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The assessment of coronary artery disease in patients with end-stage renal disease

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ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality among patients with end-stage renal disease (ESRD). Clustering of traditional atherosclerotic and non-traditional risk factors drive the excess rates of coronary and non-coronary CVD in patients with ESRD. Coronary artery disease (CAD) is a key disease process, present in ∼50% of the haemodialysis population ≥65 years of age. Patients with ESRD are more likely to be asymptomatic, posing a challenge to the correct identification of CAD, which is essential for appropriate risk stratification and management. Given the lack of randomized clinical trial evidence in this population, current practice is informed by observational data with a significant potential for bias. For this reason, the most appropriate approach to the investigation of CAD is the subject of considerable discussion, with practice patterns largely varying between different centres. Traditional imaging modalities are limited in their diagnostic accuracy and prognostic value for cardiac events and survival in patients with ESRD, demonstrated by the large number of adverse cardiac outcomes among patients with negative test results. This review focuses on the current understanding of CAD screening in the ESRD population, discussing the available evidence for the use of various imaging techniques to refine risk prediction, with an emphasis on their strengths and limitations.

Keywords: cardiovascular, chronic renal failure, coronary artery disease, dialysis, ESRD, ischaemia

INTRODUCTION

Patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) are at elevated risk of cardiovascular disease (CVD) [1]. Age-adjusted cardiovascular mortality among dialysis patients is 10–20 times higher than in the general population [2]. As estimated glomerular filtration rate (eGFR) declines, CVD accounts for an increasing proportion of mortality [3, 4], explaining up to 50% of deaths among patients with ESRD [5]. In these patients, CVD is driven by clustering of traditional risk factors such as hypertension, dyslipidaemia, age, smoking and diabetes and non-traditional risk factors such as arteriosclerosis, vascular calcification, endothelial dysfunction and low-grade inflammation [6–8]. These drive both coronary artery disease (CAD) and non-CAD-related processes such as left ventricular hypertrophy (LVH), diffuse fibrosis and left ventricular (LV) dilatation [6, 9–11].

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As traditional risk factors only partially explain the increased risk of coronary events in patients with ESRD, the prognostic power of traditional risk prediction tools, such as the Framingham score, is limited [12]. Patients on dialysis often do not present with classic signs and symptoms of CAD and are less likely to be correctly diagnosed with an acute coronary syndrome (ACS) compared with non-dialysis patients [13]. There are many reasons for this, including patients with ESRD are less prone to experiencing symptoms of coronary ischaemia [13]; a lower proportion of patients who present with chest pain have ST-segment changes compared with non-dialysis individuals [13]; many patients with ESRD have diabetes and a lower sensitivity to anginal pain [14]; patients with ESRD are often less physically active and may not reach the exertional threshold for experiencing anginal symptoms or fatigue [15]; symptoms of CAD, when present, may be incorrectly attributed to anaemia from CKD rather than coronary pathology [14] and cardiac troponin levels might be chronically elevated in the absence of ACS [16].

Investigations that reliably identify clinically relevant CAD in patients with advanced CKD and ESRD are severely limited, as are strategies to mitigate the excess CVD-related morbidity and mortality in these patients. While developing therapies that target the different risk factors and disease processes that drive CVD in patients with ESRD is clearly a priority, so is developing robust investigations for the appropriate identification of CAD to allow optimal intervention, risk stratification and management [11, 17]. Any benefits of screening investigations must be weighed against their cost-effectiveness and potential for harm. Investigations for CAD can broadly be classified as invasive and non-invasive, with the latter commonly used first. There is significant controversy regarding the most appropriate screening modality for CAD in patients with ESRD [14, 18], resulting in centres using a variety of different protocols. This uncertainty partly stems from the exclusion or underrepresentation of patients with ESRD in most cardiovascular clinical trials, posing a major limitation to the applicability of their results to this patient group. Doubts regarding the significance of test results have been raised given the high pretest probability of disease, meaning that a negative scan does not necessarily put the patient at low risk [14]. This review will discuss the data for the commonly available techniques for the assessment of CAD in patients with ESRD, their advantages and limitations.

ASSESSMENT OF CAD

Serum biomarkers

Serum biomarkers are an appealing tool as they can be performed quickly and cheaply. Troponin assays (both high-sensitivity Troponin-I and Troponin-T) are one of the most studied and promising biomarkers for CAD and are a sensitive indicator of myocardial necrosis. A raised troponin has been found to predict cardiovascular events [19], mortality [19–21] and obstructive CAD on invasive coronary angiography (ICA) [22]. However, its specificity is limited in patients with ESRD, as it is often persistently elevated in the presence of CKD [23–25]. This is likely due to several cardiac (LVH, diastolic dysfunction, volume overload) and non-cardiac conditions other than ACS [26]. Optimization of cut-off values for patients with CKD may be required to improve specificity while maintaining sensitivity [27]. Given the variety of different-generation assays and their different operational characteristics, conclusions regarding one assay might not necessarily be applicable to a different one [28]. Therefore there is a need for fine-tuning of clinical decision levels specific for individual assays, populations and clinical settings [27]. The established prognostic value of troponin T for risk stratification beyond the traditional use to diagnose ACS is supported by the Kidney Disease Outcomes Quality Initiative [28]. However, how troponin assays can guide clinical practice in this population remains unclear [29]. As evidence for treatment strategies informed by abnormal troponin assays is lacking [21], it is important to interpret troponin levels in the wider clinical context to inform management decisions. A range of other serum biomarkers have been associated with CVD but have no established role in CAD screening at present in patients with ESRD, primarily because of the high false positivity rates [30].

Resting and exercise electrocardiogram

The most straightforward non-invasive investigation for CAD is a 12-lead electrocardiogram (ECG). The resting ECG is often abnormal in patients with ESRD, with voltage criteria for LVH, ST-segment and T-wave changes [31–33]. These are thought to be the result of a combination of factors, including LVH, volume overload, electrolyte imbalances, anaemia and uraemic toxins [31–33]. In renal transplant candidates (RTCs), an association between an abnormal resting ECG and severe CAD has been documented, with sensitivity and specificity of 77% and 58%, respectively [31]. Among ESRD patients, non-specific ST-segment and T-wave ECG changes not attributable to LVH have been found to be significantly associated with CAD [34]. An abnormal resting ECG has also been associated with a nearly 3-times greater risk of cardiac death in this population [35].

The high prevalence of abnormalities on resting ECGs partly accounts for why exercise ECG has not been found to be predictive of severe CAD in ESRD patients, with sensitivity and specificity of 35% and 64%, respectively [31], much lower than the values of 68% and 77% in the general population [36]. The other critical factor contributing to the limited role of exercise ECG testing is the reduced exercise capacity commonly encountered in patients with ESRD stemming from a combination of factors, including mobility-limiting comorbid conditions, anaemia, muscle fatigue, arthralgia and blunted tachycardia secondary to autonomic neuropathy [31]. The role of exercise stress is therefore limited, necessitating the use of pharmacological stress for cardiac testing. These factors, combined with ECG abnormalities occurring late in the ischaemic cascade, with other investigations picking up ischaemia at an earlier stage (Figure 1), do not make ECG a suitable CAD screening modality in this population.

ICA

Catheter-based ICA is considered the gold-standard diagnostic technique for the anatomical detection of coronary stenoses. It is an invasive and costly test that requires the use of ionizing radiation and contrast media, with their associated measurable risks, although major complications are rare (2%) and mortality rates low (<0.08%) [37]. The prevalence of angiographically severe CAD (≥70% luminal reduction) in patients referred for kidney transplantation has been found to range from 25 to 59% [14, 31, 38–44]. Figures are even higher if a more liberal definition of significant CAD is adopted or if high-risk groups are studied [45, 46]. Importantly, the presence of anatomically significant defects does not always imply the functional significance of the stenoses [47].

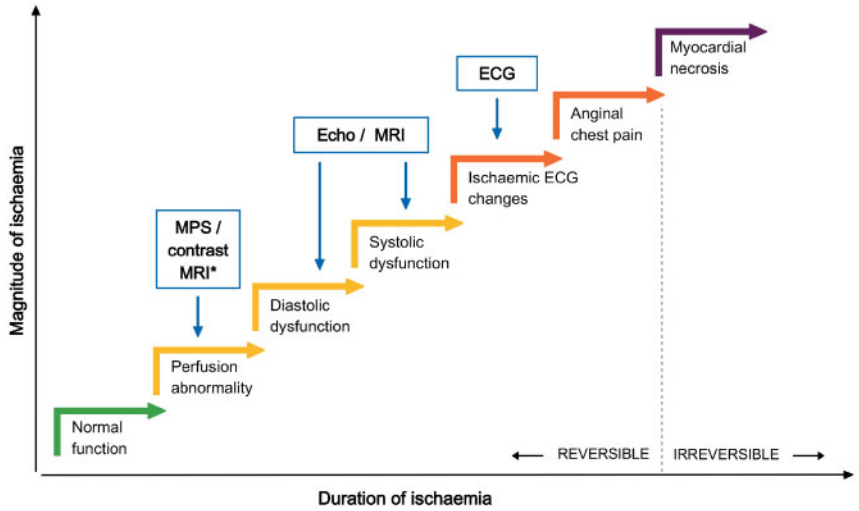

FIGURE 1: Ischaemic cascade. Sequence of pathophysiological events after a coronary artery occlusion. Different investigations can identify manifestations of disrupted coronary flow at different preclinical (yellow) and clinical (orange) stages. *Gadolinium stress cardiac MRI can identify perfusion abnormalities. However, GBCAs are contraindicated in patients with impaired kidney function (eGFR <30 mL/min/m^2). Echo, echocardiography.

Experimental evidence regarding the impact of angiographically significant CAD on clinical event rates and long-term survival in patients with ESRD is lacking and observational studies have reported variable results (Table 1). Angiographic CAD has been documented to predict major adverse cardiac events (MACE) [39, 40, 50, 52] and has been associated with increased mortality [31, 48, 49]. Sharma *et al.* [31] reported a significantly worse unadjusted 2-year survival among patients with angiographic CAD compared with patients with normal coronary arteries. However, this was non-significant when the analysis was restricted to patients with severe CAD, possibly due to the high revascularization rates in the group with severe CAD, interfering with the natural history of the disease. Alternatively, this could reflect the imperfect correlation between anatomical severity and functional significance. In contrast, several studies describing the prognostic power of ICA have reported no association between angiographic CAD and survival [41, 42, 51, 52]. A meta-analysis of potential renal transplant recipients found that for every 100 patients with abnormalities on ICA, 22 would die from CVD and 20 would experience a MACE during follow-up [53].

Gowdak *et al.* [54] found that CAD was associated with a significantly increased risk of MACE only among high-risk RTCs without diabetes. In patients with diabetes, the risk of end-points did not differ between individuals with angiographic CAD and those without. The long-term prognosis of non-diabetic patients with CAD was comparable to that of diabetic patients with or without CAD. This suggests that for diabetic patients with CKD, ICA is not a suitably sensitive risk stratification tool.

The results from these studies must be interpreted in the context of their observational nature, inherently leading to bias and confounding, and their relatively small sample sizes. Participants for most studies are RTCs, who tend to be a fitter, lower-risk population compared with general ESRD patients. In addition, patients with significant CAD often undergo revascularization procedures, confounding the association between angiographic findings and outcomes.

Fractional flow reserve

In the general population, the American Heart Association recommends the addition of physiological measurements to the anatomical assessment of CAD by ICA to accurately evaluate the clinical significance of CAD lesions [55]. These recommendations are largely informed by the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 trial, where only 2% of participants in the percutaneous coronary intervention (PCI) arm had 'renal insufficiency' [56], limiting the generalizability of these results to patients with ESRD. Pressure-derived fractional flow reserve (FFR) is an indicator of the functional significance of coronary stenoses. It is defined as the ratio of maximal blood flow in a stenotic artery to the theoretical normal blood flow in that artery, representing the fraction of normal maximal blood flow that can be achieved despite the stenosis [57]. The severity of the stenosis might be underestimated in the presence of microvascular dysfunction, LVH, diffuse CAD, vascular calcification and arteriosclerosis. These factors restrict the blood flow increase and consequent decrease in distal coronary pressure after pharmacological vasodilation, limiting the calculation of the FFR pressure gradient [57, 58]. This is an issue in the ESRD population, given the high rates of these conditions. Matsuo *et al.* [59] found that FFR did not correlate with quantitative ICA measures (minimal lumen diameter, per cent diameter stenosis) in patients on haemodialysis, while the two did correlate in non-haemodialysis patients. This supports the need for both an anatomical and a physiological assessment to determine the clinical significance of CAD lesions. In another study, the FFR was compared against myocardial perfusion scintigraphy (MPS) in 42 patients on haemodialysis with known or suspected CAD. FFR demonstrated a suboptimal performance, as patients with a normal FFR value frequently had regional myocardial ischaemia on MPS [58]. Hence the role of FFR in patients with ESRD is not well-defined at present.

Coronary artery calcium score (CACS)

The CACS is a quick, non-invasive screening test that involves low radiation exposure (1 mSv) and no contrast. It is increasingly used in the general population, for instance, to inform atherosclerotic CVD primary prevention strategies if there is uncertainty regarding the need for statin therapy [60], due to the excellent prognostic value of a CACS of 0 [61, 62]. Despite

Table 1. Studies assessing prognostic utility of ICA in patients with ESRD

Study	Patients undergoing ICA	Study design; follow-up (months)	Selection criteria for CA	Definition of obstructive CAD	Results
Charytan *et al.* [48]	67 patients on HD	Prospective cohort; 32 (median)	No ischaemic symptoms at enrolment, HD for ≥30 days, no coronary events in last 4 weeks, no ICA in previous 2 years	≥50% stenosis relative to adjacent normal reference segment	The presence of CAD was associated with an increased risk of death [HR 3.3 (95% CI 1.4–7.6)]. In multivariate analysis, only proximal CAD was associated with an increase in risk of death [HR 3.1 (95% CI 1.3–7.3)]
De Lima *et al.* [39]	106 RTCs	Prospective cohort; 26 (mean)	Moderate risk: age ≥50 years. High risk: if any of diabetes, angina, previous MI or stroke, LV dysfunction, PAD	≥70% stenosis in one or more epicardial arteries on visual inspection	Unadjusted probability of MACE[a] at 1, 2 and 4 years: 13, 39 and 46% with angiographic CAD versus 2, 6 and 6% with no CAD. Angiographic CAD was the only predictor of future MACE on multivariate analysis (P = 0.003)
Enkiri *et al.* [49]	57 RTCs with ESRD who had both MPS and ICA	Prospective; 40 (median)	Abnormal non-invasive test in intermediate-risk patients; all high-risk patients	Significant: >50%; severe: >70% stenosis in proximal or mid segment of major epicardial arteries/their branches	1- and 3-year survival: 72 and 50% for patients with severe CAD on ICA versus 91 and 73% without severe CAD. ICA discriminated survivors from non-survivors
Fabbian *et al.* [50]	63 patients on dialysis	Prospective cohort; 62 ± 20	Awaiting transplantation or clinical evidence of CAD	Severe: ≥75% luminal stenosis in epicardial arteries	On multivariate analysis, age was the only independent predictor of MACE.[b] After the removal of age from the model, severe CAD was an independent predictor of MACE [OR 7.4 (95% CI 1.8–30.2); P = 0.005]
Gowdak *et al.* [40]	301 RTCs	Prospective cohort; 22 (median)	Any of: age ≥50 years, diabetes, angina, previous MI or stroke, LV dysfunction, PAD	≥70% luminal reduction in one or more epicardial arteries on visual inspection	Incidence of MACE[c]: 45% in the presence of angiographic CAD versus 18% if no CAD (P < 0.001)
Hage *et al.* [51]	260 RTCs	Prospective cohort; 30 ± 15	Abnormal stress MPS; discretion of cardiologist based on clinical presentation	>50% lumen diameter narrowing in any of three major coronary arteries or major branches	Presence and severity of CAD by angiography was not predictive of survival (used all-cause mortality as outcome). Two-year survival for 0-, 1-, 2- and 3-vessel disease: 80, 88, 86 and 78%, respectively; P = 0.6
Hickson *et al.* [42]	134 RTCs	Prospective cohort; 6 (median)	Based on DSE result and cardiologist's evaluation	Severity scored on highest degree of stenosis of single major epicardial artery: mild <50%, moderate 50–70%, severe >70%	Severity of CAD by angiography not significantly associated with survival (P = 0.18)
Patel *et al.* [41]	99 RTCs	Prospective cohort; 32 (median)	Any of: age >50 years, ESRD due to diabetes, symptomatic IHD, positive non-invasive testing. Ultimately based on clinical judgement and patient's preference.	>75% stenosis in one major epicardial vessel	No 4-year survival difference between patients who underwent ICA compared with no ICA or ICA + intervention (P = 0.67)
Sharma *et al.* [31]	125 RTCs	Prospective; 19 ± 7	Consecutive RTCs >18 years old, with no severe aortic	Visual luminal narrowing: mild <50%, moderate 50–70%, severe >70%	Patients with CAD had significantly worse unadjusted survival than those without CAD (80% versus 100% at 2.5 years; P = 0.005)

(continued)

Table 1. Continued

Study	Patients undergoing ICA	Study design; follow-up (months)	Selection criteria for CA	Definition of obstructive CAD	Results
			stenosis or unstable angina		
Winther *et al.* [52]	154 RTCs	Prospective cohort; 44 (median)	Any of: age ≥40 years, diabetes, symptoms of CVD, dialysis duration >5 years, on kidney transplant list for >3 years without cardiac screening	≥50% reduction in luminal diameter by quantitative ICA	Event rate in patients with versus no obstructive CAD: MACE, 10.6% versus 3.5%; mortality, 7.0% versus 4.6%. On adjusted analysis, obstructive CAD was associated with MACE (HR 2.7; $P < 0.05$) but not with mortality (HR 1.1, $P = 0.90$)

[a]MACE: sudden death, MI, heart failure, unstable angina, revascularization, life-threatening arrhythmia, pulmonary oedema.
[b]MACE: sudden cardiac death, fatal and non-fatal MI, irreversible congestive heart failure.
[c]MACE: MI, unstable angina, myocardial revascularization, sudden death, stroke, revascularization for PAD, heart failure.
HD, haemodialysis; IHD, ischaemic heart disease; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease.

evidence for CACS as a predictor of future cardiac events in patients with ESRD [52, 63–65], its use for risk stratification is limited by the common and progressive nature of coronary artery calcification among patients with ESRD [66, 67], testified to by elevated CACS in up to 83% of patients on haemodialysis [68]. A study of 18 patients with ESRD found that a CACS >0 had the best sensitivity (88%), although still lower than that described in the general population (99%) [69], but poor specificity (53%) for obstructive CAD [70]. The increase in specificity (77%) found by Winther *et al.* [71] using a threshold of 400 was at the expense of sensitivity (67%). In the general population, coronary artery calcification is normally only seen in advanced atherosclerotic plaques. However, since the CACS is a measure of absolute coronary calcium, the increased arterial media calcification (Mönckenberg's arteriosclerosis) in patients with ESRD [72, 73] likely causes the reduced diagnostic accuracy of CACS [70], as this does not contribute to the development of occlusive plaques, but rather increases arterial stiffness. Nonetheless, the correlation between CACS and atherosclerotic burden in patients with kidney disease has been described [74, 75]. Among patients with ESRD, it might be helpful to combine CACS with risk factor stratification to guide the selection of further cardiac evaluation for CAD [52, 76]. A CACS of 0 could be useful to exclude significant CAD, given its excellent negative predictive value, but the role of CACS in this patient population is far from clear and adjustment of the traditional cut-off score may be necessary [70, 74, 77].

Coronary computed tomography angiography (CCTA)

The potential of CCTA as a non-invasive test for CAD has been well described [78, 79]. Its high negative predictive value makes it reliable in ruling out significant CAD in symptomatic patients with low to intermediate pretest probability of CAD in the general population [80, 81]. In 2016, the National Institute for Health and Care Excellence recommended CCTA as the first-line investigation for all patients with anginal symptoms or ischaemic ECG changes, regardless of pretest probability [82]. More recently, the Scottish Computed Tomography of the Heart trial demonstrated that CCTA-guided care led to fewer adverse outcomes [83]. However, patients with an eGFR <30 mL/min/1.73 m^2 were excluded from this trial, precluding generalization to patients with advanced CKD and ESRD. The evidence comparing the accuracy of CCTA with ICA in an ESRD population is limited [71, 77, 84]. The elevated calcification burden constitutes the major barrier to the use of CCTA in these patients, as heavily calcified plaques cause blooming artefacts and partial volume effects that blur the coronary lumen [80, 85, 86] (Figure 2). Winther *et al.* [71] reported CCTA has high sensitivity (93%) and moderate specificity (63%) for diagnosing obstructive CAD in RTCs. The poorer specificity is likely attributable to the high calcium burden in coronary arteries without obstructive CAD. Despite finding a significant correlation between higher CACS and more severe stenosis, Mao *et al.* [77] observed that many patients with very high CACS had non-significant stenosis on CCTA. They therefore suggested that CCTA could be a diagnostic option in patients with zero to low calcium burden, but this in itself makes major obstructive CAD unlikely. A recent publication might support the use of CCTA in patients on dialysis, as it found a significant difference in the incidence of cardiovascular events at 2 years between patients with and without CAD on CCTA (36% versus 0%) [87]. At present, the role of CCTA for CAD evaluation in patients with ESRD is uncertain, but worthy of systematic study.

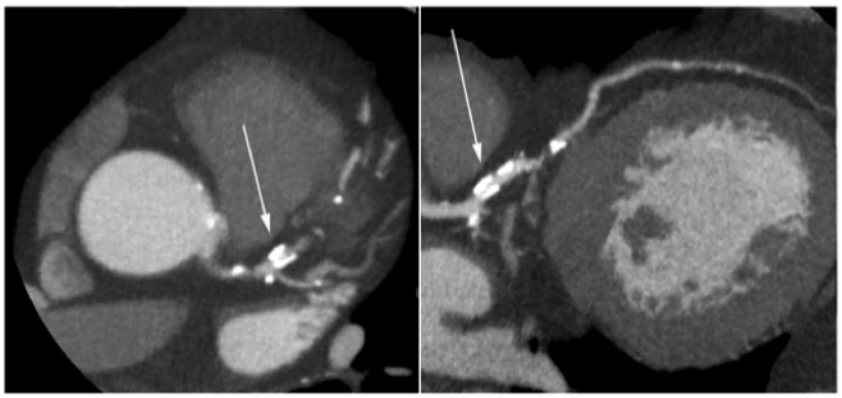

FIGURE 2: Non-interpretable lesion of the proximal left anterior descending artery on CCTA. Segment considered non-interpretable due to the extensive calcification. Left panel, axial reconstruction. Right panel, curved multiplanar reconstruction. Reproduced from 2013 De Bie *et al.* [87].

Dobutamine stress testing

Dobutamine stress echocardiography (DSE) is an established and widely available non-invasive investigation for the diagnosis and risk stratification of patients with known or suspected CAD in the general population [88–91]. It is a reliable and cost-effective imaging technique [88], independent of exercise capacity [91] and free of biohazards [89]. Dobutamine has a chronotropic and inotropic effect, provoking myocardial ischaemia chiefly by increasing myocardial oxygen demand [91]. It is contraindicated in the presence of complex arrhythmias or uncontrolled hypertension [91] and can cause minor adverse effects, which occasionally prevent test completion [92]. The hallmark of myocardial ischaemia on DSE is the induction of reduced systolic wall thickening [88]. The presence of inducible regional wall motion abnormalities (WMAs) is specific to CAD [89].

In the general population, pharmacological stress echocardiography predicted cardiac death during long-term follow-up in an international study of 7333 patients [93], with moderate accuracy for detection of angiographic CAD [94, 95]. A Cochrane meta-analysis of 13 studies of 745 RTCs found DSE to have a pooled sensitivity of 0.79 and specificity of 0.89 for angiographic CAD [96]. Factors that may affect the diagnostic performance of DSE in patients with ESRD include the high burden of hypertension, cardiomyopathy and calcific vascular disease. Both concentric remodelling (possibly due to myocardial abnormalities that influence the appearance of regional WMAs) and eccentric hypertrophy affect the accuracy of DSE, influencing false negative results [97], an important consideration when both are highly prevalent cardiomyopathic phenotypes in patients with ESRD. In terms of prognostic utility, different studies have shown that a positive DSE result is predictive of MACE [98, 99] and mortality [100] in both CKD and RTCs, while De Lima *et al.* [39] did not find DSE to predict survival in RTCs (Table 2). A meta-analysis concluded that DSE was as good as ICA at predicting cardiovascular mortality and MACE but was inferior to ICA for the prediction of all-cause mortality [53]. The prognostic ability of ICA, however, may have been falsely reduced by the interference of revascularization procedures or kidney transplantation, resulting in fewer adverse outcomes [53]. Observational studies have shown a definite role for DSE in the CAD assessment of patients with ESRD, despite its sub-optimal accuracy and imperfect prognostic utility. The lack of randomized clinical trials is an issue, but the non-invasive nature of DSE and the absence of biohazards constitute an argument for its use.

Dobutamine stress cardiac magnetic resonance (CMR) is another non-invasive functional imaging modality increasingly used to assess myocardial ischaemia, given the excellent image quality and lack of contrast or radiation exposure [47, 101]. As with DSE, it relies on the induction of WMAs in the presence of functionally significant coronary stenoses [47, 101]. It has shown significantly higher diagnostic accuracy for CAD compared with DSE [102] and excellent prognostic value for both high- and low-risk individuals in the general population [103–105]. While a recent study on 41 RTCs demonstrated its safety and feasibility in patients with ESRD [47], its diagnostic and prognostic utility in this population need further evaluation.

MPS

MPS is a well-establish non-invasive nuclear imaging test for cardiac ischaemia [106]. Through the administration of a radioactive tracer injection and pharmacological stress, myocardial viability and perfusion can be assessed. An inducible (reversible) perfusion defect that normalizes on rest images indicates a significant epicardial coronary stenosis, while a fixed defect present on both stress and rest images normally denotes an infarcted area of myocardium [107]. In the general population, its reliability for the diagnosis and risk stratification of patients with an intermediate probability of CAD make it a powerful technique for the prediction of coronary events [107] and selection of candidates who would benefit from revascularization [106–108].

The accuracy of MPS in patients with ESRD is moderate: a Cochrane meta-analysis of nine studies (582 participants) described a pooled sensitivity and specificity of 0.74 and 0.70, respectively, for angiographic CAD [96]. More recently, Winther *et al.* [71] found a sensitivity of 53% and specificity of 82% for the diagnosis of obstructive CAD. In a study of 161 RTCs, 65% of patients with significant CAD on ICA had a negative MPS for ischaemia (positive and negative predictive values, 43% and 47%, respectively), emphasizing the poor correlation between these tests [44]. Significant LVH may compromise the sensitivity of MPS, as small perfusion defects are missed [97]. Altered endothelial function in the absence of epicardial stenosis (common in patients with ESRD and diabetes) results in impaired coronary flow reserve, affecting the reliability of the scan, as the flow reserve may be abnormal in the vascular bed supplied by a non-stenosed artery [109]. Triple-vessel disease, highly prevalent

Table 2. Studies assessing the prognostic utility of DSE in patients with ESRD

Study	Patients undergoing DSE	Age (years); male (%)	Study design; follow-up (months)	Results
Bergeron *et al.* [100]	485 patients with CKD (240 on dialysis)	61 ± 14; 61%	Prospective cohort; 28 ± 22	In adjusted analysis, the percentage of ischaemic segments on DSE was an independent predictor of all-cause death [HR 1.40 (95% CI 1.16–1.68); P < 0.001]
Cai *et al.* [98]	185 RT recipients with ESRD	56 ± 11; 64%	Retrospective; 60 (mean)	Rates of MACE (cardiac death, MI, CR) at 48 months in patients with both fixed and inducible WMA compared with patients with normal DSE: 33% versus 7%; P = 0.007. In multivariate analysis, the presence of both fixed and inducible WMA was an independent predictor of MACE at 48 months [HR 5.6 (95% CI 1.5–21.2); P = 0.012]. The presence of fixed WMA alone was not a predictor of MACE
De Lima *et al.* [39]	93 RT candidates underwent DSE (total 126)	55 ± 8; 77%	Prospective cohort; 26 (mean)	DSE results correlated with the degree of coronary artery obstruction on ICA (P = 0.003). On multivariate analysis, DSE was not a predictor of cardiac events.[a] There was no significant difference in survival between patients who had a positive and negative DSE (cardiac events 16.7% versus 13%)
Tita *et al.* [99]	149 RT candidates	53 ± 11; 53%	Retrospective; 34 (mean)	On multivariate analysis, positive DSE was an independent predictor of MACE (non-fatal MI, CR, new-onset congestive heart failure, cardiac death) [HR 6.86 (95% CI 2.41–19.56); P < 0.001]

[a]Cardiac events are defined as sudden death, MI, life-threatening arrhythmia, heart failure, pulmonary oedema, unstable angina, CR.
CR, coronary revascularization; MI, myocardial infarction; OR, odds ratio; RT, renal transplant.

in patients with CKD, may result in global ischaemia, reducing the ability of MPS to pick up differences in perfusion between segments [110]. Finally, the poor spatial resolution means that subendocardial defects are easily missed [111].

Several studies have assessed the prognostic ability of MPS in patients with CKD and ESRD (Table 3). Hakeem *et al.* [121] found that a normal MPS scan in patients with CKD was associated with significantly higher unadjusted cardiac death rates compared with a normal scan in patients without CKD (2.7% and 0.8%, respectively; P = 0.001), potentially limiting the value of this technique in the ESRD population. Nevertheless, the role of MPS for the prediction of cardiac events in patients with ESRD is relatively well-established [112–118]. Data regarding survival prediction, however, are more variable. Several studies identified an abnormal finding on MPS to be an independent predictor of mortality in RTC and ESRD populations [51, 112, 115, 119], whereas others found no association between MPS results and survival [39, 49, 110, 113, 116, 120]. A meta-analysis by Wang *et al.* found that MPS was as good as ICA at predicting MACE and cardiovascular mortality, but worse than ICA for all-cause mortality [53]. Non-invasive tests (DSE and MPS) perhaps performed similarly to ICA because they can identify poor LV function and cardiomyopathy, factors that contribute to CVD in this population [53]. The evidence therefore suggests that MPS offers valuable yet imperfect prognostic information on CVD in patients with ESRD, but not necessarily because of its ability to discriminate significant CAD in this population.

OUTCOMES AFTER CORONARY REVASCULARIZATION

The only randomized evidence on outcomes following coronary revascularization (CR) is from 1992, when Manske *et al.* [122] assigned 26 RTCs with diabetes and CAD to medical therapy or CR. Cardiovascular endpoints were more common in the medical therapy group compared with the revascularization group (10 versus 2) after a median follow-up of 8.4 months. The relevance of these results to current practice, however, is limited by the advances in medical therapy. Several observational studies have reported a benefit of pre-emptive CR among RTCs [14, 44, 123]. Kumar *et al.* [123] observed excellent survival among revascularized patients who were either subsequently transplanted or on dialysis awaiting transplantation. Patients declining intervention had a poor survival (1- and 3-year survival, 75% and 37%, respectively), but these were not put forward for transplantation and consequently were likely to have been systematically unhealthier than those who were waitlisted. The lack of a similar comparison group with RTCs not undergoing pre-emptive angiography also limits interpretation of the results. Similarly, a retrospective review of 1460 renal transplant recipients found a comparable 5-year survival between patients with obstructive CAD who underwent revascularization and those with non-obstructive CAD {adjusted hazard ratio [HR] 1.24 [95% confidence interval (CI) 0.51–3.01]}, significantly worse than the 5-year survival of medically managed patients with obstructive CAD [14]. Contrary to this, revascularization has not improved outcomes in other studies [41, 51, 124]. In 300 RTCs, Patel *et al.* [41] found no difference in survival between those who underwent CR compared with those who had ICA without intervention or no ICA. The difference in mortality between patients with significant CAD who underwent PCI and those who did not (15% versus 52%) was likely to reflect the impact of transplantation, overall fitness and comorbidities rather than the effect of revascularization itself, as a lack of intervention was associated with increasing age, comorbidities and failure to waitlist for transplantation. Hage *et al.* [51] also found no impact of CR

Table 3. Studies assessing the prognostic utility of MPS in patients with ESRD

Study	Patients undergoing MPS	Study design; follow-up (months)	Imaging modality	Definition of defect on MPS	Results
Callan *et al.* [112]	138 RT candidates	Retrospective; 40 (median)	SPECT; majority dobutamine	Semi-quantitative: SSS	Higher mortality + cardiac event rate if SSS >8 (P = 0.028). Not significantly increased risk of CV events and all-cause mortality in patients with fixed perfusion defects
Chew *et al.* [113]	387 RT recipients (393 scans)	Retrospective	SPECT; tachycardic or vasodilatory	Positive scan if reversible defect (fixed defects considered negative)	Soft endpoints (inpatient admission with unstable angina, PCI, CABG): higher event rate at 5 years in group with positive MPS compared with negative MPS [20.8% versus 3.9%; HR 44 (95% CI, 2.1–9.6); P < 0.001]. Hard endpoints (inpatient admission with MI or cardiac death): no statistically significant difference between the two groups
De Lima *et al.* [39]	93 RT candidates (total 126)	Prospective cohort; 26 (mean)	SPECT; dipyridamole	Perfusion defects (fixed = fibrosis; transient = ischaemia)	On multivariate analysis, MPS was not a predictor of cardiac events.[a] There was no significant difference in survival between patients who had a positive and negative MPS
Doukky *et al.* [114]	401 RT recipients (total 581)	Retrospective; 44 ± 28	SPECT; exercise, adenosine or regadenoson	Semi-quantitative: abnormal if SSS ≥4.	Abnormal MPS provided independent and incremental predictive value for long-term MACE (cardiac death, non-fatal MI) only for patients at intermediate risk (3–4 risk factors). SDS (ischaemic burden) did not add incremental predictive value beyond risk factors
Doukky *et al.* [115]	303 with ESRD	Prospective; 35 ± 10	SPECT; regadenoson	Abnormal MPS if SSS ≥4. Inducible myocardial ischaemia if SDS ≥2.	On multivariate analysis, abnormal MPS was associated with an increased risk of composite endpoint (cardiac death, MI, late revascularization) [27.3% versus 16.7%; HR 1.88 (95% CI 1.04–3.41); P = 0.037]. Inducible myocardial ischaemia was also associated with the composite endpoint [33.3% versus 16.9%; HR 1.97 (95% CI 1.19–3.27); P = 0.008]
Enkiri *et al.* [49]	57 RT candidates with ESRD who had both MPS and ICA	Prospective; 40 (median)	SPECT; exercise ($n = 5$), adenosine ($n = 6$), dipyridamole ($n = 46$)	Abnormal perfusion: radiotracer uptake <75% of normal reference segment	Poor relation of MPS results to findings on ICA (perfusion defects present in 76% of patients without severe CAD on ICA). MPS did not provide prognostic information for the prediction of survival
Hage *et al.* [51]	2207 RT candidates with ESRD (total 3698)	Prospective cohort; 30 ± 15	SPECT; adenosine	Abnormal perfusion if reversible or fixed defects present	Myocardial perfusion abnormalities were predictive of worse survival (P < 0.001). No difference between the presence of fixed or reversible defects (P = 0.45)
Ives *et al.* [116]	819 RT recipients (total 1189)	Retrospective; 56, 40–75 (median, IQR)	MPS; exercise or vasodilator (adenosine, regadenoson)	Abnormal perfusion (perfusion defect size ≥5% LV mass) or reduced LVEF (<50%)	Annual rates of CV events (CV death, MI or revascularization): 1.5, 3.1, 4.3% (P < 0.001) and all-cause mortality: 1.8, 2.6, 3.6% (P = 0.017) for patients with no MPS, normal MPS and abnormal MPS, respectively. On multivariate analysis, abnormal MPS was an independent predictor of CV events [HR 1.78 (95% CI, 1.03–3.06) P = 0.04] but not all-cause mortality [HR 1.40 (95% CI 0.81–2.41); P = 0.2]

(continued)

Table 3. Continued

Study	Patients undergoing MPS	Study design; follow-up (months)	Imaging modality	Definition of defect on MPS	Results
Kim *et al.* [117]	165 high-risk patients with ESRD (50 low-risk patients did not have MPS)	Prospective; 50 ± 21	SPECT; adenosine	Presence of perfusion defect or SSS ≥4	Risk of cardiac events was significantly higher in high-risk patients with perfusion defects compared with high-risk patients without perfusion defects [15% versus 4.5%; HR 3.28 (95% CI 1.79–5.99); $P < 0.001$] and low-risk patients [15% versus 1.2%; HR 17.56 (95% CI 4.20–73.55); $P < 0.001$]. SPECT improved prognostic stratification ($P < 0.001$)
Marwick *et al.* [110]	45 RT candidates with ESRD	Prospective; 25 ± 14	SPECT; thallium, dipyridamole	Fixed or reversible defects	MPS did not predict prognosis. Five of six patients who died of cardiac causes had normal MPS
Patel *et al.* [118]	174 RT recipients (cohort total 600)	Prospective; 42 ± 12	SPECT; adenosine or dipyridamole	Abnormal: reversible or fixed perfusion defect	In multivariate analysis, abnormal MPS was the only predictor of cardiac events ($P = 0.006$). Cardiac event-free survival: 97% if normal MPS, 85% if abnormal MPS [RR 5.04 (95% CI 1.4–17.6); $P = 0.006$]
Venkataraman *et al.* [119]	150 RT candidates with ESRD, who had ICA within 6 months of MPS	Prospective cohort—portion of cohort in the previous study [44]; 41 ± 18	SPECT; adenosine	Perfusion defects, LVEF ≤40%	82% had CAD. Worsening survival in patients with progressively abnormal perfusion, even in patients with LVEF >40%. On multivariate analysis, abnormal MPS (low LVEF or abnormal perfusion) was the strongest predictor of all-cause mortality [adjusted OR 2.5 (95% CI 1.2–5.3); $P = 0.012$]. Chi-square of prognostic models: clinical + MPS, 7.8; clinical + MPS + ICA, 8.
Wong *et al.* [120]	126 RT candidates at high risk	Retrospective; 31 (median)	Thallium MPS; adenosine or dobutamine	Reversible or fixed perfusion defects	In unadjusted analysis, a reversible defect on MPS was associated with fatal cardiac events [HR 3.1 (95% CI 1.1–18.2)] and all-cause mortality [HR 1.92 (95% CI 1.1–4.4)]. However, in multivariate analysis, the presence of a reversible defect on MPS was not associated with all-cause mortality

[a]Cardiac events are defined as sudden death, MI, life-threatening arrhythmia, heart failure, pulmonary oedema, unstable angina, CR.

CABG, coronary artery bypass graft; CV, cardiovascular; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OR, odds ratio; RT, renal transplant; SPECT, single-photon emission computed tomography; SDS, summed difference score; SSS, sum stress score.

on 2-year survival (CR 77% versus no CR 81%) except in patients with triple-vessel disease. Observational data may point towards a benefit from CR but are ultimately inconclusive.

FUTURE PROSPECTS

CMR is an established and actively evolving non-invasive imaging modality that has the potential to comprehensively phenotype aspects of cardiac structure and function involved in the pathogenesis of CVD in patients with advanced CKD and ESRD. With regard to CAD assessment, stress CMR is excellent at identifying inducible myocardial perfusion defects through the use of gadolinium-based contrast agents (GBCAs) [47, 101]. However, GBCAs have been associated with the risk of nephrogenic systemic fibrosis (NSF) in patients with advanced kidney disease [125, 126]. Linear non-ionic or older linear ionic GBCAs are absolutely contraindicated in patients with eGFR <30 mL/min/1.73 m^2, acute kidney injury or on dialysis [127]. The Canadian Association of Radiologists suggests that macrocyclic or newer linear GBCAs can be administered in these patients if GBCA-enhanced magnetic resonance imaging (MRI) is necessary and no alternative test is available, quoting a risk of NSF of <1% [127]. There are reports of NSF after exposure to macrocyclic compounds [128]. Therefore a case-by-case risk–benefit discussion including the patient is required to consider alternative diagnostic modalities and how necessary GBCA-enhanced MRI is for patient care.

CMR adenosine stress native T1 mapping has been proposed as a method to assess myocardial blood volume changes before and after vasodilatory stress, without the need for contrast. This technique has been shown to accurately detect CAD in the general population, identifying areas of obstructive CAD or microvascular dysfunction in a study involving 60 patients with angina and 30 healthy subjects [129]. This has never been tested in patients with CKD but could represent a promising research avenue. Blood oxygen level–dependent CMR [130] is another appealing technique, as it has been shown to differentiate ischaemic myocardial segments from non-ischaemic or normal ones at rest [131] and to identify functionally significant CAD with vasodilator stress [131, 132], but it is largely untested in patients with advanced renal disease.

CONCLUSIONS

The evaluation of CAD in patients with advanced CKD and ESRD is challenging. Each screening method has its advantages and drawbacks. Even the most established imaging modalities (DSE, MPS and ICA) predict outcomes poorly [53], with a substantial number of patients experiencing adverse cardiac events despite an apparent 'negative' result. Mindful that kidney transplantation is associated with better survival regardless of CAD severity [133], some form of risk assessment is paramount to improve CVD morbidity and mortality during the peritransplant period and long term. A stepwise screening approach incorporating clinical risk stratification, non-invasive stress testing as the first-line investigation and reserving ICA for patients with signs of ischaemia seems a sensible approach that aims to avoid unnecessary exposure to invasive tests and facilitate effective resource allocation. This is, indeed, a strategy successfully employed in different centres [124, 134]. Ultimately, well-conducted RCTs are needed to determine optimal strategies for CAD investigation and management in this subgroup of patients. Given the importance of knowing the functional significance of a lesion and not only the coronary anatomy, the development of a safe and reliable stress technique to investigate myocardial ischaemia in patients with ESRD is essential.

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AUTHORS' CONTRIBUTIONS

F.E.P. contributed to manuscript drafting, figure preparation and final preparation. G.S.G. contributed to manuscript revision and figure preparation. J.O.B. and G.P.M. contributed to manuscript revision. M.P.G.-B. contributed to manuscript preparation and revision and final approval of the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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