Kidney disease 1

Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure

Alberto Ortiz, Adrian Covic, Danilo Fliser, Denis Fouque, David Goldsmith, Mehmet Kanbay, Francesca Mallamaci, Ziad A Massy, Patrick Rossignol, Raymond Vanholder, Andrzej Wiecek, Carmine Zoccali, Gérard M London, for the Board of the EURECA-m Working Group of ERA-EDTA

Patients with chronic kidney failure—defined as a glomerular filtration rate persistently below 15 mL/min per 1·73 m²—have an unacceptably high mortality rate. In developing countries, mortality results primarily from an absence of access to renal replacement therapy. Additionally, cardiovascular and non-cardiovascular mortality are several times higher in patients on dialysis or post-renal transplantation than in the general population. Mortality of patients on renal replacement therapy is affected by a combination of socioeconomic factors, pre-existing medical disorders, renal replacement treatment modalities, and kidney failure itself. Characterisation of the key pathophysiological contributors to increased mortality and cardiorenal risk staging systems are needed for the rational design of clinical trials aimed at decreasing mortality. Policy changes to improve access to renal replacement therapy should be combined with research into low-cost renal replacement therapy and optimum clinical care, which should include multifaceted approaches simultaneously targeting several of the putative contributors to increased mortality.

Lancet 2014; 383: 1831–43

See **Editorial** page 1782

This is the first in a **Series** of two papers about kidney disease

Division of Nephrology, IIS-Fundacion Jimenez Diaz, Madrid, Spain (Prof A Ortiz MD); **Department of Medicine, Universidad Autonoma de Madrid, Madrid, Spain** (Prof A Ortiz); **Red de Investigacion Renal (REDINREN), Madrid, Spain** (Prof A Ortiz); **Instituto Reina Sofia de Investigaciones Nefrológicas (IRSIN), Madrid, Spain** (Prof A Ortiz); **PaArhon University Hospital, "Grigore T Popa" University of Medicine and Pharmacy, Iasi, Romania** (A Covic MD); **Clinic for Renal and Hypertensive Disease, Saarland University Medical Centre, Homburg/Saar, Germany** (D Fliser MD); **Department of Nephrology, Nutrition, and Dialysis, Centre Hospitalier Lyon Sud, Carmen-CENS, Université de Lyon, Lyon, France** (D Fouque MD); **Renal and Transplantation Department, Guy's and St Thomas' Hospitals, London, UK** (Prof D Goldsmith FRCP); **Department of Nephrology, Istanbul Medeniyet University School of Medicine, Istanbul, Turkey** (M Kanbay MD); **Nephrology, Hypertension, and Renal Transplantation Unit, Ospedali Riuniti and CNR-IFC "Clinical Epidemiology and Pathophysiology of Renal Diseases and Hypertension", Reggio Calabria, Italy** (F Mallamaci MD, C Zoccali MD); **Division of Nephrology, Ambroise Paré Hospital, Paris Ile de France Ouest University (UVSQ), Paris, France** (Z A Massy MD); **INSERM U1088, Amiens, France** (Z A Massy); **INSERM, Centre d'Investigations Cliniques-1433 and INSERM U1116, Nancy, France** (P Rossignol MD); **Centre**

Scope of the problem

Chronic kidney failure is defined as a glomerular filtration rate (GFR) persistently below 15 mL/min per 1·73 m² and represents the end stage of chronic kidney disease.[1] Renal replacement therapy (RRT), achieved by haemodialysis, haemodiafiltration, peritoneal dialysis, or kidney transplantation, can be lifesaving. However, mortality rates in patients on RRT are high, and in developing countries RRT is initiated in less than 25% of patients with chronic kidney failure.[2] In this review, we discuss the extent and causes of chronic kidney failure and actions to improve outcomes.

Epidemiology

At age 40 years, the lifetime risk of chronic kidney failure is one in 50.[3] Each year about 440 000 patients worldwide start RRT, but 3 200 000 have no access to RRT and die prematurely (figure 1, appendix).[1] Detailed mortality data are available only from registries in developed countries. Therefore, these data might not be representative of worldwide reality. Furthermore, information about patients with chronic kidney failure who do not receive RRT is scarce. The Global Burden of Disease 2010 study[6] identified chronic kidney failure as one of the three causes of death with the greatest increase from 1990 to 2010. In some developing regions, such as Central (Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, and Venezuela) and Andean (Bolivia, Ecuador, and Peru) Latin America, chronic kidney failure is the fifth most common cause of death (appendix).[6]

Haemodialysis is the most frequent form of RRT. Mortality is highest during the first 3 months of haemodialysis (27·5 deaths per 100 person-years during the first 120 days *vs* 21·9 deaths per 100 person-years for days 121–365; p=0·002).[7] Thereafter, yearly mortality in dialysis remains around 5–27% in developed countries.[7] In patients aged 65–74 years—the most common age group in the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry[4]—life expectancy is only 5 years, which is 50% lower than in the same age group in the general population. Cardiovascular disease is the most frequent cause of death (figure 1). Cardiovascular mortality in patients on dialysis is 10–20 times higher than in the general population and seems to be more than 100 times higher in patients younger than 45 years (figure 2).[4] Figure 2 shows absolute and relative differences in mortality between the general population and the ERA-EDTA Registry. Younger patients on RRT had a higher relative risk of death than the general population, mainly from cardiovascular causes, which decreased with increasing age, although always remained several times above that of the general population. This increased risk was especially high in women. However, in view of the

Search strategy and selection criteria

We searched the Cochrane Library, Medline, Embase, and Database of Systematic Reviews (up to Nov 30, 2013). We used the search terms "mortality" or "survival" or "malnutrition" or "wasting" or "infection" or "cardiovascular" in combination with the terms "dialysis" or "end stage renal disease" or "chronic kidney disease" or "chronic kidney failure". We mostly selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles are cited to provide readers with more details and more references than there is room for in this Review. Additional publications were proposed by the authors.

d'Investigations Cliniques, CHU Nancy, Vandoeuvre lès Nancy, France (P Rossignol); Centre d'Investigations, Université de Lorraine, Vandoeuvre lès Nancy, France (P Rossignol); Association Lorraine pour le Traitement de l'Insuffisance Rénale, Vandoeuvre lès Nancy, France (P Rossignol); Nephrology Section, Department of Internal Medicine, University Hospital Ghent, Ghent, Belgium (R Vanholder MD); Department of Nephrology, Endocrinology, and Metabolic Diseases, Medical University of Silesia, Katowice, Poland (A Wiecek MD); and INSERM U970, Hopital Européen Georges Pompidou, Paris, France (G M London MD)

Correspondence to:
Prof Alberto Ortiz, IIS-Fundacion Jimenez Diaz, Av Reyes Catolicos 2, 28040 Madrid, Spain
aortiz@fjd.es

See Online for appendix

low baseline risk of death and the low number of young patients on RRT, the excess absolute number of deaths in young patients on RRT was not as high as in older patients. The greatest effect in terms of absolute number of excess deaths was from age 44 years and older and peaked in the 64–84 years age group. This finding is mainly the result of a combination of a high number of at-risk patients on RRT and a high relative risk of death, although in the 64–84 years age group the relative risk of death was much lower than in younger patients on RRT. There was a lower absolute number of excess deaths in those older than 84 years, which is misleading since the most probable cause is a low number of patients on RRT, which lowers the number of at-risk patients on RRT. Thus, the excess absolute risk of death in terms of death rate per 1000 patients was similar in those aged 75–84 years and above 84 years. The gap between 75–84 years and above 84 years in excess absolute number of RRT patient deaths can be regarded as an estimation of chronic kidney failure deaths because of limited RRT in developed countries. Aggregated non-cardiovascular deaths are even more frequent than cardiovascular deaths (appendix).[4] In relation to the general population, absolute excess mortality is greater for non-cardiovascular causes but relative excess is greater for cardiovascular deaths. Young women on RRT display the most dramatic increment in relative risk of all-cause death.

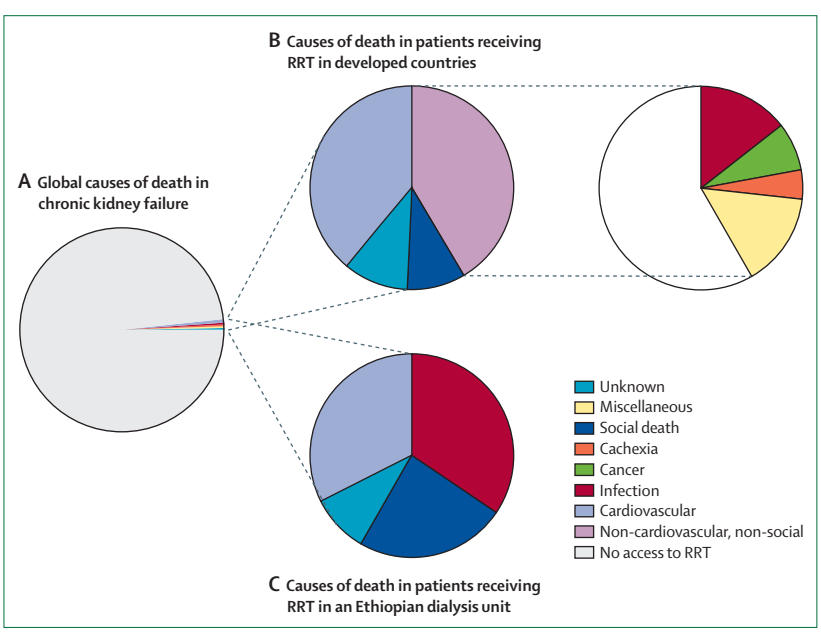

Figure 1: **Causes of death in chronic kidney failure**
(A) Global causes of mortality in chronic kidney failure.[2] (B) Causes of death in the ERA-EDTA Registry.[4] Social death includes withdrawal of dialysis, refusal of care, and suicide. (C) Causes of death in an Ethiopian dialysis centre.[5] Social death represents withdrawal of dialysis. Non-cardiovascular, non-social causes were represented exclusively by infection. Cardiovascular causes might be secondary to underdialysis. Widely cited registries from developed countries might not be fully representative of situations around the world, especially of the situation in developing countries where registry data are not available. The figure does not intend to compare registry data with single-centre data. There is a wide spectrum of economic development and RRT availability in different developing countries and the figure is not representative of all developing countries. Availability of RRT registries is in itself a sign of economic development, and data from developing countries registries might not represent the reality in other developing countries where registry data are not available. ERA-EDTA=European Renal Association–European Dialysis and Transplant Association. RRT=renal replacement therapy.

Cardiovascular death encompasses several causes with divergent pathogenic mechanisms from atherosclerosis to heart failure and sudden death. Sudden cardiac death accounts for up to 25% of haemodialysis deaths and occurs most often towards the end of the long inter-haemodialysis interval and in the 12 h immediately after haemodialysis.[8] Standardised mortality rates from pulmonary embolism, myocardial infarction, and stroke or other cardiovascular diseases were 12, 11, and eight times higher, respectively, in patients on dialysis than in the general population.[9] However, in developing countries so-called cardiovascular death can represent pulmonary oedema secondary to stopping dialysis for economic reasons.[10]

Infection is the second most common cause of death in chronic kidney failure. Mortality from septicaemia or lung infections is 50 and 15 times higher, respectively, in patients on dialysis than in the general population.[11] Also, cancer incidence in patients on dialysis is increased by 10–80% compared with the general population for about ten cancer locations, and cancer incidence is over three times higher in 20 locations in patients who have received a kidney transplantation.[12,13] Death as a result of withdrawal from dialysis is more common in the elderly, whereas refusal of care or suicide are more frequent in younger patients.[4]

Mortality on RRT is highest in the USA, lowest in Japan, and intermediate in Europe and Canada (appendix).[14,15] Per-head gross domestic product and mortality in the general population are associated with these geographical differences.[14,15] Factors associated with high mortality, such as greater use of haemodialysis catheters and shorter haemodialysis sessions or physician–patient contact times, are more prevalent in the USA than in other developed countries.[16,17] In developing countries, mortality is higher and its causes differ from those in developed countries. In an Ethiopian centre, 1-year mortality on dialysis was 58%.[5] The most frequent cause of death was septicaemia (34%), and uraemia accounted for 24% of deaths.[5] 1-year mortality in patients with catheters was 96%;[5] catheter prevalence might be as high as 92%.[18]

Despite an increase in age and comorbidities in the RRT population, mortality in patients on RRT has decreased in recent years over all age strata, although more slowly than in the general population (appendix).[19–21] Transplantation offers the lowest mortality rates, around 1·5–7% per year,[22] and is cost effective. However, access is restricted worldwide. In 2004, 23% of the world RRT population had a functioning kidney graft, ranging from 5–7% in Japan and Africa to 31% in Europe and North America.[23] Patients who have received a kidney transplant represent over 50% of the RRT population in only a few European countries.[22]

Potential pathophysiological contributors

Several factors contribute to the high risk of death in chronic kidney failure (figure 3). Common risk factors for

chronic kidney failure and mortality include diabetes, hypertension, overweight, atherosclerosis, lipid disorders, smoking, and possibly salt and phosphate intake.

Kidney failure results in accumulation of damaging molecules (uraemic toxins), volume overload, electrolyte abnormalities, metabolic acidosis, and neurohumoral and metabolic abnormalities that progress as renal function declines. Uraemic toxins, including trimethylamine-N-oxide, have been linked to cardiovascular risk in the general population,[24,25] whereas phosphate accumulation is thought to be a key driver of chronic kidney disease mineral bone disorder.[26] As discussed later, present dialysis techniques cannot replace all the different physiological functions of the kidney, and in those in whom they do offer some functional improvement, it is incomplete.

Dialysis-related factors, such as the use of central venous catheters for haemodialysis, increase the risk of death from infection and cardiovascular causes.[27] Transplantation-related factors, such as the use of immunosuppressive drugs, increase the risk of infection and cancer and impair the cardiovascular risk profile.[28]

These risk factors contribute to processes precipitating death. Chronic kidney disease results in accelerated ageing, particularly of the cardiovascular system.[29]

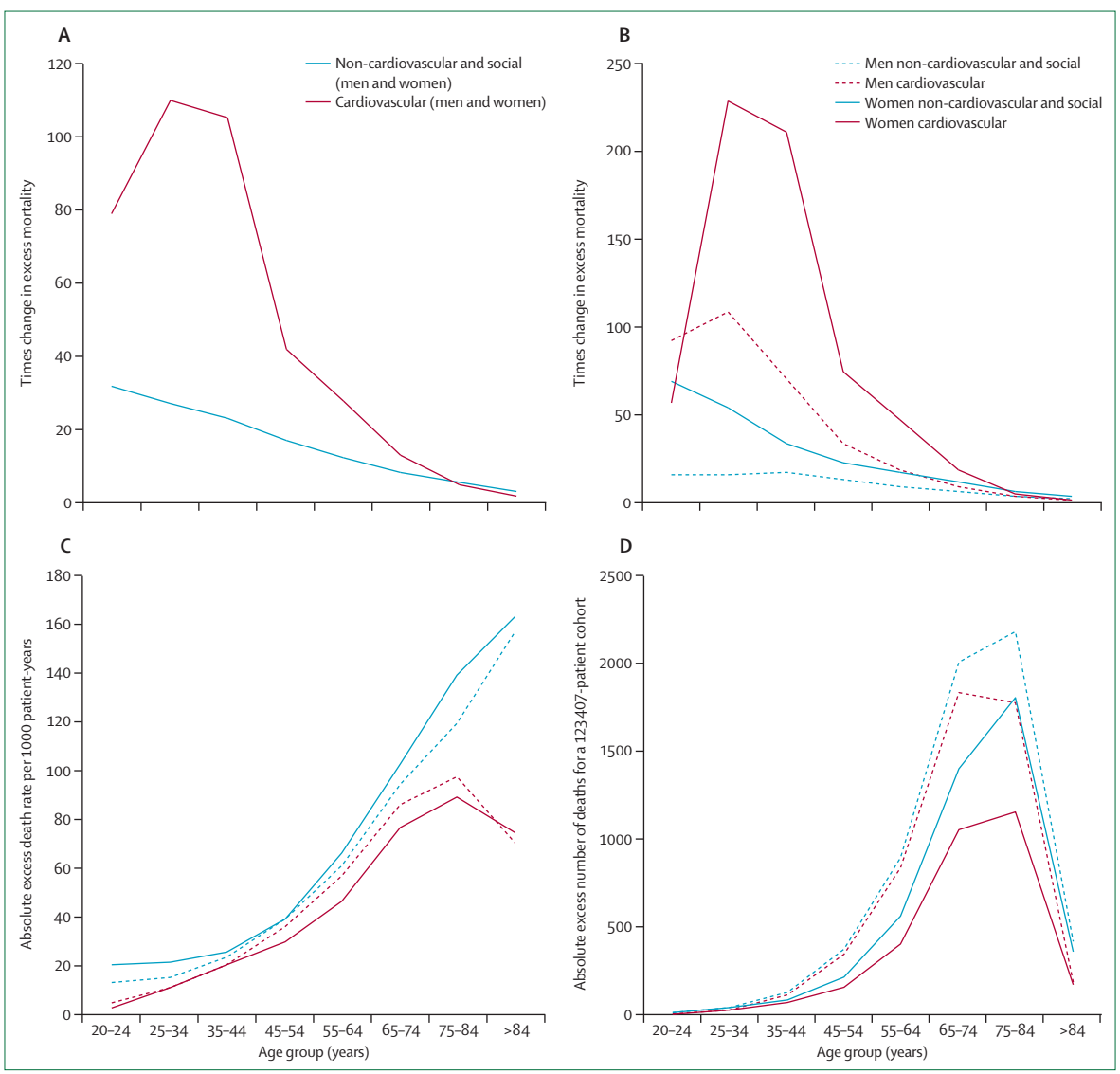

Figure 2: **Four different points of view on age-specific and sex-specific absolute and relative differences in mortality between the general population and the European Renal Association–European Dialysis and Transplant Association Registry**

Relative excess mortality of patients on RRT versus the general population per age group and stratified by cause of death: (A) overall and (B) by sex. (C) Sex-based absolute excess death rate per 1000 patient-years in patients on RRT versus the general population per age group and stratified by cause of death. (D) Sex-based absolute excess number of deaths calculated for the cohort of 123 407 patients on RRT reported by de Jager and colleagues. The number of individuals at risk in each age group of patients on RRT was multiplied by the death rate in person-years of that age group and stratified by cause of death. Figures created from data in de Jager and colleagues.[4] RRT=renal replacement therapy.

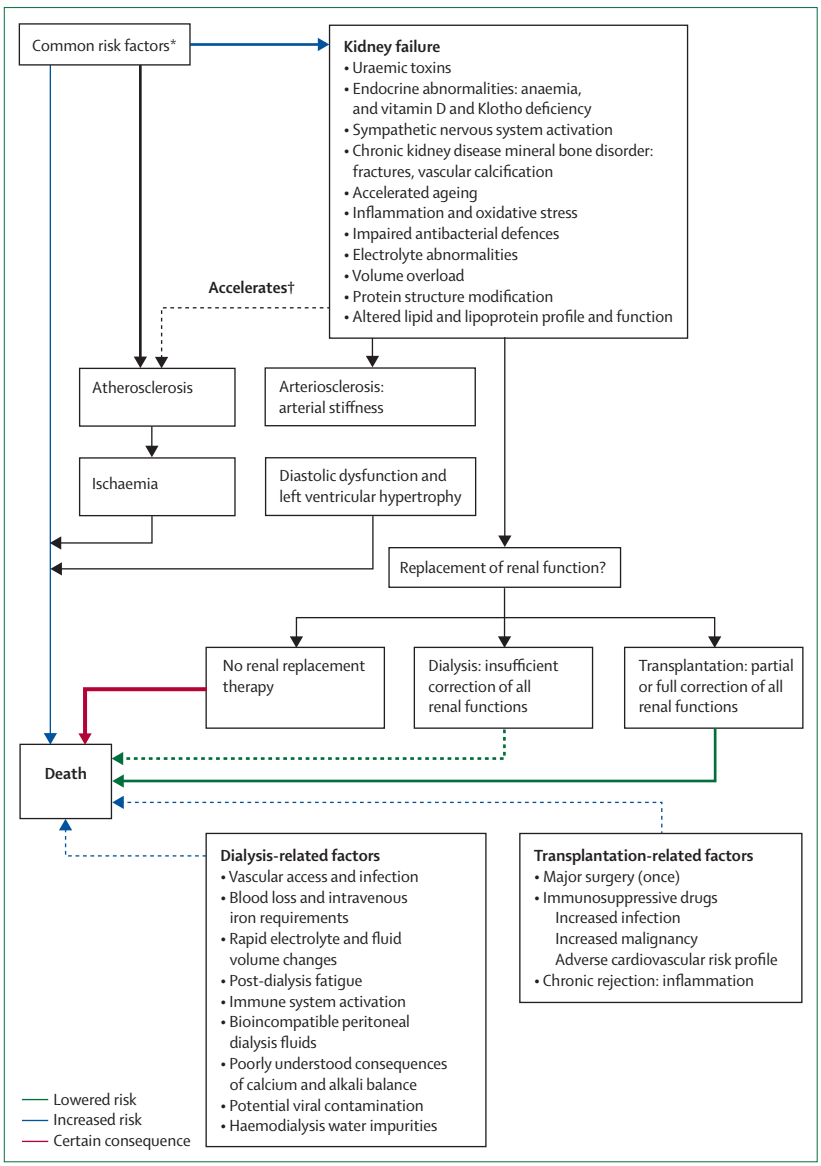

Figure 3: **Pathophysiological links between potential contributors to mortality in chronic kidney failure**
Coloured lines represent a direct effect on mortality. Line thickness shows the magnitude of effect. Dotted lines show a lesser effect than solid lines. *Diabetes, hypertension, overweight, atherosclerosis, lipid disorders, smoking, and possibly salt and phosphate intake. †The consequences of kidney failure accelerate atherosclerosis, which itself is not a direct consequence of kidney failure.

Klotho is a multifunctional protein and hormone expressed by the kidney that has phosphaturic and anti-ageing properties.[30] Klotho deficiency in chronic kidney disease is in part related to systemic and renal inflammation.[31,32]

Both atherosclerosis and arteriosclerosis contribute to cardiovascular mortality.[33] Premature arterial ageing, calcification, and stiffening are characteristic of arteriosclerosis in chronic kidney failure.[34] Aortic stiffness results in high aortic pressure and left ventricular afterload, decreased coronary perfusion, and microvascular rarefaction. Left ventricular hypertrophy and progressive cardiosclerosis are faciliatated by high left ventricular afterload and increased left ventricular preload (overhydration, arteriovenous fistulas, and anaemia), which promotes a cardiomyopathy of overload associated with systolic or diastolic left ventricular dysfunction, or both; heart failure; arrhythmias; and sudden death. Atherosclerosis is primarily a disease of the intima. Although not a specific consequence of chronic kidney failure, it is strongly aggravated by chronic kidney disease.[35]

Chronic kidney disease mineral bone disorder is often complicated by fractures or vascular arterial calcification. Negative mineral bone balance and accumulating mineral content in arteries (ie, vascular calcification) are closely and reciprocally related.[36] Cardiovascular calcification involves cellular and mineral processes, resulting from an imbalance between inducers (eg, phosphate, inflammation, and uraemic toxins) and inhibitors (eg, carboxylated matrix Gla protein, calcium sensing receptor, and pyrophosphate).[37] Although various stimuli promote dedifferentiation of vascular smooth muscle cells into osteoblast-like or chondroblast-like cells and vascular calcification in vitro,[37] such a mechanism is uncertain in vivo. Small calciparticles—extracellular particles composed of Fetuin-A, calcium, and phosphate—are possible contributors. Active vitamin D deficiency seems to affect immunity, inflammation, and vascular risk.[38] Additionally, risk factors such as coronary artery disease and heart failure, left ventricular hypertrophy, electrolyte shifts, and vascular calcification might be important contributors to sudden death.[8,37]

Sympathetic nerve activity, which contributes to hypertension and cardiovascular events, is markedly increased in chronic kidney failure due to activation of central sympathetic tone by diseased kidneys.[39,40] Nocturnal hypoxaemia due to sleep apnoea triggers sympathetic overactivity and is an independent predictor of cardiovascular death in patients on dialysis.[41] Increased concentrations of asymmetric dimethylarginine, an inhibitor of nitric oxide synthase, are associated with increased all-cause death. Both asymmetric dimethylarginine and sympathetic activity are part of the same pathophysiological pathway, which leads to an increased risk of death.

The immune system is altered in chronic kidney failure. Innate immune activation leads to systemic inflammation whereas immune suppression predisposes to infection and cancer.[42] Inflammation is associated with protein energy wasting and increased mortality.[43] Left ventricular overload and excess sodium might be proinflammatory.[44] Furthermore, haemodialysis is now the most frequent cause of catheter-related bacteraemia in the USA, after new standards of care dramatically decreased catheter-related bacteraemia in intensive care units.[45] Mortality risk remains increased for years after pneumonia or septicaemia.[46,47]

Patients with chronic kidney failure are at high risk for protein energy wasting because of anorexia, inflammation, hypothalamic appetite sensor dysregulation, unpalatable diets, or fear of kidney disease progression.[48] Reaching chronic kidney failure in a malnourished state seems to contribute to the high early mortality in dialysis.[48]

Factors predisposing to cancer include acquired renal cysts, immunosuppressive drugs, viral infection, diabetes, and diagnostic ionising radiation.[49,50] Cancer or its treatment might also provoke chronic kidney disease.[51] Frailty, poverty, depression, and social inequality further compound the complexities inherent to this population.[52]

Staging of mortality risk

Large observational databases, including the United States Renal Data System, the ERA-EDTA Registry, and the Dialysis Outcomes and Practice Patterns Study, have identified many hypothesis-generating risk factors for mortality in RRT (appendix). Randomised controlled trials (RCTs) should test whether interventions for these risk factors decrease mortality. Some traditional risk factors display a reverse epidemiology pattern, in which patients at both extremes of a given parameter have the highest mortality (U or J curve), suggesting a paradoxical link between, for example, blood pressure, serum cholesterol, or serum phosphate and mortality.[53] This finding can be explained by the presence of patients with inflammation and malnutrition in the group with low-range parameters (low blood pressure, serum cholesterol, or serum phosphate), who might be sensitive to the increased short-term risk of death conferred by inflammation over a short follow-up (<5 years), but who would be sensitive to the cardiovascular risk related to the persistence over the years of the high range of these variables (high blood pressure, serum cholesterol, or serum phosphate). Although several new biomarkers have been associated with increased risk of death, their effect on outcomes when used for therapeutic decisions has been insufficiently tested.[54]

Clinical trials of mortality in chronic kidney failure

Several RCTs have addressed overall and cardiovascular mortality in chronic kidney failure. Interventions tested so far have mainly focused on drugs that might reduce the risk of atherosclerotic complications, for example, myocardial infarction and stroke. However, most cardiovascular deaths in chronic kidney failure are attributable to non-atherosclerotic complications, especially sudden death,[8] which has rarely been targeted. No trials have systematically targeted non-cardiovascular mortality.

Several RCTs that assessed the effect of different therapeutic approaches on mortality in patients receiving treatment for chronic kidney disease have reported negative outcomes in the past few decades (table). Limited statistical power, selection of healthier patients than the general population of patients with chronic kidney disease, better quality of care during trials than standard care, high dropout rates, inadequate selection of the outcome most likely to respond to the intervention, and competing risks for mortality are all possible explanations for these negative outcomes. Most importantly, single target interventions were preferentially selected over multitarget approaches for what is a systemic, complex disease.

In patients with renal disease, the outcome after lowering cholesterol depends on chronic kidney disease stage and treatment. Findings from a meta-analysis of 51099 patients showed a marked reduction in all-cause mortality for patients with chronic kidney disease treated with statins before starting dialysis, no effect in patients on dialysis, and uncertain effects after renal transplantation.[63] In large RCTs, treatment with statins or ezetimibe plus a statin in patients on haemodialysis had no effect on cardiovascular mortality or composite endpoints that included cardiovascular mortality.[67,68,81] The question arises whether (1) statins are no longer effective once chronic kidney failure develops; (2) the high contribution of sudden death to dialysis mortality is insensitive to statins; or (3) unknown confounding factors such as competing mortality risks are responsible.

The search for an optimum haemoglobin target has been marred by the constraints of trial design. Thus, although higher achieved haemoglobin concentrations were associated with lower mortality in observational and RCT cohorts,[69] aiming for a normal haemoglobin concentration (about 130 g/L) in RCTs was associated with an increased risk of hypertension (relative risk 1·67, 95% CI 1·31–2·12) and stroke (1·51, 1·03–2·21) compared with lower haemoglobin level targets (90–110 g/L); the differences in risks for mortality (relative risk 1·09, 95% CI 0·99–1·20) and serious cardiovascular events (1·15, 0·98–1·33) were not statistically significant.[57,69] In this regard, high epoetin doses are also associated with increased mortality, independent of targeted or achieved haemoglobin concentration.[58]

Regarding chronic kidney disease mineral and bone disorders, a meta-analysis[59] of 11 RCTs including more than 4000 patients with chronic kidney disease reported a 22% reduction in overall mortality (12% in patients on dialysis) when using non-calcium phosphate binders versus calcium-based ones. Findings from a major trial[72] and a Cochrane systematic review comprising over 7000 patients[60] did not provide evidence of an effect of cinacalcet, a calcium receptor agonist used to treat hyperparathyroidism, on all-cause or cardiovascular mortality in patients on dialysis.

Findings from a meta-analysis[61] of antioxidant treatment (ubidecarenone, acetylcysteine, recombinant superoxide dismutase, and vitamin E) in chronic kidney failure and chronic kidney disease did not show a significant effect on all-cause mortality. Some benefit might be present in patients on dialysis, but studies were small and generally suboptimum. A meta-analysis did not identify an effect of

	Primary endpoints	Population	Drug or intervention	Number	Follow-up (years)	Mortality result	Comment
Meta-analyses							
Agarwal and Sinha (2009)[55]	Cardiovascular events	Haemodialysis	Antihypertensive drugs	5 studies, 1202 patients	..	HR 0·69 (95% CI 0·56–0·84) using a fixed-effects model. HR 0·62 (95% CI 0·45–0·86) using a random-effects model	All-cause mortality reduced significantly when calculated by the fixed-effects model (RR 0·79, 95% CI 0·65–0·96) but not when estimated by the random-effects model (0·77, 0·56–1·04)
Palmer et al (2012)[56]	All-cause and cardiovascular mortality	Chronic kidney disease	Statins *vs* placebo	51 099	..	Reduced all-cause mortality and cardiovascular mortality in patients not receiving dialysis; no effect in dialysis	None
Palmer et al (2010)[57]	All-cause mortality	Chronic kidney disease	Haemoglobin target trials or trials of erythropoiesis-stimulating drug *vs* no treatment	10 452	..	No effect	Targeting higher haemoglobin levels in chronic kidney disease increased risks for stroke, hypertension, and vascular access thrombosis
Koulouridis et al (2013)[58]	All-cause and cardiovascular mortality	Chronic kidney disease	Erythropoiesis-stimulating drugs	12 956	..	High erythropoiesis-stimulating drug dose associated with increased mortality	None
Jamal et al (2013)[59]	All-cause mortality	Chronic kidney disease	Non-calcium *vs* calcium containing phosphate binders	4622	..	22% reduction in all-cause mortality	None
Palmer et al (2013)[60]	All-cause and cardiovascular mortality	Chronic kidney disease stage 3–5 and dialysis	Cinacalcet *vs* placebo	7446	..	No effect	Reduces the need for parathyroidectomy
Jun et al (2012)[61]	All-cause and cardiovascular mortality	Chronic kidney disease	Antioxidants *vs* placebo	1979	..	No effect	Some benefit might be present in patients on dialysis, but studies were small and generally of suboptimum quality
Pan et al (2012)[62]	All-cause mortality	Chronic kidney disease	Homocysteine-lowering treatment *vs* placebo	4836	..	No effect	None
Palmer et al (2013)[63]	All-cause and cardiovascular mortality	Chronic kidney disease	Antiplatelet treatment *vs* placebo	21 460	..	No effect	Reduced the risk of myocardial infarction, increased the risk of bleeding
Randomised controlled trials							
Cice et al (2010)[64]	(A) All-cause mortality and (B) cardiovascular death	Haemodialysis and chronic kidney disease	Telmisartan *vs* placebo	332	3	(A) RR 0·51 (95% CI 0·32–0·82; p=0·004); (B) RR 0·42 (95% CI 0·38–0·61; p<0·0001)	None
Zannad et al (2006)[65]	Combined fatal and non-fatal first major cardiovascular events (cardiovascular death, resuscitated death, non-fatal stroke, heart failure, myocardial infarction, or revascularisation)	Haemodialysis and left ventricular hypertrophy	Fosinopril *vs* placebo	397	2	No effect	Adjusted RR 0·79 (95% CI, 0·59–1·10; p=0·099) in per-protocol analysis (n=380)
Matsumoto et al (2014)[66]	Composite of cardiovascular or cerebrovascular death or hospital admission	Oligoanuric haemodialysis	Spironolactone *vs* usual care	309	3	0·40 (95% CI 0·20–0·81)	None
Wanner et al (2005)[67]	Cardiovascular mortality (composite of death from cardiac causes, non-fatal myocardial infarction, and stroke)	Haemodialysis and type 2 diabetes	Atorvastatin *vs* placebo	1255	4	No effect	None
Fellstrom et al (2009)[68]	Cardiovascular mortality (composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke)	Haemodialysis	Rosuvastatin *vs* placebo	2776	3·8	No effect	None
Besarab et al (1998)[69]	All-cause mortality	Haemodialysis	Haematocrit at 42% *vs* 30%	1233	14 months	No effect	Terminated because of safety concerns

(Table continues on next page)

	Primary endpoints	Population	Drug or intervention	Number	Follow-up (years)	Mortality result	Comment
(Continued from previous page)							
Di Iorio et al (2013)[70]	All-cause mortality, arrhythmia, cardiovascular mortality	Incident haemodialysis	Sevelamer *vs* calcium-based phosphate binders	466	28 months	Reduction in arrhythmia and all-cause and cardiovascular mortality	None
Suki et al (2007)[71]	All-cause and cause-specific mortality	Prevalent haemodialysis	Sevelamer *vs* calcium-based binders	2103	20 months	No effect	Lower mortality in patients aged >65 years who received sevelamer *vs* those who received calcium-based binders
Chertow et al (2012)[72]	All-cause mortality	Haemodialysis	Cinacalcet *vs* placebo	3883	64 months	No effect	None
Cheung et al (2003)[73]	All-cause mortality	Haemodialysis	Equilibrated Kt/V urea 1·45 high-flux dialyser	1846	..	No effect	None
Locatelli et al (2009)[74]	All-cause mortality	Haemodialysis	High-flux *vs* low-flux dialyser	738	3–7·5	No effect	Only small benefit in patients with albumin <40 g/L
Ok et al (2013)[75]	All-cause mortality	Haemodialysis	Postdilution online haemodiafiltration *vs* high-flux haemodialysis	782	Mean 22·7 months (SD 10·9)	No effect	Better cardiovascular and overall survival in online haemodiafiltration subgroup with substitution volume >17·4 L per session
Grooteman et al (2012)[76]	All-cause mortality	Haemodialysis	Postdilution online haemodiafiltration *vs* high-flux haemodialysis	714	3	No effect	None
Maduell et al (2013)[77]	All-cause and cardiovascular mortality	Haemodialysis	Postdilution online haemodiafiltration *vs* high-flux haemodialysis	906	3	Online haemodiafiltration 30% lower risk of all-cause mortality and 33% lower risk of cardiovascular mortality	No intention-to-treat analysis
Cano et al (2007)[78]	All-cause mortality	Haemodialysis	Intradialytic parenteral nutrition plus oral supplements *vs* oral supplements	186	2	No effect of intradialytic parenteral nutrition	Improved nutrition in both arms (both on oral nutrition)
Paniagua et al (2002)[79]	All-cause mortality	Peritoneal dialysis	Peritoneal creatinine clearance 60 L per week per 1·73 m^2 *vs* peritoneal exchange volume of 8 L per day	965	2	No effect	None
Cooper et al (2010)[80]	All-cause mortality	Chronic kidney failure initiating dialysis	Early (eGFR 10–14 mL/min per 1·73 m^2) *vs* late start (eGFR 5–7 mL/min per 1·73 m^2)	828	3·6	No effect	None

..=not applicable. eGFR=estimated glomerular filtration rate. HR=hazard ratio. RR=relative risk.

Table: **Summary of key randomised controlled trials and meta-analyses that assessed mortality in chronic kidney failure as a primary endpoint**

treatment of hyperhomocysteinaemia by administration of vitamins on all-cause mortality.[62] In a meta-analysis,[63] antiplatelet drugs had no effect on all-cause or cardiovascular mortality, but did reduce the risk of myocardial infarction while increasing the risk for major bleeding in patients with chronic kidney disease.

The dose of dialysis and the size of molecules removed represent old but still tempting targets for treatment of chronic kidney failure. Findings from the Hemodialysis (HEMO) study[73] did not show any difference of a higher compared with lower dialysis dose (equilibrated Kt/V_{urea} of 1·45 *vs* 1·05) on outcome in an intention-to-treat analysis. Similarly, there was no improvement in all-cause mortality when using high-flux dialysers, apart from in patients with hypoalbuminaemia.[74] Findings from two initial studies did not show any reduction of overall mortality by haemodiafiltration (a more efficient dialysis technique)[82] versus conventional haemodialysis.[75,76] In a third, open-label, trial,[77] all-cause mortality was 30% lower for high-exchange-volume haemodiafiltration compared with high-flux haemodialysis, although no intention-to-treat analysis was provided and patients who did not reach the preset exchange volumes were censored. Only benefits on surrogate or composite endpoints could be shown by RCTs that tested the effect of long and frequent dialysis[83] or long nocturnal dialysis[84] compared with conventional haemodialysis. The Lung Water by Ultra-Sound Guided Treatment (LUST) trial explores the effect on mortality of adjusting fluid status on the basis of lung water content in high-risk patients on haemodialysis.

For the **LUST trial** see http://www.era-edta.org/eureca-m/LUST_eureca-m.html

All-cause and cardiovascular death were reduced in patients on haemodialysis who had severe heart failure and reduced ejection fraction and who were treated with carvedilol and renin-angiotensin aldosterone system blockers (secondary endpoints)[85] or with the combination of an angiotensin-converting enzyme inhibitor with the angiotensin II receptor blocker telmisartan (coprimary endpoints).[64] The Fosinopril in Dialysis study[65] was a large trial of an antihypertensive drug in patients on haemodialysis with left ventricular hypertrophy but was underpowered and findings were not significant. However, findings from a meta-analysis[55] suggested that overall antihypertensive drugs seem to improve cardiovascular outcomes in haemodialysis. However, the optimum blood pressure target (and how best to represent the blood pressure burden) remains controversial. A promising target could be mineralocorticoid receptor inhibition.[86] In the open-label Dialysis Outcomes Heart Failure Aldactone Study (DOHAS),[66] spironolactone was compared with usual care in 309 oligoanuric patients assessed for 3 years, with a composite primary outcome of cardiovascular or cerebrovascular death or admission to hospital. The hazard ratio for spironolactone compared with usual care was 0·40 (95% CI 0·20–0·81). A larger double-blind RCT (ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial [ALCHEMIST]) is ongoing (NCT01848639).

Findings from a meta-analysis[45] showed that both topical and intraluminal antibiotics reduced the rate of bacteraemia in patients with haemodialysis catheters. However, no trials have assessed mortality after antibiotic prophylaxis or oral nutritional management in RRT. Addition of intradialytic parenteral nutrition to oral nutritional supplements did not decrease mortality in malnourished patients on haemodialysis.[78]

Lessons learned for early stages of chronic kidney disease and disease in the elderly

Chronic kidney disease has been generally recognised as a major cardiovascular risk factor, independent of the amount of kidney failure. The risk of death and cardiovascular risk are increased even in early stages.[87,88] Even in patients with minor kidney dysfunction—ie, stage 2 chronic kidney disease corresponding to an estimated GFR (eGFR) of 60–89 mL/min—cardiovascular outcome is worse than when the eGFR is normal. Advanced chronic kidney disease conveys an even higher risk for incident myocardial infarction than diabetes mellitus[88] and thus deserves appropriate treatment and public health attention. Both traditional and non-traditional cardiovascular risk factors occur in patients with chronic kidney disease.[89] The latter comprise a long list of uraemia-induced changes such as anaemia, inflammation, and disturbances of lipoprotein metabolism, resulting in pathophysiological mechanisms for cardiovascular disease, which differ from those in the general population.[90] This factor might explain, at least in part, why traditional strategies to improve cardiovascular outcome failed in chronic kidney disease, especially chronic kidney failure. Future research in chronic kidney disease should focus on changes of the cardiovascular system induced by even mild reduction of kidney function to improve our understanding of pathophysiology and provide new treatment options to reduce cardiovascular mortality.

eGFR decreases with ageing even in the absence of major confounding factors such as diabetes or hypertension. As a result, many of the apparently healthy elderly in developed countries are categorised as having mild chronic kidney disease. Whether this age-related decline of kidney function conveys an additional cardiovascular risk on top of that linked to age per se is unknown.

A call to action: how to decrease worldwide mortality due to chronic kidney failure

In addition to preventing progression to chronic kidney failure, key issues to be tackled to decrease mortality due to chronic kidney failure range from optimisation of care before progression to chronic kidney failure to improvement of access to RRT. Optimisation of care before chronic kidney failure can delay the development of chronic kidney failure and ensure that patients are in the best possible clinical condition when they reach chronic kidney failure, with improved nutrition, better controlled bone mineral metabolism, and milder cardiovascular disease. Thus, optimised care will control comorbidities and prepare patients for RRT initiation in a timely manner. Optimised care will avoid the need for central venous haemodialysis catheters, and, if possible, will allow pre-emptive kidney transplantation to be planned. All of these factors have been associated with improved outcomes. Optimisation of non-RRT care for chronic kidney failure might improve survival and quality of life for patients who do not have access to RRT or who are unwilling to receive RRT. Patient education and frequent physician contact are important. Correction of acidosis[91] or reduction of protein intake in patients with chronic kidney disease not on dialysis seems to improve uraemic manifestations and reduce the incidence of a composite of RRT and death.[92,93] Ketoacid-supplemented very-low-protein diets are well tolerated and their potential to prolong survival in the absence of RRT should be explored.

Optimisation of RRT

In the IDEAL (Initiating Dialysis Early and Late) trial,[80] there was no advantage of an early start (mean eGFR at start of dialysis 12·0 mL per min) of RRT in asymptomatic patients compared with a late start (mean eGFR at start of dialysis 9·8 mL per min). This study was characterised by a large number of patients randomly assigned to late start not reaching their target, because uremic symptoms necessitated an earlier start. Consequently, the start of

dialysis should be based on symptoms rather than the eGFR. Higher eGFR at that start of dialysis was associated with higher mortality risk, independent of nutritional status.[94] Together with prevention of chronic kidney failure, a later start of RRT might contribute to a decreased need for RRT.

Patients on dialysis remain uraemic. Haemodialysis and peritoneal dialysis provide a time-averaged creatinine clearance of around 10 mL/min. This is even lower in patients who receive haemodialysis once or twice weekly for economic reasons. The kinetics of urea are used to assess the dose of dialysis. However, increasing thresholds above standard targets do not benefit either patients with haemodialysis or those with peritoneal dialysis. Urea kinetics can be considered as a baseline parameter of dialysis adequacy, but many other aspects such as nutritional factors or residual renal function should be considered.[95,96] Defining additional parameters to assess dialysis dose might improve outcome.

The endocrine function of the kidneys is not substituted by dialysis. Thus, substitution of hormones, such as erythropoietin, which can be expensive and risky, and calcitriol, may be needed. Additional factors secreted by the kidneys, such as Klotho, are not yet sufficiently characterised and are not available for supplementation.

In healthy individuals, blood purification by normal kidneys is based on the function of glomeruli, which passively filter water-containing solute, and on active tubular transport. However, dialysis replaces only the function of the glomerulus. Therapeutic options that have functional similarities to tubules, such as adsorption or hybrid organs containing tubular cells (renal bio-replacement treatment), are experimental. Enhancement of tubular cell pump function might improve removal of renal excreted solutes and protect against the solute's cardiovascular effects.[97]

Successful kidney transplantation is cost effective, replaces all renal functions, and is associated with improved survival. Living donation has better outcomes than optimum dialysis[98] and, if pre-emptive, can avoid the need for dialysis. Transplantation should be promoted through educational campaigns, legislation changes that follow the opting-out model, and training of physicians. The recent differentiation of human pluripotent cells into ureteric-bud-committed renal progenitor-like cells might set the stage one day for kidney tissue engineering.[99]

RRT-linked complications are estimated to be the primary cause of death in 2% of patients on RRT.[100] Health-care-associated infection contributed to 10% of all deaths.[100] Additionally, dialysis-related bleeding, release of plastic material, blood contamination via dialysate, inappropriate calcium:phosphate balance, and over-correction of anaemia have been linked to morbidity and mortality. For peritoneal dialysis, the gradual failure of the peritoneal membrane is detrimental. Thus, RRT should be made safer, but such countermeasure interventions have rarely been assessed with hard endpoints in RCTs. In a recent RCT,[101] a glucose-sparing peritoneal dialysis regimen improved the metabolic profile in patients with diabetes, but was associated with increased mortality and serious adverse events (safety outcome) compared with a glucose-based regimen.

Medical treatment

Absence of differences on mortality in trials of drugs for treatment of chronic kidney disease or its consequences has been suggested to show that in patients on RRT the intervention comes too late. This finding led to a pessimistic attitude and insufficient interest by non-nephrologists in drug treatment to reduce mortality. In observational studies, drugs such as β blockers or diabetes treatment in patients with diabetes with glycated haemoglobin greater than 9% were underused,[102,103] despite observational evidence for a survival advantage of β blockers and avoidance of high glycated haemoglobin concentrations in chronic kidney failure (appendix). Additionally, research is needed on incompletely identified non-traditional factors that also affect outcomes, in part related to solutes retained by the failing kidneys.[104] Definition of their actions should lead to treatments that antagonise their effects.

Large trials with focus on factors underlying the high risk for sudden death and on non-cardiovascular mortality in chronic kidney failure are urgently needed. In view of the disappointing results of previous RCTs, their high costs, and the multifactorial pathophysiology of chronic kidney disease and its complications, future attempts should target several factors simultaneously. A way forward would be the implementation of randomised registry trials through structures such as the ERA-EDTA Registry.[105] Research is also needed into mechanisms, markers, and prevention of progression and complications of chronic kidney disease.

Improvement of access to RRT

The population of patients who need RRT largely exceeds available health-care resources. In countries in which health-care costs are not fully reimbursed to the patient, RRT costs can exhaust family reserves.[18] In developed countries, previous reimbursement policies have become untenable, resulting in drastic restrictions[106] or bundling of dialysis and drug costs, which increase the risks for patient selection.

In developing countries, limited resources, infra-structure, and adequately trained health-care personnel present severe challenges that are difficult to overcome.[18] Even if dialysis is locally available, subsequent trans-plantation is often not possible. Both technical and organisational aspects should be explored, including recycling of dialysis material. Supranational or non-governmental organisations should play a key part in facilitating physician training and supporting research into low-cost RRT. However, local governments have a key responsibility. Labour cost is low but hardware

expensive, resulting in an inverse ratio of cost of peritoneal dialysis over haemodialysis.[107] Here, efforts should focus on local production of hardware. Finding a balance between the high expenses for few with RRT versus the low cost for many with prevention, for example, of diabetes, hypertension, or malaria, which are frequent causes of chronic kidney failure in developing countries, will be difficult.[108] However, experience from developed countries suggests that even preventive action will not avoid the need to offer RRT to some of the population.

In developed countries, transplantation and home dialysis are most cost effective. However, home strategies are not widely used despite patient and physician preference. In most countries, living and cadaveric donor transplantation rates lag behind demand, and some patients die on the waiting list. The community at large might profit from a shift from benefit-driven renal medicine to patient-driven and society-driven incentives.[109]

Research on adequacy and technical improvement of RRT remains important, but should become more socioeconomically oriented by distribution of specific RRT types, including kidney transplantation, and by directing efforts to test and use less expensive solutions, thus directly tackling the real costs of RRT and how to

Panel: **Reduction of mortality in chronic kidney failure: actions needed and research needs**

Needed actions

1 National or international programmes for prevention of deterioration of chronic kidney disease to chronic kidney failure.
2 National or international programmes for a holistic approach to cardiovascular risk in patients with chronic kidney disease.
3 National or international education programmes for the general population and health-care personnel, covering prevention of chronic kidney disease and alternative treatments after chronic kidney failure (including transplantation). Developing nations are important targets because of the expected increase in incidence of chronic kidney failure and the low availibility of resources for treatment.
4 Legislative changes that encourage kidney transplantation.
5 Improved care before dialysis and logistics before transplantation.
6 Increase in the number of nephrologists and other necessary health-care personnel in developing countries.
7 Avoidance of negative attitudes about non-renal treatment for patients with chronic kidney failure.

Research needs

1 Definition of the optimum moment to start dialysis, especially in the elderly and people with failed transplants.
2 Definition and implementation of strategies to decrease early mortality after the start of dialysis.
3 Definition of optimum logistics for dialysis centres, including size, caseload, and patient–doctor contact times.
4 Characterisation of risk factors for sudden cardiac death and arrhythmia and exploration of corrective strategies.
5 Optimisation of vascular access management.[110]
6 Definition of the optimum medical and interventional management of each cardiovascular cause of death.
7 Optimisation of immunosuppressive regimens to reduce cardiovascular, infection, and cancer risk.
8 Low-cost treatments: investment in low-cost RRT techniques and exploration of the effect of infrequent dialysis.
9 Definition of the optimum dialysate composition regarding sodium, potassium, calcium, and bicarbonate.
10 Definition of the optimum glycated haemoglobin range in patients on RRT.
11 Identification of the causes and study of the effect of the lower than expected use of drugs to reduce cardiovascular risk and treat diabetes in patients on RRT.
12 Optimisation of the dialysis schedule to reduce the peak mortality rates on particular days of the week.
13 Optimisation of management of chronic kidney failure in elderly patients and role of different RRT modalities.
14 Investigation of the role of inflammation and other new biomarkers in patient risk staging and individualisation of treatment.
15 Optimisation of mode and timing of nutritional support to delay RRT and decrease mortality.
16 Optimisation of management of lipid abnormalities in chronic kidney failure.[111]
17 Optimisation of non-RRT care for chronic kidney failure.
18 Optimisation of management of different aspects of chronic kidney disease mineral bone disorder, including magnesium concentrations and the effect of warfarin.[112]
19 Optimisation of supplementation strategies for vitamin D and water soluble vitamins.
20 Optimisation of diuretic use.
21 Further refinement of dialysis dose assessment and effect on mortality.
22 Optimisation of patient education techniques.
23 Optimisation of the use of stimulation of erythropoiesis and target haemoglobin concentrations.[113]
24 Optimisation of the use of convective treatments, including haemodiafiltration, and long and frequent dialysis.
25 Exploration of adsorption as extracorporeal treatment.
26 Exploration of sex differences in risk and cause of death, sex-individualised treatment, and the role of testosterone supplementation.
27 Optimisation of use of implanted cardioverter-defibrillator devices.[8]
28 Optimisation of replacement of all renal functions: renal bioreplacement therapy.
29 Increase of the pool of transplantable kidneys: bioengineered kidneys.

RRT=renal replacement therapy.

decrease them. Education of the general population, doctors, and health-care planners remains vital. The panel summarises research needs and needed actions.

Only a combination of health-care policy changes, education, and research will reduce the high rates of mortality from chronic kidney failure. Chronic kidney disease is often not regarded as a key non-communicable disease.[114] The nephrology community should at all costs advocate the inclusion of chronic kidney failure in non-communicable chronic disease programmes.[115]

Contributors

All authors contributed to the design and concept; did the searches needed for their assigned sections; wrote a section; read, revised, and critiqued the successive versions; and approved the final manuscript. AO coordinated the Review and integrated the sections and comments.

Declaration of interests

AO has received honoraria from Fresenius, AbbVie, Sanofi, Shire, and Novartis. AC has received honoraria from Amgen, Fresenius, Sandoz, and Vifor. DFo has received honoraria from Abbott, Amgen, Astellas, Baxter, Fresenius Kabi, Keryx, Sanofi, and Shire. DG has received honoraria from AbbVie, Amgen, Astellas, Fresenius, Keryx, Sandoz, and Sanofi. FM has received honoraria from Shire and Amgen. ZAM has received honoraria from Sanofi, Fresenius, Vifor, Abbott, and Chigai; and research support from Fresenius, Baxter, Amgen, and Sanofi. PR has received honoraria from Baxter-Gambro, Fresenius, and Relypsa. RV has received research grants from Fresenius Medical Care (except for Fresenius Kabi), Baxter Healthcare, Gambro, Roche, and Amgen; and is President of the ERA-EDTA. AW has received honoraria from Abbott, Amgen, Roche, Teva, Fresenius, Boehringer Ingelheim, Affymax, and Vifor. CZ has received honoraria from AbbVie, Sanofi, Amgen, and Shire. GML has received honoraria from Amgen, Sandoz, and Sanofi. DFl and MK declare that they have no competing interests.

Acknowledgments

AO receives support from Programa Intensificacion (ISCII, Spanish Government), RETIC REDINREN 012/0021, and CYTED IBERERC.

References

1 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* 2013; **3** (suppl)**:** 1–150.

2 Anand S, Bitton A, Gaziano T. The gap between estimated incidence of end-stage renal disease and use of therapy. *PLoS One* 2013; **8:** e72860.

3 Turin TC, Tonelli M, Manns BJ, et al. Lifetime risk of ESRD. *J Am Soc Nephrol* 2012; **23:** 1569–78.

4 de Jager DJ, Grootendorst DC, Jager KJ, et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA* 2009; **302:** 1782–89.

5 Shibiru T, Gudina EK, Habte B, Derbew A, Agonafer T. Survival patterns of patients on maintenance hemodialysis for end stage renal disease in Ethiopia: summary of 91 cases. *BMC Nephrol* 2013; **14:** 127.

6 Institute for Health Metrics and Evaluation. GBD arrow diagram. http://www.healthmetricsandevaluation.org/gbd/visualizations/gbd-arrow-diagram (accessed July 30, 2013).

7 Bradbury BD, Fissell RB, Albert JM, et al. Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol* 2007; **2:** 89–99.

8 Green D, Roberts PR, New DI, Kalra PA. Sudden cardiac death in hemodialysis patients: an in-depth review. *Am J Kidney Dis* 2011; **57:** 921–29.

9 Ocak G, van Stralen KJ, Rosendaal FR, et al. Mortality due to pulmonary embolism, myocardial infarction, and stroke among incident dialysis patients. *J Thromb Haemost* 2012; **10:** 2484–93.

10 Eghan BA, Amoako-Atta K, Kankam CA, Nsiah-Asare A. Survival pattern of hemodialysis patients in Kumasi, Ghana: a summary of forty patients initiated on hemodialysis at a new hemodialysis unit. *Hemodial Int* 2009; **13:** 467–71.

11 Sarnak MJ, Jaber BL. Pulmonary infectious mortality among patients with end-stage renal disease. *Chest* 2001; **120:** 1883–87.

12 Maisonneuve P, Agodoa L, Gellert R, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. *Lancet* 1999; **354:** 93–99.

13 Stengel B. Chronic kidney disease and cancer: a troubling connection. *J Nephrol* 2010; **23:** 253–62.

14 Kramer A, Stel VS, Caskey FJ, et al. Exploring the association between macroeconomic indicators and dialysis mortality. *Clin J Am Soc Nephrol* 2012; **7:** 1655–63.

15 Yoshino M, Kuhlmann MK, Kotanko P, et al. International differences in dialysis mortality reflect background general population atherosclerotic cardiovascular mortality. *J Am Soc Nephrol* 2006; **17:** 3510–19.

16 Tentori F, Zhang J, Li Y, et al. Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2012; **27:** 4180–88.

17 Kawaguchi T, Karaboyas A, Robinson BM, et al. Associations of frequency and duration of patient-doctor contact in hemodialysis facilities with mortality. *J Am Soc Nephrol* 2013; **24:** 1493–502.

18 Swanepoel CR, Wearne N, Okpechi IG. Nephrology in Africa—not yet uhuru. *Nat Rev Nephrol* 2013; **9:** 610–22.

19 Mitsnefes MM, Laskin BL, Dahhou M, Zhang X, Foster BJ. Mortality risk among children initially treated with dialysis for end-stage kidney disease, 1990–2010. *JAMA* 2013; **309:** 1921–29.

20 Steenkamp R, Shaw C, Feest T. UK Renal Registry 15th annual report: chapter 5 survival and causes of death of UK adult patients on renal replacement therapy in 2011: national and centre-specific analyses. *Nephron Clin Pract* 2013; **123** (suppl 1)**:** 93–123.

21 Roberts MA, Polkinghorne KR, McDonald SP, Ierino FL. Secular trends in cardiovascular mortality rates of patients receiving dialysis compared with the general population. *Am J Kidney Dis* 2011; **58:** 64–72.

22 ERA-EDTA Registry. Annual report 2011. http://www.era-edta-reg.org/files/annualreports/pdf/AnnRep2011.pdf. (accessed April 2, 2014).

23 Grassmann A, Gioberge S, Moeller S, Brown G. ESRD patients in 2004: global overview of patient numbers, treatment modalities and associated trends. *Nephrol Dial Transplant* 2005; **20:** 2587–93.

24 Tang WH, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med* 2013; **368:** 1575–84.

25 Duranton F, Cohen G, De Smet R, et al. Normal and pathologic concentrations of uremic toxins. *J Am Soc Nephrol* 2012; **23:** 1258–70.

26 Gutierrez OM. Fibroblast growth factor 23 and disordered vitamin D metabolism in chronic kidney disease: updating the "trade-off" hypothesis. *Clin J Am Soc Nephrol* 2010; **5:** 1710–16.

27 Lok CE, Foley R. Vascular access morbidity and mortality: trends of the last decade. *Clin J Am Soc Nephrol* 2013; **8:** 1213–19.

28 Bottomley MJ, Harden PN. Update on the long-term complications of renal transplantation. *Br Med Bull* 2013; **106:** 117–34.

29 Stenvinkel P, Larsson TE. Chronic kidney disease: a clinical model of premature aging. *Am J Kidney Dis* 2013; **62:** 339–51.

30 Kurosu H, Yamamoto M, Clark JD, et al. Suppression of aging in mice by the hormone Klotho. *Science* 2005; **309:** 1829–33.

31 Hu MC, Shi M, Zhang J, et al. Klotho deficiency causes vascular calcification in chronic kidney disease. *J Am Soc Nephrol* 2011; **22:** 124–36.

32 Moreno JA, Izquierdo MC, Sanchez-Nino MD, et al. The inflammatory cytokines TWEAK and TNFalpha reduce renal Klotho expression through NFkappaB. *J Am Soc Nephrol* 2011; **22:** 1315–25.

33 London GM, Drueke TB. Atherosclerosis and arteriosclerosis in chronic renal failure. *Kidney Int* 1997; **51:** 1678–95.

34 Briet M, Pierre B, Laurent S, London GM. Arterial stiffness and pulse pressure in CKD and ESRD. *Kidney Int* 2012; **82:** 388–400.

35 Lindner A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 1974; **290:** 697–701.

36 London GM. Bone-vascular cross-talk. *J Nephrol* 2012; **25:** 619–25.

37 Massy ZA, Drueke TB. Vascular calcification. *Curr Opin Nephrol Hypertens* 2013; **22:** 405–12.

38 Rojas-Rivera J, De La Piedra C, Ramos A, Ortiz A, Egido J. The expanding spectrum of biological actions of vitamin D. *Nephrol Dial Transplant* 2010; **25:** 2850–65.

39 Converse RL Jr, Jacobsen TN, Toto RD, et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; **327:** 1912–18.

40 Zoccali C, Mallamaci F, Parlongo S, et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation* 2002; **105:** 1354–59.

41 Zoccali C, Mallamaci F, Tripepi G. Nocturnal hypoxemia predicts incident cardiovascular complications in dialysis patients. *J Am Soc Nephrol* 2002; **13:** 729–33.

42 Kato S, Chmielewski M, Honda H, et al. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008; **3:** 1526–33.

43 Zoccali C, Mallamaci F, Tripepi G. Inflammatory proteins as predictors of cardiovascular disease in patients with end-stage renal disease. *Nephrol Dial Transplant* 2004; **19** (suppl 5): V67–72.

44 Wu C, Yosef N, Thalhamer T, et al. Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. *Nature* 2013; **496:** 513–17.

45 James MT, Conley J, Tonelli M, Manns BJ, MacRae J, Hemmelgarn BR. Meta-analysis: antibiotics for prophylaxis against hemodialysis catheter-related infections. *Ann Intern Med* 2008; **148:** 596–605.

46 Slinin Y, Foley RN, Collins AJ. Clinical epidemiology of pneumonia in hemodialysis patients: the USRDS waves 1, 3, and 4 study. *Kidney Int* 2006; **70:** 1135–41.

47 Foley RN, Guo H, Snyder JJ, Gilbertson DT, Collins AJ. Septicemia in the United States dialysis population, 1991 to 1999. *J Am Soc Nephrol* 2004; **15:** 1038–45.

48 Ikizler TA, Cano NJ, Franch H, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int* 2013; **84:** 1096–107.

49 Shebl FM, Warren JL, Eggers PW, Engels EA. Cancer risk among elderly persons with end-stage renal disease: a population-based case-control study. *BMC Nephrol* 2012; **13:** 65.

50 De Mauri A, Brambilla M, Chiarinotti D, Matheoud R, Carriero A, De Leo M. Estimated radiation exposure from medical imaging in hemodialysis patients. *J Am Soc Nephrol* 2011; **22:** 571–78.

51 Salahudeen AK, Bonventre JV. Onconephrology: the latest frontier in the war against kidney disease. *J Am Soc Nephrol* 2013; **24:** 26–30.

52 Kurella TM, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS, McCulloch CE. Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med* 2009; **361:** 1539–47.

53 Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 2003; **63:** 793–808.

54 Ortiz A, Massy ZA, Fliser D, et al. Clinical usefulness of novel prognostic biomarkers in patients on hemodialysis. *Nat Rev Nephrol* 2012; **8:** 141–50.

55 Agarwal R, Sinha AD. Cardiovascular protection with antihypertensive drugs in dialysis patients: systematic review and meta-analysis. *Hypertension* 2009; **53:** 860–66.

56 Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012; **157:** 263–75.

57 Palmer SC, Navaneethan SD, Craig JC, et al. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. *Ann Intern Med* 2010; **153:** 23–33.

58 Koulouridis I, Alfayez M, Trikalinos TA, Balk EM, Jaber BL. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a metaregression analysis. *Am J Kidney Dis* 2013; **61:** 44–56.

59 Jamal SA, Vandermeer B, Raggi P, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. *Lancet* 2013; **382:** 1268–77.

60 Palmer SC, Nistor I, Craig JC, et al. Cinacalcet in patients with chronic kidney disease: a cumulative meta-analysis of randomized controlled trials. *PLoS Med* 2013; **10:** e1001436.

61 Jun M, Venkataraman V, Razavian M, et al. Antioxidants for chronic kidney disease. *Cochrane Database Syst Rev* 2012; **10:** CD008176.

62 Pan Y, Guo LL, Cai LL, et al. Homocysteine-lowering therapy does not lead to reduction in cardiovascular outcomes in chronic kidney disease patients: a meta-analysis of randomised, controlled trials. *Br J Nutr* 2012; **108:** 400–07.

63 Palmer SC, Di Micco L, Razavian M, et al. Antiplatelet agents for chronic kidney disease. *Cochrane Database Syst Rev* 2013; **2:** CD008834.

64 Cice G, Di Benedetto A, D'Isa S, et al. Effects of telmisartan added to angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure a double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2010; **56:** 1701–08.

65 Zannad F, Kessler M, Lehert P, et al. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. *Kidney Int* 2006; **70:** 1318–24.

66 Matsumoto Y, Mori Y, Kageyama S, et al. Spironolactone reduces cardio- and cerebrovascular morbidity and mortality in hemodialysis patients. *J Am Coll Cardiol* 2014; **63:** 528–36.

67 Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; **353:** 238–48.

68 Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009; **360:** 1395–407.

69 Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; **339:** 584–90.

70 Di Iorio B, Molony D, Bell C, et al. Sevelamer versus calcium carbonate in incident hemodialysis patients: results of an open-label 24-month randomized clinical trial. *Am J Kidney Dis* 2013; **62:** 771–78.

71 Suki WN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 2007; **72:** 1130–37.

72 Chertow GM, Block GA, Correa-Rotter R, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012; **367:** 2482–94.

73 Cheung AK, Levin NW, Greene T, et al. Effects of high-flux hemodialysis on clinical outcomes: results of the HEMO study. *J Am Soc Nephrol* 2003; **14:** 3251–63.

74 Locatelli F, Martin-Malo A, Hannedouche T, et al. Effect of membrane permeability on survival of hemodialysis patients. *J Am Soc Nephrol* 2009; **20:** 645–54.

75 Ok E, Asci G, Toz H, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. *Nephrol Dial Transplant* 2013; **28:** 192–202.

76 Grooteman MP, van den Dorpel MA, Bots ML, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *J Am Soc Nephrol* 2012; **23:** 1087–96.

77 Maduell F, Moreso F, Pons M, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol* 2013; **24:** 487–97.

78 Cano NJ, Fouque D, Roth H, et al. Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, randomized study. *J Am Soc Nephrol* 2007; **18:** 2583–91.

79 Paniagua R, Amato D, Vonesh E, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol* 2002; **13:** 1307–20.

80 Cooper BA, Branley P, Bulfone L, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010; **363:** 609–19.

81 Baigent C, Landray MJ, Reith 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:** 2181–92.

82 Blankestijn PJ, Ledebo I, Canaud B. Hemodiafiltration: clinical evidence and remaining questions. *Kidney Int* 2010; **77:** 581–87.

83 Chertow GM, Levin NW, Beck GJ, et al. In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 2010; **363:** 2287–300.

84 Culleton BF, Walsh M, Klarenbach SW, 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:** 1291–99.

85 Cice G, Ferrara L, D'Andrea A, et al. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol* 2003; **41:** 1438–44.

86 Pitt B, Rossignol P. Mineralocorticoid receptor antagonists in patients with end stage renal disease (ESRD) on chronic hemodialysis. *J Am Coll Cardiol* 2014; **63:** 537–38.

87 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351:** 1296–305.

88 Tonelli M, Muntner P, Lloyd A, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet* 2012; **380:** 807–14.

89 Shlipak MG, Fried LF, Cushman M, et al. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA* 2005; **293:** 1737–45.

90 Speer T, Rohrer L, Blyszczuk P, et al. Abnormal high-density lipoprotein induces endothelial dysfunction via activation of Toll-like receptor-2. *Immunity* 2013; **38:** 754–68.

91 Loniewski I, Wesson DE. Bicarbonate therapy for prevention of chronic kidney disease progression. *Kidney Int* 2014; **85:** 529–35.

92 Fouque D, Laville M. Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database Syst Rev* 2009; **3:** CD001892.

93 Fouque D, Pelletier S, Mafra D, Chauveau P. Nutrition and chronic kidney disease. *Kidney Int* 2011; **80:** 348–57.

94 Susantitaphong P, Altamimi S, Ashkar M, et al. GFR at initiation of dialysis and mortality in CKD: a meta-analysis. *Am J Kidney Dis* 2012; **59:** 829–40.

95 Eloot S, Van BW, Glorieux G, Neirynck N, Dhondt A, Vanholder R. Does the adequacy parameter kt/v_{urea} reflect uremic toxin concentrations in hemodialysis patients? *PLoS One* 2013; **8:** e76838.

96 Bargman JM, Thorpe KE, Churchill DN. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J Am Soc Nephrol* 2001; **12:** 2158–62.

97 Toyohara T, Suzuki T, Morimoto R, et al. SLCO4C1 transporter eliminates uremic toxins and attenuates hypertension and renal inflammation. *J Am Soc Nephrol* 2009; **20:** 2546–55.

98 Pauly RP, Gill JS, Rose CL, et al. Survival among nocturnal home haemodialysis patients compared to kidney transplant recipients. *Nephrol Dial Transplant* 2009; **24:** 2915–19.

99 Xia Y, Nivet E, Sancho-Martinez I, et al. Directed differentiation of human pluripotent cells to ureteric bud kidney progenitor-like cells. *Nat Cell Biol* 2013; **15:** 1507–15.

100 Bray BD, Boyd J, Daly C, et al. How safe is renal replacement therapy? A national study of mortality and adverse events contributing to the death of renal replacement therapy recipients. *Nephrol Dial Transplant* 2014; **29:** 681–87.

101 Li PK, Culleton BF, Ariza A, et al. Randomized, controlled trial of glucose-sparing peritoneal dialysis in diabetic patients. *J Am Soc Nephrol* 2013; **24:** 1889–900.

102 Abbott KC, Trespalacios FC, Agodoa LY, Taylor AJ, Bakris GL. Beta-blocker use in long-term dialysis patients: association with hospitalized heart failure and mortality. *Arch Intern Med* 2004; **164:** 2465–71.

103 Ramirez SP, McCullough KP, Thumma JR, et al. Hemoglobin A(1c) levels and mortality in the diabetic hemodialysis population: findings from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Diabetes Care* 2012; **35:** 2527–32.

104 Vanholder R, Massy Z, Argiles A, Spasovski G, Verbeke F, Lameire N. Chronic kidney disease as cause of cardiovascular morbidity and mortality. *Nephrol Dial Transplant* 2005; **20:** 1048–56.

105 Lauer MS, D'Agostino RB Sr. The randomized registry trial—the next disruptive technology in clinical research? *N Engl J Med* 2013; **369:** 1579–81.

106 Vanholder R, Davenport A, Hannedouche T, et al. Reimbursement of dialysis: a comparison of seven countries. *J Am Soc Nephrol* 2012; **23:** 1291–98.

107 Karopadi AN, Mason G, Rettore E, Ronco C. Cost of peritoneal dialysis and haemodialysis across the world. *Nephrol Dial Transplant* 2013; **28:** 2553–69.

108 Sumaili EK, Krzesinski JM, Zinga CV, et al. Prevalence of chronic kidney disease in Kinshasa: results of a pilot study from the Democratic Republic of Congo. *Nephrol Dial Transplant* 2009; **24:** 117–22.

109 Cleemput I, De Laet C. Analysis of the costs of dialysis and the effects of an incentive mechanism for low-cost dialysis modalities. *Health Policy* 2013; **110:** 172–79.

110 Solid CA, Carlin C. Timing of arteriovenous fistula placement and Medicare costs during dialysis initiation. *Am J Nephrol* 2012; **35:** 498–508.

111 Massy ZA, de Zeeuw D. LDL cholesterol in CKD—to treat or not to treat? *Kidney Int* 2013; **84:** 451–56.

112 Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). *Kidney Int* 2009; **76** (suppl 113)**:** S1–S130.

113 Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl* 2012; **2:** 279–335.

114 Beaglehole R, Ebrahim S, Reddy S, Voute J, Leeder S. Prevention of chronic diseases: a call to action. *Lancet* 2007; **370:** 2152–57.

115 Tonelli M, Agarwal S, Cass A, et al. How to advocate for the inclusion of chronic kidney disease in a national noncommunicable chronic disease program. *Kidney Int* 2013; published online Feb 13. DOI:10.1038/ki.2012.488.