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Routine cardiac stress testing in kidney transplant candidates is only appropriate in symptomatic individuals: CON

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Cardiovascular disease is a leading cause of death in patients with end-stage kidney disease (ESKD) both before and after transplantation, accounting for 30% of mortality in post-transplant patients, with the highest rates of death occurring in the peri-transplant period\(^1,2\). It is imperative to accurately identify which patients are at elevated risk for cardiac complications pre- and post-transplant, by means of non-invasive cardiac stress testing. However, to date, there is no single consensus among the major scientific societies on criteria to determine whether kidney transplant candidates with no cardiac symptoms should undergo cardiac stress testing. As such, there is wide variability across centers in practices regarding cardiac stress testing in kidney transplant patients.

Some argue that cardiac stress testing is a limited resource that should be reserved for kidney transplant candidates who have active cardiac symptoms, such as exertional chest pain [placeholder to cite PRO side article]. In this debate, we argue that there is an important role for cardiac stress testing in kidney transplant candidates with no cardiac symptoms, because cardiac symptoms have a remarkably poor negative predictive value in the ESKD population, significant coronary artery disease is highly prevalent in the ESKD population, pre-operative guidelines for the general population are based on evidence from studies that excluded ESKD patients, and the perioperative period of interest differs in transplant candidates compared to the general population.

First, reliance on a history of cardiac symptoms may be deceptive in ESKD patients, as the absence of cardiac symptoms has a poor negative predictive value in this population. In a study
of 534,395 dialysis and non-dialysis patients who developed acute MI, only 55% of dialysis patients were diagnosed with acute coronary syndrome on admission, compared to 79% of non-dialysis patients. Contributing to the delayed diagnosis, only 44% of dialysis patients presented with chest pain, compared to 68% of non-dialysis patients; 19% of dialysis patients presented with ST elevation, compared to 36% of non-dialysis patients. The relative lack of symptoms may play a role in poor outcomes. Cardiac arrest was twice as frequent in dialysis patients (11%) than in non-dialysis patients (5%). In another study of 4,482 patients with and without chronic kidney disease (defined as estimated glomerular filtration rate < 60 mL/min/1.73 m$^2$) who developed acute MI, patients with kidney disease were less likely to report chest pain (adjusted odds ratio [aOR] 0.57; 95% confidence interval: 0.46-0.70). Patients with kidney disease were also less likely to report arm pain, shoulder pain, or neck pain, although they were more likely to report shortness of breath.

There are several hypotheses as to why cardiac symptoms are less prevalent in dialysis patients. ESKD patients, who are often quite deconditioned, may unconsciously learn to avoid chest pain and shortness of breath by avoiding prolonged physical exertion, translating into what is perceived as a negative history for chest pain. It is also possible that dialysis patients truly experience chest pain of a different quality than non-dialysis patients due to the metabolic derangements in ESKD, including uremic neuropathy and diabetic autonomic neuropathy. Additionally, given the myriad of symptoms experienced in ESKD and common comorbidities, patients may misattribute chest pain or shortness of breath to non-cardiac etiologies such as acid reflux or COPD.
Second, the prevalence of significant coronary artery disease is high in ESKD patients compared to age-matched controls and exceeds the prevalence that would be expected based on Framingham risk factors alone. In a study that performed coronary angiography at the time of initiation of dialysis on 30 asymptomatic stage 5 CKD patients with no prior history of angina or MI, it was found that 53% of patients had angiographically significant coronary artery stenosis (defined as >50% stenosis in this study). Among the patients with diabetes in the study, the prevalence increased even further to 83%. In a population that carries a high prevalence of the disease of interest, screening should be adjusted accordingly.

Third, the traditional recommendation that stress testing be reserved for patients with active cardiac symptoms or who cannot perform 4 METS of activity is based on foundational studies that do not apply to the kidney transplant candidate population. Proponents of limiting preoperative stress testing to only symptomatic individuals point to randomized, controlled trials showing no mortality benefit to pre-operative coronary artery revascularization. However, the benefits of coronary revascularization, are not known in transplant candidates, because ESKD patients have generally been excluded from randomized trials of coronary revascularization.

Fourth, the duration of the “perioperative period” is more prolonged when considering ESKD patients on the transplant list. Standard risk calculators are applied within 30 days prior to the surgery, and are designed to predict 30 day post-operative major adverse cardiovascular
In contrast, patients awaiting transplant routinely wait longer than 30 days before they are offered a transplant. Furthermore, there is a need to avoid cardiac complications and cardiac interventions that might damage the transplanted kidney in the months following the transplant, especially since delayed graft function is not an uncommon occurrence.

Finally, patients with ESKD have risk factors for coronary artery disease that are not fully captured by standard risk calculators when assessing perioperative risk of MACE. In addition to a high prevalence of hypertension, hyperlipidemia, and diabetes mellitus, ESKD patients also have accelerated vascular calcifications\textsuperscript{11}, impaired endothelial function\textsuperscript{12}, systemic inflammation from circulating uremic toxins and oxidative stress\textsuperscript{13}, and post-translational modifications of LDL and HDL that are associated with activation of pro-atherogenic pathways\textsuperscript{14}. Duration of ESKD or CKD is not a variable included in standard risk calculators for CAD.

To address these unique factors not taken into account by the guidelines for preoperative testing in the general population, major scientific societies have released guidelines specific to the transplant population over the last two decades\textsuperscript{10}. This includes the 2001 American Society of Transplantation (AST) clinical practice guidelines on the evaluation of renal transplant candidates\textsuperscript{15}, the 2005 Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines for cardiovascular disease in dialysis patients\textsuperscript{16}, the 2007 Lisbon Conference report on the care of the kidney transplant recipient\textsuperscript{17}, and most recently, the 2012 American Heart Association/American College of Cardiology (AHA/ACC) scientific statement on cardiac disease...
evaluation and management among kidney and liver transplant candidates. All of the aforementioned guidelines make an allowance for testing kidney transplant candidates with no active cardiac conditions, as long as they have risk factors, although each guideline differs in the number of risk factors needed to proceed to testing and the specific risk factors (Table 1).

In a retrospective study of 204 renal transplant candidates including 178 patients who underwent noninvasive stress testing, and in whom ischemic heart disease was found in 10% of patients, the authors retrospectively applied four guidelines: the 2001 AST guidelines, the 2005 K/DOQI guidelines, the 2007 Lisbon guidelines, and the 2007 ACC/AHA guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery (note the 2012 ACC/AHA scientific statement had not been published at that time). The 2007 ACC/AHA guidelines, which are non-specific to transplant patients (and has since been replaced by 2014 guidelines) would have only identified 4 of the 10 patients who required revascularization, as it would have recommended testing in only 20% of the cohort. Although they vary in the proportion of the population they would have recommended stress testing in, the 2001 AST, 2005 K/DOQI, and 2007 Lisbon approaches would have identified all patients who required revascularization. In any case, the study demonstrates that general perioperative guidelines for the non-ESKD population are not appropriate for use in the ESKD population.

Of note, the recommendations made in the 2012 AHA/ACC scientific statement were class IIb, level of evidence C, denoting that based on consensus opinion, case studies or standard of care, the benefit seems to outweigh the harm. Further studies are needed to show that a
strategy of stress testing in asymptomatic kidney transplant patients with cardiovascular risk factors leads to improved survival. The ideal risk stratification algorithm would require a randomized, controlled trial. Until then, we should not deny stress testing to asymptomatic ESKD patients awaiting transplant as the absence of symptoms has a poor negative predictive value in this population, and standard perioperative risk calculators do not take into account non-traditional risk factors seen in ESKD patients. Absence of evidence should not be taken as evidence of absence.

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Lissa Sugeng: Conceptualization; Supervision; Writing - review and editing.
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Table 1: Comparison of major society guidelines on risk factors that warrant non-invasive stress testing in kidney transplant candidates with no active cardiac conditions

| Guideline                                                                 | Testing is indicated in kidney transplant candidates with no cardiac conditions if there is: | Number of Risk Factors Needed | Risk Factors                                                                 |
|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------|------------------------------------------------------------------------------|
| 2001 AST Clinical Practice Guidelines on the Evaluation of Renal Transplant Candidates | prior DM, ASCVD, or CAD risk factors                                                            | ≥2                            | >45 years of age (men); >55 years of age (women)                               |
|                                                                          |                                                                                               |                               | Women with premature menopause but no estrogen replacement therapy            |
|                                                                          |                                                                                               |                               | Family history of premature CAD                                             |
|                                                                          |                                                                                               |                               | Smoking                                                                      |
|                                                                          |                                                                                               |                               | Hypertension                                                                 |
|                                                                          |                                                                                               |                               | Dyslipidemia                                                                 |
| 2005 K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients | prior DM, ASCVD, LVEF ≤ 40%, or peripheral vascular disease.                                   | ≥ 2                            | “Traditional risk factors”, not specified                                    |
| 2007 Lisbon Conference on the Care of the Kidney Transplant Recipient    | prior DM, ASCVD, or CAD risk factors                                                            | “Multiple”, but does not specify number | >1 year on dialysis                                                        |
|                                                                          |                                                                                               |                               | LV hypertrophy                                                              |
|                                                                          |                                                                                               |                               | >60 years of age                                                             |
|                                                                          |                                                                                               |                               | Smoking                                                                      |
|                                                                          |                                                                                               |                               | Hypertension                                                                 |
|                                                                          |                                                                                               |                               | Dyslipidemia                                                                 |
| 2012 AHA Scientific Statement on Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates | multiple CAD risk factors, regardless of functional status                                     | Undetermined, but ≥3 is “reasonable” | Diabetes mellitus                                                            |
|                                                                          |                                                                                               |                               | Prior cardiovascular disease                                                |
|                                                                          |                                                                                               |                               | >1 year on dialysis                                                        |
|                                                                          |                                                                                               |                               | LV hypertrophy                                                              |
|                                                                          |                                                                                               |                               | >60 years of age                                                             |
|                                                                          |                                                                                               |                               | Smoking                                                                      |
|                                                                          |                                                                                               |                               | Hypertension                                                                 |
|                                                                          |                                                                                               |                               | Dyslipidemia                                                                 |

Abbreviations: AST: American Society of Transplantation; AHA: American Heart Association; K/DOQI: Kidney Disease Outcomes Quality Initiative; LV: left ventricle; LVEF: left ventricular ejection fraction