ORIGINAL RESEARCH

Prognostic Value of Exercise Capacity in Kidney Transplant Candidates

Sean Tan, MBBS; Yi Wen Thang, MBBS; William R. Mulley, BMed, PhD; Kevan R. Polkinghorne, MBChB, PhD; Satish Ramkumar, MBBS, PhD; Kevin Cheng, MBBS; Jasmine Chan, BSc, MBBS; John Galligan, MBBS; Mark Nolan, MBBS, PhD; Adam J. Brown, BSc, MB BChir, PhD; Stuart Moir, MBBS, PhD; James D. Cameron, MD, MEngSc; Stephen J. Nicholls, MBBS, PhD; Philip M. Mottram, MBBS, PhD; Nitesh Nerlekar, MBBS, MPH, PhD

BACKGROUND: Exercise stress testing for cardiovascular assessment in kidney transplant candidates has been shown to be a feasible alternative to pharmacologic methods. Exercise stress testing allows the additional assessment of exercise capacity, which may have prognostic value for long-term cardiovascular outcomes in pre-transplant recipients. This study aimed to evaluate the prognostic value of exercise capacity on long-term cardiovascular outcomes in kidney transplant candidates.

METHODS AND RESULTS: We retrospectively evaluated exercise capacity in 898 consecutive kidney transplant candidates between 2013 and 2020 who underwent symptom-limited exercise stress echocardiography for pre-transplant cardiovascular assessment. Exercise capacity was measured by age- and sex-predicted metabolic equivalents (METs). The primary outcome was incident major adverse cardiovascular events, defined as cardiac death, non-fatal myocardial infarction, and stroke. Cox proportional hazard multivariable modeling was performed to define major adverse cardiovascular events predictors with transplantation treated as a time-varying covariate. A total of 429 patients (48%) achieved predicted METs. During follow-up, 93 (10%) developed major adverse cardiovascular events and 525 (58%) underwent transplantation. Achievement of predicted METs was independently associated with reduced major adverse cardiovascular events (hazard ratio [HR] 0.49; [95% CI 0.29–0.82], \(P=0.007\)), as was transplantation (HR, 0.52; [95% CI 0.30–0.91], \(P=0.02\)). Patients achieving predicted METs on pre-transplant exercise stress echocardiography had favorable outcomes that were independent (HR, 0.78; [95% CI 0.32–1.92], \(P=0.59\)) and of similar magnitude to subsequent transplantation (HR, 0.97; [95% CI 0.42–2.25], \(P=0.95\)).

CONCLUSIONS: Achievement of predicted METs on pre-transplant exercise stress echocardiography confers excellent prognosis independent of and of similar magnitude to subsequent kidney transplantation. Future studies should assess the benefit on exercise training in this population.

Key Words: exercise testing • kidney transplantation • major adverse cardiovascular events • stress echocardiography

Correspondence to: Nitesh Nerlekar, MBBS, MPH, PhD, Monash Cardiovascular Research Centre, Monash Health, Melbourne, Victoria, Australia.
Email: nitesh.nerlekar@monash.edu
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.025862
For Sources of Funding and Disclosures, see page 10.
© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made. JAMA is available at: www.ahajournals.org/journal/jama

Journal of the American Heart Association

ORIGINAL RESEARCH

Prognostic Value of Exercise Capacity in Kidney Transplant Candidates

Sean Tan, MBBS; Yi Wen Thang, MBBS; William R. Mulley, BMed, PhD; Kevan R. Polkinghorne, MBChB, PhD; Satish Ramkumar, MBBS, PhD; Kevin Cheng, MBBS; Jasmine Chan, BSc, MBBS; John Galligan, MBBS; Mark Nolan, MBBS, PhD; Adam J. Brown, BSc, MB BChir, PhD; Stuart Moir, MBBS, PhD; James D. Cameron, MD, MEngSc; Stephen J. Nicholls, MBBS, PhD; Philip M. Mottram, MBBS, PhD; Nitesh Nerlekar, MBBS, MPH, PhD

BACKGROUND: Exercise stress testing for cardiovascular assessment in kidney transplant candidates has been shown to be a feasible alternative to pharmacologic methods. Exercise stress testing allows the additional assessment of exercise capacity, which may have prognostic value for long-term cardiovascular outcomes in pre-transplant recipients. This study aimed to evaluate the prognostic value of exercise capacity on long-term cardiovascular outcomes in kidney transplant candidates.

METHODS AND RESULTS: We retrospectively evaluated exercise capacity in 898 consecutive kidney transplant candidates between 2013 and 2020 who underwent symptom-limited exercise stress echocardiography for pre-transplant cardiovascular assessment. Exercise capacity was measured by age- and sex-predicted metabolic equivalents (METs). The primary outcome was incident major adverse cardiovascular events, defined as cardiac death, non-fatal myocardial infarction, and stroke. Cox proportional hazard multivariable modeling was performed to define major adverse cardiovascular events predictors with transplantation treated as a time-varying covariate. A total of 429 patients (48%) achieved predicted METs. During follow-up, 93 (10%) developed major adverse cardiovascular events and 525 (58%) underwent transplantation. Achievement of predicted METs was independently associated with reduced major adverse cardiovascular events (hazard ratio [HR] 0.49; [95% CI 0.29–0.82], \(P=0.007\)), as was transplantation (HR, 0.52; [95% CI 0.30–0.91], \(P=0.02\)). Patients achieving predicted METs on pre-transplant exercise stress echocardiography had favorable outcomes that were independent (HR, 0.78; [95% CI 0.32–1.92], \(P=0.59\)) and of similar magnitude to subsequent transplantation (HR, 0.97; [95% CI 0.42–2.25], \(P=0.95\)).

CONCLUSIONS: Achievement of predicted METs on pre-transplant exercise stress echocardiography confers excellent prognosis independent of and of similar magnitude to subsequent kidney transplantation. Future studies should assess the benefit on exercise training in this population.

Key Words: exercise testing • kidney transplantation • major adverse cardiovascular events • stress echocardiography

Correspondence to: Nitesh Nerlekar, MBBS, MPH, PhD, Monash Cardiovascular Research Centre, Monash Health, Melbourne, Victoria, Australia.
Email: nitesh.nerlekar@monash.edu
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.025862
For Sources of Funding and Disclosures, see page 10.
© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made. JAMA is available at: www.ahajournals.org/journal/jama

Journal of the American Heart Association
may still be utility for cardiac stress testing to identify at risk patients who may benefit from lifestyle and medica
tal preventative measures to improve long-term cardio-
vacular outcomes.

Cardiac stress testing in the CKD population is rou-
tinely performed by pharmacological methods due to a perceived inability of this population to exercise ade-
quately.7 Despite this, exercise stress echocardiography (ESE) has been shown to be feasible, safe and well tol-
erated in patients with CKD8 and allows measurement of exercise capacity, a recognized marker of long-term cardiovascular risk in the general population.9,10 Studies have reported that patients with CKD have reduced exercise capacity11 due to a combination of sedentary lifestyle, chronic inflammation and maladaptive left ventricular (LV) remodeling.12-14 However, the prognostic

value of exercise capacity on long-term cardiovascular

outcomes in the CKD population remains unclear.

We aimed to evaluate the prognostic utility of ex-

ercise capacity, quantified by metabolic equivalents (METs) on pre-operative ESE, on long-term

cardiovascular outcomes among kidney transplant candidates. This is with view of identifying a poten-
tially modifiable risk factor that could be targeted with lifestyle intervention. We hypothesized that ability to achieve age and sex predicted METs on pre-operative ESE is associated with better long-term cardiovascular outcomes independent of other known cardiovascular risk factors and subsequent kidney transplantation.

CLINICAL PERSPECTIVE

What Is New?
• Better exercise capacity on pre-transplant exercise stress echocardiography is associated with reduced major adverse cardiovascular events.
• Patients who achieve predicted metabolic equivalents for age and sex had excellent long-term prognosis of similar magnitude to and ir-

respective of future kidney transplantation.
• Ability to achieve predicted metabolic equivalents for age and sex could be a better dis-

criminator than an unadjusted threshold of 7 metabolic equivalents or achievement of target heart rate.

What Are the Clinical Implications?
• Ability to achieve age and sex predicted meta-

bolic equivalents could be used as a new metric to predict cardiovascular outcomes in kidney transplant candidates.
• Future studies could evaluate exercise training to improve long-term cardiovascular outcomes in patients with chronic kidney disease.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Definition |
|--------------|------------|
| ESE          | exercise stress echocardiography |
| LVEF         | left ventricular ejection fraction |
| MACE         | major adverse cardiovascular events |
| METs         | metabolic equivalent |

CLINICAL PERSPECTIVE

What Is New?
• Better exercise capacity on pre-transplant exercise stress echocardiography is associated with reduced major adverse cardiovascular events.
• Patients who achieve predicted metabolic equivalents for age and sex had excellent long-term prognosis of similar magnitude to and irrespective of future kidney transplantation.
• Ability to achieve predicted metabolic equivalents for age and sex could be a better discriminator than an unadjusted threshold of 7 metabolic equivalents or achievement of target heart rate.

What Are the Clinical Implications?
• Ability to achieve age and sex predicted metabolic equivalents could be used as a new metric to predict cardiovascular outcomes in kidney transplant candidates.
• Future studies could evaluate exercise training to improve long-term cardiovascular outcomes in patients with chronic kidney disease.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Definition |
|--------------|------------|
| ESE          | exercise stress echocardiography |
| LVEF         | left ventricular ejection fraction |
| MACE         | major adverse cardiovascular events |
| METs         | metabolic equivalent |

may still be utility for cardiac stress testing to identify at risk patients who may benefit from lifestyle and medical preventative measures to improve long-term cardiovascular outcomes.

Cardiac stress testing in the CKD population is routinely performed by pharmacological methods due to a perceived inability of this population to exercise adequately.7 Despite this, exercise stress echocardiography (ESE) has been shown to be feasible, safe and well tolerated in patients with CKD8 and allows measurement of exercise capacity, a recognized marker of long-term cardiovascular risk in the general population.9,10 Studies have reported that patients with CKD have reduced exercise capacity11 due to a combination of sedentary lifestyle, chronic inflammation and maladaptive left ventricular (LV) remodeling.12-14 However, the prognostic value of exercise capacity on long-term cardiovascular outcomes in the CKD population remains unclear.

We aimed to evaluate the prognostic utility of exercise capacity, quantified by metabolic equivalents (METs) on pre-operative ESE, on long-term cardiovascular outcomes among kidney transplant candidates. This is with view of identifying a potentially modifiable risk factor that could be targeted with lifestyle intervention. We hypothesized that ability to achieve age and sex predicted METs on pre-operative ESE is associated with better long-term cardiovascular outcomes independent of other known cardiovascular risk factors and subsequent kidney transplantation.

CLINICAL PERSPECTIVE

What Is New?
• Better exercise capacity on pre-transplant exercise stress echocardiography is associated with reduced major adverse cardiovascular events.
• Patients who achieve predicted metabolic equivalents for age and sex had excellent long-term prognosis of similar magnitude to and irrespective of future kidney transplantation.
• Ability to achieve predicted metabolic equivalents for age and sex could be a better discriminator than an unadjusted threshold of 7 metabolic equivalents or achievement of target heart rate.

What Are the Clinical Implications?
• Ability to achieve age and sex predicted metabolic equivalents could be used as a new metric to predict cardiovascular outcomes in kidney transplant candidates.
• Future studies could evaluate exercise training to improve long-term cardiovascular outcomes in patients with chronic kidney disease.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Definition |
|--------------|------------|
| ESE          | exercise stress echocardiography |
| LVEF         | left ventricular ejection fraction |
| MACE         | major adverse cardiovascular events |
| METs         | metabolic equivalent |

methods

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Study Population

This was a retrospective analysis of a prospectively curated registry of consecutive patients above 18 years old with stage 4 or 5 CKD7 (including those on dialysis) who were referred for ESE for cardiovascular risk stratification as part of routine assessment for kidney transplantation suitability at Monash Health, Melbourne, Australia. As part of local guidelines, all kidney transplant candidates were required to undergo non-invasive coronary artery disease (CAD) screening prior to eligibility for waitlisting. All patients referred for ESE attempted ESE unless there were significant contraindications to ESE such as musculoskeletal disease affecting mobility, use of a gait aid, and/or prior leg amputation. Those without contraindications underwent a 40-m gait assessment immediately prior to testing with the final decision on exercise versus pharmacologic testing at the discretion of the supervising cardiologist. Patients who were unable to exercise underwent dobutamine stress echocardiography and were excluded from the study. Prospective registry data collection of eligible patients commenced on February 1, 2013 and retrospective analysis was performed in July 2020, with follow-up from the date of ESE to July 31, 2020. Patient consent was not required for this study. Institutional ethics approval was obtained for the study.

Exercise Stress Echocardiography

All ESE were performed according to American Society of Echocardiography guidelines.15 Patients were asked to withhold any beta-blocker use for at least 48 hours prior to the test, but beta-blocker usage did not preclude testing. ESE was performed using the standard Bruce protocol to assess exercise capacity in METs. Exercise was not ceased when target heart rate was attained but was performed as a symptom-limited test. The test was prematurely aborted at supervising physician discretion if any of the following occurred: limiting symptoms (angina, dyspnea), ST depression
≥3 mm, ventricular tachycardia, decline in blood pressure by ≥30 mm Hg, rise in systolic blood pressure to ≥230 mm Hg.

Baseline and stress imaging were performed using views from the parasternal long and short axis; apical 4 chamber, 2 chamber, and long axis. All echocardiographic studies were performed, supervised and reported by a specialist non-invasive imaging cardiologist. Baseline LV dysfunction was defined as left ventricular ejection fraction (LVEF) <50% by modified Simpson biplane method on resting images prior to exercise. Tests were considered abnormal if they were non-diagnostic due to poor imaging, had global failure of LV augmentation or fall in LVEF at peak stress, or inducible regional wall motion abnormalities. A decision on the necessity for post-test coronary angiography and revascularization was discussed at a multi-disciplinary cardiology and cardiothoracic surgical conference with additional input from the renal transplant department. Non-MI revascularization was defined as revascularization for stable angina or asymptomatic patients following abnormal ESE results. All subjects with normal ESE results were allowed to be wait-listed for kidney transplantation from a cardiovascular perspective without further cardiac testing, whilst those with abnormal ESE results were only cleared after review by a specialist cardiologist in clinic either with or without post-test revascularization. If a patient underwent multiple ESE for pre-transplant cardiovascular assessment, the earliest ESE was recorded for study purposes. Inter-reader and intra-reader variability were assessed in a subset of 20 randomly selected cases.

Clinical Data
Clinical data were collated from the patients’ medical records and prospective local and national dialysis and transplant registries (ANZDATA [Australian and New Zealand Dialysis and Transplant Registry]). Achieved METs were automatically calculated by a computer-generated algorithm according to the Bruce protocol. Predicted METs for age and sex for each patient was calculated using previously published formulas: for women, predicted METs=14.7−(0.13×age); and for men, predicted METs=18−(0.15×age). Secondary analyses were performed using METs as a continuous variable, a non-adjusted cut-off of 7 METs which has previously been defined as threshold for “good” exercise capacity, and ability to achieve 85% of maximal predicted heart rate (MPHR) which is the standard target heart rate for ESE.

End Points
The primary outcome of the study was major adverse cardiovascular events (MACE), defined as a composite of cardiac death, non-fatal MI, and stroke. Each individual endpoint was analyzed as a secondary outcome.

Outcomes were obtained from ANZDATA and reported at the pre-specified 7-year follow-up from start of enrolment, which represents the end of the study period from 2013 to 2020.

Statistical Analysis
Categorical data are presented as absolute numbers and percentages and compared with chi-square test or Fishers exact test as appropriate. Continuous data are displayed as mean±SD if data were normally distributed, or medians (interquartile range [IQR]) for non-Gaussian data and compared with t tests or Mann–Whitney tests as appropriate. Inter-reader and intra-reader variability were assessed by Kappa statistic.

Cox proportional hazards models were used to assess achievement of age and sex predicted METs, achieved METs, and achievement of 7 METs separately on time to first MACE. The date of ESE was used as time of study entry. If a patient experienced more than one MACE during follow-up (eg, non-fatal MI followed by death, the first event defined the MACE recorded, and the time of study exit). In patients without MACE, the date of last follow-up or July 31, 2020, whichever came last, was considered to be the censoring date. Achievement of age and sex predicted METs and achievement of 7 METs were modeled as dichotomous variables, whilst achieved METs was modeled continuously. Kidney transplantation was treated as a time-dependent covariate in order to account for the wait time between ESE and transplantation. Graphical time-to-event plots were constructed and the Mantel-Byar test used to assess the differences in equality of curves due to the use of time-varying data as previously recommended for transplant data. Model covariates included those with P<0.20 on univariable assessment and variables of clinical relevance such as age. The final included covariates were: age, sex, diabetes, hypertension, hyperlipidemia, history of smoking, history of ischemic heart disease (IHD), previous kidney transplantation, body mass index (BMI), baseline LV dysfunction, abnormal ESE result, non-MI revascularization prior to transplantation, achievement predicted METs, and transplantation. Multicollinearity between covariates was excluded by assessing variance inflation factors. Conditional proportional hazards assumptions were visually inspected by plotting Schoenfield residuals. Results were reported as hazard ratio (HR) with 95% CI. A two-sided P-value of <0.05 was considered statistically significant. Statistical analysis was performed using Stata MP/14 (StataCorp, College Station, TX).

RESULTS
Demographics
There were 974 patients with CKD referred for stress echocardiography for cardiovascular risk evaluation
testing during the study period. A total of 76 patients were excluded due to an inability to exercise (musculoskeletal disease affecting mobility [n=49], use of a gait aid [n=14], leg amputation [n=13]), accordingly 898 patients were included in the study cohort. Patient characteristics are shown in Table 1. The mean age of the cohort was 51.8±11.3 years and 69% had renal replacement therapy at baseline.

There were 525 (58%) patients who received kidney transplantation during the study. Baseline characteristics stratified by transplantation status are shown in Table S1. Median time to transplantation was 1.5 years (IQR 0.8–2.8 years). Follow-up duration was mean 5.0±1.9 years after ESE.

Exercise Capacity
The mean achieved exercise capacity was 9.2±2.8 METs (Table 1). At time of ESE, 139 (15%) patients were in their long interdialytic period (2-day hemodialysis-free interval due to weekend gap on a thrice weekly schedule), whilst 379 (42%) performed the test on beta-blockers. A total of 429 (48%) patients achieved age and sex predicted METs, whilst 734 (82%) patients achieved ≥7 METs. Patients who achieved predicted METs were older (53.7±10.8 versus 50.2±11.6 years, P<0.001), more likely to be female (41% versus 29%, P<0.001), had lower BMI (25.6±4.6 versus 28.5±5.5 kg/m², P<0.001), less beta-blocker use (36% versus 48%, P=0.001), less diabetes (30% versus 47%, P<0.001), lower prevalence of smoking (29% versus 38%, P=0.002), and less baseline LV dysfunction on ESE (10% versus 21%, P<0.001). Patients who achieved predicted METs were less likely to have non-MI revascularization (1% versus 5%, P=0.005) and were more likely to receive subsequent kidney transplantation (65% versus 52%, P<0.001). Population characteristics stratified by ability to achieve ≥7 METs are shown in Table S2.

The majority of ESE results were normal (755 [84%]). There was excellent inter-reader (κ=0.93) and intra-reader agreement (κ=0.95). Of the 143 abnormal ESE results, 32 (22%) were non-diagnostic, 53 (37%) had a fall in post-stress LVEF or a failure of LV contractile reserve, and 58 (41%) had inducible regional hypokinesis in a single coronary territory. A total of 56 patients with abnormal ESE results (39%) underwent coronary angiography after abnormal ESE results and 28 (50%) were subsequently revascularized. All remaining patients were treated with guideline directed medical therapy. Patients who achieved predicted METs had fewer abnormal ESE results (10% versus 22%, P<0.001) due to reduced non-diagnostic studies (1% versus 7%, P=0.003), but similar incidences of global failure of LV contractile reserve and inducible regional wall motion abnormalities. Similar rates of coronary angiography were performed in both groups (4% versus 9%, P=0.87), but there was more non-MI revascularization in the group that failed to achieve predicted METs (1% versus 5%, P=0.005).

Major Adverse Cardiovascular Events
A total of 106 MACE were recorded in 93 patients (21 cardiac deaths, 53 non-fatal MI, and 32 strokes) over the follow-up period (cumulative event rate of 2.4% per year). In the 525 patients who received a kidney transplant during the follow-up period, there were 50 MACE (10%): 13 events (26%) prior to the transplant and 37 events (74%) post-transplantation. Of the 37 post-transplant events, 5 events occurred within 30 days of surgery (peri-operative MACE incidence 1%) (Figure 1). In the 373 patients who did not receive a kidney transplant, there were 43 MACE (12%).

Univariable and Multivariable Analysis
Several parameters were associated with future MACE at a univariable level (Table S3). Those with a crude increased risk of MACE included diabetes, hyperlipidemia, history of smoking, history of IHD, baseline LV dysfunction, and non-MI revascularization. Variables associated with a reduction in MACE included female sex, ability to achieve predicted METs, and subsequent transplantation. Multivariable analysis demonstrated significant associations between MACE and diabetes, hyperlipidemia, ability to achieve predicted METs, and transplantation (Table 2). Both diabetes (HR, 1.78; [95% CI 1.11–2.87], P=0.02) and hyperlipidemia (HR, 1.70; [95% CI 1.03–2.82], P=0.04) were associated with an increased risk of MACE, while achievement of predicted METs (HR, 0.49; [95% CI 0.29–0.82], P=0.007) and subsequent kidney transplantation (HR, 0.52; [95% CI 0.30–0.91], P=0.02) conferred lower risk.

Similar results were found on secondary analysis when achieved METs was analyzed as a continuous variable, with 12% reduction in MACE for each unit increase in achieved METs (HR, 0.88; [95% CI 0.80–0.96], P=0.007) (Table S4, Figure S1). Results were also unchanged when a cut-off of ≥7 METs was analyzed, with the ability to achieve ≥7 METs associated with a significant reduction in MACE (HR, 0.55; [95% CI 0.32–0.95], P=0.03) (Table S5). Sensitivity analysis was performed with categorization of METs in groups ≤4 METs (very poor capacity), 4 to 7 METs (intermediate capacity), 7 to 10 METs (good capacity), and ≥10 METs (excellent capacity). This demonstrated a reduction in MACE with each increasing exercise capacity group (P<0.001) (Figure S2).

The Combined Impact of Exercise Capacity and Transplantation
When stratified according to achievement of predicted METs and subsequent kidney transplantation, the
primary outcome occurred in 42 patients who did not achieve predicted METs and did not achieve prevented METs but did not receive transplantation, 13 patients who did not achieve predicted METs but received transplantation, 14 patients who achieved predicted METs but did not receive transplantation, and 24 patients who achieved predicted METs and received transplantation (Figure 2). Patients who did not achieve predicted METs and did not receive a kidney transplant had the worst outcomes (Figure 2). In contrast, patients who did not receive transplantation but achieved predicted METs had better outcomes (HR, 0.33; [95% CI 0.18–0.61], \(P<0.001\), which were similar to both other groups of patients who received transplantation (Figure 2). Differences in baseline demographics among the 4 patient groups are reported in Tables S6 and S7.

When secondary analysis at \(\geq 7\) METs was performed, subsequent kidney transplantation conferred better outcomes irrespective of achievement of 7 METs on pre-operative ESE (Figure 3). In patients who
did not receive transplantation, patients who achieved ≥7 METs on pre-transplant ESE had better outcomes than those who did not (HR, 0.41; [95% CI 0.24–0.71], P=0.001) (Figure 3, Table S8). Further secondary analysis using ability to achieve a target heart rate of 85% MPHR on pre-operative ESE demonstrated that patients who received subsequent kidney transplantation had similar outcomes irrespective of achievement of 85% MPHR on pre-operative ESE (HR, 0.74; [95% CI 0.34–1.60], P=0.44) (Figure 4). In patients who did not receive subsequent transplantation, ability to achieve 85% MPHR conferred better outcomes (HR, 0.49; [95% CI 0.29–0.83], P=0.01), although this benefit was declined after 5 years of follow-up (Figure 4).

Individual secondary outcomes stratified by ability to achieve predicted METs and transplantation status are shown in Table 3.

**DISCUSSION**

In this analysis of 898 ambulatory patients with stage 4 or 5 CKD who underwent cardiovascular risk stratification for potential kidney transplantation with ESE, we have demonstrated the prognostic benefit of good exercise capacity on long-term cardiovascular outcomes. The major findings of this study are: (1) ability to achieve predicted METs for age and sex on pre-operative ESE confers excellent long-term cardiovascular prognosis, (2) exercise capacity is an independent predictor of MACE with a 12% relative reduction for each 1-unit increment in METs, and (3) ability to achieve predicted METs for age and sex may be a better discriminator than a threshold of 7 METs or ability to achieve 85% MPHR for long-term cardiovascular outcomes in kidney transplant candidates. This is the largest contemporary study evaluating exercise stress testing in a CKD population.

Conventionally, the goals of pre-operative kidney transplant cardiovascular risk assessment are to assess for the presence of significant CAD, to predict
peri-operative cardiovascular risk at transplantation, and to predict long-term cardiovascular outcomes. The role of pre-operative cardiac stress testing with view of revascularization for stable or asymptomatic CAD has been recently challenged by the ISCHEMIA CKD trial, which demonstrated that revascularization for stable CAD in CKD patients did not reduce mortality and non-fatal MI regardless of kidney transplant wait-list status. Furthermore, revascularization following abnormal cardiac stress testing may not improve

Figure 2. Cumulative major adverse cardiovascular event free proportion stratified by achievement of predicted METs and transplantation status.
Graph demonstrates cumulative MACE free proportion stratified by achievement of predicted METs and transplantation status at 7 years. Transplantation was treated as a time-dependent variable and curves reflect univariable modeling. MACE indicates major adverse cardiovascular event; and METs, metabolic equivalents.

Figure 3. Cumulative major adverse cardiovascular event free proportion stratified by ≥7 MET threshold and transplantation status.
Graph demonstrates cumulative MACE free proportion stratified by achievement of 7 METs and transplantation status at 7 years. Transplantation was treated as a time-dependent variable and curves reflect univariable modeling. MACE indicates major adverse cardiovascular event; and METs, metabolic equivalents.
angina-related health status in this patient population as kidney transplant candidates are often asymptomatic at the time of pre-operative testing.6 The ongoing CARSK trial will address this issue by evaluating the utility of screening for asymptomatic CAD after kidney transplant wait-list entry.21 Although the role of cardiac stress testing with goal of revascularization remains in contention, there may be a role for cardiac stress testing to identify patients with CKD at risk of CVD who may benefit from lifestyle intervention and risk factor modification, as well as patients of very high cardiovascular risk who may not prognostically benefit from transplantation.

The primary goal of this study was to assess the utility of pre-operative exercise capacity assessment using ESE in predicting long-term cardiovascular outcomes in kidney transplant candidates, which is a metric that is not assessed on pharmacological stress testing. Exercise capacity represents an integrated measure of multiple prognostic variables and has been suggested as a useful modality to assess long-term cardiovascular risk in the general population.22 Similarly, exercise capacity may be a more reliable metric in predicting long-term cardiovascular outcomes in kidney transplant candidates. Poor exercise capacity is also a potential modifiable risk factor that could be improved with lifestyle measures and exercise training, an intervention which has previously been shown to be safe and effective in improving exercise capacity in patients with CKD without any adverse outcomes.23

Although cardiac stress testing conventionally utilizes a target of 85% MPHR to improve detection of coronary ischemia, target heart rate may not be an adequate indicator of exercise capacity, which is a marker of functional

Table 3. Primary and Secondary Outcomes

| Outcome          | Did not achieve predicted METs (n=469) | Achieved predicted METs (n=429) |
|------------------|----------------------------------------|---------------------------------|
|                  | Not transplanted                      | Transplanted*                   | Not transplanted | Transplanted* |
|                  | (n=223)                               | (n=246)                         | (n=150)        | (n=279)       |
| MACE             | 42 (18%)                              | 13 (5%)                         | 14 (9%)        | 24 (9%)       |
| Cardiac death    | 9 (4%)                                | 3 (1%)                          | 2 (1%)         | 7 (3%)        |
| Non-fatal MI     | 18 (8%)                               | 8 (3%)                          | 11 (7%)        | 12 (4%)       |
| Stroke           | 15 (7%)                               | 2 (1%)                          | 1 (1%)         | 5 (2%)        |

MACE indicates major adverse cardiovascular event; METs, metabolic equivalents; and MI, myocardial infarction.

*Transplantation was treated as a time-dependent covariate.
status and better quantified with achievement of METs. Traditionally, a threshold of 7 METs has been described as “good” exercise capacity in pre-operative assessment, however this is unadjusted for age and sex. The findings of this study propose that the ability to achieve age and sex predicted METs may be a more practical discriminator for exercise capacity in predicting long-term cardiovascular outcomes. In the study population, only 48% of patients achieved predicted METs, compared with 82% of patients achieving ≥7 METs and 60% of patients achieving 85% MPHR on pre-transplant ESE.

The importance of exercise in potential kidney transplant candidates for long-term cardiovascular prognosis has been investigated in previous studies. Patel et al performed exercise treadmill testing in 268 candidates as part of a cardiovascular screening program and reported a poorer survival in patients exercising <6 minutes. Ting et al performed cardiopulmonary exercise testing (CPET) in 240 patients and demonstrated that reduced anaerobic threshold <40% of alveolar oxygen uptake (VO₂) conferred a significantly worse prognosis. Other observational studies have also demonstrated the association of peak VO₂ on CPET with future cardiac events and all-cause mortality in kidney and/or pancreas transplant candidates and patients receiving hemodialysis. Our study supports and mirrors these findings and is further enhanced by a much larger sample size and consequently more events. However, the patients in this study achieved above expected exercise capacity when compared with a conventional CKD population, reflective of a fitter study cohort. This needs to be considered when interpreting this study’s results.

The finding of better long-term cardiovascular prognosis with achievement of age and sex predicted METs may not appear novel, but it is remarkable that patients who achieved predicted METs on pre-operative ESE or received subsequent transplantation during follow-up had similar favorable outcomes. These findings suggest that the prognostic benefit seen with achievement of predicted METs is independent of and has similar magnitude to receiving a kidney transplant in patients with advanced CKD. This result may provide clinicians with reassurance if there is delay to transplantation in patients who are able to achieve predicted METs whilst they remain on the wait-list. Conversely, those with a poorer exercise capacity may warrant more expedited assessment for transplantation. Finally, this raises the possibility of using predicted METs for age and sex as a target for future studies exploring exercise training as a treatment modality to improve long-term cardiovascular outcomes in CKD patients awaiting transplantation.

Study Limitations

Our results represent one of the largest kidney transplant centers in Australia, but are limited by the single-center setting and observational design. Additionally, there could have been selection bias in the study cohort as we only included patients referred for stress echocardiography for pre-transplant cardiovascular assessment but cannot account for patients who were referred solely for nuclear myocardial perfusion imaging. The cohort would also have excluded patients deemed unsuitable for transplantation on other clinical grounds and hence not referred for pre-transplant cardiac stress testing. This selection bias may explain the younger patient population (52±11 years) with better exercise capacity (82% achieving 7 METs) in this study, leading to lower than expected MACE incidence which could affect the generalizability of these findings to an unselected CKD cohort. Hence, the results reported in this single-center study may be indiscriminate and may not represent standard practice in other centers where standardized cardiovascular screening is performed for all-comer CKD patients. Furthermore, some patients may not have been waitlisted for transplantation following ESE and cardiovascular clearance due to non-cardiac reasons, which could introduce further selection bias into the transplanted cohort.

CONCLUSIONS

In patients with CKD undergoing cardiovascular assessment for kidney transplantation, exercise capacity as assessed on pre-operative ESE is associated with reduced likelihood of long-term MACE. Patients who are able to achieve predicted METs for age and sex have good long-term cardiovascular prognosis that is independent of and of similar magnitude to receiving a kidney transplant. Further studies are required to prospectively assess exercise training as a treatment modality to improve long-term cardiovascular outcomes in CKD patients awaiting transplantation.

ARTICLE INFORMATION

accepted May 3, 2022 Received March 2, 2022.

Affiliations

Monash Cardiovascular Research Centre, Victorian Heart Institute, Monash University, Melbourne, Victoria, Australia (S.T., S.R., K.C., J.C., J.G., A.J.B., S.M., J.D.C., S.J.N., P.M.M., N.N.); Monash Heart (S.T., S.R., K.C., J.C., J.G., A.J.B., S.M., S.J.N., P.M.M., N.N.); and Department of Nephrology (Y.W.T., W.R.M., K.R.P.), Monash Health, Melbourne, Victoria, Australia; Department of Medicine, Monash University, Melbourne, Victoria, Australia (W.R.M., K.R.P.; and Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia (M.N., N.N.).

Acknowledgments

The authors wish to thank Professor Thomas Marwick (Baker Heart and Diabetes Institute, Melbourne, Australia) for his guidance, and Dr Caitlin Cheshire (Monash Heart, Melbourne, Australia), Dr Hashrul Rashid (Monash Heart, Melbourne, Australia), and Ms Orla Maney (Department of Nephrology, Monash Health, Melbourne, Australia) for their assistance in data collection.

Sources of Funding

This work was not supported by any funding. Dr Nerlekar is supported by an Emerging Leader Fellowship from the National Health and Medical Research Council.
REFERENCES

1. Johansen KL, Chertow GM, Foley RN, Gilbertson DT, Herzog CA, Ishani A, Israni AK, Ku E, Kurella Tamura M, Li S, et al. US renal data system 2020 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2021;77:A7–A8. doi: 10.1053/j.ajkd.2021.01.002

2. Briggs JD. Causes of death after renal transplantation. Nephrol Dial Transplant. 2001;16:1545–1549. doi: 10.1093/ndt/16.8.1545

3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Clinical practice guideline on the evaluation and management of candidates for kidney transplantation. Transplantation. 2020;101:S1-S103. doi: 10.1097/TP.0000000000003138

4. Lentile KL, Costa SP, Weir MR, Robb JF, Fleisher LA, Kasiske BL, Carithers RL, Ragosta M, Bolton K, Auerbach AD, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation; endorsed by the American Society of Transplant Surgeons, American Society of Transplantation, and National Kidney Foundation. Circulation. 2012;126:617–663. doi: 10.1161/CIR.0b013e31823eb07a

5. Bangalore S, Maron DJ, O’Brien SM, Fleg JL, Kretov EI, Briguori C, Aldridge N, Iyengar KA, Kheir S, Holmes DR Jr, et al. Exercise capacity in kidney transplant candidates for coronary artery disease in patients with advanced kidney disease. N Engl J Med. 2020;382:1608–1618. doi: 10.1056/NEJMoai1915925

6. Spertus JA, Jones PG, Maron DJ, O’Brien SM, Reynolds HR, Rosenberg Y, Stone GW, Harrell FE Jr, Boden WE, Weintraub WS, et al. Health-status outcomes with invasive or conservative care in coronary disease. N Engl J Med. 2020;382:1408–1419. doi: 10.1056/NEJMoai1613670

7. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.

8. Nerlekar N, Mulley W, Rehmani H, Ramkumar S, Cheng K, Vasanathakumar SA, Rashid H, Barton T, Nasis A, Meredith IT, et al. Feasibility of exercise stress echocardiography for cardiac risk assessment in chronic kidney disease patients prior to renal transplantation. Clin Transplant. 2016;30:1209–1215. doi: 10.1111/ctt.12796

9. Fleisher LA, Fleischmann KE, Auerbach AD, Sarnason SA, Beckman JA, Bolzurt B, Davila-Roman VG, Gerhard-Herman MD, Holy TA, Kane GC. 2014 ACC/AHA guideline on peripерoperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Circulation. 2014;130:2215–2245. doi: 10.1161/CIR.0000000000000105

10. Poldermans D, Bax JJ, Boersma E, De Hert S, Eckehout E, Fowkes FGR, Gorenek B, Hennerci MK, Jung B, Kelm M. Guidelines for pre-operative cardiac risk assessment and perioperative cardiovascular management in non-cardiac surgery. Eur Heart J. 2009;30:2769–2812. doi: 10.1093/eurheartj/ehp337

11. Reese PP, Cappola AR, Shults J, Townsend RR, Gadegbeku CA, Anderson C, Baker JF, Carlow D, Sulk MJ, Lo JC, et al. Physical performance and frailty in chronic kidney disease. Am J Nephrol. 2015;38:307–315. doi: 10.1159/000355568

12. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Patsy BM. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. Circulation. 2003;107:87–92. doi: 10.1161/01.cir.0000042700.48769.59

13. Ting SM, Hamborg T, McGregor G, Oxborough D, Lim K, Koganti S, Aldridge N, Imray C, Bland R, Fletcher S, et al. Reduced cardiovascular reserve in chronic kidney failure: a matched cohort study. Am J Kidney Dis. 2015;66:274–284. doi: 10.1053/j.ajkd.2015.02.335

14. Gan GCH, Kadappu KK, Bhat A, Fernandez F, Esho S, Thomas L. Exercise E/E’ is a determinant of exercise capacity and adverse cardiovascular outcomes in chronic kidney disease. JACC Cardiovasc Imaging. 2020;13:2485–2494. doi: 10.1016/j.jacc.2020.05.044

15. Pelikka PA, Naguwa SF, Eihendy AA, Kuehl CA, Sawada SG. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr. 2007;20:1021–1041. doi: 10.1016/j.echo.2007.07.003

16. Kim ES, Ishwaran H, Blackstone E, Lauer MS. External prognostic validations and comparisons of age- and gender-adjusted exercise capacity predictions. J Am Coll Cardiol. 2007;50:1867–1875. doi: 10.1016/j.jacc.2007.09.003

17. Patel AY, Eagle KA, Vaishnava P. Cardiac risk of noncardiac surgery. J Am Coll Cardiol. 2015;66:2140–2148. doi: 10.1016/j.jacc.2015.09.026

18. Hicks KA, Mahaffey KW, Mehran R, Nissen R, Slivitz SD, Dunn B, Solomon SD, Marlter JR, Teerlink JR, Farb A, et al. 2017 cardiovascular and stroke endpoint definitions for clinical trials. Circulation. 2018;137:961–972. doi: 10.1161/CIRCULATIONAHA.117.35502

19. Mantel N, Byar DP. Evaluation of response-time data involving transient state survival. J Am Stat Assoc. 1966;71:81–86. doi: 10.2307/2282550

20. Herzog CA, Smegen MA, Xu Y, Costa SR, Mathew RO, El-Hajjar MC, Gulati S, Maldonado RA, Daugas E, Madero M, et al. Kidney transplant list status and outcomes in the ISCHEMIA-CKD trial. J Am Coll Cardiol. 2021;78:348–361. doi: 10.1016/j.jacc.2021.05.001

21. Ying T, Gill J, Webster A, Kim SJ, Morton R, Klarenbach S, Kelly J, Burton S, Hall B, et al. Reduced cardiovascular and fibrinogen levels in kidney transplant candidates for coronary artery disease—a trial protocol for the CARSK study. Am Heart J. 2019;214:175–183. doi: 10.1016/j.ahj.2019.05.008

22. Dagianti A, Penco M, Agati L, Sciomer S, Dagianti A, Rosario S, Fedele F. Stress echocardiography: comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease. J Am Coll Cardiol. 1995;26:18–25. doi: 10.1016/0735-1097(95)00121-F

23. Hiwse S, Jacobson SH. Exercise training in adults with CKD: a systematic review and meta-analysis. Am J Kidney Dis. 2014;64:383–393. doi: 10.1053/j.ajkd.2014.03.020

24. Patel R, Mark P, Johnston N, McGeoch R, Lindsay M, Kingsmore D, Dargie H, Jardine A. Prognostic value of cardiovascular screening in potential renal transplant recipients: a single-center prospective observational study. Am J Transplant. 2008;8:1673–1683. doi: 10.1111/j.1600-6143.2008.02281.x

25. Ting SM, Iqbal H, Kanji H, Hamborg T, Aldridge N, Krishnan N, Imam CH, Banerjee P, Bland R, Higgins R, et al. Functional cardiovascular reserve predicts survival pre-kidney and post-kidney transplantation. Am J Nephrol. 2014;39:187–195. doi: 10.1055/asn.2013040348

26. Chakka HA, Angadi SS, Heilman RL, Kaplan B, Scott RL, Bollempalli H, Cha SS, Khamash HA, Huskey JL, Mour GK, et al. Cardiorespiratory fitness (peak oxygen uptake): safe and effective measure for cardiovascular screening before kidney transplantation. J Am Heart Assoc. 2018;7:e008662. doi: 10.1161/JAHA.118.008662

27. Sietsma KE, Amato A, Adler SG, Brass EP. Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. Kidney Int. 2004;65:719–724. doi: 10.1111/j.1523-1755.2004.00411.x
Table S1. Baseline characteristics stratified by transplantation status

| Demographics                  | Not Transplanted (n=373) | Transplanted (n=525) | p-value |
|-------------------------------|--------------------------|----------------------|---------|
| Age (years)                   | 51.7±11.9                | 52.1±10.9            | 0.607   |
| Male sex                      | 234 (63%)                | 352 (67%)            | 0.181   |
| BMI (kg/m²)                   | 27.3±5.7                 | 27.0±5.0             | 0.412   |
| Cardiovascular risk factors   |                          |                      |         |
| Diabetes                      | 141 (38%)                | 210 (40%)            | 0.506   |
| Hypertension                  | 319 (86%)                | 472 (90%)            | 0.046   |
| Hyperlipidaemia               | 183 (49%)                | 238 (45%)            | 0.270   |
| History of smoking            | 148 (40%)                | 155 (30%)            | 0.002   |
| History of IHD                | 85 (23%)                 | 113 (22%)            | 0.652   |
| Previous transplantation      | 53 (14%)                 | 57 (11%)             | 0.131   |
| On renal replacement therapy  | 213 (57%)                | 409 (78%)            | <0.001  |
| Peritoneal Dialysis           | 65 (17%)                 | 134 (26%)            | 0.004   |
| Haemodialysis                 | 148 (40%)                | 275 (52%)            | <0.001  |
| Cause of kidney disease       |                          |                      |         |
| Diabetes                      | 125 (34%)                | 130 (25%)            | 0.004   |
| IgA nephropathy               | 59 (16%)                 | 91 (17%)             | 0.548   |
| Reflux nephropathy            | 25 (7%)                  | 46 (9%)              | 0.260   |
| Polycystic kidney disease     | 33 (9%)                  | 70 (13%)             | 0.038   |
| Glomerulonephritis            | 73 (20%)                 | 112 (21%)            | 0.520   |
| Renovascular                  | 26 (7%)                  | 23 (4%)              | 0.092   |
| Miscellaneous                 | 32 (9%)                  | 53 (10%)             | 0.444   |

Exercise stress echocardiography results
| Test during long interdialytic interval | 61 (46%) | 78 (33%) | 0.011 |
| Test performed on beta blockers | 170 (46%) | 209 (40%) | 0.085 |
| Exercise duration (min) | 7.1±2.9 | 7.9±2.5 | <0.001 |
| Reached ≥85% MPHR | 209 (56%) | 326 (62%) | 0.068 |
| METs | 8.8±2.9 | 9.5±2.7 | <0.001 |
| Achieved 4 METs | 364 (98%) | 520 (99%) | 0.082 |
| Achieved 7 METs | 280 (75%) | 454 (86%) | <0.001 |
| Achieved predicted METs | 150 (40%) | 279 (53%) | <0.001 |
| Baseline LVEF <50% | 70 (19%) | 71 (14%) | 0.033 |
| Abnormal Stress | 68 (18%) | 75 (14%) | 0.111 |
| Echocardiogram | | | |
| Non-diagnostic | 19 (5%) | 15 (3%) | 0.265 |
| Global failure in LV contractile reserve | 28 (8%) | 23 (4%) | 0.190 |
| Inducible regional wall motion abnormalities | 21 (6%) | 37 (7%) | 0.025 |
| Underwent coronary angiography | 27 (40%) | 29 (39%) | 0.899 |
| Non-MI revascularization | 11 (3%) | 17 (3%) | 0.806 |
| Outcomes | | | |
| MACE | 43 (12%) | 50 (10%) | 0.331 |
| Cardiac Death | 14 (4%) | 7 (1%) | 0.018 |
| Non-fatal MI | 23 (6%) | 30 (6%) | 0.777 |
| Stroke | 16 (4%) | 16 (3%) | 0.323 |

Values are mean ± standard deviation, median (Q1-Q3) or n (%).
BMI – body mass index, IHD – ischaemic heart disease, LV – left ventricular, LVEF – left ventricular ejection fraction. MACE – major adverse cardiovascular outcomes, METs – metabolic equivalents, MI – myocardial infarction, MPHR – maximum predicted heart rate.
Table S2. Population characteristics stratified by 7 metabolic equivalents

| Demographics          | <7 METs (n=164) | ≥7 METs (n=734) | p-value |
|-----------------------|-----------------|-----------------|---------|
| Age (years)           | 56.4±9.8        | 50.9±11.4       | <0.001* |
| Male sex              | 91 (55%)        | 495 (68%)       | 0.004   |
| BMI (kg/m²)           | 28.9±5.7        | 26.7±5.1        | <0.001  |
| Cardiovascular risk factors |                 |                 |         |
| Diabetes              | 96 (59%)        | 255 (35%)       | <0.001  |
| Hypertension          | 148 (90%)       | 643 (88%)       | 0.345   |
| Hyperlipidaemia       | 77 (47%)        | 344 (47%)       | 0.984   |
| History of smoking    | 66 (40%)        | 237 (32%)       | 0.051   |
| History of IHD        | 54 (33%)        | 144 (20%)       | <0.001  |
| Previous transplantation | 18 (11%)    | 92 (13%)        | 0.582   |
| On renal replacement therapy | 118 (72%)   | 504 (69%)       | 0.410   |
| Peritoneal Dialysis   | 45 (27%)        | 154 (21%)       | 0.072   |
| Haemodialysis         | 73 (45%)        | 350 (48%)       | 0.462   |
| Cause of kidney disease |               |                 |         |
| Diabetes              | 82 (50%)        | 173 (24%)       | <0.001  |
| IgA nephropathy       | 18 (11%)        | 132 (18%)       | 0.030   |
| Reflux nephropathy    | 9 (5%)          | 62 (8%)         | 0.204   |
| Polycystic kidney disease | 8 (5%)     | 95 (13%)        | 0.003   |
| Glomerulonephritis    | 22 (13%)        | 163 (22%)       | 0.012   |
| Renovascular          | 11 (7%)         | 38 (5%)         | 0.435   |
| Miscellaneous         | 14 (9%)         | 71 (10%)        | 0.691   |
**Exercise stress echocardiography results**

|                          | Test during long interdialytic interval |  |
|--------------------------|----------------------------------------|--|
|                          | 24 (37%)                               | 115 (38%) | 0.891 |
| Exercise duration (min)  | 3.7±1.4                                 | 8.5±2.1   | <0.001 |
| Reached ≥85% MPHR        | 44 (27%)                                | 491 (67%) | <0.001 |
| METs                     | 5.2±1.0                                 | 10.1±2.3  | <0.001 |
| Baseline LVEF <50%       | 44 (27%)                                | 97 (13%)  | <0.001 |
| Abnormal Stress          | 54 (33%)                                | 89 (12%)  | <0.001 |

**Echocardiogram**

|                          | Non-diagnostic                        |  |
|--------------------------|----------------------------------------|--|
|                          | 24 (15%)                               | 4 (1%)   | <0.001 |
| Global failure in LV contractile reserve | 11 (7%)                                | 40 (5%)  | 0.003  |
| Inducible regional wall motion abnormalities | 18 (11%)                               | 40 (5%)  | 0.170  |
| Non-MI revascularization | 10 (6%)                                | 18 (2%)  | 0.015* |
| Transplanted             | 71 (43%)                               | 454 (62%) | <0.001 |
| Median time to transplantation | 1.5 [0.9-2.3]                       | 1.5 [0.7-2.9] | 0.964 |

Values are mean ± standard deviation, median (Q1-Q3) or n (%).

*BMI* – body mass index, *IHD* – ischaemic heart disease, *LV* – left ventricular, *LVEF* – left ventricular ejection fraction, *METs* – metabolic equivalents, *MI* – myocardial infarction, *MPHR* – maximum predicted heart rate.
Table S3. Univariate associations of clinical factors, echocardiographic parameters, ability to achieve predicted metabolic equivalents and major adverse cardiovascular events

| Variable                                      | Hazard ratio | 95% CI    | p-value |
|-----------------------------------------------|--------------|-----------|---------|
| Age                                           | 1.01         | 0.99-1.03 | 0.327   |
| Sex (female referent)                         | 0.58         | 0.34-0.96 | 0.035   |
| Diabetes                                      | 2.40         | 1.54-3.74 | <0.001  |
| Hypertension                                  | 2.43         | 0.89-6.63 | 0.084   |
| Hyperlipidemia                                | 2.25         | 1.42-3.57 | 0.001   |
| History of smoking                            | 1.97         | 1.27-3.05 | 0.003   |
| History of ischaemic heart disease            | 1.92         | 1.23-3.01 | 0.004   |
| Previous kidney transplantation               | 0.49         | 0.20-1.21 | 0.123   |
| Body mass index                               | 1.03         | 0.99-1.07 | 0.200   |
| Current renal replacement therapy             | 1.22         | 0.72-2.07 | 0.451   |
| LV hypertrophy                                | 1.25         | 0.80-1.95 | 0.330   |
| LV ejection fraction<50%                      | 2.04         | 1.25-3.33 | 0.004   |
| Abnormal stress echocardiogram                | 1.52         | 0.92-2.52 | 0.105   |
| Non-MI revascularization                      | 3.08         | 1.48-6.40 | 0.003   |
| Achieved Predicted METs                       | 0.41         | 0.25-0.66 | <0.001  |
| Kidney Transplant*                            | 0.48         | 0.28-0.81 | 0.006   |
Hazard ratio for age was calculated per one year. Hazard ratio for body mass index was calculated per 1kg/m² increase.

* Transplantation was treated as a time-dependent covariate

CI – confidence interval, LV – left ventricle, METs – metabolic equivalents, MI – myocardial infarction
Table S4. Multivariable associations of clinical factors, echocardiographic parameters, metabolic equivalents as a continuous variable and major adverse cardiovascular events

| Variable                              | Hazard ratio | 95% CI      | p-value |
|---------------------------------------|--------------|-------------|---------|
| Age                                   | 0.99         | 0.97-1.01   | 0.336   |
| Sex (female referent)                 | 0.62         | 0.35-1.09   | 0.093   |
| Diabetes                              | 1.72         | 1.06-2.78   | 0.027   |
| Hypertension                          | 1.55         | 0.55-4.36   | 0.406   |
| Hyperlipidaemia                       | 1.73         | 1.05-2.86   | 0.031   |
| History of smoking                    | 1.41         | 0.89-2.23   | 0.144   |
| History of ischaemic heart disease    | 1.11         | 0.67-1.82   | 0.689   |
| Previous kidney transplantation       | 0.53         | 0.21-1.34   | 0.179   |
| Body mass index                       | 1.00         | 0.95-1.04   | 0.846   |
| LV ejection fraction<50%              | 1.41         | 0.81-2.44   | 0.220   |
| Abnormal stress echocardiogram        | 0.94         | 0.53-1.63   | 0.815   |
| Non-MI revascularization              | 1.92         | 0.89-4.11   | 0.095   |
| METs                                  | 0.88         | 0.80-0.96   | 0.007   |
| Kidney transplant*                    | 0.53         | 0.30-0.92   | 0.024   |

Hazard ratio for age was calculated per one year. Hazard ratio for body mass index was calculated per 1kg/m² increase.

* Transplantation was treated as a time-dependent covariate

CI – confidence interval, LV – left ventricle, METs – metabolic equivalents, MI – myocardial infarction
Table S5. Multivariable associations of clinical factors, echocardiographic parameters, ability to achieve 7 metabolic equivalents and major adverse cardiovascular events

| Variable                              | Hazard ratio | 95% CI     | p-value |
|---------------------------------------|--------------|------------|---------|
| Age                                   | 0.99         | 0.97-1.01  | 0.447   |
| Sex (female referent)                 | 0.64         | 0.36-1.13  | 0.126   |
| Diabetes                              | 1.75         | 1.08-2.84  | 0.023   |
| Hypertension                          | 1.50         | 0.53-4.21  | 0.444   |
| Hyperlipidaemia                       | 1.78         | 1.08-2.95  | 0.024   |
| History of smoking                    | 1.42         | 0.89-2.24  | 0.138   |
| History of ischaemic heart disease    | 1.06         | 0.64-1.74  | 0.822   |
| Previous kidney transplantation       | 0.53         | 0.21-1.33  | 0.177   |
| Body mass index                       | 1.01         | 0.96-1.05  | 0.808   |
| LV ejection fraction<50%              | 1.50         | 0.86-2.61  | 0.151   |
| Abnormal stress echocardiogram        | 0.97         | 0.55-1.71  | 0.903   |
| Non-MI revascularization              | 1.94         | 0.90-4.18  | 0.092   |
| Achieved ≥7 METs                      | 0.55         | 0.32-0.95  | 0.033   |
| Kidney transplant*                    | 0.52         | 0.30-0.91  | 0.021   |

Hazard ratio for age was calculated per one year. Hazard ratio for body mass index was calculated per 1kg/m² increase.

* Transplantation was treated as a time-dependent covariate

CI – confidence interval, LV – left ventricle, METs – metabolic equivalents, MI – myocardial infarction
Table S6. Population characteristics comparing patients who achieved predicted metabolic equivalents who did and did not receive transplantation

| Demographics                        | Achieved Predicted METs and not transplanted (n=150) | Achieved Predicted METs and transplanted (n=279) | p-value |
|-------------------------------------|-----------------------------------------------------|-------------------------------------------------|---------|
| Age (years)                         | 53.7±11.8                                           | 53.7±10.2                                       | 0.952   |
| Male sex                            | 85 (57%)                                            | 170 (61%)                                       | 0.391   |
| BMI (kg/m²)                         | 25.5±4.9                                            | 25.7±4.4                                        | 0.716   |
| Cardiovascular risk factors         |                                                     |                                                 |         |
| Diabetes                            | 26 (17%)                                            | 104 (37%)                                       | <0.001  |
| Hypertension                        | 127 (85%)                                           | 250 (90%)                                       | 0.135   |
| Hyperlipidemia                      | 69 (46%)                                            | 130 (47%)                                       | 0.906   |
| History of smoking                  | 49 (32%)                                            | 74 (27%)                                        | 0.180   |
| History of IHD                      | 26 (17%)                                            | 63 (23%)                                        | 0.201   |
| Previous kidney transplantation     | 23 (15%)                                            | 32 (11%)                                        | 0.254   |
| On renal replacement therapy        | 69 (46%)                                            | 222 (80%)                                       | <0.001  |
| Peritoneal Dialysis                 | 20 (13%)                                            | 79 (28%)                                        | <0.001  |
| Hemodialysis                        | 49 (33%)                                            | 143 (51%)                                       | <0.001  |
| Cause of kidney disease             |                                                     |                                                 |         |
| Diabetes                            | 23 (15%)                                            | 58 (21%)                                        | 0.169   |
| IgA nephropathy                     | 35 (23%)                                            | 46 (16%)                                        | 0.084   |
| Reflux nephropathy                  | 15 (10%)                                            | 26 (9%)                                         | 0.819   |
| Polycystic kidney disease           | 19 (13%)                                            | 38 (14%)                                        | 0.781   |
| Glomerulonephritis                  | 40 (27%)                                            | 73 (26%)                                        | 0.910   |
| Renovascular  | 9 (6%) | 15 (5%) | 0.789 |
|---------------|--------|---------|-------|
| Miscellaneous | 9 (6%) | 23 (8%) | 0.267 |
| Test during long interdialytic interval | 19 (46%) | 44 (37%) | 0.290 |
| Test performed on beta-blockers | 56 (37%) | 100 (36%) | 0.759 |
| Baseline LVEF <50% | 17 (11%) | 27 (10%) | 0.590 |
| Abnormal Stress Echocardiogram | 18 (12%) | 24 (9%) | 0.259 |
| Non-diagnostic | 2 (1%) | 1 (0%) | 0.387 |
| Global failure in LV contractile reserve | 11 (7%) | 8 (3%) | 0.073 |
| Inducible regional wall motion abnormalities | 5 (3%) | 15 (5%) | 0.026 |
| Underwent coronary angiography | 8 (5%) | 8 (3%) | 0.463 |
| Non-MI revascularization | 1 (1%) | 5 (2%) | 0.344 |

Values are mean ± standard deviation or n (%).

*BMI – body mass index, IHD – ischaemic heart disease, LVEF – left ventricular ejection fraction, METs – metabolic equivalents, MI – myocardial infarction.*
Table S7. Population characteristics comparing patients who achieved predicted metabolic equivalents who did not receive transplantation and patients who did not achieve predicted metabolic equivalents and received transplantation

| Demographics                        | Did Not Achieve Predicted METs and transplanted (n=246) | Achieved Predicted METs and not transplanted (n=150) | p-value |
|-------------------------------------|--------------------------------------------------------|-----------------------------------------------------|---------|
| Age (years)                         | 50.1±11.4                                              | 53.7±11.8                                           | 0.003   |
| Male sex                            | 182 (74%)                                              | 85 (57%)                                            | <0.001  |
| BMI (kg/m²)                         | 28.5±5.2                                               | 25.5±4.9                                            | <0.001  |
| Cardiovascular risk factors         |                                                        |                                                     |         |
| Diabetes                            | 106 (43%)                                              | 26 (17%)                                            | <0.001  |
| Hypertension                        | 222 (90%)                                              | 127 (85%)                                           | 0.096   |
| Hyperlipidemia                      | 108 (44%)                                              | 69 (46%)                                            | 0.684   |
| History of smoking                  | 81 (33%)                                               | 49 (33%)                                            | 0.957   |
| History of IHD                      | 50 (20%)                                               | 26 (17%)                                            | 0.463   |
| Previous kidney transplantation     | 25 (10%)                                               | 23 (15%)                                            | 0.126   |
| On renal replacement therapy        | 187 (76%)                                              | 69 (46%)                                            | <0.001  |
| Peritoneal Dialysis                 | 55 (22%)                                               | 20 (13%)                                            | 0.026   |
| Hemodialysis                        | 132 (54%)                                              | 49 (33%)                                            | <0.001  |
| Cause of kidney disease             |                                                        |                                                     |         |
| Diabetes                            | 72 (29%)                                               | 23 (15%)                                            | 0.002   |
| IgA nephropathy                     | 45 (18%)                                               | 35 (23%)                                            | 0.226   |
| Reflux nephropathy                  | 20 (8%)                                                | 15 (10%)                                            | 0.525   |
| Polycystic kidney disease           | 32 (13%)                                               | 19 (13%)                                            | 0.922   |
| Condition                          | Group 1 | Group 2 | P-value |
|-----------------------------------|---------|---------|---------|
| glomerulonephritis                | 30 (12%)| 35 (23%)| 0.004   |
| Renovascular                      | 8 (3%)  | 9 (6%)  | 0.191   |
| Vasculitides                      | 9 (4%)  | 5 (3%)  | 0.865   |
| Miscellaneous                     | 30 (12%)| 9 (6%)  | 0.025   |
| Test during long interdialytic    | 34 (29%)| 19 (46%)| 0.040   |
| interval                          |         |         |         |
| Test performed on beta-blockers   | 109 (44%)| 56 (37%)| 0.172   |
| Baseline LVEF <50%                | 44 (18%)| 17 (11%)| 0.080   |
| Abnormal Stress                   | 51 (21%)| 18 (12%)| 0.026   |
| Echocardiogram                    |         |         |         |
| Non-diagnostic                    | 14 (6%) | 2 (1%)  | 0.158   |
| Global failure in LV contractile reserve | 15 (6%) | 11 (7%) | 0.017   |
| Inducible regional wall motion abnormalities | 22 (9%) | 5 (3%)  | 0.251   |
| Underwent coronary angiography    | 21 (9%) | 8 (5%)  | 0.809   |
| Non-MI revascularization          | 12 (5%) | 1 (1%)  | 0.023   |

Values are mean ± standard deviation or n (%).

**BMI** – body mass index, **IHD** – ischaemic heart disease, **LVEF** – left ventricular ejection fraction, **METs** – metabolic equivalents, **MI** – myocardial infarction.
Table S8. Population characteristics comparing patients who achieved <7 metabolic equivalents and received transplantation with patients who achieved ≥7 metabolic equivalents and did not receive transplantation

| Demographics                  | <7 METs and transplanted (n=71) | ≥7 METs and not transplanted (n=280) | p-value |
|-------------------------------|---------------------------------|--------------------------------------|---------|
| Age (years)                   | 57.1±10.3                       | 50.2±12.2                            | <0.001  |
| Male sex                      | 43 (61%)                        | 186 (66%)                            | 0.354   |
| BMI (kg/m²)                   | 28.4±4.4                        | 26.7±5.2                             | 0.013   |
| Cardiovascular risk factors   |                                 |                                      |         |
| Diabetes                      | 41 (58%)                        | 86 (31%)                             | <0.001  |
| Hypertension                  | 70 (99%)                        | 241 (86%)                            | 0.003   |
| Hyperlipidaemia               | 32 (45%)                        | 138 (49%)                            | 0.526   |
| History of smoking            | 24 (34%)                        | 106 (38%)                            | 0.527   |
| History of IHD                | 19 (27%)                        | 50 (18%)                             | 0.092   |
| Previous renal transplantation| 7 (10%)                         | 42 (15%)                             | 0.264   |
| On renal replacement therapy  | 55 (77%)                        | 150 (53%)                            | <0.001  |
| Peritoneal Dialysis           | 21 (30%)                        | 41 (15%)                             | 0.003   |
| Haemodialysis                 | 34 (48%)                        | 109 (39%)                            | 0.170   |
| Cause of kidney disease       |                                 |                                      |         |
| Diabetes                      | 29 (41%)                        | 72 (26%)                             | 0.012   |
| IgA nephropathy               | 10 (14%)                        | 51 (18%)                             | 0.412   |
| Reflux nephropathy            | 6 (8%)                          | 22 (8%)                              | 0.869   |
| Polycystic kidney disease     | 5 (7%)                          | 30 (11%)                             | 0.356   |
|                        | Group 1 | Group 2 | p-value |
|------------------------|---------|---------|---------|
| Glomerulonephritis     | 11 (15%)| 62 (22%)| 0.218   |
| Renovascular           | 4 (6%)  | 19 (7%) | 0.726   |
| Miscellaneous          | 6 (8%)  | 24 (9%) | 0.948   |
| Test during long interdialytic interval | 7 (25%) | 44 (46%) | 0.044   |
| Baseline LVEF <50%     | 15 (21%)| 41 (15%)| 0.183   |
| Abnormal Stress        | 23 (32%)| 37 (13%)| <0.001  |
| Echocardiogram         |         |         |         |
| Non-diagnostic         | 10 (14%)| 4 (1%)  | 0.004   |
| Global failure in LV contractile reserve | 3 (4%)  | 20 (7%) | 0.001   |
| Inducible regional wall motion abnormalities | 10 (14%)| 13 (5%) | 0.518   |
| Underwent coronary angiography | 11 (15%)| 15 (5%) | 0.580   |
| Non-MI revascularization | 5 (7%)  | 6 (2%)  | 0.034   |

Values are mean ± standard deviation or n (%).

BMI – body mass index, IHD – ischaemic heart disease, LV – left ventricular, LVEF – left ventricular ejection fraction. METs – metabolic equivalents, MI – myocardial infarction
Graph demonstrates relative hazard of MACE with associated 95% CI for METs fitted from multivariable modelling at 7 years, using age, sex, diabetes, hypertension, hyperlipidemia, history of smoking, history of ischaemic heart disease, previous kidney transplantation, body mass index, baseline left ventricular dysfunction, abnormal exercise stress echocardiography result, non-myocardial infarction revascularization prior to transplantation, ability to achieve predicted METs, and transplantation (treated as time-dependent covariable). Results demonstrate a reduction of 12% in hazard for each increasing unit of METs (p=0.01).

CI – confidence interval, HR – Hazard ratio, MACE – Major adverse cardiovascular events, METs – metabolic equivalents
Figure S2. Cumulative MACE free proportion stratified by MET groups

With increasing categories of METs, patients have an improved freedom from MACE (p<0.001).

MACE – Major adverse cardiovascular events, METs – metabolic equivalents