ORIGINAL RESEARCH

Prognostic Value of Exercise Capacity in Kidney Transplant Candidates

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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

Cardiovascular disease (CVD) is the leading cause of mortality in patients with chronic kidney disease (CKD) regardless of transplantation status.[1,2] Therefore, risk stratification by cardiac stress testing is often performed in the work-up for kidney transplantation with consideration of revascularization to reduce this risk.[3,4] However, the ISCHEMIA-CKD study demonstrated that revascularization does not reduce death or non-fatal myocardial infarction (MI) in patients with

CKD, questioning the role of routine cardiac stress testing in this vulnerable population.[5] Furthermore, the majority of CKD patients referred for cardiac stress testing prior to transplantation are asymptomatic, and may not have improved angina-related health status if they undergo coronary revascularization following abnormal cardiac stress testing results.[6] Although current literature suggests less need for cardiac stress testing to guide revascularization in patients with CKD, there

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

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 CKD[8] 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 capacity[11] 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.

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 CKD[7] (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 nondiagnostic 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).[16] 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,[17] and ability to achieve 85% of maximal predicted heart rate (MPHR) which is the standard target heart rate for ESE.[15]

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.[18] 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.[19] 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/m^2, $P<0.001$), 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 increment 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

Table 1. Population Characteristics

Demographics	Total (n=898)	Did not achieve predicted METs (n=469)	Achieved predicted METs (n=429)	P value
Age, y	51.8±11.3	50.2±11.6	53.7±10.8	<0.001
Male sex	586 (65%)	331 (71%)	255 (59%)	<0.001
BMI, kg/m^2	27.1±5.3	28.5±5.5	25.6±4.6	<0.001
Cardiovascular risk factors				
Diabetes	351 (39%)	221 (47%)	130 (30%)	<0.001
Hypertension	791 (88%)	414 (88%)	377 (88%)	0.856
Hyperlipidemia	421 (47%)	222 (47%)	199 (46%)	0.776
History of smoking	303 (34%)	180 (38%)	123 (29%)	0.002
History of IHD	198 (22%)	109 (23%)	89 (21%)	0.368
Previous kidney transplantation	110 (12%)	55 (12%)	55 (13%)	0.618
On renal replacement therapy	622 (69%)	331 (71%)	291 (68%)	0.373
Peritoneal dialysis	199 (22%)	100 (21%)	99 (23%)	0.527
Hemodialysis	423 (47%)	231 (49%)	192 (45%)	0.177
Cause of kidney disease				
Diabetes	255 (28%)	174 (37%)	81 (19%)	<0.001
IgA nephropathy	150 (17%)	69 (15%)	81 (19%)	0.094
Reflux nephropathy	71 (8%)	30 (6%)	41 (10%)	0.080
Polycystic kidney disease	103 (11%)	46 (10%)	57 (13%)	0.102
Glomerulonephritis	185 (20%)	72 (15%)	113 (26%)	<0.001
Renovascular	49 (5%)	25 (5%)	24 (6%)	0.862
Miscellaneous	85 (9%)	53 (11%)	32 (7%)	0.036
Exercise stress echocardiography results				
Test during long interdialytic interval	139 (15%)	76 (36%)	63 (39%)	0.554
Test performed on beta-blockers	379 (42%)	223 (48%)	156 (36%)	0.001
Exercise duration, min	7.6±2.7	5.9±2.2	9.4±1.9	<0.001
Reached ≥85% MPHR	535 (60%)	221 (47%)	314 (73%)	<0.001
METs	9.2±2.8	7.4±2.1	11.2±2.0	<0.001
Baseline LVEF <50%	141 (16%)	97 (21%)	44 (10%)	<0.001
Abnormal stress echocardiogram	143 (16%)	101 (22%)	42 (10%)	<0.001
Non-diagnostic	32 (4%)	31 (7%)	3 (1%)	0.003
Global failure in LV contractile reserve	53 (6%)	32 (7%)	19 (4%)	0.123
Inducible regional wall motion abnormalities	58 (6%)	38 (8%)	20 (5%)	0.268
Underwent coronary angiography	56 (6%)	40 (9%)	16 (4%)	0.866
Non-MI revascularization	28 (3%)	22 (5%)	6 (1%)	0.005
Transplanted	525 (58%)	246 (52%)	279 (65%)	<0.001
Median time to transplantation	1.5 [0.8–2.8]	1.6 [0.7–2.7]	1.5 [0.8–2.9]	0.752

Values are mean±SD, median (Q1–Q3) or n (%). BMI indicates body mass index; IHD, ischemic heart disease; LV, left ventricular; LVEF, left ventricular ejection fraction; METs, metabolic equivalents; MI, myocardial infarction; and MPHR, maximum predicted heart rate.

primary outcome occurred in 42 patients who did not achieve predicted METs and 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 ≥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
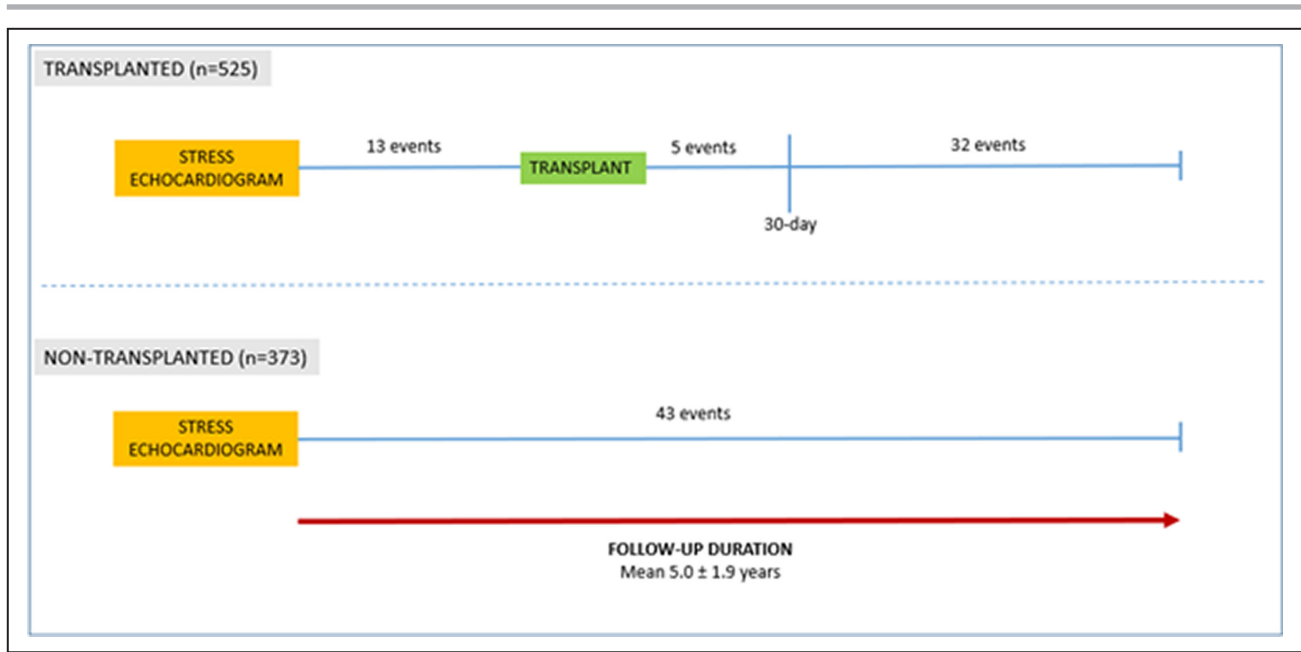
Figure 1.   Major adverse cardiovascular events in patients stratified by transplantation status.
Results shown are for follow-up duration from time of stress echocardiogram until July 2020.

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

Table 2.   Multivariable Analysis for Major Adverse Cardiovascular Events

Variable	Hazard ratio	95% CI	P value
Age	1.00	0.98–1.03	0.890
Sex (female referent)	0.79	0.45–1.36	0.403
Diabetes	1.78	1.11–2.87	0.017
Hypertension	1.54	0.55–4.34	0.414
Hyperlipidemia	1.70	1.03–2.82	0.038
History of smoking	1.39	0.88–2.20	0.161
History of ischemic heart disease	1.14	0.69–1.87	0.616
Previous kidney transplantation	0.56	0.22–1.40	0.215
Body mass index	1.00	0.96–1.04	0.889
LV ejection fraction<50%	1.47	0.85–2.53	0.164
Abnormal stress echocardiogram	0.98	0.56–1.72	0.954
Non-MI revascularization	2.07	0.97–4.43	0.061
Achieved predicted METs	0.49	0.29–0.82	0.007
Kidney transplant*	0.52	0.30–0.91	0.021

Hazard ratio for age was calculated per 1 year. Hazard ratio for body mass index was calculated per 1 kg/m² increase. LV indicates left ventricle; METs, metabolic equivalents; and MI, myocardial infarction.

*Transplantation was treated as a time-dependent covariate.

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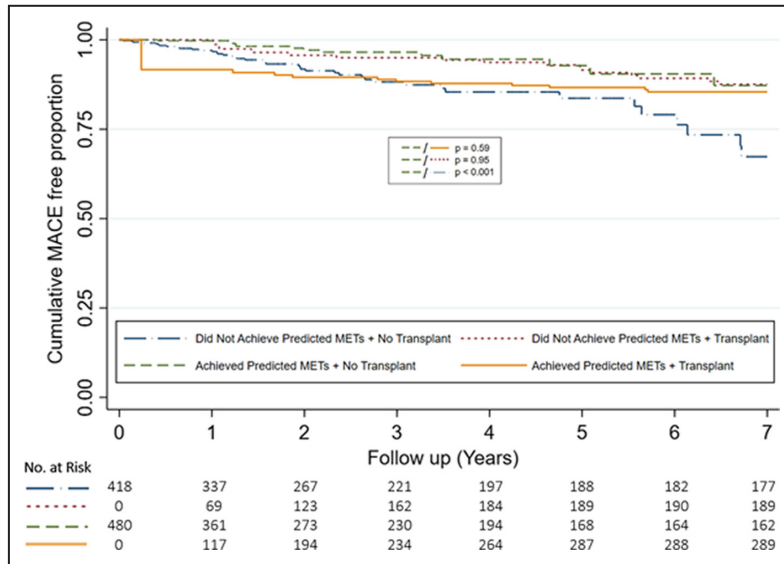
Figure 2. Cumulative major adverse cardiovascular event free proportion stratified by achievement of predicted METs and transplantation status.
Graph demonstrates cumulative MACE free proportion stratified by achievement of predicted METs and transplantation status at 7 years. Transplantation was treated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

peri-operative cardiovascular risk at transplantation, and to predict long-term cardiovascular outcomes.[3] 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.[5,20] Furthermore, revascularization following abnormal cardiac stress testing may not improve
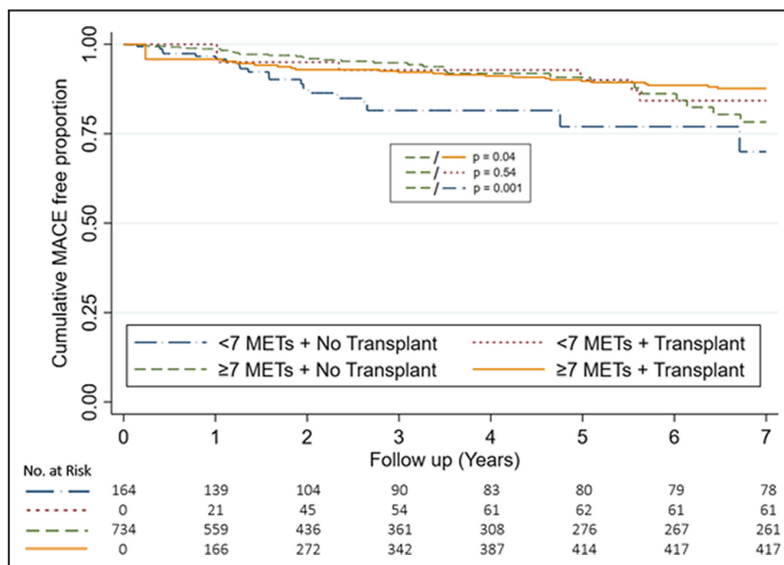
Figure 3. Cumulative major adverse cardiovascular event free proportion stratified by ≥7 MET threshold and transplantation status.
Graph demonstrates cumulative MACE free proportion stratified by achievement of 7 METs and transplantation status at 7 years. Transplantation was treated as a time-dependent variable and curves reflect univariable modeling. MACE indicates major adverse cardiovascular event; and METs, metabolic equivalents.
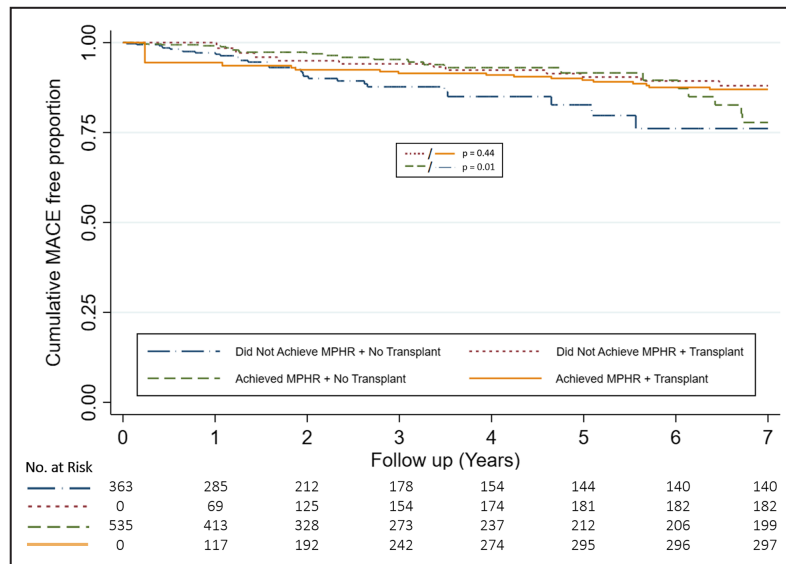
Figure 4. Cumulative major adverse cardiovascular event free proportion stratified by ability to achieve 85% maximal predicted heart rate and transplantation status.
Graph demonstrates cumulative MACE free proportion stratified by achievement of 85% maximal predicted heart rate and transplantation status at 7 years. Transplantation was treated as a time-dependent variable and curves reflect univariable modeling. MACE indicates major adverse cardiovascular event; and MPHR, maximal predicted heart rate.

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 (n=223)	Transplanted* (n=246)	Not transplanted (n=150)	Transplanted* (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.[17] 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.[24] Ting et al performed cardiopulmonary exercise testing (CPET) in 240 patients and demonstrated that reduced anerobic threshold <40% of alveolar oxygen uptake (VO_2) conferred a significantly worse prognosis.[25] Other observational studies have also demonstrated the association of peak VO_2 on CPET with future cardiac events and all-cause mortality in kidney and/or pancreas transplant candidates[26] and patients receiving hemodialysis.[27] 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.

Disclosures

The authors have no disclosures, conflicts of interest, or relationships to industry to report.

Supplemental Material

Tables S1–S8
Figures S1–S2

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SUPPLEMENTAL MATERIAL

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/m^2)	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 Echocardiogram	68 (18%)	75 (14%)	0.111
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/m^2)	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 Echocardiogram	54 (33%)	89 (12%)	<0.001
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 $1kg/m^2$ 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 $1kg/m^2$ 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 $1kg/m^2$ 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/m^2)	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/m^2)	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

Other 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 interval	34 (29%)	19 (46%)	0.040
Test performed on beta-blockers	109 (44%)	56 (37%)	0.172
Baseline LVEF <50%	44 (18%)	17 (11%)	0.080
Abnormal Stress Echocardiogram	51 (21%)	18 (12%)	0.026
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/m^2)	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

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 Echocardiogram	23 (32%)	37 (13%)	<0.001
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
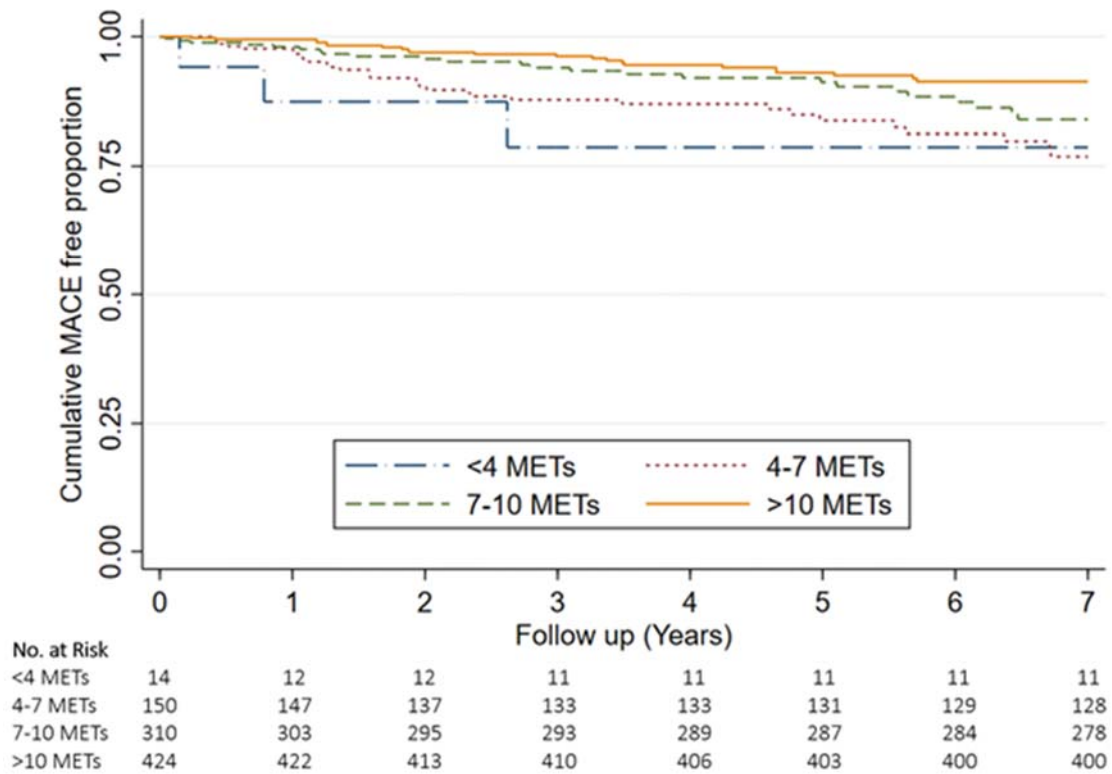
Figure S1. Relationship between relative hazard of MACE with METs
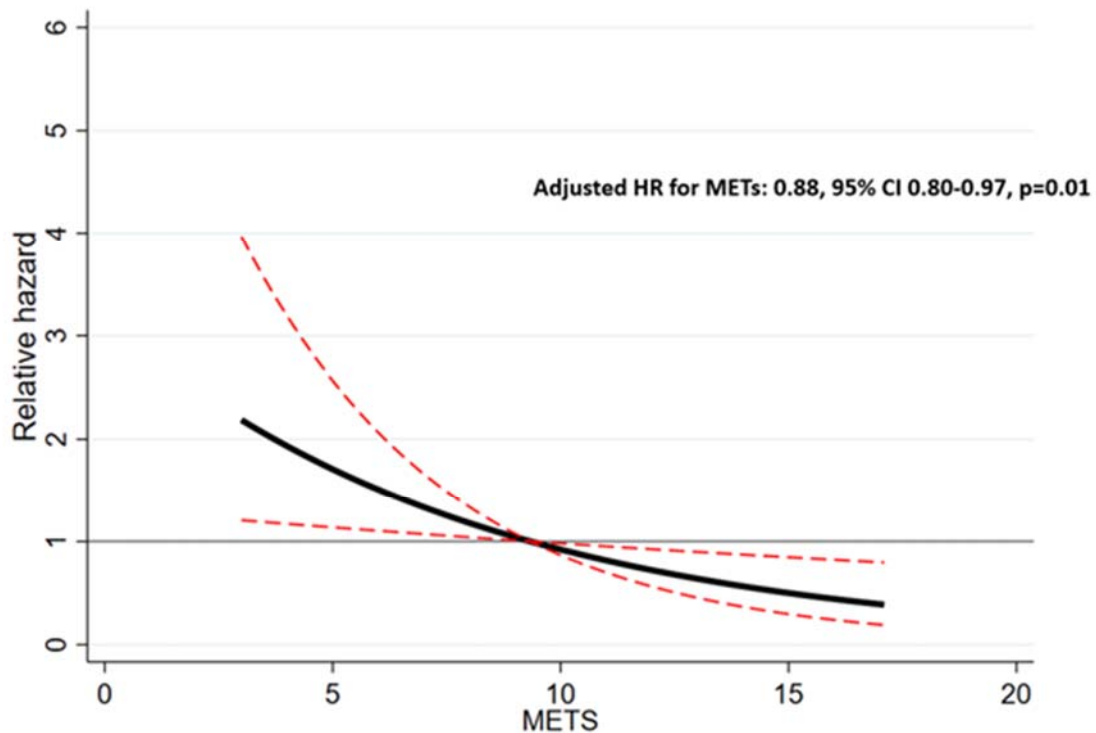
Graph demonstrates relative hazard of MACE with associated 95% CI for METs fitted from multivariable modelling at 7 years, using age, sex, diabetes, hypertension, hyperlipidemia, history of smoking, history of ischaemic heart disease, previous kidney transplantation, body mass index, baseline left ventricular 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

No. at Risk							
<4 METs	14	12	12	11	11	11	11	11
4-7 METs	150	147	137	133	133	131	129	128
7-10 METs	310	303	295	293	289	287	284	278
>10 METs	424	422	413	410	406	403	400	400

With increasing categories of METs, patients have an improved freedom from MACE

(p<0.001).

MACE – Major adverse cardiovascular events, METs – metabolic equivalents