Dialysis 1

The heart and vascular system in dialysis

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This is the first in a Series of three papers about dialysis

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The heart and the vascular tree undergo major structural and functional changes when kidney function declines and renal replacement therapy is required. The many cardiovascular risk factors and adaptive changes the heart undergoes include left ventricular hypertrophy and dilatation with concomitant systolic and diastolic dysfunction. Myocardial fibrosis is the consequence of impaired angio-adaptation, reduced capillary angiogenesis, myocyte-capillary mismatch, and myocardial micro-arteriopathy. The vascular tree can be affected by both atherosclerosis and arteriosclerosis with both lipid rich plaques and abundant media calcification. Development of cardiac and vascular disease is rapid, especially in young patients, and the phenotype resembles all aspects of an accelerated ageing process and latent cardiac failure. The major cause of left ventricular hypertrophy and failure and the most common problem directly affecting myocardial function is fluid overload and, usually, hypertension. In situations of stress, such as intradialytic hypotension and hypoxaemia, the hearts of these patients are more vulnerable to developing cardiac arrest, especially when such episodes occur frequently. As a result, cardiac and vascular mortality are several times higher in dialysis patients than in the general population. Trials investigating one pharmacological intervention (eg, statins) have shown limitations. Pragmatic designs for large trials on cardio-active interventions are mandatory for adequate cardioprotective renal replacement therapy.

Introduction

Nearly four centuries ago the English physician Thomas Sydenham (1624–89) commented that "a man is as old as his arteries". Of all the common diseases, uraemia imposes the most dramatic divergence between biological age and chronological age. Declining renal function, independent of a patient's age, is the main driver of cardiovascular ageing. If the kidneys are incapable of excreting water and waste products (uraemic toxins), the heart and vasculature are exposed to toxins, which contribute to accelerated ageing.[1] Cardiac and vascular alterations also arise from endocrine failure (eg, deficiency of erythropoietin and vitamin D, or excess of parathyroid hormone), which causes anaemia and secondary hyperparathyroidism. The final consequences have been termed uraemic cardiomyopathy, vascular calcification, and calciphylaxis or calcific uraemic arteriolopathy. Development of dialysis technologies have affected the survival of patients with uraemia by improving many aspects of the pathophysiological abnormalities of end-stage kidney disease. However, unsolved problems in the cardiovascular system caused by uraemia still exist (only a fraction of uraemic toxins are removed by dialysis), because dialysis-related medications and later treatments cause hypotension and reactive sympathetic overactivity. Investigations of the nature of cardiomyopathy and calcification will help in the development of new treatments for dialysis patients, and the results might also lead to cardiovascular anti-ageing strategies in general.

Search strategy and selection criteria

We searched MEDLINE for articles published up to Jan 31, 2016. We used the search terms "heart", "artery", "vascular", "cardiovascular", "atherosclerosis", or "arteriosclerosis" in combination with "dialysis", "end stage renal disease", "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 Series paper. Additional publications included were proposed by the authors and the reviewers.

Scope of the problem

The large number of patients with chronic kidney disease who require dialysis has become a major clinical problem because it has led to a disproportionally high prevalence of cardiovascular disease, including congestive heart

Key messages

- Left ventricular hypertrophy and failure are the most common problems
- The major cause of left ventricular hypertrophy and failure is fluid overload and, usually, hypertension
- Myocardial fibrosis is the consequence of impaired angio-adaptation, reduced capillary angiogenesis, myocyte-capillary mismatch, and micro-arteriopathy
- The vascular tree is affected by both arteriosclerosis and atherosclerosis with abundant media calcification and lipid rich plaques
- For many patients receiving dialysis, use of longer treatments or more frequent short treatments might be a preferable option
- The error of trying to achieve immediate euvolaemia in conventional haemodialysis therapy causes more harm than benefit

failure, and mortality.[2] Cardiovascular mortality is about nine times more frequent in individuals on dialysis than in the age-matched and sex-matched population without renal disease,[3] and cardiovascular disease is up to three times more frequent than that observed in other groups at risk of cardiovascular disease—eg, in individuals with diabetes.[4] In particular coronary artery calcification is common and progressive in young adults on dialysis.[5] In addition to this negative epidemiology, cardiac and vascular disease in patients with chronic kidney disease are different, in many respects, from the same diseases in patients without renal disease, so treatment for these conditions is much more complex in patients with chronic kidney disease. The search is ongoing for pharmacological interventions to treat vascular disease and related mineral and bone disorders, both on the basis of effectiveness and patient adherence to treatment. Few cardioprotective dialysis strategies have been tested in studies with small sample sizes. Thus, whether to provide treatment with more frequent or longer dialysis or haemodiafiltration currently depends on the individual cases on the basis of tolerance or resources available. Randomised, multinational effectiveness trials investigating pragmatic approaches (eg, dialysate sodium concentrations; use of drugs such as β blockers, aldosterone antagonists, or angiotensin receptor blockers; removal of larger uraemic toxins) to improve cardiovascular outcomes have not been undertaken on the scale required.

Pathology

Uraemia and the heart

The most characteristic and specific changes associated with chronic kidney disease that lead to cardiac and vascular pathology are early-onset left ventricular hypertrophy (LVH); impaired angio-adaptation, which leads to reduced capillary supply; myocardial microarteriopathy; and pronounced myocardial fibrosis. Overall, these structural changes induce a mismatching between myocytes and capillaries, with large intercapillary distances that compromise the supply of blood and oxygen to myocardial tissues.[6,7]

Use of animal models has been extremely valuable in investigation of the pathogenesis and relevance of cardiovascular changes in renal disease. A rat with a subtotal nephrectomy exhibits mild-to-moderate renal failure, which perfectly mimics human cardiac and vascular pathologies.[8] In this animal model, cardiac interstitial fibroblasts are activated as early as 2 weeks after the subtotal nephrectomy-induced renal failure. About 3–4 weeks later, LVH develops and capillary rarefaction and arterial changes occur at 8–12 weeks after initial induction. Furthermore, all these cardiovascular lesions progress as renal failure progresses. Of note, cardiovascular alterations have already been shown in animal models of uninephrectomy—eg, with only mild renal impairment.[9]

Experimental models of renal failure also showed a significant loss of cardiomyocytes, due to increased apoptosis, activation of cyclin D2, and increased expression of proliferating cell nuclear antigen.[10] Moreover, a reduction in cyclin-dependent kinase inhibitor activity caused a progressive loss of cardiac contractility.[11] In the model of renal failure caused by subtotal nephrectomy, the loss of cardiomyocytes was prevented by long-term treatment with angiotensin-converting-enzyme inhibitor (ACE) and rapamycin,[11,12] but apoptosis could be induced by administration of a soluble vascular endothelial growth factor (VEGF) receptor (s-Flt).[13]

Some of the first animal models used to study renal failure suggested that angio-adaptation to ischaemia was impaired in both the myocardium and skeletal muscle. That finding pointed to a potential role of pro-angiogenic or anti-angiogenic factors, particularly an impaired capacity to form new capillaries in chronic kidney disease that contributes to the severity of cardiovascular disease. Capillary angiogenesis is an essential adaptive process that restores perfusion to organs affected by processes such as macrovascular stenosis or occlusion or cardiac hypertrophy. In the rat model of subtotal nephrectomy, a 25% reduction in myocardial capillary supply after 8 weeks of renal failure was associated with a significantly greater area of myocardial infarction than in control animals without renal dysfunction (30 [SD 6·7] *vs* 18·8 [SD 6·6]).[8] This result indicated that renal failure increased myocardial susceptibility to ischaemic damage,[14] which was confirmed in a study[15] of patients with chronic kidney disease. Jefferies and colleagues[16] also showed that two-thirds of adults and children receiving dialysis experienced repeated episodes of intradialytic impairments in cardiac function (eg, cardiac stunning), accompanied by elevated concentrations of serum troponin T.

In patients with chronic kidney disease microvascular disorders and capillary rarefaction are not restricted to the myocardium, but are also observed in other vascular systems such as the cutaneous vasculature and in skeletal muscle where changes do not occur as early as in the myocardium.[17,18] However, skeletal muscles show impairments in angio-adaptation after ischaemia, with reduced new vessel formation.[19]

By contrast, patients with chronic kidney disease have increased burdens of comorbidities that arise from peripheral artery occlusive diseases, which worsen their overall prognosis.[20] To date, the detailed causes and pathological mechanisms of impaired angio-adaptation in chronic kidney disease remain unknown. Animal data have indicated a diminished or even disturbed adaptive up-regulation of VEGF and its receptors, both in the heart and in ischaemic skeletal muscle;[21] sympathetic overactivity might have a role because it interferes with local VEGF mRNA production.[22] In experimental models of renal failure various strategies for inhibiting the sympathetic system have restored myocardial capillary supply and prevented LVH to some extent.[23] Impaired mobilisation of bone marrow-derived cells in chronic kidney disease or uraemia is another possible cause of impaired angiogenesis.[23]

In 2015, data from patients with chronic kidney disease point to a potential role of sFlt-1, because binding to the soluble receptor does not lead to pathway activation.[13] The presence of sFlt-1 inhibits ischaemia-induced angiogenesis and favours apoptosis of endothelial cells and cardiomyocytes.[13,24] Consistent with these findings, serum from patients with chronic kidney disease showed antiangiogenic effects in vitro, with increased endothelial cell apoptosis and reduced nitric oxide production.[24] In addition to VEGF signalling, pro-angiogenic gene regulation by hypoxia-induced factors might be important in adaptive angiogenesis after ischaemia. Low basal concentrations of gene expression mediated by hypoxia-induced factors were found in skeletal muscle from rats that had undergone subtotal nephrectomies.[25]

Dialysis and the heart

Initially, cardiac death in patients who were undergoing dialysis was assumed to be caused by accelerated coronary atherosclerosis. However, studies[26] have shown that more than half of these patients experienced cardiac arrhythmias or acute heart failure, and less than a quarter died from myocardial infarction.

Of the cardiac abnormalities we have described, LVH is clinically the most prominent. Development of LVH after the initiation of haemodialysis is associated with and independently predicts mortality (hazard ratio 2·1, 95% CI 1·1–4·1; figure 1).[27] Early work by Foley and colleagues[28] in 1996 showed that LVH was present in more than 80% of patients at the time they entered a dialysis programme, and 17% of young patients (mean age 31·5 years) had no significant comorbidities. LVH is associated with systolic and, particularly, diastolic dysfunction in patients with chronic kidney disease and congestive heart failure. The time spent in haemodialysis is positively correlated with the prevalence of LVH,[29] but LVH is somewhat less prevalent in patients who undergo peritoneal dialysis.[30] In addition to left ventricular failure, renal disease is associated with an increased prevalence of lung diseases (chronic obstructive pulmonary disease and sleep apnoea[31]), which might also be relevant in terms of nocturnal hypoxia and sympathetic activation. Sleep apnoea is common in the dialysis population and has been associated with concentric LVH and cardiovascular mortality.[32,33] In the PEPPER study (prevalence of precapillary pulmonary arterial hypertension in patients with end-stage renal disease),[31] 90% of patients with stages 4 and 5 chronic

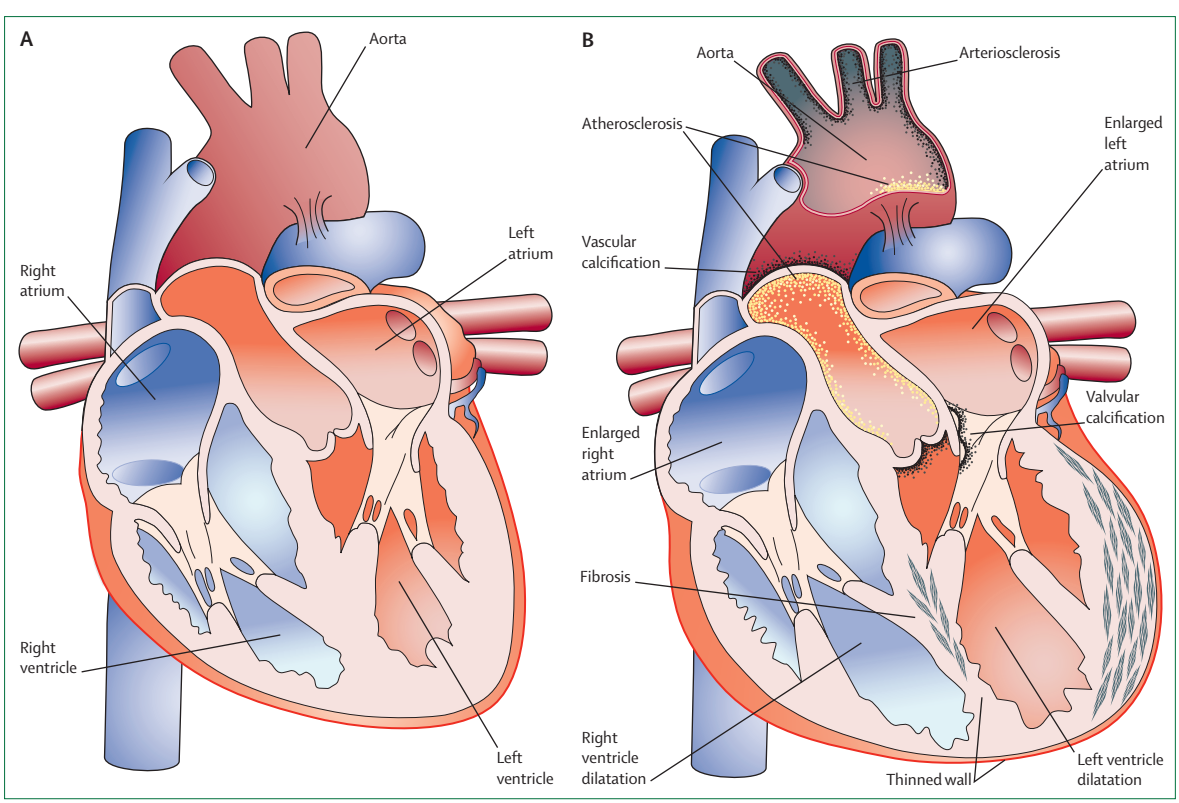

Figure 1: **The heart and arteries in (A) a healthy individual and (B) a representative patient on haemodialysis with left ventricular hypertrophy**
Uraemic cardiomyopathy is characterised by marked dilatation of the left and right ventricle with thickening of the ventricular walls, endocardial fibrosis, and, particularly, myocardial fibrosis, reduction of myocardial capillary supply, and thickening of intramyocardial arteries. Extracardiac vessels show various structural alterations depending on the site of the vessel, with the more muscular vessels (such as the carotid artery) showing thickening of the intima and media and, most characteristically, media calcification. By contrast the aorta, which is a more elastic artery, has thicker walls and shows reduced elastic fibre content and plaque-forming atherosclerosis with characteristic calcified plaques.

kidney disease[34] showed increased left ventricular filling pressures, indicative of left ventricular diastolic failure. However, 10% of patients presented with so-called unexplained pulmonary hypertension and right ventricular failure. Intradialytic hypotension as a result of ultrafiltration in patients with diastolic heart failure is one of the most common manifestations of cardiac problems in patients undergoing dialysis.

Uraemia and the microvascular and macrovascular systems

Structural and functional alterations of the heart and intramyocardial vasculature are accompanied by major changes in extracardiac elastic and muscular arteries and veins. More than 40 years ago Lindner and colleagues[35] noted that patients undergoing dialysis had pronounced atherosclerosis with specific calcification and lipid patterns. Chronic kidney disease is also associated with marked fibrous or fibro-elastic thickening of elastic and muscular arteries and with a loss of elastic fibre content. This condition leads to increased vascular stiffness (ie, premature vasculature ageing in patients in predialysis or undergoing regular dialysis),[36,37] and pronounced peripheral artery disease. The hallmarks of vascular alterations are increased thickening of the media and intima with loss of elastin fibre integrity and pronounced vascular calcification (figure 1),[38] and endothelial characterised by increased numbers of circulating microparticles in the presence of reduced numbers of endothelial progenitor cells.[39] Arterial changes are present even in children with chronic kidney disease—which suggests an absence of age-associated risk factors—and these changes do not worsen substantially during subsequent dialysis treatment. However, some studies[40] reported that vascular wall thickening tended to decline after renal transplantation, which could be interpreted as the healing of early changes. A recent study by Matsui and colleagues[41] showed an inverse relationship between sFlt-1 and atherosclerosis, which contrasted with the myocardial pathology observed.[13]

These structural alterations of the heart and vasculature, and the large differences in extent of cardiac disease between patients from southeast Asia and those from western Europe and the USA, could be due to genetic differences or modification by genetic differences, and other established cardiovascular risk factors—eg, diabetes or hypertension—might have synergistic effects on myocardial fibrosis.[5]

Potential pathophysiological contributors

Many factors have been identified that contribute to the complex, multifaceted pathophysiology of cardiac and vascular changes in patients with late-stage chronic kidney disease or those undergoing dialysis (appendix).[2] Volume overload, almost always the consequence of excessive interdialytic or intradialytic sodium loading (ie, excessive extracellular volume), leads to cardiac dilatation, increase in left ventricular mass, and deterioration of systolic and diastolic functions. Lung oedema and congestive heart failure are frequent in haemodialysis patients. Sympathetic overactivity, including norepinephrine spillover, is prominent and has been associated with concentric LVH.[42] Patients with type 2 diabetes might have long undetected hypoglycaemic episodes during sleep at night, leading to hypoxia, atrial fibrillation, and more complex arrhythmias. Of the other factors that might contribute to cardiac and vascular alterations, only a few have been tested in randomised controlled trials (RCTs). Many factors have been proposed, and several factors have been supported by epidemiological studies, but further studies should be done in cohort or interventional studies. The plasma concentrations of most of these so-called biomarkers are either increased or decreased on activation of the acute phase response, a condition highly prevalent in patients in areas other than from east Asia and Japan undergoing dialysis. Cardiovascular risk factors adversely affect the heart and blood vessels, increase the risk of cardiovascular events, and cause or contribute to cardiovascular and all-cause deaths.

Imaging studies can capture changes in surrogate or intermediate factors such as LVH, atrial and ventricular function, intima–media thickness, aortic stiffness, and vascular calcification. Effect modifiers—factors that modify another factors' effect on clinical outcomes—include the presence of inflammation, history of cardiovascular disease, and ethnic origin (appendix). Haemodialysis does not remove many uraemic toxins—such as p-cresyl sulphate and indoxyl sulphate—effectively because they are largely protein bound. AST-120 (an orally administered intestinal sorbent) reduces the production of some uraemic toxins, but no RCT of AST-120 has been done in dialysis populations. In this Series paper we discuss only a few factors, which are supported with relatively solid evidence.

Some of the most intensively studied risk factors for cardiovascular disease are lipoproteins and lipids (LDL cholesterol and HDL cholesterol). However, chronic kidney disease causes substantial changes in the associations between lipoprotein cholesterol levels and outcomes of cardiovascular disease. Plasma lipoprotein composition and concentrations are different in chronic kidney disease stages 3–5D, and are modified by inflammation. Additionally, ethnic origin and time of exposure (ie, duration of baseline arterial and cardiac complications) affect the association between lipoproteins and outcomes in patients with chronic kidney disease. This association weakens as the estimated glomerular filtration rate decreases, and LDL cholesterol contributes little to the incidence of myocardial infarction.[43] Furthermore, in stage 5 chronic kidney disease, LDL cholesterol can no longer be used to predict myocardial infarction.[44] Consistent with these findings, carotid artery atheroma growth was slower in advanced chronic kidney disease than in the early stages of kidney disease.[45] One explanation for the absence of the classic relationship between lipoproteins and cardiovascular risk in chronic

See Online for appendix

kidney disease is that lipoproteins, particularly HDL particles, are modified in chronic kidney disease. In inflamed conditions, HDL particles lose their anti-inflammatory and anti-atherogenic components and gain inflammatory and atherogenic factors.[46] Additionally, LDL is modified by urea-derived carbamylation, oxidation, and glycation, in the same way that albumin is.[47,48] Thus, modified acute phase HDL predicted adverse clinical outcomes in patients with chronic kidney disease.[49,50]

An interesting example of the complex changes associated with chronic kidney disease is the effect of race on the lipoprotein-associated outcome in patients undergoing dialysis. In Japanese patients, the incidence of myocardial infarction in those undergoing dialysis with no history of cardiovascular disease was independently associated with high non-HDL cholesterol and low HDL cholesterol serum concentrations.[51] On average, Japanese and other southeastern or eastern Asian patients who require haemodialysis have less inflammation, live for much longer, and probably have less lipoprotein functionality modifications than do patients from western Europe and the USA. Consistent with lipid biomarker data, cardiovascular outcomes in Japanese patients are more dependent on traditional risk factors than outcomes in white patients.

In patients who need haemodialysis, the risk of cardiac events largely depends on the extent of coronary artery disease at the initiation of haemodialysis treatment.[52] A 1997 study[53] showed that more than half of patients starting dialysis had undiagnosed coronary artery stenosis.[53] A 2014 report by the same group[54] showed that the proportion of patients with undiagnosed coronary artery disease had decreased from 69% to 25% during the past two decades. Similarly, the prevalence of undiagnosed coronary artery disease at start of dialysis treatment was closely inversely associated with the frequency of use of renin-angiotensin system blockers for treatment of hypertension, and with the frequency of erythropoiesis-stimulating agents for renal anaemia in the predialysis period. On the basis of these observational data, it is tempting to speculate that adequate treatment of the classic risk factors and risk factors associated with chronic kidney disease might reduce the atherosclerotic burden at dialysis initiation, and thus improve clinical outcomes in patients on dialysis.

High oxidative stress is a plausible factor for increasing the risk of cardiovascular disease in chronic kidney disease and patients undergoing dialysis, but only a few cohort studies provide evidence that oxidative stress was linked to cardiovascular outcomes in patients undergoing dialysis. This absence of sufficient evidence might have arisen from the methodological difficulties involved in quantification of oxidative stress in biomaterials from patients in cohort studies.

Telomere shortening, a marker of biological ageing, was associated with cardiovascular disease in a cohort of more than 5000 patients with chronic kidney disease.[55] Although a longitudinal association between telomere length and cardiovascular disease incidence has not been reported to date, telomere length might serve as a surrogate marker for the cumulative effects of inflammation, oxidative stress, and accelerated ageing in patients with renal dysfunction undergoing dialysis.

Phosphate is a candidate causative factor for premature ageing. High serum phosphate concentrations were associated with all-cause mortality in patients who required haemodialysis. The potential toxicity of phosphate might not be specific to chronic kidney disease, because serum phosphate concentrations—particularly postprandial concentrations—can independently predict mortality in the general population.[56] Phosphate, calcium, and fetuin-A can form nanosized particles in extracellular fluids, called fetuin mineral complexes or calciprotein particles. These particles are highly cytotoxic and pro-inflammatory.[57] Propensity of serum for calciprotein particle formation has been shown to predict mortality in predialysis patients[58] and in those who have renal transplants.[59]

Serum concentrations of fibroblast growth factor 23 (FGF23) predicted mortality in patients with chronic kidney disease.[60] FGF23 was shown to induce LVH via the FGF receptor 4 on myocytes in an animal model.[61] However, in chronic kidney disease FGF23 effects were dependent on the presence of Klotho deficiency and phosphotoxicity.[62] Other predictors of all-cause mortality related to mineral bone disorders in chronic kidney disease included high serum calcium, high intact parathyroid hormone concentrations, and the absence of exogenous vitamin D receptor activators[63] and phosphate binders.[64]

An increased susceptibility to death after a cardiovascular event contributes to the increased cardiovascular mortality in patients with chronic kidney disease.[65] In patients undergoing haemodialysis, survival was low after myocardial infarction[66] and stroke[67] compared with the general population who had also had a myocardial infarction or stroke. The major, pervasive effect of fluid overload has not been sufficiently analysed separately from factors associated with fatality risk such as older age, elevated C-reactive protein concentrations, low serum albumin concentrations, low body-mass index, diabetes, raised serum calcium concentrations, elevated serum phosphate concentrations, and an absence of exogenous phosphate binders.[68]

Prevention and treatment

Atherosclerotic and non-atherosclerotic cardiovascular diseases

Atherosclerotic and non-atherosclerotic cardiovascular disease involve different factors that cause distinct changes in the risk factor profile and contribute differently to outcomes during the course of chronic kidney disease. The burden of atherosclerotic cardiovascular disease increases in the early stages of chronic kidney disease, and the burden of non-atherosclerotic cardiovascular disease increases in the more advanced stages of chronic kidney disease (figure 2). Additionally,

the risk of fatality is increased in patients with low glomerular filtration rates. Thus, the risk of cardiovascular disease in patients who require haemodialysis depends largely on their cardiovascular health at haemodialysis initiation. Consequently, during screening and interventions for chronic kidney disease, risk factors for cardiovascular disease should be managed intensively in the predialysis period, during transition, and at dialysis initiation. In patients with healthy arteries, the predialysis management strategy should be continued to prevent new cardiovascular lesions.

Cardioprotective haemodialysis

Because of the development of dialysis technologies, patients with uraemia can survive for longer and the number of patients worldwide who require treatment with dialysis is growing. About half of the population that needs haemodialysis in high-income countries is aged older than 65 years, and the average age of those needing dialysis in these countries has tended to increase with time. Due to cardiovascular comorbidities, the biological age of these patients is often substantially older than their chronological age. Frailty, protein energy wasting, and sarcopenia are becoming increasingly frequent in the older dialysis patients, and these are associated with impaired physical performance, disability, poor quality of life, and reduced survival. Prevention and treatment of these conditions often need a multifaceted approach and are being focused on increasingly to mitigate the symptomatic burden. Observational studies, such as the EQUAL study, are investigating whether cardiac and vascular risk might be reduced by administering lower than expected drug doses (ie, statins) or whether to create a pragmatic polypill.

Outcomes of haemodialysis treatment can be gravely affected by wrongly prescribed high ultrafiltration rates, leading to intermittent hypotensive episodes and intradialytic hypoxaemia.[68] These rates are sometimes ordered in view of a target weight instead of aiming at a gradual decrease in post-dialysis weight with time—ie, too much fluid is removed in too few treatments. Haemodialysis-associated cardiomyopathy with fibrotic pathology might render the heart more susceptible to ischaemic injury and subsequent arrhythmias. Dialysis-based interventions can be specifically designed to maintain vascular stability to avoid hypotensive episodes and to mitigate the cumulative ischaemic insults that result from conventional haemodialysis treatments. Several approaches to this problem have been proposed including control of the patient's thermal balance with use of individualised dialysate cooling,[69,70] measurements of intradialytic haemoglobin oxygen saturation, change in position, and adaptation of the ultrafiltration rate to the patient's condition in longer or more frequent maintenance haemodialysis sessions.[71,72]

In the past year studies using tagged cardiovascular magnetic resonance have shown that patients new to haemodialysis have many cardiac and aortic abnormalities. These findings suggest that pharmacological cardioprotective interventions might be needed before the transition phase to haemodialysis and that slow, incremental dialytic treatment during the 90-day phase after the start of maintenance haemodialysis treatment might be needed.[73]

The almost inevitable excess of extracellular fluid load and high blood pressure are traditionally treated with sodium restriction and ultrafiltration. As a result, reduction in cardiac preload in patients with diastolic cardiac dysfunction might reduce cardiac output and cause hypotension. Aggressive fluid removal can induce circulatory stress, so-called cardiac stunning, and multiorgan injury.[17] Consequently, the error of trying to achieve immediate euvolaemia in conventional haemodialysis therapy causes more harm than benefit. Many

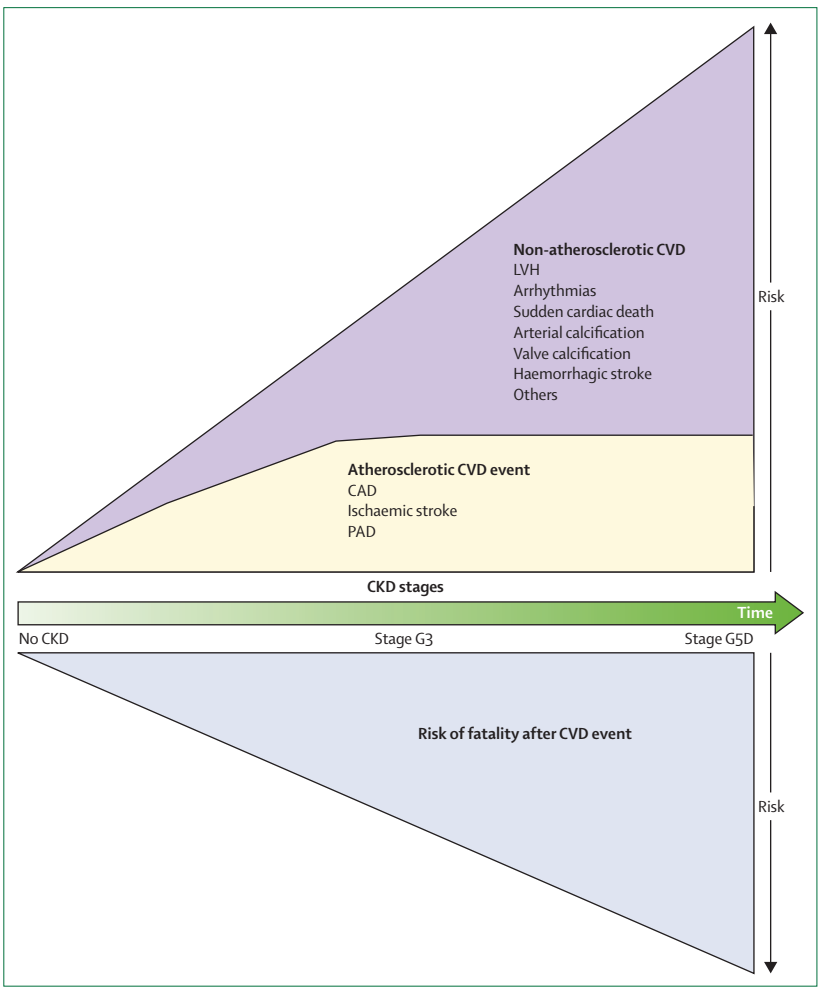

Figure 2: **Change in cardiovascular risk during chronic kidney disease progression**
Cardiovascular disease (CVD) event (upper triangle); contributions of atherosclerotic CVD (yellow); non-atherosclerotic CVD (purple), and risk of fatality after CVD event (blue). Time is an important factor—ie, the time a patient spends in each stage of chronic kidney disease (CKD) before initiating dialysis. For example, acute onset of kidney disease, which causes rapid, progressive kidney failure, will not expose the patient to the burden of accumulated vascular damage. CKD stages are according to the KDIGO (Kidney Disease: Improving Global Outcomes Group) guidelines, 2012.[34] LVH=left ventricular hypertrophy. PAD=peripheral artery disease. CAD=coronary artery disease.

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dialysis facilities practise so-called incremental dialysis as a preventive measure at the start of renal replacement therapy. Other dialysis facilities permit a degree of initial overhydration to maintain residual renal function, and have reported improved outcomes.[73] By contrast, increased frequency or duration of haemodialysis sessions, which reduces extracellular fluid load more effectively than conventional dialysis—in addition to dietary salt restriction and low dialysate sodium—has been shown to control high volume status, left ventricular mass, and blood pressure effectively over 12 months.[74]

Pharmacological intervention

Many patients with comorbidities who transition into a dialysis programme appear to reach a plateau in atherosclerotic events through interventions to address traditional risk factors. A good example is use of statin treatment. Statins are very effective in prevention of cardiovascular events in patients with normal renal function, but appear not to have comparable efficacy in patients undergoing dialysis.[75,76] Nevertheless, the Study of Heart and Renal Protection (SHARP)[77] reduced the risk of atherosclerotic events through a combination of simvastatin plus ezetimibe (an inhibitor of intestinal cholesterol absorption). This trial[77] recruited a wide range of patients with advanced chronic kidney disease before and during dialysis treatment, and showed positive outcomes without heterogeneity between pre-dialysis and dialysis patients. The multiplicity of factors involved suggested that much larger trials are needed to dissect the beneficial effect of an intervention, particularly during the later course of the disease, when the patient population is more heterogeneous in underlying risk factors, vasculopathy, and cardiomyopathy. The SHARP trial[77] used ezetimibe as part of the cholesterol lowering intervention on the basis of previous cohort studies[78] in patients undergoing haemodialysis, which showed that poor cardiovascular outcomes were predicted by low hepatic synthesis and increased intestinal absorption of cholesterol.

Other intervention studies in patients receiving haemodialysis have reported disappointing data. Relatively small RCTs have tested various strategies for preventing cardiovascular disease, including β blockade, ACE inhibition, or supplementation with vitamin E, acetyl cysteine, folic acid, or n-3 polyunsaturated fatty acid. Positive results were expected from these interventions because patients undergoing haemodialysis have high sympathetic activity, oxidative stress, and deficient n-3 fatty acid profiles.[79] An RCT[80] of n-3 polyunsaturated fatty acid versus olive oil showed no significant effect on the primary composite cardiovascular endpoint, although the group receiving n-3 polyunsaturated fatty acid had a lower rate of myocardial infarction. Another study[81] compared atenolol (β blocker) to lisinopril (ACE inhibitor) in patients with hypertension and LVH who received dry-weight adjusted, sodium restricted, maintenance haemodialysis. They found that an atenolol-based antihypertensive therapy might be better than lisinopril-based therapy in prevention of cardiovascular morbidity and all-cause admissions to hospital.[81]

Two other smaller RCTs[82,83] showed carvedilol treatment had a positive effect on dilated cardiomyopathy and heart failure as well as all-cause mortality, pointing to the importance of the sympathetic system in haemodialysis patients. Several large trials were designed on the basis that cinacalcet and sevelamer induce a positive change in serum concentrations of a marker (eg, calcium, phosphate, fibroblast growth factor 23 [FGF23], and parathyroid hormone) or hard outcomes (eg, all-cause mortality, cardiovascular complications) in haemodialysis patients, but none showed a significant reduction in the primary composite endpoint.[84,85] Other interventions have caused harm (eg, epoetin therapy[86]) or been implicated in a potential for causing harm (eg, vitamin K depletion through use of warfarin; lowering of serum phosphate with a phosphate binder; or excessive intravenous iron).

All these trials have provided useful information about the ability to intervene in cardiovascular risk for dialysis patients and many promising hypotheses remain to be tested. Ongoing trials are testing whether a wearable cardioverter defibrillator (WED-HED; NCT02481206) can prevent sudden cardiac death or whether antagonism of the mineral corticoid receptor with spironolactone (NCT01691053; NCT01848639) can prevent intermediate (eg, left ventricular hypertrophy) and hard outcomes in patients undergoing haemodialysis. Continuing to investigate potential strategies such as these is important because operative vascular procedures—eg, angioplastic and bypass surgeries—are not associated with improved outcomes and prognoses.[87]

Conclusions

Because of the multiplicity of pathologies involved, treating patients with chronic kidney disease can be difficult. Treatable factors such as anaemia, hyperphosphataemia, hypercalcaemia, hyperparathyroidism, cannot completely explain the broad spectrum of cardiovascular disease in this patient population.[88] To date, studies have not identified effective drug treatments that can control cardiac and vascular outcomes. For many patients receiving dialysis, use of longer treatments or more frequent short treatments might be a preferable option. Conventional haemodialysis can bring its own problems, especially in the elderly, who are at increased risk of cardiac pathologies and underlying diseases such as heart failure, arrhythmias, diabetes, and peripheral arterial disease. Thus, many treatment care teams have focused more pragmatically on advance care planning, delivering supportive care, and providing volume controlled cardioprotective dialysis treatment.[89] This change might ultimately turn into a better quality of life before or during dialysis treatment.

Contributors

TS and CW took part in the literature search. All authors drafted and revised the manuscript.

Declaration of interests
CW has received personal fees from Amgen, Boehringer Ingelheim, Sanofi Genzyme, GlaxoSmithKline, Janssen, and Novo Nordisk, outside the submitted work. TS has received personal fees and research grant from Astellas, Chugai, Daiichi Sankyo, and Takeda; and has received personal fees from Bayer, Boehringer Ingelheim, Fuso, Kyowa Hakko Kirin, Mochida, Merck Sharp & Dohme, Novo Nordisk, and Pfizer. KA declares no competing interests.

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References

1 Kooman JP, van der Sande FM, Leunissen KM. Kidney disease and aging: a reciprocal relation. *Exp Gerontol* 2016; published online Feb 2. DOI:10.1016/j.exger.2016.02.003.
2 Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation* 2003; **108:** 2154–69.
3 DeJager DJ, Grotendorst DC, Jager KJ, et al. Cardiovascular and noncardiovascular morality among patients starting dialysis. *JAMA* 2009; **302:** 1782–89
4 Foley RN, Parfrey PS, Sarnak M. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; **32** (suppl 3)**:** S112–19
5 Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000; **342:** 1478–83.
6 Amann K, Breitbach M, Ritz E, et al. Myocyte/capillary mismatch in the heart of uremic patients. *J Am Soc Nephrol* 1998; **9:** 1018–22.
7 Amann K, Wanner C, Ritz E, et al. Cross-talk between the kidney and the cardiovascular system. *J Am Soc Nephrol* 2006; **17:** 2112–19.
8 Amann K, Wiest G, Zimmer G, et al. Reduced capillary density in the myocardium of uremic rats-a stereological study. *Kidney Int* 1992; **42:** 1079–85.
9 Buzello M, Törnig J, Faulhaber J, Ehmke H, Ritz E, Amann K. The (apo)E knockout mouse—a model documenting accelerated atherogenesis in uremia. *J Am Soc Nephrol* 2003; **14:** 311–62.
10 Amann K, Tyralla K, Gross ML, et al. Cardiomyocyte loss in experimental renal failure: prevention by ramipril. *Kidney Int* 2003; **63:** 1708–13.
11 Siedlecki AM, Jin X, Muslin AJ. Uremic cardiac hypertrophy is reversed by rapamycin but not by lowering of blood pressure. *Kidney Int* 2009; **75:** 800–08.
12 Dikow R, Kihm LP, Zeier M, et al. Increased infarct size in uremic rats: reduced ischemia tolerance? *J Am Soc Nephrol* 2004; **15:** 1530–36.
13 Di Marco GS, Kentrup D, Reuter S, et al. Soluble Flt-1 links microvascular disease with heart failure in CKD. *Basic Res Cardiol* 2015; **110:** 30.
14 Ix JH, Shlipak MG, Brandenburg VM, et al. Association between renal insufficiency and inducible ischemia in patients with coronary artery disease: the heart and soul study. *J Am Soc Nephrol* 2003**; 14:** 3233–38.
15 Wetmore JB, Broce M, Malas A, et al. Painless myocardial ischemia is associated with mortality in patients with chronic kidney disease. *Nephron Clin Pract* 2012; **122:** 9–16.
16 Jefferies HJ, Virk B, Schiller B, et al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). *Clin J Am Soc Nephrol* 2011; **6:** 1326–32.
17 Hothi DK, Rees L, Marek J, et al. Pediatric myocardial stunning underscores the cardiac toxicity of conventional hemodialysis treatments. *Clin J Am Soc Nephrol* 2009; **4:** 790–97.
18 Stewart J, Kohen A, Brouder D, et al. Noninvasive interrogation of microvasculature for signs of endothelial dysfunction in patients with chronic renal failure. *Am J Physiol Heart Circ Physiol* 2004; **287:** H2687–96.
19 Arismendi-Morillo G, Fernandez-Abreu M. Ultrastructural cutaneous microvascular pathology of young adults aged up to 50 years with chronic kidney disease and cognitive impairment. *Ultrastruct Pathol* 2010; **34:** 214–18.
20 Jacobi J, Porst M, Cordasic N, et al. Subtotal nephrectomy impairs ischemia-induced angiogenesis and hindlimb reperfusion in rats. *Kidney Int* 2006; **69:** 2013–21.
21 O'Hare AM, Bertenthal D, Shlipak MG, et al. Impact of renal insufficiency on mortality in advanced lower extremity peripheral arterial disease. *J Am Soc Nephrol* 2005; **16:** 514–19.
22 Wiley LA, Berkowitz BA, Steinle JJ. Superior cervical ganglionectomy induces changes in growth factor expression in the rat retina. *Invest Ophthalmol Vis Sci* 2006; **47:** 439–43.
23 Amann K, Odoni G, Benz K, et al. Sympathetic blockade prevents the decrease in cardiac VEGF expression and capillary supply in experimental renal failure. *Am J Physiol Renal Physiol* 2011; **300:** F105–12.
24 Di Marco GS, Reuter S, Hillebrand U, et al. The soluble VEGF receptor sFlt1 contributes to endothelial dysfunction in CKD. *J Am Soc Nephrol* 2009; **20:** 2235–45.
25 Jacobi JM, Tam BY, Wu G, et al. Adenoviral gene transfer with soluble vascular endothelial growth factor receptors impairs angiogenesis and perfusion in a murine model of hindlimb ischemia. *Circulation* 2004**; 110:** 2424–29.
26 Flisinski M, Brymora A, Bartlomiejczyk I, et al. Decreased hypoxia-inducible factor-1alpha in gastrocnemius muscle in rats with chronic kidney disease. *Kidney Blood Press Res* 2012; **35:** 608–18.
27 de Bie MK, van Dam B, Gaasbeek A, et al. The current status of interventions aiming at reducing sudden cardiac death in dialysis patients. *Eur Heart J* 2009; **30:** 1559–64.
28 Foley RN, Parfrey PS, Kent GM, et al. Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant* 1996; **11:** 1277–85.
29 Sise ME, Courtwright AM, Channick RN. Pulmonary hypertension in patients with chronic and end-stage kidney disease. *Kidney Int* 2013; **84:** 682–92.
30 Issa N, Krowka MJ, Griffin MD, et al. Pulmonary hypertension is associated with reduced patient survival after kidney transplantation. *Transplantation* 2008; **86:** 1384–88.
31 Pabst S, Hammerstingl C, Hundt F, et al. Pulmonary hypertension in patients with chronic kidney disease on dialysis and without dialysis: results of the PEPPER-study. *PLoS One* 2012; **7:** e35310.
32 Zoccali C, Benedetto FA, Mallamaci F, et al. Left ventricular hypertrophy and nocturnal hypoxemia in hemodialysis patients. *J Hypertens* 2001; **19:** 287–93.
33 Zoccali C, Mallamaci F, Tripepi G. Nocturnal hypoxemia predicts incident cardiovascular complications in dialysis patients. *J Am Soc Nephrol* 2002; **13:** 729–33.
34 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.
35 Lindner A, Charra B, Sherrard DJ. Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 1974; **290:** 697–701.
36 Schwarz U, Buzello M, Ritz E, et al. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. *Nephrol Dial Transplant* 2000; **15:** 218–23.
37 London GM, Safar ME, Pannier B. Aortic aging in ESRD: structural, hemodynamic, and mortality implications. *J Am Soc Nephrol* 2015; published online Oct 16. DOI:10.1681/ASN.2015060617.
38 Paloian NJ, Giachelli CM. A current understanding of vascular calcification in CKD. *Am J Physiol Renal Physiol* 2014; **307:** F891–900.
39 Soriano S, Carmona A, Triviño F, et al. Endothelial damage and vascular calcification in patients with chronic kidney disease. *Am J Physiol Renal Physiol* 2014; **307:** F1302–311.
40 Litwin M, Wühl E, Jourdan C, et al. Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. *J Am Soc Nephrol* 2005; **16:** 1494–500.
41 Matsui M, Takeda Y, Uemura S, et al. Suppressed soluble Fms-like tyrosine kinase-1 production aggravates atherosclerosis in chronic kidney disease. *Kidney Int* 2014; **85:** 393–403.
42 Zoccali C, Mallamaci F, Tripepi G, et al. CREED investigators. Norepinephrine and concentric hypertrophy in patients with end-stage renal disease. *Hypertension* 2002; **40:** 41–46.
43 Levin A, Rigatto C, Barrett B, et al. Biomarkers of inflammation, fibrosis, cardiac stretch and injury predict death but not renal replacement therapy at 1 year in a Canadian chronic kidney disease cohort. *Nephrol Dial Transplant* 2014; **29:** 1037–47.

44 Tonelli M, Muntner P, Lloyd A, et al. Association between LDL-C and risk of myocardial infarction in CKD. *J Am Soc Nephrol* 2013; **24:** 979–86.

45 Rigatto C, Levin A, House AA, Barrett B, Carlisle E, Fine A. Atheroma progression in chronic kidney disease. *Clin J Am Soc Nephrol* 2009; **4:** 291–98.

46 Speer T, Zewinger S, Fliser D. Uraemic dyslipidaemia revisited: role of high-density lipoprotein. *Nephrol Dial Transplant* 2013; **28:** 2456–63.

47 Drechsler C, Kalim S, Wenger JB, et al. Protein carbamylation is associated with heart failure and mortality in diabetic patients with end-stage renal disease. *Kidney Int* 2015; **87:** 1201–08.

48 Berg AH, Drechsler C, Wenger J, et al. Carbamylation of serum albumin as a risk factor for mortality in patients with kidney failure. *Sci Transl Med* 2013; **5:** 175ra29.

49 Kopecky C, Genser B, Drechsler C, et al. Quantification of HDL proteins, cardiac events, and mortality in patients with type 2 diabetes on hemodialysis. *Clin J Am Soc Nephrol* 2015; **10:** 224–31.

50 Zewinger S, Drechsler C, Kleber ME, et al. Serum amyloid A: high-density lipoproteins interaction and cardiovascular risk. *Eur Heart J* 2015; **36:** 3007–11.

51 Shoji T, Masakane I, Watanabe Y, Iseki K, Tsubakihara Y. Elevated non-high-density lipoprotein cholesterol (non-HDL-C) predicts atherosclerotic cardiovascular events in hemodialysis patients. *Clin J Am Soc Nephrol* 2011; **6:** 1112–20.

52 Hase H, Tsunoda T, Tanaka Y, et al. Risk factors for de novo acute cardiac events in patients initiating hemodialysis with no previous cardiac symptom. *Kidney Int* 2006; **70:** 1142–48.

53 Joki N, Hase H, Nakamura R, Yamaguchi T. Onset of coronary artery disease prior to initiation of haemodialysis in patients with end-stage renal disease. *Nephrol Dial Transplant* 1997; **12:** 718–23.

54 Iwasaki M, Joki N, Tanaka Y, et al. Declining prevalence of coronary artery disease in incident dialysis patients over the past two decades. *J Atheroscler Thromb* 2014; **21:** 593–604.

55 Raschenberger J, Kollerits B, Titze S, et al. Association of relative telomere length with cardiovascular disease in a large chronic kidney disease cohort: the GCKD study. *Atherosclerosis* 2015; **242:** 529–34.

56 Chang AR, Grams ME. Serum phosphorus and mortality in the Third National Health and Nutrition Examination Survey (NHANES III): effect modification by fasting. *Am J Kidney Dis* 2014; **64:** 567–73.

57 Kuro-o M. Klotho Phosphate and FGF-23 in ageing and disturbed mineral metabolism. *Nat Rev Nephrol* 2013; **9:** 650–60.

58 Smith ER, Ford ML, Tomlinson LA, et al. Serum calcification propensity predicts all-cause mortality in predialysis CKD. *J Am Soc Nephrol* 2014; **25:** 339–48.

59 Keyzer CA, de Borst MH, van den Berg E, et al. Calcification propensity and survival among renal transplant recipients. *J Am Soc Nephrol* 2016; **27:** 239–48.

60 Isakova T, Xie H, Yang W, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA* 2011; **305:** 2432–39.

61 Grabner A, Amaral AP, Schramm K, et al. Activation of cardiac fibroblast growth factor receptor 4 causes left ventricular hypertrophy. *Cell Metab* 2015; **22:** 1020–32.

62 Hu MC, Shi M, Cho HJ, et al. Klotho and phosphate are modulators of pathologic uremic cardiac remodeling. *J Am Soc Nephrol* 2015; **26:** 1290–302.

63 Kovesdy CP, Kalantar-Zadeh K. Vitamin D receptor activation and survival in chronic kidney disease. *Kidney Int* 2008; **73:** 1355–63.

64 Isakova T, Gutierrez OM, Chang Y, et al. Phosphorus binders and survival on hemodialysis. *J Am Soc Nephrol* 2009; **20:** 388–96.

65 Nishizawa Y, Shoji T, Ishimura E. Paradox of risk factors for cardiovascular mortality in uremia: is a higher cholesterol level better for atherosclerosis in uremia? *Am J Kidney Dis* 2001; **38** (suppl 1)**:** S4–7.

66 Smith GL, Masoudi FA, Shlipak MG. Renal impairment predicts long-term mortality risk after acute myocardial infarction. *J Am Soc Nephrol* 2008; **19:** 141–50.

67 Iseki K, Fukiyama K. Long-term prognosis and incidence of acute myocardial infarction in patients on chronic hemodialysis. The Okinawa Dialysis Study Group. *Am J Kidney Dis* 2000; **36:** 820–25.

68 Meyring-Wösten A, Zhang H, Ye X, et al. Intradialytic hypoxemia and clinical outcomes in patients on hemodialysis. *Clin J Am Soc Nephrol* 2016; **11:** 616–25.

69 Maggiore Q, Pizzarelli F, Santoro A, et al, and the Study Group of Thermal Balance and Vascular Stability. The effects of control of thermal balance on vascular stability in hemodialysis patients: results of the European randomized clinical trial. *Am J Kidney Dis* 2002; **40:** 280–90.

70 Odudu A, Eldehni MT, McCann GP. Randomized controlled trial of individualized dialysate cooling for cardiac protection in hemodialysis patients. *Clin J Am Soc Nephrol* 2015; **10:** 1408–17.

71 Levin NW, Raimann JG, Rocco MV. Should the knowledge gained from the Frequent Hemodialysis Network (FHN) trials change dialysis practice? *Curr Opin Nephrol Hypertens* 2011; **20:** 577–82.

72 Rocco MV, Lockridge RS Jr, Beck GJ, et al. The effects of frequent nocturnal home hemodialysis: Frequent Hemodialysis Network (FHN) Trial Group. *Kidney Int* 2011; **80:** 1080–91.

73 Obi Y, Streja E, Rhee CM, et al. Incremental hemodialysis, residual kidney function, and mortality risk in incident dialysis patients: a cohort study. *Am J Kidney Dis* 2016; published online Feb 8. DOI:10.1053/j.ajkd.2016.01.008.

74 Ok E, Asci G, Chazot C, Ozkahya M, Dorhout Mees EJ. Dialysis 2. Controversies and problems of volume control and hypertension in haemodialysis. *Lancet* 2016; published online May 22. DOI:10.1016/S0140-6736(16)30389-0.

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

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

77 Baigent C, Landray MJ, Reith C, et al, on behalf of the SHARP Investigators. 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.

78 Silbernagel G, Fauler G, Genser B, et al. Intestinal cholesterol absorption, treatment with atorvastatin, and cardiovascular risk in hemodialysis patients. *J Am Coll Cardiol* 2015; **65:** 2291–98.

79 Shoji T, Kakiya R, Hayashi T, et al. Serum n-3 and n-6 polyunsaturated fatty acid profile as an independent predictor of cardiovascular events in hemodialysis patients. *Am J Kidney Dis* 2013; **62:** 568–76.

80 Svensson M, Schmidt EB, Jorgensen KA. N-3 fatty acids as secondary prevention against cardiovascular events in patients who undergo chronic hemodialysis: a randomized, placebo-controlled intervention trial. *Clin J Am Soc Nephrol* 2006; **1:** 780–86.

81 Agarwal R, Sinha AD, Pappas MK. Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial. *Nephrol Dial Transplant* 2014; **29:** 672–81.

82 Cice G, Ferrara L, Di Benedetto A, et al. Dilated cardiomyopathy in dialysis patients—beneficial effects of carvedilol: a double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2001; **37:** 407–11.

83 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.

84 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.

85 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.

86 Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355:** 2085–98.

87 Pinkau T, Hilgers KF, Veelken R, et al. How does minor renal dysfunction influence cardiovascular risk and the management of cardiovascular disease? *J Am Soc Nephrol* 2004; **15:** 517–23.

88 Ortiz A, Covic A, Fliser D, et al, for the Board of the EURECA-m Working Group of ERA-EDTA. Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure. *Lancet* 2014; **383:** 1831–43.

89 Davison SN, Levin A, Moss AH, et al. Executive summary of the KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease: developing a roadmap to improving quality care. *Kidney Int* 2015; **88:** 447–59.

Dialysis 2

Controversies and problems of volume control and hypertension in haemodialysis

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Extracellular volume overload and hypertension are important contributors to the high risk of cardiovascular mortality in patients undergoing haemodialysis. Hypertension is present in more than 90% of patients at the initiation of haemodialysis and persists in more than two-thirds, despite use of several antihypertensive medications. High blood pressure is a risk factor for the development of left ventricular hypertrophy, heart failure, and mortality, although there are controversies with some study findings showing poor survival with low—but not high—blood pressure. The most frequent cause of hypertension in patients undergoing haemodialysis is volume overload, which is associated with poor cardiovascular outcomes itself independent of blood pressure. Although antihypertensive medications might not be successful to control blood pressure, extracellular volume reduction by persistent ultrafiltration and dietary salt restriction can produce favourable results with good blood pressure control. More frequent or longer haemodialysis can facilitate volume and blood pressure control. However, successful volume and blood pressure control is also possible in patients undergoing conventional haemodialysis.

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Introduction

It is estimated that there are more than 3 million patients with end-stage renal disease worldwide, and two-thirds are treated with haemodialysis. Although haemodialysis is a life-saving treatment, these patients have increased mortality, with nearly 50% of deaths due to cardiovascular causes. Cardiovascular mortality in patients starting dialysis is 8·8 times higher than in the general population (95% CI 8·6–9·0).[1] Volume overload, hypertension, left ventricular hypertrophy, and congestive heart failure are frequent in these patients, and play an important part in their high cardiovascular mortality.

Hypertension is very common in patients undergoing haemodialysis. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend a target pre-dialysis blood pressure of less than 140/90 mm Hg, and a target post-dialysis blood pressure of less than 130/80 mm Hg.[2] In a cohort of 2535 patients undergoing haemodialysis, the frequency of hypertension (defined as systolic blood pressure >150 mm Hg, diastolic blood pressure >85 mm Hg, or the use of antihypertensive medications) was reported as 86%.[3] According to the Dialysis Outcomes and Practice Patterns Study (DOPPS) data,[4] the frequency of patients with systolic blood pressure more than 140 mm Hg is 55% in Europe, Australia, and New Zealand, 69% in the USA and Canada, and 75% in Japan, suggesting inadequate control of blood pressure across the world. By contrast, two centres practising strict volume control (Tassin, France, and Ege University, Izmir, Turkey) report blood pressure of less than 140/90 mm Hg in 98% (Tassin) and 96% (Izmir) of patients without using antihypertensive medication, suggesting that these differences are related to the treatment strategies.[5,6]

Search strategy and selection criteria

We searched for articles and reviews published between Jan 1, 1968, and Dec 31, 2015, without language restriction in MEDLINE and the Cochrane Library database using the terms: "dialysis patients" or "hemodialysis patients" or "haemodialysis patients" AND "blood pressure" or "hypervolemia" or "hypovolemia"or "hypertension" or "hypotension" or "extracellular fluid volume" or "overhydration" or "salt intake". In addition to 4329 articles identified by this search strategy, we also searched the reference lists of those articles and selected relevant papers.

Key messages

- About 2 million patients with end-stage renal disease in the world are treated with haemodialysis. Haemodialysis saves lives, but patients starting haemodialysis have 8·8-times higher cardiovascular mortality than the general population.
- Volume overload and hypertension are common and play an important part in the pathogenesis of greater cardiovascular mortality.
- Although two-thirds of patients on haemodialysis use antihypertensives, systolic blood pressure measured just before dialysis session is above 140 mm Hg in 55–75% of patients, indicating that antihypertensive medications do not provide successful blood pressure control.
- The major cause of hypertension in patients undergoing haemodialysis is extracellular fluid volume overload, which leads to congestive heart failure and lung oedema. Volume control strategies (gradual reduction of post-dialysis bodyweight and dietary salt restriction) can offer successful blood pressure control without use of antihypertensive medications in 90% of patients undergoing either intensive or conventional haemodialysis.
- Neither absence of oedema nor occurrence of intradialytic hypotension is a reliable sign of euvolaemia. The presence of hypertension can be a marker of volume overload in most patients. Bioimpedance spectroscopy, lung ultrasonography, relative plasma volume slope monitoring, echocardiography (vena cava and left atrium diameter), and chest radiography can be helpful to evaluate volume status.

The objective of this Series paper is to discuss the controversies about volume and blood pressure control in patients undergoing haemodialysis, with a focus on treatment strategies.

Blood pressure in haemodialysis

Maintenance haemodialysis is generally done three times a week for 3–4·5 h per session, during which time the fluid accumulated between dialyses is removed (usually 2–4 L). As a result of these substantial fluctuations in extracellular fluid volume, blood pressure shows large variability at different timepoints during the week. The measurement of bodyweight before and after haemodialysis is a cornerstone of fluid management.

Blood pressure can be measured before or after haemodialysis in the dialysis unit, at home or using ambulatory blood pressure recordings, all of which result in different values. The blood pressure measurement that best predicts left ventricular hypertrophy, cardiovascular events, and cardiovascular and overall mortality is debated. Findings from observational studies yield conflicting results. Foley and colleagues[7] found that post-haemodialysis systolic blood pressure, but not pre-haemodialysis blood pressure, was associated with overall mortality. Another study showed a strong correlation between pre-haemodialysis systolic blood pressure and 24 h systolic ambulatory blood pressure; both blood pressures equally correlated with left ventricular mass on echocardiography, whereas post-haemodialysis blood pressure did not.[8] Agarwal reported that 44 h ambulatory and home systolic blood pressures were associated with all-cause mortality, whereas blood pressure recordings taken on the dialysis unit were of no prognostic importance.[9] Recently, Merchant and colleagues[10] investigated the relationships of different blood pressure measurement methods with left ventricular hypertrophy determined by cardiac MRI, a more reliable technique. Left ventricular hypertrophy was best predicted by systolic blood pressure after haemodialysis and during initial dialysis (within the first 15 min of the session). Blood pressure variability and 44 h ambulatory blood pressure did not predict left ventricular hypertrophy. Although the measurement method might be important for optimising treatment, we feel that it does not play a major part in poor blood pressure control, and that pre-haemodialysis and post-haemodialysis measurements targeted in KDOQI guidelines can be used for clinical practice.

When extracellular fluid volume is reduced by ultrafiltration, the most frequent complication is intradialytic hypotension. Depending on the state of overhydration, the removal of 2–4 L of extracellular fluid is accompanied by a 10–30% decrease in blood volume in a few hours. The decrease of plasma volume below a critical threshold leads to intradialytic hypotension. There is remarkable interindividual variation in the degree of plasma volume decrease during constant ultrafiltration due to variance in refill rate, from only 1% to as much as 22%.[11] The refill rate of plasma volume is related to the hydration state and decreases when extracellular fluid approaches normal volumes.[12] A high ultrafiltration rate (caused mostly by large interdialytic weight gain [IDWG] and shorter session duration) that exceeds the refill rate leads to intradialytic hypotension, despite the patient still having excess extracellular fluid volume and in some cases even oedema.

By contrast with intradialytic hypotension, blood pressure can increase in some patients despite ultrafiltration (referred to as paradoxical or intradialytic hypertension), which is associated with poor survival.[13] No increase has been reported in plasma renin and catecholamine concentrations[14] and paradoxical hypertension is not prevented by treatment with angiotensin-converting enzyme inhibitor (ACE-I).[12] In a small, uncontrolled study[15] of patients with paradoxical hypertension refractory to medications and who had cardiac enlargement, their paradoxical hypertension was successfully treated by reduction in post-haemodialysis bodyweight by a mean of 6·7 kg. Another observational study reported an increase in cardiac index measured by echocardiography during the episode of increased blood pressure.[16] These results suggest that the paradoxical hypertension might be caused by increased cardiac output through improved cardiac contractility, and that it might be treatable by intensified ultrafiltration. Findings from a randomised controlled trial[17] supported the notion that intradialytic hypertension improved with reduction in post-haemodialysis bodyweight.

Hypertension, cardiovascular disease, and mortality

In patients undergoing haemodialysis, hypertension has been reported to be associated with left ventricular hypertrophy, left ventricular systolic and diastolic dysfunction, cardiac enlargement, cardiac failure, ischaemic heart disease, myocardial infarction, sudden cardiac death, stroke, and increased cardiovascular and overall mortality.[9,18–24]

However, findings from several other observational studies have shown that low blood pressure, rather than high blood pressure, is a risk factor for increased mortality, and have even shown that high blood pressure is associated with improved survival.[4,25–27] In 5433 prevalent dialysis patients undergoing haemodialysis during a mean follow-up of 2·6 years, Zager and colleagues[27] showed that cardiovascular mortality was associated with systolic blood pressure of more than 180 mm Hg after haemodialysis, and less than 110 mm Hg before or after haemodialysis, and proposed the existence of a U-shaped curve in the association between blood pressure and cardiovascular mortality. Findings from the DOPPS study involving 24525 prevalent dialysis patients with a mean follow-up of 1·7 years showed that, for patient-level systolic blood pressure, mortality was raised at low

(<130 mm Hg) and not high (≥180 mm Hg) systolic blood pressure.[4]

Duration of follow-up and interaction between cardiac functions and blood pressure are likely to contribute to those discrepancies.

In a cohort of 405 patients undergoing haemodialysis,[23] low diastolic blood pressure before dialysis was a predictor of early mortality (<5 years of dialysis), whereas high systolic blood pressure predicted late mortality (≥5 years of dialysis). Among the early deaths, cardiac causes were less frequent, and malignant disease and withdrawal of treatment were more frequent, compared with late deaths. Patients who died in the early period were older and had more comorbidities. Another retrospective study reported the association between high blood pressure and mortality after 3 years, whereas low blood pressure was associated with mortality in the first 2 years.[28] These data could explain why hypertension was not reported as a risk factor for mortality in studies with short follow-up.

The largest prospective observational study, by Foley and colleagues,[18] clarifies the relationship between blood pressure, cardiac function, and survival in patients undergoing haemodialysis. In this cohort, 432 patients were followed up for an average of 41 months with annual echocardiography. The frequency of antihypertensive drug use was 90%. Each 10 mm Hg rise in mean arterial blood pressure was associated with left ventricular hypertrophy, change in left ventricular mass index and cavity volume, and development of de-novo cardiac failure and ischaemic heart disease. However, low blood pressure was associated with earlier death, whereas high blood pressure was not. The investigators reported that mean arterial blood pressure fell from 103 mm Hg (SD 10) to 98 mm Hg (SD 13) with the development of cardiac failure, after which median survival was 20 months. These data show that although hypertension causes left ventricular hypertrophy, ischaemic heart disease, and heart failure, relatively low blood pressure that develops after deterioration in cardiac function is associated with earlier death.

It is not certain whether severely reduced cardiac function, sometimes called uraemic cardiomyopathy, can be improved. Findings from a small, uncontrolled prospective study[29] showed that in patients with severe heart failure and low left ventricular ejection fraction, average ejection fraction increased from 31% to 50% after a 12 kg (SD 10) reduction in post-haemodialysis bodyweight with persistent ultrafiltration within 4 months.[29] Blood pressure increased in patients with low blood pressure at baseline, as a result of improvement in left ventricular systolic function. Similarly, findings from a larger observational study[30] showed an increase in blood pressure after reduction of post-haemodialysis bodyweight in patients with systolic blood pressure less than 120 mm Hg. These data indicate the role of extracellular fluid overload in pathogenesis of deteriorated myocardial function and the reversibility of depressed left ventricular systolic dysfunction.

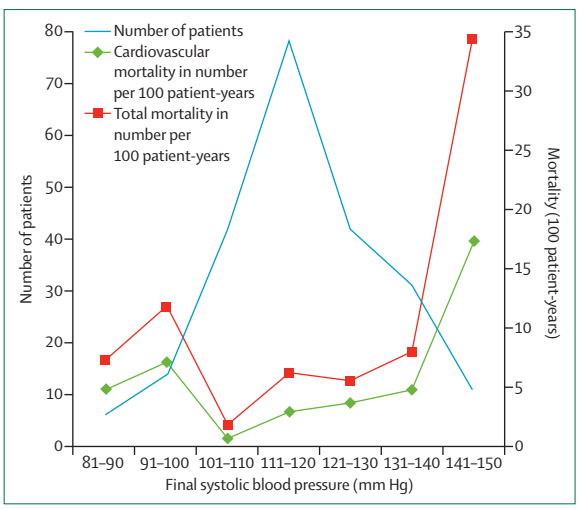

Figure 1: **Systolic blood pressure and mortality in patients treated with a strict volume control strategy**
Reproduced from Ozkahya et al[6] by permission of Oxford University Press.

With a strict strategy for volume control, patients with mean arterial blood pressure less than 99 mm Hg (according to the Tassin results)[5] and patients with systolic blood pressure of 101–110 mm Hg (according to the Izmir results)[6] were reported to have the highest survival rates (figure 1).

It seems that the association between low blood pressure and mortality is due to poor cardiac and general health status, rather than the result of overtreatment. Therefore, the association between low blood pressure and mortality should not discourage physicians from treating hypertension.

Treatment of hypertension in patients undergoing haemodialysis

The following algorithm is recommended by KDOQI[2] for treatment of hypertension in patients undergoing haemodialysis: achieve dry weight; prescribe an ACE-I or angiotensin receptor blocker (ARB) if blood pressure is still more than 140/90 mm Hg, or prescribe an ACE-I/ARB and a calcium channel blocker (CCB) if blood pressure is more than 160/100 mm Hg; and add a β blocker or clonidine if blood pressure still remains more than 140/90 mm Hg.

Although several clinical and laboratory parameters have been proposed for the definition of dry weight, absence of oedema and occurrence of intradialytic hypotension are considered as signs of dry weight achieved by nephrologists in routine practice; anti hypertensive medications are usually prescribed to patients who still have high blood pressure.

To date, there is no conclusive evidence that documents the superiority of one class of antihypertensive medication over another.[31] Findings from several

randomised controlled trials[32,33] have shown a decrease in the occurrence of cardiovascular complications with the use of ACE-I or ARB. A meta-analysis,[34] however, showed no change in the risk of fatal and non-fatal cardiovascular events with these two drug classes. In another meta-analysis[35] including eight randomised controlled trials, blood pressure-lowering treatment (β blocker, ACE-I, ARB, and CCB) reduced the risk of cardiovascular events and all-cause and cardiovascular mortality. However, the studies in this meta-analysis were not homogeneous, and most did not have a blood pressure target. Additionally, findings of two large studies in this meta-analysis did not show a decrease in cardiovascular events and mortality with active treatment.[36,37] A small (but well designed) double-blind randomised controlled trial[38] in haemodialysis patients found no significant effect of irbesartan on blood pressure (a similar decrease of blood pressure in the groups compared with placebo) and several intermediate cardiovascular endpoints.

In a cohort of 326 patients undergoing haemodialysis, 74% had used antihypertensive medications (ACE-I or ARB in two-thirds, and β blocker in half), although the mean home systolic blood pressure was 150 mm Hg (SD 24), with the lowest mortality between 120 mm Hg and 130 mm Hg.[9] The DOPPS II study[39] suggests that the prevalence of antihypertensive medication use in patients undergoing haemodialysis in 12 countries is at 66%, although pre-haemodialysis systolic blood pressure is still above 140 mm Hg in 55–75% of patients.[4]

These data suggest that blood pressure control by antihypertensive medication is far from reaching its target, probably due to the lack of success in achieving actual dry weight—ie, being in normal fluid status, with a normal extracellular fluid volume. For example, Katzarski and colleagues[40] documented that blood volume was significantly higher in hypertensive patients undergoing haemodialysis (in whom it was thought that dry weight had been attained) compared with patients undergoing haemodialysis with normal blood pressure. These results, however, might not be that surprising, as the major cause of hypertension in patients undergoing haemodialysis is volume overload. Antihypertensive medications might be effective in reducing high blood pressure only in the minority of patients in whom mechanisms other than extracellular fluid volume overload contribute to hypertension. By contrast, strict volume control provides optimal blood pressure control in most patients (table 1).[5,6]

	Year	Number of patients	Control rate of hypertension
Vertes et al[41]	1969	40	88%
Curtis et al[42]	1969	25	92%
Charra et al[43]	1992	445	98%
Salem et al[25]	1996	649	28%
Agarwal et al[3]	2003	2535	14%
Ozkahya et al[6]	2006	218	96%
Robinson et al (DOPPS)[4]*	2012	24 525	25–45%
Ok et al[44]†	2013	782	84%

Table shows observational studies unless otherwise stated. DOPPS=Dialysis Outcomes and Practice Patterns Study. *Only patients with systolic blood pressure <140 mm Hg, including those who achieved this with antihypertensive use; diastolic blood pressure not included. †Baseline data for patients enrolled in a randomised controlled trial, which had no exclusion criteria regarding blood pressure. Adapted from Charra[45] by permission of John Wiley and Sons.

Table 1: **Hypertension control by haemodialysis alone**

	Treatment of hypertension with antihypertensive medications (n=204)	Treatment of hypertension with ECV reduction (n=190)	p value
Systolic blood pressure, mm Hg	126 (21)	126 (15)	NS
Diastolic blood pressure, mm Hg	76 (11)	75 (12)	NS
Anti-hypertensive use	86 (42%)	13 (7%)	0·001
IDWG, kg	3·31 (1·12)	2·29 (0·83)	<0·001
Intradialytic hypotension (per 100 sessions)	27	11	0·009
Left atrium volume index, mL/m^2	36·7 (21·7)	29·5 (10·0)	<0·001
Left ventricle mass index to height (2·7), g/m$^{2·7}$	74 (27)	59 (16)	<0·001
Left ventricular ejection fraction, %	63 (9)	68 (10)	<0·001

Table shows data from a cross-sectional study.[46] Data are mean (SD) or n (%). IDWG=interdialytic weight gain. ECV=extracellular volume. NS=not significant. Adapted from Kayikcioglu et al[46] by permission of Oxford University Press.

Table 2: **Comparison of two different strategies in the treatment of hypertension in haemodialysis**

Volume overload, cardiovascular disease, and mortality

It is not clear whether persistent extracellular fluid overload can still cause poor outcomes if blood pressure is normalised through use of antihypertensives in mild hypertension (which is not likely to be achieved in severe hypertension). A cross-sectional study[46] compared two strategies for blood pressure control, based either on antihypertensive medication or on extracellular fluid volume reduction by dietary salt restriction and persistent ultrafiltration. Despite similar blood pressures achieved by these two different strategies, IDWG, frequency of intradialytic hypotension, left atrium volume index, and left ventricular mass index were all higher in the patients who received the pharmacological strategy, and these patients also had lower left ventricular ejection fraction (table 2). These findings suggest that persistent overhydration might lead to cardiac dilatation, increase in left ventricular mass, and deterioration of systolic and diastolic left ventricular functions.

As a manifestation of volume overload, lung oedema and congestive heart failure are frequent in patients receiving haemodialysis. In a prospective observational study[47] of 432 patients starting dialysis, the frequency of congestive heart failure was as high as 31% at the initiation of dialysis and recurred in 56% of patients during 41 months of follow-up. Moreover, de-novo congestive heart failure developed in 25% of patients, with hypertension as a risk factor. Findings from a retrospective study[48] showed that 14% of 176 790 patients undergoing

haemodialysis were admitted to hospital a mean of 1·64 times for heart failure, fluid overload, or pulmonary oedema over 2·5 years of follow-up, corresponding to a hospitalisation rate of 137 per 1000 patient-years.

Overload of extracellular fluid volume before dialysis (assessed by several methods)[6,49–52] and large IDWG[53–55] are frequent and also predict mortality independent of blood pressure.

Pathogenesis of hypertension

Interestingly, blood pressure and volume control were excellent in the early era of haemodialysis. In 1960s and early 1970s, the treatment of hypertension was based on the gradual reduction of extracellular fluid volume by ultrafiltration during long hours haemodialysis, dietary salt restriction, and relatively low dialysate sodium. The success rate of blood pressure control without antihypertensive medications was around 90%.[41,42,56]

Unfortunately, nowadays, control of both blood pressure and volume seems to be unsuccessful. We feel that the knowledge procured on the pathophysiology of hypertension in end-stage renal disease may be underutilised for guiding treatment.

There is an incontestable relationship between extracellular fluid volume and salt balance. Increased salt intake results in an unavoidable thirst that is subsequently satisfied by water ingestion, which leads to an increase in extracellular fluid volume. Kidney disease reduces the sodium excretion capacity of kidneys, leading to increased salt sensitivity and volume retention.[57,58] Expansion of extracellular fluid volume (and thereby of blood volume) causes an increase in cardiac output, which ultimately elicits a rise in blood pressure. The overperfusion of the tissues due to increased cardiac output leads to the downregulation of blood flow by vasoconstriction, called autoregulation.[59] The increase in total peripheral resistance by vasoconstriction further escalates blood pressure. Koomans and colleagues[58] documented increases in extracellular fluid volume, blood volume, and blood pressure, and decreased plasma renin activity, after salt load in patients with different degrees of renal insufficiency.

Although renin secretion is not completely abolished in the non-functioning kidney, and can sometimes be inappropriately high, the influence of the renin-angiotensin system seems to be trivial in patients undergoing haemodialysis as long as overhydration is present.[12] Compared with healthy controls, sympathetic nerve discharge was higher in haemodialysis patients who had not undergone bilateral nephrectomy, along with higher vascular resistance and mean arterial blood pressure.[60] However, Vertes and colleagues[41] showed that blood pressure normalised in 35 (88%) of 40 patients starting dialysis with hypertension undergoing haemodialysis after extracellular fluid volume reduction. Current practice shows that the widespread use of ACE-I, ARB, β blocker, and CCB does not provide successful blood pressure control,[9,39] wheras extracellular fluid volume reduction can achieve normal blood pressure without use of antihypertensive drugs.[5,6,41,42] These results suggest that the primary cause of hypertension in patients undergoing haemodialysis is volume overload and that increased sympathetic activity or renin activity (or both) might be the primary responsible factor in a minority of hypertensive patients undergoing haemodialysis.

Implementation of volume control strategy in long and conventional haemodialysis

Introduction of shorter dialysis sessions in the late 1970s clearly resulted in increased rates of ultrafiltration and intradialytic hypotension episodes. Utilisation of higher dialysate sodium level to overcome intradialytic hypotension led to positive sodium balance during haemodialysis sessions. Extracellular fluid volume control, and resultantly blood pressure control, became much more difficult.[61] By contrast, the Tassin group continued to practice long haemodialysis sessions and reduction of extracellular fluid volume to treat hypertension instead of using blood pressure medications, resulting in survival rates of 87% at 5 years.[59] They used controlled ultrafiltration to achieve normal post-haemodialysis and pre-haemodialysis blood pressure, low salt diet, and discontinuation of anti-hypertensive medications.[43,45,62] In a report of 876 patients undergoing haemodialysis, 90% had high blood pressure at the initiation of dialysis.[5] Post-haemodialysis bodyweight was reduced by ultrafiltration within the first month, with a corresponding decrease in blood pressure. Bodyweight then increased by several kilograms but blood pressure continued to fall gradually between the third and 12th months, suggesting an anabolic weight gain.[63] This progressive and slow reduction in blood pressure observed in the absence of further reduction in extracellular fluid volume was explained by delayed regression of peripheral vascular resistance developed in response to chronic fluid overload, the so-called lag phenomenon (figure 2).[45,63,64] The mean systolic and diastolic blood pressure recorded in

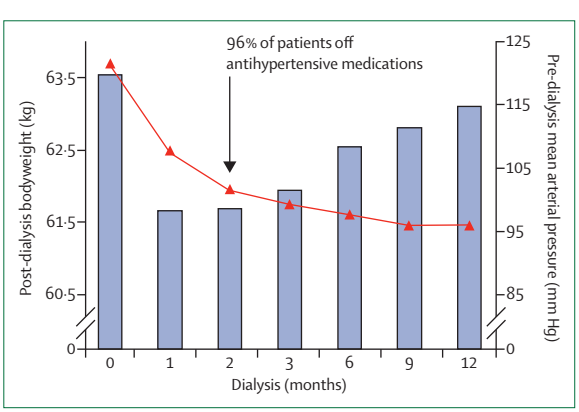

Figure 2: **The time-lag phenomenon in post-dialysis bodyweight and pre-dialysis mean arterial pressure**
Figure shows data for 712 patients undergoing haemodialysis at Tassin during 12 months of follow-up. Reproduced from Charra[45] by permission of John Wiley and Sons.

ambulatory monitoring were close to those of normotensive individuals.[65]

In Ege University, the strict volume control strategy has been achieved in conventional haemodialysis for the past 20 years (by contrast with Tassin, where long haemodialysis sessions have been practised). It consists of dietary salt restriction (4–5 g/day), discontinuation of all antihypertensive medications, intensified ultrafiltration during dialysis, and occasional isolated ultrafiltration sessions. Post-haemodialysis bodyweight is reduced until blood pressure falls to 140/90 mm Hg or less and cardiothoracic index less than 0·50, at a rate of 0·5–1·5% per week according to blood pressure and cardiac function. The renin dependency of hypertension is assessed by response to a test dose of captopril.[6] Patients and their families are advised not to add salt during cooking or eating, to restrict consumption of processed food with high salt content, and not to drink more (or less) water than indicated by thirst.

Although a meta-analysis[34] showed that treatment with ACE-I or ARB could decrease left ventricular mass by 15·4 g/m², this finding was somewhat surprising because no change in blood pressure was shown with these drugs and five of the six studies in the analysis did not show a statistically significant decrease in left ventricular mass. In a retrospective study, the Ege group showed a sharp decrease in left ventricular mass index (by 70 g/m²) through strict volume control,[66] and also complete or partial correction of valvular insufficiencies (mitral and tricuspid).[67] This strategy has been gradually accepted throughout Turkey. Supporting this, the prevalence of hypertension was found to be 16% in a multicentre trial.[44] One might argue that the successful blood pressure control in Turkey could be attributed to the Mediterranean diet, but the daily average salt intake in the country has been reported to be about 18 g/day.[68]

Barriers to achieve volume control

Overview

Despite the favourable effects of the Tassin and Ege approaches compared with use of antihypertensive drugs, surprisingly few nephrologists have attempted to follow policies of sodium restriction and gradual post-haemodialysis bodyweight reduction. Recently, in a pilot trial from the USA,[30] pre-haemodialysis bodyweight was successfully reduced by 3·9 kg, resulting in a 15·7 mm Hg decrease of systolic blood pressure in patients with high baseline systolic blood pressure (≥160 mm Hg) and an 11·2 mm Hg increase of systolic blood pressure in patients with low baseline systolic blood pressure (<120 mm Hg). These results are promising for the feasibility of implementing volume control policy worldwide.

We have identified three barriers to successful volume control in patients undergoing haemodialysis: problems in the assessment of volume status, difficulties in reducing post-haemodialysis bodyweight, and conviction and willingness of the dialysis team.

Problems in the assessment of volume status

Defining true dry weight is certainly one of the most important factors for determining the success of blood pressure control. Several litres of excess extracellular fluid may be present without visible oedema, and intradialytic hypotension reflects an ultrafiltration rate that exceeds the refill rate rather than a below-normal extracellular fluid volume.

A cardiothoracic index of more than 0·50 based on chest radiograph,[66] a left atrial volume index more than 32 mL/m² of body surface area or more than 12 mL/m$^{2·7}$ of height on echocardiography,[49,69] flat slopes (<1·33%/h) on relative plasma volume slope monitoring,[70] a collapse index less than 40% or vena cava diameter at least 11·5 mm/m² body surface area on echocardiography,[71] an extracellular fluid volume excess more than 15% of extracellular fluid volume on whole body bioimpedance spectroscopy,[51] and a B-lines score more than 5 on lung ultrasound[52] have been proposed for the diagnosis of extracellular fluid overload.

The presence of hypertension has been used as a marker of extracellular fluid overload by the Tassin and Ege groups. Charra and colleagues[72] defined dry weight as the post-haemodialysis bodyweight at which the patient can remain normotensive until the next haemodialysis session without antihypertensive medication or clinical signs of overhydration or dehydration. With this approach, less than 5% of the patients undergoing haemodialysis required antihypertensive medication.[72]

Difficulties in reducing post-haemodialysis bodyweight

Reduction of post-haemodialysis bodyweight is not easy because of intradialytic hypotension due to high ultrafiltration rate, which can be associated with vascular access thrombosis, decline of residual renal function, ischaemic events, cardiac damage, and increased mortality.[2,73–75] Two studies[76,77] in which antihypertensive medication use and IDWG remained unchanged during reduction of post-haemodialysis bodyweight, showed an increase in the frequencies of intradialytic hypotension and vascular access problems. Conversely, two other observational studies[78,79] applying dietary salt restriction and cessation of antihypertensive medication documented a decrease in intradialytic hypotension frequency (from 22% to 7% in one study and from 18% to 11% in the other). Intradialytic hypotension is also a risk factor for decline in residual function.[73] In case of earlier loss of residual renal function by extracellular fluid volume reduction, this unwanted effect is probably counterbalanced by favourable cardiovascular outcomes such as regression of left ventricular hypertrophy with better control of extracellular fluid volume and blood pressure.[78]

Decreasing IDWG and increasing frequency or duration of haemodialysis sessions are two ways to reduce ultrafiltration rate, and thereby reduce post-haemodialysis bodyweight safely and comfortably.

The major determinant of IDWG is dietary salt intake. Other factors include dialysate sodium, hyperglycaemia,

and fluid intake for habitual and social reasons, including both alcoholic and non-alcoholic beverages. Dietary advice should be focused on salt restriction and not on fluid intake (which is a natural consequence of salt intake).[80] McCausland and colleagues[81] reported that higher dietary sodium intake was independently associated with greater mortality in a dose-dependent manner in patients undergoing haemodialysis (figure 3), as well as in the general population.[82] In an observational study, reduction of dietary sodium intake by 33–44 mmol/day (equivalent to 1·9–2·6 g/day salt) was found to decrease cardiovascular events by 30% in general population.[83] Taste papillae take several weeks to adapt to a lower level of salt, so patients (and doctors) are reluctant to change dietary salt habits. The dialysis team has first to be convinced of its feasibility, and a coordinated program must be started. It is difficult to find low-salt food in most societies. Another determinant of IDWG is positive dialysate sodium gradient with the use of high dialysate sodium concentration.[84] Reduction or individualisation of dialysate sodium level reduced IDWG and facilitated blood pressure control.[85,86]

Increasing frequency or duration (or both) of haemodialysis sessions is an efficient way to achieve blood pressure and volume control, but intensive haemodialysis might have its own barriers, such as financial burden and patient compliance. Two randomised controlled trials[87,88] and one meta-analysis[89] showed that more frequent or longer haemodialysis sessions improved blood pressure control and also reduced left ventricular mass. However, it should be noted that an action on the part of the nephrologist is needed to reduce post-haemodialysis bodyweight.

Conviction and willingness of the dialysis team

For example, in a randomised controlled trial,[90] after 12 months of six-times weekly nocturnal haemodialysis (30·8 h/week), the mean number of antihypertensive medications was still 1·41 (SD 1·92) with no significant decrease in left ventricular mass, by contrast with findings from a previous randomised controlled trial.[87] In this trial, post-haemodialysis bodyweight was not reduced to reach normal blood pressure without blood pressure medication,[91] whereas a weekly haemodialysis duration of 30·8 h would make post-haemodialysis bodyweight reduction much easier, considering a very low ultrafiltration rate (3–4 mL/h per kg bodyweight, which is completely safe).

It is our belief that physicians might be insufficiently convinced of the role of extracellular fluid overload in hypertension in these patients and do not appreciate that hypertension can be treated by extracellular fluid volume reduction in most patients undergoing haemodialysis. Physicians might also be concerned about the possible side-effects of this strategy, but by hoping to stay on the safe side they forego the potential benefits. This is perhaps the most important reason for unsatisfactory blood pressure and volume control.

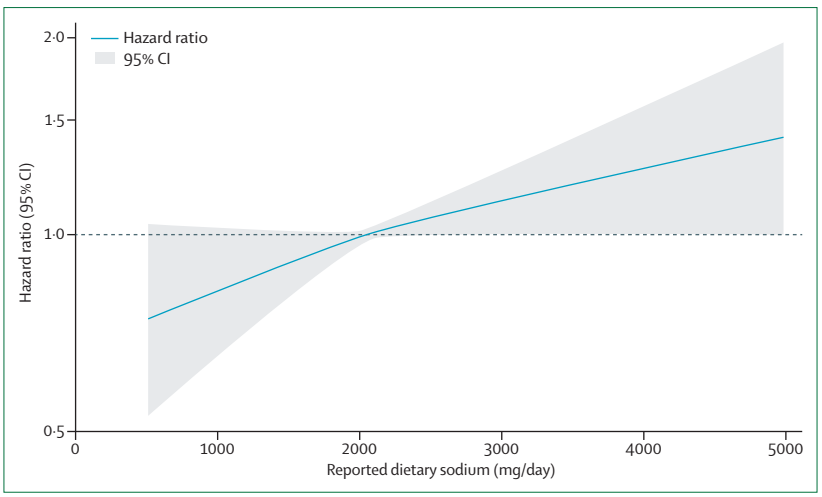

Figure 3: **Dietary sodium and all-cause mortality**
Figure shows dietary sodium intake (in mg/day) adjusted by age, sex, race, post-dialysis weight, dialysis vintage, vascular access, congestive heart failure, diabetes, ischaemic heart disease, urine volume, dialysis session length, serum sodium, albumin, creatinine, and ultrafiltration requirement. Estimates are presented for dietary sodium intakes of 500–5000 mg/day. The hazard ratio is represented by the solid line and the 95% CI by the shaded area. The y axis presents a log-scale. Reproduced from McCausland and colleagues[81] by permission of Elsevier.

It is essential to assure the nephrology community that volume and blood pressure control do not usually require antihypertensive medications. More frequent or longer dialysis is one option which facilitates these objectives, but successful volume and blood pressure control is also possible in conventional haemodialysis. Dietary salt restriction must be achieved in patients undergoing dialysis as well as in the whole population with the help of government policies.

We are well aware that the data showing the effectiveness of these volume control strategies are derived from observational studies rather than randomised trials, which are more convincing but difficult to conduct in these settings. However, the substantial number of observational studies provide a very clear message; certainly, no observational studies of sodium restriction and gradual loss of post-haemodialysis bodyweight have suggested contrary results.

Medicine did not wait for randomised controlled trials to take action against smoking. We hope for the same approach from the dialysis community for the treatment of hypertension with volume reduction and salt restriction, instead of prescribing antihypertensive medication for their patients undergoing haemodialysis.

Contributors
EO and GA did the literature search and wrote the first draft. All authors contributed to manuscript revision and approved the final version. All authors had access to all data and were responsible for the decision to submit for publication. EO confirms that all authors have seen and approved of the final text.

Declaration of interests
We declare no financial competing interests. EO, GA, and MO are affiliated with the Ege University Dialysis Center; CC is affiliated with the Tassin Dialysis Center. There was no funding source.

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References

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

2 K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005; **45** (4 suppl 3)**:** S1–153.

3 Agarwal R, Nissenson AR, Batlle D, Coyne DW, Trout JR, Warnock DG. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. *Am J Med* 2003; **115:** 291–97.

4 Robinson BM, Tong L, Zhang J, et al. Blood pressure levels and mortality risk among hemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 2012; **82:** 570–80.

5 Laurent G, Charra B. The results of an 8 h thrice weekly haemodialysis schedule. *Nephrol Dial Transplant* 1998; **13** (suppl 6)**:** 125–31.

6 Ozkahya M, Ok E, Toz H, et al. Long-term survival rates in haemodialysis patients treated with strict volume control. *Nephrol Dial Transplant* 2006; **21:** 3506–13.

7 Foley RN, Herzog CA, Collins AJ. Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. *Kidney Int* 2002; **62:** 1784–90

8 Conlon PJ, Walshe JJ, Heinle SK, Minda S, Krucoff M, Schwab SJ. Predialysis systolic blood pressure correlates strongly with mean 24-hour systolic blood pressure and left ventricular mass in stable hemodialysis patients. *J Am Soc Nephrol* 1996; **7:** 2658–63.

9 Agarwal R. Blood pressure and mortality among hemodialysis patients. *Hypertension* 2010; **55:** 762–68.

10 Merchant A, Wald R, Goldstein MB, et al. Relationship between different blood pressure measurements and left ventricular mass by cardiac magnetic resonance imaging in end-stage renal disease. *J Am Soc Hypertens* 2015; **9:** 275–84.

11 Koomans HA, Geers AB, Mees EJ. Plasma volume recovery after ultrafiltration in patients with chronic renal failure. *Kidney Int* 1984; **26:** 848–54.

12 Braam B, Jindal K, Dorhout Mees EJ. Hypertension and cardiovascular aspects of dialysis treatment. Clinical management of volume control. Lengerich: Pabst Science Publishers, 2011.

13 Inrig JK, Patel UD, Toto RD, Szczech LA. Association of blood pressure increases during hemodialysis with 2-year mortality in incident hemodialysis patients: a secondary analysis of the Dialysis Morbidity and Mortality Wave 2 Study. *Am J Kidney Dis* 2009; **54:** 881–90.

14 Chou KJ, Lee PT, Chen CL, et al. Physiological changes during hemodialysis in patients with intradialysis hypertension. *Kidney Int* 2006; **69:** 1833–38.

15 Cirit M, Akcicek F, Terzioglu E, et al. 'Paradoxical' rise in blood pressure during ultrafiltration in dialysis patients. *Nephrol Dial Transplant* 1995; **10:** 1417–20.

16 Gunal AI, Karaca I, Celiker H, Ilkay E, Duman S. Paradoxical rise in blood pressure during ultrafiltration is caused by increased cardiac output. *J Nephrol* 2002; **15:** 42–47.

17 Agarwal R, Light RP. Intradialytic hypertension is a marker of volume excess. *Nephrol Dial Transplant* 2010; **25:** 3355–61.

18 Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney Int* 1996; **49:** 1379–85.

19 Paoletti E, Specchia C, Di Maio G, et al. The worsening of left ventricular hypertrophy is the strongest predictor of sudden cardiac death in haemodialysis patients: a 10 year survey. *Nephrol Dial Transplant* 2004; **19:** 1829–34

20 Tozawa M, Iseki K, Iseki C, Takishita S. Pulse pressure and risk of total mortality and cardiovascular events in patients on chronic hemodialysis. *Kidney Int* 2002; **61:** 717–26.

21 Degoulet P, Legrain M, Réach I, et al. Mortality risk factors in patients treated by chronic hemodialysis. Report of the Diaphane collaborative study. *Nephron* 1982; **31:** 103–10.

22 Lynn KL, McGregor DO, Moesbergen T, Buttimore AL, Inkster JA, Wells JE. Hypertension as a determinant of survival for patients treated with home dialysis. *Kidney Int* 2002; **62:** 2281–87.

23 Mazzuchi N, Carbonell E, Fernández-Cean J. Importance of blood pressure control in hemodialysis patient survival. *Kidney Int* 2000; **58:** 2147–54.

24 De Lima JJ, Vieira ML, Abensur H, Krieger EM. Baseline blood pressure and other variables influencing survival on haemodialysis of patients without overt cardiovascular disease. *Nephrol Dial Transplant* 2001; **16:** 793–97.

25 Salem MM, Bower J. Hypertension in the hemodialysis population: any relation to one-year survival? *Am J Kidney Dis* 1996; **28:** 737–40.

26 Salem MM. Hypertension in the haemodialysis population: any relationship to 2-years survival? *Nephrol Dial Transplant* 1999; **14:** 125–28.

27 Zager PG, Nikolic J, Brown RH, et al. "U" curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic, Inc. *Kidney Int* 1998; **54:** 561–69.

28 Stidley CA, Hunt WC, Tentori F, et al. Medical Directors of Dialysis Clinic Inc. Changing relationship of blood pressure with mortality over time among hemodialysis patients. *J Am Soc Nephrol* 2006; **17:** 513–20.

29 Töz H, Ozkahya M, Ozerkan F, Aşçi G, Ok E. Improvement in "uremic" cardiomyopathy by persistent ultrafiltration. *Hemodial Int* 2007; **11:** 46–50.

30 Raimann JG, Williams C, Gupta S, et al. Systematic reduction of interdialytic weight gain and posthemodialysis weight lowers systolic and diastolic blood pressure: Preliminary results of a quality improvement project. *Nephrol Dial Transplant* 2015; **30** (suppl 3)**:** ii276–97.

31 Levin NW, Kotanko P, Eckardt KU, et al. Blood pressure in chronic kidney disease stage 5D-report from a Kidney Disease: Improving Global Outcomes controversies conference. *Kidney Int* 2010; **77:** 273–84.

32 Takahashi A, Takase H, Toriyama T, et al. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis—a randomized study. *Nephrol Dial Transplant* 2006; **21:** 2507–12.

33 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.

34 Tai DJ, Lim TW, James MT, Manns BJ, Tonelli M, Hemmelgarn BR; Alberta Kidney Disease Network. Cardiovascular effects of angiotensin converting enzyme inhibition or angiotensin receptor blockade in hemodialysis: a meta-analysis. *Clin J Am Soc Nephrol* 2010; **5:** 623–30.

35 Heerspink HJ, Ninomiya T, Zoungas S, et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. *Lancet* 2009; **373:** 1009–15.

36 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.

37 Iseki K, Arima H, Kohagura K, et al, Olmesartan Clinical Trial in Okinawan Patients Under OKIDS (OCTOPUS) Group. Effects of angiotensin receptor blockade (ARB) on mortality and cardiovascular outcomes in patients with long-term haemodialysis: a randomized controlled trial. *Nephrol Dial Transplant* 2013; **28:** 1579–89.

38 Peters CD, Kjaergaard KD, Jensen JD, et al. No significant effect of angiotensin II receptor blockade on intermediate cardiovascular end points in hemodialysis patients. *Kidney Int* 2014; **86:** 625–37.

39 Lopes AA, Bragg-Gresham JL, Ramirez SP, et al. Prescription of antihypertensive agents to haemodialysis patients: time trends and associations with patient characteristics, country and survival in the DOPPS. *Nephrol Dial Transplant* 2009; **24:** 2809–16.

40 Katzarski KS, Nisell J, Randmaa I, Danielsson A, Freyschuss U, Bergström J. A critical evaluation of ultrasound measurement of inferior vena cava diameter in assessing dry weight in normotensive and hypertensive hemodialysis patients. *Am J Kidney Dis* 1997; **30:** 459–65.

41 Vertes V, Cangiano JL, Berman LB, Gould A. Hypertension in end-stage renal disease. *N Engl J Med* 1969; **280:** 978–81.

42 Curtis JR, Eastwood JB, Smith EK, et al. Maintenance haemodialysis. *Q J Med* 1969; **37:** 49–89.

43 Charra B, Calemard E, Ruffet M, et al. Survival as an index of adequacy of dialysis. *Kidney Int* 1992; **41:** 1286–91.

44 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.

45 Charra B. Fluid balance, dry weight, and blood pressure in dialysis. *Hemodial Int* 2007; **11:** 21–31.

46 Kayikcioglu M, Tumuklu M, Ozkahya M, et al. The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis. *Nephrol Dial Transplant* 2009; **24:** 956–62.

47 Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS. Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. *Kidney Int* 1995; **47:** 884–90.

48 Arneson TJ, Liu J, Qiu Y, Gilbertson DT, Foley RN, Collins AJ. Hospital treatment for fluid overload in the Medicare hemodialysis population. *Clin J Am Soc Nephrol* 2010; **5:** 1054–63.

49 Ozdogan O, Kayikcioglu M, Asci G, et al. Left atrial volume predicts mortality in low-risk dialysis population on long-term low-salt diet. *Am Heart J* 2010; **159:** 1089–94.

50 Agarwal R. Hypervolemia is associated with increased mortality among hemodialysis patients. *Hypertension* 2010; **56:** 512–7.

51 Wizemann V, Wabel P, Chamney P, et al. The mortality risk of overhydration in haemodialysis patients. *Nephrol Dial Transplant* 2009; **24:** 1574–79.

52 Zoccali C, Torino C, Tripepi R, et al. Lung US in CKD Working Group. Pulmonary congestion predicts cardiac events and mortality in ESRD. *J Am Soc Nephrol* 2013; **24:** 639–46.

53 Katzarski KS, Charra B, Luik AJ, et al. Fluid state and blood pressure control in patients treated with long and short haemodialysis. *Nephrol Dial Transplant* 1999; **14:** 369–75.

54 Saran R, Bragg-Gresham JL, Rayner HC, et al. Nonadherence in hemodialysis: associations with mortality, hospitalization, and practice patterns in the DOPPS. *Kidney Int* 2003; **64:** 254–62.

55 Kalantar-Zadeh K, Regidor DL, Kovesdy CP, et al. Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. *Circulation* 2009; **119:** 671–79.

56 Scribner BH, Buri R, Caner JE, Hegstrom R, Burnell JM. The treatment of chronic uremia by means of intermittent hemodialysis: a preliminary report. *Trans Am Soc Artif Intern Organs* 1960; **6:** 114–22.

57 Guyton AC. Kidneys and fluids in pressure regulation: small volume but large pressure changes. *Hypertension* 1992; **19** (suppl 1)**:** 12–18.

58 Koomans HA, Roos JC, Boer P, Geyskes GG, Mees EJ. Salt sensitivity of blood pressure in chronic renal failure. Evidence for renal control of body fluid distribution in man. *Hypertension* 1982; **4:** 190–97.

59 Guyton AC. Arterial pressure and hypertension. London: WB Saunders Company, 1980.

60 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.

61 Sellars L, Robson V, Wilkinson R. Sodium retention and hypertension with short dialysis. *BMJ* 1979; **1:** 520–21.

62 Laurent G. How to keep the dialysis patients normotensive? What is the secret of Tassin? *Nephrol Dial Transplant* 1997; **12:** 1104.

63 Charra B, Bergström J, Scribner BH. Blood pressure control in dialysis patients: importance of the lag phenomenon. *Am J Kidney Dis* 1998; **32:** 720–24.

64 Twardowski ZJ. Sodium, hypertension, and an explanation of the "lag phenomenon" in hemodialysis patients. *Hemodial Int* 2008; **12:** 412–25.

65 Chazot C, Charra B, Laurent G, et al. Interdialysis blood pressure control by long haemodialysis sessions. *Nephrol Dial Transplant* 1995; **10:** 831–37.

66 Ozkahya M, Ok E, Cirit M, et al. Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. *Nephrol Dial Transplant* 1998; **13:** 1489–93.

67 Cirit M, Ozkahya M, Cinar CS, et al. Disappearance of mitral and tricuspid regurgitation in haemodialysis patients after ultrafiltration. *Nephrol Dial Transplant* 1998; **13:** 389–92.

68 Erdem Y, Arici M, Altun B, et al. The relationship between hypertension and salt intake in Turkish population: SALTURK study. *Blood Press* 2010; **19:** 313–18.

69 Tripepi G, Mattace-Raso F, Mallamaci F, et al. Biomarkers of left atrial volume: a longitudinal study in patients with end stage renal disease. *Hypertension* 2009; **54:** 818–24.

70 Sinha AD, Light RP, Agarwal R. Relative plasma volume monitoring during hemodialysis AIDS the assessment of dry weight. *Hypertension* 2010; **55:** 305–11.

71 Cheriex EC, Leunissen KM, Janssen JH, Mooy JM, van Hooff JP. Echography of the inferior vena cava is a simple and reliable tool for estimation of 'dry weight' in haemodialysis patients. *Nephrol Dial Transplant* 1989; **4:** 563–68.

72 Charra B, Laurent G, Chazot C, et al. Clinical assessment of dry weight. *Nephrol Dial Transplant* 1996; **11** (suppl 2)**:** 16–19.

73 Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT, for the NECOSAD Study Group. Predictors of the rate of decline of residual renal function in incident dialysis patients. *Kidney Int* 2002; **62:** 1046–53.

74 Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 2009; **4:** 914–20.

75 Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int* 2011; **79:** 250–57.

76 Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. *Hypertension* 2009; **53:** 500–07.

77 Curatola G, Bolignano D, Rastelli S, et al. Ultrafiltration intensification in hemodialysis patients improves hypertension but increases AV fistula complications and cardiovascular events. *J Nephrol* 2011; **24:** 465–73.

78 Ozkahya M, Toz H, Qzerkan F, et al. Impact of volume control on left ventricular hypertrophy in dialysis patients. *J Nephrol* 2002; **15:** 655–60.

79 Ozkahya M, Töz H, Unsal A, et al. Treatment of hypertension in dialysis patients by ultrafiltration: role of cardiac dilatation and time factor. *Am J Kidney Dis* 1999; **34:** 218–21.

80 Tomson CR. Advising dialysis patients to restrict fluid intake without restricting sodium intake is not based on evidence and is a waste of time. *Nephrol Dial Transplant* 2001; **16:** 1538–42.

81 McCausland FR, Waikar SS, Brunelli SM. Increased dietary sodium is independently associated with greater mortality among prevalent hemodialysis patients. *Kidney Int* 2012; **82:** 204–11.

82 Tuomilehto J, Jousilahti P, Rastenyte D, et al. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. *Lancet* 2001; **357:** 848–51.

83 Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* 2007; **334:** 885–88.

84 Penne EL, Sergeyeva O. Sodium gradient: a tool to individualize dialysate sodium prescription in chronic hemodialysis patients? *Blood Purif* 2011; **31:** 86–91.

85 de Paula FM, Peixoto AJ, Pinto LV, Dorigo D, Patricio PJ, Santos SF. Clinical consequences of an individualized dialysate sodium prescription in hemodialysis patients. *Kidney Int* 2004; **66:** 1232–38.

86 Santos SF, Peixoto AJ. Revisiting the dialysate sodium prescription as a tool for better blood pressure and interdialytic weight gain management in hemodialysis patients. *Clin J Am Soc Nephrol* 2008; **3:** 522–30.

87 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.

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

89 Susantitaphong P, Koulouridis I, Balk EM, Madias NE, Jaber BL. Effect of frequent or extended hemodialysis on cardiovascular parameters: a meta-analysis. *Am J Kidney Dis* 2012; **59:** 689–99.

90 Rocco MV, Lockridge RS Jr, Beck GJ, et al. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. *Kidney Int* 2011; **80:** 1080–91.

91 Kaysen GA, Greene T, Larive B, et al. The effect of frequent hemodialysis on nutrition and body composition: frequent Hemodialysis Network Trial. *Kidney Int* 2012; **82:** 90–99.

Dialysis 3

Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and haemodialysis practices

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More than 2 million people worldwide are being treated for end-stage kidney disease (ESKD). This Series paper provides an overview of incidence, modality use (in-centre haemodialysis, home dialysis, or transplantation), and mortality for patients with ESKD based on national registry data. We also present data from an international cohort study to highlight differences in haemodialysis practices that affect survival and the experience of patients who rely on this therapy, which is both life-sustaining and profoundly disruptive to their quality of life. Data illustrate disparities in access to renal replacement therapy of any kind and in the use of transplantation or home dialysis, both of which are widely considered preferable to in-centre haemodialysis for many patients with ESKD in settings where infrastructure permits. For most patients with ESKD worldwide who are treated with in-centre haemodialysis, overall survival is poor, but longer in some Asian countries than elsewhere in the world, and longer in Europe than in the USA, although this gap has reduced. Commendable haemodialysis practice includes exceptionally high use of surgical vascular access in Japan and in some European countries, and the use of longer or more frequent dialysis sessions in some countries, allowing for more effective volume management. Mortality is especially high soon after ESKD onset, and improved preparation for ESKD is needed including alignment of decision making with the wishes of patients and families.

Introduction

An estimated 2·6 million people worldwide were treated for end-stage kidney disease (ESKD) in 2010, and one to three times that number might have died because they reached ESKD but renal replacement therapy (RRT) was declined or could not be accessed.[1] Our Series paper first provides an overview of incidence, modality use (in-centre dialysis, home dialysis, or transplantation), and mortality for patients with ESKD based on data from many national registries. In addition to population differences in the incidence of kidney failure, these data illustrate disparities in access to RRT of any kind, and disparities in the use of transplantation or home dialysis, widely considered preferable to in-centre haemodialysis for many patients with ESKD where infrastructure permits. Worldwide, most patients with ESKD are treated with in-centre haemodialysis, and, though survival outcomes are poor overall, survival in some Asian countries substantially exceeds survival elsewhere. In this Series paper we then present international cohort study data that demonstrate differences in key in-centre haemodialysis practices, highlighting opportunities to improve survival and the experience of the millions of patients who rely on this therapy, which is both life-sustaining and profoundly disruptive to their lives.

Search strategy and selection criteria

We searched MEDLINE for articles published between Jan 1, 2006, and Jan 1, 2016, with terms related to specific content areas (including worldwide treatment end-stage renal disease [ESRD]; dialysis conservative care; APO L1 and kidney disease; haemodialysis treatment time; Frequent Haemodialysis Network; and HEMO trial). We also searched for relevant information in national ESRD or renal society registry reports, and for particular relevant health initiatives in some countries (UK: end of life planning; US Renal Physicians Association: shared decision making and dialysis withdrawal). We also cited selected publications from the Dialysis Outcomes and Practice Patterns Study, as this was a particular focus for this Series paper. We largely selected publications from the past 5 years, but did not exclude commonly referenced older publications. Reviews are cited to provide readers with more details and references than this Series paper has room for.

Comparisons of national ESKD registries

Data sources

We collected data from the US Renal Data System (USRDS) Annual Data Report,[2] which compiles and publishes incidence and prevalence data annually from more than 50 national registries. National ESKD registry data are not available for countries that include at least half of the world's population, such as in many low-income and middle-income countries in Africa and in the world's two most populous nations China and India. In China, regional registries are in place and efforts towards a national registry are underway.

Key messages

- Although the majority of patients reaching end-stage kidney disease (ESKD) worldwide die because renal replacement therapy (RRT; eg, dialysis or transplantation) cannot be accessed, the incidence of ESKD treated with RRT is rising rapidly in many countries because of increased availability of these services and increasingly older populations with multiple comorbidities.
- ESKD incidence is stable or declining in many countries with long-standing access to RRT, presumably due, in part, to increased success in prevention of chronic kidney disease or slowing of its progression to avoid end-stage kidney failure.
- Transplantation or home dialysis are widely considered preferable to in-centre haemodialysis for many patients with ESKD, yet use of these modalities ranges from more than two-thirds of patients in some countries to fewer than 10% in many others.
- Worldwide survival is poor in most patients with ESKD who are treated with in-centre haemodialysis, but generally survival is improving, and is longest in some Asian countries.
- International variation in haemodialysis practices and outcomes highlights opportunities to improve care; commendable practice patterns include exceptionally high use of surgical vascular access in Japan and some European countries, and high use of longer or more frequent dialysis sessions in countries such as Germany, Australia, and New Zealand, allowing for more effective management of volume status.
- Mortality is especially high soon after onset of ESKD therapy, and improved preparation for ESKD is needed, including alignment of decision making (eg, modality selection, patient choice to decline or withdraw from dialysis, and timing of RRT initiation) with wishes of patients and their families.

ESKD incidence

Registry data are provided for patients with ESKD treated by RRT (defined here as chronic dialysis or kidney transplantation). Table 1 summarises some factors that might affect incidence of treated ESKD. Gross domestic product (GDP) per person and percentage of GDP spent on health care are positively associated with incidence of treated ESKD,[3] reflecting the reality that many countries have unrecognised diagnoses of ESKD or reduced access to RRT. As a result, reported ESKD incidence almost certainly underestimates the incidence of kidney failure in these countries. Even in countries where RRT is widely available, ESKD incidence probably underestimates irreversible kidney failure to some extent because some patients choose to decline dialysis or transplantation. The term "conservative kidney management" has been applied to the choice to forego or postpone RRT while continuing active medical care by nephrologists and other providers. Conservative kidney management has been promoted for some time in Australia, the UK, and other countries, and has become an increasingly visible option worldwide.[4–7]

Both absolute rates of treated ESKD and trends in these rates are informative. Of higher-income countries, ESKD incidence is lowest in Nordic countries, other European countries, Australia, and New Zealand (figure 1). These countries have nearly universal access to RRT, so these rates are presumably due to relatively low incidence or progression of chronic kidney disease. Selection of conservative kidney management in lieu of RRT is probably not a major determinant of low ESKD incidence, although the extent of its use is not well known. By contrast, ESKD incidence is much higher in the USA and high-income eastern or southeastern Asian countries, presumably reflecting high burden of chronic kidney disease and antecedent risk factors such as diabetes, hypertension, obesity, and glomerular diseases (eg, IgA nephropathy in Asian populations).

Also in higher-income countries, ESKD incidence rates have plateaued during the past decade, not only in Nordic and other European countries but also in the USA, which has a much higher ESKD incidence.[2] Stabilisation of ESKD incidence might suggest increased success in prevention of chronic kidney disease or slowing its progression to avoid kidney failure. In support of either possibility, incidence of ESKD due to diabetes has plateaued or declined in nearly all of these countries in 2008–13.[2] Both reasons would be important public health achievements. Other factors that might have contributed to reductions in the observed incidence rates of ESKD are increases in the delay to start RRT or in patients who choose to avoid RRT entirely in favour of conservative kidney management. By contrast, incidence of ESKD continues to rise in higher-income eastern and southeast Asian countries.

In lower-income countries, reported incidence of ESKD varies greatly (figure 1) and substantial increases in recent years have been reported. From 2000 to 2013, increases of 13 times in Thailand, seven times in Bangladesh, and almost four times in Russia were reported, whereas rises of two to three times were seen in the Philippines, Malaysia, the Jalisco region of Mexico, as well as South Korea. As a whole, expansion of governmental support for dialysis programmes was the largest contributor to the rise in ESKD incidence counts, with smaller contributions from increased population size, rise in ageing populations, and growing prevalence of hypertension and diabetes.[8] Although expanded access to RRT in many countries is commendable, reduced or no access to RRT is all too common in other countries. The substantially lower incidence reported for ESKD in Indonesia, the Philippines, and Bangladesh than in higher-income countries in east and southeast Asia presumably reflects, at least in part, reduced access to RRT. Worldwide, and as previously noted, the number of people who reach ESKD without access to RRT is estimated at up to three times higher than the number who receive RRT.[1]

In many countries, the incidence of ESKD due to diabetes has risen much faster than the overall rise in ESKD incidence, presumably reflecting the rising population burden of diabetes and improving survival for people with diabetes. Diabetes was the primary cause of ESKD in 32% of incident patients in the median country in 2013 from 46 national registries,[2] varying from 15–25% in many European countries to about 60% in Malaysia,

	Comments
ESKD incidence	Net trend in ESKD incidence varies (from strongly positive to weakly negative) across countries
Factors favouring higher incidence	
Increase in population size	Affects incident counts, not rate
Increase in population and age, and in prevalence of diabetes, hypertension, and obesity	Greater burden of risk factors for ESKD
Longer survival with chronic kidney disease	Yielding more people who can progress to ESKD
Increase in access to renal replacement therapy	In many low-income and middle-income countries
Larger percentage of gross domestic product spent on health care	Via effect on several other factors listed
Earlier start of dialysis therapy	Earlier as defined by higher eGFR at dialysis start
Factors favouring lower incidence	
Better treatment of diabetes and hypertension	Decreasing incidence of CKD or rates of CKD progression
Later start of dialysis therapy	Later as defined by lower eGFR at dialysis start
Greater use of conservative kidney management	Conservative kidney management is management without dialysis, for patients reaching ESKD
ESKD prevalence	Net trend in ESKD prevalence is increasing in nearly all countries providing data
Factors favouring higher prevalence	
Rising incidence of treated ESKD	Occurring in most countries
Increasing proportion of ESKD patients receiving a kidney transplant	On average patients with kidney transplant survive longer than dialysis patients
Longer survival for dialysis and transplant recipients	Documented in many countries
Fewer voluntary withdrawals from dialysis	Trends in dialysis withdrawals are uncertain in most countries
Factors favouring lower prevalence	
Stable or lower incidence of treated ESKD	Occurs in a few countries
Time-limited payment for dialysis	Occurs in some countries, where government support for payment is limited to, for example, 1 year of dialysis

ESKD=end-stage kidney disease. eGFR=estimated glomerular filtration rate. CKD=chronic kidney disease.

Table 1: **Examples of factors affecting incidence and prevalence of treated ESKD**

Singapore, and the Jalisco region of Mexico. The global rise in diabetes and its end-organ complications has also affected the burden of comorbidities and overall frailty of patients with ESKD. The complexity of disease management and risks for adverse outcomes (ie, mortality, admission to hospital, cardiovascular events, stroke, vascular access complications, infections, amputations, and others) are higher in patients with ESKD and diabetes than in those without diabetes.[2,9–11]

ESKD prevalence

Reported ESKD prevalence varies by almost 50 times between countries (figure 1)[2] and is strongly correlated with ESKD incidence (regression coefficient [R^2]=0·66 across all countries). Unlike trends in ESKD incidence which vary from strongly positive to negative, the prevalence of ESKD per million population has increased in all 32 registries contributing data,[2] with a median increase of 50% (range 29–839) during 2000–13. Several observations are pertinent to this Series paper. First, increases in ESKD prevalence in countries with little change in the incidence are strongly indicative of declines in ESKD mortality, now generally confirmed by data from registries that publish mortality trends. Second, in countries such as Indonesia, the Philippines, and Bangladesh, ESKD prevalence is disproportionately very low in relation to the incidence. In these countries, government or third party payment for dialysis is limited to a finite period of time. Third, overall upward trends in ESKD prevalence, and similar projections for the near future, support the need for expanded access to in-centre dialysis, home dialysis, and kidney transplantation services to meet the growing worldwide burden of ESKD.[2,8]

ESKD treatment modalities

Kidney transplantation is the treatment of choice for eligible patients with ESKD, which results in a substantially improved quality of life and median survival similar to survival for patients without ESKD. Stark differences exist in access to and use of kidney transplantation. In 2013, transplantation use for patients with ESKD ranged from 57–72% in Nordic countries, Estonia, and the Netherlands, to less than 10% in some Asian and eastern European countries (figure 2). A striking observation is that the countries with the highest proportion of kidney transplants in patients with ESKD—mostly Nordic and several other European countries—also have some of the lowest incidence rates of ESKD. One implication, of public health importance, is that efforts to slow progression of chronic kidney disease might have additional downstream benefits, namely that kidney transplantation can be offered to a higher proportion of patients with ESKD because of a relatively low number of incident cases. Some European countries have a much larger proportion of incident ESKD cases who receive a pre-emptive kidney transplant (18–40% in Denmark, Iceland, Norway, Sweden, the Netherlands, and the UK) than other countries (1–2% in the USA;[12] Kramer A and Pippias M, European Renal Association/European Dialysis and Transplant Association (ERA-EDTA) Registry, personal communication). As such, these countries provide a substantial fraction of their incident patients with ESKD the opportunity to avoid dialysis as their first treatment for this disease, and potentially altogether. The optimum timing of pre-emptive transplantation remains controversial, because it balances dialysis avoidance with early exposure to chronic immunosuppressive therapy.

Of dialysis modalities, home dialysis options (peritoneal dialysis or home haemodialysis) are considered to have clinical outcomes that are better or at least comparable to in-centre haemodialysis, and are substantially less disruptive to patients' lives.[13] Countries that provide home dialysis to at least 20% of patients with ESKD include Hong Kong (45%), and New Zealand, Colombia, Thailand, and the Jalisco region of Mexico

(23–31%; figure 2). These countries' performances suggest that a large pool of patients receiving in-centre haemodialysis in other countries could use home dialysis if it were made more widely available. For example, peritoneal dialysis use in the USA has risen from 8% in 2009, to 10% in 2015, attributed principally to changes in reimbursement favouring use of peritoneal dialysis. Although this increase can be viewed enthusiastically, this 2% absolute increase could almost certainly be higher still if the culture of in-centre dialysis were less entrenched.

By providing kidney transplantation or home dialysis to a substantial fraction of patients, several nations use in-centre haemodialysis for fewer than a third of their patients with ESKD. These countries include Hong Kong (the lowest use of in-centre haemodialysis at 15%), Estonia, the Netherlands, New Zealand, and some Nordic countries (figure 2). By contrast, in many countries in eastern and southeastern Asia, at least 85% of patients with ESKD receive in-centre haemodialysis. Of these, Japan is notable because it has a large and mature ESKD treatment programme with excellent clinical outcomes, but very low use of transplantation and home dialysis. In-centre dialysis is favoured over home dialysis in Japan partly for historical reasons (many dialysis facilities are available and are easily accessible, with many placed explicitly near public transportation stops), and kidney donation rates are low, which might be because of spiritual or religious beliefs.

ESKD and dialysis mortality

Although most ESKD registries report incidence and prevalence data, survival data are preponderantly from higher-income countries. For those with ESKD onset from 2004 to 2008, unadjusted 5-year survival of all patients with ESKD (treated with dialysis or transplantation) was 41% in the USA, 48% in Europe, and 60% in Japan, despite patients being 2–3 years older on average in Europe and Japan than in the USA, and Japan having very few transplant patients.[2,12–15] The survival difference between the USA and Europe is smaller than in previous years, because mortality has declined in both regions but to a greater extent in the USA. In 1996–2000, 5-year survival in patients with incident ESKD was 36% in the USA and 48% in Europe[2,12,15] (in Europe, unadjusted survival was 47·6% in 2004 *vs* 48·3% in 2008; countries in the ERA-EDTA Registry differed slightly).[16]

Japan substantially outperforms other countries in survival of patients receiving dialysis. Unadjusted 5-year survival was 60% in Japan, 39% in the USA, and 41% in Europe for patients starting dialysis in 2004–08.[2,14,15] Where data are available, survival is good in other countries with populations of predominantly Asian ethnicity: unadjusted 5-year survival was 52% in Malaysia (2004–08)[17] and 44% in Taiwan (2000–09).[18] National dialysis outcomes data are, to our knowledge, not yet available from China or south Asian countries, although steps are underway to obtain such data.[19]

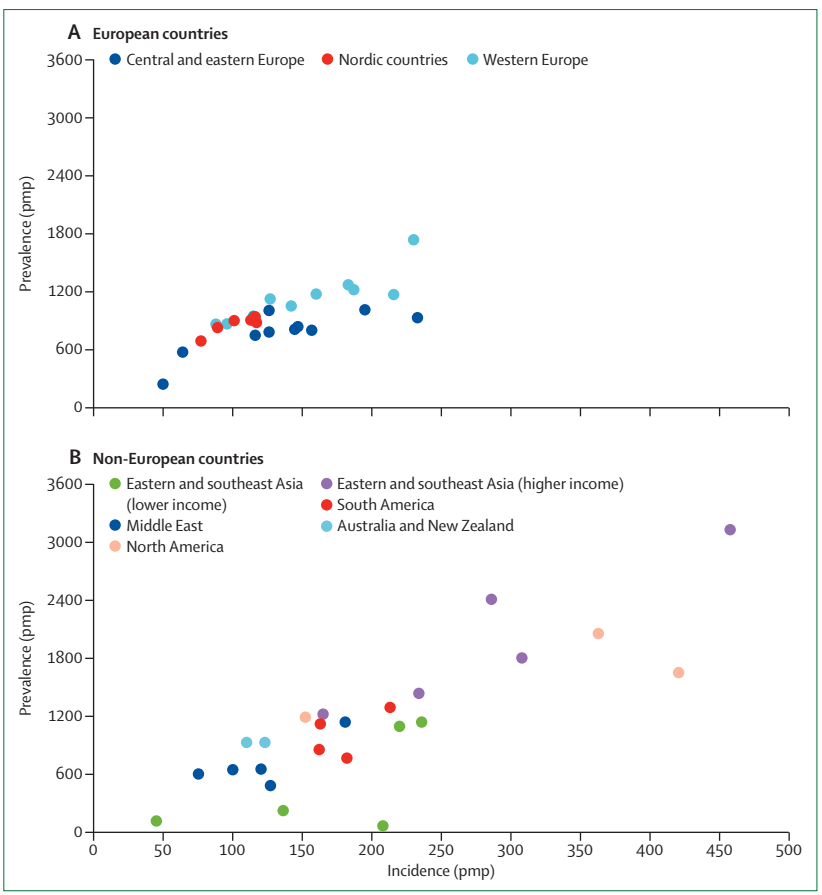

Figure 1: **Treated end-stage kidney disease incidence and prevalence by country in 2013**
End-stage kidney disease (ESKD) incidence and prevalence calculated for patients using either maintenance dialysis or a kidney transplant for ESKD. Countries listed in order of lowest to highest incidence within each region. (A) Central and eastern Europe: Russia, Estonia, Bosnia and Herzegovina, Poland, Slovenia, Romania, Serbia, Croatia, Czech Republic, and Hungary; Nordic countries: Iceland, Finland, Norway, Sweden, and Denmark; and western Europe: Ireland, Scotland, UK (excluding Scotland), Netherlands, Spain, Austria, France, Belgium (French speaking), Belgium (Dutch speaking), Greece, and Portugal. (B) Eastern and southeastern Asia (gross national income <US$25 000): Bangladesh, Philippines, Indonesia, Thailand, and Malaysia; eastern and southeastern Asia (gross national income ≥$25 000): Hong Kong, South Korea, Japan, Singapore, and Taiwan; the Middle East: Iran, Qatar, Oman, Saudi Arabia, and Israel; South America: Argentina, Uruguay, Brazil, and Chile; North America: Canada, USA, and Mexico (Jalisco). pmp=per million population. Data are from the US Renal Data System.[2]

The reasons for international differences in the survival of dialysis populations are not completely understood. First, patients receiving dialysis in countries with the highest transplantation rates are relatively older and less healthy than those in countries with lower rates of transplantation, so these countries tend to have a lower dialysis population survival. The opposite is true for Japan, which has very few transplant patients and thus retains its healthiest patients on dialysis. However, differences between patient characteristics explain only part of the international variation in survival.[10,20] A substantial part of the variability seems to be attributable to variation in cardiovascular[21] and all-cause[22] background mortality in the general populations. Investigations of the relative frequencies of types of stroke by ethinic origin showed a

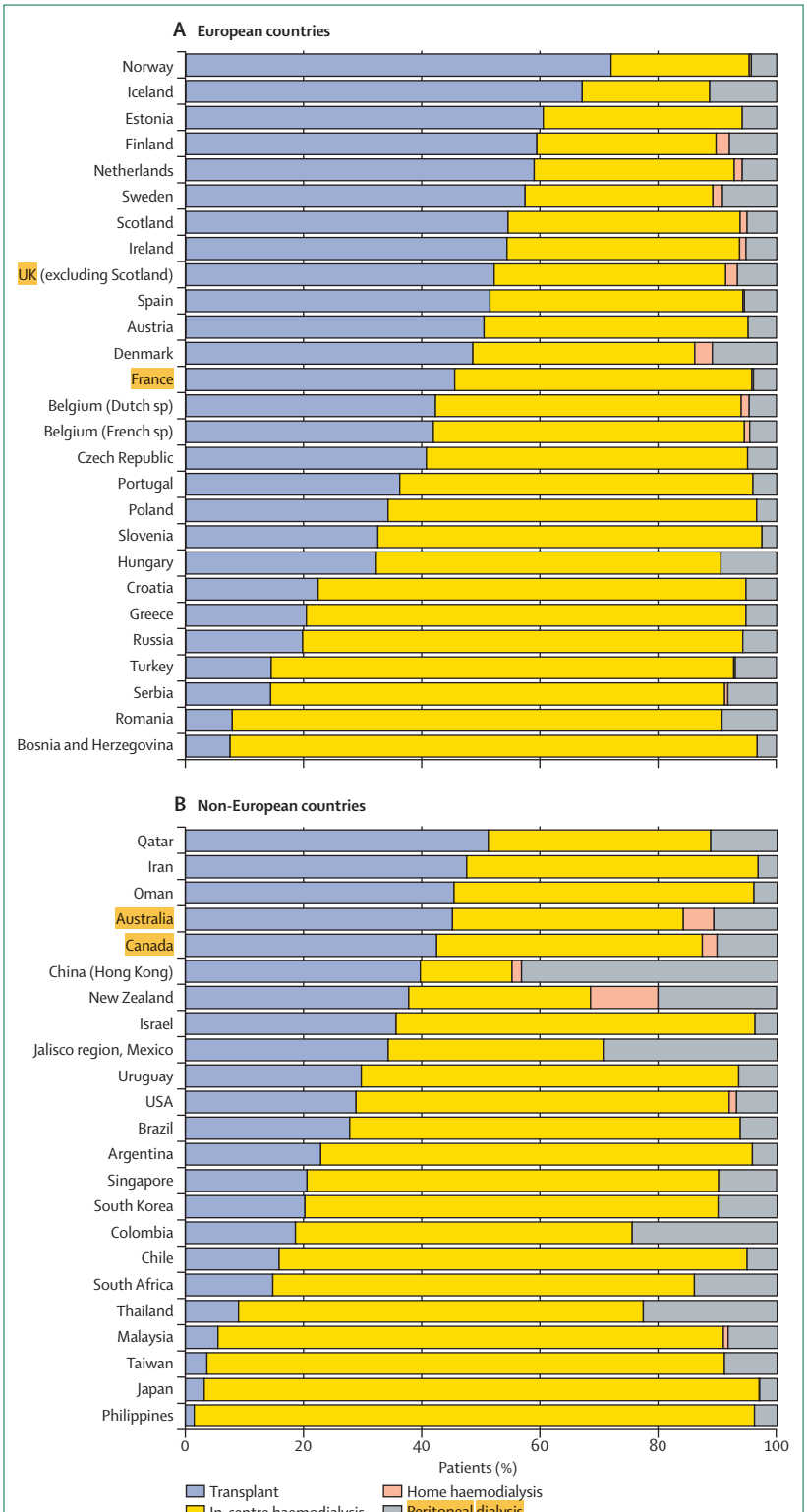

Figure 2: **Renal replacement therapy modality used for patients with end-stage kidney disease, by country, in 2013**

Modality use is shown for all patients reported in each country who received either chronic dialysis or a kidney transplant for treatment of end-stage kidney disease in 2013. Data are from the US Renal Data System.[2]

higher proportion of haemorrhagic versus thrombotic stroke in eastern and southeast Asian populations than in European and US populations,[11,23] implying differences in vascular biology or pathophysiological responses to hypertension in different populations.

Intriguingly, adjusted survival on dialysis in Europe and North America is generally shortest in white individuals.[2,24–26] In the UK, survival is longer in those of south Asian origin and those who are black compared with white patients. Similarly, in the USA, patients who are Asian, black, or Native American have longer survival than white patients, as do those of Hispanic origin than non-Hispanics. In the USA, nutritional status is healthier and muscle mass is greater in black than in white dialysis patients.[26] In the past 5 years, high ESKD incidence in black patients has been attributed to functional variants of the *APOL1* gene, which is most common in people of west African descent, and is believed to have evolved as protection from trypanosomal parasitic infections.[27–30] Whether *APOL1*-associated ESKD has a role in explaining racial differences for survival of patients receiving dialysis in the USA is unknown.

International variation in dialysis practices

While international differences in dialysis outcomes derive in part from variation in patient characteristics, evidence over the years indicates that survival differences are, to some extent, affected by modifiable variation in dialysis practices. With regards to in-centre haemodialysis, many data supporting this assertion are from the Dialysis Outcomes and Practice Patterns Study (DOPPS), a series of consecutive, international, prospective cohort studies. The DOPPS is now in its 20th year and is still motivated by the hypothesis that differences in patient longevity, morbidity, and patient experiences are influenced by measurable differences in dialysis facility practices.[31–52] The DOPPS studies a random sample of in-centre haemodialysis patients within a random sample of dialysis units in each participating country, stratified to represent facility types (eg, free-standing, hospital-based, or satellite facilities) and geographical regions in each country.[53–55] The DOPPS was launched in the USA in 1996, and was expanded to Japan, seven European countries, Canada, Australia, and New Zealand in 1998–2002, China in 2010, and Russia, Turkey, and six Gulf Cooperation Council countries in 2012.[31–52,56–58]

Contrasting Japanese practices with those of other countries

Because haemodialysis mortality is much lower in Japan than most other countries in the DOPPS, many differences in practices and clinical measures have been studied (table 2). Anaemia management is less intensive, with lower erythropoietin stimulating agent doses and less intravenous iron use; targets for haemoglobin, serum ferritin, and parathyroid hormone are lower; dialysate composition is produced centrally without the

chance to modify it at the bedside; dialysate water standards are stricter; and cardiovascular screening tests in the dialysis unit are routine. C-reactive protein concentrations, measured routinely in dialysis units outside the USA, are five times lower in Japan than in Europe, likely reflecting both genetic influences[60] and dialysis practices (eg, high use of surgical vascular access and ultrapure water). Although the previously stated differences are of interest, for many the causal associations with survival are uncertain, illustrating the dearth of definitive clinical trial data in the field.[61] We discuss selected high profile practice areas with some support from higher-level evidence.

The crucial role of vascular access

Of haemodialysis practices, variation in vascular access is undoubtedly one of the most important determinants of patient outcomes.[42] The native arteriovenous fistula (AVF) is widely recognised as the access of first choice for most patients, providing better outcomes than arteriovenous grafts or central venous catheters (CVCs). CVC use has been associated with substantially higher mortality, medical complications, and costs.[42,62–69] Since joining the DOPPS more than 15 years ago, AVF use has been highest in Japan—at more than 90%—than any other country except for Russia, which had more than 90% AVF use at study entry in 2012–13 (table 2; figure 3).[70] (Of note, mortality in patients receiving haemodialysis in the Russian registry is very low at 7·2 deaths per 100 patient-years during 2009–13; although this mortality might reflect excellent practice, patient selection for dialysis could contribute, and greater understanding is needed.[71]) In the late 1990s to early 2000s, AVF use was lower in the USA (24% in 1997) than all other DOPPS countries.[52,70] Shorter survival in the USA compared with Europe was explained largely by differences in vascular access use.[42]

Because high AVF use is of crucial clinical importance and has been achieved in some countries for many years, practice guidelines, policy changes, and quality initiatives have been directed toward this goal in countries with lower rates of AVF use in the past 10–15 years.[72–76] However, in 2013,[70] AVF use in prevalent haemodialysis patients varied from 49% to 92% across 20 countries, and catheter use ranged from 2% to 45% (figure 3A). In countries such as the UK and USA, changes spurred by policy interventions have had commendable effects. In the UK, CVC use declined from 28%[70,77,78] to 16% after application of a tariff to CVC use in 2011–12·[79] In the USA, greater AVF use is largely attributed to the Centers for Medicare & Medicaid Services' (CMS) Fistula First Breakthrough Initiative (FFBI) launched in 2003. From 2003 to 2013, AVF use increased from 32% to 68%, arteriovenous graft use declined from 38% to 18%, and CVC use declined from 27% to 15%.[2,70] The FFBI spurred quality initiatives by dialysis companies, regional ESKD quality networks, and by the CMS.[73,80] By contrast, fistula use has fallen and catheter use has risen in other countries.[77] CVC use is now 38% in Belgium and 45% in Canada, roughly three times higher than in the USA and some European countries.

	Japan	Europe*	USA
Vascular access			
Higher arteriovenous fistula use	91%	69%	68%
Anaemia			
Lower epoetin dose† (median units per week)	5000	7176	9000
Lower intravenous iron use‡	27%	69%	66%
Lower haemoglobin (g/dL)	10·5	11·3	10·9
Lower ferritin (ng/mL)	144	523	758
Mineral bone disorder			
Lower intravenous vitamin D use (*vs* USA)	36%	18%	60%
Lower parathyroid hormone (ng/L)	118	240	303
Dialysis prescription			
Lower blood flow rate (mL/min)	208	333	419
Lower Kt/V_{urea}	1·42	1·57	1·57
Longer dialysis session length (*vs* USA; min)	239	244	218
Dialysis routinely in supine position§	93%	53%	3%
Dialysate composition			
Higher dialysate sodium¶ (mmol/L)	140	139	138
Lower dialysate bicarbonate|| (mmol/L)	29	34	36
Dialysate water			
JSDT standard for dialysis fluid is <0·050 EU/mL of endotoxin and a bacterial count <100 colony forming units per mL, the strictest in the world[15,59]	..	..	..
Cardiovascular factors			
Higher blood pressure (mm Hg)	146	138	145
Lower median CRP concentrations** (mg/L)	1·0	5·2	..
Use of tests			
Routine measurement of CRP** (% of facilities)	73%	70%	0
Routine chest radiographs†† (% of facilities)	98%	59%	40%
Yearly screening for vascular calcification†† (% of facilities)	38%	35%	7%
Patient preparation for dialysis‡‡			
Higher proportion with pre-dialysis care§§	70%	76%	69%
Higher proportion with arteriovenous fistula use at haemodialysis initiation§§	84%	50%	28%
Lower estimated glomerular filtration rate at dialysis start¶¶ (mL/min per 1·73 m^2)	6·8	9·5	10·1

Data are from the initial cross-section of patients enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS) phase 5 (2012–15). Unless otherwise noted, values in the table represent the mean or prevalence weighted by the fraction of patients sampled in each participating facility. Kt/V_{urea}=a unitless measure representing clearance of urea (K) over the duration of a haemodialysis treatment (t), divided by the urea volume of distribution (V_{urea}). JSDT=Japanese Society for Dialysis Therapy. CRP=C-reactive protein. *DOPPS phase 5 European countries were Belgium, Germany, Italy, Spain, Sweden, and the UK. France was excluded because of low DOPPS phase 5 enrolment at time of publication. †Converted to intravenous epoetin equivalent dose; darbepoetin doses converted in ratio of 250:1; pegylated epoetin β (MIRCERA) doses converted in ratio of 208:1; subcutaneous doses converted in ratio of 1·15:1. ‡Prescription in the month before DOPPS enrolment. §On the basis of DOPPS 3 (2006) enrolment data. ¶Excluding patients in whom dialysate sodium concentrations varied during treatment (sodium modelling or profiling). ||Does not account for dialysate acetate concentration; median of 8·0 mmol/L for Japan, 3·0 mmol/L for Europe, and 4·0 mmol/L for the USA. **Restricted to facilities routinely measuring CRP at least once every 4 months for more than 75% of facility patients during DOPPS phase 5 follow-up. ††Used data from DOPPS phase 5 year 3 (2014) medical director survey. ‡‡≥4 months of prenephrology care. §§Among patients on dialysis ≤60 days at DOPPS enrolment. ¶¶In patients enrolled in DOPPS within 120 days of starting dialysis; estimated glomerular filtration rate calculated with the Modification of Diet in Renal Disease (version 4) variable formulae, with variables of creatinine concentration, age, black ethnicity, and sex; qualitatively similar results obtained when also adjusting for Japanese ethnic origin.

Table 2: **Haemodialysis practice areas and clinical measures that differ in Japan from Europe and the USA**

For more information about the **Fistula First Breakthrough Initiative** see http://www.fistulafirst.org

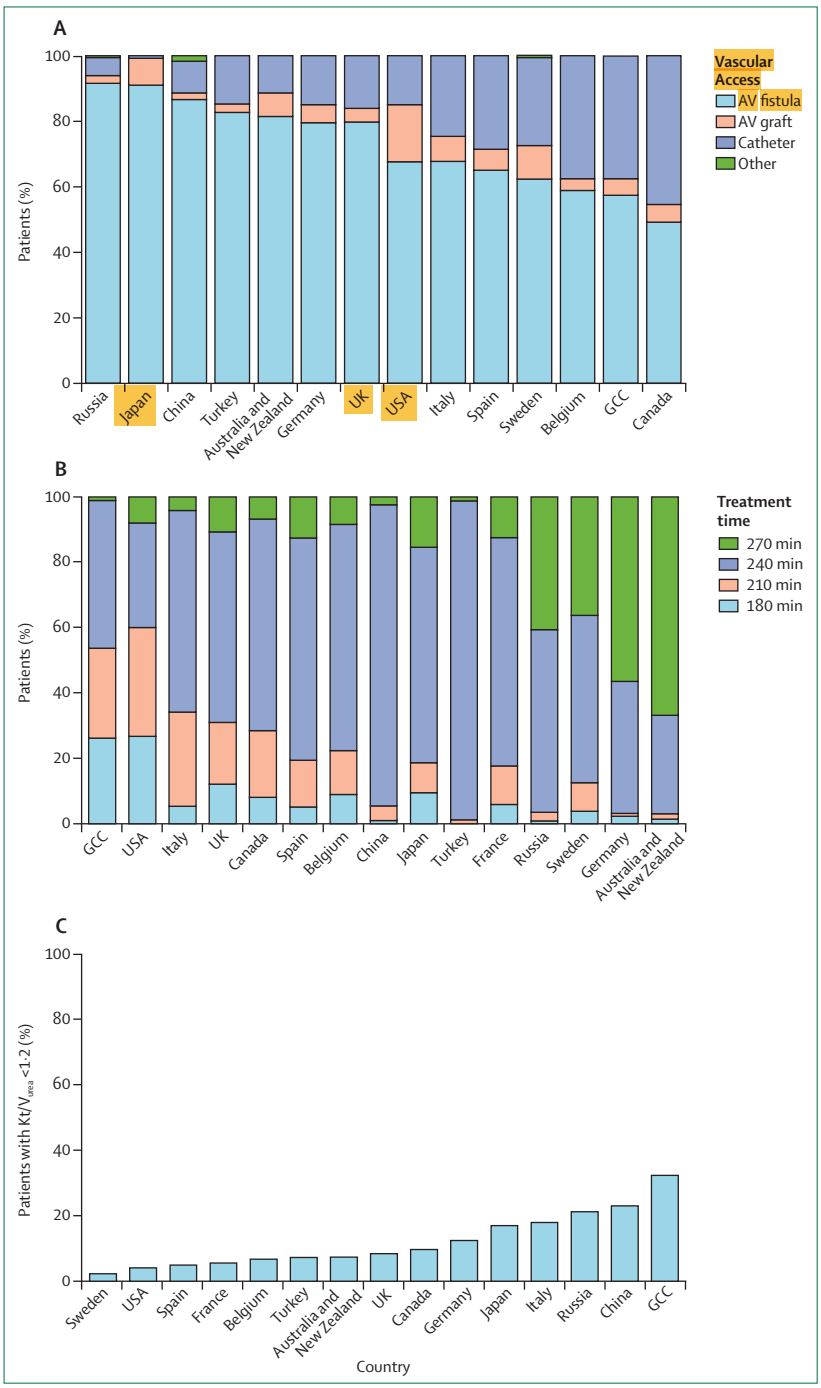

Figure 3: **Selected practices or measures in prevalent haemodialysis patients, by country (2012–15)**
(A) Type of vascular access used. Catheter is a central venous catheter. Data from Gulf Cooperation Council (GCC; Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates), Russia, Turkey, Belgium, Sweden, and China are based on vascular access at the initial cross-section of the Dialysis Outcomes and Practice Patterns Study (DOPPS) phase 5; data from remaining countries based on cross-section of haemodialysis patients in August, 2013. (B) Haemodialysis session duration (treatment time) in patients receiving dialysis three times a week; treatment time was defined as a categorical variable (<200, 200–225, 226–250, and >250 min). Because treatment time for most patients was at exactly 30 min intervals, these categories are labelled as 180, 210, 240, and 270 min, respectively. (C) Single pool Kt/V_{urea} in patients receiving haemodialysis three times a week, and receiving dialysis for at least 1 year. AV=arteriovenous. Kt/V_{urea}=a unitless measure representing clearance of urea (K) over the duration of an haemodialysis treatment (t), divided by the urea volume of distribution (V_{urea}). Some countries are omitted from some figures because of missing data. Figure adapted from Pisoni and colleagues,[70] by permisson of Elsevier.

Drivers of vascular access success, or underperformance, are complex. Social determinants and the dialysis unit culture might be a factor. Although some patients state a preference for CVCs—perhaps because surgical vascular access (AVF or arteriovenous grafts) requires large-needle venipuncture three times a week, often bleeds after dialysis, and can be physically disfiguring[81]—these preferences are more common in CVC users at dialysis centres with high CVC use, suggesting that these centres foster a culture of catheter use. Many additional observations and questions about current vascular access practice remain regarding: why differences in AVF failure rates between centres and countries are so large;[34] whether use of upper arm AVFs (now more common than forearm AVFs in the USA[82]) accelerates loss of sites for future surgical vascular access; why vascular access procedure rates have risen dramatically, and the implications for AVF durability;[83] whether vascular access outcomes can be improved by better coordination of care between the dialysis unit, surgeon, and interventional suite; what are the best approaches to vascular access for dialysis patients with a very short life expectancy; and how patients' preferences can be honoured through the complex and frequently invasive processes associated with establishment and use of vascular access.

Dialysis adequacy and dialysis session duration

Dialysis session length for in-centre haemodialysis has received considerable attention because in the past decade sessions have become longer in most DOPPS countries, but have shortened in the USA (figure 3B). Reasons for these changes reflect interplay between clinical practice recommendations, reimbursement incentives, unit policies, and clinician and patient preferences, all in absence of definitive evidence from clinical trials. For many years, dialysis adequacy in everyday clinical practice has been measured primarily by dialytic clearance of blood urea, expressed typically as Kt/V_{urea} (a unitless measure representing clearance of urea [K] over the duration of a haemodialysis treatment [t], divided by the urea volume of distribution [V_{urea}]). Clinical trial data support achievement of single pool (unequilibrated) Kt/V_{urea} values of more than 1·2, but not necessarily a cutpoint greater than 1·2 for most patients.[50,84,85] Kt/V_{urea} can be raised by increasing the dialyser size or blood flow rate through the dialyser (to increase K_{urea}), or by lengthening the dialysis session (ie, increase in treatment time).

In the absence of definitive clinical trial data, widespread opinion holds that longer treatment time confers clinical benefits beyond Kt/V_{urea}, including clearance of toxins substantially larger than urea (so-called middle molecules) and removal of target fluid volume while reducing haemodynamic instability (ie, intradialytic hypotension).[86,87] Observational data indicate that longer treatment time is associated with longer survival, better volume management, better blood

pressure control, better phosphorus control, and fewer cardiovascular events than shorter dialysis sessions.[23,88–90] In this context, median dialysis treatment time in those patients receiving in-centre dialysis three times weekly is now 4 h (total of 12 h per week) or longer in many high-income countries, despite the logistical challenges to management of dialysis shifts for health-care staff in busy dialysis units.[35,48] Dialysis session duration of 4 h or more was tied to reimbursement measures in Japan in 2008, and Germany in 2009,[91] and sessions in both these countries are now some of the longest in DOPPS countries (figure 3B).

By contrast, performance measures are not pegged to session duration in the USA, but instead to Kt/V_{urea}[72] achieved in dialysis units in the USA via short dialysis sessions, but high blood flow rate and large dialyser size (figure 3C). Shorter dialysis sessions yield many operational advantages for patient flow over three shifts a day in busy dialysis units. Although treatment time is nearly the shortest in the USA of DOPPS countries, average blood flow rate is roughly 50% higher than in Europe and double that used in Japan (table 2).[34] Japanese practice guidelines stress the importance of dialysis that is longer and gentler (ie, uses a lower blood flow rate), on the premise that this approach best ensures haemodynamic stability, despite greater likelihood of having Kt/V_{urea} values of less than 1·2.[33,49,92] Uncertainty about optimum dialysis session length, and metrics for dialysis adequacy and fluid volume management in general, continue to merit research and policy attention. Results from an ongoing pragmatic trial in the USA of dialysis session duration in incident haemodialysis patients (NCT02019225), with randomisation at the centre level to standard session length or 4·25 h, will be of interest.

Use of haemodiafiltration for chronic dialysis has gained much attention with its rapidly increased use in many countries, spurred by the availability of on-line replacement fluid, dialysis machines that can be readily adapted to haemodiafiltration, and accompanying industry interests.[87] Haemodiafiltration use in the DOPPS countries is now 26% in Europe and 7% in Japan, but less than 1% in North America. Haemodiafiltration relies on convective dialysis, which might more closely mimic glomerular filtration than conventional diffusive-based dialysis. Despite widespread uptake of haemodiafiltration, com parative effectiveness studies have, so far, reported mixed results.

Extended duration dialysis

Haemodialysis is an intermittently delivered therapy, and thus an inherently unnatural approach to replacement of kidney function. Approaches to substantially extend haemodialysis duration—eg, from 4 h three times a week to a total of 15 h or more per week—include frequent dialysis (more than three sessions a week), long dialysis (≥5 h per session), or combinations thereof, provided during the day or overnight, and in the dialysis unit or at home. Despite the theoretical benefits of extended duration dialysis, supporting evidence is derived from observational data and from the relatively small, and logistically challenging, Frequent Hemodialysis Network (FHN) trials in the USA.[93–96] The two trials[6,94] in this network showed better composite outcomes for short daily (in-centre) dialysis versus conventional three times a week haemodialysis, and did not show a survival benefit for long-hours dialysis (predominantly home nocturnal dialysis). Higher mortality rates were reported for the long-hours dialysis group during the year after study completion.[97,98] Although conclusive data are absent, use of extended duration haemodialysis is very common in countries experienced with this technique (eg, Canada, Australia, and New Zealand; figure 2), where practitioners believe in its beneficial effects on dialysis outcomes and patients' everyday experiences.

For most patients with ESKD who are still undergoing standard dialysis three times a week, the once weekly 2-day interval between dialysis sessions (long gap) is now recognised to have increased risk of complications and mortality (often volume overload related).[40,99] Beyond counselling patients to restrict salt and water intake at weekends, the practice of dialysing every other day, rather than three times a week, is physiologically appealing but rare due to scheduling challenges. A notable exception is Australia where 6–15% of haemodialysis patients receive dialysis on alternate days and predominantly in the home setting.[100]

By contrast, some authorities now advocate incremental dialysis, typically twice a week, for people starting dialysis principally as a strategy to reduce dialytic complications and help preserve residual kidney function. Although residual kidney function is associated with increased

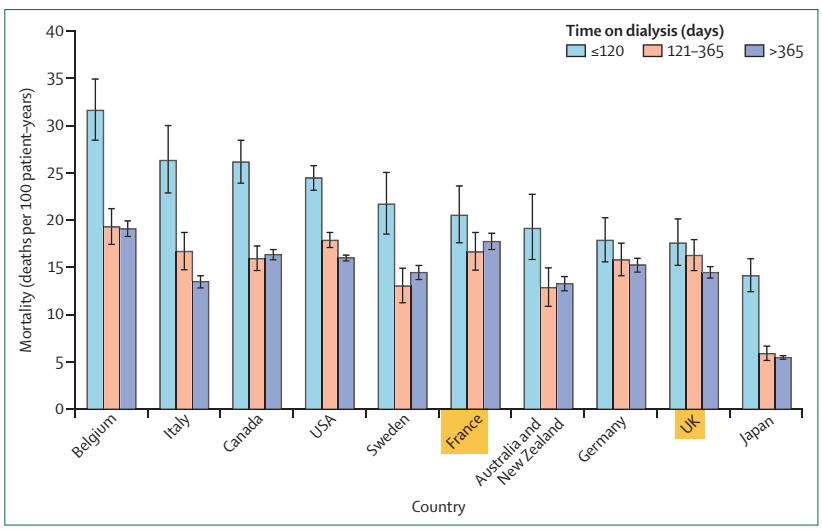

Figure 4: **Mortality in time periods after the start of haemodialysis, by country in the Dialysis Outcomes and Practice Patterns Study (2002–15)**

Countries ordered by mortality at 120 days. Error bars show 95% CIs, calculated with the Byar approximation. Data are of 86 886 patients at facilities participating in the Dialysis Outcomes and Practice Patterns Study, phases 2–5 (2002–15). Figure adapted from Robinson and colleagues,[33] by permission of Elsevier.

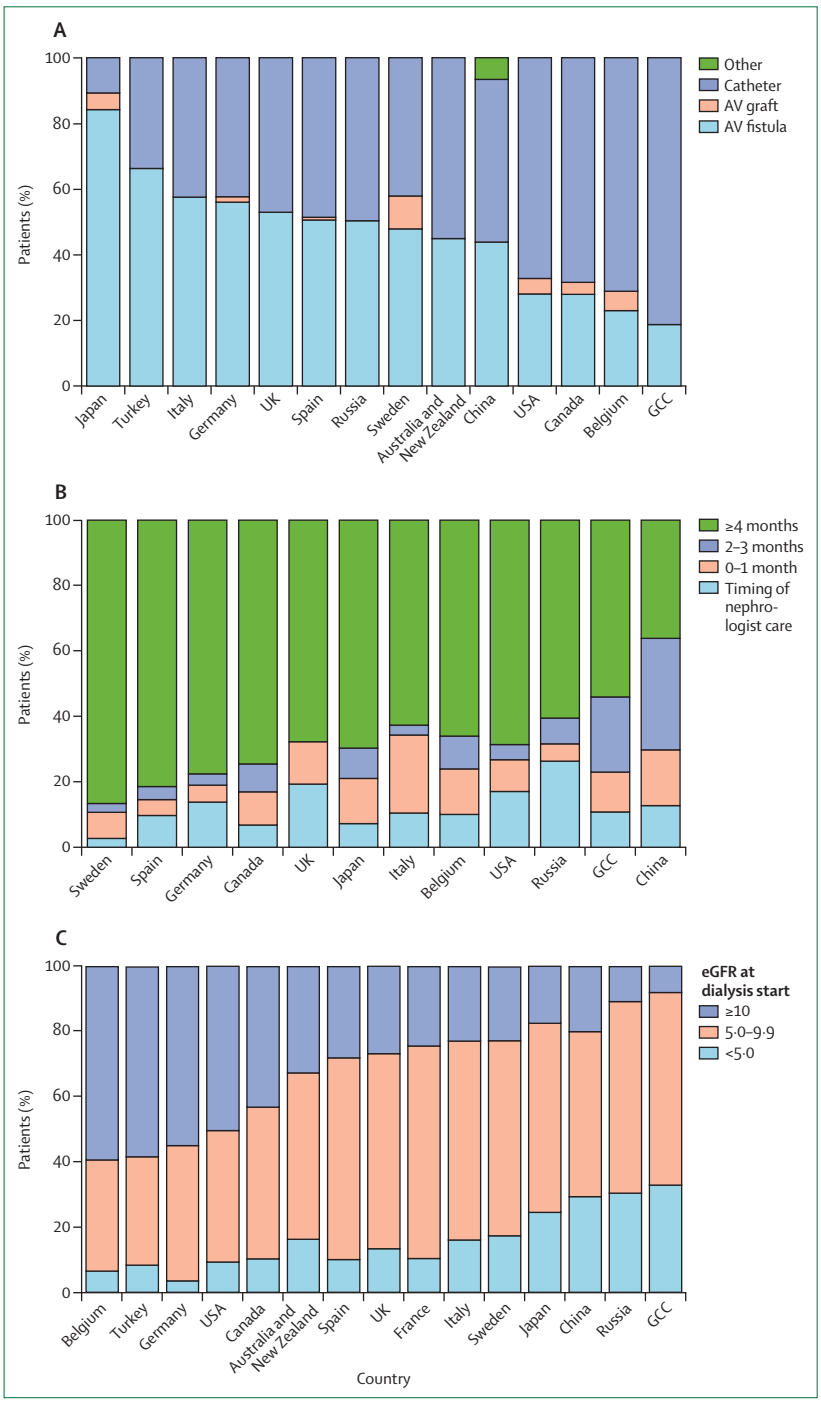

Figure 5: **Selected practices or measures in incident haemodialysis patients, by country (2012–15)**
(A) Type of vascular access used in patients on dialysis ≤60 days at Dialysis Outcomes and Practice Patterns Study (DOPPS) enrolment. (B) Timing of first nephrology care before dialysis initiation in patients on dialysis ≤60 days at DOPPS enrolment; on the basis of responses to the question, "How many months before start of chronic dialysis did the patient first see a nephrologist?", collected at enrolment. (C) Estimated glomerular filtration rate just before patients started haemodialysis. Some countries are omitted from some figures because of missing data.Figure reproduced from Pisoni and colleagues,[70] by permission of Elsevier. AV=arteriovenous. GCC=Gulf Cooperation Council (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates).

survival and a favourable patient experience, the value of incremental dialysis is uncertain and controversial.[101] Twice weekly dialysis is also common in countries with reduced access to dialysis or where patients have to pay for dialysis treatment. Use of dialysis twice weekly is less than 3% in Europe, Japan, and North America, but is 20% in China, and is more common in China among patients who report lower incomes.[102]

Outcomes in the early dialysis period

Patients starting chronic haemodialysis are faced with very high mortality rates in the first few months (figure 4).[33,103,104] As with overall dialysis mortality, mortality in the early dialysis period is lowest in Japan, and is higher in the USA than in many European DOPPS countries.[33] However, early mortality, if adjusted for age, is also especially high in Belgium and Canada. Catheter use by incident patients receiving dialysis is particularly high, and use of AVF is low in Canada, Belgium, and the USA (figure 5A).[2,70]

Early and frequent pre-ESKD nephrology care is associated with improved patient preparedness, experiences, and survival in the early dialysis period. However, in many countries a high proportion of patients start dialysis within a few months of their first visit to a nephrologist—ie, too soon to establish surgical vascular access for use at dialysis initiation (figure 5B).[45,105,106] And even early nephrological care does not guarantee readiness for dialysis. In the USA, AVF use at dialysis incidence is low (38%) even in patients who had seen a nephrologist 4 months or more before ESKD.[2,70] This poor performance is partly due to disincentives in payment structure, as patients aged younger than 65 years become eligible for Medicare reimbursement at 90 days after ESKD onset.[107]

Recognition that many patients are poorly prepared to start dialysis has led to scrutiny of estimated glomerular filtration rate (eGFR) at dialysis start. The IDEAL clinical trial,[108] corroborated by observational studies, demonstrated no clinical benefit in starting dialysis at higher or lower eGFR concentrations (ie, earlier *vs* later start).[109–111] Yet the mean eGFR concentration at dialysis start rose in the USA and elsewhere in the first decade of this century, in part in response to practice guidelines (now altered), but perhaps in some places also driven by practitioners' desire to keep dialysis clinics operating at high capacity.[112] Mean eGFR at dialysis start in the USA has been stable since roughly 2010,[113] but the difference between DOPPS countries in mean eGFR at dialysis start of 3–4 mL/min per 1·73 m² in eGFR concentration at dialysis start (figure 5C, table 2) conservatively indicates that some patients might start dialysis 6 months earlier than needed or more. Multidisciplinary programmes to start dialysis when the patient is prepared, rather than on the basis of eGFR concentrations alone, might help reduce urgent or unnecessarily early dialysis starts and improve patient outcomes.[114,115]

Future perspectives and conclusions

The upward trends in ESKD prevalence, and projections for the near future, support the need for expanded dialysis and kidney transplantation services to meet the disease's growing burden in much of the world. In some high-income countries progress is being made in slowing the development of kidney failure, an important public health achievement. At the same time, because patients with ESKD are surviving for longer and demand for transplantation is met by supply only in a few countries, the numbers of patients needing dialysis and transplantation will continue to rise even in countries with stable ESKD incidence. In many low-income and middle-income countries incremental increases in governmental support for chronic dialysis are positive developments. However, inequities in access to this life-saving therapy remain a major challenge in the context of competing priorities for resources.

In countries with universal access to ESKD therapies, large differences exist in the proportional use of transplantation or home dialysis (widely considered preferable to in-centre haemodialysis for many patients with ESKD). Overall survival of patients with ESKD is longer in Europe than in the USA, although this gap has been largely closed by incrementally greater improvements in the USA in the past few decades. Survival of patients receiving dialysis in Japan, and several other eastern or southeastern Asian countries with available data, substantially exceeds other regions partly due to lower background mortality and fewer transplant recipients. However, major differences in dialysis practices between countries highlight opportunities to improve outcomes. A commendable achievement is the exceptionally high use of surgical vascular access in Japan, some European countries, and some centres in countries with less favourable overall surgical access use, showing that excellence is a realistic expectation. Another laudable progression in some countries is the very common use of longer dialysis sessions, allowing for more gradual fluid removal and achievement of target weight with greater haemodynamic stability. By contrast, in countries where short dialysis sessions are the norm, complications of chronic volume overload remain a predominant concern. Mortality is especially high soon after onset of ESKD. Improved access to care and coordination of care to assure patients are adequately prepared to start dialysis are both feasible and necessary.

Modern dialysis is an expensive, intrusive, and physiologically inadequate treatment, and most uraemic toxins are only partly removed by the dialysers used. Nanotechnology and miniaturisation might simplify blood purification and bioengineered kidneys might provide restorative kidney functions, but these technologies are all in their infancy.[116] Until game-changing innovations are successfully developed and become widely available dialysis will remain life-saving but incredibly disruptive to patients' lives. A priority should be to improve patients' experiences by extending access to kidney transplantation, providing true choice between dialysis modalities, rehabilitating frail and poorly nourished patients, and aligning decision making with the wishes of patients and families, including the options to forego or stop dialysis if desired.

Contributors

BMR, TA, KJJ, PGK, RS, and RLP had the original research idea and for study design. BMR, TA, KJJ, RS, and RLP did data acquisition. BMR, TA, KJJ, PGK, RS, and RLP did data analysis, data interpretation, and contributed to the writing of the manuscript. BMR, KJJ, PGK, RS, and RLP did statistical analysis.

Declaration of interests

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References

1 Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* 2015; **385:** 1975–82.

2 US Renal Data System. 2015 USRDS Annual Data Report: epidemiology of kidney disease in the United States, vol 2. Bethesda, MD: National Institutes of Health and National Institute of Diabetes and Digestive and Kidney Diseases, 2015.

3 Caskey FJ, Kramer A, Elliott RF, et al. Global variation in renal replacement therapy for end-stage renal disease. *Nephrol Dial Transplant* 2011; **26:** 2604–10.

4 van de Luijtgaarden MW, Noordzij M, van Biesen W, et al. Conservative care in Europe--nephrologists' experience with the decision not to start renal replacement therapy. *Nephrol Dial Transplant* 2013; **28:** 2604–12.

5 UK NHS. End of life care in adavanced kidney disease: a framework for Implementation. http://www.ncpc.org.uk/sites/default/files/EndOfLifeCareInAdvancedKidneyDisease.pdf (accessed March 7, 2016).

6 Watanabe Y, Hirakata H, Okada K, et al, for the Japanese Society for Hemodialysis Therapy Guideline Commission of Maintenance Hemodialysis Investigation, Subgroup Commission on withholding and withdrawal from dialysis. Proposal for the shared decision-making process regarding initiation and continuation of maintenance hemodialysis. *Ther Apher Dial* 2015; **19** (suppl 1)**:** 108–17.

7 The Renal Physicians Association. Shared decision-making in the appropriate initiation of and withdrawal from dialysis, second edition. 2010. http://www.thaddeuspope.com/images/RPA_-_2010_no_dialysis_PVS_or_dementia.pdf (accessed March 7, 2016).

8 Thomas B, Wulf S, Bikbov B, et al. Maintenance dialysis throughout the world in years 1990 and 2010. *J Am Soc Nephrol* 2015; **26:** 2621–33.

9 Combe C, Albert JM, Bragg-Gresham JL, et al. The burden of amputation among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Am J Kidney Dis* 2009; **54:** 680–92.

10 Goodkin DA, Bragg-Gresham JL, Koenig KG, et al. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003; **14:** 3270–77.

11 Herrington W, Haynes R, Staplin N, et al. Evidence for the prevention and treatment of stroke in dialysis patients. *Semin Dial* 2015; **28:** 35–47.

12 Pippias M, Jager KJ, Kramer A, et al. The changing trends and outcomes in renal replacement therapy: data from the ERA-EDTA registry. *Nephrol Dial Transplant* 2016; **31:** 831–41.

13 Thodis ED, Oreopoulos DG. Home dialysis first: a new paradigm for new ESRD patients. *J Nephrol* 2011; **24:** 398–404.

14 ERA-EDTA Registry. ERA-EDTA Registry annual report 2013. Amsterdam: The European Renal Association–European Dialysis and Transplant Association, 2015.

15 Masakane I, Nakai S, Ogata S, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2013). *Ther Apher Dial* 2015; **19:** 540–74.

16 ERA-EDTA Registry. ERA-EDTA Registry 2005 annual report. Amsterdam: The European Renal Association–European Dialysis and Transplant Association, 2007.

17 Seng WH, Meng OL. Chapter 3: death and survival on dialysis. In: Goh BL, Ong LM, Lim YM, eds. 21st report of the Malaysian dialysis and transplant registry 2013. Kuala Lumpur, 2014.

18 Wu M-S, Wu I-W, Hsu K-H. Survival analysis of Taiwan renal registry data system (TWRDS) 2000–2009. *Acta Nephrol* 2012; **26:** 104–08.

19 Jha V, John O, Joshi R, et al. Dialysis outcomes in India: a pilot study. *Nephrology (Carlton)* 2015; **20:** 329–34.

20 van Manen JG, van Dijk PC, Stel VS, et al. Confounding effect of comorbidity in survival studies in patients on renal replacement therapy. *Nephrol Dial Transplant* 2007; **22:** 187–95.

21 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.

22 van Dijk PC, Zwinderman AH, Dekker FW, et al. Effect of general population mortality on the north-south mortality gradient in patients on replacement therapy in Europe. *Kidney Int* 2007; **71:** 53–59.

23 Ueshima H, Sekikawa A, Miura K, et al. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation* 2008; **118:** 2702–09.

24 Roderick P, Byrne C, Casula A, et al. Survival of patients from South Asian and Black populations starting renal replacement therapy in England and Wales. *Nephrol Dial Transplant* 2009; **24:** 3774–82.

25 van den Beukel TO, Dekker FW, Siegert CE. Increased survival of immigrant compared to native dialysis patients in an urban setting in the Netherlands. *Nephrol Dial Transplant* 2008; **23:** 3571–77.

26 Robinson BM, Joffe MM, Pisoni RL, Port FK, Feldman HI. Revisiting survival differences by race and ethnicity among hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study. *J Am Soc Nephrol* 2006; **17:** 2910–18.

27 Genovese G, Friedman DJ, RossMD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; **329:** 841–84.

28 Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol* 2011; **22:** 2129–37.

29 Rosset S, Tzur S, Behar DM, Wasser WG, Skorecki K. The population genetics of chronic kidney disease: insights from the MYH9-APOL1 locus. *Nat Rev Nephrol* 2011; **7:** 313–26.

30 Kruzel-Davila E, Wasser WG, Aviram S, Skorecki K. APOL1 nephropathy: from gene to mechanisms of kidney injury. *Nephrol Dial Transplant* 2016: **31:** 349–58.

31 Tentori F, Wang M, Bieber BA, et al. Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS Study. *Clin J Am Soc Nephrol* 2015; **10:** 98–109.

32 Bailie GR, Larkina M, Goodkin DA, et al. Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality. *Kidney Int* 2015; **87:** 162–68.

33 Robinson B, Zhang J, Morgenstern H, et al. Worldwide, mortality is a high risk soon after initiation of hemodialysis. *Kidney Int* 2014; **85:** 158–65.

34 Asano M, Thumma J, Oguchi K, et al. Vascular access care and treatment practices associated with outcomes of arteriovenous fistula: International comparisons from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephron Clin Pract* 2013; **124:** 23–30.

35 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 DOPPS. *Nephrol Dial Transplant* 2012; **27:** 4180–88.

36 Robinson BM, Bieber B, Pisoni RL, Port FK. Public policy series. Dialysis Outcomes and Practice Patterns Study (DOPPS): its strengths, limitations, and role in informing practices and policies. *Clin J Am Soc Nephrol* 2012; **7:** 1897–905.

37 Robinson B, Tong L, Zhang J, et al. Blood pressure levels and mortality risk among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 2012; **82:** 570–80.

38 Lopes AA, Tong L, Thumma J, et al. Phosphate binder use and mortality among hemodialysis patients in the DOPPS: evaluation of possible confounding by nutritional status. *Am J Kidney Dis* 2012; **60:** 90–101.

39 Jadoul M, Thumma J, Fuller DS, et al. Modifiable practices associated with sudden death among hemodialysis (HD) patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol* 2012; **7:** 765–74.

40 Zhang H, Schaubel DE, Kalbfleisch JD, et al. Dialysis outcomes and analysis of practice patterns suggests the dialysis schedule affects day-of-week mortality. *Kidney Int* 2012; **81:** 1108–15.

41 Hecking M, Karaboyas A, Saran R, et al. Dialysate sodium concentration and the association with interdialytic weight gain, hospitalization, and mortality. *Clin J Am Soc Nephrol* 2012; **7:** 92–100.

42 Pisoni RL, Arrington CJ, Albert JM, et al. Facility hemodialysis vascular access use and mortality in countries participating in DOPPS: An instrumental variable analysis. *Am J Kidney Dis* 2009; **53:** 475–91.

43 Ramirez SP, Albert JM, Blayney MJ, et al. Rosiglitazone is associated with mortality in chronic hemodialysis patients. *J Am Soc Nephrol* 2009; **20:** 1094–101.

44 Lopes AA, Bragg-Gresham JL, Ramirez SPB, et al. Prescription of antihypertensive agents to hemodialysis patients: time trends and associations with patient characteristics, country, and survival in the DOPPS. *Nephrol Dial Transplant* 2009; **24:** 2809–16.

45 Hasegawa T, Bragg-Gresham JL, Yamazaki S, et al. Greater first-year survival on hemodialysis in facilities in which patients are provided earlier and more frequent pre-nephrology visits. *Clin J Am Soc Nephrol* 2009; **4:** 595–602.

46 Mendelssohn DC, Pisoni RL, Arrington CJ, et al. A practice-related risk score (PRS): a DOPPS-derived aggregate quality index for haemodialysis facilities. *Nephrol Dial Transplant* 2008; **23:** 3227–33.

47 Tentori F, Blayney MJ, Albert JM, et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2008; **52:** 519–30.

48 Saran R, Elder SJ, Goodkin DA, et al. Enhanced training in vascular access creation predicts arteriovenous fistula placement and patency in hemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study. *Ann Surg* 2008; **247:** 885–91.

49 Port FK. Practice-based versus patient-level outcomes research in hemodialysis: the DOPPS (Dialysis Outcomes and Practice Patterns Study) experience. *Am J Kidney Dis* 2014; **64:** 969–77.

50 Port FK, Wolfe RA, Hulbert-Shearon TE, Ashby VB, McCullough KP, Held PJ. High dialysis dose is associated with lower mortality among women but not among men. *Am J Kidney Dis* 2004; **43:** 1014–23.

51 Mapes DL, Lopes AA, Satayathum S, et al. Health-related quality of life as a predictor of mortality and hospitalization: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int* 2003; **64:** 339–49.

52 Pisoni RL, Young EW, Dykstra DM, et al. Vascular access use in Europe and the United States: Results from the DOPPS. *Kidney Int* 2002; **61:** 305–16.

53 Young EW, Goodkin DA, Mapes DL, et al. The Dialysis Outcomes and Practice Patterns Study (DOPPS): an international hemodialysis study. *Kidney Int* 2000; **57:** S74–81.

54 Pisoni RL, Gillespie BW, Dickinson DM, Chen K, Kutner MH, Wolfe RA. The Dialysis Outcomes and Practice Patterns Study (DOPPS): Design, data elements, and methodology. *Am J Kidney Dis* 2004; **44:** 7–15.

55 Port FK, Wolfe RA, Held PJ, Young EW. Random sample (DOPPS) versus census-based registry approaches to kidney disease research. *Blood Purif* 2003; **21:** 85–88.

56 Hecking M, Karaboyas A, Saran R, et al. Predialysis serum sodium level, dialysate sodium, and mortality in maintenance hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2012; **59:** 238–48.

57 Fuller DS, Bieber BA, Pisoni RL, et al. International comparisons to assess effects of payment and regulatory changes in the United States on anemia practice in patients on hemodialysis: The Dialysis Outcomes and Practice Patterns Study. *J Am Soc Nephrol* 2015; published online Nov 18. DOI:10.1681/ASN.2015060673.

58 Hasegawa T, Bragg-Gresham JL, Pisoni RL, et al. Changes in anemia management and hemoglobin levels following revision of a bundling policy to incorporate recombinant human erythropoietin. *Kidney Int* 2011; **79:** 340–46.

59 Sehulster L, Chinn RY, US Centers for Disease Control and Prevention, Healthcare Infection Control Practices Advisory Committee. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). *MMWR Recomm Rep* 2003; **52:** 1–42.

60 Kelley-Hedgepeth A, Lloyd-Jones DM, et al. Ethnic differences in C-reactive protein concentrations. *Clin Chem* 2008; **54:** 1027–37.

61 Inrig JK, Califf RM, Tasneem A, et al. The landscape of clinical trials in nephrology: a systematic review of Clinicaltrials.gov. *Am J Kidney Dis* 2014; **63:** 771–80.

62 Astor BC, Eustace JA, Powe NR, Klag MJ, Fink NE, Coresh J. CHOICE study. Type of vascular access and survival among incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study. *J Am Soc Nephrol* 2005; **16:** 1449–55.

63 Bradbury BD, Chen F, Furniss A, et al. Conversion of vascular access type among incident hemodialysis patients: description and association with mortality. *Am J Kidney Dis* 2009; **53:** 804–14.

64 Xue JL, Dahl D, Ebben JP, Collins AJ. The association of initial hemodialysis access type with mortality outcomes in elderly Medicare ESRD patients. *Am J Kidney Dis* 2003; **42:** 1013–19.

65 Polkinghorne KR, McDonald SP, Atkins RC, Kerr PG. Vascular access and all-cause mortality: a propensity score analysis. *J Am Soc Nephrol* 2004; **15:** 477–86.

66 Allon M, Daugirdas J, Depner TA, Greene T, Ornt D, Schwab SJ. Effect of change in vascular access on patient mortality in hemodialysis patients. *Am J Kidney Dis* 2006; **47:** 469–77.

67 Lacson E Jr, Wang W, Hakim RM, Teng M, Lazarus JM. Associates of mortality and hospitalization in hemodialysis: Potentially actionable laboratory variables and vascular access. *Am J Kidney Dis* 2009; **53:** 79–90.

68 Engemann JJ, Friedman JY, Reed SD, et al. Clinical outcomes and costs due to *Staphylococcus aureus* bacteremia among patients receiving long-term hemodialysis. *Infect Control Hosp Epidemiol* 2005; **26:** 534–39.

69 Lee H, Manns B, Taub K, et al. Cost analysis of ongoing care of patients with end-stage renal disease: the impact of dialysis modality and dialysis access. *Am J Kidney Dis* 2002; **40:** 611–22.

70 Pisoni RL, Zepel L, Port FK, Robinson BM. Trends in US vascular access use, patient preferences, and related practices: an update from the US DOPPS practice monitor with international comparisons. *Am J Kidney Dis* 2015; **65:** 905–15.

71 Bikbov BT, Tomilina NA. Renal replacement therapy for ESRD patients in Russian Federation, 1998–2013. Report of Russian RRT registry. Part 2. *Nephrol Dial* (in press).

72 US Centers for Medicare & Medicaid Services. Technical specifications for ESRD QIP measures. www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/ESRDQIP/061_TechnicalSpecifications.html (accessed March 4, 2016).

73 Vassalotti JA, Jennings WC, Beathard GA, et al. Fistula first breakthrough initiative community education committee (2012) fistula first breakthrough initiative: targeting catheter last in fistula first. *Semin Dial* 2012; **25:** 303–10.

74 National Kidney Foundation. The National Kidney Foundation kidney disease outcomes quality initiative, 2006. Vascular access guidelines http://www.kidney.org/professionals/kdoqi/pdf/12–50–0210_JAG_DCP_Guidelines-VA_Oct06_SectionC_ofC.pdf (accessed July 23, 2013).

75 Kumwenda M, Mitra S, Reid C. Clinical practice guideline: vascular access for haemodialysis. Hampshire: UK Renal Association, 2015.

76 The Japanese Society for Dialysis Therapy. Guidelines pertaining to creating and repairing vascular access for chronic hemodialysis. *J Jpn Soc Dial Ther* 2011; **44:** 855–937.

77 Rayner HC, Pisoni RL. The increasing use of hemodialysis catheters: evidence from the DOPPS on its significance and ways to reverse it. *Semin Dial* 2010; **23:** 6–10.

78 UK NHS Department of Health. Payment by results guidance for 2011–12. http://webarchive.nationalarchives.gov.uk/20130402234253/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_126157.pdf (accessed March 8, 2016).

79 Abma I, Jayanti A, Bayer S, et al. Perceptions and experiences of financial incentives: a qualitative study of dialysis care in England. *BMJ Open* 2014; **4:** e004249.

80 Fistula First: Fistula first national vascular access improvement initiative. http://www.fistulafirst.org (accessed March 4, 2016).

81 Fissell RB, Fuller DS, Morgenstern H, et al. Hemodialysis patient preference for type of vascular access: variation and predictors across countries in the DOPPS. *J Vasc Access* 2013; **14:** 264–72.

82 Pisoni R, Zepel L, Tentori F, et al. International variability in arteriovenous fistula maturation and placement: The Dialysis Outcomes and Practice Patterns Study. *J Am Soc Nephrol* 2015; **26:** 285A–86A.

83 Lok CE, McCullough K, Fluck RJ, et al. Rising vascular access (VA) procedure rates over time internationally: findings from the DOPPS. *J Am Soc Nephrol* 2012; **23:** 268A.

84 Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM. The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* 1993; **329:** 1001–06.

85 Depner T, Daugirdis J, Greene T, et al. Dialysis dose and the effect of gender and body size on outcome in the HEMO Study. *Kidney Int* 2004; **65:** 1386–94.

86 McIntyre CW, Burton JO, Selby NM, et al. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol* 2008; **3:** 19–26.

87 Ok E, Asci G, Chazot C, Ozkahya M, Dorhout Mees EJ. Dialysis 2. Controversies and problems of volume control and hypertension in haemodialysis. *Lancet* 2016; published online May 22. DOI:10.1016/S0140-6736(16)30389-0.

88 Flythe JE, Curhan GC, Brunelli SM. Shorter length dialysis sessions are associated with increased mortality, independent of body weight. *Kidney Int* 2013; **83:** 104–13.

89 Brunelli SM, Chertow GM, Ankers ED, Lowrie EG, Thadhani R. Shorter dialysis times are associated with higher mortality among incident hemodialysis patients. *Kidney Int* 2010; **77:** 630–36.

90 Daugirdas JT. Dialysis time, survival, and dose-targeting bias. *Kidney Int* 2013; **83:** 9–13.

91 Kleophas W, Karaboyas A, Li Y, et al. Changes in dialysis treatment modalities during institution of flat rate reimbursement and quality assurance programs. *Kidney Int* 2013; **84:** 578–84.

92 Watanabe Y, Kawanishi H, Suzuki K. Japanese Society for Hemodialysis therapy clinical guideline for proposal for "Maintenance Hemodialysis; Hemodialysis Prescriptions". *Ther Apher Dial* 2015; **19** (suppl 1)**:** 67–92.

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

94 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.

95 Nesrallah GE, Lindsay RM, Cuerden MS, et al. Intensive hemodialysis associates with improved survival compared with conventional hemodialysis. *J Am Soc Nephrol* 2012; **23:** 696–705.

96 Marshall MR, Hawley CM, Kerr PG, et al. Home hemodialysis and mortality risk in Australian and New Zealand populations. *Am J Kidney Dis* 2011; **58:** 782–93.

97 Rocco MV, Daugirdas JT, Greene T, et al, for the FHN Trial Group. Long-term effects of frequent nocturnal hemodialysis on mortality: the Frequent Hemodialysis Network (FHN) Nocturnal Trial. *Am J Kidney Dis* 2015; **66:** 459–68.

98 Rocco MV, Lockridge RS Jr, Beck GJ, et al. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. *Kidney Int* 2011; **80:** 1080–91.

99 Foley RN, Gilbertson DT, Murray T, Collins AJ. Long interdialytic interval and mortality among patients receiving hemodialysis. *N Engl J Med* 2011; **365:** 1099–107.

100 ANZDATA Registry. Chapter 4: haemodialysis. In: The 37th annual ANZDATA report. Adelaide: Australia and New Zealand Dialysis and Transplant Registry, 2014.

101 Kalantar-Zadeh K, Unruh M, Zager PG, et al. Twice-weekly and incremental hemodialysis treatment for initiation of kidney replacement therapy. *Am J Kidney Dis* 2014; **64:** 181–86.

102 Bieber B, Qian J, Anand S, et al. Two-times weekly hemodialysis in China: frequency, associated patient and treatment characteristics, and quality of life in the China Dialysis Outcomes and Practice Patterns Study. *Nephrol Dial Transplant* 2014; **29:** 1770–77.

103 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.

104 Foley RN, Chen SC, Solid CA, Gilbertson DT, Collins AJ. Early mortality in patients starting dialysis appears to go unregistered. *Kidney Int* 2014; **86:** 392–98.

105 Gillespie BW, Morgenstern H, Hedgeman E, et al. Nephrology care prior to end-stage renal disease and outcomes among new ESRD patients in the USA. *Clin Kidney J* 2015; **8:** 772–80.

106 Watanabe Y, Yamagata K, Nishi S, et al. Japanese Society for Dialysis therapy clinical guideline for "Hemodialysis Initiation for Maintenance Hemodialysis". *Ther Apher Dial* 2015; **19:** 93–107.

107 Allon M, Dinwiddie L, Lacson E Jr, et al. Medicare reimbursement policies and hemodialysis vascular access outcomes: a need for change. *J Am Soc Nephrol* 2011; **22**: 426–30.

108 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.

109 Crews DC, Scialla JJ, Liu J, et al. Predialysis health, dialysis timing, and outcomes among older United States adults. *J Am Soc Nephrol* 2014; **25:** 370–79.

110 Crews DC, Scialla JJ, Boulware LE, et al. Comparative effectiveness of early versus conventional timing of dialysis initiation in advanced CKD. *Am J Kidney Dis* 2014; **63:** 806–15.

111 Mehrotra R, Rivara M, Himmelfarb J. Initiation of dialysis should be timely: neither early nor late. *Semin Dial* 2013; **26:** 644–49.

112 NKF-DOQI clinical practice guidelines for peritoneal dialysis adequacy. National Kidney Foundation. *Am J Kidney Dis* 1997; **30** (3 suppl 2)**:** S67–136.

113 US Renal Data System. USRDS 2010 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. Bethesda, MD: National Institutes of Health and National Institute of Diabetes and Digestive and Kidney Diseases, 2010.

114 Lacson E Jr, Wang W, DeVries C, et al. "Effects of a nationwide predialysis educational program on modality choice, vascular access, and patient outcomes." *Am J Kidney Dis* 2011; **58:** 235–42.

115 National Kidney Foundation. KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update. *Am J Kidney Dis* 2015; **66:** 884–930.

116 Remuzzi G, Benigni A, Finkelstein FO, et al. Kidney failure: aims for the next 10 years and barriers to success. *Lancet* 2013; **382:** 353–62.