

## CLINICAL RESEARCH

# Exercise E/e' Is a Determinant of Exercise Capacity and Adverse Cardiovascular Outcomes in Chronic Kidney Disease

Gary C.H. Gan, BSc, MBBS,<sup>a,b,c</sup> Krishna K. Kadappu, MBBS, MD, PhD,<sup>c,d,e,f</sup> Aditya Bhat, BMEDSci, MBBS, MPH,<sup>a,c</sup> Fernando Fernandez, AMS, BSc,<sup>a</sup> Suzanne Eshoo, MBBS, PhD,<sup>a</sup> Liza Thomas, MBBS, PhD<sup>a,b,c,g</sup>

## ABSTRACT

**OBJECTIVES** This study sought to assess the relationship between E/e' and exercise capacity in patients with chronic kidney disease (CKD) and evaluate its prognostic role.

**BACKGROUND** Patients with CKD have diastolic dysfunction, reduced physical fitness, and elevated risk of cardiovascular disease.

**METHODS** Patients with stage 3 and 4 CKD without previous cardiac disease underwent resting and exercise stress echocardiograms with assessment of exercise E/e'. Patients were compared to age-, sex-, and risk factor-matched control individuals and were followed annually for 5 years for cardiovascular death and major adverse cardiovascular event(s) (MACE). Exercise capacity was assessed as metabolic equivalents (METs), with reduced exercise capacity defined as METs of  $\leq 7$ . Raised exercise E/e' was defined as  $> 13$ .

**RESULTS** A total of 156 patients with CKD (age  $62.8 \pm 10.6$  years; male: 62%) were compared to 156 matched control individuals. Patients with CKD were more likely to be anemic ( $p < 0.01$ ) and had increased left ventricular mass ( $p < 0.01$ ), larger left atrial volumes ( $p < 0.01$ ), and higher resting ( $p < 0.01$ ) and exercise E/e' ( $p < 0.01$ ). Patients with CKD achieved lower exercise METs ( $p < 0.01$ ), and more patients with CKD had METs of  $\leq 7$  ( $p < 0.01$ ). Receiver-operating characteristic curves showed exercise E/e' (area under the curve [AUC]: 0.89; 95% CI: 0.84 to 0.95;  $p < 0.01$ ) as the strongest predictor of reduced exercise capacity in patients with CKD. Over a follow-up period of 41.4 months, a raised exercise E/e' of  $> 13$  was an independent predictor of cardiovascular death and MACE on unadjusted and adjusted hazard models.

**CONCLUSION** E/e' is a strong predictor of exercise capacity and METs achieved by patients with CKD. Exercise capacity was reduced in patients with CKD, presumably consequent to diastolic dysfunction. Elevated exercise E/e' in patients with CKD is an independent predictor of cardiovascular death and MACE. (J Am Coll Cardiol Img 2020;■:■-■)  
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From the <sup>a</sup>Department of Cardiology Blacktown Hospital, Sydney, New South Wales, Australia; <sup>b</sup>Department of Cardiology Westmead Hospital, Sydney, New South Wales, Australia; <sup>c</sup>University of New South Wales, Sydney, New South Wales, Australia; <sup>d</sup>Department of Cardiology Liverpool Hospital, Sydney, New South Wales, Australia; <sup>e</sup>Department of Cardiology Campbelltown Hospital, Sydney, New South Wales, Australia; <sup>f</sup>Western Sydney University, Sydney, New South Wales, Australia; and the <sup>g</sup>Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia. Dr. Kadappu is supported by an National Health and Medical Research Council Scholarship (GNT1018215). Dr. Gan is supported by a University of New South Wales University Postgraduate Award (UNSW3080080). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## ABBREVIATIONS AND ACRONYMS

**A** = late velocity

**AUC** = area under the curve

**CI** = confidence interval

**CKD** = chronic kidney disease

**E** = early velocity

**E/e'** = ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity

**eGFR** = estimated glomerular filtration rate

**LAVI** = left atrial volume indexed

**LV** = left ventricular

**LVEF** = left ventricular ejection fraction

**LVMi** = left ventricular mass indexed

**MACE** = major adverse cardiovascular event(s)

**MET** = estimated metabolic equivalent

**OR** = odds ratio

In addition to a disproportionately elevated risk of cardiovascular disease, patients with chronic kidney disease (CKD) also have reduced physical fitness and lower physical activity levels (1-4). Although the reduced physical fitness can, in part, be attributed to the increasingly sedentary lifestyle that accompanies the progression of CKD, patients with CKD also have poor cardiorespiratory capacity, which further attenuates their physical capacity (3,4).

Diastolic dysfunction at rest, a common finding in patients with CKD (5,6), is an important prognostic determinant and has been linked to a reduced exercise capacity (5). Noninvasively determined echocardiographic ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/e') is an integral part of diastolic function assessment (7) and has been shown to correlate closely with left ventricular (LV) filling pressures measured invasively at cardiac catheterization (8-10).

Assessment of E/e' after exercise has been useful in unmasking latent diastolic dysfunction. This has particular utility in the subset of patients who may have normal resting E/e' but experience exertional symptoms, such as in a subset of patients with heart failure with preserved ejection fraction (11,12). Few studies, however, have evaluated the utility of resting and exercise E/e' in patients with CKD and their correlation with exercise capacity.

The aim of our study was to assess the utility of resting and exercise E/e' in patients with CKD and to determine its relationship to exercise capacity in these patients. Additionally, we sought to determine the prognostic impact of an elevated exercise E/e' on clinical outcomes in these patients.

## METHODS

**PATIENT SELECTION.** Patients with stage 3 and stage 4 CKD, defined as an estimated glomerular filtration rate (eGFR) of 30 to 60 ml/min/1.73 m<sup>2</sup> and eGFR of 15 to 30 ml/min/1.73 m<sup>2</sup>, respectively, by the Modification of Diet in Renal Disease formula, were prospectively recruited from the nephrology outpatient clinics of Blacktown Hospital and Liverpool Hospital from January 2011 to December 2017. All patients were required to be in sinus rhythm, have no prior cardiac history, and be able to provide informed consent and perform an exercise stress test. Patients with CKD were also required to have stable renal function, which was defined as a change of ≤5% in

baseline eGFR over the preceding 3 months before enrollment. Stable renal function was independently adjudicated by the patient's treating nephrologist.

Any patients with atrial fibrillation or flutter, cardiac device in situ, pre-existing coronary artery disease or cardiomyopathy, active malignancy, disabling stroke, or concomitant medical comorbidity limiting lifespan to <12 months were excluded. Patients with valvular disease of greater than mild severity, those with greater than mild mitral annular calcification, and those with evidence of ischemia during stress testing were also excluded.

**STUDY PROTOCOL.** Included participants received thorough clinical evaluation, including detailed history of coexistent cardiac risk factors and medication history. Blood pressure and electrocardiogram was recorded at rest. All patients underwent a comprehensive resting transthoracic echocardiogram and symptom-limited exercise stress echocardiogram. Demographic, clinical, and echocardiographic parameters were compared to control individuals matched for age (±2.5 years), sex, and risk factors (hypertension, diabetes mellitus, and hypercholesterolemia) with normal renal function, prospectively recruited from referrals to the echocardiography laboratory for exercise stress echocardiograms.

Patients with CKD were subsequently followed for up to 5 years, with yearly evaluation or by telephone interview, for the composite outcome of cardiovascular death and major adverse cardiovascular event(s) (MACE). Reported adverse events were corroborated from hospital medical records and general practitioner clinical records. Deaths were corroborated from the New South Wales state births and death registry. We defined MACE as a composite of myocardial infarction, myocardial revascularization, atrial fibrillation, decompensated heart failure, and nonfatal stroke. Our study was approved by the Human Research and Ethics Committee of New South Wales (HREC/14/LPOOL/304).

**TRANSTHORACIC ECHOCARDIOGRAPHY.** Comprehensive transthoracic echocardiogram was performed using commercially available ultrasonography systems (GE, Horton, Norway) with patients in the left lateral decubitus position. Echocardiographic images were obtained from the parasternal, apical, and subcostal views in accordance with the recommendations of the American Society of Echocardiography, and focused views of the left ventricle and left atrium were optimized for 2-dimensional image quality and were acquired at high frame rates (~60 frames/s). All images were saved in digital format for off-line analysis.

LV end-diastolic and end-systolic volumes were traced in the apical 4- and 2-chamber views, and left ventricular ejection fraction (LVEF) was calculated by the Simpsons biplane method. Preserved LVEF was defined as  $\geq 52\%$  for men and  $\geq 54\%$  for women (13). LV mass was calculated using the Devereux formula— $0.8[1.04((LV \text{ end diastolic diameter} + \text{interventricular septal diameter} + \text{posterior wall diameter})^3 - LV \text{ end diastolic diameter}^3)] + 0.6$ —at end diastole and indexed to body surface area to derive the LV mass index (LVMI). Increased LVMI was defined as  $\geq 95 \text{ g/m}^2$  for women and  $\geq 115 \text{ g/m}^2$  for men (13).

LV diastolic function was evaluated from trans-mitral early (E) velocity, late (A) velocity, and the E/A ratio measured from the apical 4-chamber view with the sample volume placed at the tips of the mitral valve leaflets. Tissue pulsed Doppler velocities were measured with the sample volume placed at the septal and lateral mitral annulus, and average e' velocity was obtained. The E/e' ratio was assessed as the ratio of the E velocity/average e' velocity and served as a surrogate of LV filling pressures. Patients were placed into 3 groups based on baseline E/e', as previously defined (normal E/e':  $\leq 8$ ; indeterminate E/e': 8 to 14; elevated E/e':  $>14$ ) (7). LV diastolic dysfunction was graded in accordance with current recommendations (7).

Biplane left atrial maximum volume was evaluated by the modified Simpson method of discs at end systole just before mitral valve opening and was indexed to body surface area.

**EXERCISE ECHOCARDIOGRAPHY.** Following resting transthoracic echocardiogram, symptom-limited exercise treadmill testing was performed using standard treadmill protocols with 12-lead electrocardiographic monitoring. All patients were encouraged to exercise to maximal effort. The duration of exercise was measured, and the estimated metabolic equivalents (METs) were calculated from the peak exercise intensity from treadmill speed and grade. The rate pressure product was calculated as the product of heart rate and systolic blood pressure at peak exercise. Reduced exercise capacity was estimated METs of  $\leq 7$  as previously defined (14). Protocol-based 2-dimensional LV images were obtained at rest and immediately following exercise for assessment of wall motion abnormalities to evaluate ischemia. Mitral inflow E velocity and septal and lateral annular e' velocities were obtained following the acquisition of 2-dimensional images for wall motion analysis. In the case of fusion of the Doppler E and A waves at high heart rates, images were acquired after the heart rate decreased with separation of the waves. Based on

**TABLE 1 Clinical and Demographic Characteristics**

	CKD Group (n = 156)	Control Group (n = 156)	Significance (p Value)
<b>Demographics</b>			
Age, yrs	62.8 $\pm$ 10.6	61.0 $\pm$ 10.4	0.13
Male	191 (62)	191 (62)	0.99
BMI, kg/m <sup>2</sup>	29.51 $\pm$ 5.88	29.92 $\pm$ 6.37	0.56
BSA, m <sup>2</sup>	1.97 $\pm$ 0.25	1.96 $\pm$ 0.27	0.63
<b>Comorbidities</b>			
Hypertension	133 (85)	133 (85)	0.99
Hypercholesterolemia	108 (69)	108 (69)	0.99
Diabetes mellitus	61 (39)	61 (39)	0.99
Anemia	35 (22)	6 (4)	<b>&lt;0.01</b>
COPD	3 (2)	4 (3)	0.42
<b>Medications</b>			
Beta blocker	37 (24)	29 (19)	0.21
ACE inhibitor/ARB	106 (68)	86 (55)	<b>0.02</b>
Furosemide	8 (5)	0 (0)	<b>&lt;0.01</b>
Thiazide	22 (14)	21 (14)	0.87
Aspirin	34 (22)	29 (19)	0.48
Statin	91 (58)	67 (43)	<b>&lt;0.01</b>
Ezetimibe	2 (1)	11 (7)	<b>0.01</b>

Values are mean  $\pm$  SD or n (%). **Bold** values indicates significant p values.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BSA = body surface area; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease.

published reports, an exercise E/e' of  $>13$  was considered indicative of elevated LV filling pressure (8,14).

**STATISTICAL ANALYSIS.** Statistical analyses were performed by using SPSS, version 22.0 (SPSS Inc., Chicago, Illinois). All tests were 2-tailed, with a p value of 0.05 considered statistically significant. All data are presented as mean  $\pm$  SD for continuous variables and as number and percentage for categorical variables. Because our cohorts were matched for age, sex, and cardiovascular risk factors, between-group comparisons were evaluated with conditional logistic regression analysis for categorical variables and paired Student's *t*-test analyses for continuous variables, as appropriate. For analyses using a dichotomous endpoint, we defined reduced exercise tolerance as  $\leq 7$  METs, elevated resting E/e' as  $>14$ , and elevated post-exercise E/e' as  $>13$ .

Determinants of reduced exercise capacity among patients with CKD were assessed with independent *t*-tests and logistic regression analysis. Receiver-operating characteristic curves were used to evaluate the relative contributions of different variables to reduced exercise capacity, and DeLong tests were performed to compare the strengths of the areas under the curve (AUCs). Patients with normal or indeterminate E/e' at rest were further classified into subgroups based on changes in E/e' following

**TABLE 2 Echocardiographic Parameters Between Groups**

	CKD Group (n = 156)	Control Group (n = 156)	Significance (p Value)
<b>LV parameters</b>			
LV end-diastolic dimension, mm	45.9 ± 7.1	45.1 ± 5.9	0.24
LV end-systolic dimension, mm	27.2 ± 5.5	28.1 ± 5.2	0.16
Interventricular septal dimension, mm	11.2 ± 2.5	10.9 ± 1.8	0.28
Posterior wall dimension, mm	10.76 ± 2.43	10.4 ± 1.7	0.11
LVMI, g/m <sup>2</sup>	96.5 ± 29.5	86.7 ± 22.4	<b>&lt;0.01</b>
LVEF, %	59.8 ± 6.5	60.7 ± 4.9	0.19
<b>Diastolic parameters</b>			
LAVI, ml/m <sup>2</sup>	30.9 ± 8.5	24.6 ± 7.4	<b>&lt;0.01</b>
Mitral E velocity, ms	0.7 ± 0.2	0.6 ± 0.2	<b>0.01</b>
Mitral A velocity, ms	0.8 ± 0.2	0.7 ± 0.2	<b>&lt;0.01</b>
Deceleration time, s	218.2 ± 60.5	234.6 ± 55.2	<b>0.01</b>
E/A	0.9 ± 0.3	1.0 ± 0.3	<b>0.04</b>
e', m/s	0.06 ± 0.02	0.06 ± 0.02	0.43
Resting E/e'	13.6 ± 5.2	12.1 ± 4.6	<b>&lt;0.01</b>
<b>Stress test parameters</b>			
Resting heart rate, beats/min	77.3 ± 13.1	78.5 ± 15.0	0.46
Resting SBP, mm Hg	130.3 ± 17.9	133.4 ± 20.7	0.16
Resting DBP, mm Hg	76.0 ± 10.8	77.9 ± 11.4	0.12
Peak heart rate, beats/min	138.7 ± 23.5	153.2 ± 21.2	<b>&lt;0.01</b>
Peak SBP, mm Hg	161.5 ± 22.6	184.6 ± 26.6	<b>&lt;0.01</b>
Peak DBP, mm Hg	79.5 ± 14.6	73.2 ± 13.5	<b>&lt;0.01</b>
METs	6.7 ± 3.0	9.6 ± 3.3	<b>&lt;0.01</b>
Exercise duration, min	6.8 ± 3.1	9.7 ± 2.9	<b>&lt;0.01</b>
Rate pressure product	22,315.4 ± 5,380.7	27,845.2 ± 6,360.6	<b>&lt;0.01</b>
<b>Exercise diastolic parameters</b>			
Exercise E velocity, m/s	0.9 ± 0.2	0.8 ± 0.2	<b>&lt;0.01</b>
Exercise A velocity, m/s	0.9 ± 0.2	0.9 ± 0.2	0.20
Exercise deceleration time, ms	211.4 ± 53.6	216.8 ± 54.2	0.38
Exercise e', m/s	0.06 ± 0.02	0.07 ± 0.02	<b>&lt;0.01</b>
Exercise E/e'	14.2 ± 5.8	12.0 ± 4.2	<b>&lt;0.01</b>

Values are mean ± SD. **Bold** values indicates significant p values.

A = transmitral early velocity; CKD = chronic kidney disease; DBP = diastolic blood pressure; E = transmitral late velocity; e' = early diastolic mitral annulus velocity; E/e' = ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; LAVI = left atrial volume indexed; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass indexed; MET = estimated metabolic equivalent; SBP = systolic blood pressure.

exercise. METs achieved between the subgroups were assessed with independent Student's *t*-tests.

Event rates among patients with CKD were estimated by Kaplan-Meier survival analysis. Cox regression analysis was subsequently performed to determine independent predictors of adverse outcomes. We included univariate determinants of the composite outcome in the regression models.

Ethical approval has been obtained for this study from South West Sydney Local Heath District, and the reference number used by the Ethics Office for this study is HREC/14/LPOOL/304.

## RESULTS

### CLINICAL AND DEMOGRAPHIC CHARACTERISTICS.

The final cohort consisted of 312 patients: 156 patients

with CKD (mean age: 62.8 ± 10.6 years; male: 62%) were compared to 156 age-, sex- and risk factor-matched control individuals (mean age: 61 ± 10 years; male: 62%). **Table 1** shows the baseline clinical and demographic characteristics for both cohorts.

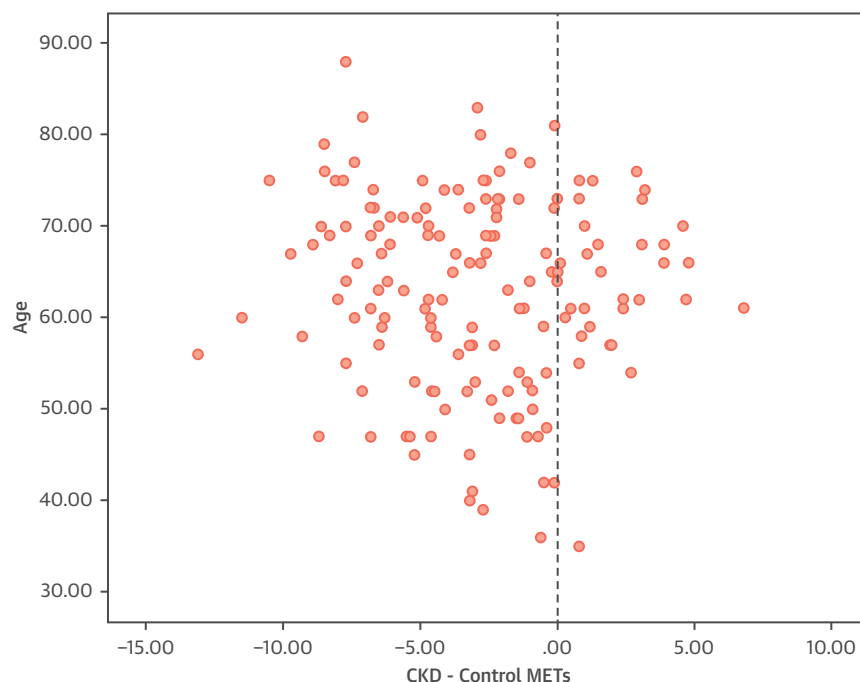
Overall, patients with CKD had significantly higher rates of anemia (defined as a hemoglobin level of <120 mg/dl for women and <130 mg/dl for men) (*p* < 0.01) and, as expected, greater angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (*p* = 0.02), diuretic agents (*p* < 0.01), and statin (*p* < 0.01) therapy.

There were 110 (70%) patients with stage 3 CKD and 46 (30%) patients with stage 4 CKD, with a mean creatinine level of 172.5 ± 95.3 μmol/l and a mean eGFR of 39.1 ± 14.6 ml/min/1.73 m<sup>2</sup>. Hypertensive nephrosclerosis (*n* = 50; 32%) accounted for the majority of patients with CKD, followed by diabetic nephropathy (*n* = 37; 24%) and primary and secondary glomerulonephropathies (*n* = 29; 19%). Other causes of renal impairment included tubulointerstitial disease (*n* = 8; 5%), polycystic kidney disease (*n* = 6; 4%), renovascular disease (*n* = 4; 3%), drug related (*n* = 1; 1%), renal calculi disease (*n* = 2; 1%), obstructive uropathy and vesicoureteric disease (*n* = 4; 3%), and single kidney (*n* = 6; 4%). Seven (5%) patients had an undifferentiated cause of renal impairment.

**BASELINE ECHOCARDIOGRAPHIC CHARACTERISTICS.** The differences in baseline echocardiographic characteristics of patients with CKD and matched control individuals are shown in **Table 2**. All patients had normal LVEF.

On paired Student's *t*-test analysis, individuals with CKD had larger indexed left ventricular mass (*p* < 0.01), higher mitral inflow peak E velocity (*p* = 0.01) and peak A velocity (*p* < 0.01), shorter deceleration time (*p* < 0.01), and lower E/A ratio (*p* = 0.04) compared to control individuals. Compared to control individuals, patients with CKD also had higher resting LV filling pressures as reflected by higher E/e' (*p* < 0.01) and larger indexed left atrial volume (LAVI) (*p* < 0.01).

**EXERCISE CAPACITY IN CKD.** Patients with CKD achieved lower METs (*p* < 0.01) compared to control individuals and had a shorter exercise duration (*p* < 0.01) and lower rate pressure product (*p* < 0.01) (**Table 2**). Because patients with CKD were matched, 1 to 1, to age-, sex-, and risk factor-matched control individuals, to delineate the true difference between a patient with CKD and his/her respective matched control, we calculated the pairwise difference in METs achieved and evaluated its association with age

**FIGURE 1** Difference in METs Achieved Between Pairwise Comparison of CKD Patients and Matched Controls

Pairwise difference in METs achieved and association with age. Regardless of age, a significant proportion of patients with CKD achieved lower METs compared to matched control individuals. CKD = chronic kidney disease; METs = metabolic equivalents.

(**Figure 1**). As shown, a substantial proportion of patients with CKD (120 of 156; 77%) achieved lower METs compared to matched control individuals, an effect observed regardless of age.

Using a cutoff of achieved METs of  $\leq 7$  to define reduced exercise capacity, 124 of 312 (40%) patients in the entire group had reduced exercise capacity. In the CKD group, 58% (90 of 156) achieved METs  $\leq 7$  compared to 22% (35 of 156) in the control individuals ( $p < 0.01$ ).

**MITRAL INFLOW AND TISSUE DOPPLER RESPONSE WITH EXERCISE.** Compared to control individuals, patients with CKD had a significantly higher E velocity ( $p < 0.01$ ) following exercise with failure to augment e' response ( $p < 0.01$ ) (**Table 2**), with a consequent higher exercise E/e' ratio ( $p < 0.01$ ). Using a cutoff value of 13, 83 of 156 (53%) patients with CKD had an exercise E/e' of  $>13$  compared to 36 of 156 (23%) matched control individuals ( $p < 0.01$ ).

**PREDICTORS OF EXERCISE CAPACITY IN CKD.** Patients with CKD with reduced exercise capacity were older ( $p < 0.01$ ), with higher body mass index ( $p < 0.01$ ), greater LVMI ( $p = 0.04$ ), higher E velocity ( $p < 0.01$ ), lower resting average e' ( $p < 0.01$ ), higher

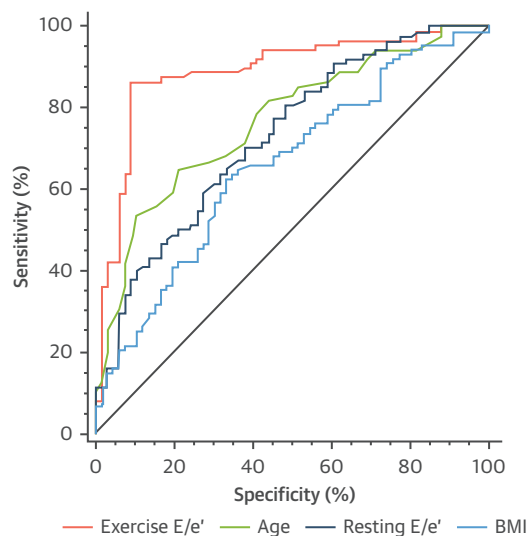
resting E/e' ( $p < 0.01$ ), and higher exercise E/e' ( $p < 0.01$ ). On logistics regression analysis, age (odds ratio [OR]: 1.08; 95% confidence interval [CI]: 1.01 to 1.12;  $p < 0.01$ ), body mass index (OR: 1.10; 95% CI: 1.04 to 1.16;  $p < 0.01$ ), resting E/e' (OR: 0.9; 95% CI: 0.81 to 1.00;  $p < 0.01$ ), and exercise E/e' (OR: 1.42; 95% CI: 1.27 to 1.60;  $p < 0.01$ ) were independent predictors of reduced exercise capacity.

Receiver-operating characteristic curve analysis for prediction of exercise capacity of  $\leq 7$  METs (**Figure 2**) showed exercise E/e' (AUC: 0.89; 95% CI: 0.84 to 0.95;  $p < 0.01$ ) to be the strongest predictor of reduced exercise capacity among the independent clinical and echocardiographic predictors. On DeLong tests, the AUC for exercise E/e' was significantly stronger than the AUC of the other independent predictors ( $p < 0.01$  for all variables). The exercise E/e' of  $>13$  had a sensitivity of 85% and specificity of 91% in identifying patients with CKD who would achieve METs of  $\leq 7$ .

**EXERCISE E/E' IN CKD.** To further evaluate the clinical utility of E/e' in patients with CKD, we sought to assess the relationship between METs achieved and the changes in E/e' with exercise in the subgroups with normal or indeterminate resting E/e'. The



**FIGURE 2** Receiver-Operating Characteristic Curves of Age, BMI, Resting E/e', and Post-exercise E/e' in Predicting Reduced Exercise Capacity



Variable	Area under curve	SE	Lower 95% confidence interval	Upper 95% confidence interval	Significance (p value)
Exercise E/e'	0.89	0.03	0.83	0.94	< 0.01
Age	0.77*	0.04	0.69	0.83	< 0.01
Resting E/e'	0.73*	0.04	0.65	0.80	< 0.01
BMI	0.66*	0.04	0.58	0.73	< 0.01

Exercise E/e' was the strongest predictor of reduced exercise capacity (METs of  $\leq 7$ ) among the independent clinical and echocardiographic predictors of reduced exercise capacity and the area under the curve of exercise E/e' was significantly stronger than the area under the curve of the other independent predictors on DeLong tests. \* $p < 0.01$  versus exercise E/e' on DeLong test. BMI = body mass index; E/e' = ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; METs = metabolic equivalents.

subgroups we assessed were: 1) normal/indeterminate resting E/e' (i.e.,  $< 8$  to  $8$  to  $14$ ) with normal exercise E/e' ( $\leq 13$ ); 2) normal resting/indeterminate E/e' (i.e.,  $< 8$  to  $8$  to  $14$ ) with raised exercise E/e' ( $> 13$ ); and 3) raised resting E/e' ( $> 14$ ).

A total of 52 of 156 (34%) patients with CKD had a raised resting E/e' of  $> 14$ . Of the 104 of 156 (66%) patients with CKD with normal/indeterminate resting E/e' ratio, 63% had a normal exercise E/e' of  $\leq 13$ , whereas 37% developed an exercise E/e' of  $> 13$ . Patients with raised exercise E/e' achieved significantly lower METs compared to patients with CKD with a normal exercise E/e' ( $5.0 \pm 2.2$  vs.  $8.8 \pm 2.5$ ;  $p < 0.01$ ). METs achieved in this group were comparable to those achieved by

patients with CKD with a raised resting E/e' of  $> 14$  ( $5.0 \pm 2.2$  METs vs.  $5.3 \pm 2.6$  METs;  $p < 0.01$ ).

#### EXERCISE E/e' AND ADVERSE OUTCOMES IN CKD.

Over a follow-up period of 41.4 months, 32 patients had the composite outcome of cardiovascular death and MACE (8 cardiovascular death, 24 MACE). Based on the 3 subgroups of resting and exercise E/e' as detailed earlier, the highest incidence of composite adverse events was observed in patients with CKD with an elevated resting E/e' of  $> 14$  (18 of 52; 35%), followed by the subgroup of patients with normal/indeterminate resting E/e' and raised exercise E/e' (9 of 37; 25%). Only 8% (5 of 61) of patients in the subgroup with normal/indeterminate resting E/e' and normal exercise E/e' suffered adverse events.

To determine factors affecting adverse outcomes, we divided patients with CKD into 2 groups based on those who had experienced the composite of death and MACE and those free of adverse events. Those who experienced events were older ( $p = 0.01$ ), had a history of diabetes mellitus ( $p = 0.05$ ), and had worse exercise capacity, with lower METs achieved with exercise ( $p < 0.01$ ). Echocardiographic parameters associated with the occurrence of the adverse outcomes included greater LVMI ( $p < 0.01$ ), larger LAVI ( $p < 0.01$ ), lower resting e' ( $p < 0.01$ ), higher resting E/e' ratio ( $p < 0.01$ ), and higher exercise E/e' ratio ( $p < 0.01$ ).

On log-rank tests (Figure 3) and unadjusted Cox proportional hazard models (Table 3), elevated exercise E/e' ( $p < 0.01$ ) was predictive of the composite endpoints of cardiovascular death and MACE. Other significant univariable predictors include raised resting E/e' ( $p < 0.01$ ), LAVI ( $p < 0.01$ ), and LVMI ( $p < 0.01$ ); reduced METs of  $\leq 7$  with exercise ( $p = 0.03$ ); age ( $p < 0.01$ ); and presence of diabetes mellitus ( $p = 0.02$ ).

Using the univariable predictors of the composite outcome identified on log-rank tests, we performed multivariable Cox regression analysis. To avoid overfitting, we performed nested regression models (Supplemental Table 1) of the clinical and echocardiographic variables (model 1: clinical variables; model 2: echocardiographic variables) followed by a third model with the independent variables identified on the first 2 models. This showed exercise E/e' to be an independent predictor of the composite outcome. A combined multivariable Cox proportional hazards model with all clinical and echocardiographic variables was also performed that similarly showed raised exercise E/e' to be an independent predictor of the composite outcomes after adjustment for the

significant clinical and echocardiographic variables on univariate analysis (Table 3).

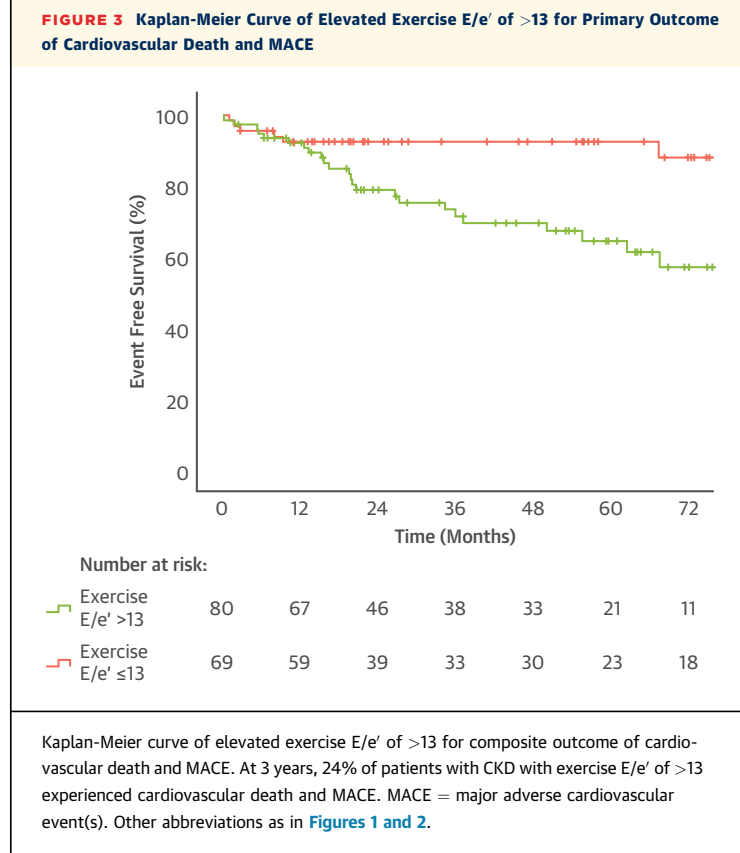
## DISCUSSION

Our study demonstrates that patients with CKD had reduced exercise capacity and achieved lower METs with exercise compared to age-, sex-, and risk factor-matched control individuals. Exercise capacity was also influenced by older age and higher body mass index. Echocardiographic parameters associated with reduced exercise capacity include greater LVMI, larger LAVI, higher E velocity, lower resting average e', and higher LV filling pressures, both at rest (resting E/e') and with exercise (exercise E/e'). Among the clinical and echocardiographic variables, exercise E/e' emerged as the strongest predictor of reduced exercise capacity in a multivariate model. Patients with elevated resting and exercise E/e' were also more likely to experience MACE and cardiovascular death (Central Illustration).

**CKD AND EXERCISE CAPACITY.** Reduced physical fitness, a key factor in chronic illness and an independent predictor of adverse cardiovascular outcomes (15), is highly prevalent among patients with CKD (16). The cause of this reduced physical fitness is multifactorial. Well-described contributory factors include associated comorbidities with CKD such as anemia; alterations in muscle function, morphology, and metabolism; and chronic inflammation (15,16). Although poor cardiorespiratory capacity has been implicated as a contributory factor as well, clinical studies evaluating specific parameters in this regard have been lacking.

In line with current published reports, our study demonstrated a high prevalence of reduced physical fitness in patients with CKD. Approximately 77% of the CKD cohort achieved lower METs with exercise relative to age-, sex- and risk factor-matched control individuals. Additionally, more than half (58%) of the recruited patients with CKD had a reduced exercise capacity, with METs of <7 achieved with exercise.

**DIASTOLIC DYSFUNCTION IN CKD.** Diastolic dysfunction is common in patients with CKD and has been reported both in patients with end-stage renal disease on dialysis (17) and in patients with CKD not on dialysis (18,19). The E/e' ratio has been demonstrated to reliably estimate LV filling pressures. Raised E/e', a consequence of diastolic dysfunction, has been shown to have a close association with exercise capacity (8,20,21), presumably due to decreased cardiac output consequent to impaired augmentation of LV relaxation relative to increases in



heart rate during exercise. Furthermore, E/e' has been linked to cardiovascular mortality (21).

In our study resting E/e' identified 33% (52 of 156) of patients with CKD with elevated LV filling pressures, whereas evaluation of E/e' post-exercise increased this to 58% (90 of 156), reflective of the high burden of latent LV diastolic dysfunction in this population.

**EXERCISE E/e'.** Although noninvasive assessment of LV filling pressures with the E/e' ratio has conventionally been performed at rest, a subset of patients with diastolic abnormalities may be asymptomatic at rest. Exercise E/e' has been shown to correlate well with simultaneously measured invasive LV pressures during exercise (8-10,22) and has been shown to improve the diagnostic accuracy for detection of latent diastolic impairment (22-24). Considering the prevalence of diastolic dysfunction in patients with CKD, we explored the role of exercise E/e' in patients with stage 3 and 4 CKD, a population known to have high rates of adverse cardiovascular outcomes.

In patients with elevated resting E/e', raised LV filling pressure persists during exercise, and thus, the incremental benefit of exercise E/e' is limited.

**TABLE 3** Unadjusted And Adjusted Cox Regression Models

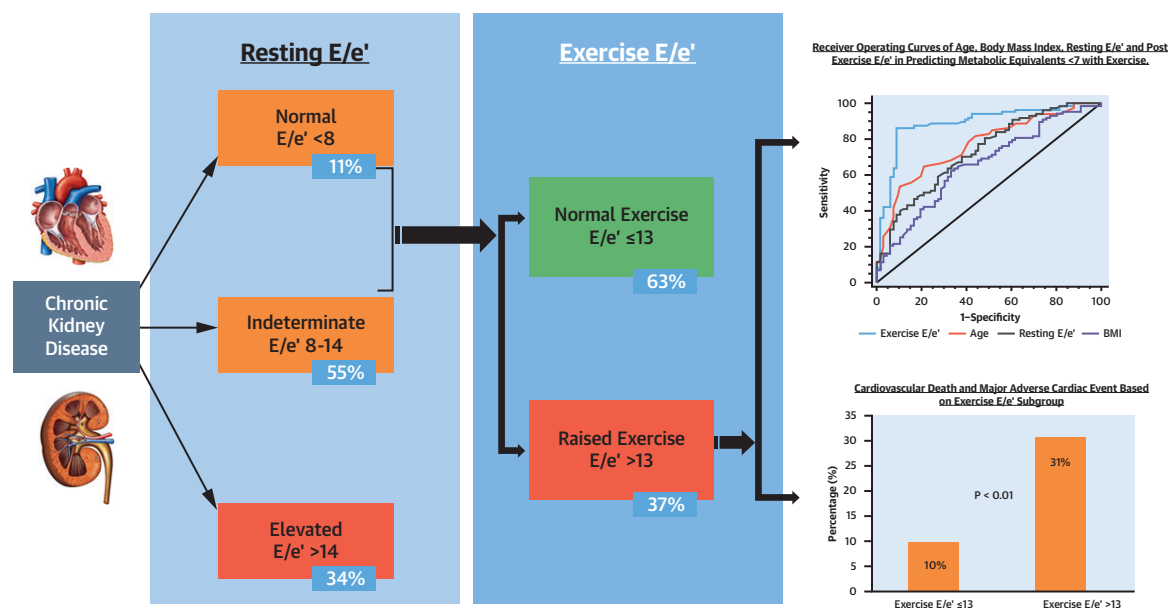
Cardiovascular Death and MACE Variables	Unadjusted Cox Regression		Multiple Cox Regression Model	
	Hazard Ratio (95% CI), Unadjusted	p Value	Hazard Ratio (95% CI), Adjusted	p Value
Age, yrs	1.06 (1.02-1.10)	<b>&lt;0.01</b>	1.03 (0.98-1.08)	0.32
DM	2.40 (1.18-4.87)	<b>0.02</b>	1.34 (0.60-2.96)	0.48
METs $\leq 7$	0.40 (0.17-0.93)	<b>0.03</b>	1.08 (0.39-2.98)	0.88
LAVI, ml/m <sup>2</sup>	1.07 (1.03-1.10)	<b>&lt;0.01</b>	1.02 (0.97-1.07)	0.37
LVMI, g/m <sup>2</sup>	1.02 (1.01-1.03)	<b>&lt;0.01</b>	1.02 (1.00-1.03)	<b>&lt;0.01</b>
Resting E/e'	1.15 (1.09-1.22)	<b>&lt;0.01</b>	1.04 (0.96-1.13)	0.36
Exercise E/e'	1.12 (1.08-1.16)	<b>&lt;0.01</b>	1.13 (1.08-1.18)	<b>&lt;0.01</b>

**Bold** values indicates significant p values.  
CI = confidence interval; DM = diabetes mellitus; MACE = major adverse cardiovascular event(s); other abbreviations as in Table 2.

However, among recruited patients with CKD with normal or indeterminate LV filling pressures at rest (i.e., E/e' of <8 or 8 to 14), abnormal diastolic response following exercise was present in 38% (38 of 98). Patients with raised exercise E/e' achieved significantly lower METs, and exercise E/e' was also the strongest predictor for reduced exercise capacity in patients with CKD. These findings highlight the

potential utility of exercise E/e' in identifying latent diastolic dysfunction in patients with CKD. Raised exercise E/e' appeared to be driven by abnormalities of both E and e' velocities. The increase in sodium and fluid retention in CKD, together with an exercise-related increase in stroke volume, can increase peak E velocity. The presence of LV hypertrophy and associated myocardial fibrosis, in turn, leads to

### CENTRAL ILLUSTRATION Exercise E/e' Refines Diagnosis of Diastolic Dysfunction and Predicts Exercise Capacity and Adverse Cardiovascular Outcomes in Chronic Kidney Disease



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Exercise E/e' identified a greater number of patients with CKD with diastolic dysfunction in the group with normal or intermediate E/e' at rest. Exercise E/e' was the strongest predictor of achieved METs of  $\leq 7$ , and patients with CKD with a raised exercise E/e' of  $\geq 13$  had higher rates of cardiovascular death and MACE. CKD = chronic kidney disease; E/e' = ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; METs = metabolic equivalents.



delayed relaxation and impaired LV compliance, with resultant lower  $e'$  velocity.

#### PROGNOSTIC VALUE OF EXERCISE E/e' IN CKD.

In addition to refining the diagnosis of diastolic dysfunction, our study also demonstrated the prognostic value of exercise E/e' in patients with CKD. Over the follow-up period, patients with raised E/e' were observed to have a significantly higher incidence for the composite endpoint of cardiovascular death and MACE. Hence, performing an exercise stress echocardiogram may be important in patients with CKD with normal or intermediate resting E/e' to identify patients at increased risk. Additionally, we have illustrated the important negative effects of left ventricular hypertrophy, diastolic dysfunction, and elevated filling pressures, which all limit exercise capacity and confer an increased risk of morbidity and mortality. Hence, these parameters need to be closely monitored, with appropriate risk factor control and lifestyle changes, to prevent their development during the course of CKD.

Our findings add to the growing body of published reports on exercise E/e' as a potential prognostic tool for patients with diastolic dysfunction. In a previous study of patients referred for exercise stress testing, patients with raised exercise E/e' demonstrated similar outcomes to patients with findings of ischemia on treadmill stress testing (12). Additionally, in patients with heart failure with preserved ejection fraction and among a cohort of patients with end-stage renal disease on dialysis, raised E/e' was a strong predictor of death, adverse cardiovascular outcomes, and cardiovascular hospitalization (17,21).

**STUDY STRENGTHS AND LIMITATIONS.** Our study had a relatively modest sample size; however, patients with CKD were carefully matched for age, sex, and risk factors to compare and validate our findings. Our inclusion criteria were strict and included only patients with stable CKD with no prior cardiac history, no significant valvular disease or more than mild mitral annular calcification on echocardiography, and no latent ischemia on exercise stress testing. Although we used achieved METs as a measure of exercise capacity as opposed to oxygen consumption, measurement of METs is a widely accepted clinical tool for determining functional capacity. Performance of maximum oxygen consumption with exercise is seldom used in clinical practice and was beyond the scope of the present study. Tissue Doppler-derived E/e' is a relatively sensitive, load-independent measure of LV relaxation and is widely used. The number of adverse events during follow-up

was a relatively small number, and therefore, nested analysis was performed.

#### CONCLUSIONS

Reduced exercise capacity is common among patients with CKD and is altered, at least in part, by poor cardiorespiratory capacity consequent to diastolic dysfunction. Exercise E/e' is a useful parameter for improved detection of latent diastolic dysfunction in patients with CKD and was the strongest predictor of exercise capacity among the clinical and echocardiographic variables assessed. Exercise E/e' was also an independent predictor of cardiovascular death and MACE in this patient group.

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**ADDRESS FOR CORRESPONDENCE:** Dr. Liza Thomas, Department of Cardiology, Westmead Hospital, Cnr Hawkesbury and Darcy Road, Westmead, NSW 2145, Sydney, Australia. E-mail: [l.thomas@unsw.edu.au](mailto:l.thomas@unsw.edu.au) OR [liza.thomas@sydney.edu.au](mailto:liza.thomas@sydney.edu.au).

#### PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Patients with CKD have reduced physical fitness relative to age, sex-, and risk factor-matched control individuals without CKD, which further contributes to the disproportionately elevated risk of cardiovascular disease in this population.

**COMPETENCY IN PATIENT CARE:** Exercise E/e' is an independent predictor of exercise capacity in patients with CKD and is able to unmask latent diastolic dysfunction in those with normal or indeterminate resting E/e'. In patients with CKD, exercise E/e' is an independent predictor of cardiovascular death and MACE.

**TRANSLATIONAL OUTLOOK:** This analysis demonstrates the utility of exercise E/e' in patients with stable CKD for the identification of reduced exercise capacity and increased morbidity and mortality. Patients with CKD warrant aggressive risk factor control and lifestyle modification to prevent the development of left ventricular hypertrophy and diastolic dysfunction.

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**KEY WORDS** chronic kidney disease, diastolic dysfunction, E/e', exercise capacity, exercise E/e'

**APPENDIX** For a supplemental table, please see the online version of this paper.