Cardiovascular complications of chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is a risk factor for premature cardiovascular disease (CVD). In patients with kidney failure requiring replacement therapy (KFRT) with dialysis or transplantation, CVD risk is greater, approximately 20 times that of the general population. Conventional cardiovascular risk factors such as diabetes, hypertension, smoking and dyslipidaemia worsen both CKD and CVD. Factors specific to CKD, such as proteinuria, impaired calcium–phosphate homeostasis, anaemia and inflammation, also contribute to cardiovascular risk. Atypical relationships exist between blood pressure, cholesterol and mortality in KFRT. Although CKD accelerates atherosclerosis, sudden cardiac death, rather than myocardial infarction, is the predominant mode of cardiac death in KFRT. Left ventricular disorders are common in this population and are associated with mortality as well as cardiac failure. Clinical trials of interventions to improve cardiovascular outcomes have been disappointing in KFRT, although two new treatments have emerged to reduce cardiovascular risk in earlier stages of CKD: sodium-glucose co-transporter 2 (SGLT2) inhibitors and the non-steroidal mineralocorticoid receptor antagonist finerenone. Tight blood pressure control and

lipid lowering for primary prevention of CVD are beneficial for patients with CKD not on dialysis. 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

Key points

- Sodium-glucose co-transporter 2 (SGLT2) inhibitors are novel evidence-based treatments to reduce cardiovascular risk and slow the progression of chronic kidney disease (CKD)
- The PIVOTAL trial (2019) showed that the proactive administration of high-dose intravenous iron is superior to low doses in reducing cardiovascular risk and reducing requirements for erythropoiesis-stimulating agents and red cell transfusions in individuals requiring haemodialysis
- The SPRINT trial (2015, further results 2021) and KDIGO 2021 blood pressure guideline update have recommended a new lower systolic blood pressure target of <120 mmHg in hypertension with CKD
- Advice about lipids remains unchanged, with cholesterol lowering recommended for cardiovascular disease prevention in people with CKD not requiring dialysis

Introduction

Chronic kidney disease (CKD) is common, affecting 5–10% of the population. It is more common in patients with known cardiovascular (CV) risk factors such as diabetes, previous CV disease (CVD), hypertension and advanced age (Figure 1). Registry studies suggest that CKD is a risk factor for CVD in the general population, as well as in patients with previous CVD, heart failure or stroke.[1] Therefore although CKD, indicated by reduced estimated glomerular filtration rate (eGFR), is a risk factor for CVD, its association with other CV risk factors makes the isolated effect of reduced eGFR on increased CV risk less clear.

Premature CVD is the leading cause of death in individuals with kidney failure requiring replacement therapy (KFRT) with dialysis, with an age-adjusted CV risk at least 20 times that of the general population (Figure 2). Although CV risk falls after successful transplantation, it remains around 3–5 times that of the general population.

Clinical manifestations of CVD in CKD

Before the development of effective kidney replacement therapies, uraemic pericarditis and pericardial effusions were common, potentially fatal manifestations of kidney failure. These are now rarely seen. CKD is associated with accelerated atherosclerosis. It is often difficult to diagnose acute myocardial infarction in individuals with advanced kidney disease and KFRT, because of the absence of symptoms, and the high prevalence of electrocardiogram abnormalities and elevated troponin concentrations in patients with reduced eGFR.

In registry data and clinical trials there are differences in CV causes of death in KFRT compared with the general population; whereas the most common mode of CV death in the general population is myocardial infarction, in KFRT sudden (presumed arrhythmic) cardiac death and death caused by heart failure predominate.[1] Left ventricular (LV) hypertrophy (LVH), the prevalence of which increases with declining eGFR, is the likely substrate for sudden cardiac death, whereas dyslipidaemia predisposes to atheromatous coronary heart disease.

Pulmonary oedema is common with declining kidney function, as salt and water retention increase. This is worsened by LV abnormalities, either LVH and diastolic dysfunction, or LV systolic dysfunction. Oedema can occur in patients with normal systolic function because of extreme fluid overload ordue to bilateral renal artery stenosis (‘flash’ pulmonary oedema).

Risk factors for CVD in CKD

Conventional CV risk factors are highly prevalent in CKD and KFRT while certain CV risk factors are specific to CKD (see Figure 1). These CKD-specific factors include albuminuria/proteinuria, anaemia, abnormal calcium/phosphate/vitamin D homeostasis (so-called ‘mineral bone disorders’) and arterial calcification (see Figure 1).

Hypertension. Hypertension is common in CKD and is a major risk factor for CVD and CKD progression. Vascular calcification is also important, with the associated reduced vascular compliance contributing particularly to systolic hypertension. Once an individual is established on dialysis, the situation is less clear: there is a 'J'-shaped relationship with mortality, reflecting 'reverse causality' and the fact that patients with co-morbid diseases can have low blood pressure (BP), probably reflecting underlying cardiac dysfunction.

Cigarette smoking and diabetes. Smoking and diabetes are both risk factors for CVD in CKD as well as for progression of CKD.. Diabetic kidney disease accounts for 20–40% of individuals with KFRT, with the proportion rising in keeping with the rising incidence of type 1 and particularly type 2 diabetes mellitus (T2DM). Diabetes also increases in prevalence after transplantation because of treatment with immunosuppressive agents. Tight glycaemic control reduces progression of microvascular complications such as nephropathy, whereas BP control reduces the progression of CKD and CV events.

Hypercholesterolaemia and dyslipidaemia. In the general population, hypercholesterolaemia and dyslipidaemia are interchangeable in terms of prevalence and risk; however, neither the pattern of dyslipidaemia nor the relationships with outcome are the same in CKD, particularly KFRT. Total and low-density lipoprotein (LDL) cholesterol can be normal or reduced, with elevated triglycerides and decreased high-density lipoprotein being the characteristic features. In KFRT, this is less evident and low total cholesterol is associated with poorer outcome.

Ischaemic heart disease. The prevalence and severity of ischaemic heart disease is a major contributor to CV mortality in KFRT. Studies assessing the prevalence of coronary artery disease in advanced CKD focus on kidney transplant candidates, who have less co-morbidity than the total KFRT population. Nonetheless, significant coronary atherosclerosis is found in approximately 30% of patients with KFRT. Conversely, symptomatic angina can occur in individuals with KFRT with normal coronary arteries. Explanations for this include subendocardial ischaemia resulting from capillary–myocyte mismatch in LVH.

LV abnormalities. LV abnormalities are strongly associated with adverse outcomes in KFRT. In KFRT there is a 50–80% prevalence of LVH, which is associated with LV wall stiffening, a precursor of diastolic heart failure. The major determinant of LVH in CKD is hypertension but anaemia, hyperparathyroidism and abnormal calcium–phosphate metabolism all promote LVH.

Microalbuminuria or proteinuria. Microalbuminuria/proteinuria predicts progression of CKD and future CVD. Proteinuria is a consequence of kidney damage, although moderately increased albuminuria can reflect endothelial injury and vascular dysfunction and is therefore a risk factor for CVD.

Anaemia. Anaemia occurs secondary to erythropoietin deficiency and functional iron deficiency, and is an almost universal finding in patients with KFRT. Anaemia is linked to the development and progression of cardiac structural changes in CKD, as well as increased mortality.

Hyperparathyroidism. Hyperparathyroidism accompanies CKD as a result of chronic hyperphosphataemia and hypocalcaemia associated with functional vitamin D deficiency. In experimental

uraemia, serum parathyroid hormone (PTH) promotes cardiac fibrosis and arteriolar thickening, and in patients with KFRT, raised PTH is a risk factor for mortality.

Hyperphosphataemia. Hyperphosphataemia is almost universal in KFRT, and is associated with mortality in KFRT and other populations. Phosphate promotes vascular calcification, inducing the transformation of vascular smooth muscle cells into an osteoblast-like phenotype. Vascular calcification on plain radiographs is common in KFRT. Coronary artery calcification is also highly prevalent and a marker of future CVD and mortality. Phosphate is also thought to exert direct effects on vascular function, specifically impaired endothelial function, which may additionally contribute to increased CV mortality.

Evidence-based therapy to improve cardiovascular outcomes

General measures

A healthy lifestyle is recommended for all patients with CKD – cessation of cigarette smoking, a low-sodium diet and moderate physical activity (Figure 3). There is no evidence to suggest that aspirin should be used for CVD primary prevention in CKD.[2]

For individuals with CKD who experience an atherosclerotic cardiac event, it is reasonable to prescribe secondary prevention with antiplatelet agents, β-adrenoceptor blockade, angiotensin-converting enzyme inhibitors and statins. Patients with CKD have poorer outcomes after myocardial infarction or coronary revascularization. There is a trend towards undertreatment in CKD and it is imperative that 'therapeutic nihilism' is avoided.

Diabetes management

Diabetes management in CKD should aim for moderately tight glycaemic control, identifying a glycated haemoglobin (HbA_{1c}) target of between 48 and 64 mmol/mol (between <6.5% and <8%) depending on individual patient factors. More intensive glycaemic control (HbA_{1c} <48 mmol/mol) has been associated with increased CV and all-cause mortality in patients with T2DM and mild to moderate CKD.

First-line pharmacological treatment for individuals with T2DM and CKD with an eGFR ≥30 ml/min/1.73 m^2 is metformin and a sodium-glucose co-transporter 2 (SGLT2) inhibitor.[2] If this first-line therapy is contraindicated or glycaemic control is not achieved, long-acting glucagon-like peptide 1 receptor agonists should be used.[2] In addition to glycaemic control, SGLT2 inhibitors reduce CV morbidity and mortality in T2DM with CKD.[3]

Dyslipidaemia

The SHARP trial showed that lipid lowering with combined simvastatin/ezetimibe reduced the risk of atherosclerotic vascular events in CKD.[4] The benefits of lipid lowering in SHARP were mainly seen in patients with pre-dialysis CKD, and lipid lowering did not significantly influence non-atherosclerotic cardiac events such as sudden death. In dialysis patients, the 4D and AURORA studies failed to show a significant effect on a CV outcomes with atorvastatin or rosuvastatin, respectively, compared with placebo.[4] However,

in kidney transplant patients, the ALERT trial demonstrated that fluvastatin reduced cardiac deaths and non-fatal myocardial infarction.[4]

A meta-analysis of the major LDL–cholesterol-lowering trials demonstrated the benefits of cholesterol-lowering therapy with statins on atherosclerotic vascular events in people with CKD; however, this falls as kidney function declines, to the point that these agents do not appear to affect CVD risk in people on dialysis (Figure 4).[4] Guidelines support the use of statins in patients with CKD not requiring dialysis.[2]

Blood pressure

Good BP control in patients with CKD stages 1–4 is associated with reduced CV risk. Based on the results of the SPRINT trial, more intensive BP lowering is now recommended in CKD, targeting a systolic BP of <120 mmHg regardless of proteinuria (with the exception of dialysis patients, kidney transplant recipients and those with postural hypotension or approaching end of life). In the SPRINT population at increased CV risk, of whom around 2600 (approximately 30%) had CKD, intensive BP lowering to a systolic pressure <120 mmHg resulted in a 40% reduction in CV death compared with the standard <140 mmHg target.

Although SPRINT was not a dedicated CKD trial, and recommendations are based on subgroup analysis for which the trial was not powered, the CKD subgroup comprising 2600 participants is larger than any trial of BP targets in CKD. SPRINT excluded participants with diabetes but until a dedicated trial is conducted in people with diabetes and CKD, the target of <120 mmHg should be applied. Authors emphasize that the <120 mmHg target depends on the use of standardized (as opposed to routine) clinic BP measurements. Renin–angiotensin system (RAS) inhibitors should be preferentially used, particularly in diabetes mellitus and/or with proteinuria.[2] Moderate dietary sodium restriction (<5 g salt/day) may help improve the outcome of RAS blockade.[2]

BP strategies become less clear once patients have been established on dialysis. The choice of agent in patients on dialysis is similarly difficult to recommend as there have been no large-scale trials. The updated 2021 Kidney Disease: Improving Global Outcomes (KDIGO) management of BP guidelines do not include patients on dialysis, and although it is reasonable to individualize therapy it is difficult to say more than to avoid extremes of BP (systolic BP >160 mmHg or <120 mmHg). BP targets in individuals with functioning kidney transplants should be more conservative than in the general CKD population and should target systolic BP <130 mmHg and diastolic <80 mmHg using a calcium channel blocker or angiotensin receptor blocker first-line.

Anaemia, hyperphosphataemia and non-traditional CVD risk factors

Although anaemia in CKD is associated with LVH, clinical trials that have studied the effect of returning haemoglobin to ‘normal’ concentrations with erythropoiesis-stimulating agents (ESAs) have not shown reduced risks of CVD. This remains a controversial area, and current guidelines suggest maintaining the haemoglobin concentration at 100–120 g/litre in CKD patients requiring ESAs. The recent PIVOTAL trial

demonstrated that a proactive intravenous iron regimen was associated with fewer CV events than a reactive iron regimen in people treated with haemodialysis.[5]

Hyperphosphataemia and elevated PTH are associated with increased mortality in observational studies of patients with KFRT. However, no specific phosphate binder has been proven to reduce CV mortality. In addition, the EVOLVE study in dialysis patients did not demonstrate a significant effect of cinacalcet on the primary composite endpoint (death, myocardial infarction, hospitalization for unstable angina, heart failure or peripheral vascular disease).

Novel pharmacological treatments for CVD in CKD

Treatment to slow the progression of CKD and reduce CV morbidity and mortality has for two decades been limited to RAS inhibition. Recent large randomized controlled trials (RCTs) have identified two new effective treatments that can be used in combination: SGLT2 inhibitors and finerenone, a non-steroidal mineralocorticoid receptor antagonist (MRA).

SGLT-2 inhibitor/. Cardioprotective effects of SGLT-2 inhibitors, such as canagliflozin, dapagliflozin and empagliflozin, have been demonstrated in trials of people with T2DM, heart failure and, more recently, CKD with and without T2DM.[3] CV benefits are largely mediated by reductions in hospitalization for heart failure with less effect on atherosclerotic disease; which is of particular relevance in CKD where heart failure and sudden cardiac death are the more common causes of CV death.

Four large RCTs have been completed in dedicated CKD populations: CREDENCE and SCORED involved exclusively T2DM populations, whereas DAPA-CKD and EMPA-KIDNEY included participants with and without T2DM. A meta-analysis of these and eight other large SGLT-2 inhibitor trials found a 23% reduction in the relative risk of a composite outcome of hospitalization for heart failure or CV death overall (relative risk 0.77, 95% confidence interval [CI] 0.74–0.81) with consistent effects in those with and without diabetes (heterogeneity p=0.67).[3] The mechanisms of action remain incompletely understood but are largely haemodynamic with associated metabolic and diuretic effects. The class effects of SGLT2 inhibitors are consistent across different levels of kidney function. SGLT2 inhibitors should now be part of routine care for many patients with CKD to reduce CVD risk and prevent CKD progression.

MRAs. The second drug class of interest is MRAs Steroidal MRAs (spironolactone and eplerenone)are established cardioprotective agents in the treatment of heart failure with reduced ejection fraction, but a significant increased risk of hyperkalaemia has limited their role in CKD. Recent trials testing finerenone, a non-steroidal MRA with a lower propensity for hyperkalaemia, in diabetic kidney disease have demonstrated relative risk reductions in composite CV outcomes; these were driven largely by effects on heart failure hospitalization (and kidney disease progression). The role of finerenone either in combination with or as an alternative to SGLT2 inhibitors in routine clinical practice for diabetic kidney disease will emerge in the near future.

Figure 1 Risk factors for CVD.

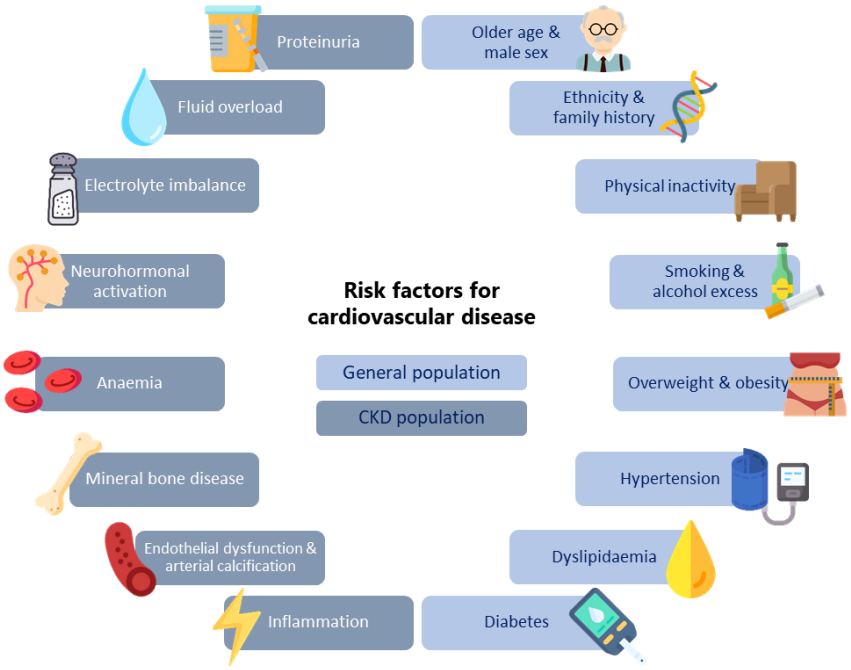

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Figure 2 CV mortality and associations with kidney function measured by (**A**) eGFR and (**B**) albuminuria. Reproduced from Gansevoort et al. (2013).[1]

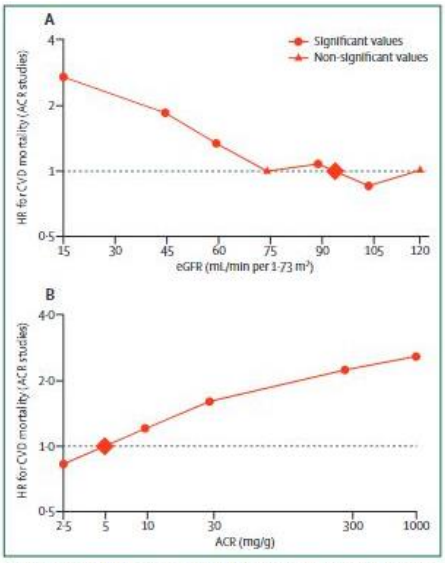
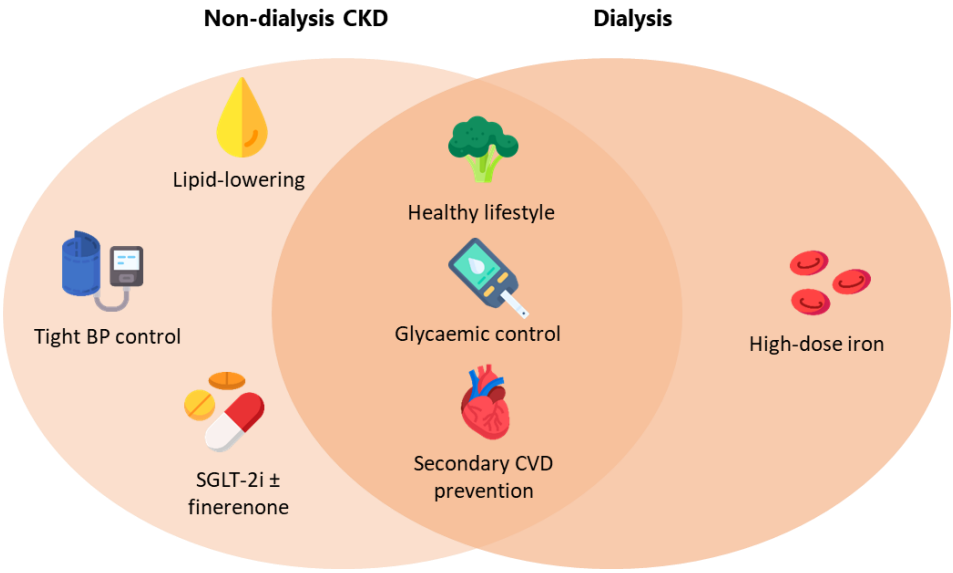


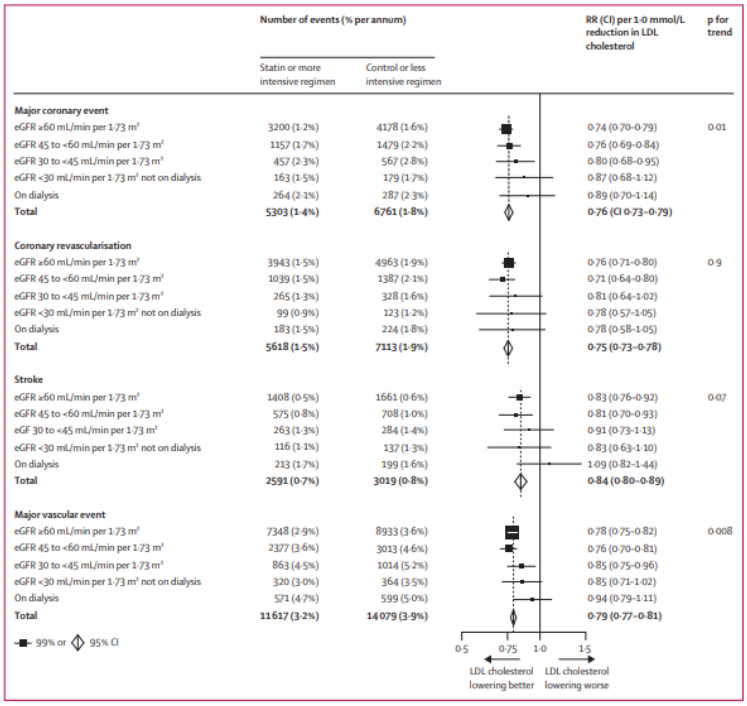
Figure 1: Independent associations of kidney function and proteinuria with cardiovascular mortality
(A) Kidney function (eGFR); reference value of 95 mL/min per 1·73 m² is shown with a diamond. (B) Albuminuria (ACR); the reference value of 5 mg/g is shown with a diamond. Hazard ratios are adjusted for each other (eGFR or ACR), age, sex, ethnic origin, and traditional cardiovascular risk factors. HR=hazard ratio. CVD=cardiovascular disease. ACR=albumin-to-creatinine ratio. eGFR=estimated glomerular filtration rate. Based on data in reference 5.

Figure 3 Key recommendations to lower CVD risk in CKD.



Designed using icons made by Freepik from www.flaticon.com. CKD, chronic kidney disease; BP, blood pressure; SGLT-2, sodium glucose cotransporter-2; CVD, cardiovascular disease.

Figure 4 Effect of LDL–cholesterol lowering on CV events according to baseline kidney function. Reproduced from Herrington et al. (2016).[4]



	Number of events (% per annum)		RR (CI) per 1·0 mmol/L reduction in LDL cholesterol	p for trend
	Statin or more intensive regimen	Control or less intensive regimen		
Major coronary event				
eGFR ≥60 mL/min per 1·73 m²	3200 (1·2%)	4178 (1·6%)	0·74 (0·70–0·79)	0·01
eGFR 45 to <60 mL/min per 1·73 m²	1157 (1·7%)	1479 (2·2%)	0·76 (0·69–0·84)	
eGFR 30 to <45 mL/min per 1·73 m²	457 (2·3%)	567 (2·8%)	0·80 (0·68–0·95)	
eGFR <30 mL/min per 1·73 m² not on dialysis	163 (1·5%)	179 (1·7%)	0·87 (0·68–1·12)	
On dialysis	264 (2·1%)	287 (2·3%)	0·89 (0·70–1·14)	
Total	**5303 (1·4%)**	**6761 (1·8%)**	**0·76 (CI 0·73–0·79)**	
Coronary revascularisation				
eGFR ≥60 mL/min per 1·73 m²	3943 (1·5%)	4963 (1·9%)	0·76 (0·71–0·80)	0·9
eGFR 45 to <60 mL/min per 1·73 m²	1039 (1·5%)	1387 (2·1%)	0·71 (0·64–0·80)	
eGFR 30 to <45 mL/min per 1·73 m²	265 (1·3%)	328 (1·6%)	0·81 (0·64–1·02)	
eGFR <30 mL/min per 1·73 m² not on dialysis	99 (0·9%)	123 (1·2%)	0·78 (0·57–1·05)	
On dialysis	183 (1·5%)	224 (1·8%)	0·78 (0·58–1·05)	
Total	**5618 (1·5%)**	**7113 (1·9%)**	**0·75 (0·73–0·78)**	
Stroke				
eGFR ≥60 mL/min per 1·73 m²	1408 (0·5%)	1661 (0·6%)	0·83 (0·76–0·92)	0·07
eGFR 45 to <60 mL/min per 1·73 m²	575 (0·8%)	708 (1·0%)	0·81 (0·70–0·93)	
eGF 30 to <45 mL/min per 1·73 m²	263 (1·3%)	284 (1·4%)	0·91 (0·73–1·13)	
eGFR <30 mL/min per 1·73 m² not on dialysis	116 (1·1%)	137 (1·3%)	0·83 (0·63–1·10)	
On dialysis	213 (1·7%)	199 (1·6%)	1·09 (0·82–1·44)	
Total	**2591 (0·7%)**	**3019 (0·8%)**	**0·84 (0·80–0·89)**	
Major vascular event				
eGFR ≥60 mL/min per 1·73 m²	7348 (2·9%)	8933 (3·6%)	0·78 (0·75–0·82)	0·008
eGFR 45 to <60 mL/min per 1·73 m²	2377 (3·6%)	3013 (4·6%)	0·76 (0·70–0·81)	
eGFR 30 to <45 mL/min per 1·73 m²	863 (4·5%)	1014 (5·2%)	0·85 (0·75–0·96)	
eGFR <30 mL/min per 1·73 m² not on dialysis	320 (3·0%)	364 (3·5%)	0·85 (0·71–1·02)	
On dialysis	571 (4·7%)	599 (5·0%)	0·94 (0·79–1·11)	
Total	**11617 (3·2%)**	**14079 (3·9%)**	**0·79 (0·77–0·81)**	

99% or 95% CI

0·5 0·75 1·0 1·5

LDL cholesterol lowering better | LDL cholesterol lowering worse

Figure 1: **Effects on major vascular events per mmol/L reduction in LDL cholesterol, by baseline renal function**
Data for participants with missing creatinine values at baseline are included in totals. Black squares and horizontal lines represent 99% CIs. White diamonds represent 95% CIs. Vertical dotted line represents overall RR for each outcome. eGFR=estimated glomerular filtration rate. RR=rate ratio.

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