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Chapter 4

Cardiovascular Disease in Dialysis Patients

Dev Jegatheesan, Wenling Yang, Rathika Krishnasamy, Carmel M. Hawley and David W. Johnson

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Abstract

Cardiovascular disease (CVD) is highly prevalent in the dialysis population, affecting up to 60% of cohorts. Cardiovascular mortality rates are reported to be ~14 per 100 patient-years, which are 10- to 20-fold greater than those of age- and gender-matched controls. CVD is the primary cause of death in up to 40% of dialysis patients in Australia, New Zealand and the United States. Dialysis patients endure a greater burden of both traditional risk factors for CVD and risk factors related to loss of kidney function that may account for the higher CVD morbidity and mortality. Many cardiology guidelines include chronic kidney disease (CKD) and end-stage kidney disease (ESKD) as coronary heart disease (CHD) risk equivalents. It is therefore important for clinicians to both recognise and optimise the cardiovascular health of patients receiving maintenance dialysis. This chapter will focus on risk factor modification, screening and prevention of CVD in dialysis patients.

Keywords: dialysis, end-stage kidney disease, cardiovascular disease, risk factors, screening, prevention

1. Introduction

Reduced kidney function (estimated or measured glomerular filtration rate <60 mL/min/1.73 m²) and proteinuria are independent predictors of future coronary events [1]. It is not surprising therefore that cardiovascular disease (CVD) is highly prevalent in the dialysis population, affecting up to 60% of cohorts [2]. It is also the most common cause of death in this group, accounting for up to 40% of deaths in dialysis patients globally [3–5]. In Australia and New Zealand, the incidence rate of cardiovascular mortality in peritoneal dialysis (PD) and haemodialysis (HD) patients is approximately 10 and 8 per 100 patient-years, respectively, some
10- to 20-fold greater than that of age and gender-matched controls [6]. The most common causes of cardiovascular mortality are sudden cardiac death, myocardial infarction and cardiac failure [6].

The increased risks of cardiovascular events and mortality in dialysis patients is partly related to an increased prevalence of traditional cardiovascular risk factors, including diabetes mellitus, hypertension, obesity, physical inactivity, smoking and dyslipidaemia (Table 1). However, these factors account for less than 50% of the excess risk of cardiovascular disease [7], leading many researchers to explore the roles of non-traditional risk factors (Table 1). Some of these factors, including anaemia, fluid overload, hyperuricaemia and chronic inflammation, are directly related to loss of residual kidney function, leading to hormonal, fluid balance and uraemic toxin dysregulation. However, dialysis-specific factors may also contribute to this risk. For example, in HD patients, dialysis catheters, membrane exposure, endotoxaemia (from intestinal hypoperfusion or dialysis water) and more rapid loss of residual kidney function may contribute to inflammation, oxidative stress and myocardial stunning, which may ultimately increase the risk of CVD [8, 9]. Moreover, the intermittent nature of HD has been reported to be associated with heightened risks of cardiovascular mortality, particularly sudden cardiac death, towards the end of the long inter-dialytic interval over weekends, possibly related to fluid

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*Risk factors that are prevalent in the dialysis population.
CVD, cardiovascular disease; CKD-MBD, chronic kidney disease mineral and bone disease. Modified from [19].

Table 1. Traditional and non-traditional cardiovascular risk factors.
overload and electrolyte disturbances [10, 11]. On the other hand, PD patients may experience inflammation and oxidative stress as a result of exposure to PD catheters, bio-incompatible PD solutions and PD-related peritonitis [12]. Abnormalities in serum potassium concentrations, particularly hypokalaemia, also disproportionately increase the risk of death in patients receiving PD [13]. Excessive exposure to glucose in PD solutions (up to 200 g/day) has also been linked to atherogenic lipid profiles, metabolic syndrome and ultimately increased CVD risk [14]. Jiang et al. noted that while ~22% of patients with end-stage kidney disease (ESKD) met the diagnostic criteria for metabolic syndrome pre-dialysis, this number rose to ~70% after commencement of PD. Similar results were reported by Johnson et al. [15]. Metabolic syndrome is an independent predictor of cardiovascular mortality in the PD population [16–18].

This chapter will focus on risk factor modification, screening and prevention of CVD in dialysis patients.

2. Risk factor modification

Whilst there is substantial research identifying the myriad CVD risk factors inherent in the dialysis population, there is less to support that treatment of the modifiable factors alters outcomes to the same extent as in the non-CKD population. The evidence surrounding CVD risk factor modification in dialysis patients is summarised below. Clinical practice guideline recommendations from National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI), Kidney Disease: Improving Global Outcomes (KDIGO) and the International Society for Peritoneal Dialysis (ISPD) have been included where appropriate.

3. Traditional risk factors

3.1. Hypertension

There is marked heterogeneity in the definition, measurement methods and epidemiology of hypertension in dialysis populations. The 2004 KDOQI guidelines define hypertension as pre-dialysis blood pressure (BP) > 140/90 mmHg or post-dialysis BP > 130/80 mmHg [20]. However, pre- and post-dialysis BP readings considerably over and underestimate inter-dialytic ambulatory BP respectively [21]. Ambulatory BP monitoring (ABPM) provides information on circadian variation, is reproducible and remains the most reliable method to diagnose hypertension in the dialysis population [22, 23]. Home BP recordings, including ABPM and self-measured readings have been shown to be greater predictors of all-cause and cardiovascular mortality than haemodialysis unit recordings [24].

The definitions of hypertension clearly have a bearing on its reported epidemiology. The prevalence of hypertension—when defined by weekly average pre-dialysis systolic blood pressure (BP) measures > 150/85 mmHg or the use of antihypertensive medications—was 86% among 2535 chronic HD patients in a multi-centre trial [25]. The prevalence of hypertension in another cohort—defined by inter-dialytic ambulatory BP measures ≥ 135/85 mmHg or
the prescription of any antihypertensive agent—was 82% among 369 chronic HD patients [26]. The prevalence of hypertension in PD populations varies from 69 to 88% (when defined as ≥140/90 mmHg) [27].

Guidelines, epidemiological studies and clinical decision-making should therefore not rely on peri-dialysis BP readings alone. Regardless of definition, hypertension remains very common in the dialysis population and an important modifiable risk factor.

The pathophysiology of hypertension is multifaceted, complex and unique in dialysis patients. Volume and sodium overload remain the predominant mechanisms of hypertension, with a graded increase in BP as fluid and sodium (and body weight) accumulate over the inter-dialytic period [28]. Sodium and volume removal through dialysis manages hypertension in a proportion of patients. Lins et al. showed that atrial natriuretic peptide concentrations decrease post dialysis in those patients whose BP responded to ultrafiltration [29]. Other reported mechanisms include increased arterial stiffness [30], renin-angiotensin-aldosterone system activation [31], sympathetic hyperactivity [32, 33], endothelial dysfunction [34, 35], sleep apnoea [36] and use of erythropoiesis-stimulating agents (ESAs) [37, 38].

Non-pharmacological measures to treat hypertension ultimately involve sodium and fluid restriction. Ultrafiltration, sodium removal and reduction of dry weight result in normalisation of the BP in ~60% of chronic dialysis patients [39]. Establishment and attainment of the patient's dry weight are the generally accepted initial goals. The dry weight has been defined as the lowest tolerated post-dialysis weight, achieved gently and gradually, at which patients experience minimal signs or symptoms of dysvolaemia [40]. Furthermore, the duration of dialysis treatment should be long enough to ensure that the required ultrafiltration (and BP control) can be attained with minimal symptoms and haemodynamic compromise. Increased duration of dialysis affords a slower rate of ultrafiltration, improves BP control and reduces the incidence of intra-dialytic hypotension [41, 42]. Minimisation of inter- and intra-dialytic sodium gain is essential to management also. KDOQI guidelines advocate a low dietary sodium intake (<2–3 g/day), which appears to be effective in limiting thirst, reducing inter-dialytic weight gain, achievement of dry weight and controlling BP [43]. Similarly, avoidance of a positive sodium balance during dialysis is also key, i.e., dialysate sodium concentrations should not exceed that of pre-dialysis serum sodium. Individualisation of the dialysate sodium prescription was shown to reduce intra-dialytic weight gain, thirst and episodes of intra-dialytic hypotension in a randomised, cross-over study [44]. Use of a low sodium PD solution has also shown promise, with increased diffusive sodium removal, reduced thirst, improved ultrafiltration and reduction in BP [45].

Pharmacological therapies have been shown to be effective in achieving BP control in dialysis patients. Importantly, pharmacological treatment of hypertension has been shown to modify CVD outcomes in the dialysis population. In a systematic review and meta-analysis of 8 randomised, controlled trials (RCTs) involving 1679 dialysis patients and 495 cardiovascular events (CVE), lowering BP with medication was associated with decreased risks of CVE (RR 0.71, 0.55–0.92, \( p = 0.009 \)), all-cause mortality (RR 0.80, 0.66–0.96, \( p = 0.014 \)) and cardiovascular mortality (RR 0.71, 0.50–0.99, \( p = 0.044 \)) [46]. If these results were broadly applicable to dialysis populations, BP treatment would be expected to prevent 2 deaths per 100 patient-years.
Angiotensin receptor blockers (ARBs) have been shown to reduce CVE in ESKD [47–49]. Suzuki et al. found that HD patients randomised to candesartan, valsartan or losartan had fewer fatal and non-fatal CVE (hazard ratio (HR) 0.51, 0.33–0.79, \( p = 0.002 \)) [47]. Similar results were seen with telmisartan in HD patients with congestive heart failure—with reductions in all-cause mortality (HR 0.51, 0.32–0.82, \( p < 0.01 \)), cardiovascular mortality (HR 0.42, 0.38–0.61, \( p < 0.0001 \)) and hospital stay (HR 0.38, 0.19–0.51, \( p < 0.0001 \)).

Angiotensin-converting enzyme inhibitors (ACEi) have been studied in RCTs including dialysis patients. Whilst effective antihypertensive agents, ACEi have not been shown to reduce CVE compared with standard therapy. Zannad et al. found no significant benefit of fosinopril in HD patients after adjusting for independent predictors of CVE [50]. Li et al. showed that ramipril, whilst slowing residual kidney function decline in PD patients, did not reduce the risk of CVEs [51]. In a prospective, open-label RCT of lisinopril versus atenolol administered three times a week after maintenance HD in 200 prevalent patients with hypertension and left ventricular hypertrophy followed for 12 months. Agarwal et al. [52] reported that lisinopril-based therapy resulted in higher rates of serious CVE (incidence rate ratio [IRR] 2.36, 95% CI 1.36–4.23) and all-cause hospitalizations (IRR 1.61, 95% CI 1.18–2.19). Moreover, a systematic review of 8 RCTs of renin angiotensin aldosterone inhibitors (RAAS inhibitors—2 ACEi, 4 ARBs, 2 ACEi versus ARBs) did not find a clear role for these agents in hypertensive HD patients [53]. Unfortunately, the small numbers of patients and trials as well as suboptimal methodologic quality severely limit the conclusions that can be drawn about these agents for preventing CVD in dialysis patients.

Mineralocorticoid antagonists (MCAs) are another form of RAAS inhibitor that may mitigate cardiovascular risk in dialysis patients. Quach et al. [54] recently reported a systematic review and meta-analysis of 9 RCTs involving 829 dialysis patients (peritoneal dialysis or haemodialysis) treated with MCAs (spironolactone 8 trials, eplerenone 1 trial). Compared with control patients, those treated with MCAs had a significantly lower cardiovascular mortality (risk ratio [RR] 0.34, 95% CI 0.15–0.75) and all-cause mortality (RR 0.40, 95% CI 0.23–0.69), although these benefits were offset by a significantly increased risk of hyperkalaemia (RR 3.05, 95% CI 1.21–7.70). Given the small sample sizes and generally poor quality of published trials, the relative benefits and harms of RAAS inhibitors, including MCAs, for preventing CVD in dialysis patients remain uncertain. An adequately powered RCT is warranted given the possible benefit shown in the small studies to date.

The roles of other specific anti-hypertensive agents also remain uncertain. Tepel et al. found that whilst amlodipine did not significantly reduce all-cause mortality, it may reduce CVE (composite secondary end-point, HR 0.53, 0.31–0.93, \( p = 0.03 \)) in HD patients [55]. Cice et al. showed that carvedilol improved LV function and reduced all-cause mortality (HR 0.51, 0.32–0.82, \( p < 0.01 \)), cardiovascular mortality (HR 0.32, 0.18–0.57, \( p < 0.0001 \)) and hospital admissions (HR 0.44, 0.25–0.77, \( p < 0.005 \)) in 114 HD patients with dilated cardiomyopathy over 2 years at a single centre [56]. These findings have yet to be replicated. Indeed, a recently published feasibility study demonstrated significant challenges with recruiting dialysis patients into β-blocker intervention studies and emphasized the need for pragmatic trial methodologies [57].
The current KDOQI and ISPD recommendations of a BP target goal < 140/90 mmHg are extrapolated from studies in the non-dialysis population [20]. There have been no published prospective, randomised trials to date evaluating the target BP in dialysis patients. Target BP and appropriate treatment options need to therefore be individualised based on patient comorbidities, residual kidney function, dialysis modality and symptoms.

3.2. Diabetes

Diabetic nephropathy remains the leading cause of ESKD globally, with the number of diabetic patients commencing dialysis increasing [3, 58–60]. When diabetes is the primary cause of ESKD, 5-year adjusted survival is only 38%, significantly lower than if hypertension (45%) or glomerulonephritis (55%) is the primary aetiology [61]. Diabetic patients on HD are at a higher risk of CVD, especially acute myocardial infarction (OR 1.36) and cardiac death (OR 1.88) [62, 63].

There is currently a paucity of high quality, randomised trials evaluating the effect of glycaemic control on outcomes in the dialysis population. However, observational data indicates that survival is influenced by glycaemic control in patients with diabetic nephropathy. Patients with HbA1c < 7.5% (58.5 mmol/mol) at dialysis initiation had a greater 5-year survival than those with poor control (31.7% vs 12.1%, adjusted HR 1.13) [64]. In maintenance HD patients, those with a HbA1c < 8% (63.9 mmol/mol) had an improved survival rate at 3 and 5 years compared to the poor control group [65]. Very poor glycaemic control (HbA1c > 10% or > 85.8 mmol/mol) is associated with higher adjusted all-cause and cardiac death (HR 1.41 and 1.73 respectively) in HD patients and increased mortality (HR 1.20) in all dialysis patients [66, 67]. Furthermore, Ramirez et al. and Ricks et al. went on to find a U-shaped association between HbA1c and mortality [68, 69]. There was a symmetric increase in adjusted all-cause mortality with low HbA1c—6.0–6.9% (42.1–51.9 mmol/mol, HR 1.05), 5.0–5.9% (31.1–41.0 mmol/mol, HR 1.08) and ≤ 5.0% (≤31.1 mmol/mol, HR 1.35) [69].

However, HbA1c has its limitations as a marker of glycaemic control in ESKD. Metabolic acidosis and elevated blood urea nitrogen have been shown to falsely elevate HbA1c whereas anaemia, ESA use, protein-energy wasting and shortened erythrocyte lifespan falsely decrease HbA1c values. Fructosamine and glycated albumin, as markers of intermediate-term glycaemic control, may therefore be more accurate metrics than HbA1c in ESKD patients [70].

KDOQI and KDIGO guidelines recognise the lack of robust evidence for glycaemic control and the limitations of HbA1C in ESKD [20] [KDIGO]. They currently recommend that individuals on dialysis and pre-dialysis, respectively, should target an HbA1C ~7% (53.0 mmol/mol), with tighter control to be avoided in patients at risk of hypoglycaemia. Furthermore, the KDOQI guidelines advise clinicians that dosing of insulin and oral hypoglycaemic agents may change markedly as patients transition onto dialysis—often with increased requirements in PD [20]. The ISPD Guidelines recommend an HbA1c target of 7% (53 mmol/mol) in PD patients with diabetes, which may be increased up to 8.5% (69 mmol/mol) in older patients [71].

Minimising dialysis-related glucose exposure may also help to mitigate cardiovascular risk in diabetic PD patients. Several observational cohort studies have reported that higher peritoneal
dialysis-related glucose exposure was associated with higher rates of technique failure and both cardiovascular and all-cause mortality [72–74]. A subsequent RCT of a glucose-sparing PD regimen (combination of dextrose-based solution, icodextrin and amino acids) versus conventional PD (dextrose solutions only) in 251 diabetic PD patients over 6 months demonstrated that the glucose sparing regimen produced modest benefits in the outcomes of HbA1c (0.5% lower, 95% CI 0.1–0.8%), serum triglycerides, very low density lipoproteins and apolipoprotein B, although this was counterbalanced by a safety signal regarding a (not statistically significant) higher rate of deaths and serious adverse events, including several related to volume expansion, in the glucose-sparing group [14]. The results suggested that glucose-sparing PD regimens may improve surrogate metabolic outcomes, albeit possibly at the expense of optimal peritoneal ultrafiltration and fluid control. The ISPD Guidelines recommend that “once daily icodextrin be considered as the long-dwell dialysis solution in diabetic peritoneal dialysis patients for better glycaemic control” [71].

3.3. Cigarette smoking

Cigarette smoking is the leading cause of preventable death in the United States and ~30% is attributed to ischaemic heart disease [75]. The prevalence of smoking in the dialysis population has been reported as high as 15% [76].

Liebman et al. conducted a systematic review and meta-analysis of smoking and cardiovascular outcomes in dialysis patients. Whilst smokers had a significant increase in all-cause mortality (HR 1.65, 1.26–2.14, \( p < 0.001 \)), surprisingly no significant increase was seen in cardiovascular events (HR 1.01, 0.98–1.05, \( p = 0.4 \)) compared with non-smokers [77]. The authors reconcile that this may be due to (a) the composite cardiovascular outcome not being influenced by smoking alone and (b) that smoking may increase mortality via non-cardiovascular means.

Though specific data in dialysis patients are lacking, smoking cessation is likely to reduce cardiovascular disease and mortality. Smoking cessation is supported by both KDOQI and ISPD guidelines, with recommendations for specialist referral if required [20, 71].

3.4. Dyslipidaemia

Dyslipidaemia has been extensively studied as a potentially modifiable risk factor in the prevention of CVD in dialysis patients. Dyslipidaemia in ESKD presents predominantly with low high-density lipoprotein (HDL) and high triglyceride levels. Importantly, total cholesterol and low-density lipoprotein (LDL) levels tend to be in the normal range or even low [78]. The relationship between serum cholesterol levels and cardiovascular risk in the dialysis population is complex. Observational studies have shown an inverse relationship between total cholesterol and survival i.e. dialysis patients with the lowest cholesterol levels had the highest mortality rates [79–81]. However, this appears to be confounded by malnutrition and chronic inflammation—as when corrected for serum albumin, C-reactive protein and interleukin 6 levels, the positive correlation between cholesterol and mortality parallels that of the non-dialysis population [82].
The pathophysiological role of cholesterol in atherosclerosis appears to differ in patients with ESKD. Coronary artery studies in the ESKD population have shown a 5-fold higher prevalence of calcification, greater deposition of inflammatory cytokines and more intense intra-plaque haemorrhage [78]. Fathi et al. studied the effect of aggressive cholesterol lowering in non-CKD and ESKD patients with established coronary artery disease (CAD) [83]. In the non-CKD group, the carotid artery intima/media thickness decreased significantly with atorvastatin therapy during the 2-year observation period. There was no such change seen in the ESKD cohort. The authors proposed that the beneficial effect of statins is likely counteracted or nullified by the uraemic state.

There is accumulation of highly atherogenic lipoproteins in dialysis patients due to deficiency of lipoprotein lipase, hepatic lipase and LDL receptor-related protein [84]. These include very low density lipoprotein (VLDL), small dense LDL, intermediate-density lipoproteins, oxidised LDL and lipoprotein (a)—which are not treatable with statin therapy [84]. This atherogenic lipid profile is also more apparent in PD patients than those on HD [85–87].

Atherosclerotic coronary artery disease only accounts for ~20% of CVD in ESKD [88]. Vascular calcification, LVH, diastolic dysfunction, cardiomyopathy, arrhythmia and sudden cardiac death are also contributory. Given that the majority of CVD mortality is not related to CAD, it seems plausible that lipid lowering therapy would not modify outcomes [84].

In the non-dialysis population, a meta-analysis of over 90,000 randomised patients demonstrated an overall 25% reduction in major cardiovascular events for each 1 mmol/L decrease in LDL cholesterol [89].

However, treatment of dyslipidaemia does not appear to confer the same benefits in the dialysis population. Palmer et al. performed a systematic review of RCTs evaluating the efficacy of statins in over 8000 dialysis patients [90]. Despite clinically relevant lowering in serum cholesterol levels, statins had no significant effects on major cardiovascular events (RR 0.95, 0.88–1.03), all-cause mortality (RR 0.96, 0.90–1.02), cardiovascular mortality (RR 0.94, 0.84–1.06) or myocardial infarction (RR 0.87, 0.71–1.07).

Hypertriglyceridaemia (fasting triglycerides > 5.65 mmol/L) should be treated through lifestyle measures, including dietary modification, weight reduction, increased physical activity, adequate glycaemic control and reduced alcohol intake [KDIGO].

Given the evidence presented, the KDOQI and KDIGO guideline recommendations advise that statins should not be initiated routinely for primary prevention in dialysis patients [20, 91]. Statin therapy should be continued in patients already on treatment at the commencement of dialysis—due to the overwhelming evidence of cardiac protection in the non-dialysis population and paucity of data in the dialysis population [91]. The role for statins in dialysis patients post coronary/cerebrovascular event (secondary prevention) and in those with LDL > 3.9 mmol/L has not satisfactorily been assessed in RCTs and thus there may be a role for therapy in these populations [84, 91].

3.5. Obesity

Higher body mass index (BMI) is associated with higher all-cause and cardiovascular mortality in the non-dialysis population. In contrast, epidemiological studies in dialysis patients...
have shown a paradoxically inverse association between BMI and mortality [92–97]. HD patients appear to have a lower BMI than age and sex-matched controls from the general population [98]. The survival advantage associated with a higher BMI appears less in patients on PD than on HD [99–101].

Theories to support this paradox include protein energy wasting (PEW), inflammation, competing risk and reverse causation [102]. PEW refers to loss of body protein and fat mass, frequently observed in ESKD patients [103]. Increased activation of inflammatory cytokines in dialysis patients may cause appetite suppression and proteolysis—overall increasing the risk of death from CVD [104]. Obesity may therefore provide a ‘functional reserve’, potentially attenuating the effect of PEW and inflammation in patients with a higher BMI. Given the high mortality of patients on dialysis, it may be that the long-term, conventionally detrimental effects of obesity may be outweighed by the competing short-term effects of PEW and inflammation. Finally, lower BMI may simply be a consequence of conditions that lead to poorer outcomes in ESKD, rather than the cause—a confounding factor limited by observational data [102].

Observational data from Ramkumar et al. showed that PD patients with high BMI/high muscle mass had lower all-cause (HR 0.90, 0.83–0.97) and cardiovascular (HR 0.88, 0.79–0.97) mortality compared with normal BMI/high muscle mass patients [105]. Patients with high BMI/low muscle mass had an increased risk of all-cause (HR 1.29, 1.17–1.42) and cardiovascular (HR 1.21, 1.06–1.39) mortality [105].

The existing evidence is not strong enough to inform decisions regarding weight management in ESKD. Larger, prospective, randomised trials are required to assess the efficacy of weight management interventions on cardiovascular outcomes in the dialysis population. At this stage weight loss measures cannot be recommended for all dialysis patients but increasing muscle mass may be beneficial in those on PD.

3.6. Sedentary lifestyle

In an observational study of 2507 incident dialysis patients, 56% reported exercising less than once a week and only 20% reported daily exercise [106]. Low aerobic activity has been identified as one of the strongest predictors of mortality among ESKD patients [107].

Many studies have validated the safety and efficacy of exercise in the CKD population. Specifically, trials in dialysis patients have utilised intra-dialytic cycling and/or progressive resistance training to show improvements in systemic inflammation, cardiovascular functioning, dialysis adequacy and muscle wasting [107]. In an observational study, Stack et al. found that mortality risks were lower for dialysis patients who exercised vigorously 2–3 times per week (RR 0.74, 0.58–0.95) compared to their less active peers [106]. In a multi-centre randomised trial, Manfredini et al. found that dialysis patients undertaking a personalised walking program had significantly improved scores on physical (6 minute walk test, 5 times sit to stand test), cognitive and quality of life measures [108].

As per Cheema: “despite overwhelming evidence of the safety, efficacy, feasibility and generalisability of these interventions, as well as comparative trials demonstrating that in-centre training results in higher adherence than training on non-dialysis days, intra-dialytic exercise
remains notably absent from standard practice” [107]. However, it should be noted that high quality RCTs evaluating exercise and cardiovascular mortality in ESKD are still lacking.

KDOQI and ISPD guidelines recommend that all dialysis patients be counselled and regularly encouraged to increase their physical activity—accumulating at least 30 min of moderate intensity physical activity on most, preferably all days of the week [20, 71]. Patients should be appropriately referred for physical therapy to ensure that exercise programs are tailored according to functional capacity. It remains uncertain whether aerobic, resistance or combination programs are most efficacious in dialysis patients.

3.7. Depression

The epidemiology of depression in ESKD is variably reported, largely dependent on the methods used for screening and diagnosis. A systematic review and meta-analysis of observational studies found that the prevalence of depression in HD and PD patients is similar ~40%, higher than in CKD (26.5%) or transplant (26.6%) patients [109]. Self-reported diagnostic tools may overestimate the prevalence of depression given the overlap of somatic symptoms in ESKD (fatigue, anorexia, sleep disturbance) [109].

A meta-analysis of cohort studies (>30,000 dialysis patients) found an increased risk of mortality in patients with depression (RR 1.40, 1.23–1.45, \( p = 0.03 \)). The risk of increased cardiovascular mortality was less clear (RR 1.88, 0.84–4.19, \( p = 0.2 \)) [110]. Randomised trials of interventions for depression in CKD have been limited by small sample size, short duration and surrogate outcomes to determine efficacy [110].

The KDOQI guidelines recommend that all patients be seen by a social worker at dialysis commencement, and at least 6 monthly thereafter to assess their psychosocial state and screen for depression and anxiety [20]. The guidelines also recommend treatment for all patients with diagnosed depression and/or anxiety. The recommendations are based on moderately strong evidence extending from the non-dialysis population.

4. Non-traditional risk factors

4.1. Anaemia

Anaemia is a known complication of CKD, primarily due to the inadequate renal production of erythropoietin, with its prevalence increasing as patients’ approach ESKD. Anaemia is an established non-traditional cardiovascular risk factor that promotes cardiac structural and functional abnormalities including left ventricular hypertrophy/dilatation, diastolic dysfunction, arrhythmias and congestive heart failure [19, 111, 112].

The Dialysis Outcomes and Practice Patterns Study (DOPPS) data showed that approximately 47% of prevalent HD patients had haemoglobin (Hb) concentrations <110 g/L and 84% were prescribed erythropoietin-stimulating agents (ESAs) [113]. DOPPS also found that higher Hb concentrations (Hb 110–120 g/L) were associated with decreased mortality (RR 0.95, 0.90–0.99,
Evidence from RCTs thereafter raised concerns about higher Hb concentrations. CHOIR investigators reported higher composite CVEs (HR 1.34, 1.03–1.74, \( p = 0.03 \)) in patients receiving ESA who achieved a higher Hb (~135 g/L) when compared with the lower Hb (~113 g/L) target group, with no between-group differences in patient reported outcomes [114]. A meta-analysis thereafter by Palmer et al. found that treatment with ESA to a higher Hb target (~130 g/L) increased the risk of stroke, worsened hypertension and vascular access thrombosis, compared with the lower Hb target (~101 g/L). There were no statistically significant differences between groups for the risk of all-cause mortality, serious CVEs or quality of life [115].

The most recent network meta-analysis of RCTs concluded that while ESAs prevent blood transfusions, their effect on survival, CVEs and symptom improvement remain unclear. There have been few direct comparisons between the different ESAs and the current studies are unable to separate the formulations based on patient-centred or hard outcome measures [116].

The KDOQI and KDIGO guidelines currently recommend that ESA therapy be initiated when Hb levels are between 90 and 100 g/L, with a view to avoiding concentrations falling to <90 g/L. They also suggest that ESAs not be used to maintain Hb concentration > 115 g/L or to intentionally increase concentration >130 g/L. Whilst anaemia itself is regarded as a non-traditional risk factor, its correction with ESA therapy does not appear to improve cardiovascular outcomes in dialysis patients. Ultimately dosing and target Hb concentrations very much need to be individualised based on patient symptoms and competing co-morbidities. The principal goal of ESA therapy is avoidance of blood transfusion.

4.2. Chronic volume overload

Chronic fluid overload remains highly prevalent in dialysis patients and is an independent predictor of all-cause and cardiovascular mortality [117, 118]. Zoccali et al. examined chronic fluid exposure using bio-impedance spectroscopy in approximately 35,000 incident HD patients across 26 countries [119]. Baseline fluid overload and cumulative 1 year fluid overload exposure predicted excess risk of mortality across all BP categories. The highest mortality risk was in those with fluid overload and systolic BP < 130 mmHg at baseline (HR 1.51, 1.38–1.65, \( p < 0.001 \)) and at 1 year (HR 1.94, 1.68–2.23, \( p < 0.001 \)) [119]. Fluid overload also independently predicted all-cause mortality (HR 12.98, 1.06–168.23, \( p = 0.042 \)) and a trend of increased CVD mortality (log-rank test 2.90, \( p = 0.089 \)) in a trial of 307 PD patients [120]. Interestingly, a multi-centre RCT of 308 patients found that bio-impedance did not appear to improve clinical management of fluid status in PD patients [121].

Treatment of fluid overload in dialysis patients has yet to be studied in the RCT setting. However, Assimon et al. performed a retrospective analysis of over 118,000 HD patients and found that ultrafiltration rates > 13 ml/kg/h were associated with increased mortality (adjusted HR 1.31, 1.28–1.34) compared with rates ≤ 13 ml/kg/h [122]. As Dasgupta and colleagues state ‘controlling the high prevalence of fluid overload in this population is considered an unmet...
clinical need, and there is a quest for clinical policies specifically aimed at optimising control of fluid overload to improve the dim prognosis of patients with ESKD’ [123]. In the interim, the traditional goals of sodium and volume restriction (as outlined in Section 3.1) remain key to controlling fluid overload and maintaining dry weight in dialysis patients.

4.3. Mineral and bone disorder

Chronic kidney disease—mineral and bone disorder (CKD-MBD) is defined as a systemic disorder encompassed by bone abnormalities, laboratory abnormalities and vascular calcification that are associated with hard outcomes such as fractures, cardiovascular morbidity and mortality [124]. The premature CVD experienced by ESKD patients is in part due to accelerated vascular calcification. With declining renal excretion of phosphorus, its accumulation in serum ultimately promotes the conversion of vascular smooth muscle cells towards the osteoblast phenotype [125].

Observational data from >40,000 HD patients showed an incremental association between serum phosphorus concentrations and mortality—RR 1.10 (1.02–1.17) and RR 2.47 (1.90–3.19) at phosphorus levels 1.62–1.78 mmol/L and ≥3.55 mmol/L respectively [126]. Similar findings were noted for serum corrected calcium and parathyroid hormone (PTH). Hyperphosphataemia and hyperparathyroidism were also significantly associated with all-cause, cardiovascular and fracture-related hospitalisation.

Many treatment modalities including vitamin D compounds, phosphate binders, cinacalcet, bisphosphonates and calcitonin have been successful in correcting the biochemical abnormalities associated with CKD-MBD [127]. However, these therapies have only weakly correlated with all-cause and cardiovascular mortality outcomes in a meta-analysis [127]. Furthermore, a recent network meta-analysis of randomised trials concluded that there is currently no evidence that phosphate binders reduce mortality compared to placebo [125]. Similarly, a cumulative meta-analysis of 18 RCTs involving 7446 patients with CKD found that cinacalcet did not influence cardiovascular or all-cause mortality [128]. There is also no compelling evidence that vitamin D influences patient-level outcomes such as CVEs and mortality [129, 130]. Overall, existing evidence shows that despite the strong association between bone and mineral parameters and CVD mortality in cohort studies, the benefits of drug effects on biochemical targets does not translate into improved health outcomes [127].

The KDOQI and KDIGO guidelines do provide recommendations on the evaluation and treatment of the abnormalities of CKD-MBD [131]. However, given the lack of definitive clinical outcome trials most of the recommendations are weak and/or discretionary. Further research is required to assess whether CKD-MBD is a truly modifiable, non-traditional cardiovascular risk factor among dialysis patients.

4.4. Hyperuricaemia

Hyperuricaemia has been associated with increased CVD mortality and CKD progression in the non-dialysis population [132–134]. The association between hyperuricaemia and cardiovascular outcomes in the dialysis population is less clear.
Latif et al. reviewed DOPPS data and found that higher uric acid levels were associated with lower risk of all-cause and CVD mortality in HD patients [135]. The adjusted HR at uric acid level ≤ 0.488 mmol/L compared with > 0.488 mmol/L was 1.24 (1.03–1.49) for all-cause mortality and 1.54 (1.15–2.07) for CVD mortality. Similar results were found by Bae et al. [136]. The authors proposed that elevated uric acid levels among HD patients may be a surrogate marker for better nutritional status, as these patients also had higher serum phosphate and BMI [135].

Dong et al. found contrasting results in their multi-centre study of over 2000 PD patients. Each 1 mg/dL (0.06 mmol/L) increase in uric acid level was associated with higher adjusted all-cause mortality (HR 1.05, 1.00–1.10) and CVD mortality (HR 1.12, 1.05–1.20). Similar results have been found by other authors [137, 138].

Further research is required to shed more light onto the relationship between uric acid and cardiovascular outcomes, especially to elucidate the apparent differences in HD and PD. Furthermore, it remains to be seen whether correction of uric acid abnormalities may alter hard outcomes in the dialysis population.

4.5. Hyperhomocysteinaemia

Homocysteine is a non-essential amino acid that plays an important role in the methionine cycle through its interaction with vitamin B12 and folic acid [139]. Disturbance of this pathway leads to accumulation of homocysteine, which is believed to play a role in vascular calcification, atherothrombosis and CVD [140]. Hyperhomocysteinaemia is seen in 85–100% of patients with ESKD and is currently regarded as an independent predictor of CVD morbidity and mortality in this population [139, 141].

Qin et al. performed a meta-analysis of 7 randomised trials involving 3886 patients with advanced or ESKD to assess whether homocysteine-lowering with folic acid reduced CVE [142]. Folic acid therapy significantly reduced the risk of CVEs (RR 0.85, 0.76–0.96, p = 0.009), with the greatest benefit seen in patients that had a longer duration of therapy, no or partial folic acid fortification and a > 20% decrease in homocysteine levels. However, a subsequent meta-analysis of 6 RCTs involving 2452 ESKD patients only found that homocysteine-lowering therapy had little or no effect on all-cause or cardiovascular mortality [143].

Folic acid therapy for hyperhomocysteinaemia per se is not specifically covered in many dialysis clinical practice guidelines. Folic acid is often supplemented in dialysis patients to avoid deficiency, particularly those at risk of malnutrition. Whether folic acid supplementation provides any additional cardiovascular benefit in replete patients is unknown. Given its cost efficacy, favourable side effect profile and potential CVD benefit, it would be reasonable to recommend folic acid therapy for ESKD patients not receiving fortification.

4.6. Chronic inflammation—oxidative stress, endotoxaemia and uraemic toxins

Elevated oxidative stress has been associated with increased CVD risk in the ESKD population [144]. ESKD patients have been shown to have an imbalance in pro-oxidant and antioxidant pathways that ultimately lead to endothelial dysfunction, chronic inflammation
and accelerated atherosclerosis [144]. The predominant mechanism of oxidative stress in HD is thought to be through inactivation of nitric oxide synthase by reactive oxygen species [145]. Anti-oxidant therapies may therefore have a role in improving CVD outcomes in dialysis patients. Tepel et al. performed a randomised, placebo-controlled trial in 134 HD patients and found that N-acetylcysteine reduced CVEs (RR 0.60, 0.38–0.95, \( p = 0.03 \)) but not all-cause or CVD mortality [146]. Similarly, Boaz et al. evaluated vitamin E in 97 HD patients and found that, compared to placebo, vitamin E reduced CVEs (RR 0.46, 0.27–0.78, \( p = 0.014 \)) but had no effect on all-cause or CVD mortality [147]. These findings are yet to be replicated in larger clinical trials.

Endotoxaemia has been proposed as a potential mechanism for the chronic inflammation seen in ESKD [148]. Endotoxins are complex polysaccharides found on the outer cell wall of gram-negative bacteria. Endotoxaemia not only occurs in sepsis, but has also been identified in congestive heart failure and in ESKD [149–151]. Current endotoxin detection assays are however limited by their poor sensitivity and validation in ESKD [152]. Potential sources of endotoxaemia that are pertinent to the ESKD population include contaminated dialysate, dialysis catheters and circuitry (HD and PD), peritoneal membrane dysfunction, gastrointestinal bacterial translocation and periodontal disease [12, 152]. Preventative strategies such as avoidance of temporary dialysis catheters and use of ultrapure water have been shown to reduce endotoxin levels [153, 154]. Initial evaluation of gut flora modulation through use of pre- and probiotics [155] as well as gastrointestinal decontamination [156] have shown some promise—their efficacy is yet to be confirmed in dialysis patients however.

Uraemic toxins, particularly indoxyl sulphate (IS) and p-cresyl sulphate (PCS), have been associated with chronic inflammation, premature CVD and mortality in ESKD [157–160]. Both toxins are produced by large bowel microbiota, which is known to be dysregulated in CKD and ESKD [161]. In a meta-analysis of 10 RCTs involving 1572 patients with CKD, PCS was significantly associated with both all-cause mortality (OR 1.16, 1.03–1.30, \( p = 0.013 \)) and cardiovascular mortality (OR 1.28, 1.10–1.50, \( p = 0.002 \)) whereas IS was only significantly associated with all-cause mortality (OR 1.10, 1.03–1.17, \( p = 0.003 \)) [157]. Importantly, there is limited but supportive evidence for the effectiveness of pre- and probiotics on reducing IS and PCS levels in CKD [161, 162]. Whether this translates to improved cardiovascular outcomes in the dialysis population remains to be seen.

5. Cardiovascular disease screening

Despite the considerable burden of CVD in the ESKD population, screening in asymptomatic individuals is not routine in clinical practice, except those being evaluated for transplantation. This may in part be due to the uncertainty regarding whether early detection and intervention improves outcomes in this population. Furthermore, CVD screening methods in themselves pose unique challenges in the dialysis cohort. The prediction of CAD risk is limited by traditional risk estimate tools, including the Framingham risk model, which can underestimate risk in ESKD by 50% [163]. The biomarkers and screening tests with the most evidence in ESKD are presented here. A summary of the limitations of screening tests in the dialysis population are shown in Table 2.
5.1. Biomarkers

The search for a novel predictive biomarker has not yielded many successful results. Markers of myocardial injury, inflammation, endothelial dysfunction, sympathetic overactivity, oxidative stress and atherosclerosis have been evaluated [165]. The most promising biomarker appears to be the cardiac troponin assay. A meta-analysis of ~4000 asymptomatic ESKD patients found that an elevated troponin T level (>0.1 ng/ml) was significantly associated with increased all-cause mortality (RR 2.64, 2.17–3.20) and CVD mortality (RR 2.55, 1.93–3.37) [166]. The American College of Cardiology Foundation highlighted the value of troponin for prognostication in ESKD but also its current limitations in guiding clinical practice [167]. This may be in part related to the lack of specificity of troponin, elevated in more than a third of patients with ESKD [165]. B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT pro-BNP) may also have a role in predicting CVD and all-cause mortality in ESKD [168]. The between-person variability of NT pro-BNP is considerable in stable HD patients, likely accounted for by differences in fluid status, residual kidney function, dialysis prescription and underlying cardiac pathologies [169]. However, the within-person variation is markedly smaller and thus may be of greater prognostic significance [169]. In a prospective cohort study of baseline serum NT pro-BNP levels in 230 PD patients, the adjusted HR for all-cause mortality and cardiovascular mortality of the fourth quartile were 4.97 (1.35–18.28, p = 0.016) and 7.50 (1.36–41.39, p = 0.021) respectively, compared with the first quartile [170]. Similar results were found in a study of 150 HD patients, where serum NT pro-BNP had a strong graded relationship with all-cause mortality (HR 1.54, p < 0.01) and cardiovascular mortality (HR 2.99, p < 0.01) [171]. Furthermore, a prospective cohort study of 113 HD patients found that an annual increase in serum BNP of 40% predicted all-cause and cardiovascular death in the subsequent year [172].

5.2. Exercise stress test

Exercise stress testing is generally a poor screening tool in the dialysis population given the high prevalence of baseline ECG abnormalities, limited exercise tolerance due to non-cardiac co-morbidities, a blunted chronotropic response from autonomic dysfunction—ultimately only 7–53% of patients achieve the target heart rate [164].
5.3. Myocardial perfusion scintigraphy (MPS)

Myocardial blood flow can be evaluated both at rest and post cardiac stress with MPS. The same limitations of exercise stress testing exist with exercise-MPS in dialysis patients, necessitating the use of pharmacological stressors. When compared to coronary angiography, its specificity and sensitivity range from 37 to 100% and 29 to 92%, respectively. The low sensitivity in dialysis patients has been attributed to equally distributed diminished coronary flow (‘balanced ischaemia’) and an impaired vasodilatory response [164]. Nevertheless, an abnormal MPS finding was a significant independent predictor of CVEs (HR 2.11, 1.05–4.24, \( p = 0.035 \)) [173]. In one prospective study of 150 dialysis patients, an abnormal MPS result was more predictive of mortality than the number of narrowed coronary vessels [174].

5.4. Dobutamine stress echocardiography (DSE)

DSE demonstrates resting and stress-induced regional wall motion abnormalities which signify scar and ischaemia respectively [165]. DSE is a valid screening test as it not only provides information on the location and extent of CAD, but also on ventricular hypertrophy, volume status and valvular disease. Its sensitivity and specificity appear similar to that of MPS [164]. An abnormal DSE result had a HR of 4.3 (1.8–10.0) for major CVE, with similar findings across many studies in ESKD [175–178].

5.5. Coronary artery calcium score

Computed tomography (CT) is a sensitive tool for the detection and quantification of calcium deposition in soft tissues, particularly coronary arteries. Coronary calcium scores do predict mortality in dialysis patients, but have poor correlation with angiogram findings [179, 180]. Though not the best tool to predict future need for coronary intervention, low or negative coronary calcium scores have been shown to have good negative predictive value [180].

5.6. CT coronary angiogram

CT coronary angiogram is presently used in the general population to evaluate CAD in low to intermediate risk patients. Its utility has not been extensively assessed in the dialysis population. In a trial of 70 maintenance HD patients, the prevalence of CAD on CT coronary angiogram at baseline was 43%. After 2 years, 36% of those with CAD had a CVE compared with none of the patients with no significant CAD (\( p < 0.01 \)) [181]. Given its high negative predictive value, Hakeem et al. concluded that ‘the potential role of CT coronary angiogram likely rests in serving as a gatekeeper for invasive angiography in patients with submaximal, equivocal or mildly abnormal stress tests’ [165].

5.7. Coronary angiography

Coronary angiography remains the gold standard for the diagnosis of CAD in dialysis patients. Its use as a screening tool is limited by its cost, invasive nature and presumed deleterious effects on residual kidney function [164]. CAD (>50% coronary stenosis) has been identified in 50–70% of asymptomatic incident HD patients, with multi-vessel involvement in up to 40% [182–184].
Coronary intervention does not appear to improve survival in asymptomatic individuals in the general population [185]. Yasuda et al. performed a prospective cohort study over 5 years in 259 HD patients with CAD to assess whether percutaneous intervention had a therapeutic advantage over medical therapy [186]. They found that after adjustment for other risk factors, effects of coronary intervention on the risk for all-cause mortality (OR 0.37, 0.26–0.54, \( p = 0.006 \)) and CVD mortality (OR 0.14, 0.08–0.25, \( p < 0.001 \)) remained significant and independent [186]. This evidence clearly needs to be clarified further through larger and ideally randomised trials.

As for any screening program, the expected benefits should outweigh the costs and side effects. Screening can only be justified when there is high asymptomatic disease prevalence within the cohort and with evidence that early intervention improves overall outcomes [164]. Early coronary intervention should be the focus of future research, which may alter screening practices in ESKD. Hakeem et al. proposed an algorithm for CAD screening and risk stratification in asymptomatic ESKD—the adapted schematic is presented below [165] (Figure 1).

6. Screening in renal transplant candidates

Patients with ESKD being considered for transplantation warrant comprehensive cardiac evaluation to assess both peri-operative and post-transplant risk. CVD remains the major cause of mortality after renal transplantation, with approximately 30% due to myocardial infarction [187, 188].
Several workgroups have published guidelines and recommendations regarding the cardiac workup of dialysis patients awaiting transplantation. A summary of the recent guidelines is presented in Table 3.

<table>
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<th>Guideline</th>
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| 2013 KHA-CARI [189] | **Recommend that:**  
- all candidates for kidney transplantation be screened for CVD risk factors. Indicators of high risk include: older age, DM, abnormal ECG, prior IHD or CCF, increased dialysis vintage, smoker  
- stress testing such as MPS or stress echocardiography be performed without concurrent β-blocker therapy  
- coronary angiography for candidates with abnormalities on screening procedures  
**Suggest that:**  
- candidates with low CVD risk do not require stress testing for CAD  
- candidates with a moderate or high clinical risk of CVD undergo stress testing prior to transplantation  
- the prognostic accuracy of cardiac stress testing diminishes after 24 months. The interval at which testing should take place not been well defined  
- the benefit of revascularisation prior to transplantation be reviewed on an individual basis |
| 2012 ACC/AHA [190] | Non-invasive stress testing may be considered in those with no active cardiac conditions: presence of multiple CAD risk factors regardless of functional status  
- Relevant risk factors include DM, prior CVD, > 1 year on dialysis, LV hypertrophy, age > 60 years, smoking, hypertension, dyslipidaemia. Reasonable to prompt stress testing with ≥ 3 risk factors  
- The usefulness of periodically screening asymptomatic subjects for ischaemia while on the waiting list to reduce the risk of CVE is uncertain |
| 2005 NKF KDOQI [20] | Non-invasive stress testing recommended for:  
- all patients with DM; repeat every 12 months  
- all patients with prior CAD:  
  - If not revascularised, repeat every 12 months  
  - If prior PCI, repeat every 12 months  
  - If prior CAGB, repeat after first 3 years and then every 12 months  
Repeat every 24 months in “high-risk” non-diabetic patients defined as:  
- ≥ 2 traditional risk factors  
- known history of CAD  
- LVEF ≤ 40%  
- peripheral vascular disease |

KHA-CARI, Kidney Health Australia Caring for Australasians with Renal Impairment; ACC/AHA, American College of Cardiology/American Heart Association; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative; CVD, cardiovascular disease; DM, diabetes mellitus; IHD, ischaemic heart disease; CCF, congestive cardiac failure; MPS, myocardial perfusion scintigraphy; CAD, coronary artery disease; LV, left ventricular; CVE, cardiovascular events; PCI, per cutaneous intervention; CAGB, coronary artery bypass grafting; LVEF, left ventricular ejection fraction.

Table 3. Summary of cardiac screening guidelines for the patient with ESKD awaiting renal transplantation.
7. Conclusion

The high incidence of multiple traditional and non-traditional risk factors predisposes dialysis patients to a considerable burden of CVD. This chapter has summarised the available evidence supporting CVD risk factor modification, prevention and screening in ESKD. Clinicians must appreciate the limitations of the current evidence and tailor specific therapeutic strategies to the individual patient. Future research into modifiable, non-traditional risk factors is warranted and we look forward to their clinical application and improvement of CVD outcomes in ESKD.

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