Cardiovascular complications of chronic kidney disease

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Abstract

Chronic kidney disease (CKD), as defined by low levels of eGFR, is common and is a risk factor for premature cardiovascular disease (CVD). The risk rises incrementally with decline in eGFR and is maximal in patients with end-stage kidney disease (ESKD) requiring dialysis (to around 20 times that of the general population). Conventional factors such as diabetes mellitus, hypertension, smoking and hyperlipidaemia contribute to the risk of developing progressive CKD and CVD. Other factors, some specific to CKD, including proteinuria, left ventricular hypertrophy, impaired calcium–phosphate homeostasis (PTH and FGF-23), anaemia and inflammation, contribute to CV risk in this population. Atypical relationships exist between blood pressure, cholesterol and mortality in ESKD. Although CKD is a state of accelerated atherosclerosis, the most common presentations in ESKD are heart failure and sudden cardiac death rather than myocardial infarction; this reflects the impact of abnormalities in cardiac structure and function, rather than atheromatous coronary heart disease. Clinical trials to improve CV outcomes have failed to deliver benefits comparable to the general population. Tight blood pressure control and lipid lowering for primary prevention of CVD are beneficial for patients with CKD not on dialysis; statin therapy reduces the risk of coronary heart disease in patients with CKD but has less of an impact on overall CV risk and CVD than in other high-risk populations. Further evidence is required for interventions targeted at sudden death and other non-conventional risk factors in CKD.

Keywords Cardiovascular disease; cholesterol; chronic kidney disease; diabetes; hypertension; ischaemic heart disease; left ventricular hypertrophy; statins

Background

Chronic kidney disease (CKD) is common, affecting 5–10% of the population. Although most of these patients will not develop progressive or end-stage kidney disease (ESKD), they are at increased risk of cardiovascular disease (CVD). Whereas this may reflect the fact that CKD is more common in patients with known cardiovascular (CV) risk factors, such as diabetes mellitus, pre-existing CVD, hypertension and advanced age, registry studies have shown that CKD is a risk factor for CVD in the general population, and in patients with previous CVD, heart failure or stroke.[1,2] Although CV risk factors such as hypertension and dyslipidaemia are a common consequence of CKD, these analyses suggest that reduced GFR may have independent effects on CV risk.

The magnitude of any independent, direct effect of reduced GFR on CV risk has been difficult to quantify. Recent studies in living kidney donors suggest that there is little impact. Living kidney donors are highly selected, healthy people who undergo surgical removal of 50% of their renal mass, with the post-operative eGFR typically recovering to around 60–70% of baseline. In a large Norwegian cohort, the long-term increased risk of CVD was small. Moreover, the observed increase in CVD was driven by the risk of developing progressive kidney disease amongst living related donors (and the CV risk associated with ESKD), presumably reflecting undetected genetic risk for kidney disease in these individuals, rather than a generalized increase in CVD. As well as providing reassurance for patients undergoing nephrectomy, these data are consistent with previous observations that CV risk rises significantly only when GFR falls below 60 ml/min. Thereafter, CV risk increases progressively and is maximal in patients with ESKD requiring dialysis, with age-adjusted CV risk at least 20 times that of the general population.[1,2] Although CV risk falls after successful transplantation, it remains around three to five times that of the general population (Figure 1).[2] In this overview, we concentrate on patients with ESKD – including those requiring dialysis and transplantation – but it is important to appreciate that CKD is a continuum. The pattern of CVD in ESKD is very different from that in early CKD, where it is similar to the general population.

Clinical manifestations of CVD in CKD

Before the development of effective renal replacement therapies (RRT), uraemic pericarditis and pericardial effusions were common, potentially fatal manifestations of ESKD. These are now rarely seen, typically in patients presenting with undiagnosed ESKD. CKD is also associated with accelerated atherosclerosis, although acute myocardial infarction (aMI) is not specifically increased in patients with ESKD and it is unusual to see typical ST elevation in patients with ESKD undergoing dialysis. It is often difficult to diagnose aMI in patients with advanced kidney disease and ESKD, because of the absence of symptoms, and the high prevalence of ECG abnormalities and elevated troponin concentrations in patients with reduced GFR. In Registry data and clinical trials[1–5] there are striking differences in CV causes of death in ESKD compared to the general population; whereas the most common mode of CV death in the general population is myocardial infarction, in ESKD sudden (presumed arrhythmic) cardiac death and death due to heart failure predominate. Left ventricular hypertrophy (LVH), the prevalence of which increases with declining GFR and which is almost universal in ESKD, is the likely substrate for sudden cardiac death, whereas

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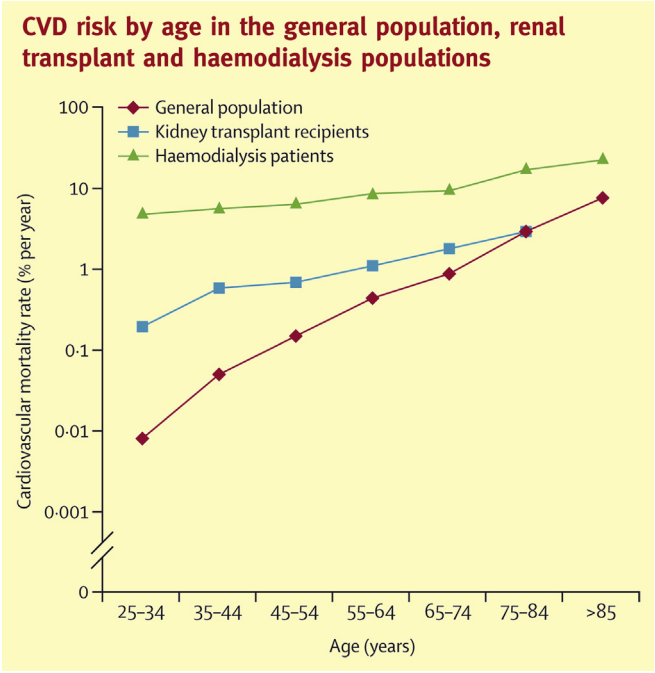

Figure 1 CVD risk by age in the general population, renal transplant and haemodialysis populations. Reprinted from Jardine AG, Gaston RS, Fellstrom BC, Holdaas H. Prevention of cardiovascular disease in adult recipients of kidney transplants. *Lancet*. 2011;**378**:1419–27, with permission from Elsevier.

dyslipidaemia predisposes to atheromatous coronary heart disease.

Pulmonary oedema is more common with declining renal function, as salt and water retention increases. This is exacerbated by LV abnormalities, either LVH and diastolic dysfunction, or LV systolic dysfunction. Oedema may occur in patients with normal systolic function due extreme fluid overload, and in patients with CKD due to bilateral renal artery stenosis ('flash' pulmonary oedema).

Risk factors, mechanisms and therapeutic targets for cardiovascular disease in CKD

Conventional CV risk factors (Table 1) are highly prevalent in CKD and ESKD.[1,2] However, certain CV risk factors are either specific to CKD or have a dominant effect in this population. These include albuminuria and proteinuria, anaemia, abnormal calcium/phosphate/vitamin D homeostasis and arterial calcification (so called 'bone mineral disorders' or BMD), and inflammation.

Hypertension is common in non-dialysis CKD and is a major risk factor for CVD as well as progression of kidney disease. The mechanism involves activation of the renin-angiotensin system, and impaired endothelial function in early CKD, but is more dependent on sodium and water retention in advanced and end-stage disease. Vascular calcification is also important, with the associated reduced vascular compliance contributing particularly to systolic hypertension. Once established on dialysis, the relationship with outcomes is less clear; there is a 'J'-shaped relationship with mortality, reflecting 'reverse causality' and the fact that patients with co-morbid diseases may have low blood pressure, probably reflecting underlying cardiac dysfunction.[1,2] This makes blood pressure targets in ESKD difficult to define.[6]

Cigarette smoking is a risk factor for CVD in CKD as well as for progression of CKD. This risk persists in patients treated by maintenance dialysis or following transplantation.[1,2] The same is true for diabetes. Diabetic nephropathy accounts for 20–40% of ESKD patients, with the proportion rising in keeping with the rising incidence of type 1, and particularly type 2 diabetes. Diabetes also increases in prevalence after transplantation; new-onset diabetes after transplantation (NODAT) is a consequence of treatment with immunosuppressive agents.[1,2] Tight glycaemic control reduces progression of microvascular complications such as nephropathy, whereas meticulous blood pressure control reduces progression of CKD and CV events.

In the general population, ***hypercholesterolaemia and dyslipidaemia*** are interchangeable in terms of prevalence and risk implication, but neither the pattern of dyslipidaemia nor the relationships with outcome are the same in CKD, particularly ESKD. Although lipids are abnormal, total and LDL cholesterol may be normal or reduced, elevated triglyceride and decreased HDL being the characteristic features. In ESKD, this is less evident and low total cholesterol is associated with poorer outcome,[1–5] the overall relationship having a J shape resembling that seen for hypertension.

Ischaemic heart disease is a major cause of CV mortality in ESKD, and significant coronary atherosclerosis is found in approximately 30% of potential renal transplant candidates. Conversely, symptomatic angina may occur in ESKD patients with normal coronary arteries, reflecting sub-endocardial ischaemia due to capillary/myocyte mismatch in the presence of LVH and microvascular dysfunction.

Left ventricular (LV) abnormalities, so-called 'uraemic cardiomyopathy', are strongly associated with adverse outcome in ESKD. Echocardiographic studies report three patterns of cardiomyopathy – LVH, LV dilatation and LV systolic dysfunction (LVSD) – affecting up to 85% of ESKD patients; the individual prevalences are 50–80% (LVH), 20–40% (LV dilatation)and approximately 16% (LVSD). LVH develops early in CKD and is associated with LV wall stiffening, a precursor to diastolic heart failure.[7,8] The major determinant of LVH in CKD is hypertension but anaemia, hyperparathyroidism and abnormal calcium –phosphate metabolism (and the resultant vascular calcification) all promote LVH.[7,8] Recently, left atrial size (left atrial volume >32 ml/m^2), which is dependent on diastolic dysfunction and intravascular volume, has been identified as a strong predictor of cardiovascular morbidity and mortality across the spectrum of CKD.

Albuminuria or proteinuria predict progression of CKD and future CVD. Proteinuria is a consequence of renal damage, although moderately increased albuminuria may reflect endothelial injury and vascular dysfunction, and is therefore a risk factor for CVD (with the kidney acting as a 'window' to the vasculature). Anaemia, secondary to erythropoietin deficiency and functional iron deficiency, is an almost universal finding in ESKD patients. Anaemia is consistently linked with development and progression of cardiac structural changes in CKD patients, in particular LVH, as well as increased mortality. However, some of the reported echocardiographic abnormalities linked to anaemia in CKD are partly artefactual. The reliance upon common