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Key Points:

Abstract:

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Routine cardiac stress testing in potential kidney transplant recipients is only appropriate in symptomatic individuals: PRO

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The desire for routine cardiac stress testing in asymptomatic kidney transplant candidates is strong. Cardiovascular causes remain the leading cause of death for kidney failure patients, due to traditional and kidney-specific risk factors. The burden of asymptomatic coronary artery disease (CAD) in this high-risk cohort is excessive, with reported prevalence between 37-53% for at least one coronary artery to have a minimum 50% stenosis,\(^1\) and post-transplant immunosuppression has cardio-metabolic side effects. Therefore, advocates for routine cardiac stress testing pre-transplantation justify the strategy by claiming it can; 1) improve counselling and decision-making process for patients and professionals; 2) facilitate intervention on asymptomatic lesions to reduce risk of peri- or post-operative harm, and/or 3) exclude very high-risk candidates from transplantation surgery to prevent wastage of a valuable resource due to early mortality risk. However, arguments have challenged these assertions\(^2\) and the subsequent publication of ISCHEMIA-CKD provides further validation to support a laissez-faire approach.

ISCHEMIA-CKD is a multi-center randomized controlled trial (RCT) that enrolled 777 patients with advanced kidney disease (defined as estimated glomerular filtration rate [eGFR] of <30 ml/min/1.73 m\(^2\) or receipt of dialysis) and moderate or severe myocardial ischemia.\(^3\) After a median follow up of 2.2 years, the investigators did not find any evidence that an initial invasive strategy, as compared with an initial conservative strategy, reduced the risk of death or nonfatal myocardial infarction or angina-related health status. However, the invasive strategy was associated with higher incidence of stroke and higher incidence of death or initiation of dialysis compared with the conservative strategy.
Combining ISCHEMIA-CKD with other revascularization RCTs, a recent systematic review and meta-analysis pooled empirical data from fourteen studies including 14,877 patients with 64,678 patient-years of follow-up. Its principal findings demonstrated routine revascularization was not associated with improved survival, but was associated with reduced risk of non-procedural myocardial infarction, unstable angina and greater freedom from angina, at the expense of higher rates of procedural myocardial infarction. Data for coronary intervention after kidney transplantation is limited but appears safe in small case series.

ISCHEMIA-CKD is a landmark study for kidney patients, but its publication has not satisfied cardiac test enthusiasts and the trial data has been probed and dissected vociferously to find crumbs of contention. Some critics argue the trial population was low-risk (surprising considering observed three-year event rates were 36.4% and 36.7% per arms) and highly selective (approximately two recruits per center per year), while others highlight differential effect sizes observed for study participants with severe ischemia favoring invasive intervention. Only 13.0% of study participants were on a kidney transplant waiting list and this is a legitimate critique, although the trial was not designed to address this particular question. However, there are other interesting observations buried within ISCHEMIA-CKD. Half of study participants randomized to the invasive-strategy group did not undergo revascularization, most frequently because they did not have obstructive CAD despite positive stress tests. ISCHEMIA-CKD has successfully provided clarity about the failure of invasive strategies for people with advanced chronic kidney disease or kidney failure with asymptomatic CAD and the failure of non-invasive stress test characteristics as a screening tool to facilitate those ineffective interventions. Others have determined an antithetical
conclusion from ISCHEMIA-CKD and other relevant RCTs (see Table 1), which reflects the
dogmatism many clinicians have on this issue.

The fundamental question is what is in the best interest of kidney failure patients? For most
people with kidney failure, in the absence of major contra-indications and regardless of
baseline demographics, kidney transplantation is the best form of therapy as it lowers all-
cause and cardiovascular mortality compared to treatment options like dialysis.\textsuperscript{6} Impaired
kidney function is a strong independent risk factor for cardiovascular disease,\textsuperscript{7} and a
spectrum of disorders with overlapping cardiovascular and kidney disease are associated
with impaired kidney function. Experimental evidence suggests hemodialysis leads to
transient declines in both cerebral blood flow (which correlates with interdialytic cognitive
dysfunction)\textsuperscript{8} and renal blood flow (which correlates with myocardial injury).\textsuperscript{9} If intradialytic
circulatory stress is associated with reduced perfusion in multiple vulnerable organs, then
dialysis is clearly a modifiable risk factor for cardiovascular disease. Removing the need for
dialysis with a working kidney transplant abrogates this risk and contributes to survival
benefits (see Figure 1).

The clinical challenge is translating population-level evidence to high-risk individuals for
personalized decision making. While kidney transplantation is the best form of therapy for
many kidney failure patients, some are more likely to suffer harm than receive benefit.
However, determination of eligibility can lack objectivity and be maligned by perception
bias. While decision making is easy in the presence of absolute or relative contra-
indications, subjective discernments which negatively influence decision making are harder
to overcome. Doctrinaire views of cardiovascular risk impede access to kidney
transplantation and subjective assessments are inferior to objective tools. For example, subjective appraisal of functional capacity before non-cardiac surgery has poor sensitivity or predictive capacity for death or myocardial infarction within 30 days of surgery. In contrast the Duke Activity Status Index (DASI), a standardised questionnaire correlated with gold-standard measures of functional capacity, demonstrates significant adjusted associations with a primary outcome of death or myocardial infarction by 30 days post-surgery in the same study. The caveat is DASI has not been validated in the context of kidney transplantation and exercise tolerance declines with advancing renal dysfunction, which limits interpretation of functional ability.

Arguments can be passionately construed both for and against cardiac screening in asymptomatic kidney transplant candidates, but for many there is significant confusion about the ultimate objective with cardiac testing. Many clinicians cite regulatory pressures rather than perceived patient benefit for their incongruous practice. Advocates of cardiac testing argue symptoms of significant CAD are masked by poor exercise tolerance which could manifest after the stress of kidney transplant surgery, exacerbated in the context of primary non-function or delayed graft function. However, recent epidemiological analyses using propensity-scored cohorts suggest cardiac screening does not predict major adverse cardiovascular events after kidney transplantation. This clinical equipoise should set the stage for an RCT, purposefully designed and adequately powered to determine whether cardiac screening asymptomatic kidney transplant candidates has any clinical benefit. However, logistical challenges and methodological constraints make this an incredibly challenging study to design and/or execute, with considerable costs and numbers required for adequate statistical power. Even if viable in theory, the biggest obstacle in practice will
be selection bias. Persuading apprehensive clinicians to recruit kidney failure patients reflective of real-world cohorts will be a significant challenge. This bias has been demonstrated in clinical trials recruiting kidney failure patients, with participants in multi-center dialysis studies shown to be younger, less co-morbid and with lower mortality rates compared to real-world cohorts.\textsuperscript{13} Therefore, prejudiced enrolment skewed towards lower-risk candidates will diminish any trial outcome and fail to win over sceptics. Ambitious studies like CARSK (http://www.carsk.org) are welcomed and may shed light on the utility of surveillance cardiac testing after joining the waiting list, but the key obstacle for high-risk candidates is joining the waiting list in the first place.

The \textit{aim} of doing something underlies the \textit{purpose} for which we do it or the result that we intend to achieve. As we debate the purpose of cardiac stress testing asymptomatic kidney transplant candidates, we must remind ourselves what aim we are striving to achieve. If our aim is to optimise outcomes for people receiving kidney transplants, then this timorous attitude will restrict access to transplantation. However, if our aim is to optimise outcomes for people living with kidney failure, then this bold attitude will broaden access to transplantation. On the balance of probabilities, more kidney transplant candidates will benefit than come to harm with a laissez-faire approach to cardiac testing. To be clear, this is not a recommendation for reckless behaviour and cavalier transplant activity. Suitability for kidney transplant surgery is important but must be fit for purpose. Assessing, validating and incorporating objective measures to assess fitness for transplant surgery, tailored to a kidney failure cohort, must override subjective bias.
For high-risk cardio-metabolic kidney transplant candidates, communication of the risks and benefits of kidney transplantation, versus the alternative therapy option of dialysis, must acknowledge probabilities and uncertainties. Improved risk communication is essential but requires a supportive regulatory environment where calculated risk is embraced to avoid cautious risk aversion. While post-transplant outcomes may be impacted by increased risk from kidney transplant candidates with significant cardio-metabolic burden, we are ignoring the risk for these high-risk individuals who are denied access to kidney transplantation. As highlighted in a recent perspective; “... we perceive greater risk in acts of commission than in acts of omission; if a patient dies during or after transplantation, it’s the doctor’s responsibility; if the patient dies from organ failure while awaiting a transplant, we can blame the indifference of the universe.” The simple truth is the best treatment for most kidney failure patients with asymptomatic CAD is transplantation, regardless of underlying risk factor characteristics and/or duration. Obstacles to that goal that are based on dogma rather than evidence, like cardiac testing in the absence of significant symptoms, should therefore be abolished.

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**Author Contributions:** Adnan Sharif: Conceptualization; Writing - original draft; Writing - review and editing.
References

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<th>Study</th>
<th>Number (CKD/overall)</th>
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<th>Primary end point</th>
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<th>Main findings</th>
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<td>Bangalore (2020)(^a)</td>
<td>777/777</td>
<td>eGFR &lt;30 m/L/min/1.72 m(^2) or kidney failure (53.4%)</td>
<td>Moderate or severe ischemia defined by site investigators using trial-defined criteria</td>
<td>Composite of all-cause mortality and non-fatal myocardial infarction</td>
<td>Site dependent (nuclear imaging, stress echo, cardiac MRI or exercise test)</td>
<td>Coronary angiogram within 30-days of randomization with PCI or CABG as indicated</td>
<td>No benefit, some harm</td>
</tr>
<tr>
<td>Frye (2009)(^b)</td>
<td>443/2,368</td>
<td>eGFR between 30-60 mL/min/1.72 m(^2)</td>
<td>Coronary artery disease defined by angiography (≥50% stenosis of a major epicardial coronary artery + positive stress test or ≥70% stenosis of a major epicardial coronary artery + classic angina)</td>
<td>All-cause mortality</td>
<td>None</td>
<td>PCI or CABG within 4-weeks of randomization as clinically indicated</td>
<td>No benefit</td>
</tr>
<tr>
<td>Boden (2007)(^c)</td>
<td>320/2,287</td>
<td>eGFR &lt;60 mL/min/1.72 m(^2) (only 16 had eGFR &lt;30)</td>
<td>Coronary artery stenosis of at least 70% in at least one proximal epicardial coronary artery and objective evidence of myocardial ischemia or at least one coronary stenosis of at least 80% and classic angina without provocative testing.</td>
<td>Composite of all-cause mortality and non-fatal myocardial infarction</td>
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<td>Target-lesion PCI attempted, and complete revascularization performed if clinically appropriate</td>
<td>No benefit</td>
</tr>
<tr>
<td>Manske (1999)(^d)</td>
<td>26/26</td>
<td>CKD stage 5 or kidney failure on dialysis (27%)</td>
<td>Coronary artery stenosis ≥75% in one or more coronary arteries, atypical or no chest pain and left ventricular ejection fraction &gt;35%</td>
<td>Composite of unstable angina, myocardial infarction or cardiovascular-related death</td>
<td>Gated-blood-pool radionuclide scan</td>
<td>PCI or CABG as clinically indicated</td>
<td>Benefit</td>
</tr>
</tbody>
</table>


**Abbreviations.** eGFR (estimated glomerular filtration rate), CKD (chronic kidney disease), PCI (percutaneous coronary intervention), CABG (coronary artery bypass grafting), MRI (magnetic resonance imaging)

**Figure legend**  
Figure 1. Dynamic risk of major adverse cardiovascular events for kidney failure patients versus the general population before, during and after kidney transplant surgery.
Figure 1. Dynamic major adverse cardiovascular event risk for kidney failure patients

Cardiovascular risk pre-op

Cardiovascular risk peri- and early post-op (~3-months)

Cardiovascular risk post-op (≥ ~3-months)

*TX = Kidney transplant