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Cardiac screening prior to renal transplantation – good intentions, rather than good evidence, dictate practice.

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Running title: Cardiac screening prior to transplantation- intentions versus evidence

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Abstract

Cardiovascular disease is the leading cause of death in kidney transplant recipients in many transplant registries. An analysis of transplant recipients from the United Kingdom using propensity score matching suggests there are limited or no benefits to cardiovascular screening prior to listing. We suggest that short of a randomised controlled trial in this area, these data are enough to suggest transplant centres should reflect on their current protocols for cardiovascular workup required prior to transplantation.

Main article

The rationale for screening for coronary artery disease (CAD) in individuals being considered for renal transplantation is clear. Patients with advanced chronic kidney disease (CKD) are at increased cardiovascular risk with a high incidence of significant CAD even in the absence of symptoms¹. Kidney transplantation is associated with a relatively high peri-operative cardiovascular mortality (1.1% compared to 0.7% for other major abdominal surgery)² and there is a higher risk of cardiovascular events in the first year post-transplant compared to patients remaining on the waiting list³. However, the benefits of screening patients for CAD remains unproven, while negative consequences of screening are abundant: financial cost, radiation and radio-iodine contrast exposure, time delay in listing (and consequent reduction in proportion of patients receiving pre-emptive transplants), and the considerable uncertainty regarding interpretation of results and the complications of any resulting interventions.

In this issue of *Kidney International*, Nimmo *et al* ⁴ use propensity score matching (PSM) to compare the incidence of major adverse cardiovascular events (MACE) in patients who underwent screening for CAD prior to renal transplantation compared to those who did not. Screening was defined as cardiac stress testing or coronary angiogram. From a prospective cohort of 2572 renal transplant recipients, 880 patients who underwent screening were matched to 880 individuals who did not. They found no difference in MACE at 90 days, 1 year or 5 years, concluding that screening for asymptomatic CAD does not reduce the risk of MACE following kidney transplant.

This study is observational and limited by the accepted caveats of PSM ⁵. Nevertheless, in the absence of a randomised controlled trial (RCT), this prospective study of a well-defined cohort, with robust outcome assessment, is the most reliable evidence to date on which to inform decisions regarding screening for asymptomatic CAD in pre-transplant patients.

These results support the low incidence of MACE in the early post-transplant period in appropriately selected patients. At 0.9%, most clinicians and patients would find this acceptable. Defining an unacceptable level of risk is challenging, especially as those with greatest cardiovascular risk achieve the greatest risk reduction from transplantation. The authors find that age, male sex, and history of previous ischaemic heart disease emerge as clear risk factors for post-transplant MACE. This should inform clinicians to allow more personalised risk discussions and shared decision making with patients. Inevitably, it will impact on discussions regarding the balance of societal utility, individual benefit and the utilisation of a scarce resource.

The observed variability in screening practices between centres was vast: ranging from 5 to 100% of transplanted patients undergoing screening. This finding alone should challenge the nephrology and transplant community. Our patients are not receiving equal treatment. We believe that these results are sufficient to force centres that screen for asymptomatic CAD before transplant listing to ask themselves why?

Cardiovascular screening is a barrier to renal transplantation. Barriers have a disproportionate effect on the disadvantaged. A previous publication ⁶ from the same data-set demonstrates multiple factors contributing to inequity of access to transplantation. Interestingly, in the present study, white ethnicity and higher socioeconomic status were associated with increased likelihood of undergoing screening (amongst patients successfully listed for transplant). Removing unnecessary cardiovascular screening may improve equity of access to transplantation.

It is vital to keep the findings of *Nimmo et al* in context. Their study refers only to screening for CAD. The role of transthoracic echocardiography (which is radiation-free, relatively inexpensive and widely available) to screen for structural and functional cardiac disease might have a more widely applicable role in pre-transplant assessment. The results do not apply to symptomatic patients. It is not clear in this study how the investigations were deemed to be 'screening' and not driven by symptoms. These results refer to low/moderate risk patients only (see Figure 1). Across the entire cohort of 2572 patients (i.e. prior to PSM), there was a

significant increase in MACE at 5 years in those who underwent screening compared to those who did not (10.1% vs 5.3%). This is explainable by discrepancies in cardiovascular risk factors between these cohorts. Consequently, patients with greater cardiovascular risk were less likely to be matched by propensity scoring and were excluded from analysis (including 82 patients who experienced MACE within 5 years). While we are reassured by the sensitivity analyses performed, the authors accept that the rising incidence of MACE over 5 years in the screened group, even after PSM, opens the possibility that there is residual confounding from unmeasured indication bias between the groups. As such, the lack of difference in early MACE may be due to an uncaptured degree of protection attained through screening. The nature of the dataset means it was not possible to examine patients considered for transplantation but who were excluded following positive cardiac screening. This is where true equipoise exists. Does screening allow the exclusion of (and potentially risk reduction in) those who would have unacceptably high peri-operative cardiovascular risk? Or does it falsely deny higher risk patients from the treatment from which they stand to gain the most benefit?

We believe these results are sufficient to state that universal screening for CAD in low-moderate risk asymptomatic patients being considered for renal transplantation is not justified. We believe there is equipoise in relation to how to manage patients at higher cardiovascular risk and call for a RCT. Nimmo *et al* discuss the challenges in conducting such a trial, but there are data to support its feasibility ⁷. We await the results of the ongoing CARSK trial ⁸ addressing whether eliminating annual non-invasive cardiac screening is non-inferior to annual screening in transplant waitlisted

patients. However, this trial will not inform if cardiac screening is beneficial prior to waitlisting. The closest analogous trial from which we can infer evidence is ISCHEMIA-CKD⁹. This RCT examined 777 patients with advanced CKD (estimated glomerular filtration rate < 30 ml/min/1.73m²) who had stable angina and evidence of inducible ischaemia on stress testing to either medical therapy or invasive angiography and revascularisation. The trial found no difference in death or non-fatal myocardial infarction, but a greater incidence of stroke in the intervention group. The trial population is broadly comparable to those being assessed for kidney transplantation: 53% were on dialysis and median eGFR in the remainder was 23 ml/min/1.73m². Although the participants in ICHEMIA-CKD were not subsequently exposed to a major physiological stress such as transplant surgery, they were a higher risk cohort, in that ischaemia-CKD studied patients with both symptoms and inducible ischaemia, while standard practice prior to transplantation in many centres includes screening patients with neither. However, we cannot simply extrapolate the results of ISCHEMIA-CKD to the role of stress testing prior to renal transplantation without a RCT. The results of ISCHEMIA-CKD should not promote complacency with regards the very real risk of MACE in patients with CKD but encourage optimal medical management of symptomatic but stable patients. Notably, ISCHEMIA-CKD excluded patients with left ventricular ejection fraction of <35% and those whom left main stem disease was known (from previous angiogram or coronary CT scan) or suspected (based on physician discretion which is not without its own inherent bias). It could be argued that these two (easily determinable) criteria should become indications for cardiac screening before transplantation. Any future trial will have to be large and multi-centre. The CARSK trial aims to enrol 3306 participants, while previous sample size calculations

exploring cardiac screening prior to wait-listing estimated between 1700 - 4000 participants would be needed for 80% power depending on if a 20 or 30% reduction in MACE was clinically relevant ⁷. When compared to the 1760 participants in the present observational study, it is plausible that the present sample could not detect a small effect size. However, the absolute risk is low, screening has consequences and transplantation brings many advantages beyond simply reduced cardiovascular risk. Therefore, the minimal clinically relevant risk reduction is open for debate.

The results by Nimmo *et al*, while observational, are the most robust data available and are sufficient to support that routinely screening asymptomatic, unselected patients for CAD prior to renal transplantation is not justified. There are major gaps in our knowledge regarding assessing and managing peri-transplant cardiovascular risk. RCTs, while challenging, are essential to determine how we should manage patients with higher cardiovascular risk who are otherwise appropriate for renal transplantation. The risk of post-transplant MACE is genuine and we should not confuse this with the apparent futility of screening. Undoubtedly, there are some patients where the peri-transplant cardiovascular risk is unacceptably high. Within this population, some are likely to be asymptomatic and a small number may benefit from intervention to reduce their risk. However, it is not yet clear how to identify these patients, without disadvantaging many more who derive no benefit from screening. If we relax pre-transplant cardiovascular assessment too far, we will inevitably cause harm. But as current practice stands, for the majority of patients cardiac screening is a well-meaning search for a risk that we cannot reduce whilst indistinguishably depriving more patients than it protects.

Figure Legend

Figure 1: Flow chart highlighting the patient population to which the results of *Nimmo et al* are relevant to. (Diabetes and smoking are included as cardiovascular risk factors on the basis of the existing evidence outside the present study)

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