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Screening for occult coronary artery disease in potential kidney transplant recipients: time for reappraisal?

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ABSTRACT

Screening for occult coronary artery disease in potential kidney transplant recipients has become entrenched in current medical practice as the standard of care and is supported by national and international clinical guidelines. However, there is increasing and robust evidence that such an approach is out-dated, scientifically and conceptually flawed, ineffective, potentially directly harmful, discriminates against ethnic minorities and patients from more deprived socioeconomic backgrounds, and unfairly denies many patients access to potentially lifesaving and life-enhancing transplantation. Herein we review the available evidence in the light of recently published randomized controlled trials and major observational studies. We propose ways of moving the field forward to the overall benefit of patients with advanced kidney disease.

Keywords: cardiac surgery, cardiorenal syndrome, cardiovascular, guidelines, kidney transplantation, myocardial infarction

> 'If a patient asks a medical practitioner for help, the doctor does the best he can. He is not responsible for defects in medical knowledge. If, however, the practitioner initiates screening procedures, he is in a very different situation. He should have conclusive evidence that screening can alter the natural history of disease in a significant proportion of those screened.'
> Archie Cochrane, 1971

INTRODUCTION

The number of patients with kidney failure on renal replacement therapy has risen continuously since such treatments started to become widely available in the 1960s; worldwide there are 3.4 million people currently on dialysis [1–3]. This rise has been disproportionately greater in patients from ethnic minorities [4, 5] and lower socioeconomic backgrounds [4–6]. In February 2020, there were 8236 (4618 active) patients on the kidney transplant waiting list in the UK, with a median waiting time of 20 months (2014–17) [7]. In the USA, based on the Organ Procurement and Transplantation Network in April 2021, there were 90 876 patients wait-listed for a kidney transplant. In 2013, their median wait-time was 49.2 months and this was higher for Black (5 years) than for White (3.4 years) patients [8].

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The routine care of non-transplanted patients with kidney failure, especially those on dialysis, is intrinsically expensive [9, 10]. In addition, they have a high requirement for elective or emergency admission to hospital, further increasing costs [11]. Kidney transplantation confers better survival and quality of life at a much lower cost than dialysis treatment [12, 13]. There is, therefore, a strong motivation to maximize the number of patients with kidney failure listed for a kidney transplant. Limited donor organ availability, however, means that there is also an imperative not to risk an organ by transplanting subjects with kidney failure who are unlikely to gain either symptomatic or prognostic benefit because of their high level of comorbidity. Such patients have a high risk of adverse perioperative and post-operative health events. The current strong focus on preoperative evaluation and disease screening of potential recipients has grown out of these concerns.

Patients with advanced chronic kidney disease (CKD), and especially those on dialysis, have a greatly increased risk of cardiovascular (CV) morbidity and mortality [9, 10, 14]. The increase in relative risk (RR) is age-dependent but is between 10 and 100 times higher than control subjects [14]. While much of this increased risk is due to sudden death and heart failure rather than myocardial infarction (MI), the risk of coronary artery disease is increased in CKD [14, 15]. Somewhere between 9% and 17% of patients on the kidney transplant waiting list will suffer from an MI within 3 years of being listed [16–18]. The risk of MI is highest immediately post-transplant and declines in the subsequent year [18–20]. Furthermore, patients with kidney failure will often not display classic symptoms of myocardial ischaemia, making the diagnosis of significant coronary artery disease difficult to make on history alone [21]. Despite improvements in emergency treatment, the outcome of MI in dialysis patients remains very poor, with 1 year mortality rates of around 40% [22].

Therefore, it has become commonplace for patients being assessed for kidney transplantation to undergo non-invasive stress testing, usually myocardial perfusion scintigraphy (MPS) or dobutamine stress echocardiography (DSE), both of which are used to detect significant, but usually occult myocardial ischaemia due to coronary artery disease. Protocols requiring these investigations have been applied in many developed countries and are now generally considered to be the standard of care [13, 21, 23–27]. They are performed with the laudable aim of detecting individuals at high perioperative risk and ultimately of reducing peri-transplant cardiac events and mortality. This approach has, however, never been evidence-based and evidence is accumulating that it has important limitations. Screening for coronary artery disease in kidney failure may not only lack cost and clinical efficacy but it may also be harmful, delaying or even preventing listing for a kidney transplant and giving rise to revascularization procedures that carry risk without clear prognostic benefit. Furthermore, it may be exacerbating inequalities of care for patients from ethnic minorities and deprived socioeconomic backgrounds.

Several new sources of evidence on coronary artery disease in kidney failure have become available since most of the current protocols were designed and in view of these and the potential for unintended adverse effects, we believe that the time has come to re-evaluate the approach of screening and intervention for occult coronary artery disease in asymptomatic patients before being wait-listed for kidney transplantation (Table 1). We further propose a way forward to ensure efficient use of available cardiac investigations and fairer allocation of the scarce and precious resources of donor organs.

Limitations of the conventional approach to cardiac screening

Problems with tests for myocardial ischaemia in potential transplant candidates

The sensitivity and specificity of MPS and DSE are lower in patients with kidney failure than in patients without CKD. False-negative results are more likely, probably because coronary flow reserve is impaired [34] and there is a high prevalence of multivessel coronary artery disease with balanced ischaemia [35]. False-positive results are also more likely because of increased left ventricular mass, concentric remodelling and increased afterload [35–37]. Currently, there is no strong evidence, nor consensus, to support the use of one non-invasive test over another [35, 38]. In patients without CKD, magnetic resonance perfusion imaging is superior to MPS but is not applicable to patients with kidney failure due to concerns over the use of gadolinium contrast [39]. The choice of test is usually determined by local availability and expertise. Both non-invasive tests (and coronary angiography) predict outcomes poorly. Similar proportions of patients will experience adverse coronary events after an abnormal screening result compared with a normal result, while most patients with abnormal test results do not have adverse cardiac outcomes and may be disadvantaged by current screening practices [40].

Coronary artery calcification (CAC) assessed non-invasively by non-enhanced computed tomography (CT) is a powerful predictor of obstructive coronary events in the general population, where a score of more than 400 Agatston Units is associated with high risk [41, 42]. CAC is extremely common and extensive in patients on dialysis [15]. Indeed, in 1996, Braun *et al.* [43] showed high levels of CAC in patients on long-term haemodialysis, with a mean score of 4290 Agatson Units. As a consequence, the predictive power of CAC scoring in patients with kidney failure is poor [44–46]. Coronary CT angiography has been shown to be useful in diagnosing coronary artery stenosis in the general population [47]. However, the requirement to administer nephrotoxic contrast dye, and the high prevalence of severe CAC obscuring the contrast-filled coronary arterial lumen severely limit its use in patients with kidney failure [35].

Value of screening for coronary artery disease in asymptomatic patients

There is no evidence showing that screening for coronary artery disease in asymptomatic patients with kidney failure improves outcomes. Even in the general population the evidence is weak. Several randomized controlled trials (RCTs) have been conducted in patients with diabetes mellitus, another population at high risk of asymptomatic coronary artery disease [48]. The largest of these is the Detection of Ischaemia in Asymptomatic Diabetics study, in which 1123 asymptomatic participants with Type 2 diabetes were randomized to either adenosine-stress nucleotide myocardial perfusion imaging or medical therapy [49]. There were no differences in cardiac events between groups [hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.45–1.1; $P = 0.14$]. Similar findings were observed in the FACTOR-64 study, which randomized 900 asymptomatic participants with Type 1 or 2 diabetes to either CT coronary angiography or optimal medical care [50]. There was no difference between the two groups for the primary outcome of all-cause mortality, non-fatal MI or unstable angina requiring hospitalization (HR 0.80, 95% CI 0.49–1.32; $P = 0.38$), nor for the secondary outcome of major adverse CV events (MACEs; HR 1.15, 95% CI 0.60–2.19;

Table 1. Key RCTs and observational studies published since 2020

Study	Study design	N	Outcomes	Notes
RCTs				
Maron *et al.* (2020) ISCHEMIA Trial [28]	Patients with stable coronary disease with moderate to severe ischaemia randomized to an initial invasive strategy of coronary angiography and revascularization or medical therapy alone	5179 (2588 invasive strategy; 2591 conservative strategy)	All-cause mortality or non-fatal MI occurred in 318 patients in the invasive strategy group and 352 patients in the conservative strategy group after a median follow-up of 3.2 years (aHR 0.93, 95% CI 0.80–1.08)	eGFR >30 mL/min/1.3 m^2
Bangalore *et al.* (2020) ISCHEMIA-CKD Trial [29]	As for ISCHEMIA Trial except all patients had advanced CKD (eGFR <30 mL/min/1.73 m^2 or on dialysis)	777 (388 invasive strategy; 389 conservative strategy)	All-cause mortality or non-fatal MI occurred in 123 patients in the invasive strategy group and 129 patients in the conservative strategy group after a median follow-up of 2.2 years (aHR 1.01, 95% CI 0.79–1.29)	Incidence of AKI, death or intuition of dialysis in patients who were not receiving dialysis at baseline was higher in the invasive strategy group
Herzog *et al.* (in press) *Post hoc* analysis of ISCHEMIA-CKD trial [30]	Analysis of subset of patients listed for kidney transplantation	194	All-cause mortality or non-fatal MI occurred in 27/94 (28%) of those in the invasive strategy group and 30/100 (30%) in the conservative strategy group (aHR 0.91, 95% CI 0.54–1.54)	
Observational studies				
Deak *et al.* (2020) [31]	Retrospective study of the implementation of a comprehensive screening programme for CV disease in potential KTR implemented in 2007 in Austria	551 KTR	No difference in 2-year occurrence of MACE 2003–07, 2008–11 and 2012–15	Significantly more cardiac CTs and coronary angiograms performed after 2007 Age of KTR constant in contrast to increasing age of KTR in other countries
Nimmo *et al.* 2021 [32] ATTOM Study	National UK prospective cohort of KTR between 2011 and 2017 Cohort divided into those that did or did receive CV screening before transplantation	1760 KTR (880 KTR in each group after PSM)	No difference in MACE at 90 days, 1 year or 5 years after transplantation	Proportion of patients undergoing CV screening varied widely between centres 5–100%
Kanigicherla *et al.* (2020) [33]	Single-centre retrospective analysis of CV screening in potential KTR 2009–14	1053 evaluated for kidney transplantation	Non-invasive CV screening added limited benefit and was not associated with death or MACE in listed patients	CV screening contributed to significant delays in transplant listing Transplantation was the most significant factor associated with improved outcomes
Studies in progress				
Ying *et al.* (2019) CARSK Trial [18]	Randomized 1:1 to either repeated screening for coronary artery disease or to no further screening after listing	3306 adults active on kidney transplant waiting list	Not applicable	Results not expected until 2025 at the earliest

ATTOM, Access to Transplant and Transplant Outcome Measures Study.

P = 0.68). A meta-analysis of these two [49, 50], and a further three [51–53] RCTs published in 2017 [54] concluded that there were no differences between the non-invasive coronary artery screening and control groups in all-cause mortality (RR 0.97, 95% CI 0.66–0.95), cardiac events (RR 0.72, 95% CI 0.49–1.06), non-fatal MI (RR 0.65, 95% CI 0.41–1.02), hospitalization for heart failure (RR 0.66, 95% CI 0.33–1.10) and myocardial revascularization (RR 1.08, 95% CI 0.83–1.41). A subsequent meta-analysis of the

same five trials in 2018 also concluded that non-invasive coronary artery screening did not decrease the individual outcomes of all-cause death, cardiac death, non-fatal MI and hospitalization for heart failure [55]. However, they did conclude that non-invasive coronary artery screening reduced a composite outcome of cardiac events consisting of cardiac death, non-fatal MI, unstable angina and hospitalization for heart failure (RR 0.73, 95% CI 0.55–0.97). This positive result was driven by non-significant decreases in non-fatal MI and hospitalization for heart failure and was not associated with improved patient survival over the mean follow-up of over 4 years. The CT Coronary Angiography for the Prevention of MI (The SCOT-HEART2) trial (NCT04156061) is re-examining the value of screening high-risk subjects by CT coronary angiography and aims to complete in 2027. However, in common with previous trials, it excludes patients with advanced kidney disease.

Value of revascularization in stable ischaemic heart disease

Patients without CKD

When severe ischaemia due to coronary artery disease is found in potential transplant recipients, there is often pressure to revascularize and reduce myocardial ischaemia and improve prognosis. Recent trial data have, however, made the value of this approach highly questionable even in symptomatic chronic stable coronary disease. Several studies have tested the incremental effect of revascularization in addition to medical therapy [56–58]. They have consistently failed to show a significant reduction in either death or incidence of MI. For example, in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial, 2287 participants with objective evidence of myocardial ischaemia and significant coronary artery disease were randomized to undergo percutaneous coronary intervention (PCI) and optimal medical therapy or optimal medical therapy alone [56]. While PCI effectively reduced ischaemia, there were no differences in major CV outcomes between groups. These findings were consistent with previous smaller studies of PCI showing a reduction in angina symptoms but no reduction in death or MI [59]. Commonly postulated explanations for this include that there is only a minority of patients with moderate to severe ischaemia for whom revascularization might have been beneficial, and recruitment bias, as the angiographic evidence of obstructive coronary artery disease prior to study entry might have led to the exclusion of patients with 'high-risk' anatomical features .

To address this, The Initial Invasive or Conservative Strategy for Stable Coronary Disease (ISCHAEMIA) trial was set up to address whether adding cardiac catheterization and revascularization when feasible to medical therapy is beneficial in patients with stable coronary artery disease and moderate or severe ischaemia without left main stem disease [28]. The trial enrolled 8518 patients of which 5179 were randomized, making it the largest study of this type to date. Patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 were excluded. This large (US$100 million) trial showed no difference in the primary outcome of CV death, MI, hospitalization for unstable angina, heart failure or resuscitated cardiac arrest either at 6 months or 5 years of follow-up. Furthermore, the amount of ischaemia at baseline was of no value in predicting treatment effect. These results led to a major paradigm shift in the management of coronary artery disease. It has become evident that while the extent of chronic myocardial ischaemia is associated with coronary risk, it is not causative, and correction of ischaemia does not reduce risk. The extent of ischaemia is merely a surrogate for the extent of coronary artery disease, plaque burden and the risk of MI, but is not a direct cause of CV mortality.

Patients with CKD

The same questions were examined in patients with advanced kidney disease in the ISCHEMIA-CKD trial, which followed an identical protocol to the ISCHEMIA trial and enrolled 802 patients, of which 777 patients had advanced CKD, defined as an eGFR <30 mL/min/1.73 m^2, and stable coronary artery disease with moderate to severe ischaemia [29]. Of these, 404 were on dialysis at enrolment. At a median follow-up of 2.2 years, the primary outcome event, a composite of death and non-fatal MI, occurred in very similar numbers of patients: 123 in the invasive strategy group (of whom 85% had undergone angiography and 50% revascularization, mainly by PCI) and 129 in the conservative strategy group (31% angiography and 20% revascularization). Similarly, the key secondary outcome of CV death, non-fatal MI or hospitalization for unstable angina, heart failure or resuscitated cardiac arrest, occurred in 132 patients in the invasive strategy group and 138 patients in the conservative-strategy group [adjusted HR (aHR) 1.01, 95% CI 0.79–1.29]. Thus, in patients with advanced kidney disease, there is also strong evidence of lack of prognostic benefit from revascularization for stable coronary artery disease.

Value of revascularizing to reduce perioperative mortality

It might be argued that the stress of transplant surgery with its increased risk of acute coronary events might unmask the value of pre-procedural revascularization for stable coronary disease. The value of coronary artery revascularization as a method of reducing perioperative mortality for non-cardiac surgery is, however, also unproven. The Coronary Artery Revascularization Prophylaxis (CARP) study randomized 510 patients at increased risk for perioperative cardiac complications (based on combined clinical risk factors) and clinically significant coronary artery disease (based on non-invasive stress testing) to either revascularization [PCI with bare-metal stents in 59% and coronary artery bypass graft (CABG) in 41%] or no revascularization before high-risk vascular surgery (expanding abdominal aortic aneurysm in 33%, advanced lower extremity arterial occlusive disease in 67%) [60]. Within 30 days of vascular surgery, neither mortality (3.1% in the coronary revascularization group and 3.4% in the control group) nor risk of MI (11.6% in the coronary revascularization group and 14.3% in the control group) were significantly different. Longer term follow-up also failed to show benefit; at a median of 2.7 years, mortality was 22% in the coronary vascularization group and 23% in the control group. Of relevance to a population gaining prognostic benefit from a surgical procedure, the median time to surgery was markedly delayed at 54 days in the coronary revascularization group compared with only 18 days in the control group ($P < 0.001$).

Evidence of screening for, or revascularization of, stable coronary artery disease to improve outcomes in kidney transplant recipients

A single RCT conducted over 30 years ago has examined outcomes of prophylactic revascularization in prospective kidney

transplant recipients (KTRs) [61]. Over a 3.5-year period from February 1987 to August 1990, 26 asymptomatic patients with Type 1 diabetes mellitus who had a coronary angiogram as part of their work-up for kidney transplantation listing and who were found to have a left ventricular ejection fraction (LVEF) >35% and a coronary artery lesion felt to be suitable for revascularization agreed to be randomized to either medical therapy (aspirin and a calcium-channel blocker) or revascularization (PCI if possible or CABG). Ten of the 13 patients allocated to medical management suffered a cardiac endpoint (two fatal MI, seven non-fatal MI and one unstable angina) whereas only 2 of the 13 patients randomized to revascularization suffered a cardiac endpoint (both non-fatal MI). This study was terminated early because of slow recruitment and imbalanced outcomes. However, despite the low numbers of participants (only 26) and the now outdated cardioprotective medical therapy, this study has had, and continues to have, a major impact on current protocols for cardiac assessment for potential KTRs. This is despite very significant improvements in the medical management of coronary artery disease over the past two decades [14].

A *post hoc* analysis of the ISCHEMIA-CKD RCT reported that 25% ($n = 194$) of the cohort were on a kidney transplant waiting list, of which 51 (26%) received a kidney during the follow-up period of 2.4 years [30]. Among those listed for transplant, the primary outcome of all-cause mortality or non-fatal MI occurred in 27/94 (28%) of those in the invasive strategy group and 30/100 (30%) in the conservative strategy group (aHR 0.91, 95% CI 0.54–1.54) [30]. These data do not support the use of routine coronary angiography or revascularization in patients with CKD and myocardial ischaemia on stress testing listed for kidney transplantation.

Although there are no other RCTs examining whether more screening for asymptomatic coronary artery disease in prospective KTR improves survival or reduces CV events after transplantation, two important observational studies have reported recently. An intensive CV risk stratification protocol implemented nationwide in Austria in 2007 resulted in over 50% of transplanted patients having a coronary angiogram but failed to demonstrate any improvement in patient survival or a reduction in coronary events in patients transplanted directly after (2008–11) or 5 years after (2012–15) compared with historical data (2003–07) [31, 33]. A prospective study of 2572 UK KTR who received a transplant in 2011–17 in 18 centres found that 51% underwent cardiac screening pre-transplantation with screening by centre varying from 5% to 100% [32]. The incidence of major MACEs was 0.9%, 2.1% and 9.4% at 90 days, 1 year and 5 years after transplantation, respectively. After propensity score matching (PSM) based on the presence or absence of screening (880 KTR per group) there was no statistically significant association between screening and MACE at 90 days (HR 0.80, 95% CI 0.31–2.05), 1 year (HR 1.12, 95% CI 0.51–2.47) or 5 years (HR 1.31, 95% CI 0.86–1.99). Based on these data the authors called for the practice of screening of transplant recipients to be reviewed.

To summarize so far, non-invasive testing for coronary artery disease in asymptomatic populations has never been shown to reduce adverse outcomes in the era of modern medical CV risk reduction in either patients from the general population or those with kidney failure. Furthermore, there is no evidence in any setting, including KTRs, that revascularizing stable coronary artery disease improves survival. These data have led to a major reappraisal of the natural history of coronary artery disease in which it is now clear that while chronic myocardial ischaemia is associated with mortality in coronary artery disease, it is not causative. The detection and relief of chronic ischaemia is not associated with survival benefit, while drugs that prevent acute ischaemia due to plaque rupture/erosion and thrombus formation are highly effective. The primary role of revascularization procedures is the relief of disabling symptoms. Given this realization, it is hardly surprising that two recently published studies of screening for myocardial ischaemia in KTR demonstrated no benefit to either patient survival or reduced CV events. This is reflected in the 2020 Kidney Disease: Improving Global Outcomes guidelines, which recommend asymptomatic patients do not undergo revascularization solely to reduce perioperative risk [13].

Evidence that conventional approach to cardiac screening causes harm

The value of detection, and subsequent invasive intervention of asymptomatic coronary artery disease, is highly questionable as part of a cardiac screening programme for patients waiting to be listed for a kidney transplant, and further, there is evidence of a potential risk of harm.

Interventions themselves cause harm

There is increasing evidence that coronary interventions may be harmful because they delay treatment and because there is a risk of procedural mortality, stroke and MI. For example, in the CARP study, 10 patients in the intervention arm, and 1 in the non-intervention arm, died before their vascular surgery [60]. The incidence and consequences of procedural MI in PCI and CABG are highly sensitive to definition and hotly debated, but there is no doubt that large MIs with clinical consequences do occur, probably in 1–2% of elective cases [62]. In the ISCHEMIA RCT, there were more procedural MI and hospitalizations for heart failure in the intervention arm; early procedural MIs occurred in 2.6–7.7% (according to definition) of the invasive group and accounted for 20% to >40% of MIs in the trial, again according to definition [28]. In the ISCHEMIA-CKD trial, there was a 3-fold increase in stroke in the intervention arm [29]. Finally, the risk of major cardiac surgery such as CABG in dialysis patients is high with perioperative mortality in the region of 8% [63].

In addition, the use of contrast agents is associated with acute kidney injury (AKI). In the ISCHEMIA-CKD RCT, AKI precipitated the periprocedural initiation of dialysis in 2.1% of participants in the interventional arm [29]. Registry data from the USA between 2009 and 2011 reported that PCI precipitated AKI in 4.3% of patients with an eGFR <30 mL/min/1.73 m^2, of whom 26.1% required dialysis [64]. Furthermore, the use of radiological investigations in many patients is not without its problems, exposing patients to unnecessary radiation [65].

Delays in transplantation

There is consensus that pre-emptive transplantation and early transplantation of suitable patients improve clinical outcomes [66, 67]. Waiting for non-invasive tests, waiting for a decision on management of detected asymptomatic coronary artery disease, waiting for coronary angiography and waiting for potential interventions may all delay transplant listing by several months, if not years. This is especially pertinent in patients potentially suitable for pre-emptive transplantation in which coronary angiography is often delayed until they have started dialysis. In addition, coronary artery stenting will often

mandate dual antiplatelet treatment for at least 6 months further delaying transplant listing. A recent meta-analysis found that the risk of a major haemorrhagic complication in the perioperative period after kidney transplantation was increased by >50% in KTRs receiving dual rather than single antiplatelet therapy (RR 1.58, 95% CI 1.19–0.09; P = 0.001) [68].

Patients denied transplantation

There is emerging evidence that having a positive non-invasive cardiac stress test results in an otherwise potentially suitable patient never being listed for transplantation [69]. Patients with CKD and coronary artery disease are consistently less likely to be revascularized either because they are considered at higher risk of complications or because they have diffuse coronary artery disease without suitable targets for intervention [17, 18]. Therefore, asymptomatic potential KTRs who could benefit from transplantation are denied this treatment because of a positive screening test. This is more than a theoretical consideration. For example, during the implementation of a 'stricter' CV screening process in Austria, the median age and prevalence of comorbidities of KTRs in that country were unchanged over a 13-year observation period [31]. Elsewhere, international trends were those of an ageing KTR population [70–74].

The very considerable differences in screening practices both within [33] and between countries raise concern about whether patients in many centres are being denied access to a kidney transplant without supportive evidence while patients with similar characteristics in other centres are wait-listed promptly [75]. In the UK, a recent study found that the proportion of KTRs that had undergone CV screening with either a stress test or coronary angiogram ranged between 5% and 100% [33]. An important and uncomfortable question is raised: how many patients in the centres with high screening rates were, potentially unnecessarily, denied access to transplantation [76]?

Ethnic minority patients and low socioeconomic groups disproportionately affected

Screening for occult coronary artery disease is arguably another barrier to kidney transplantation and barriers have a disproportionate effect on the disadvantaged [76]. Even in the UK, with a well-established universal healthcare system that should overcome several of the socioeconomic barriers to transplantation found in other healthcare systems such as the USA, although patients from ethnic minorities and lower socioeconomic backgrounds have a higher incidence of end-stage kidney disease (ESKD) [4, 6, 77] they are less likely to be wait-listed for transplantation [78–81]. Reducing, or indeed removing, the need for CV screening may serve to improve equity in access to transplantation.

Current trials

In a survey of 15 Canadian Transplant centres conducted to inform the design of the Canadian-Australasian Randomized trial of Screening Kidney transplant candidates for coronary artery disease (CARSK) trial, 13 centres (87%) responded that screening for coronary artery disease was essential prior to transplant listing and would therefore not support randomization of patients into a trial of screening versus no screening before listing [18]. However, all units were prepared to randomize patients to continued screening versus no further screening for coronary artery disease after wait-listing. This was based on the greater variation in practice in terms of timing and frequency of screening, and the greater cost of screening patients multiple times after listing.

The CARSK trial will therefore test the hypothesis that eliminating screening tests for occult coronary artery disease 'after' wait-listing is not inferior to regular screening for the prevention of major adverse cardiac events, defined as the composite of CV death, non-fatal MI, urgent coronary revascularization and hospitalization for unstable angina [18]. Secondary outcomes will include the transplant rate, safety measures and the cost-effectiveness of screening. Enrolment of 3306 patients over 3 years with a follow-up period of 5 years after wait-listing and 1 year after transplantation. Although this study will provide useful information when completed, unfortunately, it will not answer the more fundamental question of whether screening for coronary artery disease in asymptomatic patients with kidney failure results in net benefit or harm. The CARSK study is facing problems with recruitment and is unlikely to complete before 2025 [10, 82].

The way forward

Small steps

For all the reasons so far listed, we suggest that there is an imperative to begin to reduce unnecessary screening and interventions for asymptomatic coronary artery disease with the aim of improving access (and equality of access) to transplantation for all patients with kidney failure.

It is recognized that the current screening practices are not only engrained in the current practice of transplanting centres across developed countries but are also advocated in national and international guidelines, albeit on the basis of expert opinion rather than an evidence base [13, 21, 23–27]. In the absence of a landmark randomized clinical trial conclusively demonstrating the lack of benefit of the current system, change is likely to come in small steps, carefully monitored and audited, perhaps through regional and national registries, to ensure safe practice. As such we propose small, incremental changes to current cardiac transplant work-up protocols for patients referred for kidney transplant listing (Figure 1). The overarching aims are to minimize harm, minimize delay to listing and improve access to transplantation for all patients.

The initial small steps would revolve around reducing unnecessary blanket screening by incorporating a measure of functional capacity to allow more targeted screening of candidates regardless of age as recommended by the American College of Cardiology and American Heart Association as well as the European Society of Cardiology and European Society of Anaesthesiology Guidelines [83, 84]. Irrespective of the presence or absence of coronary artery disease, high functional capacity is a well validated predictor of a good prognosis [85]. Functional capacity can usually be estimated from activities of daily living and is expressed in terms of metabolic equivalents (METS) [86], where one MET is the resting or basal oxygen consumption of a 40-year-old, 70-kg man. An exercise capacity of >10 METs indicates an excellent survival group, despite the extent of coronary artery disease or left ventricular function [86]. In the literature, functional capacity is often classified as excellent (>10 METs), good (7–10 METs), moderate (4–6 METs), poor (<4 METs) or unknown [83, 84]. Perioperative cardiac and long-term risks are increased in patients unable to perform 4–6 METs of work during daily activities. Examples of activities associated with <4 METs are slow ballroom dancing, golfing with a cart, playing a musical

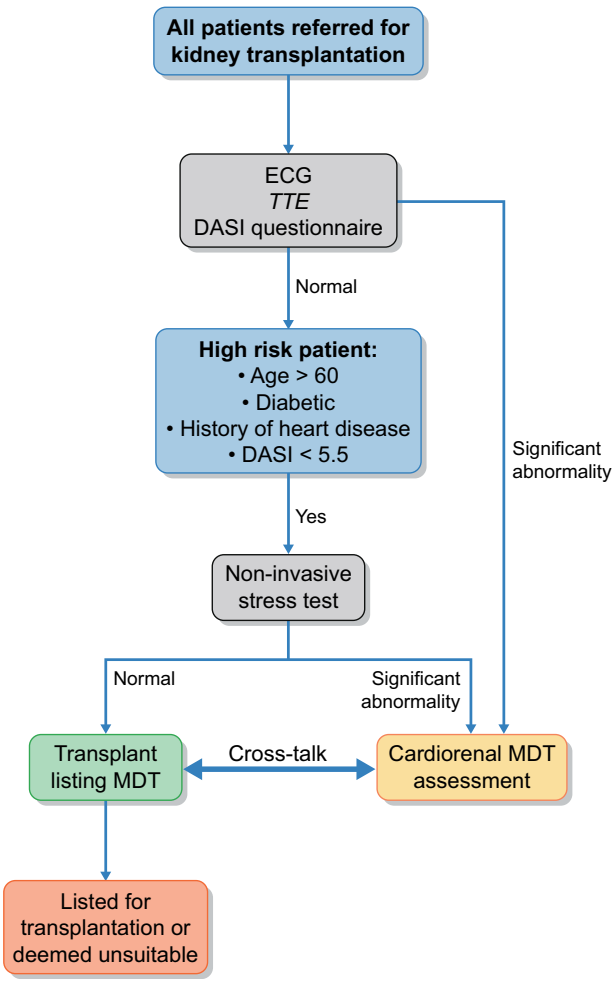

FIGURE 1: Proposed pathway for CV assessment of potential KTRs with suggested areas for gradual relaxation of criteria. Patients with ESKD are assessed by their physician to be potentially suitable candidate to receive a kidney transplant have some basic investigations including an ECG, chest X-ray and TTE, and complete a DASI questionnaire with their physician. Referral to Cardiorenal MDT is made if: any cardiac history; any symptoms thought to be caused by ischaemic or structural heart disease; DASI score <5.5; ECG shows a significant abnormality not commonly seen in patients with ESKD such as LVH, lateral T wave inversion or left axis deviation; TTE shows moderate-to-severe valvular dysfunction, LVEF <35%, regional wall abnormalities, high risk of pulmonary hypertension or other incidental findings causing concern including right ventricular dysfunction, intra-cardiac mass or pericardial effusion. After discussion at Cardiorenal MDT, patients can either be referred back for transplant listing with no cardiac contra-indication to transplantation; further investigations arranged including perfusion imaging/stress testing; further clinical assessment in a combined cardiorenal clinic or a decision made that patient is unsuitable for transplant listing on cardiac grounds and is unlikely to ever be so. There are multiple points on this pathway that can gradually be altered to reduce the need for cardiac investigations. These are in *italics* and include need for everyone to have a TTE; cut-off age of 60 years; cut-off age for diabetics; DASI score. ECG, electrocardiogram; LVH, left ventricular hypertrophy; MDT, multidisciplinary team; TTE, transthoracic echocardiogram.

instrument and walking at ~2–3 mph. Examples of activities associated with >4 METs are climbing a flight of stairs or walking up a hill, walking on level ground at 4 mph and performing heavy work around the house.

Functional status can also be assessed more formally by activity scales, such as the Duke Activity Status Index (DASI; Table 1) [87, 88] and the Specific Activity Scale [89]. In 600 consecutive patients undergoing non-cardiac surgery, perioperative myocardial ischaemia and CV events were more common in those with poor functional status (defined as the inability to walk four blocks or climb two flights of stairs) even after adjustment for other risk factors [86]. The likelihood of a serious complication was inversely related to the number of blocks that could be walked ($P = 0.006$) or flights of stairs that could be climbed ($P = 0.01$). Analyses from the American College of Surgeons National Surgical Quality Improvement Programme dataset have shown that dependent functional status, based on the need for assistance with activities of daily living rather than on METs, is associated with significantly increased risk of perioperative morbidity and mortality [90, 91].

While we acknowledge that many candidates for a kidney transplant have poor functional status for a variety of reasons, those with good status should be rapidly and inexpensively assessed and listed for transplantation without further investigation for myocardial ischaemia. The indication for such testing would then fall more appropriately on those at greater risk. If tests of myocardial ischaemia are used in this group, decisions about treatment including coronary revascularization need to be taken with full appreciation of current trial data on outcomes after procedures and the risk of such procedures in dialysis patients. In many cases of extensive coronary artery disease, the evidence base would suggest medical management rather

Box 1: Summary of why the current approach to screening for occult coronary artery disease in potential KTRs is flawed with the level of evidence supporting this assertion

Limitations of the conventional approach to cardiac screening

1. Problems with tests for myocardial ischaemia in potential transplant candidates
   a. Reduced sensitivity and specificity of non-invasive stress tests in patients with kidney failure
   b. Similar proportions of patients will experience an adverse coronary event after an abnormal screening result compared with a normal result while most patients with an abnormal test do not have adverse cardiac outcomes
2. No evidence of value of screening for coronary artery disease in asymptomatic patients
   a. Consistent findings in RCTs and meta-analyses in patients without CKD
3. No evidence of benefit of revascularization in stable ischaemic heart disease
   a. RCTs in patients without CKD including the ISCHEMIA RCT
   b. ISCHEMIA-CKD RCT in patients with advanced CKD and ESKD
4. No evidence that revascularization reduces perioperative mortality
   a. RCTs in patients without CKD
5. No evidence that screening for, or revascularization of, stable coronary artery disease improves outcomes in KTRs in the current era
   a. *Post hoc* analysis of ISCHEMIA-CKD RCT
   b. Large nationwide observational studies

Evidence that current conventional approach causes harm

1. Interventions themselves cause harm
   a. Increased risk of procedural mortality, stroke and MI reported in RCTs
   b. Increased risk of procedure-related AKI reported in RCTs
   c. Increased use of ionizing radiation
2. Delays in transplantation
   a. Observational studies
3. Patients denied transplantation
   a. Observational studies
4. Ethnic minority and low socioeconomic groups disproportionately affected by barriers to transplantation
   a. Observational studies

than revascularization. We should beware of subjecting patients to procedures that reduce myocardial ischaemia and reassure treating clinicians, but which do not appear to be associated with either prognostic benefit or reduced operative risk.

The cardiorenal multidisciplinary team

The bi-directional links between kidney disease and CV disease have long been established, as have the calls for cardiologists and nephrologists to develop expertise in cardiorenal medicine and work together to provide optimal management of cardiorenal patients [92, 93]. Such teams have been reported to reduce the number of investigations and improve the cost-effectiveness of pre-wait-listing CV screening with no increase in peri-transplant CV events [94, 95]. As such, these cardiorenal teams and specialists would be ideally placed to oversee the gradual and sustained changes in practice. The team at the Queen Elizabeth Hospital Birmingham UK, a transplant centre serving almost 10% of the UK population, has developed a protocol (Figure 1) and instituted bi-weekly meetings to review the CV risk stratification data on all candidates referred for transplantation.

CONCLUSIONS

The current situation regarding CV screening of prospective KTR by the detection of myocardial ischaemia is untenable even though it is supported by several guidance documents. It is wasteful, harmful, discriminatory and not supported by the available evidence (Box 1). There are, however, no current RCTs addressing this topic and future studies are going to come up against significant resistance. Change is likely to come from small, staged and progressive changes in practice that are carefully monitored using national and international registries. Closer integrated working between nephrologists and cardiologists is likely to be key to the successful and safe continuation of transplantation programmes. Screening strategies should be in place to improve the outcomes of our patients, not to serve the interests of the professionals caring for them.

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CONFLICT OF INTEREST STATEMENT

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