the treatment of hypotonic hypervolaemic (US) and euvolaemic (US and Europe) hyponatraemia. In particular, in patients with mild-to-moderate symptomatic hyponatraemia, or in those with asymptomatic hyponatraemia, the use of these drugs appears to be an appropriate treatment strategy as an alternative to traditional treatments. The use of conivaptan is limited to short-term therapy of hospitalised patients; in the US, conivaptan is the only vaptan available in patients who cannot receive oral therapy because it can be administered intravenously. Furthermore, conivaptan appears to be particularly useful in patients affected by HF because it has a dual selectivity, i.e. for V1a and V2 receptors. Tolvaptan can also be used for long-term treatment provided that a careful evaluation of possible signs suggesting adverse events is carried out. Admittedly, the cost of this drug may very well be a current limit for its prolonged use. Further studies are required in order to clarify the effective advantages of this class of drugs in terms of cost-effectiveness and patient outcomes.

REFERENCES

1. Upadhyay A et al. Incidence and prevalence of hyponatremia. Am J Med. 2006;119(7 Suppl 1):30-5.

2. Hoorn EJ et al. Development of severe hyponatremia in hospitalized patients: treatment-related risk factors and inadequate management. Nephrol Dial Transplant. 2006;21(1):70-6.

3. Gill G et al. Characteristics and mortality of severe hyponatremia – a hospital-based study. Clin Endocrinol (Oxf). 2006;65(2):246–9.

4. Renneboog B et al. Mild chronic hyponatremia is associated with falls, unsteadiness and attention deficits. Am J Med. 2006;119(1):71.e1-8.

5. Gankam KF et al. Mild hyponatremia and risk of fracture in the ambulatory elderly. QJM. 2008;101(7):583-8.

6. Kinsella S et al. Hyponatremia independent of osteoporosis is associated with fracture occurrence. Clin J Am Soc Nephrol. 2010;5(2):275-80.

7. Verbalis JG et al. Hyponatremia-induced osteoporosis. J Bone Miner Res. 2010;25(3):554-63.

8. Barsony J et al. Osteoclast response to low extracellular sodium and the mechanism of hyponatremia-induced bone loss. J Biol Chem. 2011;286(12): 10864-75.

9. Waikar SS et al. Mortality after hospitalization with mild, moderate, and severe hyponatremia. Am J Med. 2009;122:857–65.

10. Klein L et al. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Study. Circulation. 2005;111(19):2454–60.

11. Kim WR et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008;359(10):1018–26.

12. Zilberberg MD et al. Hyponatremia and hospital outcomes among patients with pneumonia: a retrospective cohort study. BMC Pulm Med. 2008;8:16.

13. Terzian C et al. Admission hyponatremia in the elderly: factors influencing prognosis. J Gen Intern Med. 1994;9(2):89-91.

14. Stelfox HT et al. The epidemiology of intensive care unit-acquired hyponatremia and hypernatraemia in medical-surgical intensive care units. Crit Car. 2008;12(6):R162.

15. Corona G et al. Moderate hyponatremia is associated with increased risk of mortality: evidence from a meta-analysis. PLoS One. 2013;8(12):e80451.

16. Verbalis JG et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126(10 Suppl 1):S1-42.

17. Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med. 2000;342(21):1581-9.

18. Adrogué HJ. Consequences of inadequate management of hyponatremia. Am J Nephrol. 2005;25(3):240-9.

19. Peri A et al. Hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). J Endocrinol Invest. 2010;33(9):671-82.

20. Peri A, Combe C. Considerations

regarding the management of hyponatraemia secondary to SIADH. Best Pract Res Clin Endocrinol Metab. 2012;26(Suppl 1):S16-26.

21. Furst H et al. The urine/plasma electrolyte ratio: a predictive guide to water restriction. Am J Med Sci. 2000;319(4):240-4.

22. Yamamura Y et al. OPC-21268, an orally effective, nonpeptide vasopressin V1 receptor antagonist. Science. 1991;252(5005):572-4.

23. Ohnishi A et al. Potent aquaretic agent. A novel nonpeptide selective vasopressin 2 antagonist (OPC-31260) in men. J Clin Invest. 1993;92(6):2653-9.

24. Robertson GL. Vaptans for the treatment of hyponatremia. Nat Rev Endocrinol. 2011;7(3):151-61.

25. Peri A. Clinical review: the use of vaptans in clinical endocrinology. J Clin Endocrinol Metab. 2013;98(4):1321-32.

26. Sørensen JB et al. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease. J Intern Med. 1995;238(2):97-110.

27. Zeltser D et al. Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. Am J Nephrol. 2007;27(5):447-57.

28. Schrier RW et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med. 2006;355(20):2099-112.

29. Berl T. Treating hyponatremia: damned if we do and damned if we don't. Kidney Int. 1990;37(3):1006-18.

30. Shoaf SE et al. Effects of CYP3A4 inhibition and induction on the pharmacokinetics and pharmacodynamics of tolvaptan, a non-peptide AVP antagonist in healthy subjects. Br J Clin Pharmacol. 2012;73(4):579-87.

31. Shoaf SE et al. Effect of grapefruit juice on the pharmacokinetics of tolvaptan, a non-peptide arginine vasopressin antagonist, in healthy subjects. Eur J Clin Pharmacol. 2012;68(2):207-11.

32. Shoaf SE et al. Tolvaptan administration does not affect steady state amiodarone concentrations in patients with cardiac arrhythmias. J Cardiovasc Pharmacol Ther. 2005;10(3):165-71.

33. Shoaf SE et al. In vitro P-glycoprotein interactions and steady-state pharmacokinetic interactions between tolvaptan and digoxin in healthy subjects. J Clin Pharmacol. 2011;51(5):761-9.

34. Verbalis JG et al. Assessment of the efficacy and safety of intravenous conivaptan in patients with euvolaemic hyponatraemia: subgroup analysis of a randomized, controlled study. Clin Endocrinol (Oxf). 2008;69(1):159-68.

35. Verbalis JG et al. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. Eur J Endocrinol. 2011;164(5):725-32.

36. Berl T et al. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol. 2010;21(4):705-12.

37. Gheorghiade M et al. Vasopressin v(2) receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. Am J Cardiol. 2006;97(7):1064-7.

38. Rossi J et al. Improvement in hyponatremia during hospitalization for worsening heart failure is associated with improved outcomes: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) trial. Acute Card Care. 2007;9(2):82-6.

39. Konstam MA et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007;297(12): 1319-31.

40. Pang PS et al. Effects of tolvaptan on physician-assessed symptoms and signs in patients hospitalized with acute heart failure syndromes: analysis from the efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan (EVEREST) trials. Am Heart J. 2011;161(6):1067-72.

41. Vaduganathan M et al. Efficacy of oral tolvaptan in acute heart failure patients with hypotension and renal impairment. J Cardiovasc Med (Hagerstown). 2012;13(7):415-22.

42. Otsuka America Pharmaceutical Inc. SAMSCA tolvaptan tablet. 2014. Available at: http://medlibrary.org/lib/rx/meds/samsca-1/.

43. Malhotra I et al. Unpredictable nature of tolvaptan in treatment of hypervolemic hyponatremia: case review on role of vaptans. Case Rep Endocrinol. 2014;2014:807054.

44. Torres VE et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012;367(25):2407-18.

CARDIOVASCULAR REMODELLING IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Left ventricular (LV) structure and function abnormalities are frequent in patients with chronic uraemia; these disorders increase the risk of cardiovascular (CV) and overall morbidity and mortality in the predialysed population, during dialysis treatment, and in renal transplant recipients. Since the first description of the association between chronic kidney disease (CKD) and heart disease, many epidemiological studies have confirmed and extended this finding. The risk of cardiovascular disease (CVD) is notably increased in patients with CKD. When adjusted for traditional CV risk factors, impaired kidney function increases the risk of CVD 2 to 4-fold. CVD is frequently underdiagnosed and undertreated in patients with CKD. This review will attempt to summarise current knowledge of the prevalence and pathophysiological mechanisms of LV disease in chronic uraemia, and to discuss useful medical strategies in this population.

Keywords: Chronic kidney disease, cardiovascular remodelling, risk factors.

INTRODUCTION

Left ventricular hypertrophy (LVH) is the most frequent cardiac complication in patients with chronic kidney disease (CKD), and carries a poor prognosis.[1] Nearly 75% of adult patients have LVH at the time of initiation of dialysis therapy. The development of LVH is associated with decreased survival in patients with CKD. The reason for this is that LVH may cause cardiac arrhythmias, diastolic dysfunction, ischaemic heart disease, and progression to overt heart failure (HF). The high risk of cardiovascular disease (CVD) results from multiple factors, including haemodynamic overload and metabolic and endocrine abnormalities.[2]

PATHOLOGICAL CARDIAC REMODELLING

Cardiac remodelling is frequently identified in patients with CKD. Remodelling can be defined as molecular, cellular, interstitial, and genomic expression changes that manifest as myocyte hypertrophy, intramyocardial cell fibrosis, and decreased capillary density.[3] Cardiac remodelling is clinically manifested by changes in cardiac size, shape, and function in response to cardiac injury or increased cardiac load. The cardiac cells involved in the remodelling process are cardiomyocytes and fibroblasts. Fibroblast stimulation increases collagen synthesis and causes fibrosis of both the infarcted and non-infarcted regions of the ventricle.[3] This leads to a loss of cardiomyocytes by apoptosis or necrosis. Eventually these cardiomyocytes are replaced by fibroblasts and extracellular collagen. Marked remodelling of the heart has also been observed in CKD patients.[3]

There is a high rate of both eccentric (ventricular dilatation owing to volume overload) and concentric (increased ventricular wall thickness secondary to pressure overload) hypertrophy in patients with CKD. Additionally, in the setting of renal insufficiency there are many non-

haemodynamic factors that promote both hypertrophy and fibrosis. Cardiac remodelling can be both adaptive and destructive.[4] Pathologic remodelling develops as a response to prolonged stress on the heart from chronic volume overload, pressure overload, and non-haemodynamic factors. This pathologic remodelling involves diffuse fibrosis and hypertrophy, which lead to increased myocardial stiffness and impaired diastolic relaxation. Remodelling under these conditions is associated with HF progression and poor prognosis.[5]

The prevalence of LVH is strikingly increased in patients with early or advancing CKD. When the estimated glomerular filtration rate (GFR) is <30 mL/min per 1.73 m^2, around 50% of patients develop LVH, of which most is concentric hypertrophy.[6] Both preload and afterload-related processes affect the heart simultaneously and likely affect both patterns of hypertrophy. There appears to be an additive or even synergistic effect in promoting LVH. Additionally, many present in CKD have direct hypertrophic effects that are independent from their haemodynamic effects (e.g. renin-angiotensin-aldosterone system [RAAS] activation, increased sympathetic output, oxidative stress, inflammation, increased endothelin activity, hyperparathyroidism, and fibroblast growth factor 23 [FGF-23]).

Increased CV risk in individuals with CKD is due partly to the high prevalence of traditional risk factors. Also, non-traditional kidney-specific mechanisms make notable contributions to cardiovascular (CV) risk. Clarification of these mechanisms could reveal ways to lessen the CV risk in patients with CKD.[7]

Hypertension is a well-known and strong risk factor for development of CKD. Nevertheless, the cause-effect association can also be in the opposite direction. Even in the early phases CKD can cause hypertension, which is likely to increase CV risk in affected patients. A target blood pressure (BP) of <140/90 mmHg is deemed appropriate to prevent CV events in patients with CKD; a lower target BP of <130/80 mmHg is recommended only in patients with increased albuminuria (>30 mg/g).[8]

The primary structural component of the extracellular matrix (ECM) is fibrillar collagen. There are five types of fibrillar collagen; Type 1 and Type 3 are the predominant isoforms in the heart, accounting for approximately 80% of the myocardial collagen.[9] Collagen forms a structural scaffold that provides both strength and elasticity. This scaffold is important in maintaining structural integrity of the myocardium and actively participates in force generation and transmission across the LV wall. Taken in whole, the ECM is the primary determinant of ventricular stiffness and passive relaxation during diastole. An imbalance between collagen production by myofibroblasts results in a net accumulation of fibrillar collagen and myocardial fibrosis. Oxidative stress, inflammation, and excess hypertrophic growth factors are involved early-on in the course of CKD haemodynamic overload. At the same time, with progressive CKD, chronic anaemia, hyperphosphataemia, and uraemic toxins also play a role in promoting fibrosis.

In a recent study, Martin et al.[10] demonstrated early myocardial fibrosis with impaired diastolic function in an experimental model of mild renal insufficiency produced by unilateral nephrectomy. Nephrectomy rats in the investigational group showed a significant increase in myocardial fibrosis compared to the control group after 4 weeks. These findings were independent of any change in BP, sodium retention, activation of aldosterone, GFR, proteinuria, or plasma B-type natriuretic peptide (BNP) level. After 16 weeks these changes progressed to more global remodelling and dysfunction with increases in LV mass, LV end diastolic diameter, and plasma BNP, with a modest decrease in LV ejection fraction (LVEF).

FUNCTIONAL CONSEQUENCES

Diastolic dysfunction is the predominate physiology seen in patients with CKD and is associated with a higher mortality rate than systolic dysfunction.[11] CKD can lead to adverse cardiac remodelling and fibrosis (LV dysfunction, HF, etc.). At this stage, the clinical syndrome is typically progression and is a common cause of hospitalisation and suddenly death. All of the features and complications manifested by low LVEF have been described and found to be increased with progressively lower levels of GFR including increased symptoms, decreased exercise tolerance, reduced peak oxygen consumption, higher risks of arrhythmias, thromboembolism, device failure, and death.[12]

Over the last two decades, with the development of highly sensitive and cost-effective assays, serum biomarkers have become integral tools in all phases of diagnosis, management, and prognosis

of HF.[13] Many commonly used biomarkers are substances released upon damage to or stress on the myocardium (including troponin and BNP); these can be considered to be bystander biomarkers as they are not actively involved in promoting disease progression. It is considered that there are other biomarkers that appear to be helpful in risk stratification of patients with HF, particularly after an acute myocardial infarction (e.g. serum levels of soluble ST2 receptor and interleukin-33 [IL-33]).[14]

Except hypertension, renal anaemia and increased vascular stiffness might play key roles in the development of LVH that leads to reduced coronary reserve.[15] The latter could be aggravated by reduced cardiac capillary density in CKD and impaired coronary dilatory responses, as has been shown in animal studies. Expression of endothelial nitric-oxide (NO) synthase is down-regulated, which suggests a possible mechanism for coronary endothelial dysfunction in the early stages of CKD.[7] The high prevalence of LVH, with its associated risk of cardiac rhythm disturbances, could at least partly explain why the prevalence of sudden cardiac death is increased in people with CKD. In the general population, sudden cardiac death accounts for roughly one death per 1,000 person-years and for 6–13% of all deaths, whereas among individuals with kidney failure, the rates are 59 deaths per 1,000 person-years and 26% of total mortality.[16] Besides the high prevalence of LVH, abnormal electrolyte concentrations and increased prevalence of coronary artery disease (CAD) are predisposing factors for sudden cardiac death in patients with CKD. Electrolyte disturbance, especially hyperkalaemia, may cause severe arrhythmias, including ventricular fibrillation and asystole. Dyslipidaemia and inflammation are also caused by CKD.[17] In patients with impaired kidney function and high albuminuria, lipid profiles become atherogenic. Mechanisms of increased systemic inflammation in CKD are unclear, but the increased production of inflammatory mediators has been attributed to raised oxidative stress and the accumulation of post-synthetically modified proteins and toxins that are cleared with normal renal function.[18]

Other factors that raise CV risk in patients with CKD include increased activity of the renin–angiotensin system and sympathetic nerve activity in CKD. Bioavailability of NO, which is involved in vascular smooth-muscle contraction and growth, platelet aggregation, and leukocyte adhesion to the endothelium, becomes decreased. Albuminuria can be interpreted as a sign of, but also as a consequence/marker of, endothelial dysfunction.[18] Another key factor for endothelial function seems to be asymmetric dimethylarginine (ADMA), the concentration of which is a predictor of mortality and CV complications in patients with CKD.[18] ADMA is an endogenic inhibitor of NO; it reduces cardiac output and raises systemic vascular resistance and BP. Increased concentrations of ADMA and sympathetic overactivity are associated with concentric LVH, which fits with the hypothesis that these factors may be associated with cardiac abnormalities in CKD.[19]

Vascular calcification is increasingly recognised to be a frequent complication in patients with CKD.[20] In the general population electron beam computed tomography evidence of vascular calcification is a useful index of atherosclerotic burden. It not only predicts adverse coronary events, but it is also associated with a lower event-free survival.[21] The significant correlation observed between valvular calcification and aortic atheroma[22] suggests that valvular calcification may be a manifestation of generalised atherosclerosis.[23] The calcified regions of the cardiac valves not only share common features with arterial atherosclerotic plaque with infiltration of inflammatory cells, lipoproteins, and calcium deposits, but also express 'bone' matrix proteins,[24] suggesting that the process of valvular calcification simulates bone formation. Interstitial cells with osteoblastic characteristics identified in cardiac valves were suggested to be partly responsible for the increased expression of 'bone' matrix proteins. The protein deposition 'bone' matrix in vascular calcification in uraemic patients[25] suggests that valvular and vascular calcification are likely associated syndromes, both involving an active cell-mediated process and not just passive accumulation of minerals.

Atherosclerosis is frequently seen in patients with kidney failure but also occurs in those with early CKD. The key modulators in this field have not been elucidated in intervention trials, but might include calcification inhibitors (e.g. fetuin-A and matrix Gla protein), promotors (e.g. hyperphosphataemia), calcium-phosphate product, parathyroid hormone (PTH), and leptin.[26]

FGF-23 is a recently discovered regulator of phosphate and mineral metabolism.[27] FGF induces phosphaturia by reducing the number of Na-P co-transporters on renal tubular cells, as well as

mitigating the effects of calcitriol on intestinal absorption.[28] The biological effects of FGF-23 are exerted through activation of FGF receptors (FGF-R). Klotho is a transmembrane protein originally described in mice with a phenotype of accelerated aging and atherosclerosis. Klotho directly interacts with FGF-R, allowing it to bind FGF-23 with a higher affinity and increased specificity. The activation of FGF-23 therefore occurs in a Klotho-dependent manner.[29] The main known physiological role of FGF-23 is to regulate urinary phosphate excretion and maintain a stable serum phosphate. An important secondary role is the counter-regulation (against PTH) of vitamin D biosynthesis. The main stimuli for increased expression of FGF-23 are high dietary phosphate, calcitriol, and persistent hyperphosphataemia. In CKD, recently reported clinical studies support a phosphate-centric, FGF-23 mediated pathogenesis of secondary hyperparathyroidism, and findings suggest that FGF-23 plays an active role in CKD. There is also growing evidence of the association between CVD and FGF-23 levels. In an observational study of 833 patients with early CKD and stable CAD, elevated FGF-23 was independently associated with mortality and CV events.[30] Association between arterial stiffness and FGF-23 has also been demonstrated once in a cohort of 967 patients with early CKD, where arterial stiffness was measured with ShygmoCor.[31]

Patients with impaired kidney function frequently develop a deficiency of active vitamin D because of a lack of its precursor, impaired activity of the kidney enzyme 1-α-hydroxylase, which converts this precursor to the active hormone, or both.[33] Observational studies in patients with CKD have shown associations between vitamin D deficiency and increased risk of CV events, and experimental data suggest that the vitamin D pathway is involved in modifying cardiac structure and function.[33]

The complex interaction between the kidneys and the heart has been termed the cardiorenal syndrome (CRS), in which five types have been defined.[34] Type IV CRS is classified as CKD contributing to decreased cardiac function, cardiac hypertrophy, and increased risk of adverse CV events, and is referred to as chronic reno-cardiac syndrome. As CKD progresses and kidney-specific risk factors become more and more relevant the risk of CVD is amplified. However, traditional risk factors remain the major determinants of CV remodelling in CKD.

PREVENTION

CVD can be prevented by lifestyle and pharmacological interventions. In view of the progressive increase in CV risk as kidney function declines, however, prevention of loss of kidney function should be viewed as a target by itself. Treatment strategies that slow or even halt the progressive loss of kidney function might not only postpone the need for dialysis or kidney transplantation, but also attenuate CV risk. Thus, the assignment of strength and grade to recommendations balances CV and renal protective effects.

PHARMACOLOGICAL INTERVENTIONS

Treatment of high BP in patients with any stage of CKD is of paramount importance to slow or prevent disease progression, and is the mainstay of CV protection.[35] In such patients, drugs to control BP, especially RAAS inhibitors, should be titrated until the target BP is reached and baseline albuminuria is reduced by at least 50%.[35] Lipid-lowering therapies have undoubtedly contributed to a reduced incidence of CV events in the general population.[36] A meta-analysis of all statin trials in individuals with CKD showed that the CV protective effect of these drugs is attenuated in those with low estimated GFR values and limited in patients undergoing dialysis.[37]

Diabetes is an important cause of CKD and significantly increases CV risk in these patients. Optimum glycaemic control slows the progression of microvascular complications, but the evidence for CV or mortality outcomes is of much lower quality.[38] New oral glucose-lowering drugs have become available for clinical use (e.g. GLP-1 analogues), but their long-term effects on CV and kidney outcomes are not yet established so they are not approved for use in dialysis patients or advanced CKD. Targeting future therapies at the underlying cellular mechanisms of CV remodelling, such as the insulin resistance (IR) pathway, may begin to reduce the burden of this disease. Thioglitazones, some of which are currently used to treat diabetes, are thought to be able to manipulate the IR pathway and to have the potential to be an effective therapy for cardiomyopathy in CKD. It should be noted, however, that some thioglitazones have been associated with increased risk of congestive HF, which might complicate their role in the treatment of this disease.[39]

CV protection with antiplatelet and anticoagulant therapy has been documented in secondary prevention trials. Because patients with CKD are at increased CV risk they might benefit from antiplatelet therapy, but they also have abnormal platelet function that raises the risk of haemorrhagic events when treated with anticoagulants, including antiplatelet therapies.[40]

Much attention has been paid to the targeted treatment of specific kidney-related CV risk factors to improve renal and CV health, but results have been mixed. For instance, on the basis of the observation that low haemoglobin concentrations were associated with CV outcomes, erythropoiesis stimulating agents were assessed. Unfortunately, no benefit was seen with the correction of haemoglobin concentrations to >120 g/L, and an increased risk of stroke has been proven.[41]

Vitamin D deficiency can activate the intracardiac renin-angiotensin system (RAS), and active vitamin D supplementation can cause regression of LVH and/or cardiac fibrosis. Lowering greatly elevated PTH levels seen in experimental uraemia by calcimimetics (cinacalcet) decreases cardiac fibrosis but does not affect LV mass. Calcitriol also reduces cardiac fibrosis and microvascular remodelling in experimental models of renal failure.[42]

The identification of clinical manifestations of CVD is challenging in patients with CKD, especially identification of ischaemic heart disease. Some patients with CKD present with classic symptoms, but many are asymptomatic, with no pain or adrenergic manifestations, or develop atypical manifestations despite a major acute ischaemic event.[43] People with diabetes might be particularly prone to asymptomatic ischaemic heart disease because of visceral neuropathy.

Clinicians must be fully aware of the atypical presentations of acute coronary syndromes in patients with CKD to avoid under-diagnosis of potentially life-threatening CV events. This consideration is particularly relevant because patients with Stage 3–5 CKD have notably higher rates of and worse prognoses from comorbidities, conduction abnormalities, and anterior infarctions than do individuals without CKD.[44]

In our opinion there are at least two approaches to prevent CV events in patients with CKD. First, treatment should be started in early stages of CKD. Screening for albuminuria and treatment with angiotensin-converting enzyme inhibitors in patients who have increased albuminuria might be a cost-effective approach to prevent CV events and renal failure, especially in patients at high risk of developing CKD, such as those with diabetes, hypertension, or old age.[45] Such an approach should be formally investigated. Second, in late-stage CKD, intensified, multifactorial interventions may be mandatory. Gaede and colleagues[46] showed benefits with multimodal treatment that included strict glucose management, statins, angiotensin-converting enzyme inhibitors, etc.

Antihypertensive agents and lifestyle interventions (smoking cessation, increased physical activity, and dietary changes) compared with standard care according to national guidelines. The rate of macrovascular complications was halved after 8 years of follow-up, as was CV mortality after 13 years. A similar multimodal strategy was safely and effectively applied to normalise albuminuria and prevent loss of kidney function in patients otherwise predicted to rapidly progress to renal failure.[47]

Rapamycin, targeting mammalian target of rapamycin (mTOR) downstream of protein kinase B (Akt), has been shown to reduce LVH and fibrosis in uraemic mice. It has the potential to be an effective and simple therapy for uraemic cardiomyopathy.[48]

CONCLUSIONS

Identification of the pathophysiological mechanisms underlying CV remodelling will allow for a better understanding of the clinical consequences of these diseases. Mechanisms specific to CKD promote vascular disease and, therefore, substantially increase the burden of CVD in patients with CKD. Experimental and interventional studies designed to test whether biomarkers are not only markers but also aetiological risk factors may provide further information that could lead to novel treatment options. Patients with CKD have a high risk of CVD that requires special attention and monitoring.

Finally, further research into the specific derangements will open the door for development of novel therapeutic targets aimed at treating the underlying disease aetiology and, thus, preventing initiation of the disease. Targeting future therapies at the underlying cellular mechanisms of CV remodelling may finally start to reduce the burden of CV changes in the CKD population.

REFERENCES

1. Foley RN et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int. 1995;47(1):186–92.

2. London GM. Cardiovascular disease in chronic renal failure: pathophysiologic aspects. Semin Dial. 2003;16(2):85–94.

3. Gansevoort RT et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382(9889): 339-52.

4. Pelliccia Aet al. Remodeling of left ventricular hypertrophy in elite athletes after long-term deconditioning. Circulation. 2002;105(8):944-9.

5. Konstam MA et al. Left ventricular remodeling in heart failure. JACC Cardiovasc Imaging. 2011;4(1):98-108.

6. Levin A, Foley RN. Cardiovascular disease in chronic renal insufficiency. Am J Kidney Dis. 2000;36(6 suppl 3):S24–30.

7. Schiffrin EL et al. Chronic kidney disease: effects on the cardiovascular system. Circulation. 2007;116(1):85–97.

8. Upadhyay A et al. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann Intern Med. 2011;154(8): 541-8.

9. Manabe I et al. Gene expression in fibroblasts and fibrosis involvement in cardiac hypertrophy. Circ Res. 2002;91(12):1103-13.

10. Martin FL et al. Experimental mild renal insufficiency mediates early cardiac apoptosis, fibrosis, and diastolic dysfunction: a kidney-heart connection. Am J Physiol Regul Integr Comp Physiol. 2012;302:R292-3.

11. Ahmed A et al. Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity match study. Am J Cardiol. 2007;99(3):393-8.

12. McCullough PA et al. Impact of reduced kidney function on cardiopulmonary fitness in patients with systolic heart failure. Am J Nephrol. 2010;32(3):226-33.

13. Ohshiro K et al. Troponin in both smooth and striated muscles of Ascidian *Ciona intestinalis* functions as a Ca2+-dependant accelerator of actin-myosin interaction. Biochemistry. 2010;49(44):9563-71.

14. Sanada S et al. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest. 2007;117(6):1538-49.

15. Pannier B et al. Stiffness of capacitive and conduit arteries prognostic significance for end-stage renal disease patients. Hypertension. 2005;45(4): 592-6.

16. Green D et al. Sudden cardiac death in hemodialysis patients: an in-depth review. Am J Kidney Dis. 2011;57(6):921-9.

17. Krane V, Wanner C. Statins, inflammation and kidney disease. Nat Rev Nephrol. 2011;6:1573–9.

18. Ochodnicky P et al. Microalbuminuria and endothelial dysfunction: emerging targets for primary prevention of end-organ damage. J Cardiovasc Pharmacol. 2006;47(Suppl 2):S151–62.

19. Kielstein JT, Zoccali C. Asymmetric dimethylarginine: a cardiovascular risk factor and a uremic toxin coming of age? Am J Kidney Dis. 2005;46(2):186–202.

20. Zoccali C et al. Left ventricular hypertrophy, cardiac remodeling and asymmetric dimethylarginine (ADMA) in hemodialysis patients. Kidney Int. 2002;62(1):339–45.

21. Leskinen Y et al. Valvular calcification and its relationship to atherosclerosis in chronic kidney disease. J Heart Valve Dis. 2009;18(4):429-38.

22. Keelan PC et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. Circulation. 2001;104:412–7.

23. Adler Y et al. Association between mitral annulus calcification and aortic atheroma: a prospective transesophageal echocardiographic study. Atherosclerosis. 2000;152:451–6.

24. Pohle K et al. Progression of aortic valve calcification. Association with coronary atherosclerosis and cardiovascular risk factors. Circulation. 2001;104:1927–32.

25. Mohler ER 3rd et al. Bone formation and inflammation in cardiac valves. Circulation. 2001;103:1522–8.

26. Moe SM et al. Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. Kidney Int. 2002;61:638–47.

27. Ketteler M et al. Calcification and cardiovascular health: new insights into an old phenomenon. Hypertension. 2006;47(6):1027–34.

28. Urakawa I et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature. 2006;444:770-4.

29. Baum M et al. Effect of fibroblast growth factor-23 on phosphate transport in proximal tubules. Kidney Int. 2005;68:1148-53.

30. Kurosu H et al. Regulation of fibroblast growth factor-23 signaling by klotho. J Biol Chem. 2006;281:6120-3.

31. Parker BD et al. The associations of fibroblast growth factor 23 and uncarboxylated matrix Gla protein with mortality in coronary artery disease: the Heart and Soul Study. Ann Intern Med. 2010;152:640-8.

32. Mirza MA et al. Circulating fibroblast growth factor-23 is associated with vascular dysfunction in the community. Atherosclerosis. 2009;205:385-90.

33. Quarles LD. Endocrine functions of bone in mineral metabolism regulation. J Clin Invest. 2008;118(12):3820–28.

34. Ronco C et al. Cardiorenal syndrome. J Am Coll Cardiol. 2008;52(19):1527–39.

35. De Galan BE et al. Lowering blood pressure reduces renal events in type 2 diabetes. J Am Soc Nephrol. 2009;20(4):883–92.

36. Baigent C et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181–92.

37. Palmer SC et al. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med. 2012;157(4):263–75.

38. Boussageon R et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ. 2011;343:d4169.

39. Wong AK et al. Insulin sensitization therapy and the heart: focus on metformin and thiazolidinediones. Heart Fail Clin. 2012;8:539–50.

40. Weigert AL, Schafer AI. Uremic bleeding: pathogenesis and therapy. Am J Med Sci. 1998;316(2):94–104.

41. Pfeffer MA et al. A trial of darbepoietin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361(21):1–14.

42. Glassock JR et al. Left ventricular mass in chronic kidney disease and ESRD. Clin J Am Soc Nephrol. 2009;4(1):S79-91.

43. Dasmahapatra P et al. Subclinical atherosclerotic changes related to chronic kidney disease in asymptomatic black and white young adults: the Bogalusa Heart Study. Ann Epidemiol. 2011;21(5):311–7.

44. Szummer K et al. Relation between renal function, presentation, use of therapies and in-hospital complications in acute coronary syndrome: data from the SWEDEHEART register. J Intern Med. 2010;268(1):40–9.

45. Crews DC et al. Albuminuria: is it time to screen the general population? Adv

Chronic Kidney Dis. 2011;18(4):249–57.

46. Gaede P et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358(6): 580–91.

47. Ruggenenti P et al. The Remission Clinic approach to halt the progression of kidney disease. J Nephrol. 2011;24:274–81.

48. Semple D et al. Uremic cardiomyopathy and insulin resistance: a critical role for akt? J Am Soc Nephrol. 2011;22:207–15.

Icy frontiers explored in kidney transplantation

"The benefits of minimally invasive surgery in removing donor kidneys has been well established in earlier studies, but the use of robot-assisted surgery in transplanting those kidneys is comparatively a frontier."

Dr Mani Menon,
Henry Ford's Vattikuti Urology Institute,
Detroit, USA

ICED kidneys were transplanted into the chilled abdomens of 50 frail patients using minimally invasive robotic surgery.

Since kidney dysfunction occurs when blood flow to the organ is disrupted for longer than 30 minutes during transplant, a team of surgeons from two institutes, the Henry Ford Hospital, Detroit, Michigan, USA, and Medanta Hospital, Gurgaon, India, have introduced a method of minimally invasive robotic surgery, which involves chilling the organ and transplant site with ice slush prior to surgery.

"To our knowledge, ours is the first study to use renal cooling during robotic kidney transplant," stated Dr Mani Menon, co-author of the study and Chair of Henry Ford's Vattikuti Urology Institute. "It had already proved useful during minimally invasive prostate surgeries."

The experienced surgeons, who have collectively carried out over 10,000 robotic procedures and 2,500 standard kidney transplants, simulated the procedure for 3 years before carrying out 50 robotic kidney transplants.

Their method involved chilling the patients' abdomen, held open with gauze, and subsequently filling the kidney cavity with sterile ice slush before transplanting the donor kidney, which had blood vessels attached using standard suturing.

Post-surgery, all grafted kidneys functioned normally, and creatinine levels - an indicator of function - were normal. Patients reported no complications from surgical wounds, neither did they have any blood or urine leakage, nor did they need dialysis after surgery.

At 6-month follow-up, 3 out of 28 patients developed complications, while the 25 remaining patients were well.

"The benefits of minimally invasive surgery in removing donor kidneys has been well established in earlier studies, but the use of robot-assisted surgery in transplanting those kidneys is comparatively a frontier," explained Dr Menon.

The researchers attribute their success to excellent collaboration and preparation, and hope to expand their research in order for the procedure to be accepted as an alternative to traditional open surgery.

25 years of improvement for child kidney recipients

DEATH, hazard of graft loss, and odds of delayed or primary non-function are among the outcomes that have been substantially improved in paediatric kidney transplantation over the last 25 years.

Dr Dorry L. Segev, Associate Professor of Surgery and Epidemiology, Johns Hopkins School of Medicine, Baltimore, Maryland, USA, and colleagues gathered data from the Scientific Registry of Transplant Recipients on 17,446 children who received kidney transplants from 1987 to 2012. 10 years post-transplant the patient survival rates were 90.5% (2001) versus 77.6% (1987). Graft survival rates showed a similar increase of nearly 15%.

The results revealed that outcomes after paediatric kidney transplantation have greatly improved over time for all recipient subgroups. Subgroups with fewer robust improvements included adolescent and female patients, as well as those receiving pre-transplant dialysis or suffering from focal segmental glomerular sclerosis.

"Strategies to improve paediatric kidney transplant outcomes today include greater attention to the detection of elevated blood pressure, and the institution of aggressive therapy when it is detected, along with continued efforts to address medication non-adherence in the adolescent population,"

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"Strategies to improve paediatric kidney transplant outcomes today include greater attention to the detection of elevated blood pressure, and the institution of aggressive therapy when it is detected, along with continued efforts to address medication non-adherence in the adolescent population."

Dr Brad Warady, Children's Mercy Hospital, Kansas City, USA

described Dr Brad Warady, Division Director of Paediatric Nephrology and Director of Dialysis and Transplantation, Children's Mercy Hospital, Kansas City, Kansas, USA.

Emphasis has been placed on the need to magnify the current progress as some suggest this analysis may have other avenues of interpretation.

Long-term graft survival rates did not reflect the same increases as the short-term graft survival over time, "meaning most paediatric recipients will eventually face either re-transplantation or a return to dialysis," wrote Dr Segev and colleagues.

"Continued progress in outcomes after paediatric [kidney transplant] ... is therefore needed to reach the goal in which a child with [end-stage renal disease] may receive a single kidney transplant that will last a lifetime," the authors added.

Oxygen starved cells promote kidney cancer

"Just by putting SPOP into the cytoplasm, we got great big tumours, but we also saw that the cells get addicted to it. When we knock it down, they die. Our hope is that cytoplasmic SPOP might turn out to be a good drug target."

Dr Kevin White, University of Chicago, Chicago, USA

MIGRATION of nuclear speckle-type POZ protein (SPOP) to the cytoplasm of kidney cells, as a result of hypoxia, is found to lead to the inhibition of pathways which protect against cancer.

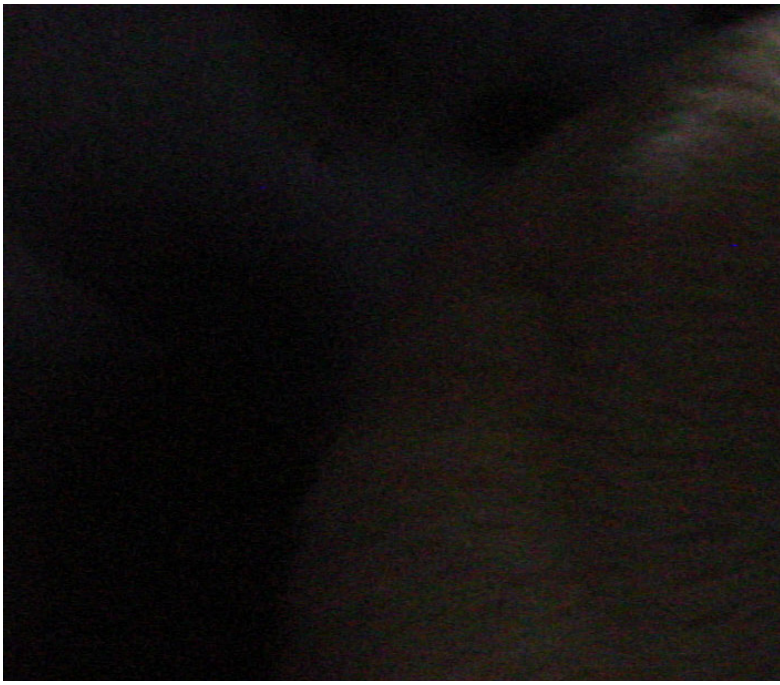
SPOP, ordinarily found in the nucleus as a tumour-suppressor protein, is induced into overexpression when rapidly metastasising tumour growths become starved of oxygen due to their growing mass. Notably, while SPOP does not mutate, it becomes targeted by hypoxia-inducible factors and is redirected outside of the nucleus. There, its function is changed and it shuts down protective pathways that restrict tumour growth.

Among the tumour-suppressor proteins degraded by the accumulation of cytoplasmic SPOP was phosphatase and tensin homolog (PTEN), a gene lost or damaged in many types of cancer. Cancerous cell samples showed consistently high levels of SPOP and low levels of PTEN, while normal cells had the reverse.

"These results clearly demonstrate that SPOP is acting as a critical hub in a network involving multiple cancer-related pathways," the study authors wrote. "In doing so, SPOP appears to be both necessary and sufficient for tumorigenic phenotypes."

Often detected late, and highly resistant to chemotherapy, kidney cancer has a high mortality rate. Unfortunately, for most patients urine in the blood is the first indicator as there are currently no reliable screening tests.

"We found that this normal protein, found in the wrong place and acting in the wrong way, was sufficient to drive the formation of tumours," said Dr Kevin White, Professor, Human Genetics and Ecology and Evolution, Director, Institute for Genomics and Systems Biology, University of Chicago, Chicago, Illinois, USA. "Just by putting SPOP into the cytoplasm, we got great big tumours, but we also saw that the cells get addicted to it. When we knock it down, they die. Our hope is that cytoplasmic SPOP might turn out to be a good drug target."



Battle of the bulge

BELLY fat of rats has been unveiled as a novel feature in the treatment for chronic kidney disease (CKD). Stem cells from the omentum (an organ in the abdomen naturally enriched with them) of a CKD patient could be used to ameliorate their kidney function.

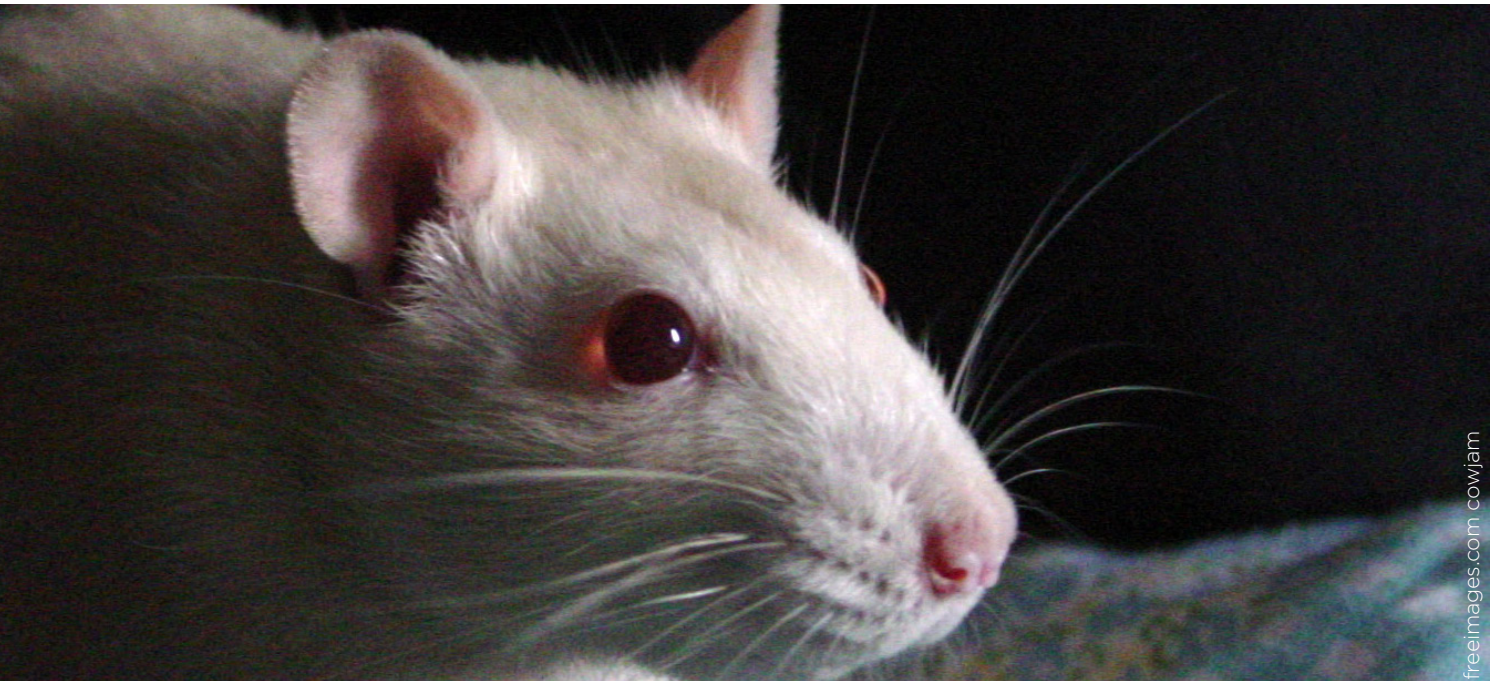
Dr Ashok Singh, study author, John H. Stroger Jr. Hospital of Cook County, Chicago, Illinois, USA, and colleagues linked the omentum, a fatty fold of tissue, to the kidney, which lies in close proximity. After 3 months, continuous migration of stem cells from the abdomen to the diseased kidney had the power to slow CKD, indicating that there could be further healing - and perhaps reversion of CKD - if the stem cells sustained contact with the diseased kidney over time.

"Attaching the omentum, a supposedly useless organ lying close to the kidney, to the diseased kidney could be put into practice after some more developmental work," said Dr Singh. "By this technique, patients would be using their own stem cells lying in the omentum to cure their kidneys without depending on outside sources of stem cells."

Due to the short lifespan of stem cells after removal from the body, it is unclear whether this treatment can be applied to clinical cases; the treatment would involve repeated stem cell injections over the course of many months, or potentially years. As a result, the technique has received mixed reviews.

Dr Christof Westenfelder, Professor of Medicine, University of Utah Health Sciences Center, Salt Lake City, Utah, USA, posited that the research is: "Novel and scientifically interesting," but that "further studies are needed to fully define the complex nature of the omentum's ability to heal injured organs and to establish its potential utility in patients with renal diseases."

> "Patients would be using their own stem cells lying in the omentum to cure their kidneys..."
>
> *Dr Ashok Singh, Hospital of Cook County, Chicago, USA*



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Increased risk of kidney disease to kidney donors

"It would be easy to misinterpret the findings of Muzaale et al. as suggesting that kidney donation is a risky procedure. In reality, the authors have shown that the absolute risk of ESRD among living donors is extremely low; this is their key finding and does not imply the need to alter existing clinical practice."

Dr John S. Gill,
University of British Columbia,
Vancouver, Canada

LIFETIME risk of developing end-stage renal disease (ESRD) is real for kidney donors, though still lower than in the general population.

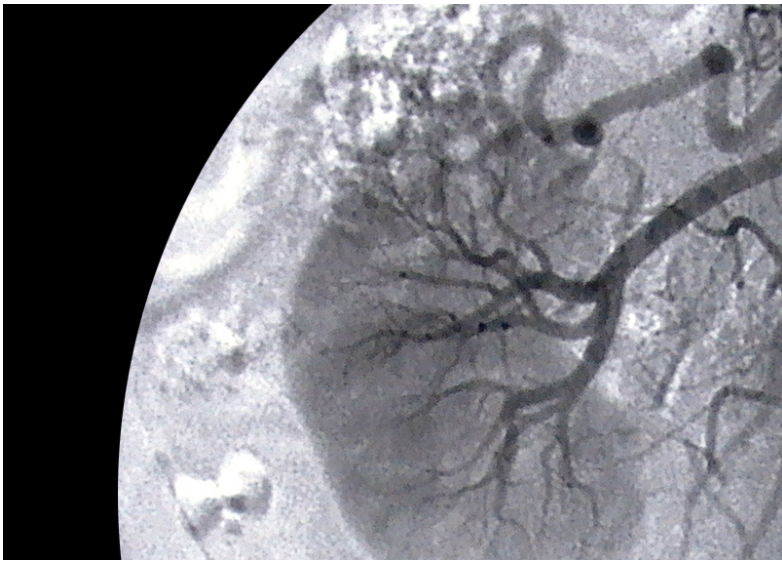
The current study entitled: *Understanding rare adverse outcomes following living kidney donation*, aimed to evaluate the risk of developing ESRD in donors versus healthy non-donors. The analysis involved close to 100,000 kidney donors, and found that 15 years after donation, the cumulative incidence of ESRD was 30.8 per 10,000 in donors against 3.9 per 10,000 in healthy non-donors. This does, however, represent a lower risk for live donors than seen in the general population: 326 per 10,000.

"This makes biological sense, of course, because kidney disease is a progressive, chronic deterioration of kidney function, so if you start with less, you'll get failure faster," Dr Dorry Segev, Associate Professor of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, explained. "However, this study reassures us that the risk of this happening in healthy, screened donors is extremely low."

Every year in the USA, nearly 6,000 healthy adults donate kidneys to help those in need. Though presenting minimal risk to these donors, the study does bring to light the necessity for discussions on informed consent.

The opinion of Dr Segev and colleagues is that: "It is imperative that the transplant community, in due diligence to donors, understands the risk of donation to the fullest extent possible, and communicates known risks to those considering donation."

However, Dr John S. Gill, Assistant Professor, University of British Columbia, Vancouver, Canada, states that: "It would be easy to misinterpret the findings of Muzaale et al. as suggesting that kidney donation is a risky procedure. In reality, the authors have shown that the absolute risk of ESRD among living donors is extremely low; this is their key finding and does not imply the need to alter existing clinical practice."



No stone left unturned in single operation to treat double nephrolithiasis

PIONEERING bilateral simultaneous ureteroscopy procedure allows surgeons to remove stones from both kidneys of nephrolithiasis sufferers at once, and sees patients sent home the same day.

Mr Bhaskar Somani, Consultant Urological Surgeon, Southampton General Hospital, Hampshire, UK, has been the lead in this new technique, which uses a ureteroscope to visualise and reposition kidney stones that are then destroyed by a laser. The technique is usually attempted separately on each kidney.

"Performing them separately means they have more hassle, more time off work and, logically, if both stones can be removed at the same time then why do it at different times and prolong discomfort for these patients," explained Mr Somani.

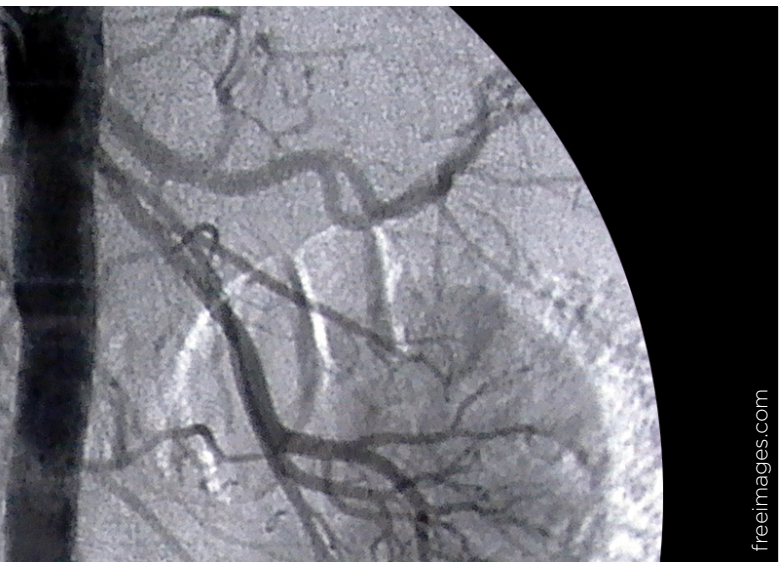
Kidney stones are deposits of salt which crystallise into solid masses that the body cannot easily rid itself of. They commonly affect men over 30 but are also seen less commonly in women (10-15% versus 2-7%). Though small stones may go undetected as they pass through the urine, larger stones can block the urethra leading to pain in the groin or abdomen, urinary tract infection, or sepsis.

Mr Somani noted: "In particular, for patients with urinary tract infections who have stones in both kidneys, it is sensible to try and clear everything at once as you can't be sure which side is causing the infection."

A related study has already seen the procedure achieve a colossal success rate of 92% in a trial of 22 patients with nephrolithiasis. Of these patients, over 75% were released from the hospital on the same day, while others experienced minimal complications.

Mr Somani added: "Many surgeons may be fearful of attempting both sides due to the risk and worry of causing trauma to the kidneys.

"But, with the right expertise, confidence, and experience, the benefits of a single procedure far outweigh the risks of performing more work in a single session."



"The benefits of a single procedure far outweigh the risks of performing more work in a single session."

Mr Bhaskar Somani,
Southampton General Hospital,
Southampton, UK

Acute kidney injury sufferers on dialysis face higher mortality rates

"Dialysis for AKI may cause more harm than good in the subgroup of people who are frail and have lower muscle mass, and more benefit than harm in more robust patients."

Dr F. Perry Wilson, University of Pennsylvania, Philadelphia, USA

NEGATIVE results were revealed in an assessment of the benefit of dialysis for acute kidney injury (AKI) sufferers.

There is an increasing prevalence of AKI (the unexpected, short-term loss of kidney function); this complication is estimated to arise in around 10% of critically ill hospital patients. However, an unfortunately high rate of mortality, 50-80%, accompanies figures of those who receive dialysis for its treatment.

The current data support a lack of robust evidence used to determine which patients would benefit from acute dialysis initiation.

In a comparison of nearly 600 AKI patient records, from those who received dialysis immediately following the incident and those who did not, Dr F. Perry Wilson, lead study author and Instructor of Medicine, Renal, Electrolyte, and Hypertension Division, University of Pennsylvania, Philadelphia, Pennsylvania, USA, and his team, found that AKI patients with lower levels of creatinine (<2.8 mg/dl) – a sign of reduced muscle mass and weakness - had increased mortality after dialysis (64% did not receive dialysis and died, versus 78% who received dialysis and died).

The initiation of dialysis is already known to be a multifactorial decision, ordinarily based on patient choice and the practitioner's analysis. However, it was of interest that males, people of black ethnicity, those who gave orders not to resuscitate, and those who were scheduled for dialysis on a Sunday, had negative associations with initiation of dialysis.

"Many clinicians feel that, although acute dialysis may not help a critically ill patient, it is unlikely to cause any harm. Through this study, we have been able to show for the first time among an equally matched group of patients that dialysis for AKI may cause more harm than good in the subgroup of people who are frail and have lower muscle mass, and more benefit than harm in more robust patients," said Dr Wilson.

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Nephrology

With its headquarters in Connecticut, USA, Alexion is a global company with more than 1,800 employees worldwide helping patients in nearly 50 countries. Since 1992, Alexion has developed from a biotech start-up into one of the world's largest biopharmaceutical companies. The company is focused on developing life-altering therapies for patients with extremely rare, severe, and life-threatening diseases. Alexion's first commercial product was Soliris (eculizumab); the only approved terminal complement inhibitor currently available worldwide. Soliris is approved in USA, EU, and Japan, among others, as a treatment for patients with atypical haemolytic ureamic syndrome.

As one of the largest companies on the global healthcare stage, Baxter aims to fuel the treatment of a range of complex medical conditions by assisting healthcare professionals and their patients. Baxter exhibits impressive knowledge in medical devices, pharmaceuticals, and biotechnology, creating medical products that help patients globally. Some of these include haemophilia, immune disorders, infectious diseases, kidney disease, trauma, and a range of other chronic and acute conditions. Baxter employs hundreds of scientists who focus heavily on recombinant and plasma-based therapeutics, vaccines, biosurgery, kidney dialysis, and parenteral nutrition.

Dedicated to unearthing and distributing game-changing therapies to patients with exceptional medical requirements, Genzyme has been fulfilling these targets for over 30 years to become one of the world's leading biotech companies, with more than 40 global locations serving patients in over 100 countries. The Boston-based firm was further boosted by the 2011 acquisition by global pharmaceutical giant Sanofi, adding clout to its reach and resources. Genzyme's main clinical investigative focus is on rare genetic diseases, including lysosomal storage disorders, and has pushed the boundaries into other disease areas such as thyroid cancer and multiple sclerosis.

Novartis has one outstanding mission: to discover, design, and deliver state-of-the-art healthcare to patients worldwide. Founded in 1996 and based in Basel, Switzerland, this world-leading pharmaceutical company has consistently produced medical breakthroughs, developing innovative products for patients and consumers. A host of ground-breaking pharmaceuticals, generics, vaccines, and consumer health products have provided pain relief and boosted patient quality of life since the company's inception. Operating in 140 countries, the seismic ambitions of Novartis have attracted a total of 135,000 associates, including top experts in research and development.

Vifor Pharma is a global pharmaceutical company that researches, develops, and markets its own brand of pharmaceutical products worldwide with a focus on iron replacement. Vifor has managed to generate sales from approximately 100 countries in 4 key franchises: iron, Vifor Fresenius Medical Care Renal Pharma Ltd., infectious diseases/OTX, and consumer healthcare. The company has always strived to make a positive impact on the lives of its customers by continuously building on its expertise in the fields of iron deficiency, infectious diseases, and consumer healthcare. The company has an increasing global presence, with manufacturing sites in Switzerland, the UK, and Portugal.

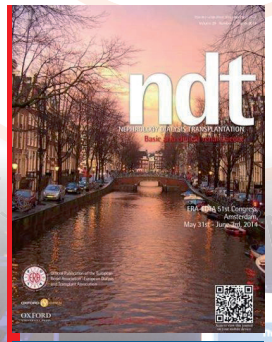
ERA-EDTA's Mission

Promoting Kidney Health and Increasing the Standard of Care

The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) is one of the fastest growing medical associations in Europe and - with nearly 7,000 members - one of the biggest nephrology associations worldwide. It supports basic and clinical research in the fields of clinical nephrology, dialysis, renal transplantation and related subjects. Many studies and research groups are funded by the ERA-EDTA and it stimulates research by awarding prizes and scholarships, some are for research achievements in nephrology, while others foster young talents. The association's journals, NDT (Nephrology, Dialysis, Transplantation) and CKJ (Clinical Kidney Journal), are currently the leading nephrology journals in Europe.

The ERA-EDTA also has an established Registry, a large epidemiologic database comparing countries by assessing nephrology practice throughout Europe, has been established. Besides, ERA-EDTA is member of the European Kidney Health Alliance (EKHA), a consortium of renal societies that actively interacts with the European Parliament.

ERA-EDTA's educational program is extremely comprehensive: there are several series of CME-courses, an electronic Journal (NDT-Educational) and the annual congress offers an attractive scientific programme that is attended by more than 8,000 delegates. Besides, the ERA-EDTA has established various Working Groups to promote the collaboration of nephrologists with other medical disciplines. Finally ERA-EDTA has an extensive program for young members including the YNP (Young Nephrologists' Platform) one of its most active committees.



www.era-edta.org

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- EMODIAL
- ERA-EDTA
- ERBP
- ETROPAL
- EUROCLINIC S.P.A
- EUROPEAN MEDICAL JOURNAL (EMJ)
- FARMASOL
- FRESENIUS KABI
- FRESENIUS MEDICAL CARE
- FRESENIUS MEDICAL CARE & FRESENIUS JOINT VENTURE VIFOR
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Nephrology

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World Transplant Congress (WTC) 2014

26th–31st July 2014

San Francisco, USA

The WTC Congress will provide a forum for the exchange of new scientific and clinical information relevant to solid organ and tissue transplantation. It will bring together transplant physicians, nurses, organ procurement personnel, and other transplant professionals. Attendees have the opportunity to learn about cutting-edge advances in research, and the exchange of ideas and practice in the field of solid organ and tissue transplantation.

Federation of American Societies for Experimental Biology (FASEB)-Polycystic Kidney Disease (PKD)

3rd-8th August 2014

Barga, Italy

This 'From Molecular Mechanism to Therapy' Conference will focus on recent advances in the understanding of the pathogenic mechanisms underlying the cystic renal diseases, and the development of therapies to slow down their progression. PKD research is presently one of the most exciting areas of renal research. It attracts a wide range of healthcare specialists, including basic scientists and clinical researchers who are at the forefront of PKD research.

15th Congress of the International Society of Peritoneal Dialysis (ISPD) 2014

7th-10th September 2014

Madrid, Spain

This Congress will be an opportunity to realise the changes in the field, and to envision new perspectives for basic and clinical research. The translational programme aims to draw experts from all over the world, and will encompass innovations in diagnosis, advances in clinical practice, novel therapeutic approaches, and new insights into cellular and animal models. It also aims to provide a strong networking opportunity for its attendees.

47th Annual Scientific Meeting of the European Society for Paediatric Nephrology (ESPN) 2014

18th-20th September 2014

Porto, Portugal

This annual meeting aims to provide a high quality and diverse programme, which will include the latest developments and ideas in basic science, transitional, and clinical science. These will be presented in the form of lectures, mini-lectures, symposia, and courses. There will also be industry-sponsored symposia. Topics to be covered include transplantation, chronic kidney disease, kidney injury, and nephrotic syndrome.

Primary Care: Nephrology Essentials and Case Studies - Mediterranean Cruise Conference

20th September–2nd October 2014

Barcelona, Spain

This event will aim to provide a clear understanding of the different stages of chronic kidney disease. Upon completion, participants should be able to enumerate the common disease entities that result in chronic disease, as well as recognise common complications of chronic kidney disease along with their pathophysiology and management. The programme is aimed at urologists, nephrologists, renal specialists, and internists.

American Society of Nephrology (ASN) Kidney Week 2014

11th–16th November 2014

Philadelphia, USA

This event will focus on late-breaking information relating to basic, translational, and clinical research discoveries in the field of nephrology. The scientific programme, aimed at practicing nephrologists and delivered by internationally recognised scientists, will include a wide range of clinical conferences, symposia, presentations, and state-of-the-art lectures. The event will also provide ample scientific networking.

Nephrologisches Jahresgespräch (Nephrology Annual Meeting) 2014

21st–23rd November 2014

Mannheim, Germany

This annual meeting will allow practicing nephrologists to exchange information concerning a variety of topics relating to kidney disease. The total spectrum of nephrology includes basic research on the causes of kidney disease, its prevention and treatment, the introduction of renal replacement therapy in end-stage renal disease, and kidney transplant. There will also be discussions on the latest policy developments to improve patient care.

International Society of Nephrology (ISN) World Congress of Nephrology 2015

13th–17th March 2015

Cape Town, South Africa

The scientific programme at this Congress will include topics addressing the practical, social, and economic challenges across the world. Key scientific themes to be discussed throughout the Congress include communicable (HIV, etc.), non-communicable (Hypertension, etc.) and other renal risk factors. Further material will cover acute kidney injury (AKI), translational and clinical nephrology, dialysis, and transplantation.