Does screening for asymptomatic coronary artery disease predict cardiac events in kidney transplant recipients? A propensity score matched analysis.

Journal:	*Kidney International*
Manuscript ID	KI-06-20-1127.R2
Article Type:	Clinical Investigation
Date Submitted by the Author:	09-Sep-2020
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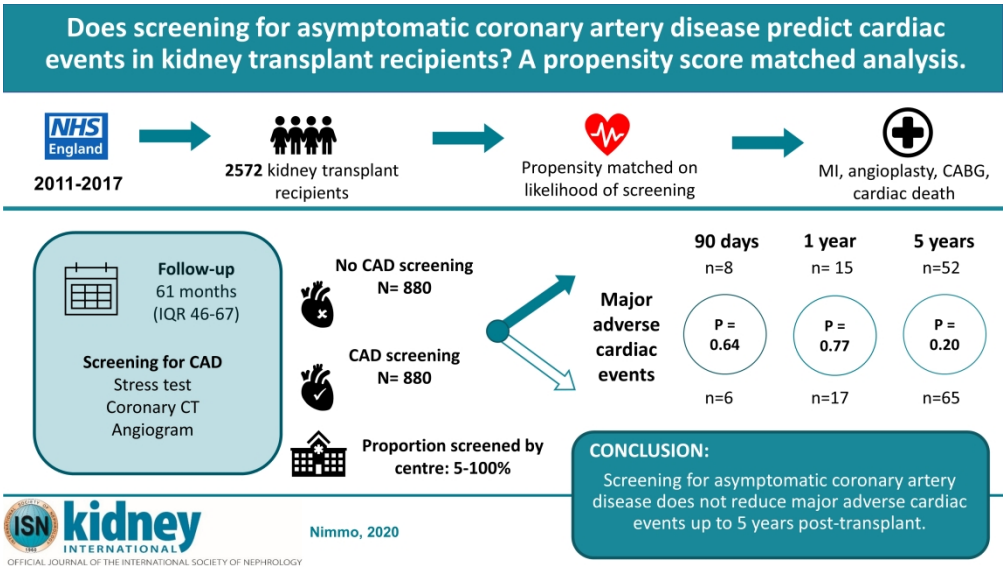
Keywords:	cardiovascular disease, transplantation
Subject Area:	Transplantation



Graphical abstract TIFF

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Does screening for asymptomatic coronary artery disease predict cardiac

NHS England

2011-2017

2572 kidney transplant recipients

Propensity matched on likelihood of screening

MI, angioplasty, CABG, cardiac death

Follow-up
61 months
(IQR 46-67)

Screening for CAD
Stress test
Coronary CT
Angiogram

No CAD screening
N= 880

CAD screening
N=880

Proportion screened by centre: 5-100%

Major adverse cardiac events

	90 days	1 year	5 years
	n=8	n= 15	
	P = 0.64	P = 0.77	P = 0.20
	n=6	n=17	
	n=65		

Nimmo, 2020

CONCLUSION:
Screening for asymptomatic coronary artery disease does not reduce major adverse cardiac events up to 5 years post-transplant.

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Title:

Does screening for asymptomatic coronary artery disease predict cardiac events in kidney transplant recipients? A propensity score matched analysis.

Running title:

Cardiac screening prior to kidney transplantation

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Sources of support: Nil

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AN performed the analyses, produced the figures and tables and wrote the manuscript under the supervision of DMT, RAR and PJR. James Fotheringham assisted with manipulation of HES data, statistical analyses and contributed to manuscript preparation. All other authors were members of the ATTOM research group who gave editorial and methodological advice and contributed to manuscript preparation.

Abstract

Screening for asymptomatic coronary artery disease prior to kidney transplantation aims to reduce peri- and postoperative cardiac events. It is uncertain if this is achieved. We investigated whether pre-transplant screening with a stress test or coronary angiogram associates with any difference in major adverse cardiac events (MACE) up to 5 years post-transplantation. We examined a national prospective cohort recruited to the Access to Transplant and Transplant Outcome Measures study who received a kidney transplant between 2011-2017, and linked patient demographics and details of cardiac screening investigations to outcome data extracted from the Hospital Episode Statistics dataset and UK Renal Registry. Propensity score matched groups were analysed using Kaplan-Meier and Cox survival analyses. Overall, 2572 individuals were transplanted in 18 centres; 51% underwent screening. The proportion undergoing screening by centre ranged from 5-100%. The incidence of MACE at 90 days, 1 and 5 years was 0.9%, 2.1% and 9.4% respectively. After propensity score matching based on the presence or absence of screening, 1760 individuals were examined (880 in screened and unscreened groups). There was no statistically significant association between screening and MACE at 90 days (hazard ratio [HR] 0.80, 95% CI 0.31-2.05), 1 year (HR 1.12, 95% CI 0.51–2.47) or 5 years (HR 1.31, 95% CI 0.86-1.99). Age, male sex and history of ischaemic heart disease were associated with MACE. There is no association between screening for asymptomatic coronary artery disease and MACE up to 5 years post-transplant. Practices involving unselected screening of transplant recipients should be reviewed.

Keywords

Coronary artery disease, screening, kidney transplantation, cardiovascular events

Introduction

Cardiovascular disease is common in people with chronic kidney disease (CKD): those on dialysis have a risk of cardiovascular death 20 times that of the general population. [1] Significant coronary artery disease (CAD) is often asymptomatic in these individuals. [2] Although kidney transplantation offers dramatically improved long-term cardiovascular outcomes and survival compared to dialysis, [3,4] cardiovascular disease remains common, accounting for 20% of deaths with a functioning graft. [5] Further, the benefits of kidney transplantation come at the expense of increased perioperative cardiovascular risk [3] relating to surgical and anaesthetic stress. [6]

Clinicians aim to reduce peri- and postoperative risk by selecting individuals who are likely to achieve improved quality and quantity of life with an acceptably low risk of adverse cardiac events and premature death. To aid recipient selection, current practice is to consider screening for occult CAD pre-transplantation. [7] If screening investigations are abnormal, revascularisation may be performed to attempt to reduce cardiovascular risk, or patients may be deemed too high-risk to proceed.

It is unclear if abnormal stress-tests in asymptomatic transplant candidates predict cardiovascular outcomes, [2,8] and although patients with occult CAD have a higher rate of post-transplant cardiac events [9] there is no clear evidence that revascularisation in asymptomatic individuals reduces myocardial infarction and death. [2,10,11,12] Additionally, the cardiac outcomes of individuals excluded from transplantation based on abnormal screening tests are unknown, as is whether any individuals are unnecessarily deprived of this superior treatment option.

This lack of high-quality evidence leads to inconsistency between international guidelines' recommendations on screening [13] and variation between centres in patient selection for cardiovascular assessment, investigations used, and subsequent actions taken. [14,15] Patients may be selected based on perceived or calculated risk, or screened universally. [16,17] Screening investigations are not standardised and include stress tests (exercise tolerance test (ETT), myocardial perfusion

scan (MPS) or dobutamine stress echocardiogram (DSE)), coronary computed tomography (CT) and invasive coronary angiograms, [9,12] used according to local availability.

Interpretation of the observational data in this field is challenging: good cardiovascular outcomes in transplant recipients may suggest screening is unnecessary, [18] or reflect a successful screening programme. Full evaluation is limited by the lack of data on those deemed unfit for transplantation through screening. Furthermore, the screening process may be harmful or wasteful through unnecessary exposure to ionising radiation, exacerbating inequities in access to transplant by unjustified exclusion or delay to listing, [11,19] and consumption of non-evidence-based resources.

We used data from the Access to Transplant and Transplant Outcome Measures (ATTOM) study of prospective kidney transplant recipients in England [20] linked to national hospitalisation data to examine the impact of pre-transplant screening on 5 year cardiovascular outcomes.

Results

Patient population (Figure 1)

ATTOM recruited both 'incident transplant' patients within 90 days of kidney transplantation and 'waitlisted' patients active on the deceased-donor waiting list. Patients in the 'waitlisted' group subsequently transplanted before 31st December 2017 were examined alongside 'incident transplant' patients.

In total, 2853 patients received a transplant in England and 2723 were matched to their Hospital Episode Statistics (HES) record. Of those unmatched, 49 had non-English postcodes and are likely to have received treatment in other parts of the UK. The 151 patients receiving multi-organ transplants were excluded. Overall, 2572 patients were examined: 1661 (64.6%) 'incident transplant' and 911 (35.4%) 'waitlisted'. Median time from recruitment to transplant in the 'waitlisted' group was 17 months [IQR 9-29]. Median age at transplant was 51 years (range 20-76 years).

Ethnicity data were available in 92.3% of cases from ATTOM, increasing to 99.7% with HES data. Baseline comorbidity information was available in 99.5% of cases from ATTOM, increasing to 100% with HES data.

In the 'waitlisted' group, 2.8% of individuals underwent first screening investigations after recruitment to ATTOM (Supplementary Figure 1).

Incidence of MACE

Median follow-up was 61 months [IQR 46-67], over which time 202 patients experienced MACE (145 from the 'incident transplant' group and 57 from the 'waitlisted' group). The incidence of MACE was 0.9% at 90 days (n=23), 1.3% at 6 months (n=32), 2.1% at 1 year (n=52), 3.6% at 2 years (n=82) and 9.4% (n=199) at 5 years post-transplant.

Of those experiencing MACE, 55% underwent coronary intervention (angioplasty or CABG) alone and 32% had two or more categories of MACE (Supplementary Figure 2). Only 4% of MACE were based on a clinical diagnosis of MI or unstable angina alone.

Over follow up, 254 patients died. Cause of death was available in 94% of cases; 32 (13%) deaths were cardiac in nature and counted as MACE. Of the 108 in-hospital deaths, 11 were cardiac and 4 individuals experienced another MACE during the terminal admission.

Patterns of cardiovascular workup (Figure 2)

Combinations of screening investigations varied (Figure 2). No investigations were performed in 17% and an echocardiogram alone was performed in 32% (not counted as CAD screening). An echocardiogram and stress test (ETT, MPS or DSE) was performed in 29%. Overall, 51% of patients underwent CAD screening in some form.

Factors associated with CAD screening (Tables 1 and 2)

Individuals undergoing screening were older (median age 56 years [IQR 47-63] vs. 46 years [IQR 36-55]), more likely to be male, have a history of diabetes, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease and smoking (Table 1). By univariable analysis, significant variation was observed with ethnicity, socioeconomic status and primary renal disease (PRD); white ethnicity, higher socioeconomic status and renovascular disease were associated with the highest likelihood of screening. In addition to differences in screening investigations used, there was significant variation in the proportion of patients tested between transplant centres. The median percentage of patients undergoing screening by centre was 58% [IQR 26-68, range 5-100%].

Following multivariable analysis (Table 2), factors independently associated with likelihood of screening comprised age (OR 1.08, 95% CI 1.07-1.09), ethnicity (white ethnicity vs. black ethnicity OR 1.62, 95% CI 1.05-2.51), history of ischaemic heart disease (OR 2.93, 95% CI 1.76-4.86) and diabetes (OR 3.11, 95% CI 1.84-5.25). Significant variation between centres persisted following adjustment

for all other factors. There was no association between screening and prior renal replacement therapy (RRT) modality, socioeconomic status or PRD.

Propensity score matching and non-matched individuals

Prior to propensity-score matching, patients undergoing screening had a higher incidence of MACE at 1 and 5 years (52 patients had an event at 1 year with 65% in the screened group; 199 patients had an event at 5 years with 67% in the screened group). No difference was observed at 90 days post-transplant (Table 1).

The covariables used to generate the propensity score comprised age, sex, ethnicity, socioeconomic status, smoking history, history of diabetes, ischaemic heart disease, peripheral vascular disease, and cerebrovascular disease. Matching based on propensity for screening allowed assessment of 1760 patients (880 in each screened and unscreened groups).

Characteristics of the 812 patients who were not propensity matched are shown in Supplementary Table 1. Of these, 440 underwent screening. Non-propensity matched individuals were more likely to be male, of Asian ethnicity, of lower socioeconomic status, and have a history of diabetes, ischaemic heart disease, peripheral vascular disease and cerebrovascular disease. Variation was observed between centres, reflecting differing screening practices. There were no statistically significant differences in age, smoking history or prior RRT modality.

Associations between CAD screening and MACE with propensity score matching (Table 3 and Figure 3)

In the propensity score matched cohort, baseline covariables were balanced between groups with a standardised mean difference (SMD) of 0.2 or less for all variables (Supplementary Table 2). There was variation in SMD, though all variables were more evenly balanced following the propensity score matching process. Ethnicity, PRD, Index of Multiple Deprivation (a marker of socioeconomic status), smoking and history of ischaemic heart disease each had an SMD of greater than 0.1, though

ischaemic heart disease and smoking were more prevalent in the unscreened group within the propensity matched cohort.

In the propensity matched cohort, 14 individuals experienced MACE by 90 days (incidence 0.9%), 32 by 1 year (incidence 1.9%) and 117 by 5 years (incidence 8.0%) (Figure 3). The pattern of screening was similar to the whole study population: 696 (39.5%) had a stress test without angiogram and 184 (10.5%) had a coronary angiogram with or without a stress test.

In the Cox models, proportionality assumptions were met. There was no statistically significant association between screening and MACE in univariable or multivariable analyses at 90 days (multivariable HR 0.80, 95% CI 0.31-2.05; p=0.64), 1 year (HR 1.12, 95% CI 0.51-2.47; p=0.77) or 5 years post-transplant (HR 1.31, 95% CI 0.86-1.99; p=0.20) (Table 3).

In the multivariable Cox model, factors independently associated with MACE at 1 year were age (HR 1.02, 95% CI 1.00-1.05; p=0.02) and history of ischaemic heart disease (HR 4.06, 95% CI 1.73-9.55; p<0.001). An association between MACE and one socioeconomic quintile (Index of Multiple Deprivation quintile 2) was observed but there was no association with other socioeconomic quintiles and this observation was not noted at the other timepoints. At 5 years, age (HR 1.05, 95% CI 1.04-1.06; p<0.001), male sex (HR 1.60, 95% CI 1.08-2.37; p=0.02) and history of ischaemic heart disease (HR 2.15, 95% CI 1.19-3.87; p=0.01) were positively associated with MACE. The incidence of MACE at 5 years did not correlate with transplant centre (Supplementary Table 3).

Sensitivity analyses

Four sensitivity analyses were performed. In the first analysis examining the 'incident transplant' cohort only, and the second analysis using a competing risk model for non-cardiovascular death, there remained no association between screening and MACE (Supplementary Tables 4 and 5).

The third sensitivity analysis investigated the likelihood that an unmeasured confounder eliminated a 'true' protective effect of screening. If at 1 year, screening were protective against MACE with a

hazard ratio of 0.95 and upper limit of the 95% confidence interval of 1.0, to explain the observed hazard ratio of 1.12 the 'inverse' E value for the point estimate is 1.64 and for the confidence interval 1.49. Agreed interpretation of this statistic is that for an unmeasured confounder (associated with both screening and MACE) to bias a true hazard ratio of 0.95 or below to the observed hazard ratio of 1.12, the confounder would have to be associated with screening and MACE with a risk ratio of 1.64 or above. To put this in perspective, the confounder would need to be associated with screening and MACE at a magnitude equal to or greater than the association between MACE at 1 year and a 10-year increment in age (adjusted HR 1.57, 95% CI 1.17-2.10). Significant unmeasured confounding therefore seems unlikely. A value of 0.95 was chosen as for any stronger association between screening and MACE, the 'inverse' E-value would need to be even greater.

The final sensitivity analysis examined the effect of screening on MACE in the whole population using an adjusted Cox regression model with inverse probability of treatment weighting. The weighted hazard ratios were similar to those for the propensity matched cohort (Supplementary Table 6). There remained no statistically significant association between screening and MACE at 90 days (weighted HR 0.70, 95% CI 0.29-1.68; p=0.43) or 1 year (weighted HR 0.99, 95% CI 0.51-1.91; p=0.98). Five year results did not meet the proportionality assumption of the Cox model due to the rate of MACE climbing at a greater rate in the screened group, and have not been presented.

Post-transplant events

In the propensity matched cohort, there was no difference in creatinine at 1 year (screened median 125µmol/L [IQR 101-158] vs. unscreened median 125µmol/L [IQR 100-163]; p=0.73) or 5 years (median 128µmol/L [IQR 103-167] vs. unscreened median 126µmol/L [IQR 98-158]; p=0.21) post-transplant. There was no statistically significant difference in HES-documented rejection episodes prior to MACE (screened 18.0% vs. unscreened 16.7%; p=0.49) nor in incidence of post-transplant

diabetes (screened 15% vs. unscreened 11%; p=0.07). In the screened group, 30% of transplants were from a living donor compared with 29% in the unscreened group (p=0.67).

Discussion

In this national prospective study of kidney transplant recipients in England we found no association between screening for asymptomatic coronary artery disease and the development of major adverse cardiac events up to 5 years post-transplantation. By examining a national cohort and adjusting for factors associated with screening through propensity score matching, our results are less subject to regional and selection bias than previous observational studies which report variable associations between cardiac screening and MACE. [9,21,22,23,24,25] The uncertainty over the utility of screening is highlighted by the variation in uptake between centres, ranging from 5-100% of recipients.

The low incidence of post-transplant MACE is reassuring and similar to that reported previously. [26,27] This suggests individuals currently selected for transplant (with or without screening) have what most clinicians would deem an acceptable cardiac risk, but others who may benefit could have been unnecessarily excluded. Other methods to stratify risk should be considered when evaluating suitability for transplant. We found age, male sex and ischaemic heart disease to be positively associated with MACE, as previously reported, [26,27] adding weight to their use in risk-stratified algorithms. [2,28]

It seems intuitive that pre-transplant screening should improve outcomes given that significant CAD is often asymptomatic in transplant candidates, [2] but our results suggest otherwise. There are several possible explanations. First, performing and interpreting non-invasive investigations in renal patients is challenging. Less than 40% of transplant candidates reach maximal work capacity or experience symptoms during ETTs. [29,30] The sensitivity and specificity of DSE and MPS for detecting angiographically-confirmed CAD are moderate at best, with a sensitivity of 76% and 67% and specificity of 88% and 77% respectively. [31] Increased vascular calcification in CKD also limits the utility of coronary CT in identifying obstructing lesions. [32] As such, non-invasive tests may not adequately risk-stratify patients. [24]

Second, even if non-invasive tests accurately identified individuals with significant coronary lesions, it remains uncertain if revascularisation improves outcomes. [10,11,18] The ISCHEMIA-CKD randomised control trial examined individuals with an eGFR<30ml/min/1.73m^2 or on dialysis with stable symptoms and moderate to severe ischaemia on stress testing: a similar population to transplant candidates. Importantly, patients were excluded if they had unprotected left main stem disease or an ejection fraction below 35%, but in individuals without these features no reduction in death or myocardial infarction was observed with angioplasty over best medical therapy. [33] This is reflected in the 2020 KDIGO guidelines which recommend asymptomatic patients not undergo revascularisation solely to reduce perioperative risk. [34]

Third, the absence of a clear benefit from revascularisation suggests a different aetiology for cardiovascular disease in people with CKD. The high prevalence of left ventricular hypertrophy, systolic and diastolic dysfunction, myocardial fibrosis and arteriosclerosis [35] may explain why half of cardiovascular deaths in transplant recipients relate to dysrhythmias as opposed to atherosclerotic events. [36,37,38] Currently-adopted screening tools for atheromatous disease may be less suited to the CKD population. Other dynamic investigations e.g. functional cardiopulmonary exercise testing may provide superior cardiovascular risk information in this cohort. [39]

Finally, MACE post-transplantation may be influenced by transplant-specific cardiovascular risk factors such as renal function and acute rejection episodes. [40] However, our data suggest these did not play a clear role in predicting MACE over our follow-up period: there was no significant difference in creatinine between groups or frequency of HES-recorded rejection episodes which may have led to intensified immunosuppression, though there was a non-significant trend towards increased post-transplant diabetes in the screened group.

Our study has several strengths. Using a prospective cohort of patients from all units in England [20] we were able to evaluate a large propensity matched population through dataset linkage. Propensity matching was possible because of variation in practice between centres with no inter-

centre difference in incidence of MACE; by examining individuals with a similar likelihood for screening we estimate them to have comparable degrees of underlying CAD. Our baseline data, which included details of screening investigations, were collected by dedicated research nurses with specific training to seek and record such information thus improving data accuracy. Only 2.8% of 'waitlisted' individuals underwent first screening whilst on the waitlist, and similar results were observed when examining the 'incident transplant' group alone increasing confidence in our results. The coding criteria used to detect MACE in HES data also appear robust: 87% of individuals with MACE had a coronary angioplasty, CABG, or 2 or more classes of event, reducing reliance on clinical diagnosis alone [41] and dysrhythmia-related deaths should be captured. Our population is broadly representative of other high-income countries with respect to renal [42,43] and cardiovascular outcomes [44,45] making our results generalisable.

We recognise our study's limitations. Data were observational so only associations can be described and there is potential for unmeasured confounding. Individuals with the highest propensity for screening (and hence greatest cardiovascular risk factors) were less likely to be matched in our models. The highest-risk individuals are thus under-represented in our analyses and caution should be exercised extrapolating findings to this group. The inverse probability weighted analysis goes some way to mitigate this, but the greater rise in rate of MACE in screened individuals does question whether certain subgroups may derive an early benefit from screening. We do not know how many patients underwent screening and were not waitlisted. In the UK, single centre reports suggest the proportion of patients not listed after screening ranges from 13-26% [11,18] but screening results are just one factor in a complex clinical assessment and the relative impact of these in 'justifying' transplant preclusion is unclear. The proportion excluded predominantly due to screening abnormalities is probably much lower, reported as 4% by Kumar et al. [18] We do not have direct evidence that screening tests met agreed diagnostic thresholds, but have no reason to suspect that investigations would not meet established quality standards. [46,47,48] We do not have investigation results and assume that individuals listed for transplantation following screening were deemed to

have acceptable test results that ruled out significant cardiovascular risk. The rate of MACE in the early post-operative period was low, which may reduce the power to detect differences particularly at the 90 day time point, but we are reassured that no difference was seen over 5 years with a greater number of events observed. We did not have information on medical management of CAD, and whether this differed between groups. We also do not have data on all post-transplantation cardiovascular risk factors such as maintenance immunosuppression regimen and other biochemical parameters, but these may impact more on long-term cardiovascular risk so are less likely to be clinically relevant. Finally, it is not known how the availability of pre-transplant screening investigations varies between centres and whether this influences the individuals they list for transplantation.

There are likely to be health economic and practical benefits from reducing potentially unnecessary screening. Half of the individuals in our study underwent screening. Around 3600 patients are transplanted annually in the UK [49] with more being investigated and not listed. A stress echocardiogram costs £280 and an angiogram £2500, [50] providing a cost perspective. The Canadian-Australasian Randomised trial of screening kidney transplant candidates for CAD (CARSK) study is investigating if repeated screening on the waitlist reduces MACE. [51] Results are not expected until 2025, but a cost utility analysis suggests eliminating screening may increase cost due to more individuals being transplanted with improved survival [52] than because of increased MACE.

The feasibility of a prospective randomised control trial evaluating the impact of pre-listing screening on MACE should be considered. Such a study may also be able to evaluate whether individuals with higher risk of MACE have more to gain from screening. This comes with challenges: changes to practice must consider the acceptability of risk to the whole transplant community. There will likely be apprehension around anaesthetising higher-risk individuals with apparently less thorough workup, especially if some may have otherwise been excluded. With low event rates of post-transplant MACE, achieving sufficient power even with a national study may be challenging.

Standardising the timing of screening prior to transplantation is also difficult given the unpredictable time spent on the waitlist prior to deceased donor transplantation. Potential benefits however are clear: minimising screening reduces exposure to ionising radiation, post-intervention coronary events [18] and minimises delays to listing with potential to reduce time on dialysis.

In conclusion, this national observational propensity cohort study of patients listed for kidney transplantation found that screening for CAD does not reduce cardiac events post-transplantation. Unselected screening of asymptomatic patients prior to kidney transplantation is not justified. A large-scale randomised control trial of asymptomatic higher-risk individuals through increased age, history of diabetes or ischaemic heart disease, may clarify if there is benefit in selected patients.

Methods

Data sets and patient population

Data from the Access to Transplantation and Transplant Outcome Measures (ATTOM) study were linked to routinely collected Hospital Episode Statistics (HES) data, which captures activity in English hospitals. ATTOM was a UK-wide prospective cohort study that recruited patients aged 18-75 years between 1st November 2011 and 31st March 2013. Both 'incident transplant' patients within 90 days of kidney transplantation and prevalent 'waitlisted' patients active on the deceased-donor waiting list were recruited. [20] Patients in the 'waitlisted' group who were subsequently transplanted before 31st December 2017 were examined alongside the 'incident transplant' group.

Patients receiving both first and subsequent allografts were included as screening practices are generally independent of graft number. Only recipients of single organ kidney transplants were examined as different workup processes exist for dual organ transplants. As only English hospital data are included in HES, ATTOM participants from Scotland, Wales and Northern Ireland were excluded.

Baseline patient characteristics and data on inpatient or outpatient cardiovascular screening investigations performed for transplant assessment were collected by research nurses at ATTOM recruitment using a systematic note review and patient interviews. Information on the validity of screening investigations, screening investigation results and revascularisation procedures were not recorded. Missing ethnicity and comorbidity data from ATTOM were supplemented from HES data if required. Date of graft loss, date and cause of death and 1 and 5 year creatinine were obtained from NHS Blood and Transplant and the UK Renal Registry.

As individuals in the 'waitlisted' group were not immediately transplanted, HES data were interrogated to identify screening investigations occurring between recruitment and transplantation. An investigation was assumed to be for screening if performed as an outpatient or day-case with no cardiac event within the preceding 30 days.

Data from HES were available from 1st January 2006 to 31st December 2017, including NHS admitted patient care, outpatient, and emergency department attendances. Diagnoses and procedures from admitted patient care and outpatient episodes are coded using International Classification of diseases 10th revision (ICD-10) and OPCS Classification of Interventions and Procedures version 4 (OPCS-4) criteria. Data were obtained from NHS Digital, stored at NHS Blood and Transplant and linked to the ATTOM database by unique patient identifiers.

Major adverse cardiac events

Major adverse cardiovascular events (MACE) were identified from HES coding, defined as unstable angina, myocardial infarction (MI), coronary artery bypass graft (CABG), coronary angioplasty or cardiac death. [53] HES data were interrogated for corresponding ICD-10 and OPCS-4 codes using Myocardial Ischaemia National Audit Project criteria (Supplementary Table 7). [54]

Cardiac deaths comprised those caused by myocardial ischaemia and infarction, sudden death, cardiac failure, pulmonary oedema or cardiac arrest as per the ERA-EDTA coding system. [55] These are coded by clinicians at the patient's renal unit and returned to NHS Blood and Transplant and the UK Renal Registry.

Events from transplantation until the end of available HES data were identified, censored for non-cardiac death. The incidence of MACE was calculated from Kaplan-Meier analyses.

Statistical Methods

Baseline patient- and transplant-specific risk factors for cardiovascular disease were reported using descriptive statistics. Non-parametric continuous variables are expressed as median (interquartile range [IQR]) and categorical variables as frequency and percentage. Comparisons were made using the Chi-square test for categorical variables and Mann-Whitney U test for non-parametric continuous variables.

Outcome Measures

The primary outcome was time to MACE, calculated from day of transplant until first event, non-cardiac death or end of follow-up. Events following graft failure were included.

Factors associated with CAD screening

Patients were divided into those who underwent a stress test (ETT, DSE or MPS) or angiogram (CAD screening group) or had no investigation or echocardiogram alone (no screening group). Echocardiography identifies heart failure and valvular heart disease and is not a dynamic test for CAD. Whilst low ejection fraction may be a contraindication to transplantation, revascularisation can improve left ventricular function [56] and individuals are likely to proceed to further investigation. Echocardiography alone was therefore not considered a CAD screening investigation.

Logistic regression analyses were performed to identify factors associated with screening. Covariables, defined *a priori*, comprised age, sex, ethnicity, PRD, cardiovascular comorbidities, smoking history, prior RRT modality and Index of Multiple Deprivation: an area-level marker of socioeconomic status ranging from 1 (most deprived) to 5 (least deprived).

Propensity score matching and non-matched individuals

Propensity score analysis was used to balance differences in baseline cardiovascular risk between groups which may bias the association between screening and MACE. [57,58] Variables used to create the propensity matched groups were those which we clinically judged to relate to screening or MACE (other than transplant centre) and comprised age, sex, ethnicity, socioeconomic status, smoking status and history of ischaemic heart disease, diabetes, cerebrovascular disease and peripheral vascular disease. [59] Analyses included complete cases only, present in 2477 (96.3%) of cases.

Individuals were matched using a nearest-neighbour algorithm (1:1 case control) without replacement, with a radius of 0.2 standard deviations of the log odds of the estimated propensity score. SMD between groups were used to ensure covariables were balanced [58] accepting a SMD of

0.2 or below to indicate appropriate matching. [60] The characteristics of matched and unmatched individuals following the generation of the propensity score were compared using univariable analyses.

Associations between CAD screening and MACE with propensity score matching

The Kaplan-Meier method and univariable analyses followed by a doubly robust estimation using multivariable Cox regression models were used to assess factors associated with MACE at 90 days, 1 year and 5 years post-transplant. Time to event models were chosen to account for censoring events. Variables in the doubly robust multivariable model were determined *a priori* to be those used to create the propensity groups. [61] The proportionality assumption of the Cox models was tested using Schoenfeld residuals. Analyses used robust standard errors to account for clustering by centre.

As the propensity groups were not matched by transplant centre, a logistic regression model including centre was used to identify if MACE at 5 years was independently associated with unit.

Sensitivity analyses

Four sensitivity analyses were performed. These comprised (1) a propensity score matched analysis examining only the 'incident transplant' group given the potential for first screening to occur following ATTOM recruitment in the 'waitlisted' cohort, (2) a competing risks analysis using the Fine and Gray method to examine the impact of screening on MACE considering the competing risk of non-cardiovascular death [62] and (3) an assessment of how robust the 1 year results were with respect to unmeasured confounding by calculating the E-value. [63] The E-value estimates what the relative risk must be for an unmeasured confounder to overcome an observed but false association between screening and MACE, or in the event of no significant observed association for it to have eliminated a true protective effect of screening (i.e. the 'inverse' of the E-value).

The final sensitivity analysis (4) was an adjusted Cox regression model in the whole transplanted population using inverse probability of treatment weighting. Inverse probability of treatment weights were calculated from the reciprocal of the propensity score and stabilised by multiplying the weight by the proportion of the population in the treated (screened) group. The mean of the stabilised weights was 1.15 (SD 0.48). This technique creates a pseudo-population informed by all patients, where the distribution of observed covariables in screened and unscreened populations become balanced. [64] This method means previously unmatched individuals contribute to the analysis reducing any bias introduced by propensity score matching. The final Cox model was adjusted for the variables included in the generation of the propensity score.

Post-transplant events

To assess differences in transplant-specific cardiovascular risk factors in the propensity groups, creatinine 1 and 5 years post-transplant, HES-documented graft rejection, HES-documented post-transplant diabetes, and donor type (live or deceased) were compared.

Statistical tests were two-tailed with statistical significance defined *a priori* as $p<0.05$. Results of regression analyses were presented as effect ratios with 95% confidence intervals. Analyses were performed using Stata version 15 (Statacorp, College Station, TX).

Figures

Figure 1. Flow chart depicting patients included in the study.

Figure 2. Pattern of cardiovascular workup. Note an unknown number of patients will be tested and excluded from transplant based on test results. Stress test comprises exercise tolerance test, dobutamine stress echocardiogram and myocardial perfusion scan. Abbreviations: echo: echocardiogram; CT: computed tomography.

Figure 3. Kaplan-Meier estimator curve demonstrating MACE events after transplant in patients undergoing screening for coronary artery disease versus those who did not in the propensity matched cohort.

Tables

	No CAD Screening Test N=1252	CAD Screening Test N=1320	P
Age (years) (n=2572)	46 [36 – 55]	56 [47 – 63]	<0.001
Male Sex (n=2572)	734 (59)	830 (63)	0.03
Ethnicity (n=2563)			
White	892 (71)	1050 (80)	
Asian	210 (17)	147 (11)	<0.001
Black	122 (10)	101 (8)	
Mixed	23 (2)	18 (1)	
PRD (n=2555)			
GN	325 (26)	286 (22)	
Other	283 (23)	259 (20)	
PKD	196 (16)	229 (17)	
Uncertain	156 (12)	151 (12)	<0.001
PN	150 (12)	118 (9)	
Diabetes	55 (4)	159 (12)	
Hypertension	76 (6)	84 (6)	
Renovascular	6 (1)	22 (2)	
History of Diabetes (n=2572)	90 (7)	243 (18)	<0.001
History of IHD (n=2572)	40 (3)	147 (11)	<0.001
History of PVD (n=2572)	14 (1)	48 (4)	<0.001
History of CeVD (n=2572)	40 (3)	70 (5)	0.008
Ever smoker (n=2507)	358 (29)	466 (36)	<0.001
RRT modality (n=2556)			
HD	707 (57)	785 (60)	
PD	263 (21)	241 (18)	0.06
Transplant	13 (1)	5 (1)	
Pre-emptive	260 (21)	282 (21)	
IMD (n= 2572)			
1 – Most deprived	344 (27)	263 (20)	
2	247 (20)	271 (21)	
3	234 (19)	256 (19)	<0.001
4	218 (17)	287 (22)	
5 – Least deprived	209 (17)	243 (18)	
Centre (anonymised) (n=2572)			
1	118 (9)	64 (5)	
2	61 (5)	80 (6)	
3	0 (0)	264 (20)	
4	123 (10)	39 (3)	
5	62 (5)	12 (1)	
6	75 (6)	51 (4)	
7	72 (6)	163 (12)	
8	92 (7)	11 (1)	<0.001
9	25 (2)	119 (9)	
10	104 (8)	10 (1)	
11	47 (4)	81 (6)	
12	145 (12)	67 (5)	
13	20 (2)	118 (9)	
14	44 (4)	49 (4)	

15 16 17 18	99 (8) 16 (1) 111 (9) 38 (3)	95 (7) 38 (3) 6 (1) 53 (4)	
First transplant (n=1842)	795 (88)	826 (88)	0.86
Years RRT pre-transplant (n=1592)	1.7 [0.0 – 4.0]	1.9 [0.17 – 4.28]	0.10
Live donor (n=2572)	403 (32)	368 (28)	0.02
Creatinine at 1 year (n=2354)	125 [100 – 161]	124 [101 – 157]	0.42
Creatinine at 5 years (n=1235)	125 [100 – 160]	126 [103 – 163]	0.30
Post-transplant diabetes (n=2572)	154 (12.3)	172 (13.0)	0.58
Graft failure over follow-up	135 (10.8)	148 (11.2)	0.73
MACE at 90 days	10 (0.8)	13 (1)	0.62
MACE at 1 year	18 (1.5)	34 (2.6)	0.04
MACE at 5 years	66 (5.3)	133 (10.1)	<0.001

Table 1. Cardiovascular workup by patient demographic factors and transplant centre. Data are expressed as number (%) or median [interquartile range]. Abbreviations: PRD, primary renal diagnosis; GN, glomerulonephritis; PKD, polycystic kidney disease; PN, pyelonephritis; IHD, ischaemic heart disease; PVD, peripheral vascular disease; CeVD, cerebrovascular disease; RRT, renal replacement therapy; HD, haemodialysis; PD, peritoneal dialysis; IMD, Index of Multiple Deprivation; MACE major adverse cardiovascular event.

	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Age (years)	1.05 (1.05 – 1.06)	<0.001	1.08 (1.07 – 1.09)	<0.001
Male sex (Ref: Female)	1.20 (1.02 – 1.40)	0.03	1.22 (0.97 – 1.54)	0.10
Ethnicity (Ref: White)				
Asian	0.59 (0.47 – 0.75)	<0.001	0.75 (0.53 – 1.08)	0.13
Black	0.70 (0.53 – 0.93)	0.01	0.61 (0.40 – 0.94)	0.03
Mixed	0.66 (0.36 – 1.24)	0.20	0.60 (0.25 – 1.42)	0.25
PRD (Ref: PN)				
GN	1.12 (0.84 – 1.49)	0.45	0.75 (0.49 – 1.14)	0.18
Other	1.16 (0.87 – 1.56)	0.31	1.13 (0.74 – 1.74)	0.57
Uncertain	1.23 (0.89 – 1.71)	0.22	0.95 (0.59 – 1.53)	0.83
PKD	1.49 (1.09 – 2.02)	0.01	0.78 (0.50 – 1.20)	0.25
Diabetes	3.67 (2.49 – 5.43)	<0.001	1.69 (0.81 – 3.55)	0.16
Hypertension	1.41 (0.95 – 2.08)	0.09	1.13 (0.65 – 1.97)	0.66
Renovascular	4.66 (0.89 – 1.71)	0.22	1.03 (0.26 – 4.19)	0.96
Diabetes (Ref: Absent)	2.91 (2.26-3.76)	<0.001	3.11 (1.84 – 5.25)	<0.001
IHD (Ref: Absent)	3.80 (2.65 – 5.44)	<0.001	2.93 (1.76 – 4.86)	<0.001
PVD (Ref: Absent)	3.34 (1.83 – 6.08)	<0.001	1.70 (0.74 – 3.91)	0.21
CeVD (Ref: Absent)	1.70 (1.14 – 2.52)	0.007	0.62 (0.35 – 1.08)	0.09
Ever Smoker (Ref: Never)	1.36 (1.15 – 1.60)	<0.001	1.12 (0.88 – 1.43)	0.37
RRT Modality (Ref: HD)				
PD	0.83 (0.67 – 1.01)	0.06	0.84 (0.63 – 1.13)	0.26
Transplant	0.35 (0.12 – 0.98)	0.05	0.29 (0.08 – 1.11)	0.11
Pre-emptive	0.98 (0.80 – 1.19)	0.82	1.07 (0.80 – 1.43)	0.69
IMD (Ref: 1)				
2	1.43 (1.13 – 1.82)	0.003	1.17 (0.83 – 1.64)	0.38
3	1.43 (1.13 – 1.82)	0.003	0.92 (0.65 – 1.32)	0.67
4	1.72 (1.36 – 2.19)	<0.001	1.19 (0.84 – 1.70)	0.33
5	1.52 (1.19 – 1.94)	0.001	0.90 (0.62 – 1.31)	0.58
Centre (Ref: Bristol)				
1	0.41 (0.26-0.65)	<0.001	0.35 (0.20 – 0.6q)	<0.001
2	0.24 (0.15 – 0.39)	<0.001	0.16 (0.09 – 0.29)	<0.001
3	0.15 (0.07 – 0.30)	<0.001	0.07 (0.03 – 0.16)	<0.001
4	0.52 (0.32 – 0.84)	0.008	0.43 (0.25 – 0.83)	0.01
5	1.73 (1.12 – 2.66)	0.01	2.39 (1.37 – 4.14)	0.002
6	0.09 (0.04 – 0.19)	<0.001	0.06 (0.03 – 0.14)	<0.001
7	3.63 (2.10-6.25)	<0.001	4.52 (2.37 – 8.62)	<0.001
8	0.07 (0.04 – 0.15)	<0.001	0.03 (0.01 – 0.06)	<0.001
9	1.31 (0.81 – 2.24)	0.28	1.26 (0.67 – 2.35)	0.48
10	0.35 (0.23 – 0.55)	<0.001	0.27 (0.16 – 0.47)	<0.001
11	4.50 (2.52 – 8.03)	<0.001	5.70 (2.90 – 11.21)	<0.001
12	0.85 (0.50 – 1.44)	0.54	0.72 (0.37 – 1.40)	0.38
13	0.73 (0.47 – 1.13)	0.16	0.47 (0.27 – 0.82)	0.008
14	1.81 (0.92 – 3.55)	0.08	1.59 (0.70 – 3.63)	0.27
15	0.04 (0.02 – 0.10)	<0.001	0.01 (0.01-0.04)	<0.001
16	1.06 (0.62 – 1.81)	0.82	0.93 (0.48 – 1.79)	0.82

Table 2. Logistic regression of factors associated with CAD screening investigation. One transplant centre was removed as all patients underwent screening. Abbreviations: PRD, primary renal diagnosis; GN, glomerulonephritis; PKD, polycystic kidney disease; PN, pyelonephritis; IHD, ischaemic

heart disease; PVD, peripheral vascular disease; CeVD, cerebrovascular disease; RRT, renal replacement therapy; HD, haemodialysis; PD, peritoneal dialysis.

		90 day Unadjusted	90 day Adjusted	1 year Unadjusted	1 year Adjusted	5 year Unadjusted	5 year Adjusted
Screening investigation	HR	0.75	0.80	1.14	1.12	1.31	1.31
	(95% CI)	(0.33 – 1.72)	(0.31 – 2.05)	(0.56 – 2.31)	(0.51 – 2.47)	(0.85 – 2.03)	(0.86 – 1.99)
	P	0.50	0.64	0.72	0.77	0.22	0.20
Age (years)	HR	1.02	1.02	1.03	1.02	1.05	1.05
	(95% CI)	(0.99 – 1.06)	(0.98 – 1.06)	(1.01 – 1.06)	(1.00 – 1.05)	(1.04 – 1.06)	(1.04 – 1.06)
	P	0.20	0.29	**0.002**	**0.02**	**<0.001**	**<0.001**
Male sex	HR	1.24	1.35	1.14	1.13	1.51	1.60
	(95% CI)	(0.39 – 3.91)	(0.42 – 4.31)	(0.57 – 2.28)	(0.54 – 2.40)	(1.01 – 2.27)	(1.08 – 2.37)
	P	0.72	0.62	0.71	0.74	0.04	**0.02**
Asian ethnicity (Ref: White)	HR	1.85	1.61	2.53	2.20	1.75	1.61
	(95% CI)	(0.46 – 7.38)	(0.48 – 5.38)	(0.91 – 7.00)	(0.84 – 5.79)	(1.02 – 3.00)	(0.96 – 2.68)
	P	0.38	0.44	0.07	0.11	0.04	0.07
Black ethnicity (Ref: White)	HR	-	-	0.78	0.67	1.08	0.93
	(95% CI)	-	-	(0.19 – 3.27)	(0.18 – 2.53)	(0.52 – 2.22)	(0.46 – 1.88)
	P	-	-	0.73	0.56	0.84	0.84
Mixed ethnicity (Ref: White)	HR	-	-	-	-	1.79	1.85
	(95% CI)	-	-	-	-	(0.35 – 9.01)	(0.32 – 10.87)
	P	-	-	-	-	0.48	0.49
IMD 2 (Ref: 1)	HR	3.04	2.77	3.07	2.74	1.36	1.26
	(95% CI)	(0.27 – 33.71)	(0.24 – 31.59)	(1.42 – 6.64)	(1.29 – 5.89)	(0.73 – 2.48)	(0.69 – 2.30)
	P	0.37	0.41	**0.004**	**0.009**	0.33	0.46
IMD 3 (Ref: 1)	HR	2.06	1.66	1.30	1.18	1.27	1.17
	(95% CI)	(0.16 – 27.34)	(0.12 – 22.56)	(0.48 – 3.51)	(0.49 – 2.87)	(0.71 – 2.26)	(0.68 – 2.00)
	P	0.58	0.70	0.61	0.71	0.42	0.58
IMD 4 (Ref: 1)	HR	3.12	2.61	0.78	0.75	0.90	0.92
	(95% CI)	(0.26 – 37.26)	(0.22 – 31.41)	(0.26 – 2.36)	(0.27 – 2.06)	(0.37 – 2.16)	(0.43 – 1.96)
	P	0.37	0.45	0.66	0.58	0.81	0.82
IMD 5 (Ref: 1)	HR	6.09	4.62	2.46	2.17	1.24	1.12
	(95% CI)	(0.84 – 43.74)	(0.61 – 34.74)	(0.81 – 7.47)	(0.74 – 6.36)	(0.64 – 2.41)	(0.63 – 1.98)
	P	0.07	0.14	0.11	0.16	0.53	0.69
Ever smoker	HR	0.35	0.38	0.71	0.74	0.90	0.96
	(95% CI)	(0.08 – 1.62)	(0.08 – 1.74)	(0.29 – 1.73)	(0.30 – 1.85)	(0.58 – 1.39)	(0.65 – 1.41)
	P	0.18	0.21	0.45	0.52	0.63	0.82
History of cerebrovascular	HR	-	-	0.96	0.92	0.84	0.74

disease	(95% CI) *P*	- -	- -	(0.11 – 8.42) 0.97	(0.11 – 7.82) 0.94	(0.24 – 2.91) 0.79	(0.22 – 2.47) 0.62
History of peripheral vascular disease	HR (95% CI) *P*	- - -	- - -	- - -	- - -	0.80 (0.17 – 3.83) 0.78	0.63 (0.17 – 2.34) 0.49
History of diabetes	HR (95% CI) *P*	1.65 (0.33 – 8.19) 0.54	1.68 (0.39 – 7.31) 0.49	0.66 (0.15 – 2.91) 0.58	0.55 (0.14 – 2.10) 0.38	1.35 (0.70 – 2.64) 0.37	1.19 (0.54 – 2.60) 0.67
History of ischaemic heart disease	HR (95% CI) *P*	2.29 (0.34 – 15.58) 0.40	1.87 (0.4 – 10.38) 0.48	5.66 (2.39 – 13.39) **<0.001**	4.06 (1.73 – 9.55) **0.001**	2.88 (1.67 – 4.95) **<0.001**	2.15 (1.19 – 3.87) **0.01**

Table 3. Factors associated with MACE at following propensity score matching by pre-transplant CAD screening investigations. Measures of effect are expressed as hazard ratios (HR) and confidence interval (CI) and each time point. Significant P values are shown in bold. Hazard ratios marked by '-' reflect no events within the specified time period in this patient group.

Supplementary Material

Table S1. Patient and transplant characteristics in propensity score matched and unmatched individuals.

Table S2. Balance of characteristics of patients pre- and post-matching based on their propensity score for screening.

Table S3. Factors associated with MACE at 5 years in the propensity matched group with the inclusion of transplant centre.

Table S4. Factors associated with MACE following propensity score matching in the 'incident transplant' cohort only.

Table S5. Adjusted regression analysis using competing risk methodology examining risk of MACE and pre-MACE death in propensity score matched transplant recipients.

Table S6. Cox regression analysis examining effect of screening on MACE using inverse probability weighting methodology in the whole population.

Table S7. HES ICD-10 and OPCS-4 codes used to identify MACE.

Figure S1. Screening patterns in the 'waitlisted' group between ATTOM recruitment and transplantation.

Figure S2. Combinations of MACE components post-transplantation.

Disclosure Statement

The authors (other than James Fotheringham) received funding from the National Institute for Health Research (NIHR) under the Programme Grants for Applied Research scheme (RP-PG-0109-10116) for completion of the ATTOM study. James Fotheringham received personal fees from Fresenius Medical Care and grants from Vifor Pharma and Novartis outside the submitted work.

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Acknowledgements

This paper presents research from the Access to Transplantation and Transplant Outcome Measures (ATTOM) study which was funded by the National Institute for Health Research (NIHR) under the Programme Grants for Applied Research scheme (RP-PG-0109-10116). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Many thanks to the ATTOM research team, the research nurses and to the patients in the study.

Title:

Does screening for asymptomatic coronary artery disease predict cardiac events in kidney transplant recipients? A propensity score matched analysis.

Running title:

Cardiac screening prior to kidney transplantation

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Abstract

Screening for asymptomatic coronary artery disease prior to kidney transplantation aims to reduce peri- and postoperative cardiac events. It is uncertain if this is achieved. We investigated whether pre-transplant screening with a stress test or coronary angiogram associates with any difference in major adverse cardiac events (MACE) up to 5 years post-transplantation. We examined a national prospective cohort recruited to the Access to Transplant and Transplant Outcome Measures study who received a kidney transplant between 2011-2017, and linked patient demographics and details of cardiac screening investigations to outcome data extracted from the Hospital Episode Statistics dataset and UK Renal Registry. Propensity score matched groups were analysed using Kaplan-Meier and Cox survival analyses. Overall, 2572 individuals were transplanted in 18 centres; 51% underwent screening. The proportion undergoing screening by centre ranged from 5-100%. The incidence of MACE at 90 days, 1 and 5 years was 0.9%, 2.1% and 9.4% respectively. After propensity score matching based on the presence or absence of screening, 1760 individuals were examined (880 in screened and unscreened groups). There was no statistically significant association between screening and MACE at 90 days (hazard ratio [HR] 0.80, 95% CI 0.31-2.05), 1 year (HR 1.12, 95% CI 0.51–2.47) or 5 years (HR 1.31, 95% CI 0.86-1.99). Age, male sex and history of ischaemic heart disease were associated with MACE. There is no association between screening for asymptomatic coronary artery disease and MACE up to 5 years post-transplant. Practices involving unselected screening of transplant recipients should be reviewed.

Keywords

Coronary artery disease, screening, kidney transplantation, cardiovascular events

Introduction

Cardiovascular disease is common in people with chronic kidney disease (CKD): those on dialysis have a risk of cardiovascular death 20 times that of the general population. [1] Significant coronary artery disease (CAD) is often asymptomatic in these individuals. [2] Although kidney transplantation offers dramatically improved long-term cardiovascular outcomes and survival compared to dialysis, [3,4] cardiovascular disease remains common, accounting for 20% of deaths with a functioning graft. [5] Further, the benefits of kidney transplantation come at the expense of increased perioperative cardiovascular risk [3] relating to surgical and anaesthetic stress. [6]

Clinicians aim to reduce peri- and postoperative risk by selecting individuals who are likely to achieve improved quality and quantity of life with an acceptably low risk of adverse cardiac events and premature death. To aid recipient selection, current practice is to consider screening for occult CAD pre-transplantation. [7] If screening investigations are abnormal, revascularisation may be performed to attempt to reduce cardiovascular risk, or patients may be deemed too high-risk to proceed.

It is unclear if abnormal stress-tests in asymptomatic transplant candidates predict cardiovascular outcomes, [2,8] and although patients with occult CAD have a higher rate of post-transplant cardiac events [9] there is no clear evidence that revascularisation in asymptomatic individuals reduces myocardial infarction and death. [2,10,11,12] Additionally, the cardiac outcomes of individuals excluded from transplantation based on abnormal screening tests are unknown, as is whether any individuals are unnecessarily deprived of this superior treatment option.

This lack of high-quality evidence leads to inconsistency between international guidelines' recommendations on screening [13] and variation between centres in patient selection for cardiovascular assessment, investigations used, and subsequent actions taken. [14,15] Patients may be selected based on perceived or calculated risk, or screened universally. [16,17] Screening investigations are not standardised and include stress tests (exercise tolerance test (ETT), myocardial perfusion

scan (MPS) or dobutamine stress echocardiogram (DSE)), coronary computed tomography (CT) and invasive coronary angiograms, [9,12] used according to local availability.

Interpretation of the observational data in this field is challenging: good cardiovascular outcomes in transplant recipients may suggest screening is unnecessary, [18] or reflect a successful screening programme. Full evaluation is limited by the lack of data on those deemed unfit for transplantation through screening. Furthermore, the screening process may be harmful or wasteful through unnecessary exposure to ionising radiation, exacerbating inequities in access to transplant by unjustified exclusion or delay to listing, [11,19] and consumption of non-evidence-based resources.

We used data from the Access to Transplant and Transplant Outcome Measures (ATTOM) study of prospective kidney transplant recipients in England [20] linked to national hospitalisation data to examine the impact of pre-transplant screening on 5 year cardiovascular outcomes.

Results

Patient population (Figure 1)

ATTOM recruited both 'incident transplant' patients within 90 days of kidney transplantation and 'waitlisted' patients active on the deceased-donor waiting list. Patients in the 'waitlisted' group subsequently transplanted before 31st December 2017 were examined alongside 'incident transplant' patients.

In total, 2853 patients received a transplant in England and 2723 were matched to their Hospital Episode Statistics (HES) record. Of those unmatched, 49 had non-English postcodes and are likely to have received treatment in other parts of the UK. The 151 patients receiving multi-organ transplants were excluded. Overall, 2572 patients were examined: 1661 (64.6%) 'incident transplant' and 911 (35.4%) 'waitlisted'. Median time from recruitment to transplant in the 'waitlisted' group was 17 months [IQR 9-29]. Median age at transplant was 51 years (range 20-76 years).

Ethnicity data were available in 92.3% of cases from ATTOM, increasing to 99.7% with HES data. Baseline comorbidity information was available in 99.5% of cases from ATTOM, increasing to 100% with HES data.

In the 'waitlisted' group, 2.8% of individuals underwent first screening investigations after recruitment to ATTOM (Supplementary Figure 1).

Incidence of MACE

Median follow-up was 61 months [IQR 46-67], over which time 202 patients experienced MACE (145 from the 'incident transplant' group and 57 from the 'waitlisted' group). The incidence of MACE was 0.9% at 90 days (n=23), 1.3% at 6 months (n=32), 2.1% at 1 year (n=52), 3.6% at 2 years (n=82) and 9.4% (n=199) at 5 years post-transplant.

Of those experiencing MACE, 55% underwent coronary intervention (angioplasty or CABG) alone and 32% had two or more categories of MACE (Supplementary Figure 2). Only 4% of MACE were based on a clinical diagnosis of MI or unstable angina alone.

Over follow up, 254 patients died. Cause of death was available in 94% of cases; 32 (13%) deaths were cardiac in nature and counted as MACE. Of the 108 in-hospital deaths, 11 were cardiac and 4 individuals experienced another MACE during the terminal admission.

Patterns of cardiovascular workup (Figure 2)

Combinations of screening investigations varied (Figure 2). No investigations were performed in 17% and an echocardiogram alone was performed in 32% (not counted as CAD screening). An echocardiogram and stress test (ETT, MPS or DSE) was performed in 29%. Overall, 51% of patients underwent CAD screening in some form.

Factors associated with CAD screening (Tables 1 and 2)

Individuals undergoing screening were older (median age 56 years [IQR 47-63] vs. 46 years [IQR 36-55]), more likely to be male, have a history of diabetes, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease and smoking (Table 1). By univariable analysis, significant variation was observed with ethnicity, socioeconomic status and primary renal disease (PRD); white ethnicity, higher socioeconomic status and renovascular disease were associated with the highest likelihood of screening. In addition to differences in screening investigations used, there was significant variation in the proportion of patients tested between transplant centres. The median percentage of patients undergoing screening by centre was 58% [IQR 26-68, range 5-100%].

Following multivariable analysis (Table 2), factors independently associated with likelihood of screening comprised age (OR 1.08, 95% CI 1.07-1.09), ethnicity (white ethnicity vs. black ethnicity OR 1.62, 95% CI 1.05-2.51), history of ischaemic heart disease (OR 2.93, 95% CI 1.76-4.86) and diabetes (OR 3.11, 95% CI 1.84-5.25). Significant variation between centres persisted following adjustment

for all other factors. There was no association between screening and prior renal replacement therapy (RRT) modality, socioeconomic status or PRD.

Propensity score matching and non-matched individuals

Prior to propensity-score matching, patients undergoing screening had a higher incidence of MACE at 1 and 5 years (52 patients had an event at 1 year with 65% in the screened group; 199 patients had an event at 5 years with 67% in the screened group). No difference was observed at 90 days post-transplant (Table 1).

The covariables used to generate the propensity score comprised age, sex, ethnicity, socioeconomic status, smoking history, history of diabetes, ischaemic heart disease, peripheral vascular disease, and cerebrovascular disease. Matching based on propensity for screening allowed assessment of 1760 patients (880 in each screened and unscreened groups).

Characteristics of the 812 patients who were not propensity matched are shown in Supplementary Table 1. Of these, 440 underwent screening. Non-propensity matched individuals were more likely to be male, of Asian ethnicity, of lower socioeconomic status, and have a history of diabetes, ischaemic heart disease, peripheral vascular disease and cerebrovascular disease. Variation was observed between centres, reflecting differing screening practices. There were no statistically significant differences in age, smoking history or prior RRT modality.

Associations between CAD screening and MACE with propensity score matching (Table 3 and Figure 3)

In the propensity score matched cohort, baseline covariables were balanced between groups with a standardised mean difference (SMD) of 0.2 or less for all variables (Supplementary Table 2). There was variation in SMD, though all variables were more evenly balanced following the propensity score matching process. Ethnicity, PRD, Index of Multiple Deprivation (a marker of socioeconomic status), smoking and history of ischaemic heart disease each had an SMD of greater than 0.1, though

ischaemic heart disease and smoking were more prevalent in the unscreened group within the propensity matched cohort.

In the propensity matched cohort, 14 individuals experienced MACE by 90 days (incidence 0.9%), 32 by 1 year (incidence 1.9%) and 117 by 5 years (incidence 8.0%) (Figure 3). The pattern of screening was similar to the whole study population: 696 (39.5%) had a stress test without angiogram and 184 (10.5%) had a coronary angiogram with or without a stress test.

In the Cox models, proportionality assumptions were met. There was no statistically significant association between screening and MACE in univariable or multivariable analyses at 90 days (multivariable HR 0.80, 95% CI 0.31-2.05; p=0.64), 1 year (HR 1.12, 95% CI 0.51-2.47; p=0.77) or 5 years post-transplant (HR 1.31, 95% CI 0.86-1.99; p=0.20) (Table 3).

In the multivariable Cox model, factors independently associated with MACE at 1 year were age (HR 1.02, 95% CI 1.00-1.05; p=0.02) and history of ischaemic heart disease (HR 4.06, 95% CI 1.73-9.55; p<0.001). An association between MACE and one socioeconomic quintile (Index of Multiple Deprivation quintile 2) was observed but there was no association with other socioeconomic quintiles and this observation was not noted at the other timepoints. At 5 years, age (HR 1.05, 95% CI 1.04-1.06; p<0.001), male sex (HR 1.60, 95% CI 1.08-2.37; p=0.02) and history of ischaemic heart disease (HR 2.15, 95% CI 1.19-3.87; p=0.01) were positively associated with MACE. The incidence of MACE at 5 years did not correlate with transplant centre (Supplementary Table 3).

Sensitivity analyses

Four sensitivity analyses were performed. In the first analysis examining the 'incident transplant' cohort only, and the second analysis using a competing risk model for non-cardiovascular death, there remained no association between screening and MACE (Supplementary Tables 4 and 5).

The third sensitivity analysis investigated the likelihood that an unmeasured confounder eliminated a 'true' protective effect of screening. If at 1 year, screening were protective against MACE with a

hazard ratio of 0.95 and upper limit of the 95% confidence interval of 1.0, to explain the observed hazard ratio of 1.12 the 'inverse' E value for the point estimate is 1.64 and for the confidence interval 1.49. Agreed interpretation of this statistic is that for an unmeasured confounder (associated with both screening and MACE) to bias a true hazard ratio of 0.95 or below to the observed hazard ratio of 1.12, the confounder would have to be associated with screening and MACE with a risk ratio of 1.64 or above. To put this in perspective, the confounder would need to be associated with screening and MACE at a magnitude equal to or greater than the association between MACE at 1 year and a 10-year increment in age (adjusted HR 1.57, 95% CI 1.17-2.10). Significant unmeasured confounding therefore seems unlikely. A value of 0.95 was chosen as for any stronger association between screening and MACE, the 'inverse' E-value would need to be even greater.

The final sensitivity analysis examined the effect of screening on MACE in the whole population using an adjusted Cox regression model with inverse probability of treatment weighting. The weighted hazard ratios were similar to those for the propensity matched cohort (Supplementary Table 6). There remained no statistically significant association between screening and MACE at 90 days (weighted HR 0.70, 95% CI 0.29-1.68; p=0.43) or 1 year (weighted HR 0.99, 95% CI 0.51-1.91; p=0.98). Five year results did not meet the proportionality assumption of the Cox model due to the rate of MACE climbing at a greater rate in the screened group, and have not been presented.

Post-transplant events

In the propensity matched cohort, there was no difference in creatinine at 1 year (screened median 125µmol/L [IQR 101-158] vs. unscreened median 125µmol/L [IQR 100-163]; p=0.73) or 5 years (median 128µmol/L [IQR 103-167] vs. unscreened median 126µmol/L [IQR 98-158]; p=0.21) post-transplant. There was no statistically significant difference in HES-documented rejection episodes prior to MACE (screened 18.0% vs. unscreened 16.7%; p=0.49) nor in incidence of post-transplant

diabetes (screened 15% vs. unscreened 11%; p=0.07). In the screened group, 30% of transplants were from a living donor compared with 29% in the unscreened group (p=0.67).

Discussion

In this national prospective study of kidney transplant recipients in England we found no association between screening for asymptomatic coronary artery disease and the development of major adverse cardiac events up to 5 years post-transplantation. By examining a national cohort and adjusting for factors associated with screening through propensity score matching, our results are less subject to regional and selection bias than previous observational studies which report variable associations between cardiac screening and MACE. [9,21,22,23,24,25] The uncertainty over the utility of screening is highlighted by the variation in uptake between centres, ranging from 5-100% of recipients.

The low incidence of post-transplant MACE is reassuring and similar to that reported previously. [26,27] This suggests individuals currently selected for transplant (with or without screening) have what most clinicians would deem an acceptable cardiac risk, but others who may benefit could have been unnecessarily excluded. Other methods to stratify risk should be considered when evaluating suitability for transplant. We found age, male sex and ischaemic heart disease to be positively associated with MACE, as previously reported, [26,27] adding weight to their use in risk-stratified algorithms. [2,28]

It seems intuitive that pre-transplant screening should improve outcomes given that significant CAD is often asymptomatic in transplant candidates, [2] but our results suggest otherwise. There are several possible explanations. First, performing and interpreting non-invasive investigations in renal patients is challenging. Less than 40% of transplant candidates reach maximal work capacity or experience symptoms during ETTs. [29,30] The sensitivity and specificity of DSE and MPS for detecting angiographically-confirmed CAD are moderate at best, with a sensitivity of 76% and 67% and specificity of 88% and 77% respectively. [31] Increased vascular calcification in CKD also limits the utility of coronary CT in identifying obstructing lesions. [32] As such, non-invasive tests may not adequately risk-stratify patients. [24]

Second, even if non-invasive tests accurately identified individuals with significant coronary lesions, it remains uncertain if revascularisation improves outcomes. [10,11,18] The ISCHEMIA-CKD randomised control trial examined individuals with an eGFR<30ml/min/1.73m^2 or on dialysis with stable symptoms and moderate to severe ischaemia on stress testing: a similar population to transplant candidates. Importantly, patients were excluded if they had unprotected left main stem disease or an ejection fraction below 35%, but in individuals without these features no reduction in death or myocardial infarction was observed with angioplasty over best medical therapy. [33] This is reflected in the 2020 KDIGO guidelines which recommend asymptomatic patients not undergo revascularisation solely to reduce perioperative risk. [34]

Third, the absence of a clear benefit from revascularisation suggests a different aetiology for cardiovascular disease in people with CKD. The high prevalence of left ventricular hypertrophy, systolic and diastolic dysfunction, myocardial fibrosis and arteriosclerosis [35] may explain why half of cardiovascular deaths in transplant recipients relate to dysrhythmias as opposed to atherosclerotic events. [36,37,38] Currently-adopted screening tools for atheromatous disease may be less suited to the CKD population. Other dynamic investigations e.g. functional cardiopulmonary exercise testing may provide superior cardiovascular risk information in this cohort. [39]

Finally, MACE post-transplantation may be influenced by transplant-specific cardiovascular risk factors such as renal function and acute rejection episodes. [40] However, our data suggest these did not play a clear role in predicting MACE over our follow-up period: there was no significant difference in creatinine between groups or frequency of HES-recorded rejection episodes which may have led to intensified immunosuppression, though there was a non-significant trend towards increased post-transplant diabetes in the screened group.

Our study has several strengths. Using a prospective cohort of patients from all units in England [20] we were able to evaluate a large propensity matched population through dataset linkage. Propensity matching was possible because of variation in practice between centres with no inter-

centre difference in incidence of MACE; by examining individuals with a similar likelihood for screening we estimate them to have comparable degrees of underlying CAD. Our baseline data, which included details of screening investigations, were collected by dedicated research nurses with specific training to seek and record such information thus improving data accuracy. Only 2.8% of 'waitlisted' individuals underwent first screening whilst on the waitlist, and similar results were observed when examining the 'incident transplant' group alone increasing confidence in our results. The coding criteria used to detect MACE in HES data also appear robust: 87% of individuals with MACE had a coronary angioplasty, CABG, or 2 or more classes of event, reducing reliance on clinical diagnosis alone [41] and dysrhythmia-related deaths should be captured. Our population is broadly representative of other high-income countries with respect to renal [42,43] and cardiovascular outcomes [44,45] making our results generalisable.

We recognise our study's limitations. Data were observational so only associations can be described and there is potential for unmeasured confounding. Individuals with the highest propensity for screening (and hence greatest cardiovascular risk factors) were less likely to be matched in our models. The highest-risk individuals are thus under-represented in our analyses and caution should be exercised extrapolating findings to this group. The inverse probability weighted analysis goes some way to mitigate this, but the greater rise in rate of MACE in screened individuals does question whether certain subgroups may derive an early benefit from screening. We do not know how many patients underwent screening and were not waitlisted. In the UK, single centre reports suggest the proportion of patients not listed after screening ranges from 13-26% [11,18] but screening results are just one factor in a complex clinical assessment and the relative impact of these in 'justifying' transplant preclusion is unclear. The proportion excluded predominantly due to screening abnormalities is probably much lower, reported as 4% by Kumar et al. [18] We do not have direct evidence that screening tests met agreed diagnostic thresholds, but have no reason to suspect that investigations would not meet established quality standards. [46,47,48] We do not have investigation results and assume that individuals listed for transplantation following screening were deemed to

have acceptable test results that ruled out significant cardiovascular risk. The rate of MACE in the early post-operative period was low, which may reduce the power to detect differences particularly at the 90 day time point, but we are reassured that no difference was seen over 5 years with a greater number of events observed. We did not have information on medical management of CAD, and whether this differed between groups. We also do not have data on all post-transplantation cardiovascular risk factors such as maintenance immunosuppression regimen and other biochemical parameters, but these may impact more on long-term cardiovascular risk so are less likely to be clinically relevant. Finally, it is not known how the availability of pre-transplant screening investigations varies between centres and whether this influences the individuals they list for transplantation.

There are likely to be health economic and practical benefits from reducing potentially unnecessary screening. Half of the individuals in our study underwent screening. Around 3600 patients are transplanted annually in the UK [49] with more being investigated and not listed. A stress echocardiogram costs £280 and an angiogram £2500, [50] providing a cost perspective. The Canadian-Australasian Randomised trial of screening kidney transplant candidates for CAD (CARSK) study is investigating if repeated screening on the waitlist reduces MACE. [51] Results are not expected until 2025, but a cost utility analysis suggests eliminating screening may increase cost due to more individuals being transplanted with improved survival [52] than because of increased MACE.

The feasibility of a prospective randomised control trial evaluating the impact of pre-listing screening on MACE should be considered. Such a study may also be able to evaluate whether individuals with higher risk of MACE have more to gain from screening. This comes with challenges: changes to practice must consider the acceptability of risk to the whole transplant community. There will likely be apprehension around anaesthetising higher-risk individuals with apparently less thorough workup, especially if some may have otherwise been excluded. With low event rates of post-transplant MACE, achieving sufficient power even with a national study may be challenging.

Standardising the timing of screening prior to transplantation is also difficult given the unpredictable time spent on the waitlist prior to deceased donor transplantation. Potential benefits however are clear: minimising screening reduces exposure to ionising radiation, post-intervention coronary events [18] and minimises delays to listing with potential to reduce time on dialysis.

In conclusion, this national observational propensity cohort study of patients listed for kidney transplantation found that screening for CAD does not reduce cardiac events post-transplantation. Unselected screening of asymptomatic patients prior to kidney transplantation is not justified. A large-scale randomised control trial of asymptomatic higher-risk individuals through increased age, history of diabetes or ischaemic heart disease, may clarify if there is benefit in selected patients.

Methods

Data sets and patient population

Data from the Access to Transplantation and Transplant Outcome Measures (ATTOM) study were linked to routinely collected Hospital Episode Statistics (HES) data, which captures activity in English hospitals. ATTOM was a UK-wide prospective cohort study that recruited patients aged 18-75 years between 1st November 2011 and 31st March 2013. Both 'incident transplant' patients within 90 days of kidney transplantation and prevalent 'waitlisted' patients active on the deceased-donor waiting list were recruited. [20] Patients in the 'waitlisted' group who were subsequently transplanted before 31st December 2017 were examined alongside the 'incident transplant' group.

Patients receiving both first and subsequent allografts were included as screening practices are generally independent of graft number. Only recipients of single organ kidney transplants were examined as different workup processes exist for dual organ transplants. As only English hospital data are included in HES, ATTOM participants from Scotland, Wales and Northern Ireland were excluded.

Baseline patient characteristics and data on inpatient or outpatient cardiovascular screening investigations performed for transplant assessment were collected by research nurses at ATTOM recruitment using a systematic note review and patient interviews. Information on the validity of screening investigations, screening investigation results and revascularisation procedures were not recorded. Missing ethnicity and comorbidity data from ATTOM were supplemented from HES data if required. Date of graft loss, date and cause of death and 1 and 5 year creatinine were obtained from NHS Blood and Transplant and the UK Renal Registry.

As individuals in the 'waitlisted' group were not immediately transplanted, HES data were interrogated to identify screening investigations occurring between recruitment and transplantation. An investigation was assumed to be for screening if performed as an outpatient or day-case with no cardiac event within the preceding 30 days.

Data from HES were available from 1st January 2006 to 31st December 2017, including NHS admitted patient care, outpatient, and emergency department attendances. Diagnoses and procedures from admitted patient care and outpatient episodes are coded using International Classification of diseases 10th revision (ICD-10) and OPCS Classification of Interventions and Procedures version 4 (OPCS-4) criteria. Data were obtained from NHS Digital, stored at NHS Blood and Transplant and linked to the ATTOM database by unique patient identifiers.

Major adverse cardiac events

Major adverse cardiovascular events (MACE) were identified from HES coding, defined as unstable angina, myocardial infarction (MI), coronary artery bypass graft (CABG), coronary angioplasty or cardiac death. [53] HES data were interrogated for corresponding ICD-10 and OPCS-4 codes using Myocardial Ischaemia National Audit Project criteria (Supplementary Table 7). [54]

Cardiac deaths comprised those caused by myocardial ischaemia and infarction, sudden death, cardiac failure, pulmonary oedema or cardiac arrest as per the ERA-EDTA coding system. [55] These are coded by clinicians at the patient's renal unit and returned to NHS Blood and Transplant and the UK Renal Registry.

Events from transplantation until the end of available HES data were identified, censored for non-cardiac death. The incidence of MACE was calculated from Kaplan-Meier analyses.

Statistical Methods

Baseline patient- and transplant-specific risk factors for cardiovascular disease were reported using descriptive statistics. Non-parametric continuous variables are expressed as median (interquartile range [IQR]) and categorical variables as frequency and percentage. Comparisons were made using the Chi-square test for categorical variables and Mann-Whitney U test for non-parametric continuous variables.

Outcome Measures

The primary outcome was time to MACE, calculated from day of transplant until first event, non-cardiac death or end of follow-up. Events following graft failure were included.

Factors associated with CAD screening

Patients were divided into those who underwent a stress test (ETT, DSE or MPS) or angiogram (CAD screening group) or had no investigation or echocardiogram alone (no screening group). Echocardiography identifies heart failure and valvular heart disease and is not a dynamic test for CAD. Whilst low ejection fraction may be a contraindication to transplantation, revascularisation can improve left ventricular function [56] and individuals are likely to proceed to further investigation. Echocardiography alone was therefore not considered a CAD screening investigation.

Logistic regression analyses were performed to identify factors associated with screening. Covariables, defined *a priori*, comprised age, sex, ethnicity, PRD, cardiovascular comorbidities, smoking history, prior RRT modality and Index of Multiple Deprivation: an area-level marker of socioeconomic status ranging from 1 (most deprived) to 5 (least deprived).

Propensity score matching and non-matched individuals

Propensity score analysis was used to balance differences in baseline cardiovascular risk between groups which may bias the association between screening and MACE. [57,58] Variables used to create the propensity matched groups were those which we clinically judged to relate to screening or MACE (other than transplant centre) and comprised age, sex, ethnicity, socioeconomic status, smoking status and history of ischaemic heart disease, diabetes, cerebrovascular disease and peripheral vascular disease. [59] Analyses included complete cases only, present in 2477 (96.3%) of cases.

Individuals were matched using a nearest-neighbour algorithm (1:1 case control) without replacement, with a radius of 0.2 standard deviations of the log odds of the estimated propensity score. SMD between groups were used to ensure covariables were balanced [58] accepting a SMD of

0.2 or below to indicate appropriate matching. [60] The characteristics of matched and unmatched individuals following the generation of the propensity score were compared using univariable analyses.

Associations between CAD screening and MACE with propensity score matching

The Kaplan-Meier method and univariable analyses followed by a doubly robust estimation using multivariable Cox regression models were used to assess factors associated with MACE at 90 days, 1 year and 5 years post-transplant. Time to event models were chosen to account for censoring events. Variables in the doubly robust multivariable model were determined *a priori* to be those used to create the propensity groups. [61] The proportionality assumption of the Cox models was tested using Schoenfeld residuals. Analyses used robust standard errors to account for clustering by centre.

As the propensity groups were not matched by transplant centre, a logistic regression model including centre was used to identify if MACE at 5 years was independently associated with unit.

Sensitivity analyses

Four sensitivity analyses were performed. These comprised (1) a propensity score matched analysis examining only the 'incident transplant' group given the potential for first screening to occur following ATTOM recruitment in the 'waitlisted' cohort, (2) a competing risks analysis using the Fine and Gray method to examine the impact of screening on MACE considering the competing risk of non-cardiovascular death [62] and (3) an assessment of how robust the 1 year results were with respect to unmeasured confounding by calculating the E-value. [63] The E-value estimates what the relative risk must be for an unmeasured confounder to overcome an observed but false association between screening and MACE, or in the event of no significant observed association for it to have eliminated a true protective effect of screening (i.e. the 'inverse' of the E-value).

The final sensitivity analysis (4) was an adjusted Cox regression model in the whole transplanted population using inverse probability of treatment weighting. Inverse probability of treatment weights were calculated from the reciprocal of the propensity score and stabilised by multiplying the weight by the proportion of the population in the treated (screened) group. The mean of the stabilised weights was 1.15 (SD 0.48). This technique creates a pseudo-population informed by all patients, where the distribution of observed covariables in screened and unscreened populations become balanced.[64] This method means previously unmatched individuals contribute to the analysis reducing any bias introduced by propensity score matching. The final Cox model was adjusted for the variables included in the generation of the propensity score.

Post-transplant events

To assess differences in transplant-specific cardiovascular risk factors in the propensity groups, creatinine 1 and 5 years post-transplant, HES-documented graft rejection, HES-documented post-transplant diabetes, and donor type (live or deceased) were compared.

Statistical tests were two-tailed with statistical significance defined *a priori* as $p<0.05$. Results of regression analyses were presented as effect ratios with 95% confidence intervals. Analyses were performed using Stata version 15 (Statacorp, College Station, TX).

Figures

Figure 1. Flow chart depicting patients included in the study.

Figure 2. Pattern of cardiovascular workup. Note an unknown number of patients will be tested and excluded from transplant based on test results. Stress test comprises exercise tolerance test, dobutamine stress echocardiogram and myocardial perfusion scan. Abbreviations: echo: echocardiogram; CT: computed tomography.

Figure 3. Kaplan-Meier estimator curve demonstrating MACE events after transplant in patients undergoing screening for coronary artery disease versus those who did not in the propensity matched cohort.

Tables

	No CAD Screening Test N=1252	CAD Screening Test N=1320	P
Age (years) (n=2572)	46 [36 – 55]	56 [47 – 63]	<0.001
Male Sex (n=2572)	734 (59)	830 (63)	0.03
Ethnicity (n=2563)			
White	892 (71)	1050 (80)	
Asian	210 (17)	147 (11)	<0.001
Black	122 (10)	101 (8)	
Mixed	23 (2)	18 (1)	
PRD (n=2555)			
GN	325 (26)	286 (22)	
Other	283 (23)	259 (20)	
PKD	196 (16)	229 (17)	
Uncertain	156 (12)	151 (12)	<0.001
PN	150 (12)	118 (9)	
Diabetes	55 (4)	159 (12)	
Hypertension	76 (6)	84 (6)	
Renovascular	6 (1)	22 (2)	
History of Diabetes (n=2572)	90 (7)	243 (18)	<0.001
History of IHD (n=2572)	40 (3)	147 (11)	<0.001
History of PVD (n=2572)	14 (1)	48 (4)	<0.001
History of CeVD (n=2572)	40 (3)	70 (5)	0.008
Ever smoker (n=2507)	358 (29)	466 (36)	<0.001
RRT modality (n=2556)			
HD	707 (57)	785 (60)	
PD	263 (21)	241 (18)	0.06
Transplant	13 (1)	5 (1)	
Pre-emptive	260 (21)	282 (21)	
IMD (n= 2572)			
1 – Most deprived	344 (27)	263 (20)	
2	247 (20)	271 (21)	
3	234 (19)	256 (19)	<0.001
4	218 (17)	287 (22)	
5 – Least deprived	209 (17)	243 (18)	
Centre (anonymised) (n=2572)			
1	118 (9)	64 (5)	
2	61 (5)	80 (6)	
3	0 (0)	264 (20)	
4	123 (10)	39 (3)	
5	62 (5)	12 (1)	
6	75 (6)	51 (4)	
7	72 (6)	163 (12)	
8	92 (7)	11 (1)	<0.001
9	25 (2)	119 (9)	
10	104 (8)	10 (1)	
11	47 (4)	81 (6)	
12	145 (12)	67 (5)	
13	20 (2)	118 (9)	
14	44 (4)	49 (4)	

15 16 17 18	99 (8) 16 (1) 111 (9) 38 (3)	95 (7) 38 (3) 6 (1) 53 (4)	
First transplant (n=1842)	795 (88)	826 (88)	0.86
Years RRT pre-transplant (n=1592)	1.7 [0.0 – 4.0]	1.9 [0.17 – 4.28]	0.10
Live donor (n=2572)	403 (32)	368 (28)	0.02
Creatinine at 1 year (n=2354)	125 [100 – 161]	124 [101 – 157]	0.42
Creatinine at 5 years (n=1235)	125 [100 – 160]	126 [103 – 163]	0.30
Post-transplant diabetes (n=2572)	154 (12.3)	172 (13.0)	0.58
Graft failure over follow-up	135 (10.8)	148 (11.2)	0.73
MACE at 90 days	10 (0.8)	13 (1)	0.62
MACE at 1 year	18 (1.5)	34 (2.6)	0.04
MACE at 5 years	66 (5.3)	133 (10.1)	<0.001

Table 1. Cardiovascular workup by patient demographic factors and transplant centre. Data are expressed as number (%) or median [interquartile range]. Abbreviations: PRD, primary renal diagnosis; GN, glomerulonephritis; PKD, polycystic kidney disease; PN, pyelonephritis; IHD, ischaemic heart disease; PVD, peripheral vascular disease; CeVD, cerebrovascular disease; RRT, renal replacement therapy; HD, haemodialysis; PD, peritoneal dialysis; IMD, Index of Multiple Deprivation; MACE major adverse cardiovascular event.

	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Age (years)	1.05 (1.05 – 1.06)	<0.001	1.08 (1.07 – 1.09)	<0.001
Male sex (Ref: Female)	1.20 (1.02 – 1.40)	0.03	1.22 (0.97 – 1.54)	0.10
Ethnicity (Ref: White)				
Asian	0.59 (0.47 – 0.75)	<0.001	0.75 (0.53 – 1.08)	0.13
Black	0.70 (0.53 – 0.93)	0.01	0.61 (0.40 – 0.94)	0.03
Mixed	0.66 (0.36 – 1.24)	0.20	0.60 (0.25 – 1.42)	0.25
PRD (Ref: PN)				
GN	1.12 (0.84 – 1.49)	0.45	0.75 (0.49 – 1.14)	0.18
Other	1.16 (0.87 – 1.56)	0.31	1.13 (0.74 – 1.74)	0.57
Uncertain	1.23 (0.89 – 1.71)	0.22	0.95 (0.59 – 1.53)	0.83
PKD	1.49 (1.09 – 2.02)	0.01	0.78 (0.50 – 1.20)	0.25
Diabetes	3.67 (2.49 – 5.43)	<0.001	1.69 (0.81 – 3.55)	0.16
Hypertension	1.41 (0.95 – 2.08)	0.09	1.13 (0.65 – 1.97)	0.66
Renovascular	4.66 (0.89 – 1.71)	0.22	1.03 (0.26 – 4.19)	0.96
Diabetes (Ref: Absent)	2.91 (2.26-3.76)	<0.001	3.11 (1.84 – 5.25)	<0.001
IHD (Ref: Absent)	3.80 (2.65 – 5.44)	<0.001	2.93 (1.76 – 4.86)	<0.001
PVD (Ref: Absent)	3.34 (1.83 – 6.08)	<0.001	1.70 (0.74 – 3.91)	0.21
CeVD (Ref: Absent)	1.70 (1.14 – 2.52)	0.007	0.62 (0.35 – 1.08)	0.09
Ever Smoker (Ref: Never)	1.36 (1.15 – 1.60)	<0.001	1.12 (0.88 – 1.43)	0.37
RRT Modality (Ref: HD)				
PD	0.83 (0.67 – 1.01)	0.06	0.84 (0.63 – 1.13)	0.26
Transplant	0.35 (0.12 – 0.98)	0.05	0.29 (0.08 – 1.11)	0.11
Pre-emptive	0.98 (0.80 – 1.19)	0.82	1.07 (0.80 – 1.43)	0.69
IMD (Ref: 1)				
2	1.43 (1.13 – 1.82)	0.003	1.17 (0.83 – 1.64)	0.38
3	1.43 (1.13 – 1.82)	0.003	0.92 (0.65 – 1.32)	0.67
4	1.72 (1.36 – 2.19)	<0.001	1.19 (0.84 – 1.70)	0.33
5	1.52 (1.19 – 1.94)	0.001	0.90 (0.62 – 1.31)	0.58
Centre (Ref: Bristol)				
1	0.41 (0.26-0.65)	<0.001	0.35 (0.20 – 0.6q)	<0.001
2	0.24 (0.15 – 0.39)	<0.001	0.16 (0.09 – 0.29)	<0.001
3	0.15 (0.07 – 0.30)	<0.001	0.07 (0.03 – 0.16)	<0.001
4	0.52 (0.32 – 0.84)	0.008	0.43 (0.25 – 0.83)	0.01
5	1.73 (1.12 – 2.66)	0.01	2.39 (1.37 – 4.14)	0.002
6	0.09 (0.04 – 0.19)	<0.001	0.06 (0.03 – 0.14)	<0.001
7	3.63 (2.10-6.25)	<0.001	4.52 (2.37 – 8.62)	<0.001
8	0.07 (0.04 – 0.15)	<0.001	0.03 (0.01 – 0.06)	<0.001
9	1.31 (0.81 – 2.24)	0.28	1.26 (0.67 – 2.35)	0.48
10	0.35 (0.23 – 0.55)	<0.001	0.27 (0.16 – 0.47)	<0.001
11	4.50 (2.52 – 8.03)	<0.001	5.70 (2.90 – 11.21)	<0.001
12	0.85 (0.50 – 1.44)	0.54	0.72 (0.37 – 1.40)	0.38
13	0.73 (0.47 – 1.13)	0.16	0.47 (0.27 – 0.82)	0.008
14	1.81 (0.92 – 3.55)	0.08	1.59 (0.70 – 3.63)	0.27
15	0.04 (0.02 – 0.10)	<0.001	0.01 (0.01-0.04)	<0.001
16	1.06 (0.62 – 1.81)	0.82	0.93 (0.48 – 1.79)	0.82

Table 2. Logistic regression of factors associated with CAD screening investigation. One transplant centre was removed as all patients underwent screening. Abbreviations: PRD, primary renal diagnosis; GN, glomerulonephritis; PKD, polycystic kidney disease; PN, pyelonephritis; IHD, ischaemic

heart disease; PVD, peripheral vascular disease; CeVD, cerebrovascular disease; RRT, renal replacement therapy; HD, haemodialysis; PD, peritoneal dialysis.

		90 day Unadjusted	90 day Adjusted	1 year Unadjusted	1 year Adjusted	5 year Unadjusted	5 year Adjusted
Screening investigation	HR	0.75	0.80	1.14	1.12	1.31	1.31
	(95% CI)	(0.33 – 1.72)	(0.31 – 2.05)	(0.56 – 2.31)	(0.51 – 2.47)	(0.85 – 2.03)	(0.86 – 1.99)
	P	0.50	0.64	0.72	0.77	0.22	0.20
Age (years)	HR	1.02	1.02	1.03	1.02	1.05	1.05
	(95% CI)	(0.99 – 1.06)	(0.98 – 1.06)	(1.01 – 1.06)	(1.00 – 1.05)	(1.04 – 1.06)	(1.04 – 1.06)
	P	0.20	0.29	**0.002**	**0.02**	**<0.001**	**<0.001**
Male sex	HR	1.24	1.35	1.14	1.13	1.51	1.60
	(95% CI)	(0.39 – 3.91)	(0.42 – 4.31)	(0.57 – 2.28)	(0.54 – 2.40)	(1.01 – 2.27)	(1.08 – 2.37)
	P	0.72	0.62	0.71	0.74	0.04	**0.02**
Asian ethnicity (Ref: White)	HR	1.85	1.61	2.53	2.20	1.75	1.61
	(95% CI)	(0.46 – 7.38)	(0.48 – 5.38)	(0.91 – 7.00)	(0.84 – 5.79)	(1.02 – 3.00)	(0.96 – 2.68)
	P	0.38	0.44	0.07	0.11	0.04	0.07
Black ethnicity (Ref: White)	HR	-	-	0.78	0.67	1.08	0.93
	(95% CI)	-	-	(0.19 – 3.27)	(0.18 – 2.53)	(0.52 – 2.22)	(0.46 – 1.88)
	P	-	-	0.73	0.56	0.84	0.84
Mixed ethnicity (Ref: White)	HR	-	-	-	-	1.79	1.85
	(95% CI)	-	-	-	-	(0.35 – 9.01)	(0.32 – 10.87)
	P	-	-	-	-	0.48	0.49
IMD 2 (Ref: 1)	HR	3.04	2.77	3.07	2.74	1.36	1.26
	(95% CI)	(0.27 – 33.71)	(0.24 – 31.59)	(1.42 – 6.64)	(1.29 – 5.89)	(0.73 – 2.48)	(0.69 – 2.30)
	P	0.37	0.41	**0.004**	**0.009**	0.33	0.46
IMD 3 (Ref: 1)	HR	2.06	1.66	1.30	1.18	1.27	1.17
	(95% CI)	(0.16 – 27.34)	(0.12 – 22.56)	(0.48 – 3.51)	(0.49 – 2.87)	(0.71 – 2.26)	(0.68 – 2.00)
	P	0.58	0.70	0.61	0.71	0.42	0.58
IMD 4 (Ref: 1)	HR	3.12	2.61	0.78	0.75	0.90	0.92
	(95% CI)	(0.26 – 37.26)	(0.22 – 31.41)	(0.26 – 2.36)	(0.27 – 2.06)	(0.37 – 2.16)	(0.43 – 1.96)
	P	0.37	0.45	0.66	0.58	0.81	0.82
IMD 5 (Ref: 1)	HR	6.09	4.62	2.46	2.17	1.24	1.12
	(95% CI)	(0.84 – 43.74)	(0.61 – 34.74)	(0.81 – 7.47)	(0.74 – 6.36)	(0.64 – 2.41)	(0.63 – 1.98)
	P	0.07	0.14	0.11	0.16	0.53	0.69
Ever smoker	HR	0.35	0.38	0.71	0.74	0.90	0.96
	(95% CI)	(0.08 – 1.62)	(0.08 – 1.74)	(0.29 – 1.73)	(0.30 – 1.85)	(0.58 – 1.39)	(0.65 – 1.41)
	P	0.18	0.21	0.45	0.52	0.63	0.82
History of cerebrovascular	HR	-	-	0.96	0.92	0.84	0.74

disease	(95% CI) *P*	- -	- -	(0.11 – 8.42) 0.97	(0.11 – 7.82) 0.94	(0.24 – 2.91) 0.79	(0.22 – 2.47) 0.62
History of peripheral vascular disease	HR (95% CI) *P*	- - -	- - -	- - -	- - -	0.80 (0.17 – 3.83) 0.78	0.63 (0.17 – 2.34) 0.49
History of diabetes	HR (95% CI) *P*	1.65 (0.33 – 8.19) 0.54	1.68 (0.39 – 7.31) 0.49	0.66 (0.15 – 2.91) 0.58	0.55 (0.14 – 2.10) 0.38	1.35 (0.70 – 2.64) 0.37	1.19 (0.54 – 2.60) 0.67
History of ischaemic heart disease	HR (95% CI) *P*	2.29 (0.34 – 15.58) 0.40	1.87 (0.4 – 10.38) 0.48	5.66 (2.39 – 13.39) **<0.001**	4.06 (1.73 – 9.55) **0.001**	2.88 (1.67 – 4.95) **<0.001**	2.15 (1.19 – 3.87) **0.01**

Table 3. Factors associated with MACE at following propensity score matching by pre-transplant CAD screening investigations. Measures of effect are expressed as hazard ratios (HR) and confidence interval (CI) and each time point. Significant P values are shown in bold. Hazard ratios marked by '-' reflect no events within the specified time period in this patient group.

Supplementary Material

Table S1. Patient and transplant characteristics in propensity score matched and unmatched individuals.

Table S2. Balance of characteristics of patients pre- and post-matching based on their propensity score for screening.

Table S3. Factors associated with MACE at 5 years in the propensity matched group with the inclusion of transplant centre.

Table S4. Factors associated with MACE following propensity score matching in the 'incident transplant' cohort only.

Table S5. Adjusted regression analysis using competing risk methodology examining risk of MACE and pre-MACE death in propensity score matched transplant recipients.

Table S6. Cox regression analysis examining effect of screening on MACE using inverse probability weighting methodology in the whole population.

Table S7. HES ICD-10 and OPCS-4 codes used to identify MACE.

Figure S1. Screening patterns in the 'waitlisted' group between ATTOM recruitment and transplantation.

Figure S2. Combinations of MACE components post-transplantation.

Disclosure Statement

The authors (other than James Fotheringham) received funding from the National Institute for Health Research (NIHR) under the Programme Grants for Applied Research scheme (RP-PG-0109-10116) for completion of the ATTOM study. James Fotheringham received personal fees from Fresenius Medical Care and grants from Vifor Pharma and Novartis outside the submitted work.

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Acknowledgements

This paper presents research from the Access to Transplantation and Transplant Outcome Measures (ATTOM) study which was funded by the National Institute for Health Research (NIHR) under the Programme Grants for Applied Research scheme (RP-PG-0109-10116). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Many thanks to the ATTOM research team, the research nurses and to the patients in the study.

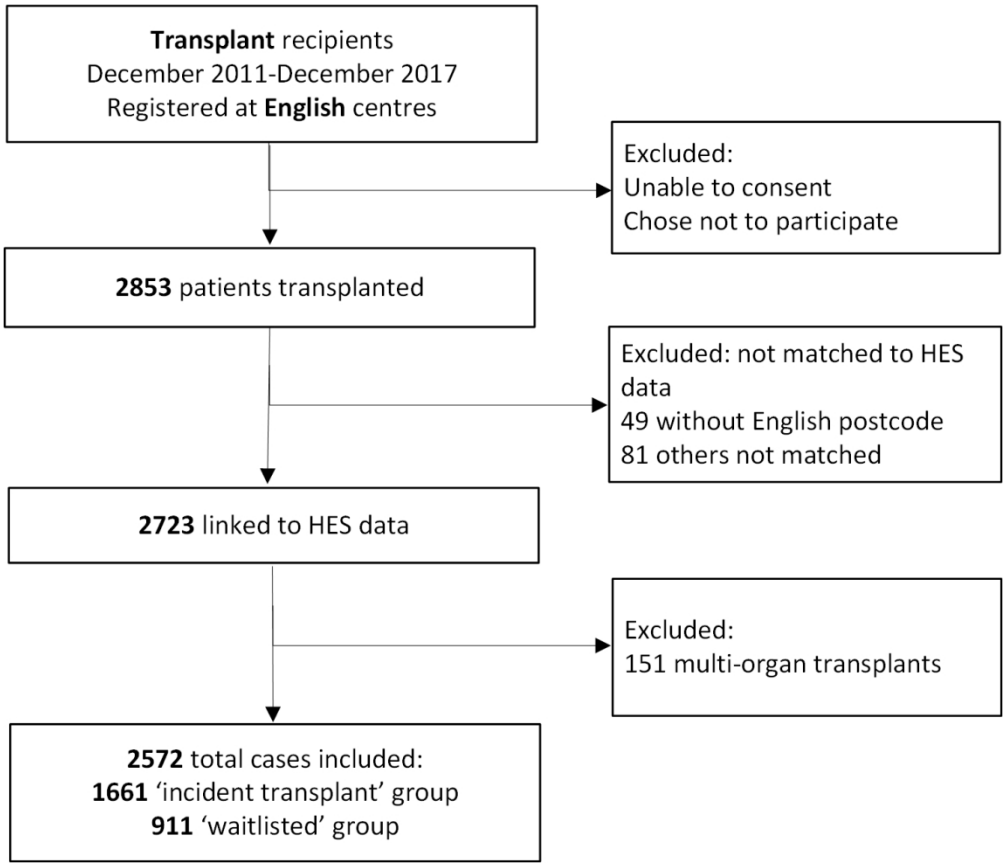

Figure 1. Flow chart depicting patients included in the study.

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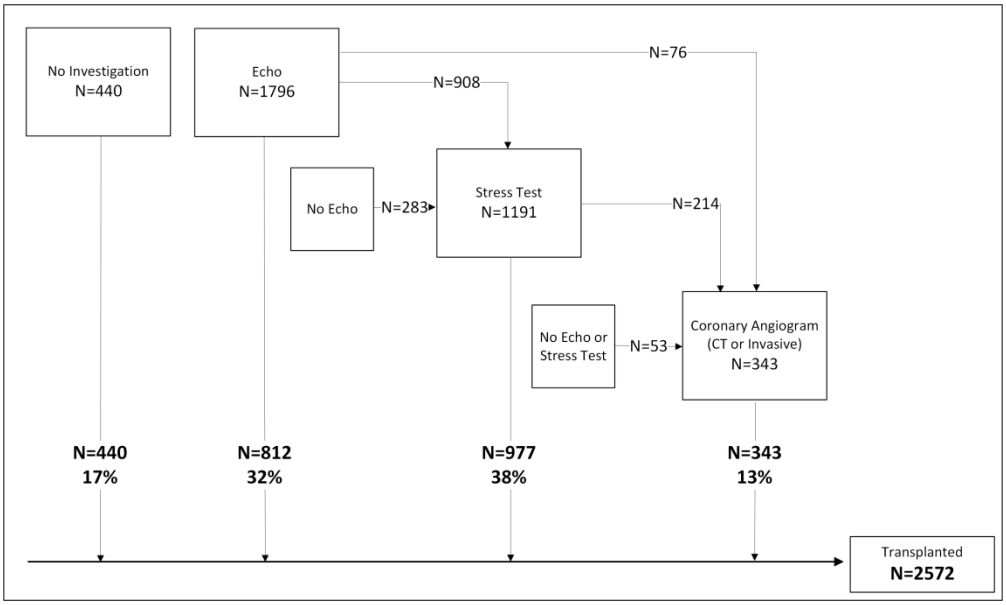

Figure 2. Pattern of cardiovascular workup. Note an unknown number of patients will have been tested and excluded from transplant based on test results. Stress test comprises exercise tolerance test, dobutamine stress echocardiogram and myocardial perfusion scan. Abbreviations: echo: echocardiogram; CT: computed tomography.

277x165mm (300 x 300 DPI)

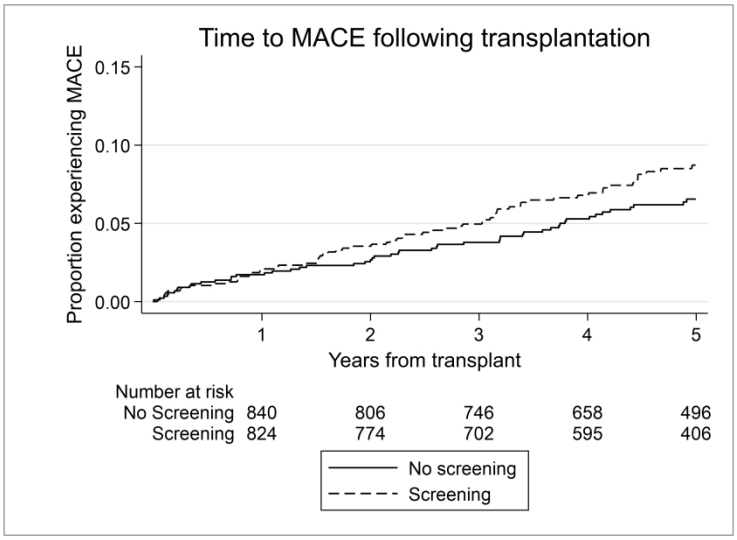

Figure 3. Kaplan-Meier estimator curve demonstrating MACE events after transplant in patients undergoing screening for coronary artery disease versus those who did not in the propensity matched cohort.

338x190mm (300 x 300 DPI)

Supplementary Material

Supplementary Tables

Table S1. Patient and transplant characteristics in propensity score matched and unmatched individuals.

	Propensity matched N=1760	Not propensity matched N=812	P value
Age (years) (n=2572)	50 [43 – 58]	54 [34 – 64]	0.09
Male Sex (n=2572)	1043 (59)	521 (64)	0.02
Ethnicity (n=2563)			
White	1376 (78)	566 (70)	
Asian	203 (12)	154 (19)	<0.001
Black	161 (9)	62 (8)	
Mixed	20 (1)	21 (3)	
PRD (n=2555)			
GN	437 (25)	174 (22)	
Other	349 (20)	193 (24)	
PKD	335 (19)	90 (11)	
Uncertain	202 (11)	105 (13)	<0.001
PN	189 (11)	79 (10)	
Diabetes	103 (6)	111 (14)	
Hypertension	121 (7)	39 (5)	
Renovascular	15 (1)	13 (1)	
History of Diabetes (n=2572)	162 (9)	171 (21)	<0.001
History of IHD (n=2572)	57 (3)	130 (16)	<0.001
History of PVD (n=2572)	18 (1)	44 (5)	<0.001
History of CeVD (n=2572)	58 (3)	52 (6)	<0.001
Ever smoker (n=2507)	563 (32)	261 (35)	0.15
RRT modality (n=2556)			
HD	1010 (58)	482 (60)	
PD	364 (21)	140 (17)	0.09
Transplant	15 (1)	3 (1)	
Pre-emptive	361 (20)	181 (22)	
IMD (n=2572)			
1 – Most deprived	372 (21)	235 (29)	
2	367 (21)	151 (19)	
3	360 (20)	130 (16)	<0.001
4	356 (20)	149 (18)	
5 – Least deprived	305 (17)	147 (18)	
Centre (anonymised) (n=2572)			
1	129 (7)	53 (7)	
2	81 (5)	60 (7)	
3	211 (12)	53 (7)	
4	119 (7)	43 (5)	<0.001
5	49 (3)	25 (3)	
6	85 (5)	41 (5)	
7	59 (3)	44 (5)	
8	162 (9)	73 (9)	

9 10 11 12 13 14 15 16 17 18	80 (5) 98 (6) 76 (4) 161 (9) 97 (6) 53 (3) 111 (6) 35 (2) 92 (50 62 (4)	34 (4) 46 (6) 52 (6) 51 (6) 41(5) 40 (5) 83 (10 19 (2) 25 (3) 29 (4)	
First transplant (n=1842)	157 (14)	64 (13)	0.77
Live donor (n=2572)	520 (30)	251 (31)	0.48
Creatinine at 1 year (n=2354)	125 [101 – 161]	123 [100 – 156]	0.21
Creatinine at 5 years (n=1235)	126 [100 – 162]	124 [103 – 161]	0.69
Graft failure over follow-up	191 (11)	92 (11)	0.72
MACE at 90 days	14 (0.8)	9 (1)	0.43
MACE at 1 year	32 (2)	20 (3)	0.28
MACE at 5 years	117 (8)	82 (13)	0.002

Table 2. Patient and transplant characteristics in propensity score matched and unmatched individuals. Data are expressed as number (%) or median [interquartile range]. Abbreviations: IMD, index of multiple deprivation; PRD, primary renal diagnosis; GN, glomerulonephritis; PKD, polycystic kidney disease; PN, pyelonephritis; IHD, ischaemic heart disease; PVD, peripheral vascular disease; CeVD, cerebrovascular disease; RRT, renal replacement therapy; HD, haemodialysis; PD, peritoneal dialysis; IMD, Index of Multiple Deprivation; MACE major adverse cardiovascular event.

Table S2. Balance of characteristics of patients pre- and post-matching based on their propensity score for screening.

		Unmatched characteristics Exposure to CAD Screening			Propensity-score matched Exposure to CAD Screening		
		No	**Yes**	**SMD**	**No**	**Yes**	**SMD**
Age (years) Median [IQR]		46 [36-55]	56 [47-63]	0.7	49 [42-58]	52 [43-57]	0.05
Male		59%	63%	0.09	60%	59%	0.02
Ethnicity	White Asian Black Mixed	71% 17% 10% 2%	80% 11% 8% 2%	0.20	80% 11% 8% 1%	77% 12% 10% 2%	0.13
IMD	1 2 3 4 5	27% 20% 19% 17% 17%	20% 21% 19% 22% 18%	0.19	21% 19% 19% 21% 20%	21% 23% 22% 20% 15%	0.17
PRD	GN Other PKD Uncertain PN Diabetes Hypertension Renovascular	26% 23% 16% 12% 12% 4% 6% 1%	22% 20% 18% 2% 9% 12% 6% 11%	0.33	26% 19% 19% 11% 11% 6% 7% 1%	24% 21% 19% 12% 10% 6% 7% 1%	0.11
Diabetes		7%	18%	0.34	10%	9%	0.03
IHD		3%	11%	0.31	4%	2%	0.11
PVD		1%	4%	0.17	1%	1%	0.05
CeVD		3%	5%	0.10	4%	3%	0.03
Ever smoker		29%	36%	0.14	34%	29%	0.12
RRT Modality	HD PD Transplant Pre-emptive	57% 21% 1% 21%	60% 18% 1% 21%	0.11	57% 22% 1% 20%	58% 20% 1% 21%	0.10

Table 3. Balance of characteristics of patients pre- and post-matching based on their propensity score for screening. Data expressed as percentages unless otherwise specified. Abbreviations: IMD, index of multiple deprivation (marker of socioeconomic status); PRD, primary renal diagnosis; GN, glomerulonephritis; PKD, polycystic kidney disease; PN, pyelonephritis; IHD, ischaemic heart disease; PVD, peripheral vascular disease; CeVD, cerebrovascular disease; RRT, renal replacement therapy; SMD, standardised mean difference.

Table S3. Factors associated with MACE at 5 years in the propensity matched group with the inclusion of transplant centre.

	Adjusted HR (95% CI)	P value
Screening investigation	1.29 (0.83 – 2.01)	0.26
Age (years)	1.03 (1.02 – 1.05)	<0.001
Male sex	1.46 (1.00 – 2.15)	0.05
Asian ethnicity (Ref: White)	1.52 (0.92 – 2.54)	0.10
Black ethnicity (Ref: White)	1.01 (0.51 – 2.00)	0.99
Mixed ethnicity (Ref: White)	0.58 (0.08 – 4.26)	0.59
History of diabetes	1.68 (1.03 – 2.73)	0.04
History of ischaemic heart disease	2.53 (1.32 – 4.84)	0.005
History of cerebrovascular disease	0.77 (0.28 – 2.12)	0.61
Centre (Ref: Bristol)		
1	0.92 (0.29 – 2.16)	0.84
2	0.45 (0.17 – 1.15)	0.10
3	0..46 (0.16 – 1.31)	0.15
4	0.97 (0.31 – 3.01)	0.96
5	0.92 (0.34 – 2.49)	0.87
6	0.82 (0.28 – 2.41)	0.72
7	0.69 (0.28 – 1.74)	0.43
8	0.50 (0.16 – 1.57)	0,24
9	0.85 (0.32 – 2.23)	0.73
10	0.43 (0.13 – 1.43)	0.17
11	0.34 (0.11 – 1.03)	0.06
12	0.70 (0.26 – 1.91)	0.49
13	0.32 (0.07 – 1.49)	0.15
14	0.83 (0.34 – 2.03)	0.69
15	1.45 (048 – 4.35)	0.51
16	0.53 (0.18 – 1.56)	0.25
17	0.56 (0.15 – 2.08)	0.39

Table S4. Cox regression of factors associated with MACE at 5 years in the propensity matched group with the inclusion of transplant centre.

Table S4. Factors associated with MACE following propensity score matching in the 'incident transplant' cohort only.

		90 day Unadjusted	90 day Adjusted	1 year Unadjusted	1 year Adjusted	5 year Unadjusted	5 year Adjusted
Screening investigation	HR (95% CI) *P*	2.01 (0.62 – 6.40) 0.25	2.27 (0.57 – 8.96) 0.24	1.76 (0.79 – 3.90) 0.16	2.10 (0.80 – 5.54) 0.13	1.29 (0.83 – 2.00) 0.26	1.36 (0.89 – 2.09) 0.15

Table S5. Factors associated with MACE following propensity score matching in the 'incident transplant' cohort only (n=1156). Measures of effect are expressed as hazard ratios (HR) and confidence interval (CI). Adjusted analyses include all variables used to generate the propensity score.

Table S5. Adjusted regression analysis using competing risk methodology examining risk of MACE and pre-MACE death in propensity score matched transplant recipients.

		90 day MACE	90 day Pre-MACE death	1 year MACE	1 year Pre-MACE death	5 year MACE	5 year Pre-MACE death
Screening investigation	SHR (95% CI) *P*	0.80 (0.31 – 2.04) 0.64	3.36 (0.73 – 15.41) 0.12	1.13 (0.52 – 2.47) 0.76	0.97 (0.39 – 2.38) 0.95	1.32 (0.88 – 1.97) 0.18	1.24 (0.93 – 1.65) 0.14

Table S6. Adjusted regression analysis using competing risk methodology examining the effect of screening on risk of MACE and pre-MACE death in propensity score matched transplant recipients. Measures of effect are expressed as subdistribution hazard ratios (SHR) and confidence interval (CI). Analyses were adjusted for all variables included in the generation of the propensity score.

Table S6. Cox regression analysis examining effect of screening on MACE using inverse probability weighting methodology in the whole population.

		Adjusted Cox model with inverse probability weights N=2502	Adjusted Cox model in propensity score matched group N=1760
Screening investigation 90 days	HR (95% CI) *P*	0.70 (0.29 – 1.68) 0.43	0.80 (0.31 – 2.05) 0.64
Screening investigation 1 year	HR (95% CI) *P*	0.99 (0.51 – 1.91) 0.98	1.12 (0.51 – 2.47) 0.77

Table S7. Cox regression analyses investigating effect of screening on MACE using inverse probability weighting methodology in the whole population in comparison to the propensity score matched group. Measures of effect are expressed as hazard ratios (HR) and confidence interval (CI) and each time point.

Table S7. HES ICD-10 and OPCS-4 codes used to identify MACE.

	Procedure Coding
Unstable angina (ICD-10)	I20.0: Unstable angina (position 1 only)
Myocardial infarction (ICD-10)	I21.0-3: STEMI (any position) I21.4 - Acute subendocardial myocardial infarction (position 1 only)
Coronary angioplasty (OPCS-4)	K49 - Transluminal balloon angioplasty of coronary artery K50 - Other transluminal operations on coronary artery K75 - Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery
Coronary artery bypass graft (OPCS-4)	K40-46: Replacement or bypass of coronary artery

Table S1. HES ICD-10 and OPCS-4 codes used to identify MACE.

Supplementary Figures

Figure S1. Screening patterns in the 'waitlisted' group between ATTOM recruitment and transplantation.

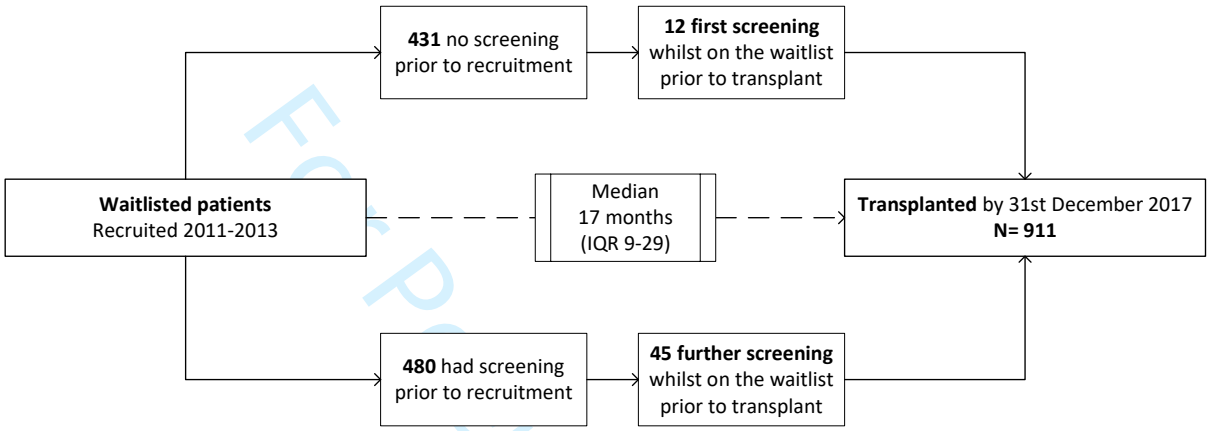

Figure S1. Screening patterns in the 'waitlisted' group between ATTOM recruitment and transplantation.

Figure S2. Combinations of MACE components post-transplantation.

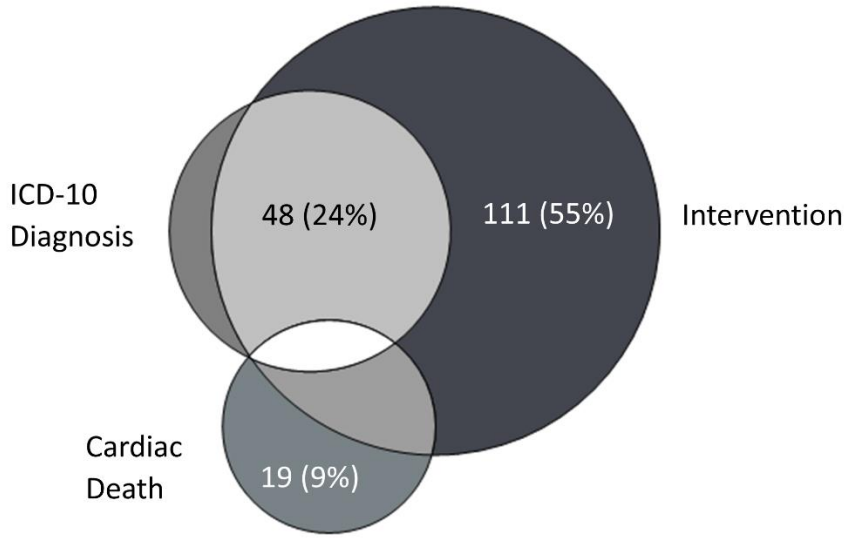

Figure S2. Combinations of MACE components in the 202 individuals experiencing an event post-transplantation. 8 patients (4%) had a medical diagnosis only recorded; 5 patients (2%) had a medical diagnosis, intervention and cardiac death recorded; 11 patients (5%) had a cardiac death and intervention recorded.

Modified STROBE Statement—checklist of items that should be included in reports of observational studies (Cohort/Cross-sectional and case-control studies)

	Item No	Recommendation	Manuscript page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	17
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	17
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	17
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and	18-19

		effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement).	17-18
Bias	9	Describe any efforts to address potential sources of bias	20-21
Study size	10	Explain how the study size was arrived at (if applicable)	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	18
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	18-21
		(*b*) Describe any methods used to examine subgroups and interactions	20-21
		(*c*) Explain how missing data were addressed	19
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	20-21
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	6

		(c) **Use of a flow diagram**	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	23 (Table 1)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8-9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from	16

		similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.