What happens to the heart in chronic kidney disease?

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Abstract

Cardiovascular disease is common in patients with chronic kidney disease. The increased risk of cardiovascular disease seen in this population is attributable to both traditional and novel vascular risk factors. Risk of sudden cardiac or arrhythmogenic death is greatly exaggerated in chronic kidney disease, particularly in patients with end stage renal disease where the risk is roughly 20 times that of the general population. The reasons for this increased risk are not entirely understood and while atherosclerosis is accelerated in the presence of chronic kidney disease, premature myocardial infarction does not solely account for the excess risk. Recent work demonstrates that the structure and function of the heart starts to alter early in chronic kidney disease, independent of other risk factors. The implications of cardiac remodelling and hypertrophy may predispose chronic kidney disease patients to heart failure, arrhythmia and myocardial ischaemia. Further research is needed to minimise cardiovascular risk associated with structural and functional heart disease associated with chronic kidney disease.

Keywords atherosclerosis, cardiovascular, chronic kidney disease, dialysis, heart, left ventricle

Declaration of interests No conflict of interests declared

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Based on a lecture given at the Renal symposium, Royal College of Physicians of Edinburgh, April 2016

Introduction

Chronic kidney disease (CKD) is a significant worldwide health problem. The diagnosis of CKD is based on either the presence of reduced kidney function, with a glomerular filtration rate (GFR) of less than 60 ml/min per 1.73m^2, or by the presence of albuminuria.[1] An individual must have either, or both, of these two features for three months or more before a diagnosis of CKD is made. The prevalence of CKD is rising: observational data from the USA suggest that the prevalence of CKD stages 1-4 rose from 10% to 13.1% over a 10-year period.[2] Part of this increase is thought to be due to the rising prevalence of diabetes and hypertension, two common causes of CKD. However, patients with early CKD are more likely to die of cardiovascular disease than of progression of their CKD to end stage renal disease (ESRD).[3] Moreover, CKD has been recognised as a risk factor for cardiovascular disease, independent of other factors and is used in the Q Risk calculator, endorsed by the Joint British Societies for prevention of cardiovascular disease, for estimating risk of cardiovascular disease.[4] However, it is perhaps not surprising that cardiovascular disease is common among patients with CKD. A large number of traditional risk factors for cardiovascular disease are common to the CKD population (Table 1). For example, obesity, dyslipidaemia, hypertension, diabetes, smoking and sedentary lifestyles are more commonly found in the dialysis population than in the general population. The excess cardiovascular risk attributable to CKD merits further study.

Key moments in our understanding of CKD-related cardiovascular disease

The link between early kidney disease and cardiovascular disease was recognised as early as three centuries ago (Figure 1). In 1836 Bright found that 22 out of 100 patients who had albuminuria had evidence of marked left ventricular hypertrophy (LVH) on autopsy.[3] With establishment of dialysis programmes as a treatment for ESRD in the latter half of the 20th century, it became clear that premature cardiovascular disease was associated with longstanding CKD. In 1974, Belding Scribner, one of the pioneers of maintenance haemodialysis therapy, described accelerated atherosclerosis in haemodialysis patients.[5] The scale and epidemiology of excess cardiovascular risk in dialysis patients was further described in 1998 by Foley, who demonstrated that risk of cardiovascular disease in dialysis patients aged 35–44 was similar to individuals in the general population aged over 75, without renal impairment, even after adjustment for traditional cardiovascular risk factors. More recently, it has become clear that excess cardiovascular risk in CKD is not limited to those on renal replacement therapy. Go et al. demonstrated in a large population-based study that reduced estimated GFR was associated with increased risks of death, cardiovascular events and hospitalisations

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Table 1 Comparison of prevalence of traditional cardiovascular risk factors between general and dialysis populations

Traditional cardiac risk factor	Prevalence within general England population (%)	Prevalence within general US population (%)	Prevalence within US dialysis population (%)
Diabetes	5.8	5	54
Hypertension	30	23	96
Total cholesterol > 5 mmol/l*	59	26**	35
HDL < 1 mmol/l	4.2	23**	45
Obesity	26	22	26
Sedentary lifestyle (failing to meet national physical exercise recommendations)	58***	67	80
Current smoker	20	15	28

US data adapted from the CHOICE study[64] English data adapted from report *Coronary Heart Disease Statistics 2012*[65]
*> 5.1 mmol/l in US data
**Prevalence for general US population not on lipid lowering agents
***Only assessed in men

that were independent of known risk factors, a history of cardiovascular disease and the presence of documented proteinuria.[6] Similarly, a recent meta-analysis showed that both falling estimated GFR (below 75 ml/min/1.73m^2) and increasing albumin creatinine ratios were each independently associated with increased cardiovascular mortality risk.[7]

Cardiovascular disease in CKD – not just accelerated atherosclerosis

Only a small proportion of the increased cardiovascular risk seen in the CKD population is attributable to the accelerated development of atherosclerosis first observed by Scribner and colleagues.[5] Nevertheless, ischaemic heart disease as a result of atherosclerotic disease is a significant problem in the CKD population. In addition to this, patients with CKD do worse than their counterparts without renal impairment when they do suffer a myocardial infarction, or undergo angioplasty or cardiac surgery.[8]

We now understand that premature atherosclerosis is not the only, or even the main, manifestation of cardiovascular disease in the CKD population.[9] Non-atherosclerotic, or non-ischaemic cardiac disease, is of much greater importance in this patient group. Patients with CKD are at a greatly increased risk of sudden cardiac death or arrhythmogenic death than their non-CKD counterparts. The risk of sudden cardiac death is particularly exaggerated in patients undergoing haemodialysis, where the risk is approximately 20 times that of the general population.[10] However, there is an increased risk of sudden cardiac death with decreasing GFR even very early in CKD. This increased risk is present even in those without known cardiovascular disease.[11] The reasons for this increased risk are not completely understood but are thought in part to be attributable to changes in structure and function of the cardiac muscle.

In 2013, half of all deaths in prevalent dialysis patients in the USA were attributable to a cardiac cause; 37% of all patients died from an arrhythmia or cardiac arrest, 6.7% of patients died following an acute myocardial infarction, 5.8% died from congestive cardiac failure and 0.5% died from another cardiac cause.[12] Evidence from the UK is similarly compelling; sudden presumed cardiac deaths are a big problem in the haemodialysis patient group.[13]

The undeniable causal association between CKD and cardiovascular risk means that, in effect, many therapies used to prevent progression of CKD also prevent cardiovascular disease.[3] In fact much of the general management of CKD also focuses on reduction of cardiovascular risk. For example, strategies such as targeting blood pressure control and improving glycaemic indices can simultaneously slow progression of CKD and reduce cardiovascular risk.[14] But what causes the increased cardiovascular risk in CKD if we cannot attribute it all to 'traditional' cardiac risk factors? This continues to be an expanding area of research but we now understand that a large number of novel cardiovascular risk factors outwith the scope of this review, such as fibroblast graft factor-23 or markers associated with vascular calcification (e.g. osteoprotegerin, matrix-gla protein) are implicated.

Abnormalities in cardiac structure in patients with CKD

Abnormalities in cardiac structure common to CKD include LVH, ventricular dilation and myocardial fibrosis.[15] Using echocardiography at initiation of renal replacement therapy, Foley showed that the majority of patients had normal cardiac function and dimensions, 32% had left ventricular dilatation with preserved systolic function and 74% had concentric LVH.[16,17] The development of these features, as well as impaired cardiac function, often in the absence of coronary artery disease, is consistent with a cardiomyopathy specifically related to renal disease; sometimes termed a 'uraemic cardiomyopathy'.[18] The presence of these features is convincingly associated with increased mortality.[19] But why are these features so bad?

The presence of LVH at dialysis initiation has been shown to be associated with significantly increased mortality.[15,20] LVH is associated with arrhythmia; observational work suggests

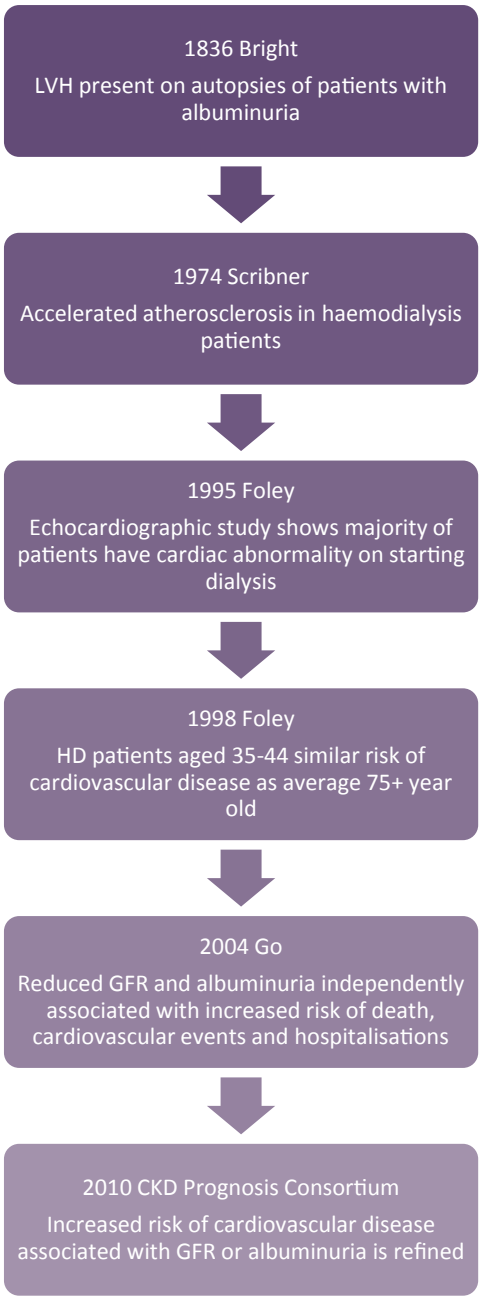

Figure 1. Our developing understanding of CKD-related cardiovascular disease

the risk of sudden cardiac death is almost trebled if LVH is present at dialysis initiation.[15] The exact mechanisms for this increased sudden cardiac death risk are not fully understood. Ventricular hypertrophy can lead to diastolic heart failure, or heart failure with preserved ejection fraction.[21] Myocyte demands are higher with greater myocardial mass and if capillary blood supply is not able to meet this increased demand, this mismatch can lead to sub-endocardial ischaemia.[22] Increased ventricular mass also promotes the development of atrial dilation which increases the risk of atrial fibrillation and cardio-embolic strokes as well as reducing coronary perfusion reserve, which may predispose to future ischaemia.[3]

In haemodialysis patients, a number of specific determinants of increased left ventricular mass (LVM) have been demonstrated using cardiac magnetic resonance imaging (MRI).[23] The main factors predisposing to increased LVM demonstrated were the traditional factor of blood pressure, as well as novel CKD-specific factors: the calcium-phosphate product and the volume of fluid removed at dialysis sessions (ultrafiltration volume).[23] Earlier studies demonstrated that the presence of anaemia (often present as a result of renal disease) was a big risk factor for LVH;[24] however now that the majority of advanced renal failure patients are treated with erythropoiesis-stimulating agents this is less of an issue. LVH is not only a problem for patients with severe CKD. LVM has been shown to be increased early in CKD.[25] However, CKD is often accompanied by other comorbid conditions and these conditions (such as obesity) may also promote the development of LVH.[19] Moreover, hypertension, present in up to 87% patients with CKD,[27] is a major driver in the development of LVH.

It is probably not surprising that regression of LVM is a common primary outcome measure in renal clinical trials,[27–30] the logic being that, as LVH is so bad, a reduction in LVM should result in improved outcomes for patients with renal

disease. This has been borne out in follow up of some clinical trials.[31] However a recent systematic review of clinical trials targeting LVM in CKD and ESRD has cast some doubt on the fact that reduced LVM necessarily equates with better cardiovascular outcomes.[31] In fact, there is some evidence that extent of myocardial fibrosis is a better predictor of outcome than LVM alone.[32]

Living kidney donation: a model for studying cardiovascular risk in CKD

Reduced kidney function, even without CKD, may predispose individuals to an increased risk of cardiovascular disease. Study of patients who undergo live kidney donation to help others with end stage renal disease provides unique insights into the effect of a fixed reduction of renal function on cardiovascular health. Historically it had been thought that while live kidney donation led to an increase in incidence of hypertension and a very small, but definite, risk of renal disease, it was not otherwise associated with reduction in lifespan. The reasons for this are complex but include the fact that kidney donors are likely to be motivated and health-aware in addition to undergoing extra health screening as part of the donation process. Additionally, there may be a psychological benefit associated with the altruism that kidney donation entails. However, a recent controversial registry study from Norway has demonstrated that live kidney donors were at increased risk of cardiovascular death compared to matched individuals from the general population.[33] A mechanistic study using cardiac MRI to measure LVM showed that when healthy individuals who had donated a kidney were compared with a matched group of potential donors who did not proceed to kidney donation, there was a significant increase in MRI-determined LVM in the group who had undergone a nephrectomy compared to the controls. This was despite these 'healthy' donors still having normal estimated GFR.[34] Whether this modest increase in LVM translates to an increased risk of cardiac disease in this particular patient group remains to be seen.

Cardiac tissue abnormalities in CKD

Histological animal studies have demonstrated that as LVM increases, tissue abnormalities in keeping with myocardial fibrosis may increase in parallel.[22] There is also considerable evidence that the extent of myocardial fibrosis is a stronger predictor of outcome in CKD than LVH alone. In a Japanese myocardial biopsy study, the degree of fibrosis was highly predictive of arrhythmic death in a haemodialysis population.[32] It is thought that this diffuse myocardial fibrosis may act as an arrhythmia substrate and this may predispose to sudden cardiac death.

MRI has emerged as the leading imaging modality for characterising myocardial tissue in CKD. Initially gadolinium contrast agents were used, with a late diffuse myocardial contrast enhancement picture considered a surrogate marker of myocardial fibrosis.[35] However, gadolinium contrast agents have fallen out of favour in the renal community because of their association with the rare, but serious, condition nephrogenic systemic fibrosis.[36] Within the last couple of years there has been a move to try and quantify myocardial fibrosis using novel non-contrast techniques such as T1. In other disease populations, increased T1 times have been demonstrated to be representative of myocardial fibrosis proven by biopsy. T1 time shows some early promise as a potential tool to quantify myocardial fibrosis in the renal population. Myocardial T1 times have been shown to be higher in early CKD than in hypertensive controls and healthy volunteers.[25] In the haemodialysis population, T1 times have also been shown to be prolonged and to correlate with LVM.[37,38] In the future T1 time may be used as a primary endpoint in renal clinical trials aiming to reduce cardiovascular risk, but at the moment its clinical utility is limited by variability in T1 times across different MRI scanners.[39]

What can we do to reduce cardiovascular risk in CKD?

In appropriately selected individuals requiring dialysis, restoration of kidney function with kidney transplantation is the single intervention associated with most dramatic reduction in cardiovascular risk. The effect cannot be tested in a randomised trial, but it should be emphasised that renal transplantation not only improves quality of life, but is associated with a much lower risk of cardiovascular disease than remaining on dialysis.[40]

In patients with CKD not requiring dialysis, the evidence to date suggests that tight control of conventional cardiovascular risk factors by controlling blood pressure, lipids, smoking cessation and maintenance of heathy lifestyle is likely to be beneficial for reduction of cardiovascular risk, although the strength of the supporting evidence is variable. Once patients are established on dialysis, the evidence for interventions to minimise cardiovascular risk are limited, outwith ensuring patients are treated broadly along the lines of national standards for care of patients needing dialysis.[41]

Lipids and CKD

While not strictly a change within the heart, lipid disorders are well established as a cardiovascular disease risk factor in the general population and so it is logical that priority should also be given to understanding and managing lipid disorders in CKD. In the general population, a significant reduction in cardiovascular risk is achieved with aggressive treatment of lipid disorders; this is accepted as standard care and is well evidenced.[42] Within the last ten years, results of large randomised trials examining the effects of lipid-lowering therapies in the CKD population have started to emerge. The SHARP (Study of Heart and Renal Protection) study demonstrated that lipid lowering therapy is associated with lower rates of major atherosclerotic events in patients with CKD not requiring dialysis.[43] Once patients are established on dialysis, clinical trials have not demonstrated benefits in lipid lowering with statins for prevention of cardiovascular disease.[44,45] This is reflected in current guidelines which do not recommend de novo commencement of lipid lowering therapy in dialysis patients to reduce cardiovascular risk.[46]

Targeting the renin angiotensin aldosterone system to reduce LVM: does this improve outcomes?

The renin angiotensin aldosterone system is over-activated in CKD, with patients having inappropriately elevated aldosterone production relative to their fluid status.[47] Therefore, aldosterone antagonism with spironolactone represents a therapeutic strategy for intervention: this approach reduces blood pressure and proteinuria, both predictors of progression to ESRD and death in CKD patients.[48] Furthermore, it has been shown that spironolactone can reduce LVM and aortic stiffness in a randomised clinical trial in CKD patients.[49] Interestingly, in an open label trial of spironolactone in Japanese patients treated with peritoneal dialysis, spironolactone prevented LVH and preserved left ventricular ejection fraction.[50] Similarly, in a separate Japanese trial, spironolactone was associated with a reduction in cardiovascular and cerebrovascular morbidity suggesting that beneficial effect on LVM may translate to clinical benefits.[51] Further large clinical trials to test this hypothesis are ongoing.[52,53] However, although attractive, spironolactone is unlikely to attract widespread use in CKD due to the risk of hyperkalaemia.[54]

Targeting non-atherosclerotic cardiovascular events in dialysis patients

As the results of trials targeting atherosclerotic events with lipid lowering therapy in dialysis patients have been disappointing,[44,45] it seems logical to consider approaches targeting cardiovascular events not directly related to atherosclerosis. A number of clinical trials have been conducted targeting aspects of haemodialysis treatment itself (HEMO),[55] phosphate balance (DCOR)[56] or secondary hyperparathyroidism (EVOLVE).[57] The logic of addressing calcium, phosphate and parathyroid metabolism, so called CKD-mineral bone disorder, is that by improving these parameters, one may see less vascular calcification, thereby improving vascular compliance, reducing cardiac afterload, in addition to experiencing less high risk calcification compromising perfusion of vascular beds. By and large these trials have been essentially negative, although in EVOLVE there was a signal of improved cardiovascular outcomes associated with intervention with the calcimimetic cinacalcet.

Alternatively, if the assumption is that sudden cardiac death is related to arrhythmia, anti-arrhythmic therapy may have a role. Again, no large outcome trials have been performed, but two single centre clinical trials have demonstrated improved outcomes with beta-blockers in haemodialysis patients.[58,59] Further understanding of the nature of sudden cardiac death in dialysis patients is necessary, as the concern is that any improvement in arrhythmia may be compounded by an exacerbation in bradycardia associated with electrolyte (especially) potassium shifts and variable drug half-life associated with reduced excretion. Thereafter, a large definitive outcome study to test whether beta blockers have a role in reducing cardiovascular mortality in dialysis patients is required.

What does the future hold for tackling heart disease in CKD?

Outwith treatment of conventional cardiovascular risk factors, other strategies to reduce cardiovascular risk are being explored. Allopurinol, conventionally used to reduce serum uric acid in gout, has recently been shown to improve LVM in CKD patients.[60] Perhaps focusing on non-atherosclerotic vascular disease may have a role in reducing risk. For example, while to date studies aimed at reducing vascular calcification have been disappointing, there is no doubt that calcification is associated with vascular morbidity and mortality.[61] Vitamin K has a key role in inhibition of vascular calcification and a number of studies are addressing whether vitamin K supplementation in CKD has cardiovascular benefits.[62] Alternatively, rather than pharmacological intervention, formal clinical intervention with lifestyle modification and exercise may have a role and has been tested with some beneficial effect in small studies.[63]

Despite these recent advances and ongoing studies, it is unlikely there will be a single intervention likely to dramatically reduce cardiovascular risk in CKD. The nature of cardiovascular disease in CKD encompasses accelerated atherosclerosis, vascular stiffness and calcification, ventricular hypertrophy and associated cardiac dysfunction. The challenge for researchers and clinicians addressing cardiovascular risk in CKD patients will be devising a strategy to address these multiple pathologies, while avoiding detrimental side-effects in a group of patients who already experience a high treatment burden.

References

1 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39: S1–266.
2 Coresh J, Selvin E, Stevens LA et al. Prevalence of Chronic Kidney Disease in the United States. *JAMA* 2007; 298: 2038–47.
3 Gansevoort RT, Correa-Rotter R, Hemmelgarn BR et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013; 382: 339–52.
4 JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart* 2014; 100: ii1–ii67.
5 Lindner A, Charra B, Sherrard DJ et al. Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 1974; 290: 697–701.
6 Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351: 1296–1305.
7 Chronic Kidney Disease Prognosis Consortium et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; 375: 2073–81.
8 2015 USRDS Annual Data Report | Volume 1 - CKD in the United States. Chapter 4: Cardiovascular Disease in Patients With CKD. *Am J Kidney Dis* 2016; 67 (suppl): S49–S56.
9 Whitman IR, Feldman HI, Deo R. CKD and sudden cardiac death: epidemiology, mechanisms, and therapeutic approaches. *J Am Soc Nephrol* 2012; 23: 1929–39.
10 Passman R, Herzog CA. End-stage renal disease: Sudden cardiac

death: stratifying risk in dialysis patients. *Nat Rev Nephrol* 2011; 7: 133–5.
11 Deo R, Sotoodehnia N, Katz R et al. Cystatin C and sudden cardiac death risk in the elderly. *Circ Cardiovasc Qual Outcomes* 2010; 3: 159–64.
12 2015 USRDS Annual Data Report | Volume 2 – ESRD in the United States. Chapter 9: Cardiovascular Disease in Patients With ESRD. *Am J Kidney Dis* 2016; 67 (suppl): S259–S264.
13 Steenkamp R, Rao A, Fraser S. UK Renal Registry 18th Annual Report (December 2015) Chapter 5: Survival and Causes of Death in UK Adult Patients on Renal Replacement Therapy in 2014: National and Centre-specific Analyses. *Nephron* 2016; 132: 111–44.
14 Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013; 158: 825–30.
15 Parfrey PS, Foley RN, Harnett JD et al. Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant* 1996; 11: 1277–85.
16 Foley R, Parfrey P, Sarnak M. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32(suppl): S112–S119.
17 Foley RN, Parfrey PS, Harnett JD et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995; 47: 186–92.
18 Kunz K, Dimitrov Y, Muller S et al. Uraemic cardiomyopathy. *Nephrol Dial Transplant* 1998; 13(suppl): 39–43.
19 Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet* 2000; 356: 147–52.
20 Stack AG, Saran R. Clinical correlates and mortality impact of left ventricular hypertrophy among new ESRD patients in the United States. *Am J Kidney Dis* 2002; 40: 1202–10.
21 London GM, Pannier B, Guerin AP et al. Alterations of Left Ventricular Hypertrophy in and Survival of Patients Receiving Hemodialysis: Follow-up of an Interventional Study. *J Am Soc Nephrol* 2001; 12: 2759–67.
22 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.
23 Patel RK, Oliver S, Mark PB et al. Determinants of left ventricular mass and hypertrophy in hemodialysis patients assessed by cardiac magnetic resonance imaging. *Clin J Am Soc Nephrol* 2009; 4: 1477–83.
24 Levin A, Thompson CR, Ethier J et al. Left ventricular mass index increase in early renal disease: Impact of decline in hemoglobin. *Am J Kidney Dis* 1999; 34: 125–34.
25 Edwards NC, Moody WE, Yuan M et al. Diffuse interstitial fibrosis and myocardial dysfunction in early chronic kidney disease. *Am J Cardiol* 2015; 115; 1311–7.
26 Muntner P, Anderson A, Charleston J et al. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 2010; 55: 441–51.
27 Thadhani R, Appelbaum E, Pritchett Y et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA* 2012: 307: 674–84.
28 Odudu A, Eldehni MT, McCann GP et al. Randomized Controlled Trial of Individualized Dialysate Cooling for Cardiac Protection in Hemodialysis Patients. *Clin J Am Soc Nephrol* 2015; 10: 1408–17.
29 Chan CT, Greene T, Chertow GM et al. Effects of frequent hemodialysis on ventricular volumes and left ventricular remodeling. *Clin J Am Soc Nephrol* 2013; 8: 2106–16.
30 Culleton B, Walsh M, Klarenbach SW et al. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis. *JAMA* 2007; 298: 1291–9.
31 Badve SV, Palmer SC, Strippoli GF et al. The validity of left ventricular mass as a surrogate end point for all-cause and cardiovascular mortality outcomes in people with CKD: a systematic review and meta-analysis. *Am J Kidney Dis* 2016; 68: 554–63.
32 Aoki J, Ikari Y, Nakajima H et al. Clinical and pathologic characteristics of dilated cardiomyopathy in hemodialysis patients. *Kidney Int* 2005; 67: 333–40.
33 Mjøen G, Hallan S, Hartmann A et al. Long-term risks for kidney donors. *Kidney Int* 2014; 86; 162–7.
34 Moody WE, Ferro CJ, Edwards NC et al. Cardiovascular effects of unilateral nephrectomy in living kidney donors. *Hypertension* 2016; 67: 368–77.
35 Mark PB, Johnston N, Groenning BA et al. Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging. *Kidney Int* 2006; 69: 1839–45.
36 Collidge TA, Thomson PC, Mark PB et al. Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis: retrospective study of a renal replacement therapy cohort. *Radiology* 2007; 245: 168–75.
37 Graham-Brown MP, March DS, Churchward DR et al. Novel cardiac nuclear magnetic resonance method for noninvasive assessment of myocardial fibrosis in hemodialysis patients. *Kidney Int* 2016; 90: 835–44.
38 Rutherford E, Talle MA, Mangion K et al. Defining myocardial tissue abnormalities in end-stage renal failure with cardiac magnetic resonance imaging using native T1 mapping. *Kidney Int* 2016; 90: 845–52.
39 Shroff GR, Raggi P. Exploring the elusive link between subclinical fibrosis and clinical events in end-stage renal disease: does cardiac magnetic resonance imaging hold the key? *Kidney Int* 2016; 90: 729–32.
40 Meier-Kriesche H-U, Schold JD, Srinivas TR et al. Kidney transplantation halts cardiovascular disease progression in patients with end-stage renal disease. *Am J Transplant* 2004; 4: 1662–8.
41 Farrington K, Warwick G. Renal Association Clinical Practice Guideline on planning, initiating and withdrawal of renal replacement therapy. *Nephron Clin Pract* 2011; 118: c189–208.
42 Cholesterol Treatment Trialists' Collaboration et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010; 376: 1670–81.
43 Baigent C, Landry MJ, Reith C et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011; 377: 2181–92.
44 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.
45 Fellström BC, Jardine AG, Schmieder RE et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009; 360: 1395–1407.
46 Wanner C, Tonelli M, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int* 2014; 85: 1303–9.
47 McQuarrie EP, Freel EM, Mark PB et al. Urinary sodium excretion is the main determinant of mineralocorticoid excretion rates in patients with chronic kidney disease. *Nephrol Dial Transplant* 2013; 28: 1526–32.
48 Currie G, Taylor AH, Fuijita T et al. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. *BMC Nephrol* 2016; 17: 127.
49 Edwards NC, Steeds RP, Stewart PM et al. Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: a randomized controlled trial. *J Am Coll Cardiol* 2009; 54: 505–512.
50 Ito Y, Mizuno M, Suzuki Y et al. Long-term effects of spironolactone in peritoneal dialysis patients. *J Am Soc Nephrol* 2014; 25: 1094–102.
51 Matsumoto Y, Mori Y, Kageyama S et al. Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. *J Am Coll Cardiol* 2014; 63: 528–36.
52 Hammer F, Krane V, Störk S et al. Rationale and design of the Mineralocorticoid Receptor Antagonists in End-Stage Renal Disease Study (MiREnDa). *Nephrol Dial Transplant* 2014; 29: 400–5.
53 Pitt B, Rossignol P. Mineralocorticoid receptor antagonists in patients with end-stage renal disease on chronic hemodialysis. *J Am Coll Cardiol* 2014; 63: 537–8.
54 Quach K, Lvtvyn L, Baigent C et al. The safety and efficacy of mineralocorticoid receptor antagonists in patients who require dialysis: a systematic review and meta-analysis. *Am J Kidney Dis* 2016; 68: 591–8.

55 Eknoyan G, Beck GJ, Cheung AK et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002; 347: 2010–9.
56 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: 1130–7.
57 EVOLVE Trial Investigators, Chertow GM, Block GA et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012; 367: 2482–94.
58 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.
59 Agarwal R, Sinha AD, Pappas MK et al. Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial. *Nephrol Dial Transplant* 2014; 29: 672–81.
60 Kao, M. P, Ang DS, Gandy SJ et al. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. *J Am Soc Nephrol* 2011; 22: 1382–9.
61 London GM, Guérin AP, Marchais SJ et al. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2003; 18: 1731–40.
62 Krueger T, Schlieper G, Schurgers L et al. Vitamin K1 to slow vascular calcification in haemodialysis patients (VitaVasK trial): a rationale and study protocol. *Nephrol Dial Transplant* 2014; 29: 1633–8.
63 Greenwood SA, Koufaki P, Mercer TH et al. Aerobic or resistance training and pulse wave velocity in kidney transplant recipients: a 12-week pilot randomized controlled trial (the Exercise in Renal Transplant [ExeRT] Trial). *Am J Kidney Dis* 2015; 66: 689–98.
64 Longenecker JC, Coresh J, Powe NR et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol* 2002; 13: 1918–27.
65 Townsend N, Wickramasinghe K, Bhatnagar P et al. Coronary heart disease statistics 2012 edition. British Heart Foundation: London; 2012. https://www.bhf.org.uk/publications/statistics/coronary-heart-disease-statistics-2012