Cardiovascular complications of chronic kidney disease

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Abstract

Chronic kidney disease (CKD), defined by low estimated glomerular filtration rate (eGFR), is common and a risk factor for cardiovascular disease (CVD). The risk rises with decline in eGFR and is maximal (around 20 times that of the general population) in patients with end-stage kidney disease (ESKD) requiring dialysis. Conventional factors such as diabetes mellitus, hypertension, smoking and hyperlipidaemia contribute to the risk of progressive CKD and CVD. Other factors including proteinuria, left ventricular hypertrophy, impaired calcium −phosphate homeostasis (PTH, FGF-23), anaemia and inflammation, contribute to cardiovascular risk in this population. Relationships between blood pressure, cholesterol and mortality in ESKD differ from the general population. Although CKD causes accelerated atherosclerosis, the most common presentations in ESKD are heart failure and cardiac death rather than non-fatal myocardial infarction. Tight blood pressure control and lipid-lowering for primary prevention of CVD benefit patients with CKD not on dialysis; statin therapy reduces the risk of coronary heart disease in patients with CKD but has less impact on overall cardiovascular risk than other high-risk populations; SGLT-2 inhibitors have benefit in patients with CKD and type 2 diabetes mellitus. However, further evidence is required for interventions targeted at sudden death and other non-conventional risk factors.

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

Key points

- Cardiovascular risk is increased in chronic kidney disease (CKD) patients, and maximal in patients with end-stage kidney disease (ESKD)
- There is a disproportionate increase in fatal compared with non-fatal cardiovascular events
- Specific risk factors for cardiovascular disease in CKD include cardiac structural abnormalities (primarily left ventricular hypertrophy) and vascular structural abnormalities (primarily vascular calcification)
- Traditional risk factor control is important in various stages of CKD but has no proven benefit in dialysis-dependent ESKD

Background

Chronic kidney disease (CKD) is common, affecting around 5 −10% of the population. Most patients with CKD do not develop progressive or end-stage kidney disease (ESKD), but they have an increased risk of cardiovascular disease (CVD). This could reflect the fact that CKD is more common in patients with known cardiovascular risk factors such as diabetes mellitus, pre-existing CVD, hypertension and advanced age. However, registry studies have identified reduced glomerular filtration rate (GFR) as having an independent effect on cardiovascular risk in the general population and in patients with previous CVD, heart failure or stroke.

The magnitude of this effect is difficult to quantify. The independent effect of reduced GFR in the early stages of CKD appears to be minimal. Living kidney donors have been studied as an ideal population of highly selected healthy people who undergo surgical removal of 50% of their renal mass, with postoperative estimated GFR (eGFR) typically recovering to around 60−70% of baseline. In a large Norwegian cohort, the long-term increased risk of CVD was small and largely driven by the small proportion of these patients who progressed to ESKD, presumably reflecting an unrecognized genetic risk for kidney disease in these individuals. These data are consistent with previous observations that cardiovascular risk rises significantly only when GFR falls to <60 ml/minute/1.73 m^2.[1] Thereafter, cardiovascular risk increases progressively and is maximal in patients with ESKD requiring dialysis, with age-adjusted cardiovascular risk at least 20 times that of the general population. Cardiovascular risk falls with successful renal transplantation, but remains 3−5 times that of the general population (Figure 1).[2] In this overview, we concentrate on patients with ESKD, including those requiring dialysis and transplantation; however, it is important to appreciate that CKD is a continuum, and that 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

Untreated ESKD presents with uraemic complications including pericarditis and pericardial effusions, although these are now rare since the development of effective renal replacement therapies (RRTs). Although ESKD is a state of accelerated atherosclerosis, acute myocardial infarction (MI) is not particularly increased in patients with ESKD, and it is unusual to see typical ST elevation in patients with ESKD undergoing dialysis. Acute MI can be difficult to diagnose in this patient group, who often have no pain, a high prevalence of baseline electrocardiogram (ECG)

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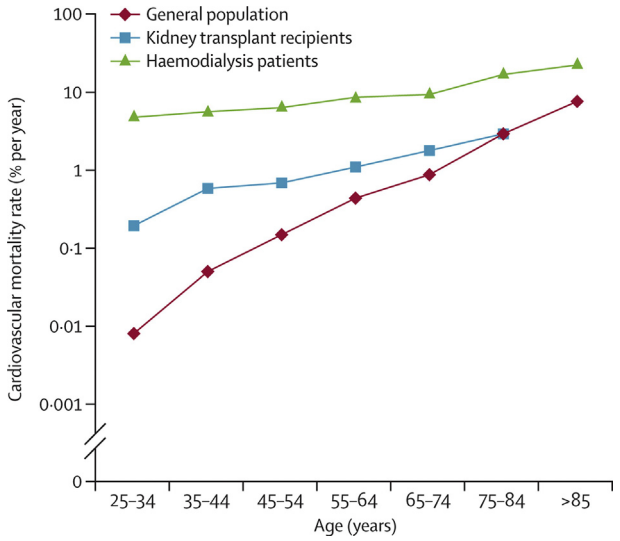

Figure 1 CVD risk by age in the general population, renal transplant and haemodialysis populations. Reprinted from Jardine et al. (2011),[2] with permission from Elsevier.

Risk factors for CVD in the general population and in ESKD

Risk factors for CVD — general population	Risk factors for CVD — ESKD population
Older age	Haemodynamic and metabolic factors of CKD
Hypertension	Proteinuria
Hyperlipidaemia	↑ Extracellular fluid volume
Diabetes	Electrolyte imbalance
Physical inactivity	Anaemia
Previous MI/CAD/PVD/CVD	FGF-23
Smoking	↑ PTH and calcium—phosphate product
Oxidative stress	Arterial calcification
	LVH/LV systolic dysfunction
	Accelerated valvular heart disease (aortic stenosis)
	Inflammation

Table 1

abnormalities and chronically elevated troponin concentrations. Perhaps as a result of this, registry data and clinical trials show striking differences in the pattern of cardiovascular events in ESKD compared with the general population. Whereas the most common mode of cardiovascular death in the general population is MI, sudden (presumed arrhythmic) cardiac death and death from heart failure predominate in ESKD.

Significant structural cardiac abnormalities develop in ESKD, with left ventricular hypertrophy (LVH) almost universal at the start of haemodialysis. LVH is the likely substrate for sudden cardiac death, presenting a vulnerable myocardium regularly insulted by large fluid and electrolyte 'shifts' as well as microscopic ischaemia during dialysis sessions. Pulmonary oedema becomes more common with declining renal function as salt and water retention increases. This is also exacerbated by left ventricular (LV) abnormalities, either LVH and diastolic dysfunction, or LV systolic dysfunction. Oedema can occur even in patients with normal systolic function because of extreme fluid overload, and in patients with CKD because of bilateral renal artery stenosis ('flash' pulmonary oedema).

Risk factors, mechanisms and therapeutic targets for CVD in CKD

Conventional cardiovascular risk factors (Table 1) are highly prevalent in CKD and ESKD. However, certain cardiovascular risk factors are either specific to or have a dominant effect in CKD. These include albuminuria and proteinuria, anaemia, abnormal calcium/phosphate/vitamin D homeostasis and arterial calcification (so-called bone mineral disorders), and inflammation.[4]

Hypertension

This is common in non-dialysis CKD and is a major risk factor for CVD as well as progression of CKD. The mechanisms involve inappropriate activation of the renin—angiotensin system, and impaired endothelial function in early CKD, but it 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 to systolic hypertension in particular. Once the individual is 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 can have low blood pressure, probably reflecting underlying cardiac dysfunction. This makes blood pressure targets in ESKD difficult to define.

Cigarette smoking

This is a risk factor for CVD in CKD as well as for progression of CKD. The risk persists in patients treated by maintenance dialysis or after transplantation.

Diabetes mellitus

Diabetes mellitus is also a risk factor for CVD in CKD as well as progression of CKD. Diabetic nephropathy is a leading cause of ESKD and accounts for 35—50% of ESKD patients, with the proportion rising in keeping with the rising incidence of type 1, but particularly type 2, diabetes. Diabetes also increases in prevalence after transplantation, new-onset diabetes after transplantation (NODAT) being a consequence of treatment with immunosuppressive agents. Tight glycaemic control reduces the progression of microvascular complications such as nephropathy, whereas meticulous blood pressure control reduces progression of CKD and cardiovascular events.

Hypercholesterolaemia and dyslipidaemia

In the general population, these 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 plasma lipids are abnormal, total and low-density lipoprotein-cholesterol can be normal or reduced, with elevated triglycerides

(triacylglycerols) and decreased high-density lipoprotein being the characteristic features. This is less evident in ESKD, and low total cholesterol is associated with poorer outcome, the overall relationship having a 'J' shape resembling that seen for hypertension.

Ischaemic heart disease

Although this is not the leading cause of mortality, it remains prevalent in ESKD, and significant coronary atherosclerosis is found in approximately 30% of potential renal transplant candidates. Symptomatic angina can occur even in the absence of coronary artery disease, reflecting subendocardial ischaemia caused by capillary–myocyte mismatch in the presence of LVH and microvascular dysfunction.

Cardiac structural abnormalities

Cardiac structural abnormalities changes in myocardial structure and valvular disease are common in CKD and ESKD. Myocardial abnormalities – 'uraemic cardiomyopathy' – are strongly associated with adverse outcome in ESKD. Echocardiographic studies report three patterns of cardiomyopathy affecting up to 85% of ESKD patients: LVH (with associated diastolic dysfunction), LV dilatation and LV systolic dysfunction, with reported prevalences of 50–80%, 20–40% and 16%, respectively.

LVH develops early in CKD and is associated with LV wall stiffening, a precursor to diastolic heart failure. The major determinant of LVH is hypertension, but anaemia, volume overload and vascular calcification (strongly influenced by hyperparathyroidism and abnormal calcium–phosphate metabolism) also contribute. Indeed, left atrial size (left atrial volume >32 ml/m^2), dependent on diastolic dysfunction and intravascular volume, has been identified as a strong predictor of cardiovascular morbidity and mortality across the spectrum of CKD. Calcific valvular abnormalities – principally aortic stenosis – the development of which is accelerated in advanced and end-stage kidney disease (reflecting bone mineral disorders; see below) are increasingly recognized. Calcific aortic stenosis is a therapeutic challenge in patients with ESKD, with substantial comorbidity, and is likely to be a factor in the very high risk of sudden cardiac death in this population.

Anaemia

This occurs secondary to erythropoietin deficiency and functional iron deficiency, and is almost universal in ESKD patients. It is consistently linked with the development and progression of LV abnormalities, particularly LVH, and increased mortality. However, some of the reported echocardiographic abnormalities linked to anaemia in CKD are partly artefactual. Common echocardiographic calculations to determine LV mass are based on chamber volume or diameter. Thus, the large fluctuations in intravascular volume that occur in ESKD, particularly interdialytic gains, result in an overestimation of LV mass. It is therefore important to schedule echocardiographic studies immediately after dialysis when patients are at their 'target' weight, and to concentrate on direct measurements such as septal and posterior wall thickness rather than on derived measures such as LV mass index.

Albuminuria and proteinuria

These predict the progression of CKD and future CVD. Proteinuria is a consequence of renal damage, although moderately increased albuminuria can reflect endothelial injury and vascular dysfunction and is therefore a risk factor for CVD (with the kidney acting as a 'window' to the vasculature).

CKD – mineral bone disorder (CKD-MBD) is the term that defines the abnormal physiological relationships between the renal, skeletal and cardiovascular systems in CKD. Key disturbances include hyperparathyroidism in the setting of chronic hyperphosphataemia and hypocalcaemia associated with functional vitamin D deficiency. Serum parathyroid hormone (PTH) is elevated in CKD, and in experimental models of uraemia promotes cardiac fibrosis and arteriolar thickening. Because of impaired excretion, hyperphosphataemia is almost universal in ESKD and is associated with mortality. Conventional thinking is that phosphate promotes vascular calcification, inducing transformation of vascular smooth muscle cells into an osteoblast-like phenotype. Recent data also support direct effects of phosphate on vascular function, specifically impaired endothelial function. Vascular calcification on plain radiographs is common in ESKD. Coronary artery calcification, demonstrated by computed tomography, and calcific valvular heart disease are also highly prevalent and act as markers for future CVD and mortality. Other determinants of vascular calcification include age, dialysis vintage, homocysteine concentration and inflammation.

Fibroblast growth factor-23 (FGF-23) is a phosphaturic hormone, levels of which are increased in AKI and CKD. In recent years, FGF-23 has been recognized as not just a biomarker of CKD, but also a key player in ESKD-associated CVD. FGF-23 acts directly on cardiac myocytes to cause LVH and cardiac fibrosis, while its actions on the distal convoluted tubule augment sodium reabsorption and increase circulating volume, also contributing to LVH. Thus, altered bone physiology in ESKD contributes to increased CVD via two major pathophysiological mechanisms. First is vascular calcification and dysfunction as a consequence of the increased calcium–phosphate product and the direct vascular effects of hyperphosphataemia. Second is fibrotic LVH, to which FGF-23 and PTH contribute, and which leads to an increased risk of heart failure and sudden, arrhythmic cardiac death.

Inflammation

ESKD is a state of chronic inflammation, and elevated circulating levels of inflammatory mediators such as C-reactive protein (CRP), interleukin 6 and decreased albumin have also been implicated in increased cardiovascular risk. In contrast to other populations with CVD, atheroma is not the main driver of inflammation and CRP levels, with infection a more important factor.

Evidence-based therapy to improve cardiovascular outcomes

General measures

To a large extent, the management of CVD in CKD has drawn on evidence from the general population, including subanalyses of clinical trials based on calculated eGFR; there are few studies on

cardiovascular outcomes in renal populations, despite the clear differences in CVD in patients with CKD and ESKD, compared with the general population. For patients with CKD who experience an atherosclerotic cardiac event, it is reasonable to prescribe secondary preventive treatment with antiplatelet agents, β-adrenoceptor blockade, angiotensin-converting enzyme inhibitors and statins. However, there is limited evidence to support their use in this setting, and patients with CKD have poorer outcomes after MI or coronary revascularization. There is a trend towards undertreatment in CKD because of drug intolerance, enhanced adverse effects or polypharmacy, and it is imperative that 'therapeutic nihilism' is avoided.

A healthy lifestyle is recommended for all CKD patients, which involves cessation of cigarette smoking, a low-sodium diet, weight management, avoidance of physical inactivity and good diabetic control. More intensive glycaemic control (glycated haemoglobin (HbA_{1c}) <47 mmol/mol (<6.5%)) has been associated with increased cardiovascular and all-cause mortality in patients with type 2 diabetes and mild to moderate CKD.

In the ESKD population on maintenance haemodialysis, daily or nocturnal haemodialysis appears to improve cardiovascular outcomes and survival. This is probably the result of better control and reduced 'swings' in intravascular volume and electrolytes. However, with the exception of small cohorts undergoing home haemodialysis, daily treatment is either impractical or unaffordable.

Dyslipidaemia

For lipid-lowering, subgroup analysis of the pravastatin trials (CARE, LIPID and WOSCOPS) demonstrated that pravastatin use was associated with reduced cardiovascular events in mild to moderate CKD. The SHARP study showed that lipid-lowering with a combination of simvastatin/ezetimibe reduced the risk of atherosclerotic vascular events in CKD. However, the benefits of lipid-lowering in SHARP were seen mainly in patients with pre-dialysis CKD, and lipid-lowering did not significantly influence non-atherosclerotic cardiac events such as sudden death. In patients given maintenance haemodialysis, the 4D study failed to show a significant effect on a composite endpoint of cardiovascular death, non-fatal MI and stroke in patients with type 2 diabetes and ESKD treated with atorvastatin 20 mg/day. In the AURORA study, rosuvastatin did not reduce cardiovascular events compared with placebo in 2800 patients with ESKD undergoing maintenance haemodialysis. However, in renal transplant recipients, the ALERT trial demonstrated that fluvastatin reduced cardiac deaths and non-fatal MI.

The lack of the expected impact of statin therapy in ESKD is consistent with the lack of a clear relationship between lipid concentration and cardiovascular events in patients with CKD and ESKD. There is general acceptance that this reflects the diminishing contribution of atheromatous CAD to the overall CVD burden as renal function declines. Nevertheless, guidelines support the use of statins in early CKD, where the pattern of CVD is similar to that in the general population, and to prevent atheromatous CAD across the range of CKD. The most recent KDIGO guidelines suggest that statins should be used, but without evidence supporting a target cholesterol these have endorsed a controversial 'fire and forget' approach to statin therapy.

Blood pressure

Good blood pressure control in patients with CKD stages 1–4 is associated with a reduced rate of decline of renal function, delay in development of ESKD and possible benefits for CVD. In general, guidelines recommend that blood pressure in patients with CKD should be <140/90 mmHg; in patients with CKD and diabetes, and those with significant proteinuria (protein:creatinine ratio ≥100 mg/mmol), target values should be <130/80 mmHg. Inhibitors of the renin–angiotensin system (angiotensin receptor blockers) should be used preferentially where tolerated, particularly in diabetes and/or in the presence of proteinuria. Recent data suggest that moderate dietary sodium restriction (<5 g salt per day) can improve the effects of renin–angiotensin system blockade.

Blood pressure strategies are less clear once patients have become established on dialysis. Blood pressure varies during and between dialysis sessions and is closely related to intravascular volume status. Measurements on non-dialysis days have been suggested as a better measure than intradialytic blood pressure, and show a linear relationship with mortality in prospective studies. The choice of agent in patients having dialysis is similarly difficult to recommend. There have been no large-scale outcome trials, although the FOSIDIAL study of fosinopril versus placebo showed a trend towards improved survival in the active treatment group. The KDIGO guidelines for blood pressure did not include patients undergoing dialysis, and although it is reasonable to follow their guidance about individualization of therapy, it is difficult to say more than to avoid extremes of blood pressure (systolic pressure >160 or <120 mmHg).

There is no specific evidence to suggest that aspirin or clopidogrel should be used specifically for primary prevention of CVD in CKD patients. For secondary prevention of CVD or after coronary intervention, aspirin or clopidogrel should be used along similar lines to the general population, despite a small increased risk of bleeding in CKD.

Anaemia

Anaemia in CKD occurs secondary to iron deficiency owing to reduced absorption and increased blood loss, as well as reduced erythropoietin concentrations. In the recent PIVOTAL trial, higher dose, proactive intravenous iron in patients on maintenance haemodialysis reduced several secondary cardiac outcomes, including MI (fatal, non-fatal), and hospitalization for heart failure.[5] However, clinical trials that have studied the effects of returning haemoglobin concentration to 'normal' with erythropoiesis-stimulating agents (ESAs) have not shown a reduction in CVD risk, and achieving a normal haemoglobin with ESAs in this context could be harmful, with an increased risk of thrombotic complications. This remains a controversial area, but current guidelines suggest that haemoglobin should be maintained between 100 and 120 g/litre in CKD patients requiring ESAs.

An interesting new development in this area is the investigation of hypoxia-inducible factor prolyl hydroxylase inhibitors, a new class of drugs that activate the hypoxia-inducible factor pathway, leading to endogenous erythropoietin secretion and increased iron availability; these are currently in Phase III clinical trials with cardiovascular outcome measurements.

Diabetes

As diabetes becomes the predominant cause of progressive and end-stage renal disease and a consequence of renal transplantation, it is a critical therapeutic target. Prevention of type 2 diabetes is likely to stem the rising numbers of patients requiring dialysis. In those with the condition, tight blood pressure control, using renin–angiotensin system blockers, is established as reducing the development of ESKD. A major breakthrough, in recent years, has been the observation that sodium—glucose co-transporter-2 (SGLT-2) inhibitors – based on trials such as EMPA-REG – reduce the risk of both ESKD and cardiovascular events by around one-third to one-half. The CREDENCE trial has recently shown that these benefits persist in patients with established CKD with eGFR as low as 30 ml/minute/1.73 m^2.[3] Although these findings have yet to be endorsed in guidelines and the mechanism is unclear, it is difficult not to endorse their use.

CKD-MBD

Hyperphosphataemia and elevated PTH are associated with increased mortality in observational studies of patients with ESKD. However, no specific phosphate binder has been shown to reduce cardiovascular mortality, and the EVOLVE study (albeit in an unbalanced population of dialysis patients) did not demonstrate a significant effect of cinacalcet on the primary composite endpoint (death, MI, hospitalization for unstable angina, heart failure or peripheral vascular disease). Nevertheless, there was a suggestion of improved survival in patients with calcific valvular disease. Currently, FGF-23 and other molecular targets involved in CKD-MBD remain speculative therapeutic targets.

Cardiovascular work-up of potential renal transplant recipients

CVD is the leading cause of death after renal transplantation, and death with a functioning graft is the leading cause of graft loss. It thus seems logical to screen for CVD before transplantation to identify and treat critical coronary artery lesions, and to guide initiation of optimal medical therapy. Controversy remains over how and whom to screen, and whether there are potential benefits from medical therapy and/or coronary artery revascularization. Assessment with echocardiography and stress testing is suggested in patients who are aged >50 years or have diabetes, pre-existing CVD, an ischaemic ECG or peripheral or cerebrovascular disease. In our experience, even aggressive screening for CVD results in a low rate of coronary revascularization (<10% of screened patients). Undue delay in transplant listing should not occur in patients who are asymptomatic patients or have low to medium risk stress test results. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 53-year-old man presented acutely with breathlessness and orthopnoea. He had end-stage kidney disease secondary to immunoglobulin A nephropathy and had been undergoing maintenance dialysis for 3 years.

On clinical examination, heart rate was 94 beats/minute, blood pressure was 180/110 mmHg, respiratory rate was 28 breaths/minute, oxygen saturation was 92% on room air, jugular venous pressure was elevated at 4 cm above the sternal angle, heart sounds were dual with nil added sounds heard, there were reduced breath sounds at both bases on auscultation of the chest, and the remainder of the examination was unremarkable.

Investigations

- Haemoglobin 95 g/litre (130–180)
- ECG showed anterolateral T wave flattening
- Initial troponin I was 0.2 micrograms/litre (<0.1); the 6-hour measurement was unchanged

What is the most likely diagnosis?

A. Non-ST elevation myocardial infarction
B. Pulmonary embolism
C. Hypertensive crisis
D. Fluid overload in the presence of uraemic cardiomyopathy
E. Acute pulmonary oedema resulting from coronary heart disease

Question 2

A 45-year-old man presented for review. He had type 2 diabetes. On clinical examination, his blood pressure was 160/110 mmHg, and body mass index was 35 kg/m^2.

Investigations

- Creatinine 150 micromol/litre (60–110)
- Estimated glomerular filtration rate (eGFR) 48 ml/minute (>60)
- Low-density lipoprotein–cholesterol 3.5 mmol/litre (<3.36)
- HbA1c 64 mmol/mol (20–42); 8.2% (4.0–6.0)
- 24-Hour urinary protein excretion 0.5 g (<0.2)

Which of the following is proven have the greatest impact on subsequent cardiovascular mortality in these circumstances?

A. Tight blood pressure control with an angiotensin receptor antagonist (ARB)
B. Tight glycaemic control
C. Weight loss
D. Initiation of an sodium–glucose transport protein 2 (SGLT-2) inhibitor
E. Statin therapy

Question 3

A 50-year-old man with type 2 diabetes mellitus presented for review. He had no symptoms He had recently commenced the angiotensin receptor blocker (ARB) irbesartan 150 mg daily for hypertension. He was also taking atorvastatin 20 mg daily.
On clinical examination, his blood pressure is 130/80 mmHg, body mass index 32 kg/m^2.

Investigations

- Creatinine 200 micromol/litre (60–110) (most recently 160)
- eGFR 33 ml/minute (>60) (most recently 43)
- Low-density lipoprotein–cholesterol 2.2 mmol/litre (<3.36)
- Urine albumin:creatinine ratio 38 (0–30) (most recently 64)

What is now the most appropriate management?

A. Add a thiazide diuretic to improve blood pressure control
B. Discontinue the ARB inhibitor as the patient has developed acute kidney injury
C. Repeat the renal function measurement at an interval and continue treatment
D. Change the ARB to a dihydropyridine calcium antagonist
E. Increase dose of atorvastatin from 20 mg to 40 mg