Welcome to the latest issue of Nephrology Research Review.

In this issue we report that the global burden of CKD is significant, rising, and unevenly distributed, and opportunities exist to reduce its burden at all levels of economic development. We also report a study of the long-term benefits of tolvaptan in patients with ADPKD, a retrospective cohort study of the value of dialysis in older adults with ESKD, and an observational study of hospitalisations and costs associated with conservative care in patients with advanced kidney failure. An analysis of the ERA-EDTA Registry examines the prevalence of ESKD secondary to scleroderma in Europe, data from a large health care system remind us that patients with both CKD and AF are at high cardiovascular risk, and a real-world study evaluates the safety and efficacy of direct oral anticoagulants for AF in patients with a range of renal function.

We hope you find these and the other selected studies interesting and look forward to any feedback you may have.

Kind Regards,

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Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016

Authors: Xie Y et al.

Summary: This analysis of data from the Global Burden of Disease study evaluated the change in global CKD burden from 1990 to 2016. Globally, the incidence of CKD increased by 89%, prevalence increased by 87%, death due to CKD increased by 98%, and disability-adjusted-life-years (DALYs) increased by 62%. Measures of burden varied markedly by level of development and geography. The increase in CKD DALYs was driven by population growth and aging. Age-standardised DALY rates decreased in most study regions, except in high-income North America, Central Latin America, Oceania, Southern Sub-Saharan Africa, and Central Asia, where the increased burden of CKD due to diabetes and to a lesser extent hypertension outpaced the burden expected by demographic expansion. 63% of the global CKD burden was in low and lower-middle-income countries. The age-standardised burden from 1990 to 2016 varied markedly by level of development and geography. The increase in CKD DALYs was driven by population growth and aging. Age-standardised DALY rates decreased in most study regions, except in high-income North America, Central Latin America, Oceania, Southern Sub-Saharan Africa, and Central Asia, where the increased burden of CKD due to diabetes and to a lesser extent hypertension outpaced the burden expected by demographic expansion. 63% of the global CKD burden was in low and lower-middle-income countries. The age-standardised CKD DALY rate was inversely associated with health care access and quality of care.

Comment: The Global Burden of Disease programme has been incredibly influential and important in helping us understand disease patterns across geographies and time, and the risk factors that can be addressed. It provides crucial information on individual conditions, but this is often difficult to extract from the vast volume of available data in the summary reports, and from the publicly available website. This paper concisely summarises the data the programme provides on the epidemiology of CKD, and the results are startling. The incidence of CKD has almost doubled in the last quarter century, as has the number of deaths due to CKD. It also highlights the burden of CKD in low- and middle-income countries, and the growing role of diabetes in driving this burden. These data are important tools we need to use for greater investment in the prevention and treatment of CKD.

Reference: Kidney Int 2018;94(3):567-81

Abstract

Long-term administration of tolvaptan in autosomal dominant polycystic kidney disease

Authors: Edwards M et al.

Summary: This study investigated the long-term use of tolvaptan in patients with ADPKD. Data for 97 patients with ADPKD who participated in the TEMPO and REPRISE clinical trials of tolvaptan were included. Patients treated with tolvaptan for ≥1 year (range 1.1–11.2 years; mean 4.6 years) had lower mean eGFR slopes from baseline (−2.20 ml/min/1.73m² per year) and from month 1 (−1.97 ml/min/1.73m² per year) compared with matched controls (−3.50 ml/min/1.73m² per year; p<0.001), and lower risk of a 33% reduction in eGFR (risk ratio, 0.63 from baseline and 0.53 from month 1). Annualised eGFR slopes of patients treated with tolvaptan did not change during follow-up.

Comment: Tolvaptan is the first treatment specifically developed for ADPKD, and has now been approved in many countries. This longer term analysis of participants in tolvaptan trials shows evidence of slowed loss of kidney function, including one-third reductions in kidney function. It also suggests that the magnitude of benefit might increase over time. More details on long-term outcomes associated with tolvaptan would be of great value.


Abstract
Survival among older adults with kidney failure is better in the first three years with chronic dialysis treatment than not

Authors: Tam-Tham H et al.

Summary: This retrospective Canadian cohort study compared survival in older adults with kidney failure who were treated vs not treated with chronic dialysis. Outcomes for 838 adults aged ≥65 years who had kidney failure in 2002–2012 were reviewed (mean age 79.1 years; 48.6% male; mean eGFR 7.8 ml/min/1.73m²). Dialysis treatment (vs no dialysis) was associated with a significantly lower risk of death in the first 3 years of follow-up (HR, 0.59), but not thereafter (HR, 1.22). However, dialysis was associated with a significantly higher risk of hospitalisation (HR, 1.40).

Comment: This interesting observational study using administrative data from Alberta, Canada addresses some of the key issues affecting observational comparisons by assessing outcomes for all older people with a documented eGFR that is sustained below 10 ml/min/1.73m². It shows that those who received dialysis were less likely to die but more likely to be hospitalised, although the differences in death were only present during the first 3 years. It supports the value of dialysis in this population, but remains subject to indication bias, in that those people who were treated with dialysis were likely to be healthier and more robust than those who were not. A randomised trial of dialysis vs optimal conservative care amongst the very elderly would appear important.

Reference: Kidney Int 2018;94(3):582-88

Association of inpatient palliative care with health care utilization and postdischarge outcomes among Medicare beneficiaries with end stage kidney disease

Authors: Chettiar A et al.

Summary: This study examined the impact of inpatient palliative care on health care utilisation and post-discharge outcomes in patients with ESKD. Medicare beneficiaries with ESKD who received inpatient palliative care in 2012–2013 were propensity score-matched to hospitalised patients who received usual care. Among the decedent cohort (n=1308), inpatient palliative care was associated with a 21% shorter length of stay and 14% lower hospitalisation costs compared with usual care. Among the nondecedent cohort (n=5024), inpatient palliative care was associated with no difference in length of stay and 11% higher hospitalisation costs compared with usual care. In the 30-day post-discharge period, patients who received inpatient palliative care had higher likelihood of hospice enrolment (HR, 8.3) and lower likelihood of rehospitalisation (HR, 0.8).

Comment: Conservative care for people with advanced kidney failure is now appropriately recognised as an important option that many people will choose if offered. There has been substantial investment in conservative care programmes around Australia and around the world, but these remain inconsistently supported by health services and funders. This analysis from the US might help, by demonstrating lower hospitalisation costs for individuals who died along with shorter hospital stays, as well as fewer readmissions for people who did not die. They add to the growing literature suggesting individual and community benefit related to wider access to formal supportive care programmes.


Characteristics and outcomes of patients with systemic sclerosis (scleroderma) requiring renal replacement therapy in Europe

Authors: Hruskova Z et al.

Summary: This analysis of the ERA-EDTA Registry examined the incidence and prevalence of ESKD secondary to systemic sclerosis (scleroderma) in Europe, and outcomes in these patients after initiation of renal replacement therapy (RRT). Data for 342 patients with scleroderma (0.14% of all RRT patients) were compared with 2 age- and sex-matched control groups without scleroderma (a group of diabetic ESKD patients and a group of non-diabetic ESKD patients). Between 2002 and 2013, the adjusted annual incidence and prevalence rates of RRT for ESKD due to scleroderma were 0.11–0.26 and 0.73–0.95 per million population, respectively. Recovery of independent kidney function was higher in the scleroderma group than in the diabetic controls and non-diabetic controls (7.6% vs 0.7% and 2.0%, respectively; both p<0.001), although time required to achieve recovery was longer. The 5-year survival probability from day 91 of dialysis among patients with scleroderma was 38.9%, whereas 5-year post-transplantation patient survival and 5-year allograft survival were 88.2% and 72.4%, respectively. Adjusted mortality from day 91 on dialysis was higher among patients with scleroderma vs controls, but patient and graft survival after kidney transplantation did not differ between groups.

Comment: Scleroderma is a rare cause of kidney failure, so good data regarding outcomes are also limited. This analysis from European registries shows the rarity of scleroderma-induced ESKD (<1 per million population) but also highlights that individuals with this cause of kidney failure appear more likely to recover kidney function than those with other causes. It also highlights the higher mortality of scleroderma-associated ESKD when treated with dialysis as compared to either diabetes or non-diabetic causes, but not when treated with transplantation.

Reference: Am J Kidney Dis 2018; published online Aug 16

Cause-specific mortality in patients with chronic kidney disease and atrial fibrillation

Authors: Airy M et al.

Summary: This study examined the association between AF and cause-specific mortality in a large CKD population. 62,459 patients with eGFR 15–59 ml/min/1.73m² (6,639 patients with AF and 55,820 without AF) were included from a large health care system. Adjusted mortality from day 91 on dialysis as compared to either diabetes or non-diabetic causes, but not when treated with transplantation.

Comment: The risk of AF increases progressively with declining kidney function, and is extremely high in people with ESKD. These people are also at very high risk of thrombotic and bleeding complications. Understanding the balance of these risks is therefore potentially important in considering the likelihood that proven treatments like anticoagulation might have net benefit rather than harm. This analysis of a large health system dataset highlights the fact that vascular causes appear to predominate as causes of excess death in CKD patients with AF; and that this is consistently true across different levels of kidney function. Cardiovascular protective therapies such as anticoagulation should therefore be a priority for future research in CKD.

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**References:**

1. Soliris® (eculizumab **rmc**) Approved Product Information (9 July 2018).
Risks and benefits of direct oral anticoagulants across the spectrum of GFR among incident and prevalent patients with atrial fibrillation

Authors: Shin J et al.

Summary: This real-world observational study evaluated the safety and effectiveness of direct oral anticoagulants across the range of renal function. The propensity score-matched cohort comprised patients with AF taking direct oral anticoagulants (n=3206) or warfarin (n=3206). Mean age of the participants was 72 years, 47% were women, and average eGFR was 69 ml/min/1.73m². 1191 bleeding events and 466 ischaemic strokes were reported during 7391 person-years of follow-up. Compared with warfarin use, the hazard ratios of bleeding associated with direct oral anticoagulant use were 1.01 and 1.23 for patients with eGFR >60 and <60 ml/min/1.73m², respectively. There were no between-group differences in the risk of ischaemic stroke.

Comment: This observational analysis assessed risks of bleeding and ischaemic stroke in people with AF treated with either direct oral anticoagulants or warfarin. It found an increased risk of bleeding with the direct oral anticoagulants in CKD compared to warfarin, but similar stroke risks. The results should be treated with caution as they run counter to the results of subgroup analyses of large randomised trials, and are prone to residual confounding due to their observational nature. But they do again highlight the importance of further randomised trials specifically addressing treatment strategies for AF in people with CKD.

Reference: Am J Nephrol 2018;48(1):4-14

Abstract

Drug coated balloon angioplasty in failing AV fistulas

Authors: Teterola S et al., for the Lutonix AV Clinical Trial Investigators

Summary: This multicentre study compared drug-coated balloon angioplasty with conventional angioplasty for the treatment of dysfunctional AV fistulas. 285 patients with dysfunctional AV fistulas at 23 centres were included. After successful angioplasty of the lesion responsible for access dysfunction, lesions were treated with either a paclitaxel-coated balloon or an uncoated control balloon of similar design. After 180 days, target lesion primary patency did not differ significantly between groups (71% for the drug-coated balloon and 63% for the control balloon; p=0.06), but fewer interventions were needed to maintain target lesion patency in the drug-coated balloon group (0.31 vs 0.44 per patient; p=0.03). Safety outcomes did not differ significantly between groups.

Comment: Drug-coated stents are now widely used in coronary angioplasty as they have been demonstrated to achieve superior outcomes to standard stents. Small trials had raised the possibility of similarly better outcomes for stents used for fistula angioplasty, however this moderately-sized trial did not show clear benefit for the primary outcome, although the results might suggest the trial was underpowered and a smaller than expected difference might still be possible.


Abstract

ABO-incompatible kidney transplant outcomes

Authors: de Weerd A & Betjes M

Summary: This meta-analysis evaluated outcomes after ABO blood group-incompatible kidney transplantation. A search of Embase, Medline, Cochrane, Web-of-Science, and Google Scholar identified 26 observational studies of ABO-incompatible kidney transplantation (1346 ABO-incompatible patients and 4943 ABO-compatible controls) that were suitable for inclusion. Meta-analysis of the data showed that 1-year uncensored graft survival was 96% in patients who were ABO-incompatible and 98% in ABO-compatible controls (relative risk [RR], 0.97; p<0.001). 49% of reported causes of death in patients who were ABO-incompatible were of infectious origin, compared with only 13% in patients who were ABO-compatible (p=0.02). Antibody-mediated rejection (RR, 3.86), severe non-viral infection (RR, 1.44), and bleeding (RR, 1.92) were also more common after ABO-incompatible transplantation.

Comment: This paper nicely reviews the available literature on ABO-incompatible renal transplant case reports and series, including over 1300 patients. While not quite as good as matched controls, the outcomes look very good overall (albeit perhaps overestimated due to reporting and publishing biases) but highlight the main challenges being the risk of infection and rejection. They suggest better immunosuppression approaches should remain a key focus.


Abstract

Gender and racial disparities in initial haemodialysis access and outcomes in incident end-stage renal disease patients

Authors: Shah S et al.

Summary: This US study examined gender and racial disparities in haemodialysis access and outcomes in patients with ESKD. 885,699 patients with ESKD who initiated haemodialysis in 2004-2014 were identified using the US Renal Data System (USRDS). Analysis of the data showed that females were less likely than males to use AV access for haemodialysis initiation (OR, 0.83). Compared with whites, the adjusted odds of AV access for haemodialysis initiation were higher in blacks (OR, 1.08) and Asians (OR, 1.11), and lower in Hispanics (OR, 0.89). There were no significant differences in mortality between males and females. Compared with whites, 1-year adjusted mortality was lower in Asians (OR, 0.55), blacks (OR, 0.67), Hispanics (OR, 0.62), and Native Americans (OR, 0.62).

Comment: This analysis is timely given that the theme of World Kidney Day in 2018 was “Kidneys and Women’s Health” – indeed there have been too few analyses highlighting some of the differences in risks, treatments and outcomes for women compared to men in kidney disease. This large analysis from the USRDS found that women were less likely to use AV access when initiating haemodialysis than men, and that Hispanics were less likely to use an AV access than whites, Asians or blacks. Mortality rates were similar across genders but the risk of death was higher in white Americans than Asians, blacks, Hispanics or Native Americans. It is not clear whether these differences reflect different characteristics of care, some sort of selection bias, or differences in treatment and outcome, but this is an area that urgently requires further exploration.

Reference: Am J Nephrol 2018;48(1):4-14

Abstract