Original Article

Dobutamine stress echocardiography and the resting but not exercise electrocardiograph predict severe coronary artery disease in renal transplant candidates

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Abstract

Background. After renal transplantation half of all deaths are cardiac, so prior detection and treatment of severe coronary artery disease (CAD) is advocated. The aim of this study was to identify non-invasive predictors of severe CAD in a group of renal transplant candidates.

Methods. One hundred and twenty-five renal transplant candidates (mean age 52 ± 12 years, 80 male, mean creatinine $608 \pm 272 \,\mu mol/l$) were studied. All had coronary angiography, dobutamine stress echocardiography, and resting and exercise electrocardiograph (ECG). Severe CAD was defined as luminal stenosis >70% by visual estimation in at least one epicardial artery. The resting ECG was recorded as abnormal if there was evidence of pathological Q waves, left ventricular hypertrophy, ST depression or elevation ≥ 1 mm, T wave inversion or bundle branch block. Total exercise time, maximal ST segment change, maximal heart rate and systolic blood pressure, limiting symptoms and Duke score were calculated during the exercise ECG test.

Results. Of the patients, 36 (29%) had severe CAD, 55% were on dialysis and 39% were diabetic. Patients with severe CAD were significantly older ($P < 0.001$), had higher total cholesterol ($P = 0.05$), higher CRP level ($P = 0.05$), larger left ventricular (LV), end systolic and end diastolic diameter ($P = 0.007$ for each), and lower LV ejection fraction ($P = 0.01$). A significantly higher percentage were diabetic ($P = 0.05$), had previous graft failure ($P = 0.05$), mitral annular calcification ($P = 0.04$), an abnormal resting ECG ($P = 0.001$) and positive stress echo result ($P < 0.001$). Cardiac symptoms and exercise ECG parameters were not significantly different in the two groups. Stepwise logistic regression identified an abnormal resting ECG (OR 7, 95% CI 2, 34, $P = 0.013$) and positive stress echo result (OR 23, 95% CI 6, 88, $P < 0.001$) as independent predictors of severe CAD.

Conclusions. In selecting which potential renal transplant candidates should undergo coronary angiography, resting ECG and dobutamine stress echocardiography are the best predictors of severe CAD.

Introduction

Cardiovascular disease is the leading cause of mortality in end stage renal disease (ESRD), accounting for ~45% of all deaths [1]. Screening of renal transplant candidates is therefore advocated to diagnose and treat severe coronary artery disease (CAD) prior to transplantation. This is especially important as their disease is often clinically silent. Many conventional cardiac risk factors such as dyslipidaemia, smoking and hypertension are less predictive of CAD in renal failure [2]. Coronary angiography for all patients is unattractive for logistical reasons and the risk of contrast nephropathy in those not on dialysis. At present, current transplantation guidelines advocate their use to those with diabetes and a past history of ischaemic heart disease. There is therefore a need to identify baseline parameters that best predict CAD in ESRD. Such higher risk cases can then be referred for angiography. In this study, we determined non-invasive parameters that differed in a group of renal transplant candidates with and without severe CAD, defined angiographically. The aim was to identify parameters that independently predict severe CAD in this patient group. Clinical, biochemical, echocardiographic, electrocardiographic, dobutamine stress echocardiography (DSE) and exercise test data were considered.

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Subjects and methods

Population

One hundred and twenty-eight consecutive patients referred for renal transplantation evaluation at St George's Hospital, London were prospectively studied. Three refused coronary angiography and so were not included in the analysis, resulting in a sample size of 125. Exclusion criteria were: age <18 years, severe aortic stenosis, unstable angina and inability to consent.

At study entry, all patients underwent full history, examination, and resting electrocardiograph (ECG). Clinical data included history of hypertension, diabetes, smoking, hypercholesterolaemia, strong family history, cause of renal failure, mode and duration of dialysis. Haematological and biochemical parameters were recorded just prior to dialysis. These included fasting total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride, glucose, cardiac troponin T (cTnT), C-reactive protein (CRP) and N-terminal pro-brain natriuetic peptide (NT-proBNP). All medications were recorded.

Assessment of peripheral vascular disease

All patients were screened for peripheral vascular disease given its high morbidity in transplant patients, especially diabetics [3]. This was done via lower limb duplex ultrasonography. If a lesion was suspected as being >50%, an angiogram was performed. Patients with significant lesions were treated accordingly with surgery or angioplasty ($n = 4$).

12 Lead ECG

This was performed on all subjects. The ECG was considered to be abnormal if any of the following criteria were met in any of the standard limb leads or precordial leads, except AVR or V1: pathological Q waves, left ventricular hypertrophy (LVH) by Sokolow–Lyon criteria or Cornell index, ST depression ≥ 1 mm, ST elevation ≥ 1 mm, T wave inversion or bundle branch block (QRS ≥ 120 ms).

Exercise testing

Patients had treadmill exercise testing according to standard Bruce protocol to limiting symptoms. The 12 lead ECG was recorded continuously and the following documented: exercise time to limiting symptom, maximal ST segment change, Duke multivariate prognostic score, maximal heart rate, maximal systolic blood pressure, limiting symptoms.

The test was stopped if any of the following occurred: limiting symptoms (angina, shortness of breath, dizziness, lethargy), ST depression ≥ 3 mm, ventricular tachycardia, drop in blood pressure ≥ 30 mmHg, rise in systolic blood pressure ≥ 230 mmHg.

Patients were given an angina score: 0 = none, 1 = non-limiting angina, 2 = limiting angina. The Duke score [4] was calculated as: total treadmill time (min) − 5 × magnitude of maximal ST depression (mm) − 4 × angina index.

Horizontal or downsloping ST depression ≥ 1 mm measured 80 ms after the J point, and ST elevation ≥ 1 mm measured 40 ms after the J point, were regarded as positive results. The test was described as inconclusive if stopped before 85% predicted heart rate could be achieved with no cardiac symptoms or significant changes at that stage.

Echocardiography

A full cross-sectional study was performed at baseline using General Electric Vingmed System 7. For those on dialysis, the studies were performed 16–24 h post dialysis, when patients were most likely to be closest to their euvolaemic state [5]. Left ventricular end diastolic diameter (LVEDD), LV end systolic diameter (LVESD), interventricular and LV posterior wall thickness at end diastole were measured from parasternal M mode recordings of the LV, with the cursor at the tips of the mitral valve leaflets. LV fractional shortening calculated from LVESD and LVEDD. LV end systolic and diastolic volumes determined by the modified biplane Simpson's rule and the standard formula applied to give LV ejection fraction (LVEF).

Transmitral inflow was recorded using pulsed wave Doppler recordings at the mitral valve leaflet tips in the apical four-chamber view. Peak velocity of early filling (E), peak velocity of atrial filling (A), the E/A ratio and E deceleration time were measured.

Flow propagation velocity (Vp) was calculated from colour M-Mode in the apical four-chamber view. From pulsed wave real-time tissue Doppler images obtained in the four-chamber view, early diastolic (Ea) velocities were measured. LV filling pressure was estimated from E/Ea and E/Vp ratios [6]. The presence of mitral annular calcification (MAC) was defined as an echodense band visualized throughout systole and diastole, distinguishable from the posterior mitral valve leaflet, and located anterior and parallel to the posterior left ventricular wall on M-mode recordings [7].

Dobutamine stress echocardiography

Images were acquired in standard parasternal long- and short-axis and apical two-, three- and four-chamber views at baseline and during stepwise infusion of dobutamine infusion. This was given according to a protocol based on 3 min stages of 5, 10, 20, 30 and 40 mg/kg/min. Atropine was administered up to a total of 1.0 mg intravenously if the target heart rate was not achieved with dobutamine alone. Blood pressure and 12 lead ECG were recorded at each infusion stage. Baseline, low-dose (heart 10–15 beats above baseline), peak and recovery (10 min after drug infusion terminated) stage images were stored and analysed in digital quad screen format. The test was stopped if (i) the target heart rate was achieved [(220 − age) × 0.85], (ii) ST depression >2 mm occurred, (iii) significant tachyarrhythmia (sustained supraventricular tachycardia or a greater than three beat run of ventricular tachycardia) occurred, (iv) symptomatic severe hypotension occurred, blood pressure exceeded 240 mmHg systolic or 140 mmHg diastolic.

All images were reported off-line by two experienced observers blinded to the rest of the study. Qualitative analysis was performed with the left ventricle divided into a 16 segment model. Regional wall motion was described as hyperkinetic, normal, hypokinetic, akinetic and dyskinetic. Results were classified as a normal response with an overall increase in wall motion or abnormal response. An abnormal response was described as the occurrence under stress of

hypokinesia, akinesia or dyskinesia in one or more resting normal segments and/or worsening of wall motion in one or more resting hypokinetic segments. The level of agreement, kappa (κ) between the two sonographers was κ = 0.82. Consensus was obtained in discordant cases.

Cardiac troponin T assay

cTnT was measured using the third generation Elecsys 2010 STAT electrochemiluminescent immunoassay (Roche Diagnostics, Lewes) [8]. The assay detection limit was <0.01 mg/l.

Sensitive C-reactive protein

This was assayed on the Immulite-1 (Diagnostic Product Corporation).

N-terminal pro-brain natriuretic peptide

This was determined by electrochemiluminescence on the Elecsys 2010 (Roche Diagnostics).

Coronary angiography

This was performed on all patients in the study via the femoral route by the standard Judkins technique. Stenosis severity of each epicardial artery was assessed visually and graded as follows: normal, mild (<50% luminal narrowing), moderate (50–70% luminal narrowing), severe (>70% luminal narrowing). Angiograms were interpreted blindly by two experienced observers and a consensus obtained for disagreement. The level of agreement was κ = 0.85.

Statistical analysis

Continuous variables were expressed as mean ± 1 SD and differences between groups determined with unpaired t-test. Categorical variables were compared using χ^2 analysis or Fisher's exact test. Stepwise logistic regression by forward selection was used to identify baseline parameters that independently predict severe coronary artery disease. Long-term survival related to severe CAD, a positive DSE result and abnormal resting ECG was analysed in a Kaplan–Meier model. The log rank test was used to evaluate the differences between Kaplan–Meier curves. All statistical tests were two-tailed with a P-value <0.05 to indicate statistical significance. The SPSS statistics package (SPSS Inc, version 12, Chicago, IL, USA) was used.

Long-term follow-up

Long-term follow-up of clinical status was obtained by review of inpatient and outpatient medical records and telephone calls to the transplant unit.

Results

The patient characteristics are shown in Table 1. Mean follow-up time was 1.61 ± 0.56 years (range, 0.19–2.52

Table 1. Baseline characteristics

Age (years)	52 ± 12
Sex	80 male, 45 female
Ethnicity	Caucasian: 63 (50%)
	Asian: 24 (19%)
	AfroCarribean: 31 (25%)
	Chinese: 4
	Other: 3
Serum creatinine (μmol/l)	608 ± 272
Serum haemoglobin (g/l)	10.2 ± 1.6
Cholesterol (mmol/l)	4.9 ± 1.8
cTnT (μg/l)	0.08 ± 0.16
NT ProBNP (pg/ml)	997.5 ± 1816.9
ESRD cause	Diabetes: 48 (39%)
	Glomerulonephritis: 29 (23%)
	Hypertension: 18 (14%)
	APCKD: 9 (7%)
	Obstructive uropathy: 9 (7%)
	Other: 12 (10%)
Dialysis modality	Predialysis: 56 (45%)
	Haemodialysis: 41 (33%)
	CAPD: 28 (22%)
Dialysis time (months)	2.73 ± 2.19
Previous transplant	16 (13%)
Chest pain	53 (42%)
Diabetes	50 (39%)
	20 Type 1 (40%)
	30 Type 2 (60%)
Hypertension	115 (91%)
Raised cholesterol	71 (56%)
Smoker	18 (14%)
Pre-existing cardiac disease	IHD: 17 (13%)
	CCF: 17 (13%)
Previous renal graft failure	15 (12%)
Severe CAD at angiography	36 (29%)
No CAD at angiography	45 (36%)
Positive DSE result	37 (30%)
Abnormal resting ECG	58 (46%)
Exercise test result	Positive: 21 (17%)
	Negative: 45 (36%)
	Inconclusive: 59 (47%)

years). Over this period, 35 patients received their renal transplant, eight had been taken off the transplant list and there had been 12 deaths, seven of which were cardiac. Mean time to death was 0.71 ± 0.59 years (range, 0.19–2.02 years). Mean age of all patients was 52 ± 12 years with a male preponderance. Of the population studied, 39% ($n = 50$) were diabetic and 55% were on dialysis. The mean time on dialysis was 2.73 ± 2.19 months. Fifteen patients (12%) had a previous renal transplant with graft failure. Of the patients, 42% had chest pain. Hypertension (91% of all patients) was the main cardiovascular risk factor. Mean cholesterol in the group as a whole was 4.9 ± 1.8 mmol/l and 71 patients (56%) were on a statin. Other medication use included aspirin in 58 patients (43%), beta blockers in 44 patients (35%), angiotensin-converting enzyme (ACE) inhibitors in 54 patients (42%), erythropoetin in 53 patients (41%) and diuretics in 56 patients (43%).

A total of 36 (29%) patients had severe CAD. Eight had severe three vessel disease, eight two vessel and 20 single vessel disease. Seventeen (14%) patients had moderate coronary disease and 27 (21%) had mild disease. Forty-five (36%) patients had normal coronary

arteries. Five of the patients with severe three vessel disease had coronary artery bypass surgery. The remaining three were taken off the transplant list. Of the patients with two vessel disease, two had coronary artery bypass surgery, one had percutaneous angioplasty and the remaining five medical therapy. Seven of the 20 patients with single vessel disease had percutaneous angioplasty.

Fifty-eight (46%) patients had an abnormal resting ECG. Of these, 34 had voltage criteria for LVH, 12 had T wave inversion, eight had bundle branch block and four had significant ST depression. Twenty-one (17%) patients had a positive exercise test and in 45 (36%) the test was normal. However, in 59 cases (47%) the result was considered to be inconclusive. Thirty-seven patients (30%) had a positive DSE result. Forty-seven patients (38%) had MAC.

Table 2 shows baseline demographic differences in those patients with and without severe CAD. Those with severe CAD were significantly older ($P < 0.001$) but there were no differences in the proportion of patients on dialysis, mode and time on dialysis and mean serum creatinine. Mean total cholesterol and LDL cholesterol was significantly higher in the group with severe CAD ($P = 0.05$) as was the proportion of patients with diabetes ($P = 0.05$). Triglyceride and HDL cholesterol levels were similar in the two groups as were blood pressure, the proportion of smokers and those with a family history of CAD. A significantly greater percentage of patients with severe CAD had peripheral vascular disease compared to those without

($P < 0.001$). Likewise, a greater proportion of patients with a previous renal transplant and graft failure had severe CAD ($P = 0.05$). Plasma cTnT, NT-proNP and haemoglobin levels were not significantly different in the two groups but CRP levels were significantly higher in those with CAD ($P = 0.05$). Aspirin and statins were used significantly more in those with severe CAD but ACE inhibitor and beta blocker use was similar in the two groups.

Table 3 shows ECG data. A significantly higher proportion of patients with severe CAD had an abnormal baseline ECG ($P = 0.001$). Patients without severe CAD had longer walking times on exercise testing ($P = 0.02$). However, maximal heart rate, maximal systolic pressure, maximal ST change and calculated Duke score were similar between the two groups. A comparison of echocardiographic parameters is shown in Table 4. Patients with severe CAD had significantly greater LVESD and LVEDD ($P = 0.007$)

Table 3. Baseline and exercise ECG data in those with and without severe CAD

	Severe CAD ($n = 36$)	Non-severe CAD ($n = 89$)	*P*-value
Abnormal resting ECG	27 (77%)	14 (26%)	0.001
Total exercise time (min)	5.2 ± 1.7	6.5 ± 2.1	0.02
Limiting angina	8 (22%)	12 (14%)	NS
Peak heart rate (beats/min)	136 ± 42	143 ± 53	NS
Peak systolic blood pressure (mmHg)	163 ± 59	174 ± 46	NS
Maximal ST change (mm)	0.25 ± 0.58	0.14 ± 0.46	NS
Duke score	2.7 ± 4.3	4.8 ± 3.8	NS

For abbreviations see text.

Table 2. Differences between patients with and without severe CAD

	Severe CAD ($n = 36$)	Non-severe CAD ($n = 89$)	*P*-value
Age (years)	57.9 ± 9.4	49.1 ± 13.1	<0.001
Sex	27 male, 9 female	53 male, 36 female	NS
Dead	6 (17%)	6 (7%)	NS
Dialysis	24 (65%)	45 (39%)	NS
Dialysis time (years)	1.83 ± 2.1	1.19 ± 1.8	NS
Creatinine (µmol/l)	656.2 ± 270.6	615.2 ± 274.3	NS
Cholesterol (mmol/l)	5.1 ± 2.1	4.4 ± 1.2	0.05
LDL cholesterol (mmol/l)	2.96 ± 1.02	2.21 ± 1.04	0.05
HDL cholesterol (mmol/l)	1.18 ± 0.41	1.25 ± 0.43	NS
Triglyceride (mmol/l)	2.15 ± 1.87	1.92 ± 1.28	NS
Systolic blood pressure (mmHg)	146 ± 18	144 ± 18	NS
Diastolic blood pressure (mmHg)	77 ± 10	79 ± 12	NS
Number diabetic	21 (61%)	29 (31%)	0.05
Smoker	5 (14%)	13 (16%)	NS
Positive family history	5 (14%)	13 (16%)	NS
Peripheral vascular disease	14 (40%)	4 (5%)	<0.001
Graft failure	8 (22%)	7 (9%)	0.05
Haemoglobin (g/l)	11.2 ± 5.6	11.7 ± 6.8	NS
cTnT (µg/l)	0.15 ± 0.25	0.07 ± 0.09	NS
CRP (mg/l)	15.7 ± 17.2	7.1 ± 15.2	0.05
NT ProBNP (pg/ml)	1661 ± 2749	776 ± 1392	NS
Aspirin	27 (77%)	31 (36%)	<0.001
Beta blocker	15 (42%)	29 (33%)	NS
ACE inhibitor	14 (37%)	40 (46%)	NS
Statin	30 (85%)	41 (38%)	<0.001

Table 4. Comparison of baseline and stress echo parameters in patients with and without severe CAD

	Severe ($n = 36$)	Non-severe ($n = 89$)	*P*-value
Baseline			
LVESD (cm)	3.36 ± 0.96	2.73 ± 0.73	0.007
LVEDD (cm)	5.22 ± 0.99	4.65 ± 0.87	0.007
LVEF (%)	60.1 ± 14.6	69.7 ± 11.9	0.011
LA (cm)	3.9 ± 0.6	3.5 ± 0.5	0.001
E/Ea	14.3 ± 6.9	11.2 ± 4.7	0.02
E/Vp	2.29 ± 0.74	1.95 ± 0.69	0.03
LVMI (g/m²)	175.1 ± 51.3	157.9 ± 79.6	NS
No. patients with resting RWMA	11 (31%)	4 (5%)	<0.001
Mean number resting abnormal segments	1.47 ± 2.64	0.26 ± 1.12	0.014
Resting RWMSI	1.11 ± 1.02	1.02 ± 0.08	0.013
Mitral annular calcification	22 (61%)	25 (28%)	0.04
Stress			
No. patients with angina	20 (55%)	9 (10%)	<0.001
No. patients with significant ECG changes	21 (58%)	5 (6%)	<0.001
Peak LVEF (%)	77.03 ± 14.69	84.43 ± 6.16	0.01
No. patients with positive DSE	32 (88%)	5 (5%)	<0.001
Mean number abnormal segments	3.00 ± 2.67	0.17 ± 0.41	<0.001
Peak RWMSI	1.30 ± 0.26	1.03 ± 0.11	<0.001

but reduced LVEF ($P = 0.011$) compared to those without. LV filling pressure as assessed by E/Ea ($P = 0.02$) and E/Vp ($P = 0.03$) ratio was also significantly higher in those with severe CAD but there was no difference in LVMI. A significantly greater proportion of patients with severe CAD had a positive DSE result ($P < 0.001$) and MAC ($P = 0.04$). Both resting ($P = 0.013$) and peak RWMSI ($P < 0.001$) were greater in those with severe CAD.

Figure 1 shows the accuracy of angina, the resting and exercise ECG and the DSE result for predicting the presence of severe CAD in this population. Both sensitivity (88%) and specificity (94%) were high for a positive DSE result. The same values for exercise testing were 35 and 64%, respectively. An abnormal resting ECG had a sensitivity of 77% but specificity of 58%. The same values for symptoms of chest pain were 51 and 59%.

Stepwise logistic regression analysis by forward selection identified an abnormal resting ECG (OR 7, 95% CI 2, 34, $P = 0.013$) and a positive DSE result (OR 23, 95% CI 6, 88, $P = <0.001$) to be the only independent predictors of severe CAD in this group of ESRD patients.

Figure 2 shows Kaplan–Meier survival curves for patients with a positive DSE result, an abnormal resting ECG, severe CAD and the presence or absence of any CAD. There were similar but non-significant trends towards worse survival in patients with severe CAD, an abnormal resting ECG and a positive DSE result. However, patients with CAD had significantly worse survival than those with normal coronary arteries ($P = 0.005$). Of the patients who died from cardiac causes, five had a positive DSE and severe CAD at angiography. Two of these had coronary artery bypass surgery and one percutaneous angioplasty. The other two had minor CAD and a normal DSE.

The results for diabetics and non-diabetics were then separately analysed. Amongst diabetics, the proportion with a positive DSE result ($P < 0.0001$) and an abnormal resting ECG ($P = 0.001$) were significantly higher in those with severe CAD compared to those

without. Diabetics with severe CAD were significantly older ($P = 0.04$), had higher LVESD ($P = 0.05$) and LVEDD ($P = 0.04$) and lower LVFS ($P = 0.03$) than diabetics without severe CAD. In the non-diabetic population, age ($P = 0.05$), the proportion with a positive DSE result ($P < 0.0001$) and an abnormal resting ECG ($P = 0.004$) were significantly higher in those with severe CAD compared to those without. LV dimensions and systolic function were similar in non-diabetics with and without severe CAD. A comparison of diabetics and non-diabetics is shown in Table 5. Diabetics were significantly older, had a higher proportion with severe CAD, higher mean cTnT concentration and higher estimated LV filling pressure compared to patients without diabetes. LV dimensions and systolic function were similar in diabetics and non-diabetics. When survival was compared (Figure 3), diabetic patients had significantly higher mortality over the follow-up period.

Discussion

In this study we have investigated differences in baseline clinical, biochemical, ECG and echocardiographic parameters, at rest and during stress, in a group of renal transplant candidates with and without severe CAD. The aim was to identify non-invasive parameters that best predicted CAD in this patient group. One hundred and twenty-five patients were studied in whom 36 (29%) had severe CAD, a similar proportion to that previously reported in renal transplant candidates [9]. Only 45 (36%) patients had normal coronary arteries. Several parameters differed in those with and without severe CAD but only an abnormal resting ECG and a positive DSE result were independent predictors. Patients with CAD had significantly worse survival than those with normal coronary arteries as described previously [10]. However, severe CAD was only associated with a non-significant trend towards worse survival. This may be explained by the small sample size, the short follow-up period and the
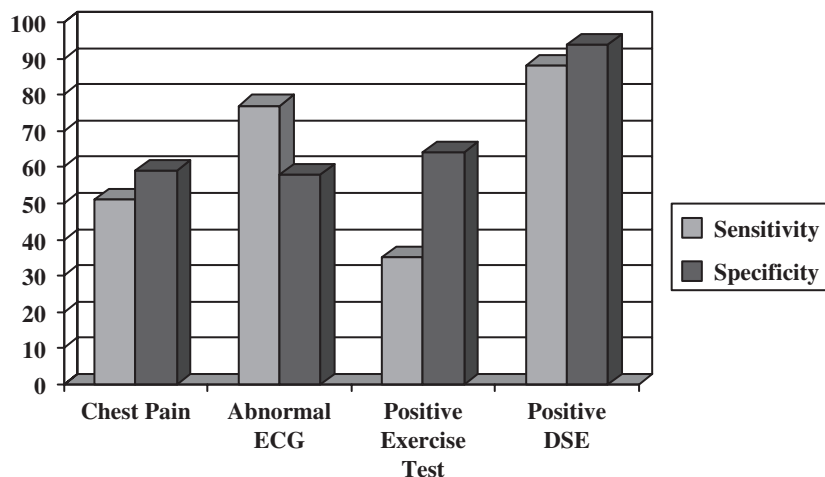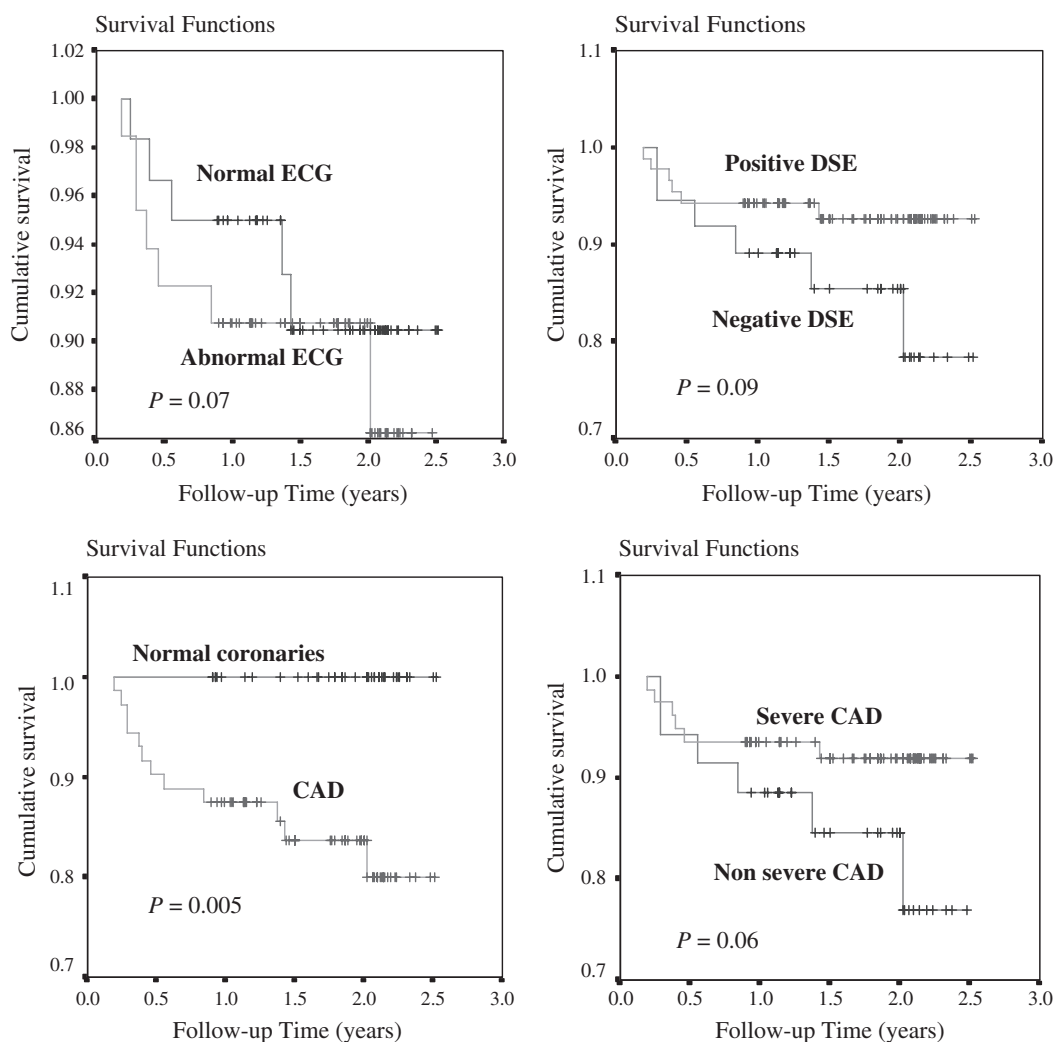
Fig. 1. Sensitivity and Specificity of chest pain, baseline ECG, exercise testing and DSE in the diagnosis of severe coronary artery disease.

Fig. 2. Kaplan–Meier survival curves according to the resting ECG, DSE result, presence of CAD and severe CAD.

Table 5. Differences between diabetics and non-diabetics

	Diabetics ($n = 50$)	Non-diabetics ($n = 75$)	*P*-value
Age (years)	56.4 ± 11.5	48.7 ± 12.7	0.001
Positive DSE result	23 (46%)	14 (20%)	0.05
Severe CAD	22 (44%)	14 (20%)	0.05
cTnT concentration (mg/l)	0.12 ± 0.08	0.04 ± 0.07	0.005
E/Ea ratio	14.7 ± 6.3	10.3 ± 4.2	0.001

high revascularization rates of patients in this study with severe CAD (15 out of 36). However, even over a short follow-up period, diabetes was associated with significantly higher mortality. Less than half the patients received a beta-blocker or ACE inhibitor despite the prognostic benefits of these drugs in high risk cardiac patients. Just over 50% received a statin. Importantly, beta-blockers and ACE inhibitors were not used significantly more in those ESRD patients with CAD.

Of the traditional cardiac risk factors only age, mean serum cholesterol and the proportion of diabetics were significantly higher in those with severe CAD. Both mean total cholesterol and LDL cholesterol were elevated despite significantly greater statin use in those with CAD, implying inadequate dosage of these drugs. Hypertension was found in 91% of patients but mean levels in those with and without CAD, though similar, were still higher than the recommended upper limit value of 130/80 for patients with ESRD [11]. Renal graft failure and the presence of peripheral vascular disease were associated with a higher prevalence of CAD in keeping with previous studies [2]. Plasma CRP levels, a marker of the inflammatory response, were significantly higher in those with CAD compared to those without. Renal failure is associated with activation of systemic inflammation and increased oxidative stress. This may contribute to the accelerated atherosclerosis seen in this patient group [12]. Plasma cTnT levels were not significantly different in those with and without severe CAD, in keeping with a previous study [13]. This suggests other mechanisms of cardiac
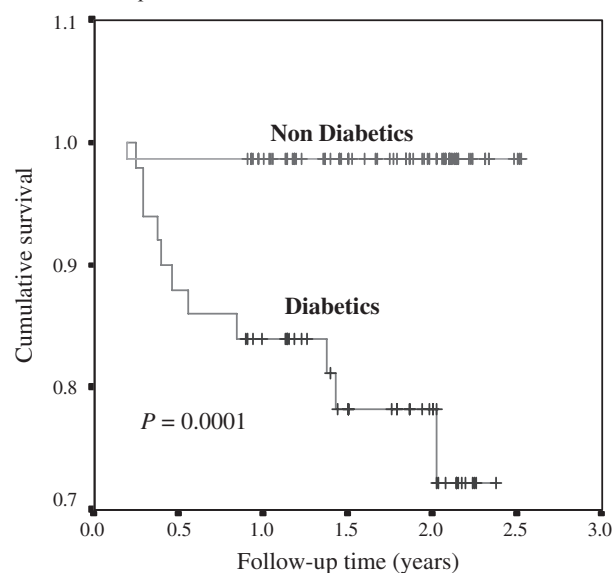
Fig. 3. Kaplan–Meier survival analysis according to diabetes.

injury may also be responsible for a raised troponin in renal failure.

When electrocardiographic data were compared, it was the resting ECG rather than changes during exercise testing that best predicted CAD in ESRD. Indeed multivariate analysis identified an abnormal baseline ECG to be independently associated with severe CAD in this patient group. Its sensitivity was 77% but specificity only 58%. An abnormal ECG was found in 46% patients studied. This high prevalence in renal failure has been previously described [14,15] and is thought to be due to left ventricular hypertrophy, volume overload and electrolyte abnormalities. In contrast, baseline ECG abnormalities are much rarer in the general population, occurring in only 8.5% men and 7.7% of women [16]. In patients with CAD, the occurrence of an abnormal baseline ECG often correlates with the severity of CAD and is a marker of poor prognosis. Exercise electrocardiography was not predictive of CAD in patients with ESRD. Maximal ST change, peak heart rate, peak systolic blood pressure and Duke prognostic score were similar in those with and without severe CAD. Only walking time was significantly reduced in those with CAD. Sensitivity was only 35% and specificity 64%, much lower than the general population. Reasons for this include the high prevalence of resting ECG abnormalities and the fact that 47% of patients were unable to achieve their target heart rate. This reduced exercise capacity in renal failure is due to muscle fatigue, arthralgia, anaemia and autonomic neuropathy causing a blunted tachycardia. Chest pain was also not predictive of CAD. Chest pain with unobstructed coronaries is described in renal failure [17]. Reasons include anaemia, reduced vasodilator reserve, micro-vascular disease and autonomic dysfunction. Likewise severe CAD is common in asymptomatic patients with ESRD, predominantly because of autonomic dysfunction and in some a sedentary lifestyle.

A positive DSE was also identified as an independent predictor of severe CAD. The sensitivity (88%) and specificity (94%) were excellent, as described previously [18]. There was a non-significant trend towards worse survival in those with a positive DSE result. Patients with severe CAD had larger LV cavity size, and more impaired LV systolic and diastolic function. These echo parameters are associated with worse outcome in ESRD. MAC was common in our patients with ESRD (38%). A significantly greater proportion of those with severe CAD had MAC, an association previously described in non-uraemic patients [19].

Current American and European renal transplantation guidelines advocate screening potential candidates for CAD in order to estimate cardiovascular risk and determine surgical risk. Patients with severe CAD are offered revascularization prior to renal transplantation. This is based largely on registry data suggesting superior survival when compared to medical therapy alone [20]. However, as shown in this study, many traditional risk factors are less predictive for CAD in patients with renal failure [2]. Consequently, there is a large variation in cardiac screening protocols used by different transplant units. Most advocate coronary angiography with subsequent revascularization to all diabetic patients. Our study would support this policy given that 44% of diabetic renal transplant candidates had severe CAD and mortality was significantly higher in this group. However, only 20% of non-diabetics had severe CAD so coronary angiography is probably not cost-effective in these patients. In this study, an abnormal baseline ECG and positive DSE result were independently associated with severe CAD in a group of renal transplant candidates. Both of these could therefore be used for cardio-vascular screening of non-diabetic patients with ESRD. Identified high risk patients would then be offered coronary angiography and revascularization where appropriate. Greater use of drugs such as aspirin, beta-blockers, ACE inhibitors and statins may also further improve the long-term survival of such high risk renal transplant candidates. However, further studies are required to validate this approach of assessing and minimizing cardiac risk in patients referred for renal transplantation.

Conflict of interest statement. None declared.

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